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NIACIN #122

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O N

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NIACIN

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NIACIN

Summary

The term "niacin" was suggested (NRC/NAS) as a generic, including both nicotinic acid and nicotinamide, in 1968. The Food Chemicals Codex applies the term to nicotinic acid and uses "niacinamide" for nicotinamide. The latter was the third member of the vitamin B-complex to be identified and was called vitamin B_3; it was isolated from heart and liver tissues, and in 1935 was found to be a component of two coenzymes, diphosphopyridine nucleotide (DPN) and nicotinamidediphosphopyridine (NAD), the end, metabolically active, product. Niacin, or a derivative, is required by all living cells and has been associated with more than 40 biochemical reactions dependent upon the enzymes incorporating it; glycolysis, pyruvate metabolism, pentose biosynthesis and high-energy phosphate bond synthesis are some of the reactions involving NAD and its triphosphate, NADP. Lipid, amino acid and protein metabolism, as well as photosynthesis, also involve the niacin enzyme systems: it has been suggested that niacin and nicotinamide are not properly classified as vitamins; tryptophan, an amino acid, is the precursor of niacin in the body and the niacin may be regarded as an intermediate metabolite between tryptophan and NAD. Goldsmith (1621) has presented a chronology of niacin research during the years 1915-1965, and a discussion of the importance of nutrition:

Highlights of Niacin Research
- 1915-1940
  - Pellagra-A deficiency disease
  - Blacktongue in dogs-Canine pellagra
  - Niacin-A coenzyme and tissue constituent
  - Niacin-The antipellagra factor
- 1940-1955
  - Tryptophan-A niacin precursor
  - Human Niacin Requirement-4.4 mg/1,000 calories
  - Corn diets-Relationship to pellagra
  - Methods for evaluation of niacin nutrition
  - Metabolic fuctions of niacin
- 1955-1965
  - Niacin deficiency induced by disease
  - Niacin deficiency induced by drugs
  - Hereditary niacin-Tryptophan abnormalities
  - Niacin-A hypocholesterolemic agent

Goldsmith (1620) has reviewed the niacin-tryptophan relationship in man up to about 1958. During the 1930's, niacin was demonstrated to be the pellagra-preventive vitamin, but certain aspects of the disease

remained unexplained. By the late 1940's, tryptophan was demonstrated to be effective in the treatment of pellagra and was suggested to be the presursor of niacin, with quinolinic acid as an intermediate metabolite or an alternate end product. Isotope (C14) studies in rats conclusively showed tryptophan to be the precursor of niacin. Studies in the mid- and late 1950's have shown dietary tryptophan conversion to niacin in the ratio of about 1 mg niacin to 55.8 mg tryptophan. Niacin and tryptophan requirements have been related to the caloric intake (about 4.4 mg niacin/1000 cal except in diets of less than 2000 cal which require 8.8 mg niacin) and to the body size of the individual. The minimum human requirement for niacin is about 9 to 12 mg daily in adults, including that formed from tryptophan.

The researcher most frequently associated with studies of niacin, particularly in regard to its therapeutic applications, has been Hoffer (1937) of the University Hospital, Saskatoon, Saskatchewan, Canada. Hoffer has presented a paper on the biochemistry of nicotinic acid and nicotinamide (1967), prefaced by a brief discussion of the biochemistry, and devoted to consideration of side effects and toxicity in the use of the substances in therapy. In 1969, Hoffer (1939) presented a more detailed study on the safety, side effects and relative lack of toxicity of nicotinic acid and nicotinamide.

Mosher (2985) reviewed the literature on nicotinic acid side effects and toxicity; it is observed that at the massive therapeutic doses employed, nicotinic acid should be classified as a drug. The toxicity stems primarily from its cholesterol-lowering effect in the treatment of atherosclerosis. The oral LD50's of nicotinic acid in mice and rats range from 5 to 7 g/kg, with nicotinamide two to three times as toxic as the acid. Mosher concludes that the question of niacin's efficacy in the treatment of schzophrenia has not been resolved. In a "letter to the editor", American Journal of Psychiatry, Newhold (3109) comments critically on Mosher's report suggesting that Mosher must have overlooked Hoffer's (1939) article noted above.

A recent review (1972) by Wittkopp and Abuzzahab (4628) of the literature covering studies of the effectiveness of nicotinic acid in the treatment of schizophrenia concludes as follows:

> 1. Nicotinic acid therapy as an adjunct added to the treatment on schizophrenia seems to have a beneficial effect, if the chronicity of the disease is not substantial. This statement is derived more from the fact that there is a lack of data contradicting it than from evidence which supports the statement. Abram Hoffer's repeated success with nicotinic acid therapy is encouraging, but aside from his work and that of his immediate associates, the use of the nicotinic acid approach in the treatment of early schizophrenia has not been subjected to a rigorous research program.

2. Neither nicotinic acid nor nicotinamide adenine dinucleotide alone in the treatment of chronic schizophrenia seems to be of benefit. The studies conducted to this date have not been encouraging. The usefulness of the vitamin in the treatment of schizophrenia would at first glance, seem to be inversely proportional to the length of illness. This is, however, assuming that nicotinic acid is, indeed, a useful tool, and this assumption cannot be confidently made without more sound studies.

Gregory (1702), two decades ago, reviewed in some detail the role of niacin in mental health and disease. Nicotinamide deficiency (pellagra), toxic psychosis, encephalopathies, organic psychoses and pychiatric disorders unrelated to nutritional deficiencies are discussed. The pharmacology and therapeutic application of nicotinic acid are discussed. A summary of the discussions is shown below:

(a) Psychiatric disorders attributed wholly to nicotinic acid defiency
  (i) Pellagra, the characteristic mental changes progressing as follows:

$$\text{Depression} \overset{\text{reversible}}{\rightleftharpoons} \text{Delirium} \xrightarrow{\text{irreversible}} \text{Dementia.}$$

  (ii) Pellagra sine pellagra, mental changes occurring in the absence of physical changes (these mental changes consisting in mild cases of psychoneurotic syndromes).
  (iii) Nicotinic acid deficiency encephalopathy, with specific neurological manifestations.

(b) Psychiatric disorders with possible relative or associated deficiency of nicotinic acid, but in which part of the therapeutic effect of nicotinic acid has also been attributed to mass action and/or vasodilatation
  (i) Atypical organic psychoses associated with malnutrition
  (ii) Organic psychoses associated with alcoholism
  (iii) Organic psychoses associated with senescence and senility.

(c) Psychiatric disorders apparently unrelated to nutritional deficiency, in which the therapeutic effect of nicotinic acid has usually been attributed to vasodilatation
  (i)Organic brain dysfunction following cerebral trauma, and hypoxic episodes.
  (ii) Organic brain dysfunction following somatic psychiatric therapies)e.g. E.C.T., prolonged insulin coma, lobotomy).
  (iii) Apparently functional depressive and anxiety reactions.

The most significant aspect of niacin lies in its relationship to pellagra, the deficiency disease. Kodicek (2345) described the problem in its universal sense, noting that the solution lies in economic and social factors. In 1929, about 200,000 pellagrins resided in the southern regions of the United States; more than 7,000 deaths were reported in that year. Public Health measures, chiefly through enrichment (niacin) policies, reduced the deaths to 2133 by 1940, and only 70 in 1956. Pellagra has been, and remains, characteristic of many

world populations. Nutritional content of various foodstuffs, and approaches to the correction of the disease are discussed.

Twenty years before Kodicek's report, Iversen (2071) reported on nicotinic acid and its therapeutic use. The introductory paragraph reads: "It is interesting that nicotinic acid and therapeutic experiments with this substance are connected with the most rapidly occurring and absolutely staggering effect on pellagra."

An early study (1939) of the acute toxicity of nicotinic acid and nicotinamide was made by Unna (4423). Mice tolerated oral doses of up to 1 g/kg without toxic symptoms; lethal doses subcutaneously administered were 1.8 g/kg nicotinamide and 3 g/kg sodium nicotinate. Extrapolation from mortality curves indicated the following LD_{50}'s: mouse, oral 4.3 g/kg nicotinic acid, 2.1 g/kg nicotinamide; subcutaneous, 5.2 g/kg nicotinic acid, 2.9 g/kg nicotinamide; for rat, oral, 5.3 g/kg nicotinic acid, 2.6 g/kg nicotinamide; subcutaneous, 7 g/kg nicotinic acid and 3.5 g/kg nicotinamide.

Chen et al. (808) in 1938 compared the toxicities of nicotinic acid and nicotine in mice, rats and guinea pigs. The LD_{50}, nicotinic acid, for mice was between 4 and 4.5 g/kg; for rat, somewhat less than 3.5 g/kg; and for guinea pig, about the same as for rats. These were intravenous doses.

Brazda and Coulson (520) determined the toxicity of nicotinic acid and some derivatives. The LD_{50}, subcutaneously administered, nicotinic acid in young rats was about 5 g/kg; for nicotinamide, about 1.68 g/kg.

Numerous examples of food poisoning due to the ingestion of meat to which unusual quantities of sodium nicotinate had been added to preserve the redness of the meat, have been reported. A typical example is that described by Press and Yeager (3474), involving a number of college students affected by typical symptoms of nicotinic acid poisoning: itching of skin, flushing of face, neck and extremities and in some instances swelling of extremities and lips and dryness of mouth. The meat for the evening meal was shown to be excessively loaded with sodium nicotinate.

In addition to the acute toxicity studies noted in the foregoing, Unna (4423) performed some chronic studies. Rats, given 1 g/kg sodium nicotinate daily orally, for 40 days; chickens given 100 mg/kg daily for 3 weeks; and dogs given 2 g/kg daily for 35 days, all showed no toxic symptoms. Metabolism, respiration and circulation appeared unaffected. Chen et al. (808) also performed chronic studies with nicotinic acid in mice (500 mg/kg daily intravenously for 4 weeks) without apparent effect; oral doses of 2 g/kg in dogs resulted in the death of one animal after 19 days, and a second at 20 days after receiving a total of 40 g nicotinic acid showed severe toxic symptoms and was sacrificed. Smaller chronic doses of up to 1 g/kg daily, orally in dogs, produced no ill effects.

Handler (1802) in early studies (1944) with rabbits and guinea pigs given large quantities (1 and 2% nicotinamide added to the diet for several weeks) produced no toxic effects. Apparently the difference in reaction of the rat, (which would have been expected to show marked toxic effects at these doses), and the rabbit and guinea pig, was due to the absence in the latter two animals of synthesis of N-methylnicotinamide which depletes the available methionine supply in the rat.

Spies et al. (4127) demonstrated that not only in pellagra does the characteristic porphyrinuria disappear after administering nicotinic acid, but in other diseases, as well. Doses of 500 mg of nicotinic acid given to hospital patients suffering porphyrinuria showed negative tests within 24 hours; in severe pellagra, several days elapsed before negative tests for porphyrinuria were obtained.

A relationship of pellagra and psychosis was established as long as 40 years ago, and both abnormalities showed improvement by nicotinic acid treatment. Sydenstricker and Clerkley (4249) demonstrated successful treatment of a number of severe psychiatric disorders with oral or intravenous doses of up to 2 g nicotinic acid.

Morgan (2965) reported successful therapy with nicotinic acid of tension headache; it is uneffective in migraine. The therapy consisted of frequent intravenous doses of 100 mg of nicotinic acid for several months, together with increasing oral doses of up to 900 mg. Forty-four of 50 cases treated responded favorably.

Rook (3666) reported success in the relief of angina in 15 cases by intravenous nicotinic acid. Doses of 25 mg were given initially six times daily, followed by variable doses, 5-50 mg, and with intervals without dosing. Rook proposed that the angina condition resulted from an inability to absorb the necessary vitamin when taken orally.

A report by the American Medical Association, Council on Drugs (108), in 1958 suggested that in spite of reported reduction in cholesterol levels by large (3-6 g) doses of nicotinic acid, the lack of evidence associating cholesterol levels with atherosclerotic cardiovascular diseases, makes the use of nicotinic acid simply experimental in other than the treatment or prevention of pellagra.

Large doses (600 mg/kg or greater) of nicotinamide given intraperitoneally to mice with implanted mammary adenocarcinoma, were shown by Shapiro et al. (3960) to be carcinostatic. At these doses, the toxicity of nicotinamide prevented other than inhibition of tumor growth; recession of tumors was not observed.

Osmond and Hoffer (3235) reported the results of a nine-year study of successful treatment of schizophrenia with niacin and advanced a theory of adrenaline metabolite cause of schizophrenia in which faulty metabolism of adrenaline was responsible. Any substance which reduces adrenaline should, in this theory - have therapeutic value in schizophrenia. Niacin was suggested as a competitor for methyl groups which

are utilized in the conversion of noradrenaline to adrenaline. The failure of doctors, in general to recognize the usefulness of niacin in the treatment of schizophrenia was deplored by the authors. Denson (1098), from the same hospital, performed similar studies with similar results. Hoffer (1940, 1941, 1942) has been outstanding in studies with niacin in the therapy of schizophrenia and has described "mega-vitamin therapy" and orthomolecular therapy". Ashby et al. (169) in 1960 and Wittenborn et al. (4627) as recently as 1973 have made studies of niacin therapy of schizophrenia, concluding that niacin was of little or no special benefit in the treatment of the disease. Heninger and Bowers (1873) reported two cases of emergent psychosis possibly accelerated or worsened by the application of niacin.

A structural analogue of nicotinamide, 6-aminonicotinamide, has been shown by studies reported by Goldstein et al. (1630), to be teratogenic and to be a competitive inhibitor of nicotinamide. Four strains of inbred mice showed genetically-based differences in the degree of malformations induced by the analogue, possibly due to factors transmitted through the egg cytoplasm.

Dreizen et al. (1164) reported a direct relationship between the nicotinic acid content of saliva and the incidence of dental caries; persons with chronic endemic pellagra have a low caries-incidence, for example. It was suggested that nicotinic acid is an essential growth factor for the lactic acid producing oral bacteria as related to dental caries.

Dietary supplements of niacin amide given to rats by Horger and Gerheim (1981) over a period of 12 weeks maximum showed no significant change in growth rate at doses of 0.1%; 0.2% niacinamide enhanced growth; and 0.4% inhibited growth.

Taylor et al. (4297) analyzed a variety of tumors for nicotinic acid content and compared the results with that of noncancerous tissues. The cancerous condition showed lowered nicotinic acid content: cancerous tissue ranged from 13 to 59 gamma/g tissue; normal tissue, 18 to 178 gamma/g.

Fecal and urinary metabolites found in mice, rats hamsters and dogs following injection with radioactive C^{14}-nicotinic acid or amide by Leifer et al. (3561) were shown to be: N'-methylnicotinamide; nicotinic acid; nicotinuric acid; N'-methyl-6-pyridone-3-carboxylamide; and nicotinamide. One unidentified metabolite was not trigonelline. All species studied produced $C^{14}O_2$ from both nicotinic acid and the amide; CO_2 should be included in a list of the known metabolites of nicotinic acid and nicotinamide.

Collins and Chaykin (911) also used radioactive C^{14}-labelled nicotinic acid and nicotinamide (7-C^{14}-labelled), in studies with mice to demonstrate that in that animal, nicotinamide serves as a precursor of NAD. In all tissues analysed after administering both the labelled acid and amide intraperitoneally, more radioactivity was found in NAD after 7-C^{14}-nicotinamide than from 7-C^{14}-nicotinic acid. When nicotinamide was given

orally or injected directly into the intestine, it appeared unchanged in the blood; nicotinic acid similarly administered appeared as nicotinamide in the blood within minutes, and after passage through the liver appeared completely converted to nicotinamide. The same authors, Collins and Chaykin (912) reported a year later in greater detail on these experiments regarding conversion of the nicotinic acid to nicotinamide in the mouse.

Numerous studies of the metabolic fate of nicotinic acid and nicotinamide have been reported: Lee et al. (2550) isolated two newly identified (in 1969) rat urine metabolites, 6-hydroxynicotinic acid and 6-hydroxynicotinamide; Lee (2548) observed the formation and degradation of NAD in the rat liver; Reddi and Kodicek (3567) developed special chromatographic techniques for the study of urinary metabolites from the ingestion of nicotinic acid, nicotinamide and tryptophan in man and rat; an early study (1942) by Sarett et al. (3801) demonstrated that trigonelline and nicotinuric acid were the sole end-products (urinary) of nicotinic acid metabolism in man; Abelson et al. (21) twenty years later, identified in human plasma two compounds, suggested to be N'-methyl-4-pyridone-3-carboxamide and N'-methyl-2-pyridone-5-carboxamide; Lee et al. (2546) using the C^{14}-labelled nicotinic acid, following urine and plasma radioactivity in a normal male human subject over a period of nearly 3 weeks, with a finding of a biphasic excretion pattern suggesting several distinct routes by which nicotinic acid is metabolized in man; Ellinger and Kader (1212) performed detailed studies of the metabolism of nicotinamide derivatives in man, dog, cat, rat and guinea pig with a view to distinguishing a species difference permitting classification based on biochemical properties; an even more detailed study with the same general goal was reported by Perlzweig et al. (3360), using man, rat, dog, pig, rabbit, guinea pig, goat, sheep and calf. Some disparities between the latter two studies with regard either to identification of the metabolites or in terminology can be seen. A comparison of these findings with those of the paper nearly twenty years later by Lee and Gholson (2550) already described in this section of the monograph, is fruitful.

Ammon and Estler (111), using white mice, investigated the influence of nicotinic acid on liver glycogenolysis; the lowering of the free fatty acid concentrations by nicotinic acid accelerates the carbohydrate breakdown to supply the energy normally provided by FFA, and indirect rather than a direct consequence of an injected nicotinic acid dose.

Carlson and Nye (685) showed that sodium nicotinate ingested subcutaneously in rats resulted in: significant reduction of plasma FFA, triglycerides and cholesterol levels. Liver triglycerides were first reduced and then elevated; liver cholesterol was not affected. The inhibition of FFA mobilization was said to be at least partly responsible for the depression of plasma triglycerides and cholesterol levels.

Alcohol-induced enhancement of alimentary lipemia in man, and the increased post-prandial plasma and liver triglycerides in rats, following ingestion of corn oil-alcohol mixture, were shown by Barboriak and Meade (252) to be effectively inhibited by nicotinic acid. The protective action was marked in both the human and in the rat studies.

Parsons (3295) presented a paper in 1963 supporting the desireability of chemotherapy in reducing cholesterol levels by the use of nicotinic acid, in the sense that even though the relationship of cholesterol levels and atherosclerosis has not been proven, a normal cholesterol level is better than an elevated one. The Physician's Desk Reference to Pharmaceutical Specialities and Biologicals (215), 1973 Edition, suggests that "several years will be required before current investigations will yield an answer to this question" (cholesterol and atherosclerosis). The doses utilized, by Parsons and others, of nicotinic acid, nicotinamide and aluminum nicotinate in therapy of hypercholesteremia range from 3 to 6 g daily over periods of a year or more. After the flush of the first week, most patients tolerate these doses in long-term therapy. Blood pressure and heart beat remain unaffected, nor is angina pectoris produced or aggravated by the treatment.

A theory suggesting that abnormality of serotonin in the brain gives rise to mental disorders was discussed briefly by Woolley (4663); nicotinamide is not specifically an serotonin antagonist but may influence serotonin action through interference with calcium ions or through transmethylation.

Large doses of nicotinic acid used in therapy by hypercholesterolemia exert a diabetogenic effect in patients with diabetes mellitus according to Molnar et al. (2942). Increased doses of insulin or hypoglycemic drugs were required; after 6 months of nicotinic acid therapy no serious effects were observed, and after cessation of the nicotinic acid treatment the diabetogenic effects promptly disappeared.

Conflicting reports of the effects of nicotinic acid on serum lipids lead Call et al. (643) in 1966 to study in man the results of a single intravenous dose of nicotinic acid and of a prolonged series of daily injections over a period of 35 days. Single doses of 100 mg, 500 mg or 1 g, and daily doses of 4 g/day in 1 g/6 hr. amounts were given to human subjects. Periodic blood samples were analyzed for blood lipid fractions; in no instance were significant variations in lipid fractions observed.

Rivin (3628) reported that hypercholesterolemic patients who were able to tolerate large (1-6 g) doses of niacin for up to 3 years have significantly reduced serum-cholesterol levels. In some patients, side effects were of sufficient severity as to warrant discontinuing treatment: nausea, severe flushing, epigastric burning, jaundice and hives. Baggenstoss et al. (210) were concerned with the effect of niacin therapy on the liver, and studied liver biopsy material in four patients undergoing nicotinic acid treatment for hypercholesterolemia. Minor abnormalities of the mitochondria were observed but the degree of abnormality was insufficient to warrant cessation of the treatment. Charman et al. (779) performed studies similar to those of Rivin and noted that the severity of side effects often precluded continued treatment of hypercholesterolemia with nicotinic acid.

The influence of nicotinic acid in lowering serum cholesterol levels in individuals with low initial, or normal, levels was investigated by Altschul and Hoffer (100). Student volunteers were given nicotinic acid,

3 g/day or alternate days, with basal metabolism rates and serum cholesterol determinations made on the days when not dosed with nicotinic acid. After 8 days, cholesterol levels were significantly reduced and basal metabolism rates elevated.

Aside from the use of niacin, or niacinamide, as dietary supplements, the most prominent application appears from the literature to lie in the field of hypercholesteremia therapy. Representative studies may be found in the following reports: Achor et al. (33) used megadoses of nicotinic acid (1.5-6 g/day) in patients for up to 1.5 years with considerable success and regarded the treatment as "highly effective, very practical to carry out, and is probably quite safe; O'Reilly (3221) treated a variety of patients, psychotic, mentally defective and schizophrenic, with 3 g/day nicotinic acid for 3 months, and postulated that the nicotinic acid has an anticoagulent effect due to the release of heparin and increased activity of lipoprotein lipase; Parsons and Flinn (3299) observed that in some hypercholestermic patients doses of 3 g nicotinic acid daily was insufficient and that 6 g/day was required for significant reduction of cholesterol levels - the mechanism by which nicotinic acid produces the observed changes in blood lipids was termed as "obscure"; Chazin (800) found results in giving patients 3 g nicotinic acid daily for up to 5 months similar to those of the foregoing investigators.

The effects of a single oral dose of 1 g nicotinic acid given to patients with uncomplicated ischemic cardiovascular diseases and moderate hyperlipoproteinemia were reported by Carlson et al. (696). Blood analyses showed an early significant reduction of the free fatty acids followed at about 3 hours by a sudden rise; cholesterol levels and glucose concentrations were not significantly altered. The triglyceride levels were markedly reduced. The absence of an effect on cholesterol levels may have been due to the short span (6 hours) of the experiment; the "overshoot" in FFA was not explained.

Kritchevsky (1560) recently (1971) reviewed the literature on the effects of nicotinic acid and derivatives on cholesterol metabolism. A summary of the sequence of events following administration of nicotinic acid is given and about 100 references are noted.

Burton et al. (602), using mice, demonstrated that nicotinamide, in combination with reserpine and chlorpromazine potentiates anesthesia induced by pentobarbitol. The nicotinamide was given intraperitoneally in combination with subcutaneous doses of reserpine and chlorpromazine, prior to intraperitoneal injection of 70 mg/kg pentobarbitol. Nicotinamide, alone-showed no potentiation of the anesthesia.

NIACIN

Chemical Information

I. Nomenclature

A. Common Names

1. Nicotinic acid
2. Nicacid
3. Nicangin
4. Niconacid
5. Nicotinipca
6. Nicyl
7. P.P. factor
8. Pellagra preventive factor
9. Anti-pellagra vitamin
10. Niacin

B. Chemical Names

1. Nicotinic acid
2. Pyridine-3-carboxylic acid
3. Pyridine-B-carboxylic acid
4. 3-Pyridinecarboxylic acid
5. Niacin

C. Trade Names

1. Akotin (Merck)
2. Nicobid (Armour)
3. Nico-400 (Marion)
4. Nicotinex (Fleming)

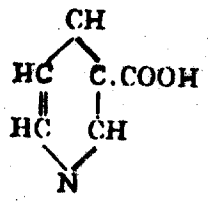
D. Chemical Abstract Registry Number

000059-67-6

II. Empirical Formula

$C_6H_5NO_2$

III. Structural Formula



IV. Molecular Weight

123.11

V. Specifications (Food Chemicals Codex)

Assay	Not less than 99.5% and not more than 101.0% of $C_6H_5NO_2$, calculated on the dried basis
Melting range	Between 234 degrees and 238 degrees
Limits of impurities	
Heavy metals (as Pb)	Not more than 20 ppm (0.002%)
Loss on drying	Not more than 1%
Residue on ignition	Not more than 0.1%

VI. Description

A. General Characteristics

White or light yellow crystals or crystalline powder; nonhygroscopic and stable in air; odorless or with slight odor.

B. Physical Properties

Soluble 1 g in 60 ml H_2O; freely soluble in boiling water and alcohol, also in solutions of alkali hydroxides and carbonates; sublimes (150 degrees) without decomposition; insoluble in ether; mp 236.6.

C. Stability

Store in well-closed containers. Niacin is exceedingly stable both in dry state and in solution; it withstands heat, oxidation, acid or alkaline media, as well as the usual methods of food preservation.

VII. Analytical Methods

From Food Chemicals Codex

IDENTIFICATION

A. Triturate a sample with twice its weight of 2,4-dinitrochlorobenzene. Gently heat about 10 mg of the mixture in a test tube until melted, and continue the heating for a few seconds longer. Cool, and add 3 ml of alcoholic potassium hydroxide T.S. A deep red to deep wine-red color is produced.

B. Dissolve about 50 mg in 20 ml of water, neutralize to litmus paper with 0.1 N sodium hydroxide, and add 3 ml of cupric sulfate T.S. A blue precipitate gradually forms.

C. The infrared absorption spectrum of a potassium bromide dispersion of the sample, previously dried at 105 degrees for 1 hour, exhibits maxima only at the same wavelengths as that of a similar preparation of N.F. Niacin Reference Standard.

D. Determine the absorbance of a solution of the sample containing 20 mcg in each ml of water, in a 1-cm cell at 237 millimicron and 262 millimicron, using water as the blank. The ratio A237/A262 is between 0.35 and 0.39.

From AOAC (4768) Sections 39.037-39.039; 39.067-39.075, pp. 763, 771.

A rapid, simple method for the specific determination of niacin and niacinamide was reported by Prosser and Sheppard (3485). Gas-liquid chromatography (GLC) was utilized after converting niacin and niacinamide to ethyl nicotinate and N-ethylnicotinamide. See Documents for details.

In the Netherlands, nicotinic acid for the preservation of the red colour of raw minced meat is permitted up to a concentration of 0.015%. Brunink and Wessels (573) have described a fluorimetric densitometric technique for the determination of nicotinic acid and nicotinamide in meat. Presumably the method is applicable in other instances. See Documents for details.

VIII. Occurrence

Found in minute amounts in all living cells; appreciable amounts in liver, yeast, milk, adrenal glands, white meat, alfalfa, legumes, whole cereals and corn. It is involved in the energy-liberating process of the organism, chiefly as a constituent of the coenzyme systems, codehydrases I and II (NAD and PNAD). Free nicotinic acid is not found in living cells, but occurs as the amide or as part of the complex enzyme systems in which it is chemically bound.

NIACINAMIDE

Chemical Information

I. Nomenclature

A. Common Names

1. Nicotinamide
2. Nicotinic acid amide
3. Vitamin PP
4. Vitamin B_3
5. Niacinamide

B. Chemical Names

1. Nicotinamide
2. 3-pyridinecarboxylic acid amide

C. Trade Names (From Merck Index)

1. Benicot
2. Aminicotin
3. Ui-Nicotyl
4. Dipegyl
5. Nicamindon
6. Nicotamide
7. Nicotilamide
8. Pelonin Amide
9. Amide PP
10. Nicofort

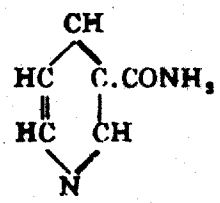
D. Chemical Abstracts Registry Number

000098-92-0

II. Empirical Formula

$C_6H_6N_2O$

III. Structural Formula



IV. Molecular Weight

122.12

V. Specifications (Food Chemicals Codex)

Assay	Not less than 98.5% and not more than the equivalent of 101.0% of $C_6H_6N_2O$ after drying
Melting Range	Between 128 degrees and 131 degrees
Limits of Impurities	
Heavy metals (as Pb)	Not more than 30 ppm (0.003%)
Loss on drying	Not more than 0.5%
Readily carbonizable substances	Passes test
Residue on ignition	Not more than 0.1%

VI. Description

A. General Characteristics

White, crystalline powder, or needles from benzene; odorless or nearly so; solutions neutral to litmus; bitter taste.

B. Physical Properties

Soluble, 1 g in 1 ml H_2O, 1.5 ml alcohol, and 10 ml glycerine; mp 128-131 degrees; forms crystalline salts with acids.

C. Stability

Store in tight containers.

VII. Analytical Methods

From Food Chemicals Codex

IDENTIFICATION

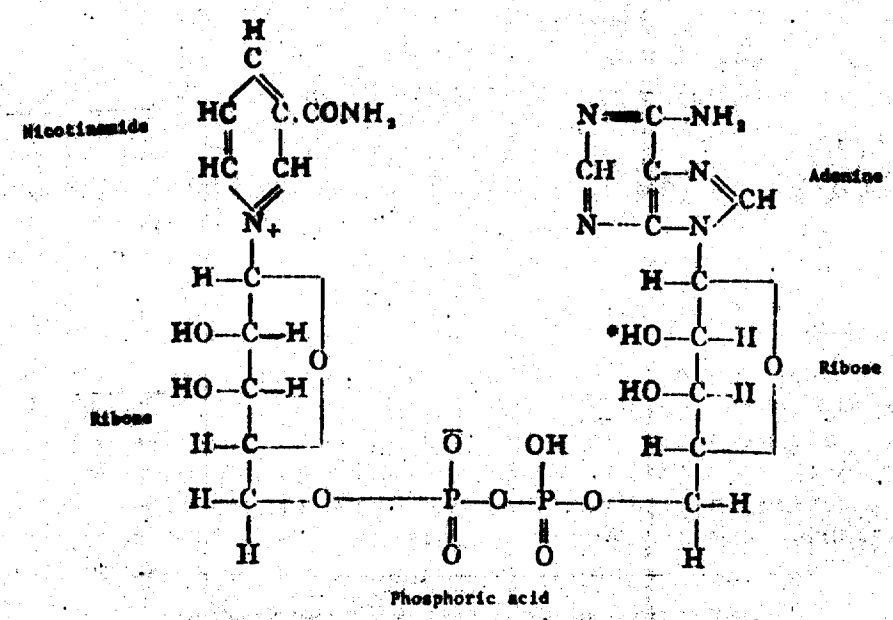
A. Transfer about 20 mg to a 1000-ml volumetric flask, dissolve and dilute with water to volume, mix, and determine the absorbance of the solution in 1-cm cells at 245 millimicron and at 262 millimicron with a suitable spectrophotometer, using water as the blank. The ratio A_{245}/A_{262} is 0.65 ± 0.02.

B. To 20 mg in a test tube add 1 pellet of sodium hydroxide T.S., and heat gently over an open flame. The odor of ammonia is perceptible. Upon heating more vigorously, the odor of pyridine is perceptible.

From AOAC (4768), Secs 39.037-39.039; 39.067-39.075, pg 763, 771. See Niacin - Analytical Methods.

VIII. Occurrence

Occurs in plants and animals, usually in conjugated form (in enzyme systems). Codehydrogenase I (DPN) consists of a complex of one molecule of niacinamide, one of adenine, two of ribose and two of phosphoric acid. Codehydrogenase II (TPN) is similar to DPN, but with three molecules of phosphoric acid. Both dehydrogenases can be synthesized in plant and animal cells from niacin. The structural formula for codehydrogenase I is shown below:



Codehydrogenase I (Diphosphopyridine nucleotide or DPN)

Dietrich (1971) in 1971 has reviewed recent biochemical relationships of nicotinamide in the living cell in a systemic pyridine nucleotide cycle and as the end product of the catabolism of nicotinamide adenine dinucleotide (NAD), as shown in the following figures:

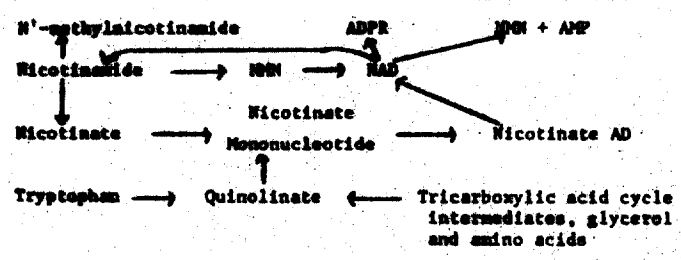


Fig. 1. Pathways of NAD metabolism. AMP = adenosine monophosphate.

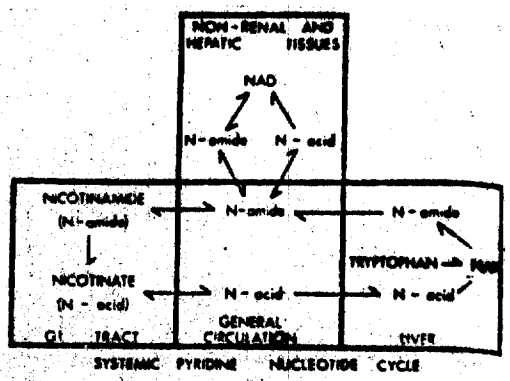


FIG. 2. Systemic pyridine nucleotide cycle.

For details of Dietrich's paper, see in Document Section, this Monograph.

Biological Data

I. Acute Toxicity

Compound	Animal	No.	Route	Dosage mg/kg Body Weight	Measurement	Ref.
Nicotinic Acid (Na-nicotinate)	Mouse	3	i.v.	2500	LD_0	808
Nicotinic Acid (Na-nicotinate)	Mouse	3	i.v.	3000	LD_0	808
Nicotinic Acid (Na-nicotinate)	Mouse	3	i.v.	4000	LD_0	808
Nicotinic Acid (Na-nicotinate)	Mouse	3	i.v.	4500	LD_{100}	808
Nicotinic Acid (Na-nicotinate)	Mouse	5-10	oral	4300	LD_{50}	4423
Nicotinic Acid (Na-nicotinate)	Mouse	5-10	s.c.	5200	LD_{50}	4423
Nicotinic Acid (Na-nicotinate)	Rat	5	i.v.	3000	LD_{40}	808
Nicotinic Acid (Na-nicotinate)	Rat	5	i.v.	3500	LD_{60}	808
Nicotinic Acid (Na-nicotinate)	Rat	5-10	oral	5300	LD_{50}	4423
Nicotinic Acid (Na-nicotinate)	Rat	5-10	s.c.	7000	LD_{50}	4423
Nicotinic Acid (Na-nicotinate)	Rat	5-10	s.c.	5000	LD_{50}	520
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	i.p.	700	LD_0	2609
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	i.p.	820	LD_{16}	2609
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	i.p.	1080	LD_{50}	2609
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	i.p.	1400	LD_{84}	2609

Compound	Animal	No.	Route	Dosage mg/kg Body Weight	Measurement	Ref.
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	i.p.	1500	LD_{100}	2609
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	s.c.	2000	LD_0	2609
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	s.c.	2050	LD_{16}	2609
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	s.c.	2550	LD_{50}	2609
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	s.c.	3125	LD_{84}	2609
Nicotinic Acid (Na-nicotinate)	Rat	5/dose level	s.c.	3200	LD_{100}	2609
Nicotinic Acid (Na-nicotinate)	Guinea Pig	3	i.v.	3000	LD_0	808
Nicotinic Acid (Na-nicotinate)	Guinea Pig	5	i.v.	3500	LD_{60}	808
Nicotinamide	Mouse	5-10	oral	2100	LD_{50}	4423
Nicotinamide	Mouse	5-10	s.c.	2900	LD_{50}	4423
Nicotinamide	Rat	5-10	oral	2600	LD_{50}	4423
Nicotinamide	Rat	5-10	s.c.	3500	LD_{50}	4423
Nicotinamide	Rat	5-10	s.c.	1680	LD_{50}	520

One of the earliest determinations of the acute toxicity of nicotinic acid and nicotinic amide was reported by Unna (4423) in 1939. The low solubility of nicotinic acid led Unna to use the sodium nicotinate in most instances, and the amide. Up to 1 g/kg was tolerated by mice without toxic symptoms; death first occurred with subcutaneous injection of 1.8 g/kg of nicotinic amide or 3 g/kg sodium nicotinate. The difference in toxicities between oral and subcutaneous administration of either compound was slight. Rats were similarly treated. The following figures show the results of giving 5 to 10 animals each dose and for each avenue of administration:

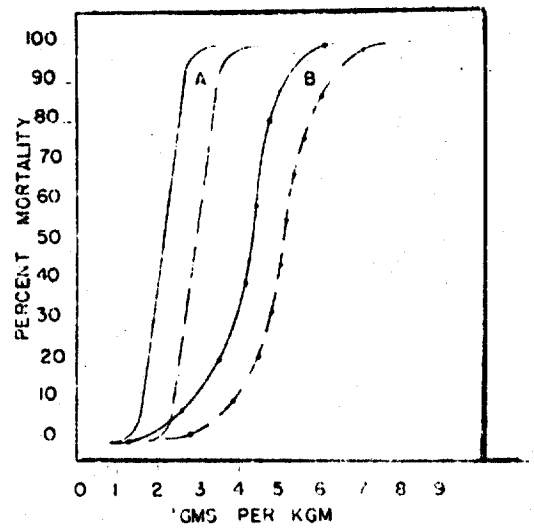


FIG. 1. TOXICITY OF NICOTINIC AMIDE AND SODIUM NICOTINATE IN MICE
A. Nicotinic amide after oral (———) and subcutaneous (— —) administration. B. Sodium nicotinate after oral (—•—) and subcutaneous (—•— —•—) administration.

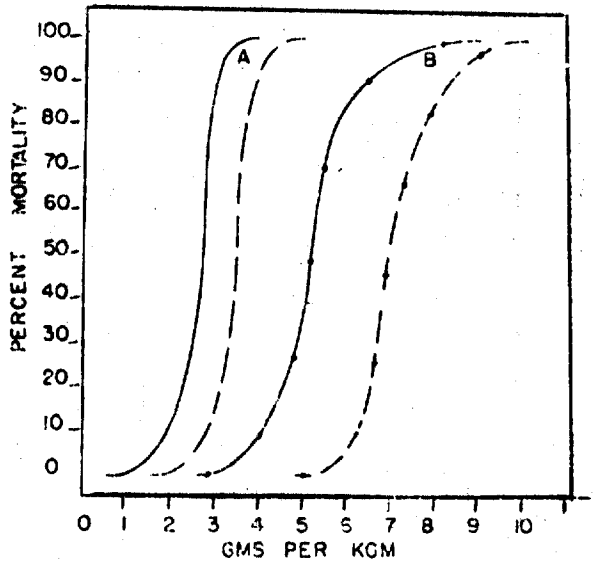


FIG. 2. TOXICITY OF NICOTINIC AMIDE AND SODIUM NICOTINATE IN RATS
A. Nicotinic amide after oral (———) and subcutaneous (— —) administration. B. Sodium nicotinate after oral (—•—) and subcutaneous (—•— —•—) administration.

A comparative study of the toxicity of nicotine and of nicotinic acid was reported by Chen et al. (808) in 1938. Mice, rats and guinea pigs were given the drugs intravenously in doses and results shown in the following table:

TABLE
Acute Toxicity of Nicotine and Nicotinic Acid.

Compound	Species	Dose, mg. per kg.	No. of Animals used	No. died	Minimal lethal dose, mg. per kg.
Nicotine	Mice	0.4	1	0	0.8
		0.5	1	0	
		0.6	6	0	
		0.7	7	0	
		0.8	10	7	
		0.9	5	5	
	Rats	0.5	1	0	1.0
		0.7	5	0	
		0.8	5	2	
		0.9	5	2	
		1.0	5	3	
		1.1	5	5	
		1.2	3	3	
	Guinea Pigs	3.0	4	1	4.5
		4.0	3	0	
		4.5	4	3	
		5.0	3	3	
Nicotinic Acid	Mice	2500.0	3	0	4500.0
		3000.0	3	0	
		4000.0	3	0	
		4500.0	3	3	
	Rats	3000.0	5	2	3500.0
		3500.0	5	3	
	Guinea Pigs	3000.0	3	0	3500.0
		3500.0	5	3	

Lyskan (2609) has reported recently (1972) on the acute toxicity of various vitamins given intraperitoneally and subcutaneously to rats. No experimental data are given - only results. The study was concerned with the pharmacodynamic effect of vitamins as used in therapy. In general, therapeutic doses are significantly less than the toxic doses of vitamins. The results of the study with regard to nicotinic acid are shown in the table presented at the beginning of this section of the monograph.

Subcutaneous, LD_{50} doses of nicotinic acid and some derivatives were determined by Brazda and Coulson (520) in 1946 for young rats of both sexes, weighing 50-100 g. The results appear in the following table:

TABLE
Relative Toxicity of Some Derivatives of Pyridine (Subcutaneous Injection).

	LD_{50}* g/kilo	Relative-order of toxicity
Pyridine	1.00	5.00
Pyridine methochloride	0.28	17.9
Nicotinic acid	5.0	1.0
Trigonelline	5.0	1.0
Nicotinamide	1.68	3.0
Nicotinamide methochloride	2.40	2.08
Coramine	0.24	20.8
Coramine methochloride	1.90	2.63

* LD_{50} = dose needed to kill one-half of the animals.

Apparently methylation decreases the toxicity of coramine and nicotinamide, increases the toxicity of pyridine, and has little or no influence on nicotinic acid toxicity.

Press and Yeager (3474) reported in 1962 an outbreak of food poisoning due to the ingestion of meat to which unduly large amounts of sodium nicotinate had been added to preserve the redness of the meat. Forty-four students at a sorority house at Northwestern University in Evanston, Illinois during an evening meal were afflicted with itching of the skin, redness and flushing of face, neck, extremities and trunk, accompanied in some cases by swelling of knees, lips, or extremities, and dryness of the mouth. The symptoms lasted only 30-40 minutes in most cases. Several ounces of sodium nicotinate had been added to the ground meat comprising the meat balls of the evening meal.

Other, similar "poisoning" episodes are described, and the authors urge better control and regulation of food additives, which in this instance of sodium nicotinate, affects millions of pounds of meat annually. The paper also outlines the history of nicotinic acid as related to pellagra and in therapy of other conditions, and as a meat additive.

II. Short-Term Studies

In addition to the acute studies, Unna (4423) described some chronic experiments. Rats, chickens and dogs were used in chronic toxicity studies. Ten six-week-old rats were fed daily 1 g/kg sodium nicotinate for 40 days; no toxic symptoms appeared, and autopsy showed no pathological changes. Five chickens were given 0.1 g/kg daily for 3 weeks; no signs

of toxicity appeared. Two adult dogs received 2 g/kg daily for 35 days without untoward symptoms.

Metabolic studies were also performed: various dosages of both the nicotinate and amide did not influence metabolism, respiration or circulation.

Chen et al. (808) also reported the following chronic studies:

A group of 5 mice given 500 mg nicotinic acid daily intravenously, for 4 weeks (except weekends) survived and gained body weight. Two adult dogs were given orally 2 g nicotinic acid daily; one animal showed severe reactions by the 11th day, became convulsed on the 12th day, died at 19 days died after a week of no medication; the second dog, given a total of 40 g nicotinic acid in 20 days, showed severe toxic reactions and was sacrificed.

Smaller, chronic doses of from 0.06 g to 1 g daily nicotinic acid were given to 4 dogs, orally - for 8 weeks; all appeared in good health at the end of the experiment.

Handler (1802) in 1944 demonstrated that the ingestion of large quantities of nicotinamide by young rabbits and guinea pigs did not impair their growth, nor were any toxic effects observed. Unlike experiments with rats in which a marked increase in urinary N'-methylnicotinamide is seen in nicotinamide feeding studies, no significant effect in urinary N'-methylnicotinamide excretion was observed in rabbit or guinea pig.

Weanling rabbits, weighing about 1250 g, were fed several diets with nicotinamide added by spraying with a 10% solution. After 20 days the animals were sacrificed; urine collected from 3 rabbits on the 15th and 16th days of feeding was analyzed for N'-methylnicotinamide and liver samples after sacrifice were analyzed for fat.

Week-old guinea pigs weighing about 124 g were similarly treated with several diets, urinalyses and liver fat after 3 weeks were determined. The following tables summarize the effects of nicotinamide feeding in rabbit and in guinea pig:

TABLE I

Effect of Nicotinamide Feeding on Rabbits

Basal diet	Test animal	Supplement to basal diet	Weight change	Liver fatty acids	F_2 excretion
			gm. per day	*per cent*	*γ per day*
A	Rabbits	None	25.3	4.5	740
"	"	1% nicotinamide	22.1	4.3	790
"	"	2% "	20.9	3.9	600
"	Rats	None	2.9	5.2	*
"	"	1% nicotinamide	1.1	11.4	*
"	"	2% "	−0.6	3.1	*
B	Rabbits	None	21.0	3.5	1030
"	"	1% nicotinamide	17.3	3.9	970
"	"	2% "	22.5	3.6	1120

* Complete data have already been published (1).

TABLE II

Effects of Nicotinamide Feeding on Guinea Pigs

Diet	Weight change	Liver fatty acids	F_2 excretion
	gm. per day	*per cent*	*γ per day*
Basal Diet 1	1.2	4.3	110
" " 1 + 1% nicotinamide	1.3	4.4	125
" " 2	1.8	3.6	155
" " 2 + 0.5% nicotinamide	1.4	4.1	
" " 2 + 1.0% "	2.2	4.0	185
" " 2 + 2.0% "	1.5	3.7	

The author suggests that the innocuous nature of nicotinamide in rabbit and guinea pig as opposed to the toxic effects in rat is due to synthesis of N'-methylnicotinamide in the rat with a consequent depletion of the available methionine supply.

III. Long-Term Studies

No relevant studies found.

IV. Special Studies

Therapy

An early study (1938) by Spies et al. (4127) demonstrated that the porphyrinuria of pellagra disappears after administration of yeast or of

nicotinic acid. This was also found in diseases other than pellagra which had associated porphyrinuria. Doses of 500 mg nicotinic acid were given to hospital patients characterized by porphyrinuria; urinalyses of persons with diseases other than pellagra showed negative tests for porphyrinuria within 24 hours of taking either yeast or nicotinic acid; severe pellagra patients required several days for negative tests results.

The relationship of pellagra and psychosis was established in the 1930's, as was the improvement of the psychoses of pellagra by treatment with nicotinic acid. Sydenstricker and Clerkley (4249) in 1971 reported successful treatment of a series of 29 cases of severe psychiatric disorder with nicotinic acid; none of the symptoms of pellagra were present. The patients were described as stuporous, comatose, confused, disoriented, delirious, irrational or manic. Other complications were frequently present, such as arterioschlerosis, pneumonia, hypertension, or infection. Other than frequently presenting dry, red or coated tongues, other signs of avitaminosis were absent.

Treatment with nicotinic acid, oral or intravenous in doses of from several hundred to several thousand milligrams, resulted in prompt and often very impressive improvement. It was proposed that "many patients whose psychiatric status suggested the diagnosis of toxic psychosis or exhaustion delirium may be relieved of their symptoms by the administration of nicotinic acid".

Nicotinic acid has been successfully used in the therapy of tension headache. Morgan (2965) in 1955 suggested criteria for differentiating migraine headache from tension headache, and proposed that only in the latter would nicotinic acid therapy be effective. The prodromata or pre-headache symptoms characteristic of migraine are usually absent in tension headache; the patient knows the causes of his tension headache which are emotional in nature, and the attack is usually followed by depression.

Ergotamine tartrate, successfully used in the treatment of migraine, is ineffective in tension headache, presumably because the latter is caused by a vasoconstriction of blood vessels.

Oral administration of nicotinic acid in insufficient dosages has discouraged its use; Morgan begins therapy by frequent intravenous doses of 100 mg over a period of months, accompanied by increasing oral doses of up to 900 mg. The author treated successfully 44 of 50 cases studied by this technique.

Rook (3666) in a "letter to the editor" in Lancet, 1944, described the successful results in 15 cases of relieving angina with nicotinic acid. Six daily doses given intravenously, starting with a 25 mg dose

followed by 5-50 mg doses are given at first, with subsequent intervals without dosing, finally reaching a maintenance dose at 4-8 week intervals. The author was of the opinion that the angina condition represents the body's loss of "capacity to absorb the necessary quantity of vitamin taken by mouth".

In 1958 the American Medical Association, Council on Drugs (108), reported that even though large doses (3-6 g) of nicotinic acid will frequently bring about a marked reduction in cholesterol levels in treating atherosclerosis, the lack of valid evidence that lowered cholesterol levels caused clinical improvement of atherosclerotic cardiovascular diseases, makes the use of nicotinic acid for other than treatment or prevention of pellagra simply experimental.

Nicotinamide in high dosage has been found to be carcinostatic; in combination with other carcinostatic compounds, a partial regression has been observed in a mouse breast carcinoma by Shapiro et al. (3960) in 1957. The 755 mammary adenocarcinoma was implanted in the axillary region of C57BL mice, 2-4 months old, weighing 18-22 g. Four to ten days after implantation, large doses of 600 mg/kg or more, twice daily, of nicotinamide were administered intraperitoneally. At the highest dose used, 1250 mg/kg twice daily, a marked degree of tumor inhibition occurred, but treatment had to be discontinued after 5 days because of toxicity. Tumor regression at these large doses of nicotinamide was not observed. The results of nicotinamide effects on the 755 tumor in mice are shown in the following table:

TABLE

EFFECT OF LARGE DOSES OF NICOTINAMIDE ON 755 TUMOR IN MICE*

Exp. no.	Sex	Group†	Dose (mg/kg)	Days of inj.	Mean tumor wt. ± S.E. (mg.)	No. animals dead/total	Per cent change in body weight
1	♂	Sac. control			24 ± 3	0/19	
		Saline		6	831 ± 87	0/20	+ 7
		Nic.	1250	6	105 ± 16	4/20	− 6
		Nic.	1000	6	207 ± 28	0/10	− 5
2	♂	Saline		11	1003 ± 90	0/19	+ 6
		Nic.	600	11	506 ± 81	0/19	− 3
3	♀	Saline		14	1310 ± 186	0/20	+ 6
		Nic.	600	14	508 ± 82	0/20	− 2
4	♂	Saline		16	1960 ± 318	1/18	+15
		Nic.	600	16	1143 ± 115	0/21	+12

* Therapy was begun on 4-10-day-old 755 mammary adenocarcinomas grown in C57BL mice. Treated animals were sacrificed on the day following the last injection.

† Sac. control = animals sacrificed when injections of other groups begun; Nic. = nicotinamide administered intraperitoneally (I.P.) twice daily; saline at 0.85 per cent administered I.P. daily.

Nicotinamide was also given the tumor-bearing mice in combination: with 8-azaguanine and testosterone, tumor growth ceased; with the former two plus deoxypyridoxine, significant tumor regression was observed. The latter combination of four compounds given for 6-8 days resulted in some deaths, and at dose-levels producing tumor regression the toxicity was too great to continue treatment to a "cure".

A nine-year study of the therapeutic value of niacin and nicotinamide in the treatment of schizophrenia was described by Osmond and Hoffer (3235) in 1962. The adrenaline metabolite theory of schizophrenia suggests that the disease is caused by a faulty adrenaline metabolism and that anything which reduces adrenaline should help; niacin was suggested as a competitor for methyl groups which are utilized in conversion of noradrenaline to adrenaline. The successful treatment of a case of acute schizophrenia lead the authors to increasingly larger investigations of comparative results of treating the disease by niacin and other treatments. The length of time spent in the hospital by the patients during the various treatments was used as the criterion of the relative success of niacin versus other treatments; during a 4-year follow-up of all patients treated for schizophrenia in Saskatchewan, Canada, patients who never had nicotinic acid spent two-fifths of year in hospital, while those receiving the nicotinic acid spent only a sixth of year. Other studies have provided similar results and the authors have become convinced that niacin is a useful adjunct in the treatment of schizophrenia. It is deplored that niacin treatment has been largely neglected possibly for lack of general information, or because it is a cheap, well-known vitamin without a campaign to promote it among doctors, or because of the influence one leader in the field who regards schizophrenia as a way of life rather than an illness.

From the same hospital in Saskatoon, Sask. and in the same year (1962), Denson (1098) published a report similar to that of Osmond and Hoffer. Forty-one cases of schizophrenia were studied in treatment with nicotinamide in a blind trial, where placebo and nicotinamide doses were indistinguishable. (Nicotinic acid, even in small doses, produces flushing and headache in some cases and could not be used in a blind trial). Ataractic drugs and other forms of treatment were carried on together with the nicotinamide; the identities of the tablets, placebo or nicotinamide remained unknown to patients and hospital staff throughout the trial. Criticisms of the criterion (length of hospital stay) are recognized, but Denson, as had Osmond and Hoffer - felt that nicotinamide therapy can shorten the length of stay in hospital for schizophrenics; his statistical treatment of the data showed significant results at the 5% level of probability. The treated patients who received the nicotinamide spent an average of ten weeks less in hospital during the test year following entry, than did the control group.

Hoffer has led the practitioners of megavitamin therapy in the treatment of schizophrenia, and has more recently used the expression "orthomolecular therapy" to describe treatment not only using megadoses

of vitamin B_3 but combinations with other vitamins and proper nutrition. Three papers included here but not abstracted describe the techniques: Hoffer (1940, 1941, 1942).

Not all studies of the effect of nicotinic acid on schizophrenia have found the treatment successful. Ashby et al. (169) in 1960 tested a group of 39 chronic schizophrenics with nicotinic acid, nicotinamide and placebo in a carefully designed experiment. Each substance was administered for 8 weeks; during the first week, dosage was increased from an initial 300 mg/day to a final 6.3 g/day, at which level the dosage was maintained for 7 weeks. Specialized psychological tests were employed, with a questionnaire to be filled in every two weeks regarding assessment of the patients' status. At the end of each 8-week period, one week without treatment was allowed, then the patient was placed on one of the remaining two substances to be tested; thus, the total time of testing lasted 26 weeks. The results of the tests, analyzed statistically (analysis of variance)," failed to show any evidence that the treatments were influencing the patients".

Wittenborn et al. (4627) recently (1973) reported results similar to those of Ashby et al. Of those treated for schizophrenia with niacin, 75 patients were maintained for 24 months. After several months on doses of 3 g niacin daily, some patients developed a superficial hyperkerotosis requiring temporary removal from treatment with the keratosis was cleared up. A comprehensive battery of laboratory tests, interviews and rating scales were employed to acquire data for an analysis of the results of the treatment; it was concluded that the use of niacin conferred no special benefit in the treatment of schizophrenia.

The usefulness of niacin in the therapy or treatment of schizophrenia is questioned in a report (Letter to the Journal) by Honinger and Bowers (1873) in JAMA, 1968. Two case-histories are described in which emergent psychosis was possibly accelerated or worsened by application by niacin. The authors viewed the cases as an example of an "iatrogenic side effect", whenever the niacin potentiated the psychotic symptoms of the two cases.

Teratogenesis

A structural analogue of nicotinamide, 6-aminonicotinamide, has been shown to be a teratogen and a competitive inhibitor of nicotinamide. Goldstein et al. (1630) in 1963 used inbred female mice (4 strains) and 6-aminonicotinamide to study the genetic basis for a strain-difference in frequency of induced malformations in specific organ systems. It was thought that a part of the strain-differences in organ response to the teratogen was cytoplasmic. Since nicotinamide, and nicotinic acid as well as tryptophan, protect against the lethal effects of 6-aminonicotinamide, the animals were treated with nicotinamide 2 hours after administering 6-aminonicotinamide to pregnant females. This technique focused the teratogen on a very precisely defined stage of pregnancy.

Mice of two highly inbred strains, A/Jax and C57BL/6J (subsequently referred to as A and C) were mated AxA, CxC, AxC and CxA, and back-crossed (AC)xA and (CA)xA. (The female parent is written first in showing crosses.) Pregnant females were treated on one of the following days of gestation: 8.5, 9.5, 10.5, 11.5, 12.5, 13.5 or 14.5. An aqueous solution (19 mg/kg) of 6-aminonicotinamide was injected intramuscularly; 2 hours later, an aqueous solution (7.3 mg/kg) of nicotinamide was injected, preventing further teratogenic action of the antimetabolite. On gestation day 18.5 the females were sacrificed and embryos observed in situ, removed and prepared for skeletal staining.

Of the variety of malformations produced, only two were dealt with in this paper - vertebral fusions and cleft palate. The results are shown in the following tables:

Table 1. *Frequencies of vertebral fusions (VF) following maternal treatment with 6-aminonicotinamide on day 8·5 or 9·5 of gestation*

Cross	Day treated	Numbers of females treated	Numbers of embryos		Percent of embryos with VF
			Resorbed	Alive	
1. A × A	8·5	9	75	7	0
	9·5	10	37	55	89
	Control	18	34	111	0
2. C × C	8·5	12	27	64	9
	9·5	12	20	73	56
	Control	12	19	72	0
3. A × C	8·5	10	61	14	14
	9·5	10	16	19 (61)†	45
	Control	10	24	52	0
4. C × A	8·5	5	1	32	37
	9·5	10	7	52 (67)†	67
	Control	10	13	65	0

† Only the numbers of mice cleared for the examination of the skeletons are included. The numbers in brackets refer to the total number of embryos.

Table 2. *Frequencies of cleft palate (CP) following maternal treatment with 6-aminonicotinamide on day 13·5 of gestation*

Cross	Day treated	Number of females treated	Numbers of embryos		Percent of embryos with CP
			Resorbed	Alive	
1. A × A	13·5	10	19	71	76·1
	Control	18	34	111	0
2. C × C	13·5	12	28	74	10·8
	Control	12	19	72	2·8
3. A × C	13·5	12	13	80	36·3
	Control	9	14	31	0
4. C × A	13·5	10	7	56	3·6
	Control	11	7	64	0
5. AC × A	13·5	9	1	76	23·7
6. CA × A	13·5	11	5	73	5·5

Crosses AxA and AxC, treatment day 8.5, showed such a high frequency of resorptions that conclusions concerning malformations could not be drawn. Crosses CxC and CxA, treatment day 8.5, showed a significantly lower frequency of vertebral fusions in the C strain than in the CxA strain (9% versus 37%). After treatment day 9.5, the frequency of vertebral fusions is significantly higher in the A strain (AxA) than in the C strain (CxC), (89% versus 56%). A less significant difference characterized the reciprocal crosses: CxA, 67%; AxC, 45%.

With regard to cleft palate, treatment day 13.5 showed frequency peaks for all four crosses. Highly significant differences were seen between AxA and CxC embryos (76.1% versus 10.8%), and significant differences between AxA and AxC (76.1% versus 36.3%). The AxC frequency of cleft palate was significantly higher than the reciprical cross CxA (36.3% versus 3.6%). Two types of F1 mothers, AC and CA were back-crossed to A strain males and treated with 6-aminonicotinamide on day 13.5. A significant difference was observed: ACxA, 24%; CAxA, 6%. It was suggested that the teratogenic response was influenced by factors transmitted through the egg cytoplasm.

Cariogenesis

A direct relationship between the nicotinic acid content of saliva and the incidence of dental caries was reported by Dreizen et al. (1164) in 1951. Earlier reports showing that persons with chronic endemic pellagra have a lower incidence of dental caries led the authors of this study to collect saliva from 43 subjects and test for nicotinic acid, correlating the findings with the caries activity of each individual. Eighty-nine percent of a series of 90 samples of saliva showed a close relationship between nicotinic acid content and dental caries activity. It is suggested that nicotinic acid, as a component of coenzymes I and II, is an essential growth factor for lactic acid producing oral bacteria.

Dietary Supplementation

Horger and Gerheim (1981) in 1958 fed rats on diets supplemented by either excess methionine or niacinamide. Several series of animals were given a variety of diets, 12 rats and 10 rats were given .1, .2 or .4% niacinamide supplements over a period of 12 weeks maximum. Four rats from each group were sacrificed at 2, 8 and 12 weeks of treatment; adrenals, liver and kidneys were removed an weighed. The .1% niacinamide caused no significant change in growth rate; the .2% level enhanced growth; the .4% level inhibited growth. Methionine also caused a decreased growth rate; a combination of methionine with niacinamide was even more effective in retarding growth than either substance alone.

Biochemical Aspects

I. Breakdown

No relevant information found.

II. Absorption-Distribution

Taylor et al. (4297) in 1942 reported an analysis of a wide variety of tumors for nicotinic acid content compared with concentrations in noncancerous tissues and found that in general, the transformation to the cancerous condition involves a decrease in nicotinic acid content. The following tables demonstrate the findings of the study:

TABLE I: NICOTINIC ACID CONTENTS OF NONCANCEROUS TISSUES

Tissue	Sex	Number of samples	Solids content, percent	Nicotinic acid content (γ per gm fresh tissue)
Liver—Wistar rat (rice-carrot diet)	♀	2	(30.5)	174
" Wistar rat (Purina diet)	♀,♂	2	30.5	178
" C57 mouse	♀	4	29.6	104
" dba "	♀	3	28.4	107
" C3H "	♀	3	32.8	93
" Human	♀	1	27.4	54
Whole heart—Wistar rat	♀,♂	2	20.6	123
" " C57 mouse	♀	3	22.2	126
" " dba "	♀	4	23.7	111
" " C3H "	♀	4	23.8	129
Myocardium—Human	♀	1	20.6	41
Whole brain—Wistar rat	♀,♂	2	21.2	64
" " C57 mouse	♀	4	22.8	68
" " dba "	♀	3	21.9	44
" " C3H "	♀	3	22.2	50
Cerebrum—Human	♀	1	24.8	20
Lung—Wistar rat	♀,♂	2	19.1	51
" Human	♀	1	21.4	18
Spleen—Wistar rat	♀,♂	2	20.2	69
" Human	♀	1	22.7	30
Kidney—Wistar rat	♀,♂	2	22.7	117
" Human	♀	1	20.3	33
Skeletal muscle—Wistar rat	♀,♂	2	24.7	81
" " Human	♀	1	26.0	50

TABLE II: NICOTINIC ACID CONTENTS OF CANCEROUS TISSUES

Sample No.	Tissue	Sex	Solids content, per cent	Nicotinic acid content (γ per gm fresh tissue)
158, 159, 160	Rat carcinosarcoma (Walker 256)	♂	13.9	19 (17–20)
176, 180, 184	C57 mouse sarcoma (methylcholanthrene)	♀	17.5	29 (26–35)
207, 208, 209	dba mouse adenocarcinoma	♀	18.3	20 (17–26)
250, 251, 252, 274, 275	C3H " "	♀	16.3	28 (18–42)
105	Human mammary carcinoma	♀	35.7	25
106	" " "	♀	27.2	27
212	" " "	♀	19.1	15
213	" " "	♀	16.1	29
214	" " "	♀	34.4	21
215	" " "	♀	16.8	28
216	" " "	♀	35.3	13
217	" " "	♀	18.0	22
218	" spindle cell sarcoma	♂	16.4	29
219	" skin carcinoma	♀	17.8	18
220	" ovarian adenocarcinoma	♀	19.5	15
225	" " "	♀	14.8	27
221	" renal adenocarcinoma	♂	19.6	18
222	" sarcoma, axilla	♀	16.7	21
223	" melanoma, orbit	♀	14.3	23
224	" lymphosarcoma, groin	♂	16.7	26
281	" melanoma, lower leg	♂	18.7	11
286	" sarcoma, back	♂	20.4	28
288	" sarcoma, neck	♂	20.0	12
289	" adenoma malignum, sigmoid colon	♀	17.5	24
290	" adenocarcinoma, rectum	♂	20.0	30

The results of the nicotinic acid assays of a variety of cancerous and noncancerous tissues showed values ranging from 18 to 178 gamma/g fresh tissue, noncancerous, and 13 to 59 gamma/g cancerous tissue.

III. Metabolism and Excretion

Six urinary metabolites were demonstrated after injection of radioactive (C^{14}) nicotinic acid or its amide into dog, rat, mouse and hamster by Leifer et al. (2561) in 1951. Female CF1 mice of about 25g weight, male Sprague-Dawley rats of 100-125 g, and hamsters of 50-60 g were given intraperitoneally 20 mg/kg radioactive nicotinic acid of nicotinamide; a single female dog of 10.4 kg was given intravenously 20 mg of C^{14}-nicotinic acid and later, the radioactive amide. Urine, feces and CO_2 samples were collected from all treated animals.

Identification of urinary metabolites was made by comparing chromatographic positions of radioactive bands (from radioautographs) with positions of known substances thought to be metabolites. The appearance of the radioautographs of chromatographic strips is shown in the following figure:

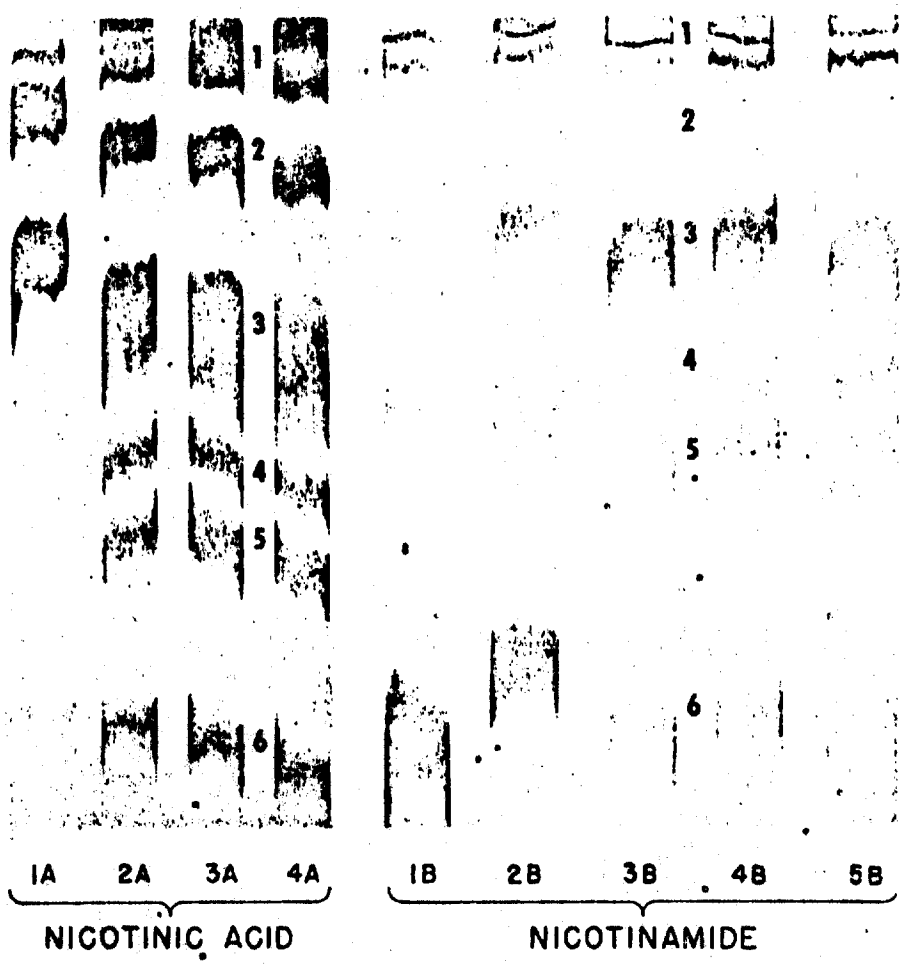


FIG. 1. Radioautographs of chromatographic strips, showing the appearance of urinary metabolites in mouse urine during various time intervals after intraperitoneal injection of C^{14}-nicotinic acid and C^{14}-nicotinamide. *1A*, 0 to 1 hour; *2A*, 1 to 9 hours; *3A*, 9 to 12½ hours; *4A*, 13½ hours after injection. *1B*, 0 to 1 hour; *2B*, 1 to 2½ hours; *3B*, 2½ to 11¾ hours; *4B*, 11¾ to 21¾ hours; *5B*, 21¾ to 24¾ hours after injection. Band 1, N^1-methylnicotinamide; Band 2, nicotinuric acid; Band 3, nicotinic acid; Band 4, unknown; Band 5, N^1-methyl-6-pyridone-3-carboxylamide; Band 6, nicotinamide.

Of the six metabolites, only five were identified: N'-methylnicotinamide; nicotinuric acid; nicotinic acid; N'-methyl-6-pyridone-3-carboxylamide; and nicotinamide. The unknown was not trigonelline, nor was trigonelline shown to be produced from either nicotinic acid or nicotinamide. All species produced $C^{14}O_2$ from the nicotinic acid and amide and CO_2 should be added to a list of known metabolites of nicotinic acid and nicotinamide.

Collins and Chaykin (911) in 1971, from preliminary experiments with mice and radioactive C^{14}-labelled nicotinic acid and nicotinamide (7-C^{14}-labelled), suggested that mouse metabolism is designed for the utilization of nicotinamide as a precursor of NAD. Adult female C3HeB/FeJ mice were injected intraperitoneally with the labelled compounds with a dose of 0.9 micromoles/mouse; at intervals of from 5 to 90 minutes after injection, the animals were sacrificed and tissues analysed for labelled

nicotinamide coenzymes and precursors by paper chromatography. In all tissues more radioactivity was found in NAD after the 7-C^{14}-nicotinamide than from 7-C^{14}-nicotinic acid; the acid was rapidly cleared from all tissues whereas the nicotinamide persisted for 90 minutes. By 20 minutes after injection, 90% of the nicotinic acid appeared as the nicotinamide in the liver. Nicotinamide given either by stomach tube or direct injection into the intestine appeared in the blood unchanged; nicotinic acid given in the same manner appeared as 30% nicotinamide in the blood within 5 minutes, and after passage through the liver was completely replaced by nicotinamide.

The foregoing, brief report was following in 1972 by a more detailed report of the same experiments by the same authors (Collins and Chaykin, (912)), and includes elaboration of experimental techniques and results. The charts taken from this report use the following terminology: des NMN, nicotinic acid mononucleotide; des DPN, nicotinic acid adenine dinucleotide; NA, nicotinic acid; NAm, nicotinamide.

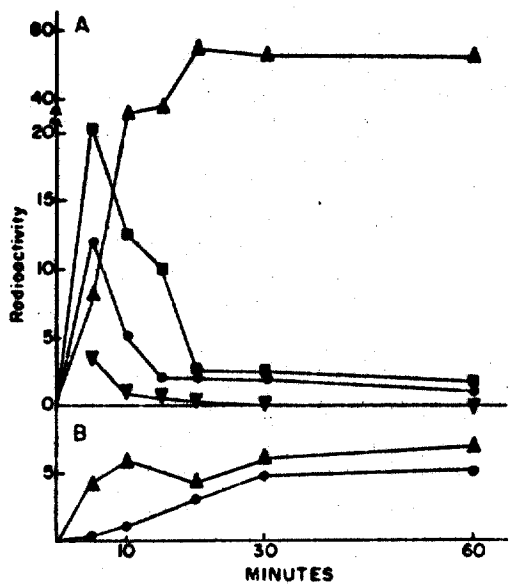


FIG. 1. Radioactive metabolites in mouse liver following the injection of 0.9 μmole of [7-^{14}C]nicotinic acid or [7-^{14}C]nicotinamide. *A*, [^{14}C]nicotinic acid injected; *B*, [^{14}C]nicotinamide injected. ▼——▼, nicotinic acid; ●——●, DPN; ■——■, desDPN; ▲——▲, nicotinamide. Each *point* represents the mean of data from two animals. Experimental procedures are described in the text. Radioactivity is expressed as (counts per min per 50 mg dry weight of tissue) × 10^{-4}.

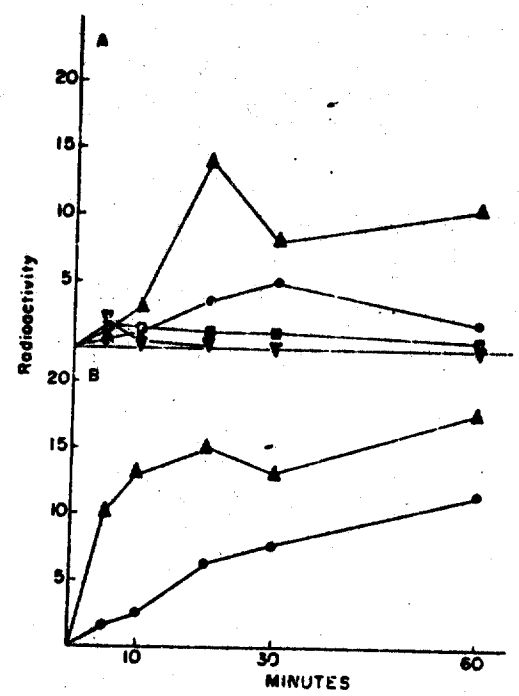


FIG. 2. Radioactive metabolites in mouse intestine following the injection of 0.9 μmole of [7-^{14}C]nicotinic acid or [7-^{14}C]nicotinamide. *A*, [^{14}C]nicotinic acid injected; *B*, [^{14}C]nicotinamide injected. ▼——▼, nicotinic acid; ●——●, DPN; ■——■, desDPN; ▲——▲, nicotinamide. Each *point* represents the mean of data from two animals. Experimental procedures are described in the text. Radioactivity is expressed as (counts per min per 50 mg dry weight of tissue) × 10^{-4}.

Table I

Major radioactive metabolites in variety of mouse tissues following intraperitoneal injection of [7-^{14}C]nicotinic acid and [7-^{14}C]-nicotinamide

Experimental procedures are described in the text.

Tissue	Time after injection	Radioactivity[a]							
		[^{14}C]Nicotinic acid injected					[^{14}C]Nicotinamide injected		
		Total[b]	DPN	desDPN	NA	NAm	Total	DPN	NAm
	min								
Kidney	5	205	5	26	86	15	75	8	60
	10	172	8	33	49	40	91	20	62
	30	150	25	13	2	90	128	65	46
	60	140	27	3		98	158	94	43
Ovaries	5	77		2	65	5	88	11	71
	10	51		5	30	6	96	13	68
	30	41	5	6	4	20	112	20	82
	60	36	5	5	1	20	74	20	45
Lung	5	39	1	7	24	1	60	5	46
	10	36	1	13	16	5	85	9	65
	30	33	3	10	2	18	84	20	52
	60	28	8	4		12	73	30	36
Heart	5	66		16	35	2	54	6	46
	10	71	1	30	23	9	93	12	67
	30	55	13	31		8	77	23	45
	60	47	22	20		12	96	42	38
Brain	5	5		1	2		23	2	16
	10	9	1	3	1	2	53	6	41
	30	18	3	2		8	61	15	39
	60	16	3	2		7	50	18	24

[a] (Counts per min per 50 mg of tissue, dry weight) $\times 10^{-3}$.

[b] Discrepancies between this value and the sum of the metabolites listed can be attributed to small amounts of label in other metabolites. An exception, however, was kidney where considerable amounts of label in nicotinuric acid were detected at 5 and 10 min after injection of nicotinic acid (6.3×10^4 and 2.3×10^4 cpm, respectively).

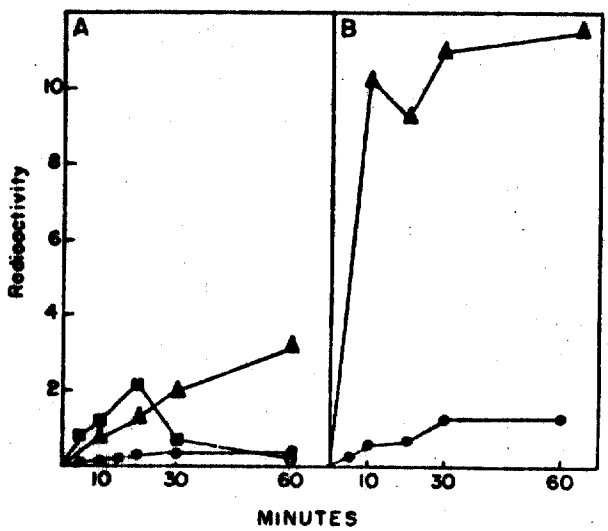


Fig. 3. Radioactive metabolites in mouse spleen following intraperitoneal injection of 0.9 μmole of [7-^{14}C]nicotinic acid or [7-^{14}C]nicotinamide. *A*, [^{14}C]nicotinic acid injected; *B*, [^{14}C]-nicotinamide injected. ●——●, DPN; ■- - -■, desDPN; ▲——▲, nicotinamide. Each *point* represents the mean of data from two animals. Experimental procedures are described in the text. Radioactivity is expressed as (counts per min per 50 mg dry weight of tissue) × 10^{-4}.

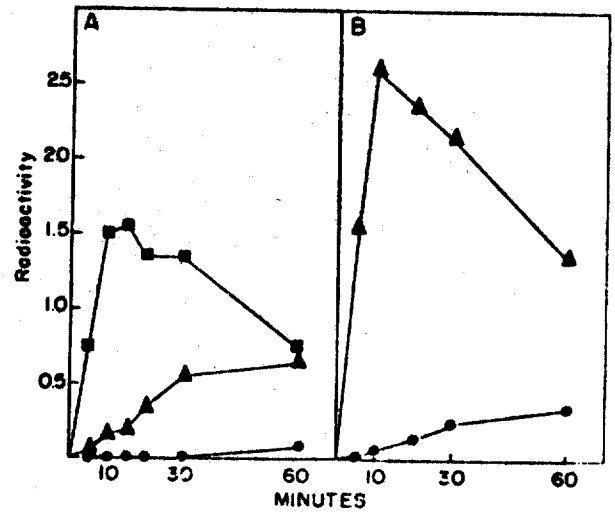


Fig. 4. Radioactive metabolites in mouse skeletal muscle following intraperitoneal injection of 0.9 μmole of [7-^{14}C]nicotinamide and [7-^{14}C]nicotinic acid. *A*, [^{14}C]nicotinic acid injected; *B*, [^{14}C]nicotinamide injected. ●- - -●, DPN; ■——■, desDPN; ▲- - -▲, nicotinamide. Each *point* represents the mean of data from two animals. Experimental procedures are described in the text. Radioactivity is expressed as (counts per min per 50 mg dry weight of tissue) × 10^{-4}.

The studies have indicated that in the mouse, both liver and intestine engage in the removal of nicotinic acid from possible circulation to the peripheral tissues by converting it to nicotinamide. Thus, nicotinamide administered either by stomach tube or by direct injection into the intestine, appears in the portal blood as nicotinamide; nicotinic acid appears as both the acid and as nicotinamide in the blood as it crossed the intestine (about 66% the acid and 33% as the amide), but upon passage through the liver most of the nicotinic acid is removed and replaced by nicotinamide.

Using carbon-14-labeled nicotinic acid and nicotinamide, Lee et al. (255) in 1969 isolated two newly identified metabolites in rat urine: 6-hydroxynicotinic acid and 6-hydroxynicotinamide.

Male Holtzman rats, weighing from 200 to 350 g were injected intraperitoneally with nicotinamide-7-C^{14} or nicotinic acid-7-C^{14}. The urine was collected and chromatographed, the radioactive areas were subjected to high voltage paper electrophoresis revealing an unidentified area. Pooled 24-hour urines from 6 rats given the radioactive nicotinamide were subjected to ion exchange chromatography and selected fractions were examined by ultraviolet, infrared, and mass spectrometry. Further studies indicated that the new metabolites are produced in the tissues rather than by the intestinal flora. About 0.6 to 1.2% of the injected dose of either nicotinic acid or nicotinamide is excreted as 6-hydroxynicotinic acid and 6-hydroxynicotinamide.

Lee (2548) in 1969 administered nicotinic acid and nicotinamide intraportally and intraperitoneally in rats, in doses of 75 or 210 millimicromoles, and observed the formation and degradation of nicotinamide adenine dinucleotide (NAD+) in the liver. Hypophysectomized rats excreted less N-methylnicotinamide and nicotinuric acid in the urine than did normal rats after intraperitoneal injections of either nicotinic acid or nicotinamide. The rate of excretion in the hypophysectomized animals was also lower than in normal animals. Two new urinary metabolites of nicotinamide were isolated and identified by mass, ultraviolet, and infrared spectrometry: 6-hydroxynicotinic acid and 6-hydroxynicotinamide. Tests with germ-free rats demonstrated that the two metabolites are formed in the animal's tissue rather than by intestinal flora.

Reddi and Kodicek (3567) in 1953 employed chromatographic techniques developed by them in studies of urinary metabolites from the ingestion of nicotinic acid, nicotinamide and tryptophan in man and rat.

Four healthy males subjects were given various nicotinyl compounds in turn at weekly intervals and their urines were collected and analyzed for nicotinyl compounds. Experimental data and results are shown in the following table:

Table 1. *Excretion of nicotinyl compounds in human urines and their distribution*

Subject	Age (years)	Dose	Excretion (mg./3 hr.): N^1-Methylnicotinamide determined chemically	Total alkali-hydrolysable nicotinic acid derivatives determined: Chemically	Micro-biologically	Approximate relative distribution of tertiary nicotinyl compounds (%)*: Nicotinic acid	Nicotinamide	Nicotinuric acid†
1	29	None	0·5	0·3	0·12	Nil	Nil	Nil
2	43		0·5	0·2	0·04	Nil	Nil	Nil
3	32		0·5	0·2	0·04	Nil	Nil	Nil
4	20		0·6	0·2	0·06	Nil	Nil	Nil
1	29	100 mg. nicotinic acid (after breakfast)	4·5	7·3	—	Nil	4	96
2	43		3·7	6·0	—	Nil	2	98
3	32		2·8	14·6	—	7	1	92
4	20		5·7	8·6	—	Nil	1	99
1	29	100 mg. nicotinic acid (before breakfast)	5·4	40·3	—	10	0·5	89·5
2	43		2·7	17·3	—	5	0·5	94·5
1	29	100 mg. nicotinamide	16·2	1·5	—	Nil	100	Nil
2	43		16·6	1·8	—	Nil	100	Nil
3	32		6·9	1·8	—	Nil	100	Nil
4	20		15·6	0·9	—	Nil	100	Nil
2	43	3 g. L-tryptophan	1·0	—	0·09	Nil	Nil	Nil
3	32		0·7	—	0·04	Nil	Nil	Nil
4	20		1·0	—	0·05	Nil	Nil	Nil

* Determined by paper chromatography (Kodicek & Reddi, 1951).
† The values for nicotinuric acid were obtained by difference.

Sixteen male piebald rats, weighing 55-60 g were divided into 2 groups and placed on different diets, one a low-protein, nicotinic acid deficient diet, and the other an adequate diet. The animals were given various nicotinyl compounds; the urine was collected and analyzed for metabolites. The results are shown in the table on the following page.

In man, nicotinic acid was excreted as nicotinuric acid, N'-methylnicotinamide and nicotinamide in decreasing order; nicotinamide was excreted as N'-methylnicotinamide and nicotinamide. The urines of untreated human subjects showed only very small amounts of nicotinamide and N'-methylnicotinamide. In the rat, nicotinic acid appeared in the urine from ingesting either nicotinic acid or nicotinamide.

An early study in 1942 by Sarett et al. (3801) showed that trigonelline and nicotinuric acid were the only known end products of nicotinic acid metabolism found in human urine. Trigonelline-free diets were tested by the authors and student volunteers, and the influence of smoking on normal daily excretion of acid hydrolyzable nicotinic acid derivatives was examined. Smoking had no influence. Oral doses of 200 mg nicotinic acid or nicotinamide increased urinary trigonelline in both instances, but no increase in hydrolyzable nicotinic acid fractions occurred from nicotinamide.

Abelson et al. (21) in 1962 reported the identification of an ultraviolet-absorbing compound which appears on chromatograms of plasma extracts. A dose of 600 mg nicotinamide was given orally to a normal, fasting subject; 3 hours later a pint of venous blood was drawn into a heparinized bottle and centrifuged. Ultraviolet and infrared spectral analysis suggested that the compound was N'-methyl-4-pyridone-3-carboxamide. An earlier identified compound which also appears on the chromatogram was identified as N'-methyl-2-pyridone-5-carboxamide.

Lee et al. (2546) in 1968 used carbon-14 labeled nicotinic acid to trace and identify the metabolites in a normal male subject (weight 71.4 kg) given 9.3 microcuries of nicotinic acid-6-C^{14} intravenously. Blood samples were taken periodically; plasma and red cell fractions were separated. All urine was collected during the 19 days of the experiment. Urine and plasma samples were counted for radioactivity; about half the injected dose appeared in the red cells within 1.5 minutes after injection, the radioactivity dropping rapidly to 8 minutes and remaining nearly constant for several hours. Urinary excretion showed an early sudden drop during the first 12 hours, a variable rate during 1st to 11th day, and a constant excretion during the remaining days to the 19th day terminating the experiment. The following figures show the blood radioactivity and the urinary excretion for the nicotinic acid-6-C^{14} and metabolites: (see page 36).

Table 2. *Excretion of nicotinyl compounds in urines of normal and deficient rats before and after dosing with nicotinic acid and related substances*

Group	Diet	No. of rats	Average wt. (g.)	Dose	Average daily excretion per rat (mg.)		Approximate relative distribution of tertiary nicotinyl compounds (%)*		
					N^1-Methyl nicotinamide	Total alkali-hydrolysable nicotinic acid derivatives	Nicotinic acid	Nicotin-amide	Nicotinuric acid
1 (deficient)	Low-protein maize (Harris & Kodicek, 1950)	8	78	None	0·01	0·01	43	57	Nil
		2	78	2·5 mg. nicotinic acid	0·42	0·53	17	2	81
		2	87	2·5 mg. nicotinamide	1·03	0·27	26	74	Nil
		2	74	100 mg. quinolinic acid	0·01	0·01	46	54	Nil
		2	88	100 mg. L-tryptophan	0·10	0·03	71	29	Nil
2 (normal)	Synthetic casein diet	8	139	None	0·24	0·04	49	51	Nil
		2	147	2·5 mg. nicotinic acid	1·27	0·98	31	6	63
		2	210	2·5 mg. nicotinamide	2·03	0·62	25	75	Nil
		2	132	100 mg. quinolinic acid	0·57	0·14	86	14	Nil
		2	130	100 mg. L-tryptophan	1·74	0·20	90	10	Nil

* Determined by paper chromatography (Kodicek & Reddi, 1951).

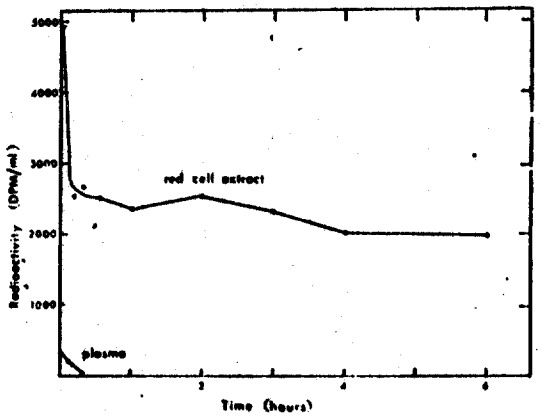


FIG. 1. Radioactivity in blood following intravenous nicotinic acid-6-^{14}C.

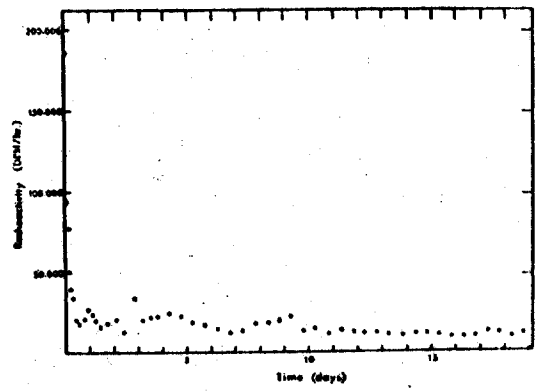


FIG. 2. Urinary excretion of nicotinic acid-6-^{14}C metabolites.

Aliquots of urine were partitioned into alkaline, acid and residue- and radioactivity determined. The first few hours of measurement showed most of the radioactivity in the residue and little in the alkaline extract; on the 12th day the situation was reversed. This biphasic excretion pattern suggests several distinct routes by which nicotinic acid is metabolized by man. The authors propose that the red cells first take up the nicotinic acid and transport it rapidly to the tissues where it enters one of two metabolic pools. One pool cycles through pyridine nucleotides and the other, which may or may not involve pyridine nucleotides, rapidly forms metabolites which are released and excreted. The distribution of the urinary radioactivity is shown in the following figure:

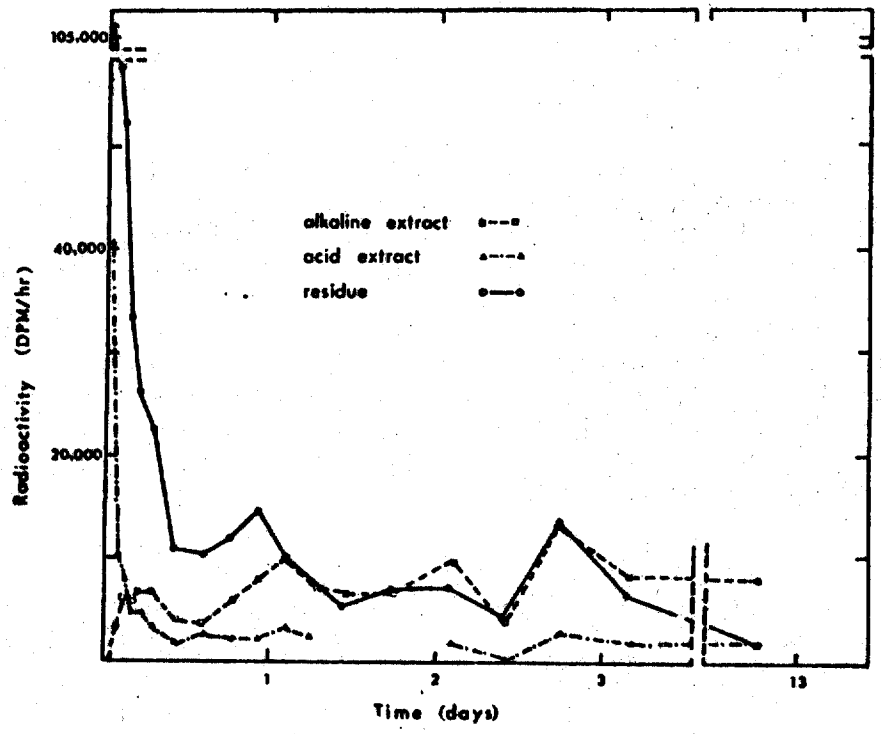


FIG. 4. Distribution of radioactivity.

The metabolism of nicotinamide derivatives in men, dogs, cats, rats, rabbits and guinea pigs was studied by Elhinger and Kader (1212) in 1948. Nicotinamide, nicotinic acid, nikethamide and in some instances, nicotinamide methochloride and nicotinuric acid were given orally, subcutaneously or intraperitoneally. Metabolites tested for were nicotinamide, nicotinic acid, nicotinuric acid, trigonelline and nicotinamide methochloride.

The following eight tables summarize the experimental results and are for the most part, self-explanatory.

Table 1. *Weights and diets of the animals used*

Species	No. of animals	Weight (kg.)	Diet (food given/day)	Dietary intake of: Nicotinic acid (mg./day)	Dietary intake of: Nicotinamide (mg./day)
Dog	2	1·8–3·5	Meat, bread and vegetables, 300 g.; milk, fresh, 200 ml.	6·1	10·0
Cat	3	0·76–0·88	Powdered milk, 15 g.; fish, 70 g.; bread, 30 g.	4·5	1·3
Rat (adult):					
Albino (stock of P.E.)	21	0·20–0·26	Grain mixture, 4·0 g.; extracted liver residue 3·5 g.; wheat germ, 1·0 g.; dried yeast 0·3 g.; salt mixture (McCallum 185), 0·5 g.; maize oil, 0·6 g.; cod-liver oil, 0·1 g.; national bread, 13·0 g.; milk powder, 1·5 g.	0·37	0·21
Hooded (Lister stock)	21	0·20–0·34			
Rat (young):					
Albino	5	Average 0·069			
Hooded	5	Average 0·039			
Rabbit	8	2·90–3·00	Either (*a*) cabbage, 200 g.; swedes, 100 g.; or (*b*) oats, 100 g.	1·00 0·34	1·60 0·21
Guinea pig	6	0·40–0·47	Pellets (containing grass meal 30%, bran 15%, ground-nut cake 15%, linseed cake 10%, barley meal 20%, meat and bone meal 8%, $CaCO_3$ 1%, NaCl 1%), 50 g.; cabbage, 50 g.	0·32	0·88

All animals obtained water *ad lib.*

Table 2*a*. *Daily elimination of nicotinamide derivatives by man*

Subject: No.	Sex	Age (yr.)	Wt. (kg.)	Metabolites eliminated (mg./24 hr.): Nicotinamide	Nicotinic acid	Nicotinamide methochloride*	Remarks
1†	♂	27	80	2·000	0·810	8·630	No smoking, no coffee
R1‡	♂	27	80	1·342	0·360	6·681	
R1§	♂	27	80	3·622	1·233	11·420	
2	♀	61	50	3·320	0·680	6·160	No smoking, coffee
3	♀	19	70	1·400	0·480	9·360	No smoking, no coffee
4	♀	19	65	2·180	0·370	9·440	
5	♂	47	67	1·980	0·215	12·040	
6	♂	22	70	1·590	0·264	12·480	
7	♀	25	58	1·175	0·190	10·840	
8	♂	53	64	2·540	0·145	6·050	
9	♂	60	68	3·000	0·440	5·040	Balanced diabetic; no smoking, no coffee
Average				2·132	0·399	8·894	

Neither trigonelline nor nicotinuric acid were eliminated.
* Absolute, not in terms of nicotinic acid.
† Average of daily output estimated on 22 control days spread over the whole period.
‡ Average of 3 days before the first injection.
§ Average of 3 days, 14 days after last injection.

Table 2b. *Response to extradietary nicotinamide derivatives by man (subject no. 1)*

Compound administered	Dose (mg.)	Route	Metabolites eliminated (% of ingested)*			
			Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Total
Nicotinamide	100	Oral	0	0	18·9 [3]	18·9
		Subcutaneous	1·8	0	24·9 [3]	26·7
Nicotinic acid	100	Oral	2·3	0·8	16·5 [2]	19·6
		Subcutaneous	2·1	0·9	21·1 [2]	24·1
Nicotindiethylamide	100	Oral	6·2	0	5·8 [2]	12·0
		Subcutaneous	6·3	0	15·5 [2]	21·8

[ ] indicates time in days over which elimination occurred.
* *Note.* Dose of administered compound is in terms of nicotinic acid. The response (percentage of ingested), also in terms of nicotinic acid, is calculated as

$$\frac{\text{(output until predosing level is reached)} - \text{(average predosing output} \times \text{days of increased output)}}{\text{dose administered}} \times 100.$$

Neither trigonelline nor nicotinuric acid was eliminated.

Table 3. *Average daily urinary elimination of nicotinamide derivatives by various mammalian species*

Species	Metabolites eliminated (Averages, limiting values in parentheses) (mg./day)		
	Nicotinamide	Nicotinic acid	Nicotinamide methochloride
Dog	4·500 (3·480–5·720)	0	5·370 (1·000–10·250)
Cat	0	0	0·290 (0·070–0·400)
Rat (albino):			
Adult	0·080 (0·054–0·130)	0	0·100 (0·030–0·260)
Young	0·035	0	0·292
Rat (hooded):			
Adult	0·140 (0·100–0·170)	0	0·060 (0·450–1·700)
Young	0·0214	0	0·150
Rabbit (On cabbage)	0	0·880 (0·500–1·350)	0*
(On oats)	0	1·190 (1·010–1·540)	0*
Guinea pig	0	0	0*

Neither trigonelline nor nicotinuric acid were eliminated.
* Indicates a small positive reaction with the acetone, but none with the König (1904) method.

Table 4. *Average response to extradietary nicotinamide derivatives by dogs*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*			
		Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Total
Nicotinamide	200	31·7 [2]	0	50·1 [2]	81·8
	500	43·0 [2]	0	31·6 [2]	74·6
Nicotinic acid	200	48·8	13·1	31·6 [2]	93·5
	500	49·0 [2]	16·7	21·5 [2]	87·2
	9000†	10·0	49·4	5·6	65·0
Nicotindiethylamide	100	43·5	0	52·1 [2]	95·5
Nicotinuric acid	67·7	31·4	41·8	18·1 [2]	91·2

[ ] indicates time in days over which elimination occurred, if more than one.
Neither trigonelline nor nicotinuric acid were eliminated.
* See note to Table 2b.
† Orally within 5 days.

Table 5. *Average response to extradictary nicotinamide derivatives by cats*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*			
		Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Total
Nicotinamide	40	34·5	0	28·3 [3]	63·3
	80	37·6 [2]	0	20·4 [2]	58·0
	200	47·0 [2]	0	34·1 [4]	81·1
Nicotinic acid	40	12·8	10·5	24·1 [2]	47·4
	100	24·1 [2]	29·0	18·7 [3]	71·8
Nicotindiethylamide	40	19·0	0	16·1 [2]	35·0

[ ] indicates time in days over which elimination occurred, if more than one.
Neither trigonelline nore nicotinuric acid were eliminated.
* See note to Table 2*b*.

Table 6. *Response to extradictary nicotinamide derivatives by two strains of rats*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*				
		Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Nicotinuric acid	Total
		Albino				
Nicotinamide	20	23·7	0	9·3	0	33·0
	20 (+30 DL-methionine)	19·2	0	12·5	0	31·7
	50	31·6	0	15·0 [2]	0	46·6
Nicotinic acid	20	23·8	26·9	1·8	0	52·5
	20 (+30 DL-methionine)	20·4	49·5	1·0 [2]	0	70·9
	50	31·9 [2]	35·4	1·0 [2]	0	68·3
Nicotindiethylamide	20	36·7	0	9·8 [2]	0	46·5
	20 (+30 DL-methionine)	48·0	0	4·9 [2]	0	52·9
	50	38·8 [2]	0	3·4 [2]	0	42·2
Nicotinamide methochloride	17·5	0	0	71·0	0	71·0
Nicotinuric acid	33·9	13·0	2·1	3·2 [2]	72·8	91·0
		Hooded				
Nicotinamide	20	15·0	0	29·7	0	44·7
	20 (+30 DL-methionine)	16·5	0	59·7*	0	76·2
	50	19·2	0	61·6 [2]	0	80·8
Nicotinic acid	20	24·1	27·7	16·0	0	67·8
	20 (+30 DL-methionine)	20·0	37·8	8·9 [2]	0	72·7
	50	25·4	19·4	5·7	0	50·5
Nicotindiethylamide	20	36·0	0	33·4 [2]	0	69·4
	50	34·4 [2]	0	13·7 [2]	0	48·1
Nicotinamide methochloride	17·5	0	0	63·2	0	63·2
Nicotinuric acid	33·9	11·4	2·0	3·1 [2]	62·2	79·6

[ ] indicates time in days over which elimination occurred, if more than one.
No trigonelline was eliminated.
* See note to Table 2*b*.

Table 7. *Average response to extradietary nicotinamide derivatives by rabbits*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*			
		Nicotinamide	Nicotinic acid	Trigonelline	Total
		Diet of cabbage			
Nicotinamide	100	2·9	3·3 [2]	5·1 [2]	11·3
	200	6·9	14·5 [3]	9·3 [3]	30·6
	400	7·5	18·6 [3]	9·4 [3]	35·5
Nicotinic acid	100	0	35·5 [2]	48·0 [2]	83·5
	200	0	63·4 [2]	33·9 [2]	97·3
Nicotindiethylamide	50	1·6	5·7	3·3	10·6†
	100	9·2	15·1	6·4	30·7†
	200	4·9	10·0 [2]	7·0 [2]	21·8†
	2 hourly doses of 100				
	600	7·5	21·7 [2]	2·7 [2]	30·9†
	6 hourly doses of 100				
		Diet of oats			
Nicotinamide	100	2·2	3·5 [2]	3·3	9·5‡
	200	7·5 [2]	13·0 [3]	6·5 [3]	27·0‡
Nicotinic acid	100	0	32·9 [2]	54·8 [2]	87·7
	200	0	52·4 [2]	29·8 [2]	82·2

[ ] indicates time in days over which elimination occurred, if more than one.
Neither nicotinamide methochloride nor nicotinuric acid were eliminated.
* See note to Table 2*b*.
† Indicates that after injection of nicotindiethylamide an unknown substance of high fluorescent efficiency was eliminated interfering with the application of the acetone method.
‡ Indicates that after injection of nicotinamide into rabbits fed on oats and possibly after that of nicotindiethylamide a substance was eliminated to a slightly increased extent giving a positive reaction with the acetone but not with the König (1904) method.

Table 8. *Average response to extradietary nicotinamide derivatives by guinea pigs*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*			
		Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Total
Nicotinamide	100	0	32·4	0*	32·4
	200	0	24·2 [2]	0* [2]	24·2
	400	0	38·9 [2]	0* [2]	38·9
Nicotinic acid	100	0	60·5 [2]	0	60·5
	200	0	82·2 [2]	0	82·2
	400	0	66·7 [2]	0	66·7
Nicotindiethylamide	25	12·9	12·7	0†	25·6
	50	10·3	20·4 [2]	0†	30·7

[ ] indicates time in days over which elimination occurred, if more than one.
Neither trigonelline nor nicotinuric acid were eliminated.
* See note to Table 2*b*.
† Indicates that after administration of nicotinamide or nicotindiethylamide a substance was eliminated to a slightly increased extent giving a positive reaction with the acetone, but not with the König (1904) method.

The authors classify the mammals examined in this report into two groups: man, dog, cat and rat which aminate nicotinic acid to nicotinamide; rabbit and guinea pig deaminate nicotinamide to nicotinic acid. Further effects to base a classification of species on biochemical properties would require more species to be examined.

A similar study by Perlzweig et al. (3360) in 1949 was more comprehensive than that of Ellinger and Kader in that a greater number of species were included in the experiments: man, rat, dog, pig, rabbit, guinea pig, goat, sheep and calf. Oral doses of nicotinamide were given; urines were analyzed for niacin derivatives. The following tables summarize the findings:

TABLE 2

The excretion of niacin and its derivatives in two adults following the ingestion of nicotinamide, N^1-methylnicotinamide and 6-pyridone. (Values are in milligrams per 24-hour urine)

URINE	N^1-METHYL-NICOTINAMIDE		6-PYRIDONE		NIACIN		TOTAL	
	F.R.	I.L.	F.R.	I.L.	F.R.	I.L.	F.R.	I.L.
Control — no supplement								
1	6	9	10	12	0.9	1.1	17 (14)[1]	22 (19)
Supplement — 500 mg nicotinamide								
2	130	185	221	280	7.1	5.3	358(282)	470(394)
3	161	165	376	279	7.5	3.7	544(451)	448(374)
4	214	278	278	271	5.6	4.5	498(418)	554(470)
5	262	245	246	238	6.1	4.7	514(436)	508(429)
6	263	191	280	228	7.4	4.4	550(465)	433(357)
Supplement — 224 mg N^1-methylnicotinamide								
12	57	35	45	41			102	76
13	70	48	37	24			107	72
14	47	34	40	48			87	82
Supplement — 25 mg 6-pyridone								
15			22	23			22	23

[1] Values in parentheses represent an equivalent amount of nicotinamide.

TABLE 3

Metabolism of nicotinamide, N^1-methylnicotinamide and 6-pyridone in the dog, rat and pig

Species	Supplement fed		Excreted in urine[1]				
	Compound	Amount	N^1-methylnicotinamide	6-Pyridone	Nicotinuric acid[2]	Total: Acct'd. for	Total: Unacct'd. for
		mg/kg					
Dog	Nicotinamide	10	80	0[3]	8	88	12
	N^1-methylnicotinamide	11	20	2[3]		22	78
	6-Pyridone	2.5–4.0		69		69	31
Rat	Nicotinamide	100–200	50	3	15	68	32
	N^1-methylnicotinamide	100	50	3		53	47
	6-Pyridone	30–50		80		80	20
Pig	Nicotinamide	75–80	7	10	9	26	74
	N^1-methylnicotinamide	10	15	20		35	65
			(3.27)	(31.9)		55	45
	6-Pyridone	1		55			

[1] Values given as per cent of total dose excreted in the urine in 24 hours.
[2] Nicotinuric acid and derivatives as measured by *L. arabinosus* assay after 1 N HCl hydrolysis of the urine.
[3] Significance questionable due to low concentration.

TABLE 4

Metabolism of nicotinamide, N^1-methylnicotinamide and 6-pyridone in the rabbit, guinea pig, goat, sheep and calf

Species	Supplement fed		Excreted in urine[1]				
	Compound	Amount	N^1-methylnicotinamide	6-Pyridone	Nicotinuric acid[2]	Total: Acct'd. for	Total: Unacct'd. for
		mg/kg					
Rabbit	Nicotinamide	90–100	0.5[3]	3	43[3]	46.5	53.5
	N^1-methylnicotinamide	100	17	25		42	58
	6-Pyridone	11–15		90		90	10
Guinea pig	Nicotinamide	150–200	0.5[3]	5	8	13.5	86.5
	N^1-methylnicotinamide	160–200	0.5[3]	4		4.5	95.5
	6-Pyridone	40–50		40		40	60
Goat	Nicotinamide	70–100	0.5[3]	0.5[3]	14	15	85
	N^1-methylnicotinamide	10	12	4		16	84
	6-Pyridone	1		35		35	65
Sheep	Nicotinamide	30–60	0.5[3]	0.3[3]	30	31	69
	N^1-methylnicotinamide	10	1[3]	3		4	96
	6-Pyridone	1		11		11	89
Calf	Nicotinamide	30–70	0.6[3]	0[3]	35	36	64
	N^1-methylnicotinamide	10	2[3]	3		5	95
	6-Pyridone	1		58		58	42

[1] Values given as per cent of total dose excreted in the urine in 24 hours.
[2] Nicotinuric acid and derivatives as measured by *L. arabinosus* assay after 1 N HCl hydrolysis of the urine.
[3] Significance questionable due to low concentration.

A comparison of these early papers by Ellinger and Kader, and Perlzweig et al., shows some disagreement regarding the identity of the metabolites of nicotinamide, or of their terminology. Reference to a more recent paper, reviewed in this section of the monograph, by Lee and Gholson (2550) reveals the following urinary metabolites: N'-methylnicotinamide, nicotinuric acid, nicotinamide-N-oxide, N'-methyl-2-pyridone-5-carboxamide, N'-methyl-4-pyridone-3-carboxamide, 6-hydroxynicotinic acid and 6-hydroxynicotinamide.

Perlzweig et al. suggested, as had Ellinger and Kader, that in man, dog, rat and pig (and possibly other omnivora and carnivora) excesses of niacin are largely disposed of by methylating processes, whereas, herbivora (rabbit, guinea pig and polygastric species) probably dispose of niacin by pathways other than through methylation.

IV. Effects on Enzymes and Other Biochemical Parameters

Ammon and Estler (111) in 1967 investigated the influence of 200 mg/kg nicotinic acid on the liver glycolytic carbohydrate breakdown in white mice. The nicotinic acid dose was administered intraperitoneally; at 1, 2, or 4 hours after injection, the mice were quick-frozen and brain muscle and liver tissues prepared; adipose tissue and blood samples were taken either immediately before or after freezing. Various carbohydrate metabolites were determined; the results are shown in the figure on the following page.

The lowering of serum free fatty acids (FFA) by nicotinic acid results in an accelerated carbohydrate breakdown to provide energy normally provided by the FFA. The glycogen content of adipose tissue remains constant even in the presence of nicotinic acid; the glycogen content however, in muscle is reduced in the absence of nicotinic acid accumulation. Thus, the increased glycogenolysis in liver and muscle is apparently indirectly due to nicotinic acid, rather than a direct consequence of the injected nicotinic acid.

The metabolic consequences of giving rats nicotinic acid (the sodium salt) in terms of plasma free fatty acids, triglycerides and cholesterol, blood glucose and liver triglycerides and cholesterol, were reported by Carlson and Nye (685) in 1966.

Male Sprague-Dawley rats, weighing 180-200 g, were given 5% sodium nicotinate solution subcutaneously, 250 mg/kg. The animals were sacrificed at intervals of up to 9 hours, and the various parameters of effect of the nicotinic acid were determined. The table on page 45 shows the results.

TABLE I. Values for plasma FFA, blood glucose, plasma triglycerides, plasma cholesterol, liver triglycerides and liver cholesterol in control and nicotinic acid-injected rats

Time after injection (hrs)		Plasma FFA (meq/l)			Blood glucose (mg/100 ml)			Plasma triglycerides (nanoles/l)			Plasma cholesterol (mg/100 ml)			Liver triglycerides (μmoles/g)			Liver cholesterol (mg/g)		
		C	NA	P	C	NA	P	C	NA	P	C	NA	P	C	NA	P	C	NA	P
0	M	0.50	–	–	70.9			0.30			75.7		–	5.01	–		4.1	–	
	SEM	0.05			3.3	–		0.028			3.5			0.51			0.1	–	
	n	9	–		9			10			10			8			10	–	
0.25	M	1.68	1.08	<0.001	55.7	56.6	>0.05	0.24	0.25	0.05	–			–	–	–	–	–	
	SEM	0.12	0.02		2.0	2.3		0.028	0.011					–	–		–	–	
	n	10	10		10	10		10	10		–			–	–		–	–	
1	M	0.46	0.22	<0.001	64.6	47.6	<0.001	0.24	0.18	0.01	81.7	85.4	–	6.05	5.92	>0.05	4.4	4.2	0.05
	SEM	0.07	0.02		3.7	1.9		0.022	0.014		3.5	2.93		0.97	0.80		0.2	0.2	
	n	9	14		9	14		10	14		10	14		10	14		10	13	
2	M	0.58	0.26	<0.01	54.2	45.6	<0.01	0.24	0.11	0.001	80.6	72.6	>0.01	4.58	3.41	<0.01	4.0	4.0	>0.05
	SEM	0.06	0.02		3.1	1.8		0.016	0.007		3.0	2.3		0.35	0.39		0.2	0.1	
	n	15	21		11	16		21	23		21	23		21	23		21	22	
3	M	0.58	0.23	<0.001	60.3	44.1	<0.001	0.22	0.09	<0.001	82.4	73.9	>0.05	6.58	2.13	<0.001	4.3	4.4	>0.05
	SEM	0.05	0.01		3.6	1.6		0.031	0.009		5.0	3.4		0.67	0.35		0.2	0.2	
	n	10	13		10	11		9	12		10	13		10	14		9	14	
6	M	0.70	0.54	>0.05	55.7	51.2	>0.05	0.25	0.08	<0.001	87.8	74.4	<0.01	4.35	1.90	<0.01	3.9	4.1	>0.05
	SEM	0.07	0.07		3.1	4.0		0.021	0.001		2.7	3.9		0.47	0.10		0.1	0.1	
	n	6	9		6	9		6	9		6	9		6	9		6	9	
9	M	0.80	0.95	>0.05	54.4	48.8	>0.05	0.20	0.17	>0.05	84.6	79.0	>0.05	3.82	8.20	<0.05	3.3	3.7	>0.05
	SEM	0.08	0.05		2.5	2.3		0.001	0.016		4.0	2.8		0.73	1.78		0.2	0.2	
	n	5	6		5	6		5	6		5	6		5	6		5	6	

C=control rats. NA=nicotinic acid-injected rats. P indicates the statistical significance for the difference between C and NA (t-test). M - mean value. SEM standard error of the mean n= number.

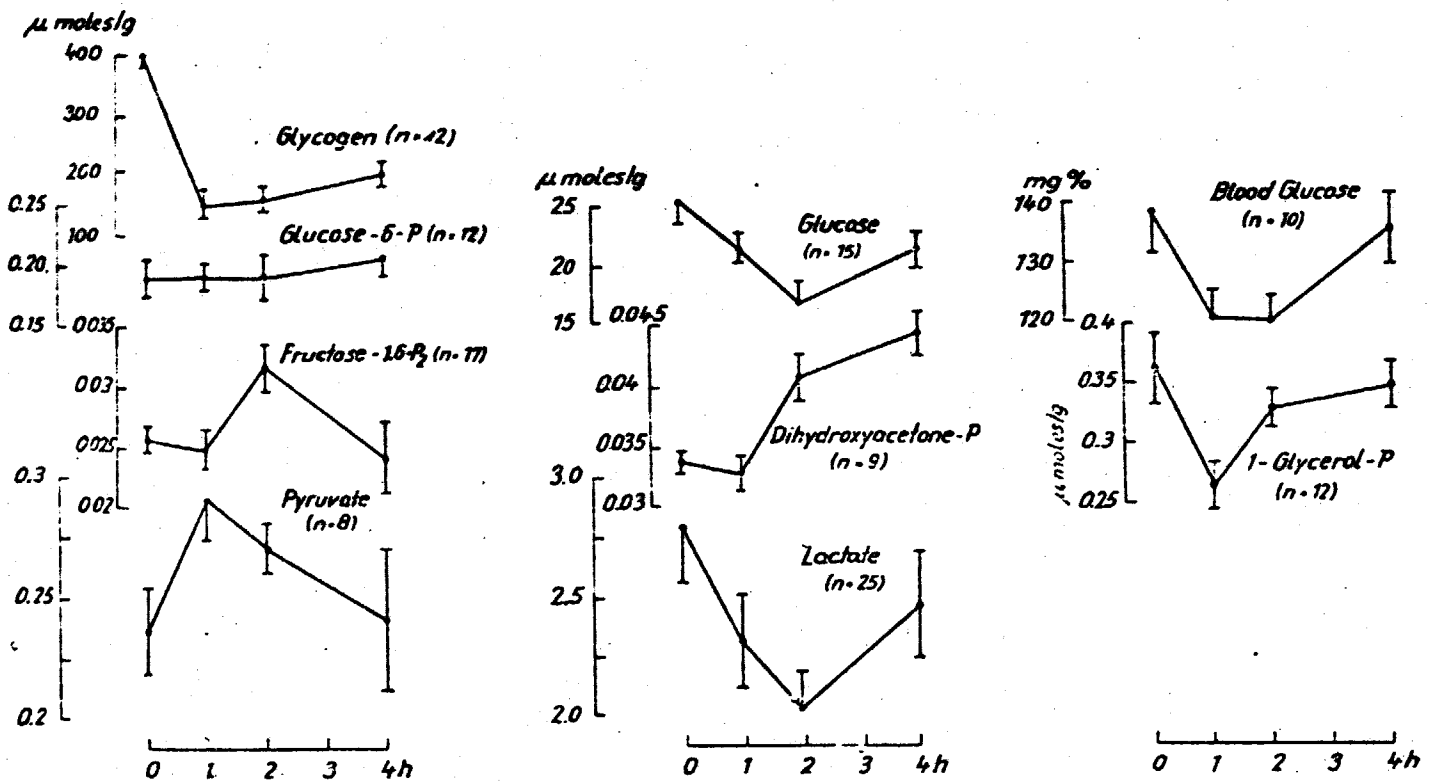


Fig.1

Contents of glycogen, glucose-6-P, glucose, fructose-1,6-P_2, dihydroxyacetone-P, 1-glycerol-P, pyruvate and lactate in the liver and blood glucose of white mice after i.p.administration of 2oo mg/kg nicotinic acid.

The plasma levels of free fatty acid were significantly reduced from 15 minutes up to 3 hours; triglycerides reduced from 1 to 6 hours, and cholesterol at 2 and 6 hours. Liver triglycerides were significantly reduced from 2 to 6 hours and elevated at 9 hours; liver cholesterol was unaffected. Free nicotinic acid rapidly appeared in adipose tissue but fell to control levels after 3 hours. The authors suggest that the action of nicotinic acid, inhibiting mobilization of free fatty acids, is at least partly responsible for the depression of plasma triglyceride and cholesterol levels.

Barboriak and Meade (252) in 1970 demonstrated that nicotinic acid effectively inhibited the usual alcohol-induced enhancement of alimentary lipemia in man, and the increased post-prandial plasma and liver triglycerides from ingestion of corn oil-alcohol mixture by rats.

Seven 24-25 year-old subjects were given 4 oz. bourbon whiskey before breakfast; one week later, the process was repeated, but with 600 mg nicotinic acid added to the breakfast meal. Venous blood samples were taken before ingestion of whiskey and 3 and 6 hours after meal. Plasma determinations of triglyceride and alcohol levels were made. The results are shown in the following figure:

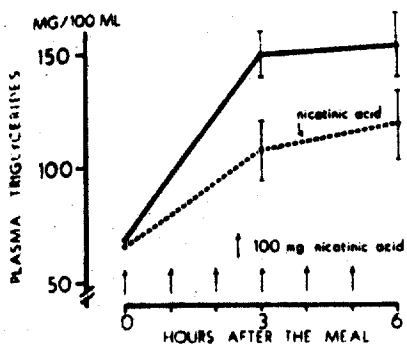


Fig. 1. Effect of nicotinic acid on alcohol-induced postprandial lipemia in man. The arrows indicate the time of nicotinic acid administration; the vertical lines represent the standard error of the mean.

Eighteen female Sprague-Dawley rats weighing about 250 g each were divided into two groups. Nine were given 200 mg/kg nicotinic acid intraperitoneally before feeding an alcohol-corn oil mixture by stomach tube; the remainder were not pretreated with nicotinic acid, serving as controls. Sixteen hours after the meal, the animals were sacrificed, blood samples were taken and livers were removed. Plasma and liver triglycerides were measured. A second experiment added trace amounts of 1-C^{14}-triolein to the control; thin-layer chromatography showed major increase in triglyceride levels in the plasma and little in the liver. The results of the first tests, without radioactive tracer, are shown in the following figure:

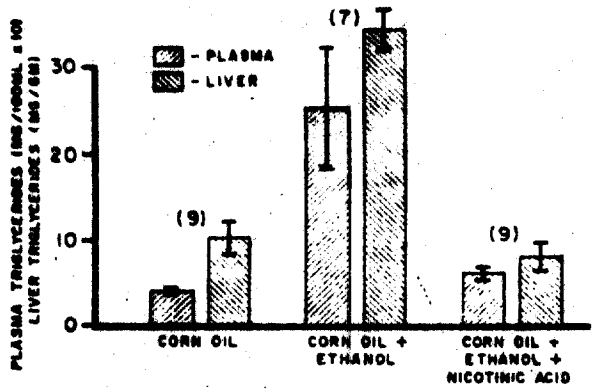


Fig. 2. Effect of nicotinic acid on postalcoholic plasma and liver triglycerides in the rats. The vertical lines represent the standard error of the mean, the number of animals is shown in parenthesis.

The protective action of the nicotinic acid was marked; the lowered plasma triglyceride levels were seen in both experiments.

Among the factors that have variously been associated epidemiologically with myocardial infarction and coronary atherosclerosis has been the incidence of hypercholesteremia; Parsons (3295) in 1961 presented a paper supporting the desireability of chemotherapy in reducing cholesterol levels by the use of nicotinic acid in view of a "consensus of informed opinion" that a normal cholesterol level is better than an elevated one, even though proof of a relationship to atherosclerosis is lacking. (It is of interest to note that the following notation may be found in the 1973 edition of the Physicians' Desk Reference to Pharmaceutical Specialities and Biologicals (215):

> "It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question."

Nicotinic acid therapy utilizes doses of 3 to 6 g taken daily; at first, and for usually a few days, an uncomfortable flush occurs which generally disappears by the end of the first week of treatment and constitutes no problem in long-term therapy. Blood pressure and heart beat are not affected nor is angira pectoris produced or aggravated by the treatment. The author has used nicotinic acid, nicotinamide and aluminum nicotinate in therapy; the amide is less effective but does not produce the "flush", and the aluminum nicotinate may be effective at lower doses than the nicotinic acid but also produces a flush and somewhat more nausea in larger doses (2-2.5 g/day).

Fifty patients, after one year of treatment, showed 80% with normal cholesterol levels and generally normal beta-lipoprotein cholesterol; 6% showed normal beta fractions and significantly reduced serum cholesterol but not quite normal. Another 12% showed reduction in both serum cholesterol and beta levels; only 2% (1 patient) remained unchanged by treatment, but some doubt existed concerning the regularity of his taking the medication. A small number of patients had upper gastro-intestinal irritation, heartburn or mild nausea and some vomiting. A few showed some abnormalities of liver function in a series of tests.

Woolley (4663) in a brief note, 1958, discussed a possible relationship between the action of massive doses of nicotinic acid or nicotinamide in therapy of schizophrenia, and the tranquilizing, antiserotonin activity of the drugs (vitamins). It was suggested that abnormality of serotonin in the brain probably gives rise to mental disorders, and though nicotinamide is not a specific antagonist to serotinin, it does act as an antagonist in smooth muscle reaction to serotinin, probably indirectly through interference with Ca++, or through the transmethylation process.

The influence of large doses of nicotinic acid used in the therapy of hypercholesteremia, in patients with known diabetes mellitus, was studied by Molnar et al. (2942) in 1964. Six diabetic volunteers were given nicotinic acid in doses of from 1 to 3 g daily together with regular therapy for diabetes. In all cases the nicotinic acid had a diabetogenic effect; increased glycemia and glycosuria were observed, as were elevated concentration of serum ketone bodies and free fatty acids. Increased doses of insulin or hypoglycemic drugs were required, and a suggestion of increased mobilization and catabolism of fat was observed.

After periods of therapy lasting 6 months, no serious deleterious effects of nicotinic acid were seen, and when the nicotinic acid treatment was stopped, the diabetogenic effects promptly disappeared.

The conflicting results of numerous investigations of the effects of nicotinic acid on serum lipids in man lead Cali et al. (643) in 1966 to study in man the effect of a single intravenous administration of nicotinic acid, and of a prolonged treatment for 35 days. Fifteen normal subjects ranging in age of from 28 to 74 years were treated in groups of 5; one group received a 100 mg dose of nicotinic acid, one a dose of 500 mg, and one of 1 g. Blood samples were taken before injection, and thereafter every hour for 8 hours, and a final one at 24 hours.

In the prolonged treatment, 9 subjects were given 1 g intravenously of sodium nicotinate every 6 hours (4 g/day) for 5 consecutive weeks. Blood samples were taken before treatment and weekly thereafter.

As can be seen in the following tables, neither the single intravenous dose nor the repeated administrations of fairly large doses of nicotinic acid produced significant variations in the blood lipid fractions:

TABLE I

TOTAL LIPIDS AND LIPID FRACTIONS OF SERUM AFTER SINGLE I.V. ADMINISTRATION OF SODIUM NICOTINATE

Mean values (g‰) of determinations in 15 subjects.

	Before injection	*After i.v. sodium nicotinate*								
		1 h	*2 h*	*3 h*	*4 h*	*5 h*	*6 h*	*7 h*	*8 h*	*24 h*
Total lipids	8.26	8.26	8.29	8.27	8.22	8.26	8.20	8.40	8.50	8.32
Triglycerides	1.37	1.34	1.36	1.34	1.35	1.36	1.33	1.38	1.47	1.39
Phospholipids	2.77	2.75	2.79	2.80	2.77	2.80	2.78	2.82	2.90	2.74
Free fatty acids	0.48	0.52	0.51	0.50	0.47	0.50	0.50	0.48	0.49	0.51
Free cholesterol	0.93	0.92	0.92	0.92	0.90	0.90	0.89	0.90	0.96	1.00
Cholesterol esters	2.71	2.73	2.71	2.71	2.73	2.70	2.70	2.82	2.77	2.68
Esterified cholesterol	1.47	1.40	1.51	1.46	1.48	1.46	1.46	1.56	1.46	1.32
Total cholesterol	2.40	2.32	2.43	2.38	2.38	2.36	2.35	2.46	2.42	2.32

TABLE II

TOTAL LIPIDS AND LIPID FRACTIONS OF SERUM BEFORE AND DURING TREATMENT WITH SODIUM NICOTINATE

1 g every 6 h for 5 weeks i.v. Mean values (g‰) of determinations in 9 subjects.

	Before treatment	*During treatment*				
		7th day	*14th day*	*21st day*	*28th day*	*35th day*
Total lipids	7.74	7.58	7.60	7.98	7.62	7.67
Triglycerides	1.10	1.06	1.08	1.14	1.14	1.05
Phospholipids	2.72	2.65	2.78	2.71	2.65	2.81
Free fatty acids	0.53	0.47	0.49	0.55	0.52	0.50
Free cholesterol	0.90	0.98	0.98	0.94	0.89	0.96
Cholesterol esters	2.49	2.42	2.27	2.64	2.42	2.35
Esterified cholesterol	1.35	1.32	1.24	1.41	1.32	1.27
Total cholesterol	2.25	2.30	2.22	2.35	2.21	2.23

Large doses (1-6 g) of niacin given daily to hypercholesterolemic patients for periods of up to 3 years have significantly reduced serum cholesterol levels in those patients able to tolerate the large doses. Rivin (3628) in 1962 reported the results of treating 31 male patients, ranging in age from 6 to 62 years, and having cholesterol levels greater than 270 mg/100 ml blood. Twenty-three of the patients had had myocardial infarction and others had cholesterol deposits in the skin or tendons (xanthomata). Only 19 of the 31 patients were treated with just niacin; 16 patients were able to continue the treatment, during which the serum cholesterol levels were reduced by 20-50% of control

levels. Side effects in some cases were of sufficient severity to warrant discontinuing treatment: nausea and vomiting, mild to severe flushing, epigastric burning, jaundice and hives.

The wisdom of using niacin therapy turns on the question of serious toxicity, particularly with regards to the liver. Baggenstoss et al. (210) in 1967 studied liver biopsy materials from patients treated with nicotinic acid for hypercholesteremia, using both light and electron microscopy. Various tests of hepatic function at the time of biopsy were normal. Light microscopy findings were essentially normal, as were the electron nicroscopic appearances from 3 untreated patients. In the treated cases (nicotinic acid therapy), dilatition of the endoplasmic reticulum with formation of vesicles and sacs was observed. Unusual shapes and elongated mitochondria were seen, but the degree of abnormality was insufficient to interfere with cell function or to contraindicate the use of nicotinic acid in the treatment of carefully supervised patients with hypercholesteremia.

Charman et al. (779) more recently, in 1972 reported studies similar to those of Rivin ten years earlier, covering 160 patients under treatment for up to more than 10 years for hypercholesterolemia. Nicotinic acid therapy began with 100 mg given after each meal and was increased by 11 days to 1 g each meal, or 3 g nicotinic acid daily. The mean percentage decrease of serum cholesterol in this study was 26%. The usual side effects, often severe - were seen and remained the major deterrent to continued use of nicotinic acid therapy. Other students of nicotinic acid therapy have observed that the mechanisms by which nicotinic acid lowers the cholesterol level are unknown; Charman et al. repeat this observation, noting that inducement of a relative lack of coenzyme A, or a direct inhibition of cholesterol synthesis, and a relationship to the lowering of free fatty acids have been hypothesized as explanations.

An experiment designed to determine whether the hypocholesteremic effect of nicotinic acid in normal persons is obtained in individuals with low initial serum cholesterol was reported by Altschul and Hoffer (100) in 1958. Twelve student volunteers were placed on a schedule of alternate treatment and testing; nicotinic acid, 3 g/day was given for 14 days, with frequent determination of basal metabolic rates and serum cholesterol. By the 8th day of treatment, cholesterol levels were significantly reduced and basal metabolic rates were significantly elevated. The relative responses of cholesterol levels to nicotinic acid appeared to be related to the dosage in terms of body weight and to the initial cholesterol level.

Doses of nicotinic acid varying from 1.5 to 6 g daily were given orally to 33 patients with hypercholesterolemia, by Achor et al. (33) in 1958 as a form of therapy. The individuals selected for the study had plasma cholesterol concentrations higher than 250 mg/100 ml before treatment with nicotinic acid. The duration of treatment varied from 3

months to 1.5 years with observations made monthly; initially, the dosage was 3 g nicotinic acid daily for about 3 months to 6 months followed by a 3-month period of placebo and then a return for 3 months to nicotinic acid. In some instances, an additional 3-month period of changed diets (in fat content) or dosage of the nicotinic acid was observed. Periodic blood samples were taken and the blood lipid concentrations were determined. The changes in plasma lipids over the study period are shown in the following table:

TABLE 1.- *Decreases in Concentration of Blood Lipids Following Treatment with Nicotinic Acid*

Patients		Study period and change	Plasma cholesterol*	Cholesterol/phospholipid ratio	Total plasma lipids†	Serum beta lipoprotein cholesterol†	Beta/alpha‡ ratio‡
All	With lipoprotein studies						
33	19	Pretreat.	337	1.15	874	238	7.7
		0-3 mo.	282	1.08	729	197	5.1
		% decrease	16	6	17	17	34
21	18	Pretreat.	339	1.09	899	238	7.7
		3-6 mo.	282	1.08	719	203	4.5
		% decrease	17	1	20	15	42
17	16	Pretreat.	322	1.08	809	216	6.5
		6-9mo. (placebo)	322	1.13	824	234	6.0
		% change	0	+4	+2	+8	—8
16	16	Placebo	323	1.15	822	234	6.0
		9-12 mo.	272	1.12	713	182	3.8
		% decrease	16	3	13	22	37

* Values are averages of all determinations on all patients treated for period indicated.
† Concentrations are in milligrams per 100 ml.
‡ Beta-lipoprotein cholesterol/alpha$_1$-lipoprotein cholesterol.

In general, those patients with the highest initial levels of plasma cholesterol obtained the greatest response to treatment with nicotinic acid, but only one failed to achieve a decrease in plasma lipid concentration. The response of women patients was nearly twice that of men in the treatment reduction of plasma cholesterol. Diets were not controlled, but the authors felt that dietary variations did not significantly influence the results of the study. The usual side effects of nicotinic acid ingestion were observed: flushing, anorexia and nausea, pruritus and mild urticaria were observed. Only in 3 of the women were the effects of treatment so disagreeable as to lead to discontinuance of treatment.

The question of whether or not therapy designed to lower abnormally high blood lipid concentrations is an effective form of treatment for atherosclerosis was not within the scope of the study, but if it were, the authors felt that nicotinic acid treatment is "highly effective, very practical to carry out, and is probably quite safe".

O'Reilly (3221) in 1958 performed a similar study with 10 patients, 3 of whom were diagnosed as psychotic with cerebral artheriosclerosis and 7 nonarteriosclerotic, of whom one was mentally defective, and the remainder (6) schizophrenic. All had been previously shown to respond well to nicotinic acid treatment by greatly lowered cholesterol levels.

Preliminary fasting total serum cholesterol was determined for each subject, who was then given 1 g nicotinic acid orally, three times daily (3 g/day) for three months; at one week and at 5 weeks of treatment the serum cholesterol was again determined. At 3 months, a period of 4 weeks without treatment was observed, and cholesterol levels were again determined. Treatment was resumed and cholesterol levels measured at 1 week and at 4 weeks. The results are shown in the following table:

TABLE

No.	Before niacin	On niacin for 6 weeks	Off niacin for 4 weeks	On niacin for 1 week	On niacin for 4 weeks	Diagnosis	Age
1	190.0	121.5	150	150	122	Schizophrenia	41
2	261.0	170.0	190	175	185	Psychosis with cerebral arteriosclerosis	67
3	288.0	213.0	290	232	215	Schizophrenia	56
4	200.0	110.0	265	175	120	Schizophrenia	31
5	208.0	149.0	220	210	120	Schizophrenia	52
6	209.0	132.5	235	150	115	Psychosis with cerebral arteriosclerosis	63
7	215.0	135.0	215	221	185	Mental deficiency	27
8	230.0	155.0	190	148	115	Schizophrenia	34
9	472.6	190.0	305	302	120	Schizophrenia	46
10	265.0	200.0	215	221	120	Psychosis with cerebral arteriosclerosis	61
Total	2590.6	1615.0	2265	1900	1417		
Mean	258.06	161.5	226.5	190.0	141.7		

Two case studies were presented in some detail and the author speculated on the action of nicotinic acid, which was postulated to have an anticoagulant effect due to release of heparin, leading to an increased activity on the part of lipoprotein lipase.

Parsons and Flinn (3299) in 1957 reported preliminary results of a study of 24 patients characterized by hypercholesteremia, with a pretreatment average level of 270 mg blood cholesterol/100 ml. Treatment consisted of oral daily doses of 3-6 g nicotinic acid for a period of from 12 to 30 weeks. Sixteen of the patients achieved a significant reduction in blood cholesterol levels; normal levels were attained in 6 of 8 patients treated for 30 weeks or longer, and in 7 of 16 additional patients followed for at least 12 weeks. More than half the patients required doses higher than 3 g nicotinic acid daily, and in 4 patients, doses of 6 g daily were required for significant reduction. Substitution of equal doses of nicotinamide resulted in a prompt return of blood cholesterol to pretreatment levels. Flushing and pruritus side effects of nicotinic acid subsided within a week of treatment in most cases, and no serious side-reactions or toxicity were observed that could be attributed to nicotinic acid.

The nicotinic acid was administered in capsule form, each capsule containing 450 mg nicotinic acid. The mechanism by which nicotinic acid produces the observed changes in blood lipids were noted by the authors as "obscure".

Chazin (800) in 1960 reported the results of giving 20 patients up to 3 g nicotinic acid daily for from 3 to 5 months, whereupon serum cholesterol levels fell significantly. The experimental details and findings parallel those described by Achor, O'Reilly and Parsons earlier in this section.

Carlson et al. (696) in 1968 studied the effects of a single dose of 1 g nicotinic acid given orally to eleven patients with uncomplicated ischemic cardiovascular diseases and moderate hyperlipoproteinemia. Blood samples were taken before and after dosing at intervals for 6 hours; plasma free fatty acids, cholesterol, triglycerides, glucose, glycerol and protein concentrations were determined. All values found were compared with those following dosing with 1 g placebo.

The free fatty acid levels were significantly reduced by nicotinic acid during the first 3 hours following administration, as were the glycerol concentrations; at about 3 hours, however, a marked "rebound" or sudden rise was observed. Cholesterol levels remained unchanged during the 6 hours of observation; triglyceride levels were significantly reduced. Blood glucose concentrations were not significantly different from controls. The findings are graphically shown in the following figures:

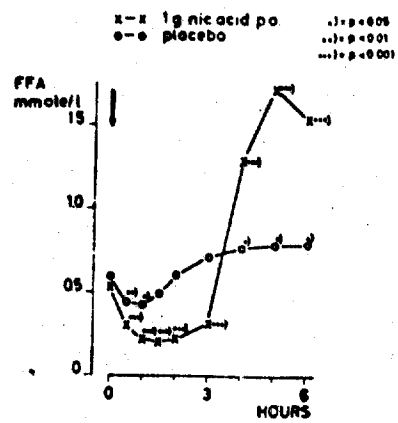


Fig. 1. Effect of nicotinic acid on free fatty acids (FFA) of blood plasma in 11 patients with ischemic-cardiovascular disease. The subjects were first given placebo (O — O) and two days later 1 g of nicotinic acid (× — ×) by mouth as indicated in the figure. The statistical calculations were made on the individual changes from the FFA concentration at zero time. The P-values indicate the statistical significance for the changes from zero time.

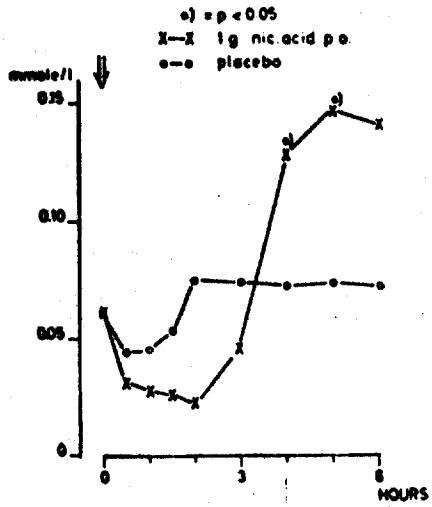


Fig. 2. Effect of nicotinic acid on plasma glycerol in 8 patients. For details see text to Fig. 1.

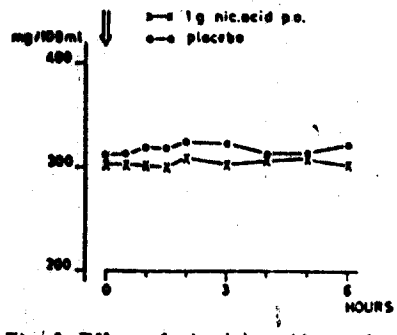


Fig. 3. Effect of nicotinic acid on plasma cholesterol in 11 patients. For details see text to Fig. 1.

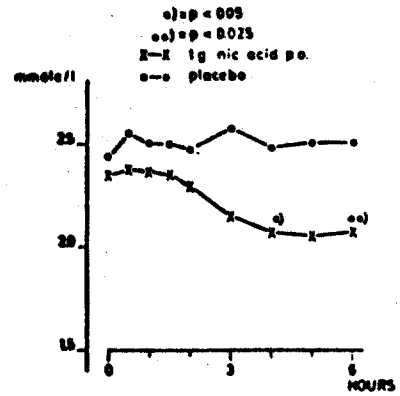


Fig. 4. Effect of nicotinic acid on plasma triglycerides in 11 patients. For details see text to Fig. 1.

Within 30 minutes to an hour, free nicotinic acid in the plasma peaked, falling at first slowly, then rapidly. Flushing in face, neck and upper part of the body was seen in 2 of the 11 patients at 30 minutes, and more markedly over whole body in 8 patients; one patient showed only faint facial flush. In all cases, flush had disappeared within 3 hours, followed by a chilly sensation. Tinnitus and vomiting were seen in a single patient each.

The absence of an effect on cholesterol levels by the 1 g dose of nicotinic acid was not explained, except that cholesterol lowering must be a later event (beyond the 6-hour limit of the study). The rebound or overshoot in the free fatty acid levels at 4-6 hours after the oral, 1 g dose of nicotinic acid was also not explained, and requires further study.

Kritchevsky (1560) recently (1971) reviewed the literature on the effect of nicotinic acid and derivatives on cholesterol metabolism. It was concluded that administration of nicotinic acid evokes the following sequence of events:

1. Inhibition of FFA mobilization
2. Reduced synthesis of liver triglycerides
3. Reduction of serum triglyceride levels
4. Reduced (or altered) lypoprotein production
5. Mobilization of sterol from body pools
6. Increased sterol excretion
7. Fall in serum cholesterol

The FFA effect is due to the inhibition of adenyl cyclase activity; how the reduction in available FFA triggers the subsequent events is not yet clear. (Nearly 100 references are given in the report).

V. Drug Interaction

Burton et al. (602) reported in 1960 that nicotinamide in combination with reserpine and chlorpromazine potentiates anesthesia induced by pentobarbitol in mice. Hybrid male mice, 8-10 weeks old, weighing 20-25 g, were placed in suspended "jiggle" cages, equipped for recording spontaneous activity of the animals. Various dosages of nicotinamide (given intraperitoneally) in combination with reserpine and chlorpromazine, administered to the mice subcutaneously prior to an intraperitoneal injection of pentobarbitol (70 mg/kg). The results and experimental data are shown in the following tables:

Table I

Effect of Nicotinamide and Chlorpromazine on Pentobarbital Anesthesia

Chlorpromazine (10 mg/kg body weight) was administered subcutaneously to mice 4 hours prior to the intraperitoneal injection of pentobarbital (70 mg/kg). When given, nicotinamide was injected intraperitoneally 30 minutes prior to the pentobarbital. The duration of anesthesia was measured by continuous observation of the animals. The value reported represents the average duration of anesthesia for each group of 10 mice.

Nicotinamide	Average Duration of Anesthesia (1)			
	Without Chlorpromazine		With Chlorpromazine	
mg per kg	Minutes ± S.E.		Minutes ± S.E.	
0	30 ± 1	—	142 ± 21	—
125	29 ± 1	−1 (2)	165 ± 7	23 (2)
250	42 ± 3	12 (2)	264 ± 18	122
500	45 ± 6	15 (2)	316 ± 11	74

(1) Time interval from the loss of the righting reflex until it is regained.
(2) Not significant at the 5 % level.

Table II

Interaction of Nicotinamide and Reserpine on Pentobarbital Anesthesia

Reserpine (5 mg/kg body weight) was administered subcutaneously to the mice 4 hours prior to the intraperitoneal injection of pentobarbital (70 mg/kg). Nicotinamide (500 mg/kg) was injected 30 minutes before the pentobarbital. Other details are as described in the legend to table I.

	Average Duration of Anesthesia (1)		Increase Due To Nicotinamide	
	Expt. 1	Expt. 2	Expt. 1	Expt. 2
	Minutes	Minutes	Minutes	Minutes
1. Pentobarbital	34	50	—	—
2. Reserpine	0	0		
3. Nicotinamide	0	0		
4. Pentobarbital plus Nicotinamide	25	41	−9 (2)	11 (2)
5. Pentobarbital plus Reserpine	101	191	—	—
6. Pentobarbital plus Reserpine plus Nicotinamide	175	187	74	46

(1) Time interval from the loss of the righting reflex until it is regained.
(2) Not significant at the 5 % level (Expt. 1, $t = 2.05$; Expt. 2, $t = 2.00$).

Nicotinamide alone showed no ability to prolong pentobarbitol anesthesia, but when given with either chlorpromazine or reserpine prolonged the anesthesia to a much greater degree than either drug alone.

VI. Consumer Exposure Information

Minute amounts of niacin occur in all living cells, appreciable amounts are found in liver, yeast, milk, adrenal glands, white meat, alfalfa, legumes, whole cereal and corn. Whole wheat flour contains about 60 micrograms per gram and enriched patent flour about 16 micrograms per gram (2852).

Both niacin and niacinamide, until 1964, were used in the United Kingdom for reddening meat; they are presently restricted to use as an additive to sausages classified as processed products. Niacin is not approved in the United States for improving the color shelf-life of fresh or cured meats; it is recognized only as a nutrient and dietary supplement.

The recommended daily dietary allowances (milligram equivalents, includes dietary source of the vitamin itself plus one milligram equivalent for each 60 milligrams of dietary tryptophan) range from about 5 for infants up to several months of age, to about 15-20 for adults. Most diets in the united States supply 500-1000 milligrams or more of tryptophan daily, and 8-17 milligrams of niacin.

The following tables were compiled from data submitted by user firms. Food consumption values for each food category were derived from the Market Research Corporation of America (MRCA) data on frequency of eating and from the USDA data on mean portion size of foods in each food category. The food consumption values thus derived were coupled with the usage level data obtained in the surveys to calculate the daily intake of each substance.

Tables 2 and 3 report the usage of niacin in foods; Table 11 reports the annual poundage data. Table 13 shows possible daily intake per food category and total dietary based on food consumption by total sample, Table 14 reports potential daily intakes per food category, based on food consumption by eaters only.

COMPREHENSIVE GRAS SURVEY -- NAS/NRC 1972 10/03/72

TABLE 11, PART A -- ANNUAL POUNDAGE DATA FOR NAS APPENDIX A SUBSTANCES (GROUPS I & II)

SUBSTANCE NAME (SURVEY NO.)	# REPORTS TO NAS 1960/1970	POUNDAGE REPORTED TO NAS (MATCHING REPORTS FOR BOTH YEARS) 1960	1970	TOTAL 1970 POUNDAGE REPORTED TO NAS	# REPORTS TO FEMA	POUNDAGE REPORTED TO FEMA-- 1970 ONLY	TOTAL 1970 POUNDAGE NAS + FEMA
NIACIN NAS 0136	23/ 29	466,033	600,392	665,148			665,148
NIACINAMIDE NAS 0137	19/ 24	90,500	135,973	145,411			145,411

COMPREHENSIVE GRAS SURVEY -- NAS/NRC 1972 10/02/72

TABLE 13, PART A -- POSSIBLE DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (GROUPS I & II), PER FOOD CATEGORY AND TOTAL DIETARY, BASED ON FOOD CONSUMPTION BY TOTAL SAMPLE - - - SEE EXPLANATORY NOTES IN EXHIBITS SECTION

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	POSSIBLE DAILY INTAKE, MG. (AGE)	AVERAGE	HIGH A	HIGH B
NIACIN NAS 0136	01 BAKED GOODS(R)	19	0-5 MO.	.150880	.223650	.217600
			6-11 MO.	1.262380	2.570460	1.625600
			12-23 MO.	2.708650	4.463060	3.688600
			2-65+ YR.	6.818840	10.120860	8.780800
NIACIN NAS 0136	02 BREAK CERLS(R)	9	0-5 MO.	.061380	.173910	.091440
			6-11 MO.	2.881250	6.117540	3.398620
			12-23 MO.	2.878030	5.207070	3.977640
			2-65+ YR.	2.040000	5.299140	3.048080
NIACIN NAS 0136	03 OTHER GRAIN(R)	15	0-5 MO.	.019750	.067150	.025980
			6-11 MO.	.383156	1.129750	.502460
			12-23 MO.	.847080	1.497050	.649820
			2-65+ YR.	1.098100	2.426800	1.440040
NIACIN NAS 0136	05 MILK PRODS(R)	*	0-5 MO.	.497340	.366400	.497340
			6-11 MO.	5.747040	27.639210	5.747040
			12-23 MO.	5.019450	16.052240	5.019450
			2-65+ YR.	3.637950	11.107260	3.637950
NIACIN NAS 0136	10 MEAT PRODS(R)	*	0-5 MO.	.176000	.464000	**********
			6-11 MO.	3.312000	8.928000	**********
			12-23 MO.	4.832000	8.304000	**********
			2-65+ YR.	12.544000	20.816000	**********

COMPREHENSIVE GRAS SURVEY -- NAS/NRC 1972 10/01/72

TABLE 2 -- USAGE LEVELS REPORTED FOR NAS APPENDIX A SUBSTANCES (GROUP I) USED IN REGULAR FOODS(R)

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO.	NAME	# FIRMS REPORTING	*** USUAL USE *** WTD MEAN, %	*** MAXIMUM USE *** WTD MEAN, %
NIACIN NAS 0136	01	BAKED GOODS(R)	19	.00497	.00640
	02	BREAK CERLS(R)	9	.01023	.01524
	03	OTHER GRAIN(R)	15	.00395	.00518
NIACIN (CONT.) NAS 0136	05	MILK PRODS(R)	*	.00921	.00921
	10	MEAT PRODS(R)	*	.01600	********
	19	SWEET SAUCE(R)	*	.01105	.01105
	22	SNACK FOODS(R)	*	.00185	.00280
	26	RECONST VEG(R)	*	.00997	.01006
NIACINAMIDE NAS 0137	01	BAKED GOODS(R)	6	.00072	.00162
	02	BREAK CERLS(R)	8	.01432	.04442
	03	OTHER GRAIN(R)	4	.00319	.00361
	05	MILK PRODS(R)	5	.00130	.00145
	10	MEAT PRODS(R)	*	.00471	.00471
	11	POULTRY(R)	*	.00900	.00900
	19	SWEET SAUCE(R)	*	.01100	.01100
	20	GELATIN PUD(R)	*	.00180	********
	22	SNACK FOODS(R)	*	.00680	.00680
	23	BEV TYPE I(R)	*	.00000	.00000
	26	RECONST VEG(R)	*	.00400	.00460
	28	IMIT DAIRY(R)	*	.01500	.01500

COMPREHENSIVE GRAS SURVEY -- NAS/NRC 1972 10/02/72

TABLE 3 -- USAGE LEVELS REPORTED FOR NAS APPENDIX A SUBSTANCES (GROUP II) USED IN INFANT FORMULA PRODUCTS & BABY FOODS(B)

NAS SURVEY NO.	SUBSTANCE NAME	FOOD CATEGORY NO.	NAME	# FIRMS REPORTING	*** USUAL USE *** WTD MEAN, %	*** MAXIMUM USE *** WTD MEAN, %
0136	NIACIN	81	BAKED GOODS(B)	*	.01300	.01500
0137	NIACINAMIDE	82	CEREALS(B)	*	.00510	.00841
		83	FORMULAS(B)	6	.00065	.00093
		93	COMB DINNER(B)	*	.00900	.00900

TABLE 13, PART A — POSSIBLE DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (GROUPS I & II), PER FOOD CATEGORY AND TOTAL DIETARY, BASED ON FOOD CONSUMPTION BY TOTAL SAMPLE - - - SEE EXPLANATORY NOTES IN EXHIBITS SECTION

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	(AGE)	POSSIBLE DAILY INTAKE, MG. AVERAGE	HIGH A	HIGH B
NIACIN NAS 0136	19 SWEET SAUCE(R)	*	0-5 MO.	.033150	.044200	.033150
			6-11 MO.	.099450	.342550	.099450
			12-23 MO.	.287300	.839800	.287300
			2-65+ YR.	.751400	1.977350	.751400
NIACIN NAS 0136	22 SNACK FOODS(R)	*	0-5 MO.	**********	.001350	**********
			6-11 MO.	.007400	.020380	.011200
			12-23 MO.	.020350	.057350	.030000
			2-65+ YR.	.024050	.068450	.036400
NIACIN NAS 0136	26 RECONST VEG(R)	*	0-5 MO.	.000000	.000000	.000000
			6-11 MO.	.000000	.000000	.000000
			12-23 MO.	.000000	.000000	.000000
			2-65+ YR.	.019940	.059820	.020120
NIACIN NAS 0136	81 BAKED GOODS(B)	*	0-5 MO.	.013000	.039000	.015000
			6-11 MO.	.039000	.039000	.045000
			12-23 MO.	**********	**********	**********
NIACIN NAS 0136	ALL CATEGORIES **********	36	0-5 MO.	.965600	1.382160	.880430
	**********		6-11 MO.	13.131710	46.790810	11.429270
	**********		12-23 MO.	16.189580	36.430870	13.632710
	**********		2-65+ YR.	26.540280	51.082780	17.714710
NIACINAMIDE NAS 0137	01 BAKED GOODS(R)	6	0-5 MO.	.024480	.032400	.055280
			6-11 MO.	.182800	.372960	.411480
			12-23 MO.	.392400	.846560	.802900
			2-65+ YR.	.507640	1.447360	2.230640
NIACINAMIDE NAS 0137	02 BREAK CERLS(R)	8	0-5 MO.	.086920	.243440	.266520
			6-11 MO.	3.193360	8.563360	9.909660
			12-23 MO.	3.737520	7.288880	11.593620
			2-65+ YR.	2.864000	7.417770	8.884060
NIACINAMIDE NAS 0137	03 OTHER GRAIN(B)	4	0-5 MO.	.015990	.054230	.018650
			6-11 MO.	.309430	.912340	.350170
			12-23 MO.	.523160	1.289010	.597040
			2-65+ YR.	.886820	1.956660	1.003560
NIACINAMIDE NAS 0137	05 MILK PRODS(R)	5	0-5 MO.	.070200	.052600	.078300
			6-11 MO.	.811200	3.501300	.904800
			12-23 MO.	.706500	2.267200	.790250
			2-65+ YR.	.913500	1.567800	.972750

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Bibliography

1. Aaron, A., C. B. Schreffler, and S. T. Lipsius. 1941. Chemical determination of nicotinic acid. Ind. and Eng. Chem. Anal. Ed. 13(1):62-63.

2. Aaron, J. J., and J. D. Winefordner. 1972. Fluorimetric and phosphorimetric characteristics of several vitamins. Talanta 19(1):21-29

3. Abbassy, A. S., M. M. Zeitoun, E. A. Hassanein, G. A. Abdel-Tawab, T. S. Khollef, and S. El-Sewedy. 1970. Tryptophan metabolism in protein-calorie malnutrition. Trans. Roy. Soc. Trop. Med. Hyg. 64(1):148-155.

4. Abbona, C., G. Peris, P. L. Gatto, G. C. Bezante, F. Indiveri, and A. Berretti. 1966. Action of nicotinic acid on some functional and histomucosal aspects of the stomach. Biopsy study. Arch. Maragliano Pat. Clin. 22:425-438.

5. Abdel-Aziz, A. M. 1966. A pressor response of the rabbit to nicotinic acid. Brit. J. Pharmacol. Chemotherapy 27(3):449-458.

6. Abdel-Aziz, A., and M. Karrar. 1969a. Analysis of a pressor response of the guinea pig to nicotinic acid. Arch. Int. Pharmacodyn. Ther. 177(2):253-277.

7. Abdel-Aziz, A., and M. Karrar. 1969b. Effect of some beta-pyridyl derivatives and of histamine on the rat uterus under different functional states. Arch. Int. Pharmacodyn. Ther. 180(3):438-443.

8. Abdel-Daim, M. H., T. S. Khollef, A. A. Konbar, and G. A. Abdel-Tawab. 1970. The functional capacity of the tryptophan-niacin pathway in pellagrous children. Trans. Roy. Soc. Trop. Med. Hyg. 64:454-459.

9. Abdel-Kader, M. M., A. Gundy, and M. M. Mahfouz. 1962. Nicotinamide methochloride excretion studies and blood coenzymes in some cancerous patients. Alexandria Med. J. 8(1):1-6.

10. Abdel-Kader, M. M., A. H. Shehata, A. H. Zaki, I. M. Fayad, and S. Nasser. 1969. Nicotinic acid metabolism in protein malnutrition syndromes. Acta Biol. Med. Ger. 23(2):329-334.

11. Abderhalden, R., and K. H. Elsaesser. 1943. The occurrence of lactoflavin, nicotinamide, and p-aminobenzoic acid in cerebrospinal fluic. Arch. Ges. Physiol. (Pflueger's) 247:325-335.

12. Abdoh, J., and K. Taeufel. 1942. Analysis of nicotinic acid and nicotinamide. Z. Untersuch. Lebensm. 84:385-392.

13. Abdulaeva-Panova, M. V. 1952. Effect of nicotinic acid on blood pressure and electrolyte content of blood in hypertension. Terap. Arkh. 24(3):30-35.

14. Abdulla, Y. H. 1969. Beta-Adrenergic receptors in human platelets. J. Atheroscler. Res. 9(2):171-177.

15. Abdurakhmanov, F. A. 1965. Influence of nicotinic acid on the metabolism of cholesterol and bile acids in atherosclerotic patients. Med. Zh. Uzbekistana 1965(12):32-35.

16. Abe, T. 1962. Fibrinolytic influence of monocarboxylic acids and some other substances. Proc. Intern. Congr. Hematol., 8th, Tokyo, 1960(3):1587-1593.

17. Abelson, D. 1962. Nicotinamide metabolites in human plasma. In: 46th Annual Meeting, Atlantic City, New Jersey, April 1962. Fed. Proc. 21(2):466.

18. Abelson, D., and A. Boyle. 1963a. Photochemical changes in nicotinic acid and its metabolites. In: 47th Annual Meeting of the Federation of American Societies for Experimental Biology, 1963.

19. Abelson, D., and A. Boyle. 1963b. Effects of ultraviolet radiation on nicotinic acid and related compounds. Biochem. J. 89(1):19-20.

20. Abelson, D., and A. Boyle. 1966. Spectrophotometric determination of plasma pyridones in man following nicotinamide administration. With a general note on the quantitative treatment of interfering substances in analytical methods. Clin. Chim. Acta 14(4):483-492.

* 21. Abelson, D., A. Boyle, and H. Seligson. 1963. Identification of N'-methyl-4-pyridone-3-carboxamide in human plasma. J. Biol. Chem. 238:717-718.

22. Abelson, D., E. Parthe, K. W. Lee, and A. Boyle. 1965. Spectral and biological changes induced in nicotinic acid and related compounds by ultraviolet light. Biochem. J. 96:840-852.

23. Aberg, G., and N. Svedmyr. 1971. Thermographic registration of flush. Arzneim. Forsch. 21(6):795-796.

24. Abolina, I. 1967. Chemical composition of Latvian black chokeberries and their products. Latv. PSR Zinat. Akad. Vestis 1967(6):74-77.

25. Abolina, I. 1970. Chemical composition of fruits of the black chokeberry and possible preservation of vitamins in some of their reprocessing products. Latv. Lauksaimn. Akad. Raksti 1970(25):26-28.

26. Abou-Donia, M. B., and D. B. Menzel. 1968. Chick microsomal oxidases. Isolation, properties, and stimulation by l embryonic exposure to 1,1,1-trichloro-2,2-bis(p'-chlorophenyl) ethane. Biochemistry 7(11):3788-3794.

27. Abraham, M. E., and G. Wilbert. 1959. Oxidation of 2,5-dialkylpyridines. U.S. Pat. 2,884,415.

28. Abrahamson, I. A., Jr., and I. A. Abrahamson, Sr. 1956. Use of Iodo-Niacin for retinal or vitreous hemorrhages and vitreous floaters. Am. J. Ophthalmol. 42:771.

29. Abramson, D. I., K. H. Katzenstein, and F. A. Senior. 1940. Effect of nicotinic acid on peripheral blood flow in man. Am. J. Med. Sci. 200(1):96-102.

30. Abramzon, M. A. 1962. The mechanism of ascorbic acid action in alimentary cholesterol atherosclerosis in rabbits. Materialy Nauchn. Konf. po Problemam Funkts. Vzaimootnosheniya Mezhdu Razlichen. Sistemami Organizma v Norme i Patol., Ivanovo Sb. 1962:683-685.

31. Abrarov, A. A., and S. Z. Isamukhamedov. 1969. Effect of vitamins A and E on some indicators in normal erythrocytes and in hemolytic (phenylhydrazine) anemia. Med. Zh. Uzb. 11:50-53.

32. Achor, R. W. P., and K. G. Berge. 1958. Treatment of hypercholesteremia with large oral doses of nicotinic acid. Med. Clins. N. Amer. 42:871-880.

* 33. Achor, R. W. P., K. G. Berge, N. W. Barker, and B. F. McKenzie. 1958. Treatment of hypercholesterolemia with nicotinic acid. Circulation 17:497-504.

34. Achor, R. W. P., N. A. Christensen, K. G. Berg, and H. L. Mason. 1961. Treatment of hypercholesteremia: Comparison of triparanol and nicotinic acid. Circulation 24(4 Pt. 2):1082.

35. Achor, R. W. P., N. A. Christensen, K. G. Berge, and H. L. Mason. 1963. Treatment of hypercholesteremia with triparanol and comparison with nicotinic acid. Proc. Staff Meetings Mayo Clin. 38(2):32-44.

36. Ackermann, D., and H. G. Fuchs. 1938. On the occurrence of nicotinic acid in beef liver. Hoppe-Seyler's Zeitschr. Physiol. Chem. 256(2/3):90-94.

37. Ackers, J. P., and J. M. Dolby. 1972. The antigen of Bordetella pertussis that induces bactericidal antibody and its relationship to protection of mice. J. Gen. Microbiol. 70(2):371-382.

38. Acocella, G. 1966. Chemotherapy of experimental lead poisoning. II. Effects of nicotinic acid on coproporphyrinuria in lead poisoned rats. Acta Vitaminol. 20(5):195-202.

39. Adachi, K. 1959. Studies on atypical acid-fast bacilli. (I) Production of nicotinic acid of atypical acid-fast bacilli in Dubos tween albumin liquid medium. Sci. Rep. Res. Inst. Tohoku Univ. (Med.) 9:18-24.

40. Adachi, T. 1970. Relation of thyroid function to NAD synthesis in mouse liver. Bitamin 42(6):364-368.

41. Adachi, T., M. Asahina, and Shiina. 1969. Change of lipid content in rat serum after administration of riboflavine tetranicotinate. Bitamin 40(2):97-100.

42. Adamek, M., K. Roth, and M. Stepankova. 1971. Consequences of long-term effect of low radiation doses in uranium miners and possibilities of preventive drug treatment. Oesterr. Z. Erforsch. Bekaempf. Krebskr. 26(3):192-200.

43. Adamo, G. 1955a. Trigonelline and niacin in coffee, tea, and cocoa. Ann. chim. (Rome) 45:274-278.

44. Adamo, G. 1955b. The nicotinic acid content of coffee. Boll. Soc. ital. Biol. Sper. 31:79-82.

45. Adamov, A. K., K. M. Mokhin, I. V. Khints, and M. S. Naumshina. 1969. Effect of nicotinic acid on the reactivity of intestinal muscle to microbial antigens. Probl. Osobo Opasnykh Infek. 1969(3):64-67.

46. Adams, D. H., and J. H. Quastel. 1956. Factors influencing the anaerobic glycolysis of brain and tumor. Proc. Roy. Soc. (London) B145:472-493.

47. Adams, R. L., et al. 1967. A study of the niacin requirement of the laying hen. Poult. Sci. 46:712-718.

48. Adams, W. L., C. S. Welch, and B. B. Clark. 1943. The effect of sodium bicarbonate on gastric secretion. Am. J. Physiol. 139(3): 356-363.

49. Adezati, L., and G. Ghigliotti. 1952a. Effects of nicotinamide on the ketogenesis from triolein. Arch. "E. Maragliano" patol. e clin. 7:851-853.

50. Adezati, L., and G. Ghigliotti. 1952b. Pyruvate metabolism. I. Effect of insulin in vivo and in vitro. Arch. "E. Maragliano" patol. e clin. 7:855-861.

51. Adler, E., H. V. Euler, and B. Skarzynski. 1943. The relation of vitamin to antivitamin. IV. Further studies on cozymase inhibition. Arkiv Kemi, Min. Och. Geol. 17A(2):5-8.

52. Adrian, J. 1953. Composition of chicken egg as related to the vitamin equilibrium of the hen. Case of the excess of pantothenic acid and that of niacin. Compt. rend. 237:273-274.

53. Adrian, J. 1958. Influence of vitamin excesses in the diet of the chicken on the amount of certain B vitamins in the egg. Arch. sci. physiol. 12:107-140.

54. Adrian, J. 1963. The synthesis of niacin during the roasting of coffee and its biological activity. Cafe, Cacao, The 7:359-367.

55. Adrian, J. 1969. Corn and pellagra. Agron. Angolana 29:29-49.

56. Adrian, J., and R. Frangne. 1969. Chemical extraction of vitamin PP from maize and its microbiological estimation. Ann. Nutrition Aliment. 23:141-150.

57. Adrian, J., and T. Terroine. 1960. Effect of quantity and quality of dietary protein on the urinary excretion of riboflavine, pyridoxine, and niacin. Compt. Rend. 250:1120-1122.

58. Adrian, J., J. Pena, J. Morais de Carvalho, A. Miranda, J. Xabregas, and A. Corte dos Santos. 1970. Coffee consumption in the treatment of pellagra. Colloq. Inst. Chim. Cafes Verts, Torrefies Leurs Deriv., 4th 1969:232-242.

59. Afanas'ev, V. I., V. S. Suleimanyan, and R. A. Kalinich. 1971. Methods for combatting hemorrhagic septicemia in carp. Veterinariya (Moscow) 48(7):59-61.

60. Agaev, B. S. 1960. Significance of vitamins C and PP in the complex therapy and normalization of oxidation-reduction processes during hepatocholecystitis. Azerb. Med. Zh. 1960(11): 43-49.

61. Agaev, B. S. 1963. The effect of nicotinic acid on oxidation-reduction processes in hepatocholecystitis. Tr. Azerb. Med. Inst. 9:81-84.

62. Agarival, P., and K. Datt. 1954. Role of nicotinic acid in healing of corneal ulcers. Am. J. Ophthalmol. 37:764-767.

63. Agarwal, P. S., K. P. Chatterjee, and S. Banerjee. 1958. Nicotinic acid-trytophan metabolism in man. Indian J. Med. Research 46:431-434.

64. Aggeler, P. M., and S. P. Lucia. 1941. Action of nicotinic acid on coagulation of the blood. Proc. Soc. Expti. Biol. Med. 47:522-525.

65. Agrawala, I. P., G. F. Huffman, R. W. Luecke, and C. W. Duncan. 1953. A quantitative study of rumen synthesis in the bovine on natural and purified rations. III. Riboflavin, panthothenic acid and niacin. J. Nutr. 49(4):631-638.

66. Ahlersova, E., I. Ahlers, A. Sedlakova, E. Tothova, and M. Praslicka. 1971. Lipomobilization in continuously irradiated rats: I. Effect of nicotinic acid in fed animals. Biologia (Bratisl.) 26(12):887-891.

67. Ahmad, B., and A. N. Sharma. 1946. A modified procedure for the estimation of nicotinic acid in biological materials. Ann. Biochem. Exp. Med. 6:35-40.

68. Aizawa, T., Y. Goto, T. Katayama, H. Nakamura, S. Hori, and Y. Tatsuzawa. 1964. Disturbance of the fatty acid metabolism of arteriosclerosis and its treatment. Proc. Asian-Pacific Congr. Cardiol., 3rd, Kyoto 1:611-615.

69. Akagi, T. 1943. Influence of vitamins and drugs upon anaphylaxis. Folia Pharmacol. Japon 39:510-520.

70. Akimov, V. G. 1967. On the problem of the study of the effect of nicotinic acid and its amide on the allergic reactivity of the skin. Sovet Med. 30:53-57.

71. Aksenova, E. N., A. Z. Knizhnik, P. L. Senov, and S. V. Churyukanova. 1968. Identification of some water-soluble vitamins by thin-layer chromatography. Farmatsiya (Moscow) 17(2):51-54.

72. Albanese, A. A., and L. A. Orto. 1963. Proteins and amino acids. Newer Methods Nutr. Biochem. 1963:1-112.

73. Albert, P. W., B. T. Scheer, and H. J. Deuel, Jr. 1948. The effect of 3-hydroxyanthranilic acid on the excretion of niacin by the rat. J. Biol. Chem. 175(1):479-480.

74. Albizati, L. D., and J. L. Hedrick. 1972. Active-site studies on rabbit liver nicotinamide deamidase. Biochemistry 12(8):1508-1517.

75. Albright, B. E., and E. F. Degner. 1968. Advances in automated vitamin analyses. Automat. Anal. Chem., Technicon Symp., 3rd 1967(1):461-465.

76. Alechinsky, A. 1947. Nicotinamide and histamine shock. Compt. rend. soc. biol. 141:524-525.

77. Aleksandrova, E. V., and V. I. Shvedova. 1968. The conservative treatment of senile cataracts with cysteine. Nauch. Tr. Irkutsk. Med. Inst. 87:85-87.

78. Alesker, E. M. 1948. The influence of nicotinic acid on diabetes mellitus. Terap. Arkh. 20(3):62-76.

79. Alesker, E. M. 1949. Effect of nicotinic acid on blood sugar during parenchymatous hepatitis. Klin. Med. (U.S.S.R.) 27(2): 70-76.

80. Alesker, E. M. 1951. Effect of nicotinic acid on gastric secretion. Terapevt. Arkh. 23(1):56-63.

81. Alessandro, G., F. Dal. Brollo, and E. Mecarelli. 1963. Separation and determination of cobalamin associated with folic acid and nicotinamide. Boll. Chim. Farm. 102:161-172.

82. Alibrandi, G. 1953. Mechanism of acute poisoning by high doses of nicotinamide. Ricerca sci. 23:245-246.

83. Alifano, A., S. Papa, F. Tancredi, M. A. Elicio, and E. Quagliariello. 1964. Tryptophan-nicotinic acid metabolism in patients with tumors of the bladder and kidney. Brit. J. Cancer 18(2):386-389.

84. Alimov, R., and K. Mavlyandzhanov. 1966. Effect of some complex compounds of cobalt on peripheral blood during radiation sickness. Med. Zh. Uzb. 1966(8):75-77.

85. Alivisatos, S. G. A., and O. F. Denstedt. 1952. Nicotinamide inhibition of tri- and diphospho pyridine nucleotide-linked dehydrogenases. J. Biol. Chem. 199:493-504.

86. Alivisatos, S. G. A., S. Kashket, and O. F. Denstedt. 1956. The metabolism of the erythrocyte. IX. Diphosphopyridine nucleotidase of erythrocytes. Canadian J. Biochem. Physiol. 34(1):46-60.

87. Allardyce, J., E. Goranson, and E. Singer. 1947. Effect on growth and basal metabolic rate of excessive amounts of some of the B vitamins in the presence of added dessicated thyroid. Trans. Roy. Soc. Canada Sect. 5. 41:35-48.

88. Allegri, G., M. Muggeo, A. De Antoni, C. Costa, and G. Crepaldi. 1972. Influence of simultaneous administration of vitamin B6 and nicotinamide on tryptophan metabolism in Hodgkin's disease. Clin. Chim. Acta 40(1):258-261.

89. Allen, D. O., and J. B. Clark. 1971. Effect of various antilipolytic compounds on adenyl cyclase and phosphodiesterase activity in isolated fat cells. Advan. Enzyme Regul. 9:99-112.

90. Allinson, M. J. C. 1943. A specific enzymatic method for the determination of nicotinic acid in blood. J. Biol. Chem. 147:785-791.

91. Alm, A. 1972. Effects of norepinephrine, angiotensin, dihydro-ergotamine, papaverine, isoproterenol, histamine, nicotinic acid, and xanthinol nicotinate on retinal oxygen tension in cats. Acta Ophthalmol. 50(5):707-719.

92. Alm, B., S. Efendic, and Low. 1970. Effect of lipolytic and antilipolytic agents on the uptake of calcium-47 into rat adipose tissue in vitro. Horm. Metab. Res. 2(3):142-146.

93. Alpatov, I. M., A. L. Germanova, and V. S. Pozdnyakov. 1968. Polytropic action of dichloroethane studied by an experimental therapeutic method. Toksikol. Nov. Prom. Khim. Veshchestv 1968(10):140-144.

94. Altea, E. 1948. Vasomotor mechanism of nicotinic acid. II. Its influence on adrenaline in vitro. Studi Sassaresi 26:43-47.

95. Altschul, R. 1956. Influence of nicotinic acid on the blood cholesterol level and on experimental atherosclerosis. Z. Kreislaufforsch. 45:573-576.

96. Altschul, R. 1960. Nicotinic acid and cholesterol metabolism. G. P. 21:115-118.

97. Altschul, R. 1964a. Niacin in Vascular Disorders and Hyperlipemia. Chas. C. Thomas, Springfield, Ill. 306 pp.

98. Altschul, R. 1964b. Influence of nicotinic acid (niacin) on hypercholesteremia and hyperlipemia and on the course of atherosclerosis. Niacin Vascular Disorders Hyperlipemia 1964:3-135.

99. Altschul, R., and M. DeMay. 1962. Passage of niacin into cerbrospinal fluid. Canadian Med. Assoc. J. 86(20):954-955.

* 100. Altschul, R., and A. Hoffer. 1958. The effect of nicotinic acid upon serum cholesterol and upon basal metabolic rate of young normal adults. Arch. Biochem. Biophys. 73:420-424.

101. Altschul, R., and A. Hoffer. 1960a. The effect of nicotinic acid on hypercholesterolemia. Can. Med. Assoc. J. 82:783-785.

102. Altschul, R., and A. Hoffer. 1960b. The effect of nicotinic acid on hypercholesterolaemia. Can. Med. Assoc. J. 83:36-37.

103. Altschul, R., and T. A. Smart. 1961. Influence of nicotinic acid on starvation hypercholesteremia in rabbits. Metabolism, Clin. and Expti. 10:231-237.

104. Altschul, R., A. Hoffer, and J. D. Stephen. 1955. Influence of nicotinic acid on serum cholesterol in man. Arch. Biochem. and Biophys. 54:558-559.

105. Amato, F. 1948. Investigations on the effects exercised on dividing cells by some organic compounds with particular regard to colchicine occasioned mitoses and to toxic effects. Caryologia 1(1):49-78.

106. Amato, F. 1949. Preprophase inhibition in root meristems. Caryologia 1(2):109-121.

107. Ambellan, E., and G. Webster. 1962. Effects of nucleotides on neurulation in amphibian embryos. Develop. Biol. 5:452-467.

* 108. American Medical Association, Council on Drugs. 1958. Use of nicotinic acid in hypercholesteremia. J. Am. Med. Assoc. 168: 1773.

109. Amery, A., J. Vermylen, and M. Verstraete. 1966. Enhancing blood fibrinolytic activity by a niacin compound. III. Study of the activation mechanism. Scand. J. Haematol. 3(1):76-84.

110. Amery, A., J. Vermylen, H. Maes, and M. Verstraete. 1961. The influence of a derivative of niacin on the fibrinolytic system of man. Proc. Congr. European Soc. Haematol. 8(Pt. II) No. 449a, 2p.

* 111. Ammon, H. P. T., and C. J. Estler. 1967. The effect of nicotinic-acid on glycolytic carbohydrate breakdown in the liver. Life Sci. 6(6pt. 2):641-647.

112. Ammon, H. P. T., and C. J. Estler. 1969. Effect of inhibition of lipolysis by nicotinic acid on glycolytic breakdown of carbohydrate in liver and skeletal musculature. Med. Ernaehrung 10:161-163.

113. Ammon, H. P. T., and J. Steinke. 1972. 6-Aminonicotinamide (6-AN) as a diabetogenic agent: in vitro and in vivo studies in the rat. Diabetes 21(3):143-148.

114. Ammon, H. P. T., C. J. Estler, and C. E. Grummt. 1971. Nicotinic acid and energy-rich phosphate esters in skeletal muscle of mice. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1971:813-817.

115. Ammon, H. P. T., C. J. Estler, and F. Heim. 1971. Ateration of carbohydrate in metabolism in liver, skeletal muscle, and brain by nicotinic acid in mice. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1971:799-809.

116. Ammon, H. P. T., C. J. Estler, F. Heim, and B. Okoronkwo. 1969. Different effects of inhibition of lipolysis by nicotinic acid on the rate of glycolytic carbohydrate breakdown in brain and skeletal muscle. Life Sci. 8(4):213-221.

117. Amor, J. H. 1947. Thiamine and nicotinic acid in bread and flour. Rev. farm. (Buenos Aires) 89:454-458.

118. Anagnostopoulos, A., M. G. B. Drew, and R. A. Walton. 1969. Crystal structure of cobalt(II) nicotinate tetrahydrate: a non-classical zwitterion. J. Chem. Soc. D 1969(21):1241-1242.

119. Ananth, J. V., L. Vacaflor, G. Kekhwa, C. Sterlin, and T. A. Ban. 1972. Nicotinic acid in the treatment of newly admitted schizophrenic patients: a placebo controlled study. Int. Z. Klin. Pharmakol. Ther. Toxikol. 5(Feb. 1972):406-410.

120. Anastasi, A., E. Mecarelli, M. L. Nebbia, and L. Novacic. 1952. Chemical determination of vitamins A, B1, B2, B6, C, PP, and calcium pantothenate contained in polyvitamin preparations. Boll. chim. farm. 91:222-226.

121. Anderson, P., and D. Schlettwein-Gsell. 1969. Lineage and nutrition in Swiss mountain areas. Int. Z. Vitaminforsch. 39(4): 492-498.

122. Anderson, E. G., H. L. Hass, and L. Hosli. 1973. Comparison of effects of naradrenaline and histamine with cyclic AMP on brain stem neurons. Brain Res. 49(2):471-475.

123. Anderson, E. G., L. J. Teply, and C. A. Elvehjem. 1944. Effect of nicotinic acid intake on the coenzyme I content of chick tissues. Arch. Biochem. 3:357-362.

124. Anderson, C., and J. L. C. Rapp. 1967. Animal nutrient. Fr. Pat. 1,490,513.

125. Anderson, W. D., and W. G. Kubicek. 1971. Effects of betahistine hydrochloride, nicotinic acid, and histamine in basilar blood flow in anesthetized dogs. Stroke 2(4):409-415.

126. Andersson, S. 1969. Side effects of drugs. 2. Gastrointestinal side effects. Lakartidningen 66:Suppl. IV:60+.

127. Andersson, S., L. A. Carlson, L. Oro, and E. A. Richards. 1971. Effects of nicotinic acid on gastric secretion of acid in human subjects and in dogs. Scand. J. Gastroenterol. 6(8): 693-698.

128. Andre, W. 1972. Experiences with Rheumasit in a balneological practice. Munch. Med. Wochenschr. 114:507-509.

129. Andreani, D. 1950. Nicotinamide and fat metabolism. Rass. fisiopatol. clin. e terap. (Pisa) 22:1059-1072.

130. Andreenko, G. V., and L. A. Migalina. 1971. Mechanism of action of nicotinic acid in vitro and in vivo. Vop. Med. Khim. 17(4):423-427.

131. Andreev, A. F. 1948. The role of certain vitamins and glucose in the prothrombin-forming function of the liver. Terapevt. Arkhiv 20(5):66-74.

132. Andrews, J. S., H. M. Boyd, and W. A. Gortner. 1942. Nicotinic acid content of cereals and cereal products. Microbiological method of assay. Indust. Eng. Chem. Anal. Ed. 14:663-666.

133. Andriadze, A. N. 1956. Combined effect of ammonium thiocyanate and nicotinic acid on blood pressure of hypertensive animals. Trudy Inst. Klin. i Ekspti. Kardiol, Akad. Nauk Gruzin. S.S.R. 4:199-212.

134. Angarano, D. R. Marano, and F. De Salvia. 1963. Metabolic modifications induced by diuretic treatment urinary elimination of some vitamins of the B complex. Acta Vitaminol. 17(2):49-53.

135. Angelino, P. F., G. Vacca, and C. Trovati. 1965. Effects of pyridoxal phosphate on some metabolic distrubances. Minerva Med. 56(55):2379-2385.

136. Anschuetz, H. F., and W. Schroeder. 1950. Effect of various pharmacological substances on the circulation in the capillaries and the arteriovenous anastomoses in the extremities of dogs. Z. ges. expti. Med. 116:291-299.

137. Antonini, F. M., and A. Sodi. 1960. Serum lipid lowering effect of nicotinic acid and 3-pyridylacetic acid and their possible mechanism of action. Drugs Affecting Lipid Metab., Proc. Symp., Milan 1960:392-411.

138. Antonini, F. M., R. Masi, and G. Verdi. 1959. Effect of nicotinic acid on the lipids and on the clearing factors of the blood. G. Geront. 7:783-792.

139. Aoe, H., I. Masuda, and T. Takada. 1967. Water-soluble vitamin requirements of carp. III. Requirement for niacin. Nippon Suisan Gakkaishi 33(7):681-685.

140. Apitz-Castro, R., K. Mickelson, K. Shriver, and E. H. Cordes. 1971. Properties of reactions catalyzed by pig brain nad glychohydrolase. Arch. Biochem. Biophys. 143(2):359-364.

141. Appelt, G.D., N.O. Walker, and R. Brown. 1968. Effect of mescaline on nicotinamide adenine dinucleotide synthesis in the central nervous system. J. Pharm. Sci. 57(3):527-528.

142. Arakawa, T., Y. Sato, T. Hashimoto, C. Morinaga, Y. Kakizaki, and A. Izurumachi. 1953. Effect of riboflavine and niacin upon lesions of the lips and the tongue in children with nutritional dystrophy. Hirosaki Med. J. 4:29-38.

143. Araki, T. 1963. Effect of nicotinamide on the depletion of ascorbic acid from the adrenal in male mice treated with ACTH or exposed to cold stress. J. Fac. Sci., Univ. Tokyo, Sect. IV 10(1):107-114.

144. Aranda Benites, M. P. 1951. Normal and pathological chloremia and variations caused by some pharmacological substances. Anales fac. farm. y bioquim., Univ. nacl. mayor San Marcos (Lima, Peru) 2:581-598.

145. Arbuzov, S. Ya. 1968. Synthesis and pharmacological investigation of some new compounds related structurally to some natural metabolites. Conf. Hung. Ther. Invest. Pharmacol., Soc. Pharmacol. Hung., 4th 1966:489-502.

146. Arditti, J. 1967. Niacin biosynthesis in germinating Laelio-cattleya or child embryos and young seedlings. Am. J. Bot. 54(3): 291-298.

147. Ardy, C., and G. Ivaldi. 1953. Nicotinamide and glucide metabolism in rats. Riv. biol. (Perugia) 45:341-349.

148. Argiroudi Akoyunoglou, J. H., H. S. Olcott, and W. D. Brown. 1963. Ferrihemochrome and ferrohemochrome formation with amino acids, amino acid esters, pyridine derivatives, and related compounds. Biochemistry 2(5):1033-1041.

149. Aries, R. 1968. Nicotinic and isonicotinic acids. Fr. Pat. 1,-509,049.

150. Aries, R. 1969. Pyridylaminonicotinic acids. Fr. Pat. 1,580,956.

151. Arima, K. 1950. Bioassay of vitamins. Kagaku no Ryoiki 4:30-44, 88-98, 143-152, 142.

152. Aring, C. D., H. W. Ryder, E. Roseman, M. Rosenbaum, and E. B. Ferris, Jr. 1941. Effect of nicotinic acid and related substances on the intracranial blood flow of man. Arch. Neurol. and Psychiat. 46(4):649-653.

153. Armellini, C., and F. Consolo. 1967. Behaviour of renal clearances during the vasomotor effects of nicotinic acid. Boll. Soc. ital. Biol. sper. 43:752-755.

154. Arnold, A., C. B. Schreffler, and S. T. Lipsius. 1941. Chemical determination of nicotinic acid. Ind. Eng. Chem., Anal. Ed. 13:62-63.

155. Arnulf, G., and Y. Grand. 1970. Value of experimental methods for measuring coronary vasomotor activity. Therapie 25(2):225-238.

156. Arora, R. B. 1949. Excretion of nicotinic acid in normal healthy human beings. Indian Med. Gaz. 84:149-151.

157. Arora, R. B. 1951. Pharmacologic basis for the correct therapeutic use of nicotinic acid, its amide and diethylamide (coramine). Antiseptic (Madras) 48:725-731.

158. Arrigo, L., and T. Montini. 1951. Vitamin B in lipid infiltration of the liver. Arch. Sci. Biol. 35(5):429-452.

159. Arrigo, L., and C. Ricci. 1954. Nicotinamide and hepatic lipides. Boll. soc. ital. biol. sper. 30:639-641.

160. Artman, M., A. Beklerkunst, and I. Goldenberg. 1964. Tissue metabolism in infection: biochemical changes in mice treated with cord factor. Arch. Biochem. Biophys. 195(1):80-85.

161. Artunkal, S. 1944. Certain effects of nicotinic acid and its amide in man. Bull. faculte med. Istanbul 7:4024-4027.

162. Arvy, L. 1969. The kidney and nicotinic acid. Laval Med. 40:571-579.

163. Asahi, Y. 1958. Polarographic determination of ascorbic acid, riboflavine, pteroylglutamic acid, 2-methyl-1,4-naphthohydroquinone diacetate, thiamine, niacinamide, and thiamine propyl disulfide in multivitamin preparations. J. Vitaminol. (Osaka) 4:118-125.

164. Asatoor, A. M. 1968. Retention of pseudouridine and 4-aminoimidazole-5-carboxamide in uremia. Clin. Chim. Acta 20(3):407-411.

165. Aschafferburg, R., M. E. Gregory, S. K. Kon, S. J. Rowland, and S. Y. Thompson. 1962. The composition of the milk of the reindeer. J. Dairy Res. 29:324-328.

166. Aschkenasy, A., and J. Mignot. 1946. Inhibition of growth and alterations in the spleen and liver in nicotinic acid hypervitaminosis; influence of dietary protein intake. Compt. Rend. Soc. Biol. 140:261-262.

167. Asenjo, C. F. 1945. The use of microbiological procedures in the determination of vitamins and amino acids. Bol. Colegio Quim. Puerto Rico 2:11-13.

168. Ashby, J. D., and J. C. Deavin. 1969. Gas chromatographic determination of nicotinamide and thiamine in vitamin preparations. J. Pharm. Pharmacol. 21(Suppl.):52-54.

* 169. Ashby, W. R., G. H. Collins, and M. Bassett. 1960. The effects of nicotinic acid, nicotinamide, and placebo on the chronic schizophrenic. J. Mental Sci. 106:1555-1559.

170. Ashford, W. R., and R. H. Clark. 1939. Comparison of colorimetric methods for the determination of nicotinic acid. Trans. Roy. Soc. Can. III, 33:29-32.

171. Askeloef, E., and C. Holmberg. 1939. Cyanogen bromide-aniline method for determining nicotinic acid. Svensk Farm. Tid. 43:301-307, 321-326.

172. Aso, Y., Y. Abe, K. Higo, T. Naruke, and T. Irikura. 1969. New nicotinic acid ester derivatives. 6. Serum cholesterol level lowering effect of 2,2,6,6-tetrakis (nicotinoyloxymethyl) cyclohexanol (K-31). J. Atheroscler. Res. 10(3):391-401.

173. Assimacoupoulos, F., and B. Jeanrenaud. 1971. Effect of nicotinic acid on isolated fat cell metabolism. Metab. Eff. Nicotinic Acid Its Deriv., Pro 1971:409-416.

174. Association of Vitamin Chemists, Inc. 1947. Methods of vitamin assay. Interscience Publishers, Inc., New York, N.Y., xviii+189pp.

175. Astaldi, G., and M. Baldini. 1948. Biology of the megaloblasts under the action of liver extract and nicotinamide on the surviving marrow of the bone. Acta Vitaminol. 2:78-81.

176. Astaldi, G., and M. Baldini. 1950. The effect of niacinamide on surviving megaloblasts in vitro. Acta Haematol. 3:255-259.

177. Astorri, P. 1954. Vitamin PP and tumors. I. Influence of vitamin PP on Ehrlich's adenocarcinoma. Boll. Soc. Med. Chir. Modena 54:8-17.

178. Atkin, L. 1949. Yeast growth factors. Wallerstein Lab. Communic. 12(37):141-151.

179. Atkin, L., A. S. Schultz, W. L. Williams, and C. N. Frey. 1943. Niacin-niacinamide differentiation in the microbiological assay procedure. J. Am. Chem. Soc. 65:992.

180. Atkinson, M. R., J. F. Jackson, and R. K. Morton. 1961. Nicotinamide mononucleotide adenylyl-transferase cf pig-liver nuclei. The effects of nicotinamide mononucleotide concentration and pH on dinucleotide synthesis. Biochem. J. 80(2):381-323.

181. Auerman, L. Ya., V. N. Bukin, Z. I. Zaitseva, L. S. Kutseva, V. F. Pashovkin, and V. V. Sheherbatenko. 1958. Maintenance and preservation of vitamins B1, B2, and pyridoxal phosphate in bread from different types of flour. Trudy Vsesoyuz. Nauch.-Issledovatel. Inst., Khlebopekar. Prom. 1958(7):79-83.

182. Auricchio, S., E. Quagliariello, and A. Rubino. 1959. Research on the interrelations of tryptophan and nicotinic acid in newborn infants during the first month of life. Boll. Soc. Ital. Biol. Sper. 35:2206-2208.

183. Auricchio, S., E. Quagliariello, and A. Rubino. 1960a. Interrelation of tryptophan and nicotinic acid in man during the first month of life. Nature 186:639-640.

184. Auricchio, S., E. Quagliariello, and A. Rubino. 1960b. Presence of metabolites of the tryptophan-nicotinic acid chain in the urine of sucklings during the first month of life. Helv. Paediat. Acta 15:479-486.

185. Auricchio, S., N. Rigillo, and R. Di Toro. 1961. The biosynthesis of nicotinic acid from tryptophan in the rat liver during pregnancy and foetal and neonatal life. Biol. Neonat. 3:149-159.

186. Auricchio, S., E. Quagliariello, A. Rubino, and L. Vecchione. 1960. Investigations on the spontaneous urinary elimination of metabolites of the tryptophan-nicotinic acid metabolism, in children affected by various illness. In: Proceedings of the Fifth Latin International Biochemical Meeting.

187. Aurich, H. 1960. B-vitamins in the waste water and the activated sludge from low-temperature carbonization in biological treatment. Wasserwirtsch Wassertechn. 10:293-295.

188. Auvergnat, R., et M. Jouenne. 1942. Action of nicotinamide on glycemia of normal and depancreated dogs. Trav. Membres Bull. Soc. Chim. Biol. 24:1227-1232.

189. Avataneo,G. 1956. Hypervitaminosis PP and histamine and lactic acid hypothermia. Ipervitaminolosi (Vitaminologia 11-13)272-289.

190. Avedikian, S. Z. 1971. Continuous manufacture of isocinchomeronic acid and nicotinic acid. Ger. Pat. 2,125,653.

191. Avetis'yan, G. M., V. A. Atsekhovskaya, and L. I. Shural. 1963. Effects of nicotinic acid on blood coagulation. Farmakol. i Toksikol. 26(2):216-219.

192. Avezzu, G. 1952. Comparison between the sensitivity of numerous types of bacteria to nicotinic acid as a growth factor, and hydrazide of isonicotinic acid as inhibiting factor. Acta Vitaminol. 6:53-55.

193. Avi-Dor, Y., and J. Mager. 1956. The effect of fluoropyruvate on the respiration of animal-tissue preparations. Biochem. J. 63(4):613-618.

194. Awata, M. 1959. Phosphorus metabolism of polished rice-fed rabbits. Nara Igaku Zasshi 10:49-60.

195. Axelrod, A. E. 1952. Role of the vitamins in antibody production. Natl. Vitamin Foundation, Nutrition Symposium Ser. No. 5:27-38.

196. Axelrod, A. E., and C. J. Martin. 1961. Water-soluble vitamins. I. Ascorbic acid, biotin, inositol, nicotinic acid, and the pyridoxine group. Ann. Rev. Biochem. 30:383-408.

197. Axelrod, A. E., E. S. Gordon, and C. A. Elvehjem. 1940. The relationship of the dietary intake of nicotinic acid to the coenzyme I content of blood. Am. J. Med. Sci. 199(5):697-705.

198. Axelrod, A. E., R. J. Madden, and C. A. Elvehjem. 1939. The effect of a nicotinic acid deficiency upon the coenzyme I content of animal tissues. J. Biol. Chem. 131:85-93.

199. Axelrod, A. E., T. D. Spies, and C. A. Elvehjem. 1941. The effect of a nicotinic acid deficiency upon the coenzyme I content of the human erythrocyte and muscle. J. Biol. Chem. 138:667-676.

200. Aykroyd, W. R., and M. Swaminathan. 1940. The nicotinic acid content of cereals and pellagra. Indian J. Med. Res. 27(3): 667-678.

201. Azarkh, R. M. 1962. Tissue respiration and amination of keto acids in liver tissue enriched in vivo with codehydrogenases. Biokhimiya 249-153.

202. Azmy, S. 1939. Observations on the effects of various modes of treatment on pellagrous patients. J. Trop. Med. Hyg. 42: 329-333.

203. Babel, J., et al. 1968. Test treatment of retinal venous thrombosis by complamine perfusion. Bibl. Ophthal. 76:104-112.

204. Babin, Ja. A., and A. I. Castov. 1970. Supplements of synthetic nicotinic acid for growing pigs. Him. Sel'sk. Hoz. 8:458-459.

205. Bader, J. P., and H. R. Morgan. 1961. Latent viral infection of cells in tissue culture. VII. Role of water-soluble vitamins in psittacosis virus propagation in L cells. J. Exptl. Med. 113:271-281.

206. Badgett, C. O., and C. F. Woodward. 1950. N-cyclohexyl nicotinamide. U. S. Patent 2,510,945.

207. Baechtold, H. P., and A. Pletscher. 1959. Decrease of the effect of noradrenalin on isolated aorta by inhibition of monoaminoxydase. Experientia 15:265-267.

208. Baethmann, A., et al. 1968. Experimental brain edema caused by 6-aminonicotinamide--an antimetabolite of nicotinic acid. Langenbecks Arch. Chir. 322:593-597.

209. Baethmann, A., H. J. Reulen, and W. Brendel. 1968. The effect of the antimetabolite 6-aminonicotinamide (6-ANA) on the water- and electrolyte content in the brain of rats and its inhibition by niacin. Z. Ges. Exp. Med. 146:226-240.

* 210. Baggenstoss, A. H., N. A. Christensen, K. G. Berge, W. P. Baldus, R. E. Spiekerman, and R. D. Ellefson. 1967. Fine structural changes in the liver in hypercholesteremic patients receiving long-term nicotinic acid therapy. Mayo Clin. Proc. 42:385-399.

211. Bailey, D. M., D. Wood, R. E. Johnson, J. P. Mc Auliff, J. C. Bradford, and A. Arnold. 1972. Lowering of serum lipid levels by "masked" nicotinic acid derivatives. J. Med. Chem. 15(4):334-348.

212. Bailey, E. A., Jr., W. J. Dann, G. H. Satterfield, and C. D. Grinnels. J. 1941. A method for the estimation of nicotinic acid in milk. J. Dairy Sci. 24:1047-1053.

213. Baker, B. E., and M. Michaelis. 1947. A correlation between redox potentials and synergisms in resting bacteria. Nature (London) 159(4032):197-198.

* 214. Baker, C. E., Jr. 1973. Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals. Medical Economics Company, Oradell, N.J., 1572pp.

215. Baker, H., and H. Sobotka. 1962. Microbiological assay methods for vitamins. Advances Clin. Chem. 5:173-235.

216. Baker, H., O. Frank, S. Feingold, and C. M. Leevy. 1967. Vitamin distribution in human plasma proteins. Nature 215 (5096):84-85.

217. Baker, H., O. Frank, I. Pasher, and H. Sobotka. 1960. Nicotinic acid assay in blood and urine. J. Protozool. 7(Suppl.):12-13.

218. Baker, H., F. Oxcar, A. D. Thomson, and S. Feingold. 1969. Vitamin distribution in red blood cells, plasma, and other body fluids. Am. J. Clin. Nutr. 22(11):1469-1475.

219. Baker, H., O. Frank, I. Pasher, S. H. Hutner, and H. Sobotka. 1960. Nicotinic acid assay in blood and urine. Clin. Chem. 6:572-577.

220. Baker, H., O. Frank, I. Pasher, H. Sobotka, and S. H. Hutner. 1961. Vitamin levels in blood and serum. Nature 191:78.

221. Baker, H., A. V. Luisada-Opper, O. Frank, S. Feingold, and C. M. Leevy. 1970. Effect of CCL4 on the vitamin-protein profile of rat liver subcellular elements. Exp. Molec. Path. 12:306-315.

222. Baker, Z., J. F. Fazekas, and H. E. Himwich. 1938. Carbohydrate oxidation in normal and diabetic cerebral tissues. J. Biol. Chem. 125:545-556.

223. Balaban, I. E., and F. Manchester. 1946. Nicotinamide. The Geigy Colour Co., Ltd. Brit. Pat. 575,119.

224. Baldini, M. 1950. Action of nicotinic acid on the lipase power of serum. Atti Accad. Fisiocrit. Siena, Studi Facolta Med. Senese 18:189-201.

225. Ball, E. G. 1939. Chemical reactions of nicotinic acid amide in vivo. Bull. Johns Hopkins Hospital 65(3):253-264.

226. Ball, E. G. 1970. Fatty acid metabolism in brown adipose tissue. Lipids. 5(2):220-223.

227. Ball, S. J., E. W. Warren, and E. W. Parnell. 1965. Anticoccidial activity of nicotinamide antagonists. Nature 208(5008):397.

228. Ballif, L., P. Jitaru, and N. Topala. 1953. Effect of nicotinic acid on circulatory flow. I. The effects of perfusion of the circulatory apparatus of a frog. Acad. Rep. Populare Romane, Filiala Iasi, Studii Cercetari Stiint. 4(1/4):379-384.

229. Bally, P. R. 1971. Effects of nicotinic acid on hormone-stimulated lipolysis. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1971:299-312.

230. Bandier, E. 1939a. Quantitative estimation of nicotinic acid in urine. Biochem. J. 33(11):1787-1793.

231. Bandier, E. 1939b. Estimation of nicotinic acid in biological material. Biochem. J. 33:1130-1134.

232. Bandier, E. 1941. The nicotinic acid content of blood and urine. Acta Med. Scand. 107:62-67.

233. Bandier, E., and J. Hald. 1939. A colorimetric reaction for the quantitative estimation of nicotinic acid. Biochem. J. 33: 264-271.

234. Banerjee, B., and C. H. Chakrabarti. 1966. Influence of niacin and inositol on faecal excretion of cholesterol and bile acid of albino rats kept on high cholesterol diet. J. Nutr. Dietetics, India, 1966(3):72-74.

235. Banerjee, S. 1947. Effect of certain substances on the prevention of diabetogenic action of alloxan. Science 106 (2745):128-130.

236. Banerjee, S., and P. S. Agarwal. 1958a. Nicotinic acid-tryptophan metabolism in certain diseases. Proc. Soc. Exptl. Biol. Med. 97:65-68.

237. Banerjee, S., and P. S. Agarwal. 1958b. Tryptophan - nicotinic acid metabolism in schizophrenia. Proc. Soc. Exptl. Biol. and Med. 97(3):657-659.

238. Banerjee, S., and R. Basak. 1955. Nicotinic acid metabolism in the rhesus monkey. J. Nutrition 55(1):179-184.

239. Banerjee, S., and R. Basak. 1957. Studies on the biosynthesis of nicotinic acid from tryptophan in the rhesus monkey. J. Nutrition 61(3):395-403.

240. Banerjee, S., and D. K. Biswas. 1957. Studies on the nutritive value of the cooked diet consumed by students of the Eden Hindu Hostel Calcutta. Indian J. Med. Res. 45(3):411-422.

241. Banerjee, B., and C. Y. Chakrabarti. 1966. Influence of niacin and inositol on fecal excretion of cholesterol and bile acid of albino rats kept on high cholesterol diet. J. Nutr. Diet. 3(3):72-74.

242. Banerjee, S., and D. P. Chattopadhyay. 1957. Studies on the role of methionine in the metabolism of tryptophan by rats treated with carbon tetrachloride. Indian J. Med. Res. 45(4): 533-537.

243. Banerjee, S., and N. C. Ghosh. 1949. Effect of nicotinamide on blood sugar and blood acetone bodies of diabetic and normal subjects. J. Biol. Chem. 177(2):789-792.

244. Banerjee, S., N. C. Ghosh, and G. Bhattacharya. 1948a. A chemical method of estimation of nicotinic acid in urine in the presence of sugar. J. Biol. Chem. 172:495-499.

245. Banerjee, S., N. C. Ghosh, and G. Bhattacharya. 1948b. Studies on the effect of nicotinic acid on the blood sugar and urinary excretion of sugar of normal and diabetic rabbits. Indian J. Med. Res. 36:341-347.

246. Banerjee, S. N. C. Ghosh, and N. Nandi. 1951. Biosynthesis of nicotinic acid. III. Effect of germination on the nicotinic acid, nicotinuric acid, N1-methylnicotinamide, and trigonelline values of pulses and cereals. Indian J. Med. Research 39: 447-451.

247. Baneyei, S., and R. Basak. 1955. Nicotinic acid metabolism in the rhesus monkey. J. Nutrition 55:179-184.

248. Banhidi, Z. G. 1964. Qualitative analytical microbiology in standardization of water-soluble vitamins and their coenzymes. Proc. Intern. Congr. Microbiol. Standardization, 9th Lisbon 1964:336-346.

249. Barahona, J. C. 1951. Action of nicotinamide on the normal blood sugar in the rabbit. Anales Fac. Farm. y Bioquim., Univ. Nacl. Mayor San Marcos (Lima, Peru) 2:498-503.

250. Barbieri, L. L., G. Marzocchi, G. Rumpianesi, and M. A. Brunelli. 1951. Excretion of thiamine, riboflavine, nicotinic acid, ascorbic acid, and 17-keto steroids in the urine after irradiation of the thyroid with x-rays. Intern. Z. Vitaminforsch. 25:261-274.

251. Barbieri, L. L., Rumpianesi, G., L. De Cesare, and M. A. Brunelli. Relations of cytochrome C and iron with B vitamins and ascorbic acid. 1955. Arch Studio Fisiopatol. e Clin. Ricambio 19:1-17.

* 252. Barboriak, J. J., and R. C. Meade. 1971. Nicotinic acid and alcohol-induced lipemia. Atherosclerosis 13(2):199-203.

253. Barboriak, J. J., R. C. Meade, J. Owenby, and R. A. Stiglitz. 1968. Blockers of free fatty acid release and postprandial lipemia. Arch. Int. Pharmacodyn. Ther. 176(2):249-254.

254. Barclay, R. K., and M. A. Phillipps. 1966. Effects of 6-diazo-5-oxo-l-norleucine and other tumor inhibitors on the biosynthesis of nicotinamide adenine dinucleotide in mice. Cancer Res. 26(2):282-286.

255. Bardhan, D. K., R. N. Bhattacharya, and S. K. Dutta. 1958. A simple physico-chemical method for estimation of thiamine, pyridoxine and nicotinamide in the presence of riboflavin and panthenol. Sci. and Culture 24(2):85-86.

256. Barenblat, I. G. 1947. Vitamins, their significance and use. Meditsin. Sestra 1947(5):3-6.

257. Barker, N. W. 1959. The effect of niacin on the blood cholesterol. Illinois Med. J. 116:138-139.

258. Barnes, A. C. 1951. The placental metabolism of vitamin A. Am. J. Obstet. Gynecol. 61:368-372.

259. Barreto, A., F. A. Gal, and H. S. R. Barreto. 1955. New method of analysis of nicotinamide and nicotinic acid. I. Nicotinamide. Rev. Quim. Ind. (Rio de Janeiro) 1955(274): 12-13.

260. Barrett, A. M. 1966. The effect of chlorophenoxyisobutyric acid on the release of free fatty acids from isolated adipose tissue in vitro. Brit. J. Pharmacol. Chemotherapy 26(2): 363-371.

261. Barsoum, G. S., and B. Girgis, 1944. Action of nicotinic acid on tissue metabolites in pellagra and its value in the treatment of some allergic conditions. J. Roy. Egypt. Med. Assoc. 27:22-24.

262. Barthelmess, A., H. Fuerst, and H. Huber. 1965. Food components as natural protective substances against x-ray-induced chromosome damage. Naturwissenschaften 52:160-161.

263. Barthen, C. L., F. F. Berg, E. B. Carter, D. M. Copley, R. J. Fosbinder, T. Lewis, and F. O. Taylor. 1939. A collaborative investigation of the spectrophotometric method for assay of vitamin A. J. Am. Pharm. Assoc. 28(10):661-672.

264. Bartlett, M. N. 1955. Red blood cell niacin and plasma riboflavin levels in a group of normal children. J. Nutrition 57:157-168.

265. Bartnicki-Garcia, S., and W. J. Nickerson. 1961. Thiamine and nicotinic acid: anaerobic growth factors for Mucor rouxii. J. Bact. 82:142-148.

266. Bartnik, J., B. Secomska, I. Trzebska-Jeske, and I. Pantorin. 1967. Nutritive value of Polish breads. IV. The content of some vitamins of B group in Polish breads as evaluated on the basis of baking formulas from 1961-1965 and the content of vitamins in flours and other components. Rocz. Panstw. Zakl. Hig. 18(4):505-511.

267. Barton-Wright, E. C. 1972. A dual-purpose basal medium for the microbiological assay of nicotinic acid (niacin) and pantothenic acid with Lactobacillus plantarum. Analyst 97(1153):300-301.

268. Barton-Wright, E. C., and R. G. Booth. 1943. The assay of riboflavin cereals and other products. 1. Microbiological assay. 2. Fluorometric assay. Biochem. J. 37:25-30.

269. Baschieri, L. 1947. The effect of nicotinamide on liver function. Acta Vitaminol. (Milan) 1:124-129.

270. Baserga, A., M. Morsiani, G. M. Mariuzzi. 1956. Haematological and histological changes caused by 6-aminonicotinamide. Acta Vitaminol. 10:195-204.

271. Bassen, F. A., A. D. Ets, and R. L. Rosenthal. 1952. Leukopenia following administration of nicotinic acid. Blood, J. Hematol. 7(6):623-630.

272. Bassi, M., and E. Liesch. 1940. Effect of nicotinic acid the movements and tonus of the stomach in nonpellagrous persons. Sperimentale 94(10-11):R37.

273. Bastomsky, C. H., V. Abbassi, and J. M. McKenzie. 1968. Effect of nicotinamide in vivo on thyroid pyridine nucleotides and radioiodine metabolism. Endocrinology 83(1):79-85.

274. Bastomsky, C. H., M. Zakarija, and J. M. McKenzie. 1971. Nicotinamide HCl and thyroid radioiodine metabolism in mice: effects due to acid. Endocrinology 88(5):1170-1174.

275. Bastrup-Madsen. P. 1963. Evaluation of aqueous vitamin B12 in long-term therapy of pernicious anaemia. Acta Med. Scand. 173(5):557-560.

276. Basualdo, R. N., P. A. Carrera, and J. C. Sanahuja. 1971. Determination of amino acids and water soluble vitamins in sunflower seed meals by microbiological methods: influence of the technological process on the content. Rev. Asoc. Bioquim. Argent. 36(192/193):1-9.

277. Batcu, A., and A. Busuioc. 1961. The influence of vitamins on the activity of phosphorus compounds in erythrocytes. Acad. Rep. Populare Romine, Inst. Biochim., Studii Cercetari Biochim. 4:223-234.

278. Bathurst, N. O. 1945. The estimation of the B vitamins: Comparison of methods. New Zealand J. Sci. and Tech. 27 A(3): 231-238.

279. Bathurst, N. O. 1947. Vitamin B content of meat cuts. New Zealand J. Sci. and Tech. 29A(2):72-74.

280. Batterham, E. S. 1970. Nutritional evaluation of diets containing meat meal for growing pigs. 3. Effects of amino acid, copper, and vitamin B supplements. Aust. J. Exp. Agr. Anim. Husb. 10(42):27-31.

281. Batunin, M. P., T. A. Glavinskaya, and V. S. Sakharova. 1965. Influence of external beta-irradiation on metabolism of thiamine, nicotinic acid, and transaminase. Med. Radiol. 10(1):62-65.

282. Batyr, D. G., and I. I. Bulgak. 1971. Iron(II) benzil dioximes with monodentate bifunctional pyridine derivatives. Izv. Akad. Nauk Mold. SSR, Ser. Biol. Khim. Nauk 1971(3):71-73.

283. Batyrov, Sh. K. 1965. Effect of nicotinic acid on gastric motility. Med. Zh. Uzbekistana 1965(9):22-24.

284. Baveja, S. K. 1966. Stability and stabilization of cyanocobalamin in vitamin B-complex injections containing, in particular, thiamine and nicotinamide. Australas. J. Pharm. 47(564):S108-S113.

285. Bavin, E. M., D. J. Drain, M. Seller, and D. E. Seymour. 1952. Further studies on tuberculostatic compounds. J. Pharm. and Pharmacol. 4:844-854.

286. Bayles, T. B., R. J. Palmer, M. F. Massod, and E. H. Judd. 1950. Vitamin B excretion studies in patients with rheumatoid arthritis. New England J. Med. 242(7):249-252.

287. Bayo Bayo, J. M. 1947. Vitamin B complex and diuresis. Farmacoterap. Actual (Madrid) 4:676-680.

288. Baxter, J. H. 1972. Histamine release from rat mast cells by dextran. Effects of adrenergic agents, theophylline, and other drugs. Proc. Soc. Exp. Biol. Med. 141(2):576-581.

289. Beal, V. A. 1955 Nutritional intake of children. III. Thiamine, riboflavin and niacin. J. Nutrition 57(2): 183-192.

290. Bean, W. B., and T. D. Spies. 1940. A study of the effects of nicotinic acid and related pyridine and pyrazine compounds on the temperature of the skin of human beings. Am. Heart J. 20:62-75.

291. Bean, W. B., R. W. Vilter, and T. D. Spies. 1939. The effect of roentgen-ray on the blood codehydrogenases I and II. Ann. Internal Med. 13(5):783-786.

292. Beard, H. H. 1941. The effect of parenteral injection of supracorcin, with and without vitamins, upon the appearance, growth and regression of the Walker sarcoma in rats. Pacific Coast Med. 8(2):44-46.

293. Beard, H. H., and P. Pizzolato. 1941. Effect of parenteral injection of crystalline vitamins upon the concentration of muscle creatine in the rat. J. Am. Dietet. Assoc. 17:446-449.

294. Beaudoin, A. R. 1973. Teratogenic activity of 2-amino-1,3, 4-thiadiazole hydrochloride in Wistar rats and the protection afforded by nicotinamide. Teratology 7(1):65-71.

295. Bebb, H. T., H. B. Houser, J. C. Witschi, A. S. Littell, and R. K. Fuller. 1971. Calorie and nutrient contribution of alcoholic beverages to the usual diets of 155 adults. Am. J. Clin. Nutr. 24(9):1042-1052.

296. Becker, D. E., J. R. Mitchel, Jr., A. H. Jensen, S. W. Terrill, and H. W. Norton. 1963. Nicotinic acid-tryptophan relationship in the nutrition of the weanling pig. In: Proceedings of the Midwestern Section of the American Society of Animal Science, Chicago, 1963. J. Animal Sci. 22(4):1117.

297. Beckett, A. H., and D. Hewick. 1967. The N-oxidation of chlorpromazine in vitro--the major metabolic route using rat liver microsomes. J. Pharm. Pharmacol. 19(2):134-136.

298. Becks, H., W. W. Wainwright, and A. F. Morgan. 1943. Comparative study of oral changes in dogs due to deficiencies of pantothenic acid, nicotinic acid and unknowns of the B vitamin complex. Am. J. Orthodontics Oral Surg. 29:183-207.

299. Begishvili, Ts. K. 1968. Pyridoxine and pantothenic and nicotinic acid levels in peas. Soobshch. Akad. Nauk Gruz. SSR 49(3):677-681.

300. Beher, W. T., and W. L. Anthony. 1953. Studies of antimetabolites III. The metabolism of 3-acetylpyridine in vivo. J. Biol. Chem. 203(2):895-898.

301. Beher, W. T., and O. H. Gaebler. 1950. Observations on niacin, riboflavin, allantoin, ascorbic acid, and vitamin A during anabolism induced by hormones. J. Nutrition 41:447-457.

302. Beher, W. T., and O. H. Gaebler. 1952. Metabolism of niacin induced growth. Federation Proc. 11:185-186.

303. Beher, W. T., E. M. Crigger, and O. H. Gaebler. 1952. The effect of testosterone propionate on niacin metabolism in rats. J. Nutrition 47:353-359.

304. Beher, W. T., W. M. Holliday, and O. H. Gaebler. 1952. Studies of antimetabolites. II. 3-Acetylpyridine. J. Biol. Chem. 198(2):573-578.

305. Behlke, J., and W. Scheler. 1964. The effect of urea on the oxidation-reduction of hemoproteins. Acta Biol. Med. Ger. 12(6):629-643.

306. Beiglboeck, W., and A. Spiess-Bertschinger. 1943. The effect of water-soluble vitamins on serous inflammation. Klin. Wochschr. 22:249-254.

307. Beiglboeck, W., and A. Spiess-Bertschinger. 1944a. On the biological and therapeutic significance of nicotinamide. Z. Klin. Med. 143:563-594.

308. Beiglboeck, W., and A. Spiess-Bertschinger. 1944b. Biological and therapeutic importance of nicotinamide. Klin. Wochenschr. 23:31.

309. Beklerkunst, A., and I. Windman. 1968. Nicotinic acid-induced NAD synthesis in polymorphonuclear leukocytes. Life Sci. (Oxford) 7(10):539-543.

310. Bekkum, D. W. van, and A. Querido. 1947. The influence of hypophysectomy on the niacin content of rat erythrocytes. Acta Brevia Neerland. 15(2/4):60-61.

311. Belavady, B., and C. Gopalan. 1966. Availability of nicotinic acid in jowar (Sorghum vulgare). Indian J. Biochem. 3(1):44-47.

312. Belavady, B., T. V. Madhavan, and C. Gopalan. 1967. Production of nicotinic acid deficiency blacktongue in pups fed diets supplemented with leucine. Gastroenterology 3(5):749-753.

313. Belavady, B., T. V. Madhavan, and C. Gopalan. 1968. Experimental production of niacin deficiency in adult monkeys by feeding jowar diets. Lab. Invest. 18(1):94-99.

314. Belen'kaya, S. L., G. P. Tikhomirova, and L. A. Prokhorenko. 1971. Use of physicochemical analytical methods for controlling stages of vitamin PP synthesis. Khim.-Farm. Zh. 5(12):4-50.

315. Belen'kii, E. E., A. S. Zaks, and T. V. Ivanovskaya. 1960. Effect of ascorbic acid and certain vitamins of the B complex and dibazol on the action of narcotics on the central nervous system. Trudy Permsk. Med. Inst. 1960(31):191-196.

316. Belen'kii, K. R., F. F. Zagafuranova, and Y. I Kiiko. 1971. Rheoophthalmological control of No-Shpa and nicotinic acid effect on glaucomatous patients. Oftal'Mol Zh. 26(7):539.

317. Belik, E. 1957. The determination of B complex vitamins in corn-steep extracts by microbiological tests. Chem. zvesti 11:51-56.

318. Bell, R. R., C. A. Blanchard, and B. E. Haskell. 1971. Metabolism of vitamin B6 in the I-strain mouse: II: Oxidation of pyridoxal. Arch. Biochem. Biophys. 147(2):602-611.

319. Bellen, N. 1973. Application of polarography in analytical control of industrial synthesis of nicotinic acid and nicotinamide from 3-picoline by the IChP (Institute of Industrial Chemistry) method. Przem. Chem. 52(3):226.

320. Beller, F. K., and W. Nagel. 1960. Thrombolysis: A new therapy of thromboembolic diseases. (II). Med. Welt 37:1928-1933.

321. Beller, F. K., and D. Sellin. 1960. Activation of fibrinolysis by a combination of nicotinic acid and heparin. Arzneimittel-Forsch. 10:758-763.

322. Bellet, S., L. Roman, H. Sandberg, and J. Kostis. 1970. Effect of nicotinic acid on the caffeine-induced serum free fatty acid increase. J. Pharmacol. Exp. Ther. 175(2):348-351.

323. Bellion, E. 1968. Rapid spectrophotometric assay for nicotinic acid. Anal. Biochem. 25(1/2/3):578-582.

324. Bellomo, G., and G. D'Urso. 1963. Profile of the hyperbilirubinemic curve induced by sodium nicotinate and modification of the pathological hyperbilirubinemia in hepatitis by ATP and DPN. Arch. Atti Soc. Med.-Chir. Messina 7(1):57-68.

325. Bellomo, G., and A. Rizzo. 1961. Comparative study on the hyperbilirubinemic action of nicotinic acid and 3-pyridine-acetic acid. Acta Vitam (Milano) 15:157-161.

326. Belova, T. V. 1970. Dynamics of the reaction of substances during the germination of peanut seeds dependent on their presowing treatment. Sb. Tr. Aspir. Molodykh Nauch. Sotrudnikov, Vses. Nauch.-Issled. Inst. Rastenievod. (10): 372-377.

327. Belsasso, E., A. Risolo, and V. Zucconi. 1951. Sideremia in the hyperbilirubinemia caused by nicotinic acid. Minerva med. II:518-520.

328. Belukha, U. K. 1969. Photoprotective and photodesensitizing properties of some pharmaceuticals. Clinical-experimental studies. Med. Zh. Uzb. 1969(10):23-25.

329. Belukha, U. K. 1970. Effect of ascorbic acid and some B vitamins on the functional state of the adrenal cortex in patients with photodermatosis. Vestn. Dermatol. Venerol. 1970(5):24-30.

330. Belvady, B., T. A. Madhavan, and C. Gopalan. 1967. Production of nicotinic acid deficiency (blacktongue) in pups fed diets supplemented with leucine. Gastroenterology 53(5):749-753.

331. Belyaev, N. I. 1970. Nicotinic acid electrophoresis in the treatment of patients suffering from hypertensive disease. Vrach Delo 5:16-17.

332. Belyaeva, N. F., I. D. Pevzner, and V. I. Telepneva. 1972. Content of nicotinamide nucleotides and the rate of NADP synthesis in rabbit muscles during embryonal and postnatal development. Zh. Evol. Biokhim. Fiziol. 8(4):375-380.

333. Benard, H., A. Gajdos, M. Gajdos-Torok, and M. Polonovski. 1948. The effect of methionine and two of its oxygenated derivatives on erythropoiesis. Le Sang 19:264-268.

334. Bencze, B. 1949/50. The estimation of nicotinamide. Zeitschr. Vitamin-, Hormon- u. Fermentforsch. 3(5/6):429-437.

335. Benedetti, G., B. Tortori-Donati, and F. Ferri. 1948. Nicotinamide and lactoflavin and carbohydrate metabolism. Rass. fisiopatol. clin. e terap. Pisa 20:233-244.

336. Benes, J., and B. Zicha. 1967. Biosynthesis of pyridine co-enzymes. Chem. Listy 61(2):203-236.

337. Benes, V., and V. Hrubes. 1968. Serum free fatty acid level after an experimentally induced emotional stress and its modification by nicotinic acid in rats with different characteristics of higher nervous activity. Activ. Nerv. Super. 10(4):395-399.

338. Benex, J. 1967. Substances capable of prolonging the survival of explants maintained in organotypic culture. C. R. Acad. Sci., Paris, Ser. D 265(7):571-574.

339. Benko, A. 1942. The combined action of nicotinic acid amide and cortigen on the porphyrinuria of lead poisoning. Chem. Zentr. Deut. med. Wochschr. 68:271-272.

340. Benn, W. R. 1963. A reinvestigation of the synthesis of pregna-5,16-diene-3beta,20alpha-diol. Nuclear magnetic spectra of some epimeric 20-hydroxypregnane derivatives. J. Org. Chem. 28(12):3557-3559.

341. Bera, G. N. 1953. Effects of niacin and niacinamide on blood sugar. Am. J. Physiol. 175:296-298.

342. Bera, G. N., and J. Chowdhury. 1958. Effects of niacin and vitamin C on blood sugar. Am. J. Physiol. 192:511-513.

343. Beran, A. V., J. Strauss, D. R. Sperling, A. C. Norton, V. P. Garwood, and J. Yamazaki. 1971. Effect of thalidomide on brain oxygenation. Pediat. Res. 5(5):199-205.

344. Bereston, E. S. 1954. Vitamins in dermatology. J. Clin. Nutrition 2(2):133-139.

345. Berg, J. R. 1950. Purification of nicotinamide. U. S. Pat. 2,496,114.

346. Berg, T. M., and H. A. Behagel. 1972. Semiautomated method for microbiological vitamin assays. Applied Microbiology 23(3): 531-542.

347. Bergamini, C. 1953. Chromatographic recognition of pantothenic acid and separation of the vitamins of the B complex. Sperimentale, Sez. chim. biol. 4:38-44.

348. Berge, K. G. 1961. Side effects of nicotinic acid in treatment of hypercholesteremia. Geriatrics 16:416-422.

349. Berge, K. G., and G. D. Molnar. 1964. Effects of nicotinic acid on clinical aspects of carbohydrate metabolism. In: R. Altschul, Editor. Niacin in Vascular Disorders and Hyperlipemia. C. C. Thomas: Springfield, Illinois, p. 136-155.

350. Berge, K. G., R. W. P. Achor, N. A. Christensen, H. L. Mason, and N. W. Barker. 1961. Hypercholesteremia and nicotinic acid. A long-term study. Am. J. Med. 31(1):24-36.

351. Berger, G. M. B., and J. D. Jones. 1971. Inhibition of corticosterone formation and 3beta-hydroxysteroid dehydrogenase activity in cell-free preparations of rat adrenals. Endocrinology 89(3):722-729.

352. Berger-Gruener, M. 1966. Changes in the riboflavine and niacin contents during manufacture of Trappist chesse. Milchwissenschaft 21(4):222-225.

353. Bergmann, F., and L. Wislicki. 1953. The pharmacological effects of massive doses of nicotinamide. Brit. J. Pharmacol. Chemotherap. 8:49-53.

354. Bergstrom, J., E. Hultman, L. Jorfledt, B. Pernow, and J. Wahren. 1969. Effect of nicotinic acid on physical working capacity and on metabolism of muscle glycogen in man. J. Appl. Physiol. 26(2):170-176.

355. Bergstrom, S., and L. A. Carlson. 1966. Prostaglandin and related factors. XLVI. Influence of the nutritional state on the inhibition of lipolysis in adipose tissue by prostaglandin E1 and nicotinic acid. Acta Physiol. Scand. 65(4):383-384.

356. Beritashvili, I. S., A. N. Bakuradze, and A. I. Kats. 1969. Image memory after administration of some drugs to lower monkeys with the frontal cortex removed. Soobshch. Akad. Nauk. Gruz. SSR 56(3):681-684.

357. Berkman, S., and S. A. Koser. 1943. Comparative effect of certain sulfonamide compounds on nicotinamide-stimulated metabolism. J. Infect. Dis. 73(1):57-64.

358. Berkowitz, D., M. W. Croll, and W. Likoff. 1962. Effects of sitosterol, nicotinic acid, and triparanol on fat tolerance. Am. J. Clin. Nutr. 10:107-110.

359. Bernardini, R. 1941. Effect of nicotinic acid on heart action and blood pressure. Riv. Patol. Sper. 25:249-256.

360. Bernasconi, E. 1961. Research on a new method of treatment of anorexia accompanying academic stress. Ther. Umsch. 18:312-314.

361. Bernhard, K., and H. J. Bollag. 1961. The vitamin B supplied by bread. A contribution to the revitaminization of food-stuffs. Schweiz. Med. Wschr. 91:208-210.

362. Bernhard, K., H. Steinhauser, and A. Matthey. 1945. Fat metabolism with the aid of deuterium as indicator. IV. Lipide synthesis from protein in albino rats. Helv. Chim. Acta 27:1134-1141.

363. Bernheim, F. 1940. Interaction of vitamins and drugs with cell catalysts. J. Lab. Clin. Med. 26:20-30.

364. Berry, L. J. 1963. Implication of tryptophan pyrrolase in endotoxin poisoning. U.S., Air Force Systems Command, Arctic Aeromed. Lab., Tech. Doc. Rept. AAL-TDR-63-13, 21pp.

365. Bertschinger, A. 1942. The effect of nicotinamide and ascorbic acid on liver parenchyma damage. Wiener Med. Wochenschr. 92 (34):625.

366. Berzewski, H. 1957. The treatment of neuro-psychiatric diseases with pyridine-beta-carboxylic acid. Med. Welt. 42:1657-1661.

367. Berzewski, H. 1971. Treatment of neuropsychiatric diseases with pyridine-beta-carboxylic acid (II). Med. Welt. 43:1705-1709.

368. Bessey, O. A. 1954. Blood levels in evaluation of vitamin adequacy. Quartermaster Food and Container Inst. Surveys Progr. Military Subsistence Problems, Ser. 2, Nutrition Aspects of Rations, No. 2, Methods for Evaluation of Nutritional Adequacy and Status: a Symposium. Advisory Board on Quartermaster Research and Development, National Research Council, Washington, D.C. 59-68pp.

369. Bessey, O. A., M. K. Horwitt, and R. H. Love. 1956. Dietary deprivation of riboflavine and blood-riboflavine levels in man. J. Nutrition 58:367-383.

370. Bessey, O. A., H. J. Lowe, and L. L. Salomon. 1953. Water-soluble vitamins. Ann. Rev. Biochem. 22:545-628.

371. Bessiere, C., B. Riche, and M. Bastide. 1959. Determination of nicotinamide in filtrates of cultures of human and bovine tubercle bacilli by microbiolical methods. Trav. soc. pharm. Montpellier 18:150-156.

372. Bevis, A., L. Lundholm, and E. Mohme-Lundholm. 1968. Cyclic amp as a mediator of hormonal metabolic effects in brown adipose tissue. Brit. J. Pharmacol. 34(1):198-199.

373. Bezuglyi, I. P. 1969. Vitamin B enrichment of mixed feed for laying hens. Ptakhivnitstvo 6:31-37.

374. Bezzi, A., M. T. Tacconi, and S. Garattini. 1966. Lowering of blood ketone bodies induced by drugs preventing free fatty acid mobilization. Experientia 22(10):664.

375. Bhagvat, K. 1943. Combined estimation of thiamine and nicotinic acid in foodstuffs by chemical methods. Indian J. Med. Research 31:145-152.

376. Bhagwat, R. V., and K. Sohonie. 1955a. The relation of vitamin B12 with thiamin, riboflavin and nicotinic acid. Ann. Biochem. and Exptl. Med. (India) 15(3):161-168.

377. Bhagwat, R. V., and K. Sohonie. 1955b. Precursor of nicotinic acid in peanuts. Ann. Biochem. and Exptl. Med. (India) 15:169-174.

378. Bhandari, B., A. Punjwani, and N. B. Saxena. 1969. Clinical study of pellagra in children. Pediat. Clins. India, 4:149-155.

379. Bhat, K. S., and Belavady. 1967. Biochemical studies in phrynoderma. I. Hemoglobin, plasma proteins, cholesterol and phospholipids in plasma and erythrocytes. Indian J. Med. Res. 55(1):80-84.

380. Bhatnagar, S. P. 1970. Release of cholinesterase from rat liver by nicotinamide and carbon tetrachloride. Biochem. Pharmacol. 19(6):2009-2016.

381. Bialecki, M. 1962. Nicotinic acid in physical stress. Polski Tygod. Lekar. 17(35):1370-1375.

382. Bialek, J., and S. Porada. 1969. Separation of a eutectic mixture of nicotinic and isonicotinic acids. Pol. Pat. 57,343.

383. Biancalana, L., N. Masera, and F. Vecchione. 1961. Cholesterol diet, cholestasia, hypocholesteremic substances, and experimental biliary lithiasis. Epatologia 7:435-448.

384. Bianchessi, M., E. Pasargiklian, E. Polli, and F. Silvestrini. 1952. Action of nicotinamide on carbohydrate metabolism. I. In normal subjects. Arch. Studio Fisiopatol. e Clin. Ricambio 16:152-159.

385. Bianchi, A. 1961. Determination of vitamin PP in pharmaceutical products by means of photometric titration in non-aqueous solvent. Farmaco (Prat) 16:476-480.

386. Bianchi-Donnasibilla, L., A. Luvara, and F. Curro. 1969. Observations on tryptophan-nicotinic acid metabolism in rats with pyridoxine deficiency after a dose of tryptophan and lysine. Acta Vitaminol. Enzymol. 23(5):165-168.

387. Biancifiori, C., and R. Ribacchi. 1962. Pulmonary tumours in mice induced by oral isoniazid and its metabolites. Nature (Lond) 194:488-489.

388. Bickers, W. 1961. Dysmenorrhea - a new therapy. Virginia Med. Monthly 88:36-39.

389. Biehl, E. R., E. Nieh, and K. C. Hsu. 1969. Substituent effects on the reactivity of arynes. Product distributions as an index of relative reactivities of arynes in methylamine and dimethylamine solvents. J. Org. Chem. 34(11):3595-3599.

390. Bielawiec, M. 1967. Clinical and experimental studies on activities of fibrinolysis. Rocz. Akad. Med. Bialymstoku, Suppl. No. 15:1-92.

391. Bieltvedt, G. 1967. The formation of formazan through dehydrogenase activity. Arzneim.-Forsch. 16(12):1686-1688.

392. Bien, E., and P. Buntrock. 1969. Effect of different petroleum fractions on experimental wound granulation. Pharmazie 24(10):629-632.

393. Bilich, I. L., and B. S. Berezovskii. 1959. Cholinesterase activity, glutathione content, and cell permeability in gastric ulcer. Kazan. Med. Zhur. 1959(6):46-51.

394. Bilich, I. L., and B. S. Berezovskii. 1962. The relation of redox processes to cell permeability in cases with peptic ulcer and hypertension. Materialy Nauchn. Konf. po Probl. Funkts. Vzaimootnoshenyia Mezhdu Razlichnymi Sistemami Organizma v Norme i Patol. 1962:114-116.

395. Binazzi, M., and P. Calandra. 1971a. Tryptophan to niacin pathway in Lupus Erythematosus. Acta Vitaminol. Enzymol. (Milano) 25:205-209.

396. Binazzi, M., and P. Calandra. 1971b. Identification of an error in the tryptophan-niacin pathway in carriers of some dermatoses conditioned or aggravated by sunlight. Arch. Klin. Exp. Dermatol. 239(4):368-376.

397. Bing, J., and B. Broager. 1938. Effects of nicotinic acid on two patients with idiopathic steatorrhea (sprue). Acta Med. Scand. 97:561-577.

398. Birch, T. W. 1939. The requirements of the dog and the rat for nicotinic acid. J. Nutrition 17:281-292.

399. Bisceglie, M. 1954. Blood levels of niacin and vitamin B2 in normal and dystrophic children. Rev. pediat. siciliana 9:67-73.

400. Bitter, H.L., D. A. Clark, and W. W. Lackey. 1967. Metabolic effects of monomethylhydrazine. Aerosp. Med. 38(12):1214-1219.

401. Bitter, H. L., D. A. Clark, and W. W. Lackey. 1969. Preferential shifts in consumption of metabolic fuels following exposure to rocket fuel substances. Aerosp. Med. 40(5):526-531.

402. Biyashev, G. Z., and L. B. Seilova. 1973. Effect of physico-chemical mutagens on microsporogenesis in sugar beets. Izv. Akad. Nauk Kaz. SSR, Ser. Biol. 11(1):25-29.

403. Bizzi, A., and S. Garattini. 1967. Effect of drugs lowering plasma FFA (free fatty acids) on the accumulation of liver triglycerides. Progr. Biochem. Pharmacol. 3:320-324.

404. Bizzi, A., and S. Garattini. 1971. Drugs lowering plasma free fatty acids. Similarities and dissimilarities with nicotinic acid effect. Metab. Eff. Nicotinic Acid Its Deriv., Pro 1971:207-220.

405. Bizzi, A., A. M. Codegoni, and S. Garattini. 1969. Hypersensitivity of adipose tissue to norepinephrine and other lipolytic agents during blockade of free fatty acids (FFA) mobilization. Biochem. Pharmacol. 18(9):2053-2060.

406. Bizzi, A., A. M. Codegoni, A. Lietti, and S. Garattini. 1968. Different responses of white and brown adipose tissue to drugs affecting lipolysis. Biochem. Pharmacol. 17(12):2407-2412.

407. Bizzi, A., A. M. Codegoni, A. Medea, and S. Garattini. 1973. Effects of antilipolytic agents on glucose utilization by adipose tissue. Biochem. Pharmacol. 22(6):763-768.

408. Bjornstad, R. T. 1972. Pellagra during treatment with isoniazid. Tidsskrift for den Norske Laegeforening 92(9):640-641.

409. Bjorntopr, P. 1965. The effect of nicotinic acid on adipose tissue metabolism in vitro. Metab., Clin. Expti. 14(7):836-840.

410. Bjorntopr, P. 1966. Inhibition of lipase activation in rat epididymal fat pads in vitro. Am. J. Physiol. 210(4):733-736.

411. Black, D. A. K., J. P. Bound, and L. P. R. Fourman. 1947. Fat absorption in tropical sprue. Quart. J. Med. 16(63):99-109.

412. Blackard, W. G., and T. Cameron. 1967. Influence of nucleotide derivatives on lipolysis and lipid peroxide formation in vitro. Metab. Clin. Exp. 16(1):91-95.

413. Blackard, W. G., and S. A. Heidingsfelder. 1969. Effect of adrenergic receptor blockade on nicotinic acid-induced plasma FFA (free fatty acids) rebound. Metab.,CClin. Exp. 18(3): 226-233.

414. Blain, J. A., J. D. E. Patterson, and M. Pearee. 1968. Carotene bleaching activity of tomato extracts. J. Sci. Fd. Agric. 19:713-717.

415. Blake, R. L. 1970. Regulation of liver tyrosine aminotransferase activity in inbred strains and mutant mice. II. Starvation-induced enzyme adaptation. Can. J. Biochem. 48(9):1043-1049.

416. Blake, R. L., and E. Kun. 1971. Enzyme induction by nicotinamide. Methods Enzymol. 18(Pt. B):113-123.

417. Blake, R. L. S. L. Blake, H. H. Loh, and E. Kun. 1967. The effect of nicotinamide and homologs on the activity of inducible enzymes and NAD content of the rat liver. Mol Pharmacol 3(5):412-422.

418. Blanchaer, M. C., D. E. Bergsagel, P. Weiss, and D. E. Jefferson. 1950. The effect of niacin on the pyridine nucleotide content of human blood cells in anemia. Can. J. Research 28E:97-105.

419. Blanchaer, M. C., B. Marlatt, S. Baldwin, and P. Weiss. 1952. Effect of nicotinamide on erythrocyte glycolysis. Rev. Can. Biol. 11:55.

420. Blaszczak, J. W. 1971. Antiviral reaction products of ascorbic acid and formaldehyde. Brit. Pat. 1,251,787.

421. Blecher, M. 1967. Evidence for the involvement of cyclic 3',5'-adenosine monophosphate in glucose utilization by isolated rat epididymal adipose cells. Biochem. Biophys. Res. Commun. 27(5):560-567.

422. Blecher, M., N. S. Merlino, and J. T. Ro'Ane. 1968. Control of the metabolism and lipolytic effects of cyclic 3',5'-adenosine monophosphate in adipose tissue by insulin, methylxanthines, and nicotinic acid. J. Biol. Chem. 243(14):3973-3977.

423. Bliss, A. R., Jr. 1938. Vitamins. Nicotinic acid and pellagra. Drug. Cosmetic Ind. 42:578-579.

424. Blok, Y. E. 1966. Influence of rabbit plasma on cellular lipoidosis in aortic culture of plasma donors. Cor Vasa 8(2): 140-147.

425. Bluemchen, G., et al. 1970. Central hemodynamic responses to xantimol-nicotinate. Arzneim. Forsch. 20:1067-1069.

426. Blugers, A., and S. A. Borovkov. 1962. The mechanism underlying the increase in enzyme activity in blood serum during pathological processes. Aktual'n. Vopr. Patogeneza, Kliniki i Lecheniya Infekts. Bolezniei, Riga, Sb. 1962:13-25.

427. Blum, J. G. 1971. Chlorocyanopyridines, intermediates for the synthesis of polysubstituted pyridines. Fr. Pat. 2,079,649.

428. Blum, K. U., D. Mehlhorn, and W. Heim. 1966. Nicotinamide as stabilizing additive in cold storage of blood. Klin. Wochenschr. 44(22):1313-1314.

429. Blumenthal, L. S., and M. Fuchs. 1960. Combined meclizine and nicotinic acid in the management of certain chronic vascular headaches. Postgrad. Med. 28:427-433.

430. Boberg, J., H. Michell, and L. Rammer. 1970a. Effect of nicotinic acid on ACTH and noradrenaline stimulated lipolysis in the rabbit. 1. In vivo studies. 2. In vitro studies including comparison with prostaglandin E1. Acta physiol. Scand. 79:153-157.

431. Boberg, J., H. Michell, and L. Rammer. 1970b. Effect of nicotinic acid on ACTH and noradrenaline stimulated lipolysis in the rabbit. II. In vitro studies including comparison with prostaglandin E1. Acta Physiol. Scand. 79(3):299-304.

432. Boberg, J., L. A. Carlson, S. O. Froberg, A. Olsson, L. Oro, and S. Rossner. 1971. Effects of chronic treatment with nicotinic acid on intravenous fat tolerance and post-heparin lipoprotein lipase activity in man. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1971:465-470.

433. Bode, H., W. Bode, and W. Schnittler. 1971. Clinical and practical experiences with Progresin, a magnesium-containing, vasoactive drug in cases with cerebral and peripheric circulatory disorders. Med. Welt 25:1044-1051.

434. Bodin, F., et al. 1969. Digestive tract hemorrhages following ingestion of anti-inflammatory drugs. Sem. Hop. Paris 45:887-892.

435. Boettcher, F., D. Birnbaum, and I. A. Samsonova. 1972. A short cut pathway of nicotinic acid synthesis in Rhodotorula glutinis. Eur. J. Biochem. 29(1):88-93.

436. Bogdanova, E. D. 1962. The effect of nicotinic acid on the growth and development of spring wheat. Izvest. Akad. Nauk. Kazaksk. SSR Ser. Bot. I Pochvovedeniya 3(15):74-80.

437. Bogdanova, E. D. 1965. Effect of nicotinic acid on the growth, development, crop yield, and sowing quality of wheat seeds. Fiziol. Rast. 12(1):152-157.

438. Bogdanova, E. D., and E. I. Omarova. 1968. Effect of nicotinic acid and its analogs on wheat growth. Tr. Inst. Bot., Akad. Nauk. Kaz. SSR 25:105-112.

439. Bogdanova, E. D., E. I. Omarova, E. A. Vorob'eva, and A. K. Krivtsanova. 1966. Effect of nicotinic and its analogs on the yield and sugar content of sugar beets. Vestn. Sel'skokhoz. Nauki (Alma-Ata) 9(7):108-111.

440. Bogdanova, E. V. 1959. Nicotinic acid and sulfidine. Trudy Vsesoyuz. Nauch.-Issledovatel. Vitamin. Inst. 6:216-219.

441. Bogentoft, C., L. Kronberg, and B. Danielsson. 1969. Medicinal chemistry of oxoquinazolines. IV. N- and O-alkylation of some 2-substituted-3,4-dihydro-4-oxoquinazolines. Acta Pharm. Suecica 6(4):489-500.

442. Boggian, B. 1948. Nicotinamide and blood-sugar curve. Acta Vitaminol. 2:35-39.

443. Bois-Joyeux, B., F. Gaudin-Harding, and J. Adrian. 1972. Diagnostic test for vitamin deficiencies and excesses by biochemical analysis of hair. Rat experiments. I. Vitamins of hair as a function of color and dietary intake of niacin and ribofavin. Int. J. Vitam. Nutr. Res. 42:33-42.

444. Boissier, J. R., and F. Mendy. 1966. Dietic compositions. Fr. Pat. M3789.

445. Bojalil, L. F., and F. Bastarrachea. 1961. Reliability of the niacin test as an aid in classifying human and bovine strains of tubercle bacilli in epidemiologic studies. Am. Rev. Resp. Dis. 84:272-275.

446. Bolewski, K., and T. Tomaszkiewicz. 1969. Chelates of poly (acrylic acid) with certain ammonium salts. Acta Pol. Pharm. 26(5):457-469.

447. Bolin, D. W., and E. Kelly. 1947. A simplified chemical method for determination of nicotinic acid in pork products. Food Res. 12:414-418.

448. Bollman, J. L. 1942. Dextrose administration and vitamin B. Proc. Soc. Exptl. Biol. Med. 50:18-22.

449. Bologov, V. P., and G. A. Uzbekov. 1966. Quantitative change in the thiol groups of proteins and low-molecular compounds of the brain under the action of cobalamine and nicotinic acid, under normal conditions and in cadmium poisoning. In: Information on the 4th Volga conference of physiologists, pharmacologists, and biochemists, with the participation of morphologists and clinicians, 1966. Saratov. 2:158-159.

450. Bombelli, R., T. Farkas, and R. Vertua. 1965. Investigations on the effect of nicotinic acid on plasma free fatty acid levels. Med. Pharmacol. Exp. 12(1):8-14.

451. Bonasera, N., G. Mangione, and V. Bonavita. 1963. Diphosphopyridine nucleotide (DPN) synthesis in brain following injection of various compounds. Biochem. Pharmacol. 12(7): 633-636.

452. Bonasera, N., G. Mangione, and V. Bonavita. 1964. Effects of reserpine on the urinary excretion of nicotinamide metabolites in mouse. Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. Nat. 34(3-4):207-212.

453. Bonati, B., G. B. Rancati, C. Ferrari, and P. Marrama. 1956. Plasma levels and urinary elimination of various vitamins in rats and rabbits in relation to age. Acta Vitaminol. 10:270-273.

454. Bonati, F., L. Cucurachi, and R. I. Portioli. 1961. The correlation and importance of the various hematochemical indexes in the clinical evaluation of blood lipid-reducing drugs. Drugs Affecting Lipid Metab., Proc. Symp. Milan 1960: 554-555.

455. Bonavita, V., S. A. Narrod, and N. O. Kaplan. 1961. Metabolites of nicotinamide in mouse urine: Effects of azaserine. J. Biol. Chem. 236(3):936-939.

456. Bondarev, G. I., et al. 1963. The supply of vitamins C, B1, B2, and PP of fish processing operators on trawlers in the North Atlantic. Vop Pitan 22:58-60.

457. Bonfiglio, G., and M. Proja. 1957. Nicotinic acid and lipide metabolism. A study on individuals with atherosclerotic alterations of central nervous system. Lavoro Neuropsichiat. 21:276-280.

458. Bongiorno, V. 1940. Nicotinic acid and blood formation. Riforma Med. 56:371-373.

459. Bonhomme, M. 1962. Fruit and vegetable preservation. Fr. Pat. 1,280,791.

460. Bonino, R. C. D'Allesio de Carnevale. 1958. Determination of nicotinic acid diethylamide. Publ. Inst. Invest. Microquim. Univ. Nacl. Litoral (Rosario, Arg.) 24(22):83-93.

461. Bonollo, L. 1969. The influence of ascorbic acid and nicotinamide on the body weight of rats treated by diphenylhydantoin. Acta Vitaminol. Enzymol. 23(6):221-224.

462. Bonollo, L., and F. B. Nicolis. 1967. Hypercholesterolemia due to pyridoxine deficiency in the rat; its relation to the metabolism of tryptophan to nicotinic acid. Acta Vitaminol. Enzymol. 21(1):24-30.

463. Bonsignore, A., and L. Bevilacqua. 1947. Studies on transmethylation. Formation of N1-methyl-nicotinamide and elimination of creatine bodies. Boll. Soc. Ital. Biol. Sper. 23:710-712.

464. Bonsignore, A., and C. Ricci. 1958. Nicotinamide and synthesis of pyridine nucleotides in the liver. Sci. Med. Ital. 6:655-670.

465. Bonsignore, A., and C. Vergano. 1958. Acute biochemical syndrome consequent to excessive administration of nicotinamide. Giorn. Biochim. 7:284-299.

466. Bonsignore, A., G. Fornaini, and E. Marinello. 1958. Formation of an activator of the phosphoglucomutase reaction in the liver of rats treated with high doses of nicotinamide. Giorn. Biochim. 7:69-77.

467. Bonsignore, A., G. Segni, G. Fornaini, and C. Antolini. 1959. The acute biochemical syndrome of overdose of nicotinamide. Variations of the heptose content of the rat's liver. Boll. Soc. Ital. Biol. Sper. 35:75-78.

468. Booher, L. E. 1942. Newer aspects of the chemical function of the vitamins. Chemistry & Industry 1942:388-392.

469. Booher, L. E., and I. T. Behan. 1949. Nutrient analyses of United States food supplies. Analyses of composited samples of our national food supplies and of the white flour and non-white flour components thereof in terms of various nutrients. J. Nutrition 39(4):495-515.

470. Bootsma, B. K. 1963. A study of the value of nicotinic acid in the treatment of hypercholesteremia. Nederl. Milit. Geneesk. T. 16:71-83.

471. Borglin, N.-E. 1947. On the excretion of choline in urine. Acta Pharmacol. et Toxicol. 3(Suppl. 1):1-123.

472. Bori, V. D., and S. Steffenoni. 1947. Relationships between nicotinamide and inorganic phosphorus in the blood. Policlin. Infantile 15(7):331-336.

473. Boriani, A. 1955. The action of nicotinic acid and some of its derivatives on the activity of serum cholinesterase. Boll. Soc. Ital. Biol. Sper. 31:135-136.

474. Boris, Ya. G. 1969a. Indexes of thyroid functional activity in experimental animals fed rations low in nicotinic acid and tryptophan against a background of iodine deficiency. Vop. Pitan. 28(2):19-23.

475. Boris, Ya. G. 1969b. Effect of nicotinic acid and tryptophan deficiency on the thyroid under conditions of adequate iodine supply. Vrach. Delo 1969(8):31-32.

476. Boris, Ya. G. 1969c. Iodine level in the thyroid gland. Faktory Vnesh. Sredy Ikh Znachenie Zdorov'ya Naseleniya 1969 (1):100-106.

477. Borisenko, Yu. B., R. M. Safiulin, and S. A. Nosovits'kaya. 1965. Preparation of tablets which contain chemically incompatible pharmaceuticals. Farm. Zh. (Kiev) 20(2):44-47.

478. Borisova, M. A. 1957. Nicotinic acid metabolism in typhoid fever patients treated with syntomycin. Terap. Arkh. 29(2): 70-76.

479. Borisova, M. A. 1960. Studies on nicotinic acid metabolism in patients with typhoid fever treated with antibiotics (synthomycin and levomycetin) with a diet rich in proteins. Vop. Pitan. 19(3):42-47.

480. Borisova, M. A. 1966a. Correlation between the metabolism of enzymes, trace elements, and vitamins in patients with abdominal typhus, acute dysentery, and infectious hepatitis. Klin. Med. (Moscow) 44(11):130-136.

481. Borisova, M. A. 1966b. Changes in metabolism of vitamins E and B1 and nicotinic acid in Botkin's epidemic hepatitis. Vop. Pitan. 25(2):80-81.

482. Boros, M. 1963. Thrombolysis with nicotinic acid. Therapia Hung. 12(2):27-29.

483. Borsuk, V. N. 1959. Phosphorus metabolism in cows in various stages of lactation. Tr. Inst. Fiziol. Pavlov 8:509-513.

484. Bortos, M. P. 1971. Effect of some analeptics on morphine analgesia. Spitalul 84(2):171-174.

485. Bosch, A. J., A. E. Harper, and C. A. Elvehjem. 1959. Factors affecting pyridine nucleotide concentration in hyperthyroid rats. Proc. Soc. Exptl. Biol. Med. 100:774-777.

486. Bose, B. C., S. S. Gupta, and H. N. De. 1955. Effect of deficiency of riboflavin and nicotinic acid on the synthesis of acetyl choline in rats. Current Sci. 24(7):231-232.

487. Botta, J. A., Jr., and W. W. Carlton. 1967. Isoniazid toxicosis in ducklings. Studies on pyridoxine, niacin, glutamic acid, and arginine supplementation. Avian Dis. 11(4):621-633.

488. Botting, R. M., and D. Burden. 1969. Potentiation of the actions of pentobarbitone by nikethamide. J. Pharm. Pharmacol. 21(6):400-401.

489. Bottomley, A. C. 1944. Chemical estimation of vitamin B6 in foodstuffs. Biochem. J. 1944:38.

490. Boulin, R., L. Justin-Besancon, Fl. Nepveux and Y. Geffroy. 1939a. A case of coproporphyrinuria treated with nicotinamide. Bull. Mem. Soc. Med. Hop. Paris 55:474-479.

491. Boulin, R., L. Justin-Besancon, Fl. Nepveux, and Y. Geffroy. 1939b. A case of uroporphyrinuria treated with nicotinamide. Bull. Mem. Soc. Med. Hop. Paris 55:480-483.

492. Bourquin, A. 1945. Observations on the ascorbic acid level of the blood plasma of women maintained on a thiamine deficient diet. Am. J. Digest. Dis. 12(5):162-166.

493. Boutwell, R. K., M. K. Brush, and H. P. Rusch. 1949. The influence of vitamins of the B complex on the induction of epithelial tumors in mice. Cancer Research 9:747-752.

494. Bovarnick, M. R. 1943. Formation of a nicotinamide-like substance from various amino acids and related compounds. J. Biol. Chem. 151(2):467-475.

495. Bowen, D. M. 1967. Studies of the mechanism of the hypocholesterolemic action of nicotinic acid. Diss. Abstr. B 27(7): 2270.

496. Bowering, J. L., and M. A. Morrison. 1967. Tryptophan utilization in a threonine-induced amino acid imbalance in weanling rats: plasma amino acid and liver pyridine nucleotide concentrations. J. Nutr. 91(4):429-440.

497. Bowery, B., and G. P. Lewis. 1973. Inhibition of functional vasodilatation and prostaglandin formation in rabbit adipose tissue by indomethacin and aspirin. Brit. J. Pharmacol. 47(2):305-314.

498. Bowman, C. G., and P. F. Bonventre. 1970. Specific reversal of diphtheria toxin mediated inhibition of protein synthesis in guinea pig tissues. Biochem. Biophys. Res. Commun. 41(5): 1148-1154.

499. Boyle, J. A., K. O. Raivio, M. A. Becker, and J. E. Seegmiller. 1972. Effects of nicotinic acid on human fibroblast purine biosynthesis. Biochim. Biophys. Acta 269(2):179-183.

500. Braasch, D., F. F. Doerr, and H. Hensel. 1961. Studies on the blood circulation of the human skin with a new thermal conductivity measurement apparatus following local application of nicotinic acid esters. Arzneimittelforsch. 11:102-104.

501. Bracco Industria Chimica S.p.A. 1970. Improvements in or relating to hepatic medicines. Brit. Pat. 1,178,984.

502. Bradford, L. W., and J. W. Brackett. 1958. Systematic procedure for the identification of dangerous drugs, poisons, and narcotics by ultraviolet spectrophotometry. Mikrochim. Acta 1958:353-382.

503. Braekkan, O. R. 1958. Vitamins in Norwegian fishes. III. Vitamins in different organs from the most important gadus-fishes (Gadidae) caught off the coast of Norway. Fiskeridirekt. Skrifter Ser. Teknol. Undersok. 3(6):1-32.

504. Braekkan, O. R., K. Hansen, and T. Skogland. 1955. Vitamins in Norwegian fish. II. Vitamins in different organs from tuna fish (Thunnus thynnus) caught off the West Coast of Norway. Fiskeridirektorat. Skrifter, Ser. Teknol. Undersok. 3(3):18.

505. Braham, J. E., R. Bressani, and M. A. Guzman. 1966. Effect of lysine and trypotophan supplementation on nicotinic acid metabolism in pigs given raw or lime-treated corn diets. Metab. (Clin Exp) 15(6):548-556.

506. Braham, J. E., A. Villabreal, and R. Bressani. 1962. Effect of lime treatment of corn on the availability of niacin for cats. J. Nutrition 76(2):183-186.

507. Brand, V. V., and W. Seitz. 1960. Inhibition of fatty acid and cholesterol syntheses in the liver in vitro and declining cholesterol content in human serum on nicotinamide administration. Med. Klin. (Munich) 55:723-725.

508. Branehog I, et al. 1967. Nicotinic acid--acanthosis nigricans. Lakartidningen 64:1449-1451.

509. Branemark, P. I. 1961. Effect of nicotinic acid and histamine on capillary circulation of bone marrow in rabbit. Acta Haematol. 25(1):71-79.

510. Bransby, E. R. 1954. The nutrition of male industrial workers with particular reference to intake and expenditure of calories. Brit. J. Nutrition 8(2):100-111.

511. Branster, M. V., and R. K. Morton. 1956. Comparative rates of synthesis of diphosphopyridine nucleotide by normal and tumour tissue from mouse mammary gland: Studies with isolated nuclei. Biochem. J. 63(4):640-646.

512. Brassard, J. A. 1964. Splenic hematopoiesis in male mice. (Mus musculus). Dissertation Abstr. 25(4):2460-2461.

513. Brattsand, R., and L. Harthon. 1971. Absorption and excretion of radioactive pentaerythritoltetranicotinate, mesoinositol-hexanicotinate and nicotinic acid after oral administration to cat. Arzneim. Forsch. 21(9):1335-1338.

514. Brattsand, R., and L. Lundholm. 1971. The effect of nicotinic acid and pentaerythritoltetranicotinate upon experimental atherosclerosis in the rabbit. Atherosclerosis 14(1):91-105.

515. Brattsand, R., T. Ekeli, E. Lindstrom, and L. Lundholm. 1971. Effect of nicotinic acid on postprandial hyperlipemia and lipoprotein lipase activity in the rat. Metab. Eff. Nicotinic Acid Its Deriv., Pro 1971:525-532.

516. Braun, K. 1949. Effect of 3-acetylpyridine and nicotinamide on the perfused heart. J. Pharmacol. Exptl. Therap. 95:58-61.

517. Braun, K., and N. Grossowicz. 1947. Excretion of nicotinic acid in typhoid. Arch. Int. Med. 80:637-643.

518. Braunsteiner, H., S. Sailer, and W. Weippl. 1959. On the influence of nicotinic acid and heparin on iron metabolism. Blut 5: 149-154.

519. Braverman, L. E., R. A. Arky, A. E. Foster, and S. H. Ingbar. 1969. Effect of physiological variations in free fatty acid concentration on the binding of thyroxine in the serum of euthyroid and thyrotoxic subjects. J. Clin. Invest. 48(5): 878-884.

* 520. Brazda, F. G., and R. A. Coulson. 1946. Toxicity of nicotinic acid and some of its derivatives. Proc. Soc. Exptl. Biol. and Med. 62(1):19-20.

521. Brazil, P., and A. P. Friedman. 1957. Further observations in craniovascular studies. Neurology 7(1):52-55.

522. Bremener, S. M., I. Y. A. Virin, E. I. Zubkova, and K. P. Rogova. 1965. Metabolism of vitamins B6, B12, C, PP and pantothenic acid in patients with gastric cancer. Vop. Onkol. 11(12):21-24.

523. Bremener, S. M., V. A. Alferova, A. S. Pipko, K. P. Rogova, and R. Ya. Seletskaya. 1964. Effects of some antibiotics on the vitamins B6, B12, PP, and C in patients with chronic cholecystiti. Antibiotiki 9(7):661-667.

524. Bremener, S. M., V. A. Alferova, G. N. Zgurskaya, E. I. Zubkova, A. S. Piko, and K. P. Rogova. 1967. Changes in metabolism of vitamins B6, B12, PP, C, and pantothenic acid in patients with chronic colitis of various etiology treated with tetracycline. Antibiotiki 12(4):343-347.

525. Brenner, G. 1970. Influence of xanthinol nicotinate on hyperlactacidemia induced by adrenaline and noradrenaline. Arzneim.-Forsch. 20(12):1860-1862.

526. Brenner, G. 1971. Effect of xanthinol nicotinate on the blood sugar level and free fatty acods of rats. Arzneim.-Forsch. 21(8):1179-1183.

527. Brenner, G., and H. Trautmann. 1969. Influence of xanthinol nicotinate on detoxification processes in the liver. Experimental study on the model of hexobarbital narcosis in the rat. Arzneim.-Forsch. 19(12):1974-1978.

528. Brenner, S., S. G. Dunlop, and V. O. Wodicka. 1948. Effect of fortification of canned bread on stability. Cereal Chem. 25(6):367-376.

529. Brenner, S., V. O. Wadicka, and S. C. Dunlop. 1949. Experimentation with dried yeast for use in army rations. J. Am. Dietetic Assoc. 25(5):409-415.

530. Bressani, R., and D. A. Navarrete. 1959. Niacin content of coffee in Central America. Food Research 24:344-351.

531. Bressani, R., L. G. Ellas, and J. E. Braham. 1968. Amino acid supplementation of corn and "tortilla." Arch. Latinoamer. Nutr. 18(2):123-134.

532. Bressani, R., R. Gomez-Brenes, and R. Conde. 1962. Changes in the chemical composition of the coffee bean and pulp during the roasting process, and the biological activity of niacin in the coffee. Arch. Venezolanos Nutr. 12(1):93-105.

533. Bressani, R., R. Gomez-Brenes, and N. S. Scrimshaw. 1961. Effect of processing on distribution and in vitro availability of niacin of corn (Zea mays). Food Technol. 15:450-454.

534. Bressani, R., D. Fiester, D. A. Navarrete, and N. S. Scrimshaw. 1961. Effect of processing method and variety on niacin and other extract content of green and roasted coffee. Food Technol. 15:306-308.

535. Bridges, J. M. 1960. The influence of dietary depletion of thiamine, riboflavine, and niacin on the induction of gliomata in mice. Brit. J. Exptl. Pathol. 41:169-175.

536. Bridges, J. M., A. M. Dalby, D. R. Hadden, H. A. Johnston, and J. A. Weaver. 1967. The effect of in vivo alteration of free fatty acids on platelet stickiness. J. Atheroscler. Res. 7(5): 695-699.

537. Briggs, A. P. 1941. Excretion of nicotinic acid in pellagra. Proc. Soc. Expti. Biol. Med. 46:374-378.

538. Briggs, A. P., S. A. Singal, and V. P. Sydenstricker. 1945. A study of nicotinic acid restriction in man. J. Nutrition 29(5):331-339.

539. Briggs, G. M. 1945. Influence of gelatin and tryptophane on nicotinic acid requirement of chicks. J. Biol. Chem. 161:749-750.

540. Briggs, G. M., and F. S. Daft. 1955. Water-soluble vitamins, I. Vitamin B12, folic acid, choline, and p-aminobenzoic acid. Ann. Rev. Biochem. 24:339-392.

541. Briggs, G. M., Jr., R. C. Mills, C. A. Elvehjem, and E. B. Hart. 1942. Nicotinic acid in chick nutrition. Proc. Soc. Expti. Biol. Med. 51:59-61.

542. Briggs, M. H., 1960. Vitamin and coenzyme content of hepatomas induced by butter yellow. Nature 187:249-250.

543. Briggs, M. H., T. W. Heard, A. Whitecroft, and M. L. Hogg. 1964. Urea-fed cattle. I. Chemical and microbiological properties of rumen fluid. Life Sci. 3(1):7-10.

544. Brink, N. E. 1953. II. Inhibition studies with compounds related to the coenzyme. Acta Scand. 1953:1090-1097.

545. Brisou, J., R. Baronnet, and J. Caussain. 1972. Bacterial degradation of nicotinamide. Pharmacological interest. J. Pharmacol. 3(3):351-354.

546. Broch, E., A. Gaudiano, and G. Petti. 1970. Effects of high doses of vitamins on experimental hepatic necrosis. Acta Vitaminol. Enzymol. 24(4/5):123-126.

547. Broch, E., A. Gaudiano, G. Petti, M. Bucci, and E. Vittori-Antisari. 1970. Effects of high doses of vitamins on experimental hepatic necrosis. Acta Vitaminol. Enzymol. 24(4-5):123-126.

548. Brodie, B. B., G. Krishna, and Hynie. 1969. Role of adenyl cyclase in the regulation of lipolysis in fasting. Biochem. Pharmacol. 18(5):1129-1134.

549. Brody, J. S., and R. F. Coburn. 1969. Carbon monoxide-induced arterial hypoxemia. Science 164(3885):1297-1298.

550. Brogioni, M. 1956. Carotenoids in wheat meal and in alimentary pastes. I. Carotenoid content of various types of Italian meals. Chimica 12:257-259.

551. Broomberg, M. M., and E. A. Bromberg. 1967. Therapeutic restorative. Brit. Pat. 1,068,546.

552. Broome, A., et al. 1967. The effect of nicotinic acid on muscle blood flow in intermittent claudication measured with xenon-133 clearance method. Scand. J. Clin. Lab. Invest. 19 (Suppl. 99):233+.

553. Brouet, G., et al. 1963. Course of the blood nicotinamide in tuberculotics treated by chemotherapy. Rev. Tuberc. (Paris) 27:871-880.

554. Brown, B. R., N. Yess, J. M. Price, H. Linkswiler, P. Swan, and L. V. Hankes. 1965. Vitamin B6 depletion in man urinary excretion of quinolinic acid and niacin metabolites. J. Nutr. 87(4):419-423.

555. Brown, D. W. 1954. Treatment of cerebral fat embolism. Dis. Nervous System. 15(10):307-311.

556. Brown, E. B., J. M. Thomas, and A. F. Bina. 1942. The nature of the interfering chromogens encountered in the determination of nicotinic acid in cereal products. Cereal Chem. 19:447-457.

557. Brown, E. B., J. M. Thomas, and A. F. Bina. 1943. The use of oxidizing agents in the removal of interfering compounds in the determination of nicotinic acid. Cereal Chem. 20(2): 201-211.

558. Brown, E. B., J. M. Thomas, and A. F. Bina. 1946. Nicotinic acid values by chemical and microbiological methods. Effect of hydrogen peroxide and infra-red rays on nicotinic acid. J. Biol. Chem. 162:221-228.

559. Brown, F. C. 1964. Nicotinamide adenine dinucleotide levels in rat brain. Canad. J. Biochem. 42:489-492.

560. Brown, G. M., et al. 1956. Symposium on vitamin metabolism. Proceedings of a symposium held under the auspices of the University of Texas and the National Vitamin Foundation, Incorporated. Nutrition Congr. Ser. No. 13. ii+118 p.

561. Brown, J. H.UU., A. Anason, and J. Jacobs. 1957. In vitro metabolism of hydrocortisone in tissues of the adult rat. Am. J. Physiol. 190:259-264.

562. Brown, L. R., Jr., L. W. Wachtel, and M. G. Wheatcroft. 1962. Diffusion of niacin through extracted human teeth and its effect on bacterial penetration into dentin. J. Dental Res. 41:684-694.

563. Brown, R. R., J. M. Price, S. W. Burney, and G. H. Friedell. 1970. Lack of effect of smoking on the excretion of tryptophan metabolites by man. Cancer Res. 30(3):611-614.

564. Brown, R. R., D. P. Rose, J. M. Price, and H. Wolf. 1969. Tryptophan metabolism as affected by anovulatory agents. Ann. N. Y. Acad. Sci. 166(Art. 1):44-56.

565. Brown, R. V. 1969. Vitamin deficiency and voluntary alcohol consumption in mice. Quart. J. Stud. Alc., Part A 30(3):592-597

566. Brox, D., and O. Selvaag. 1967. The effect of erythritol tetranicotinate on serum cholesterol levels in man. Acta Med. Scand. 182(4):437-444.

567. Bruchhausen, F. v. 1964. The mechanism of hyperglycemia in 6-aminonicotinamide poisoning in the rat. Proceedings of the German Pharmacological Society, 28th Session, Bad Nauheim, 5-8 October, 1964. Arch. Exp. Pathol. Pharmakol. (Naunyn Schmiedebergs) 250(2):241-242.

568. Bruchhausen, F. v., and H. Herken. 1966. Action of 6-aminonicotinamide on the insulin-dependent glucose absorption in epididymal adipose tissue. Arch. Pharmakol. Expti. Pathol. 254(4):388-400.

569. Brueggemann, J., G. Drepper, and U. Hadeler. 1952a. Studies of nicotinic acid metabolism. I. Estimation of nicotinic acid in the presence of nicotinamide. Biochem. Zeitschr. 322:418-425.

570. Brueggemann, J., G. Drepper, and U. Hadeler. 1952b. Studies of nicotinic acid metabolism. II. Metabolic relations between nicotinic acid, nicotinamide, and their N-methyl derivatives by in vitro experiments with rabbit and rat liver and with P. vulgaris. Biochem. Zeitschr. 322:426-438.

571. Brummer, P., T. K. Markkanen, and J. L. Kalliomaki. 1961. Effect of corticosteroids on urinary excretion and on the intestinal absorption of thiamine, riboflavine, nicotinic acid, pantothenic acid, and biotin. Acta Med. Scand. 170:183-186.

572. Brunnemann, A., and H. Coper. 1965. Hydrolysis of NAD(P) and biosynthesis of 3-APAD(P) by the brain microsomes of several species of animals. Naunyn-Schmiedebergs Arch. Pharmakol. Expti. Pathol. 250(4):469-478.

* 573. Brunink, H., and E. J. Wessels. 1972. The determination of nicotinic acid by fluorimetric densitometry. Analyst 97(1153): 258-259.

574. Brunish, V. H., H. B. McWilliams, G. D. Mason, A. D. Adams, Jr., and B. H. Ershoff. 1947. Effects of vitamin imbalance under conditions of ad libitum feeding and reduced caloric intake. Am. J. Physiol. 150(4):551-557.

575. Brus, R. 1963. Influence of nicotinic, nicotinuric and 3-puridylacetic acid on experimental atherosclerosis in white rats. In: 2nd International Pharmacological Meeting, Prague, 1962. Biochem. Pharmacol. 12(Suppl.):146.

576. Brus, R. 1966. Effect of nicotinic acid and its derivatives on arteriosclerosis. Postepy Hig. Med. Doswiadczalnej 20(1): 17-30.

577. Brus, R. 1967a. The influence of nicotinic acid and its derivatives on experimental atherosclerosis. Diss. Pharm. Pharmacol. 19(1):25-36.

578. Brus, R. 1967b. The influence of nicotinic acid and its derivatives on experimental hyperlipemia. Diss. Pharm. Pharmacol. 19(1):37-41.

579. Brusco, O. I., M. A. Oriozabala, A. M. De Ramella, R. Arakaki, and D. Stamboulian. 1968. Normal lipidemia in newborn infants. Dietologia 23(89):18,20,22.

580. Bryant, R., F. J. Burger, R. L. Henry, and F. B. Trenk. 1971. Semiautomated, simultaneous assay of thiamine, riboflavin, pyridoxine, and niacinamide in multivitamin preparations. J. Pharmaceutical Sciences 60(11):1717-1720.

581. Bryson, M. J., L. T. Samuels, and H. C. Goldthorpe. 1950. The metabolism of testosterone by liver tissue of niacin, tryptophan or thiamine deficient rats. Endocrinology 47(2): 89-96.

582. Buch, L., D. Streeter, R. M. Halpern, L. N. Simon, M. G. Stout, and R. A. Smith. 1972. Inhibition of transfer ribonucleic acid methylase activity from several human tumors by nicotinamide and nicotinamide analogs. Biochemistry 11(3):393-397.

583. Buchel, L., and J. Levy. 1962. Central action of nicotinamide. Therapie 17(2):277-286.

584. Budesinsky, Z., and E. Zikmund. 1963. Oral antidiabetics. Pharmacotherap., 1950-59 1963:31-48.

585. Budillon, G., A. Alifano, M. N. Gadaleta, and M. Coltorti. 1962. Metabolism of tryptophan, nicotinic acid in mice with leukemia. I. Action of 3-hydroxyanthranilic oxygenase. Boll. Soc. Ital. Biol. Sper. 38:1384-1385.

586. Buhler, D. R., and M. Rasmusson. 1968. The oxidation of drugs by fishes. Comp. Biochem. Physiol. 25(1):223-239.

587. Bull, H. B., and J. S. Gray. 1945. Secretion of HCl by the stomach. Gastroenterology 4:175-182.

588. Bulovskaia, L. N., S. A. Dmitrieva, A. M. Petrun'kina, L. I. Sillina. 1959. On the effect of nicotinic acid load on the content of total nicotinic acid in the blood in man. Tr. Inst. Fiziol. Pavlov 8:515-519.

589. Burch, H. B., C. A. Storvick, R. L. Bicknell, H. C. Kung, L. G. Alejo, W. A. Everhart, O. H. Lowry, C. G. King, and O. A. Bessey. 1955. J. Biol. Chem. 212(2):897-907.

590. Burchenal, J. H. 1962. Chemotherapy of leukemia. Proc. Intern. Congr. Hematol., 8th, Tokyo, 1960 1:457-461.

591. Burkard, W. P., H. Lengsfeld, and K. F. Gey. 1971a. Cyclic adenosine 3',5'-monophosphate and adenylcyclase in liver, adipose tissue, and brain of rats treated with beta-pyridylcarbinol or nicotinic acid. Metab. Eff. Nicotinic Acid its Deriv., Pro 1971:379-386.

592. Burkard, W. P., H. Lengsfeld, and K. F. Gey. 1971b. Cyclic adenosine 3',5'-monophosphate and adenylcyclase in liver, adipose tissue, and brain of rats treated with beta-pyridylcarbinol. Biochem. Pharmacol. 20(1):23-28.

593. Burke, J. C., and A. R. McIntyre. 1939. Nicotinic acid and the vitamin B complex in insulin tolerance. J. Pharmacol. 67:142-146.

594. Burkholder, P. R., and I. McVeigh. 1942. Synthesis of vitamins by intestinal bacteria. Proc. Natl. Acad. Sci. U. S. 28:285-289

595. Burnet-Merlin, J. G., B. Goldstein, I. I. Lieber, A. Herskowicz, J. C. Galeano, and J. Steinman. 1966. New interpretation of the mechanism of action of vasodilator drugs on peripheral vascular diseases. Semana Med. (Buenos Aires) 128(9):362-364.

596. Burns, J. J., and A. H. Conney. 1960. Water-soluble vitamins. I. Ascorbic acid, nicotinic acid, vitamin B6, biotin, and inositol. Ann. Rev. Biochem. 29:413-436.

597. Burns, M. J., and K. S. Self. 1969. Effects of cystine, niacin, and taurine on cholesterol and bile acid metabolism. Metab., Clin. Exp. 18(5):427-432.

598. Burroughs, W., B. H. Edgington, W. L. Robinson, and R. M. Bethke. 1950. Niacin deficiency and enteritis in growing pigs. J. Nutrition 41:51-62.

599. Burstein, J., and A. Teikka. 1962. Effect of nicotinic acid and magnesium nicotinate on cholesterol-induced atherosclerosis in cockerels. Acta Pathol. Microbiol. Scand. 56:261-265.

600. Burton, R. M. 1957. Pyridine nucleotide and diphoshopyridine nucleotidase levels of the brain of young rats. J. Neurochem. 2:15-20.

601. Burton, R. M. 1960. Alteration of tissue pyridine nucleotide levels and the central nervous system. Inhibition Nervous System Gamma-Aminobutyric Acid, Proc. Intern. Symp., Duarte, Calif. 1959:249-259.

* 602. Burton, R. M., R. A. Salvador, A. Goldin, and S. R. Humphreys. 1960. Interaction of nicotinamide with reserpine and chlorpromazine. II. Some effects on the central nervous system of the mouse. Arch. Intern. Pharmacodynamie 128:253-259.

603. Burton, R. M., R. A. Salvador, K. Smith, and R. E. Howard. 1962. Effect of chlorpromazine, nicotinamide, and nicotinic acid on pyridine nucleotide levels of human blood. Ann. N. Y. Acad. Sci. 96:185-189.

604. Burton, R. M., N. O. Kaplan, A. Goldin, M. Leitenberg, and S. R. Humphreys. 1960. Interaction of nicotinamide with reserpine and chlorpromazine. III. Some effects on the diphosphopyridine nucleotide content in liver. Arch. Int. Pharmacodyn. 123:260-275.

605. Burton, R. M., N. O. Kaplan, A. Goldin, M. Leitenberg, S. R. Humphreys, and M. A. Sodd. 1958. Effect of reserpine and promazine on diphosphopyridine nucleotide synthesis in liver. Science 127:30-32.

606. Bur'yan, N. I., L. V. Tyurina, and I. G. Maksimova. 1967. Effect of the method of juice preparation on the content of B vitamins. Vinodel. Vinograd. SSSR 27(8):4-7.

607. Buscaino, G. A. 1955. Results of cases treated with a preparation of iodine and of nicotinic acid given subarachnoidally. VII. Acta Neurol. (Naples) 10(3):304-311.

608. Buscaino, G. A., and A. Rapisarda. 1948. alpha-Ketoglutaric acid in the blood of patients with dementia praecox. Its changes after administration of nicotinic acid and nicotinamide. Acta Neurol. (Naples) 3:251-270.

609. Buscaino, G. A., V. Spadetta, and A. Carella. 1965. Methylation of nicotinamide in schizophrenics: In vitro experiments. Acta Neurol. (Naples) 20(4):453-455.

610. Businco, L. 1940. Antihistamine and antiacetylcholine action of nicotinamide on isolated guinea pig intestine. Boll. Soc. Ital. Biol. Sper. 15:826-827.

611. Businco, L. 1941. Influence of nicotinamide on the action of histaminase on histamine. Boll. Soc. Ital. Biol. Sper. 16: 497-499.

612. Butcher, F. R., and G. S. Serif. 1967. Pyridine nucleotides. III. Response of dog thyroid pyridine nucleotide to hormonal control. Biochim. Biophys. Acta 141(1):8-18.

613. Butcher, R. W. 1971. Effects of nicotinic acid on cyclic AMP levels in rat adipose tissue. Metab. Eff. Nicotinic Acid Its Deriv., Pro 1971:347-355.

614. Butcher, R. W., and C. E. Baird. 1969. Regulation of cyclic AMP and lipolysis in adipose tissue by hormones and other agents. Advan. Exp. Med. Biol. 4:5-23.

615. Butcher, R. W., and L. A. Carlson. 1970. Effects of secretion on fat mobilizing lipolysis and cyclic AMP levels in rat adipose tissue. Acta Physiol. Scand. 79(4):559-563.

616. Butcher, R. W., C. E. Baird, and E. W. Sutherland. 1968. Effects of lipolytic and antilipolytic substances on adenosine 3',5'-monophosphate levels in isolated fat cells. J. Biol. Chem. 243(8):1705-1712.

617. Butler, R. E., and H. P. Sarett. 1948. The effect of isocaloric substitution of alcohol for dietary carbohydrate upon the excretion of B vitamins in man. J. Nutrition 35(5):539-548.

618. Butturini, U. 1946. Antihistaminic and antiallergic action of nicotinamide. Giorn. Clin. Med. 27:681-701.

619. Butturini, U. 1967. Relations between glycolipid metabolism, blood insulin levels, and diabetes mellitus of obese subjects. Minerva Med. 58(24):1007-1009.

620. Buyske, D. A., J. M. Flowers, Jr., P. Wilder, Jr., and M. E. Hobbs. 1956. Nicotinic and glutamic acids, nicotinamide, and glutamine in cigaret-tobacco smoke. Science 124:1080-1081.

621. Buziassy, C., and D. E. Tribe. 1960. The synthesis of vitamins in the rumen of sheep. II. Levels of thiamine, riboflavin, and nicotinic acid in the rumen of grazing lambs. Australian J. Agric. Res. 2(6):1002-1008.

622. Buzina, R., M. Jusic, A. Brodarec, N. Milanovic, G. Brubacher, J. P. Vuilleumier, O. Wiss, and S. Christeller. 1971. The assessment of dietary vitamin intake of 24 Istrian farmers. 2. Comparison between the dietary intake and biochemical status of ascorbic acid, vitamine A, thiamine, riboflavin and niacin. International J. for Vitamin and Nutrition Research 41(3): 289-300.

623. Bykov, S. T. 1972. Effect of beta-naphthol on the level of nicotinic acid and its metabolites in the blood, liver, and urine and tryptophan in the blood serum of animals. Farmakol. Toksikol. (Moscow) 34(6):731-734.

624. Bylicki, A. 1955. Separation of pyridinecarboxylic acids from the coal tar pyridine bases. III. Roczniki Chem. 29:791-802.

625. Bylicki, A. 1963. Physicochemical study of pyridine and quinoline bases obtained from coal coking products, and preparation of nicotinic acids from these bases. Przemysl Chem. 42(12):707-711.

626. Byshevskii, A. Sh. 1963. Fibrinolysis in white rats under the influence of nicotinic acid. Vrachebnoe Delo 1963(9):149-150.

627. Byshevskii, A. Sh. 1964. Vitamin A and nicotinic acid effects on some aspects of the blood anticoagulating system in experimental hypercholesteremia. Vopr. Pitaniya 23(5):33-40.

628. Byshevskii, A. Sh. 1966. Effect of nicotinic acid and vitamins A, B12, and E on the lysis of intravascular thrombi. Vrachebnoe Delo 1966(1):38-40.

629. Byshevskii, A. Sh. 1968. Effect of some vitamins on the blood anticoagulation system. Vop. Pitan. 27(5):17-22.

630. Cagovec, R. V., and E. V. Lahno. 1970. Some aspects of the metabolism of nicotinic acid. Vitaminy v Eksperim. i Klinike. Resp. Mezved. Sb. 1970(2):12-17.

631. Cagovec, R. V., A. G. Halmuradov, and S. I. Susevic. 1968. Changes in activity of liver NAD-ase in rats given excess nicotinic acid, 3-methylpyridine and nicotinamide. Dokl. Akad. Nauk SSSR 181:245-247.

632. Cailleau, R. 1949. Cheeses and wines as sources of vitamins B. Bull. Acad. Med. (Paris) 133:204-206.

633. Cailleau, R., J. Adrain, and J. Levy. 1949. The riboflavin, niacin and pantothenic acid content of different types of cheese. Ann. Agron. (Paris) 19(3):443-447.

634. Cajthamlova, H., T. Bednarik, V. Chudomel, and D. Zmeskalova. 1968. Perfusion of the rabbit spleen in vitro. Cesk Fysiol. 17(6):585-588.

635. Calabro, Q., and R. Savini. 1948. Influence of nicotinic acid and riboflavin on metrazole shock. Boll. Soc. Ital. Biol. Sper. 24:823-824.

636. Calcutt, G., S. M. Ting, and A. W. Preece. 1970. Tissue NAD levels and the response to irradiation or cytotoxic drugs. Brit J. Cancer 24(2):380-388.

637. Calder, R. M. 1947. Effect of nicotinic acid on myocardial systole, coronary flow, and arrhythmias of the isolated heart. Proc. Soc. Expti. Biol. and Med. 65(1):76-83.

638. Calder, R. M. 1948. Effect of nicotinic acid on anoxia in rats. Proc. Soc. Expti. Biol. and Med. 68(3):642-646.

639. Calder, R. M., and G. P. Kerby. 1940. The effect of nicotinic acid on blood coagulation. Am. J. Med. Sci. 200:590-596.

640. Caley, R. M., and R. G. Jensen. 1973. Effects of parathion on lipolysis in isolated rat adipose tissue cells. Lipids 8(1): 43-44.

641. Calhoun, W. K., F. N. Hepburn, and W. B. Bradley. 1960. The distribution of the vitamins of wheat in commercial mill products. Cereal Chem. 37:755-761.

642. Cali, G., and G. Lomeo. 1953. Sodium nicotinate and endogenous creatinine clearance. Riforma med. 67:655-658.

* 643. Cali, G., E. Florentino, and C. Pietropaolo. 1966. The effect of nicotinic acid on serum lipids in normal subjects. Clin. Chim. Acta 13(4):427-430.

644. Cali, G., G. Lomeo, and L. Nasti. 1953. Effect of nicotinic acid on the oxygen desaturation in venous stasis. Riforma Med. 67:967-971.

645. Cali, G., G. Lomeo, and S. Semeraro. 1953. Action of nicotinic acid in arteriovenous anastomosis. Riforma Med. 67:1045-1046.

646. Cali, G., C. Pietropaolo, and G. Lococo. 1964. Influence of substances with a pyridine nucleus on the sideremia and bilirubinemia levels. Boll. Soc. Ital. Cardiol. 9(4):328-333.

647. Cali, G., E. Fiorentino, A. Centonze, and C. Pietropaolo. 1966. Carbohydrate metabolism after nicotinic acid administration. Boll. Soc. Ital. Biol. Sper. 42(19):1297-1301.

648. Callison, E. C., E. Orent-Keiles, and R. U. Makower. 1951. The effect of some combinations of human foods on the growth and health of the laboratory rat. J. Nutrition 43(1):131-152.

649. Calloway, D. H., E. R. Cole, and H. Spector. 1957. Nutritive value of irradiated turkey. I. Growth-promoting quality and biological value. J. Am. Dietet. Assoc. 33:1027-1029.

650. Calvery, H. O., J. H. Draize, and E. P. Lang. 1946. Metabolism and permeability of normal skin. Physiol. Rev. 26:495-540.

651. Calvet, F., and J. Bozal. 1958. Inhibition of tryptic digestion by certain drugs. Rev. Espan. Fisiol. 14:249-262.

652. Calvo, J. M., C. Boehme, and J. Goeminne. Rev. Med. y Alimentacion 8(4/5/6):88-94.

653. Cameron, E. J., R. W. Pilcher, and L. E. Clifeorn. 1949. Nutrient retention during canned food production. Am. J. Publ. Health 39(6):756-763.

654. Cameron, J. W., and H. J. Teas. 1948. Relation between nicotinic acid and carbohydrates in a series of maize endosperm genotypes. Proc. Natl. Acad. Sci. U.S. 34:390-398.

655. Cammisa, M., C. Cicconetti, and E. Ciavenzani. 1960. Observations on the behavior of the mucosal secretion of the colon of irradiated animals treated with vitamins of the B group. Note 4, Vitamin PP. Policlinico (Med) 67:177-181.

656. Campbell, J. A. 1964. Dietary factors affecting vitamin requirements. Proc. Nutr. Soc. 23:31-38.

657. Campbell, J. A., and A. B. Morrison. 1963. Factors affecting the absorption of vitamins. Am. J. Clin. Nutr. 12:162-169.

658. Campbell, J., and W. G. Tubb. 1950. Stability of ascorbic acid in solution. Can. J. Research 28E:19-32.

659. Campese, V. M., and D. Mitolo-Chieppa. 1968. Structure-activity relation of the vasorelaxant activity of nicotine studied by functional group analysis. Boll. Soc. Ital. Biol. Sper. 44(23):2112-2114.

660. Canali, G. 1949. Urinary elimination of nicotinic acid and of trigonelline after administration of caffeine and of sodium cacodylate. Boll. Soc. Ital. Biol. Sper. 25:1121-1122.

661. Cannon, M. D., G. J. Mannering, C. A. Elvehjem, and E. H. Bart. 1946. Inadequacy of certain natural diets for guinea pigs. Proc. Soc. Exptl. Biol. Med. 63:414-417.

662. Cantoni, C., R. Benatti, and V. L'Acqua. 1972. The amounts of nitrate and nitrite salts and of ascorbic acid in dry salami during seasoning and the presence of the same substances in heat-treated canned meats. Arch. Vet. Ital. 23(1):33-57.

663. Cantoni, G. L. 1951. Methylation of nicotinamide with a soluble enzyme system from rat liver. J. Biol. Chem. 189:203-216.

664. Caplan, A. 1970. Effects of the nicotinamide-sensitive teratogen 3-acetylpyridine on chick limb cells in culture. Exp. Cell. Res. 62(2-3):341-355.

665. Caplan, A. I. 1971. Teratogenic action of the nicotinamide analogs 3-acetylpyridine and 6-aminonicotinamide on developing chick embryos. J. Exp. Zool. 178(3):351-357.

666. Caplan, A. I. 1972a. Effects of a nicotinamide-sensitive teratogen, 6-aminonicotinamide, on chick limb cells in culture. Exp. Cell Res. 70(1):185-195.

667. Caplan, A. I. 1972b. The site and sequence of action of 6-aminonicotinamide in causing bone malformations of embryonic chick limb and its relationship to normal development. Dev. Biol. 28(1):71-83.

668. Caplan, A. I. 1972c. Comparison of the capacity of nicotinamide and nicotinic acid to relieve the effects of muscle and cartilage teratogens in developing chick embryos. Nicotinamide (I) Develop. Biol. 28(2):344-351.

669. Caplan, A. I., E. Zwilling, and N. Kaplan. 1968. 3-Acetylpyridine effects in vitro related to teratogenic activity in chicken embryos. Science 160(3831):1009-1010.

670. Capobianco, A., G. De Franciscis, and P. Polosa. 1953. Changes in the osmotic resistance of blood corpuscles. Experiments in vitro. I. Action of vitamins C and K1. Boll. soc. ital. biol. Sper. 29:1796-1798.

671. Cappiello, J., and C. Balacco-Gabrieli. 1970. The visual field after administration of nicotinamide. Acta Neurol. (Naples) 25(4):457-461.

672. Carbajal, C. A. P. 1947. A new spectrophotometric method for the determination of nicotinic acid (the antipellagra factor). Bol. Soc. Quim. Peru 13:172-198.

673. Cardin, A. 1940. Action of nicotinic acid on smooth muscle. Boll. Soc. Ital. Biol. Sper. 15:309-310.

674. Careddu, P., L. Mainardi, and L. T. Tenconi. 1964. Excretion of metabolites of the tryptophan-nicotinic acid chain in infants. Acta Vitaminol. 18:241-248.

675. Careddu, P., L. Mainardi, and L. T. Tenconi. 1966. Tryptophan metabolism via nicotinic acid in children with febril convulsions. Acta Vitaminol. 20(4):135-142.

676. Carlson, L. A. 1963. Effect of nicotinic acid- and catechol amine-stimulated lipolysis in adipose tissue in vitro. Acta Med. Scand. 173(6):719-722.

677. Carlson, L. A. 1966. Determination of free nicotinic acid in (human) blood plasma. Clin. Chim. Acta 13(3):349-351.

678. Carlson, L. A. 1967a. Cardiovascular and metabolic effects of prostaglandins. Progr. Biochem. Pharmacol. 3:94-109.

679. Carlson, L. A. 1967b. Consequences of inhibition of normal and excessive lipid mobilization. Studies with nicotinic acid. In: 2nd Internation Symposium on drugs affecting lipid metabolism, 1965, Milan, Italy, Part II, S. Karger: Basel, Switz. and New York. Progr. Biochem. Pharmacol. 3:151-166.

680. Carlson, L. A. 1969. Supply of free fatty acids and metabolic abnormalities in diabetes mellitus. Diabetes, Proc. Congr. Int. Diabetes Fed., 6th 1967:343-349.

681. Carlson, L. A. 1969. Effect of nicotinic acid treatment on the chemical composition of plasma lipoprotein classes in man. Advan. Exp. Med. Biol. 4:327-338.

682. Carlson, L. A. 1971. Nicotinic acid. Its metabolism and its effects on plasma free fatty acids. Metab. Eff. Nicotinic Acid Its Deriv., Pro 1971:157-165.

683. Carlson, L. A., and S. O. Liljedahl. 1963. Lipid metabolism and trauma. II. Studies on the effect of nicotinic acid on norepinephrine-induced fatty liver. Acta Med. Scand. 173(6): 787-791.

684. Carlson, L. A., and H. Michell. 1970. Characteristics of lipolysis in dog adipose tissue. Acta Physiol. Scand. 79(2): 145-152.

* 685. Carlson, L. A., and E. R. Nye. 1966. Acute effects of nicotinic acid in the rat. I. Plasma and liver lipids and blood glucose. Acta Med. Scand. 179(4):453-461.

686. Carlson, L. A., and L. Oro. 1962. The effect of nicotinic acid on the plasma free fatty acids. Demonstration of a metabolic type of sympathicolysis. Acta Med. Scand. 172:641-645.

687. Carlson, L. A., and L. Oro. 1965. Persistence of the inhibitory effect of nicotinic acid on catecholamine-stimulated lipid mobilization during prolonged treatment with nicotinic acid. J. Atherosclerosis Res. 5(4):436-439.

688. Carlson, L. A., and L. Oro. 1969. Acute effect of a sustained release pyridyl carbinol preparation, Ronicol retard, on plasma free fatty acids. Acta Med. Scand. 186(5):337-347.

689. Carlson, L. A., and J. Ostman. 1965a. Inhibition of the metabolism of free fatty acids from adipose tissue in diabetes. I. Effect of nicotinic acid on the alloxan-diabetic state in rats. Acta Med. Scand. 177(5):631-637.

690. Carlson, L. A., and J. Ostman. 1965b. Inhibition of the mobilization of free fatty acids from adipose tissue in diabetes. II. Effect of nicotinic acid and acetyl-salicylate on blood glucose in human diabetics. Acta Med. Scand. 178(1):71-79.

691. Carlson, L. A., and J. Ostman. 1966. Plasma beta-hydroxybutyric acid response to nicotinic acid-induced plasma free fatty acid decrease in man. Diabetologia 2(2):127-129.

692. Carlson, L. A., and G. Walldius. 1972. Serum and tissue lipid metabolism and effect of nicotinic acid in different types of hyperlipidemia. Advan. Exp. Med. Biol. 26:165-178.

693. Carlson, L. A., S. O. Froberg, and E. R. Nye. 1966. Nicotinic acid in the rat. II. Acute effects of nicotinic acid on plasma, liver, heart, and muscle lipids. Acta Med. Scand. 180(5):571-579.

694. Carlson, L. A., L. Levi, and L. Oro. 1968. Plasma lipids and urinary excretion of catecholamines in man during experimentally induced emotional stress, and their modification by nicotinic acid. J. Clin. Invest. 47(8):1795-1805.

695. Carlson, L. A., L. Oro, and J. Ostman. 1968a. Effect of nicotinic acid on plasma lipids in patients with hyperlipoproteinemia during the first week of treatment. J. Atheroscler. Res. 8(4):667-677.

* 696. Carlson, L. A., L. Oro, and J. Ostman. 1968b. Effect of a single dose of nicotinic acid on plasma lipids in patients with hyperlipoproteinemia. Acta Med. Scand. 183(5):457-465.

697. Carlson, L. A., U. Freyschuss, J. Kjellberg, and J. Ostman. 1967. Suppression of splanchnic ketone body production in man by nicotinic acid. Diabetologia 3(6):494-499.

698. Carlson, L. A., R. J. Havel, L. G. Ekelund, and A. Holmgren. 1963. Effect of nicotinic acid on the turnover rate and oxidation of the free fatty acids of plasma in man during exercise. Metab., Clin. Exptl. 12:837-845.

699. Carlson, L. A., C. Hedbom, E. Helgstrand, B. Sjoberg, and N. E. Stjernstrom. 1969. Pyridines affecting FFA (free fatty acid) mobilization in vivo. Advan. Exp. Med. Biol. 4:85-92.

700. Carlson, L. A., C. Hedbom, E. Helgstrand, A. Misiorny, B. Sjoberg, and N. E. Stjernstrom. 1972. Potential hypolipidemic agents: I. Syntheses of esters related to 5-fluoro- and 5-chloronicotinic acid and the corresponding alcohols: Effects on noradrenaline-stimulated free fatty acid mobilization. Acta Pharm. Suec 9(3):221-228.

701. Carlstrom, S., and S. Laurell. 1968. The effect of nicotinic acid on the diurnal variation of the free fatty acids of plasma. Acta Med. Scand. 184:121-123.

702. Carlton, B. 1944. Vitamins in beer. Am. Brewer 77(12):22,39,40.

703. Carpenter, K. J., E. Kodicek, and P. W. Wilson. 1960. The availability of bound nicotinic acid to the rat. 3. The effect of boiling maize in water. Brit. J. Nutr. 14:25-34.

704. Carrara, G., and F. M. Chiancone. 1941. Mechanism of sulfonamide activity. III. Primary data on action with oxidoreductases. Chimica e Industria 23:435-436.

705. Carrara, G., and E. Testa. 1957. Pyridoxine hydrochloride and homologous compounds. Brit. Pat. 765,526.

706. Carrara, P. M. 1958. Action of nicotinic acid on the renal function of the rat. Minerva Med. Suppl. 1:1-3.

707. Carrick, C. W., J. W. West, S. M. Hauge, and E. T. Mortz. 1952. The tryptophan requirement of young chickens as influenced by niacin. Poultry Sci. 31:479-487.

708. Carruthers, C., and V. Suntzeff. 1946. Calcium, copper, and zinc in the epidermal carcinogenesis of mouse and man. Cancer Research 6:296-297.

709. Carruthers, C., and V. Suntzeff. 1952. Nicotinamide content of some normal and malignant tissues; the apparent absence of niacin in epidermis. Cancer Research 12:879-885.

710. Carter, C. W., and J. R. P. O'Brien. 1945. The nicotinic acid content of blood in health and disease. Quart. J. Med. 14:197-205.

711. Carter-Wallace, Inc. 1968. Antiinflammatory aspirin composition. Fr. Pat. M. 6335.

712. Cartwright, G. E., B. Tatting, and M. M. Wintrobe. 1948. Niacin deficiency anemia in swine. Arch. Biochem. 19:109-118.

713. Caruso, P., S. La Rocca, and C. Materia. 1957-58. Vitamins and levels of lysozyme, antistreptolysin and antistaphylosin in childhood. Atti Soc. Peloritana. 4(Suppl.):115-119.

714. Carvalho da Silva, A., and M. A. Pontes. 1957. Diphosphopyridine nucleotide, total body water, and blood volume in niacin-deficient cats. Rev. Hosp. Clin. Fac. Med.

715. Carvalho da Silva, A., R. Fried, and R. C. de Angelis. 1952. The domestic cat as a laboratory animal for experimental nutrition studies. 3. Niacin requirements and tryptophan metabolism. J. Nutrition 46:399-409.

716. Carvalho da Silva, A., R. C. De Angelis, M. A. Pontes, and M. F. Mansur Guerios. 1955. The domestic cat as a laboratory animal for experimental nutrition studies. IV. Folic acid deficiency. J. Nutrition 56(2):199-214.

717. Carvalho da Silva, A., A. M. Giesbrecht, M. A. Pontes, and R. C. de Angelis. 1963. The domestic cat as a laboratory animal for experimental nutrition studies. IX. The influence of thiamine, riboflavine, niacin, pyridoxine, and pantothenate deficiencies on blood pyruvate and lactate levels. Folia Clin. Biol. (Sao Paulo) 32(1):24-35.

718. Casasola, M., and B. Di Lenarda. 1962. Experiences with a new geriatric drug with circulatory effect. Ther. Gegenw. 101:73-74

719. Casassas, E., and J. Fuentes Duchemin. 1971. Photometric determination of nicotinic acid and nicotinamide by reaction with cyanogen bromide and 4,4'-diaminostilbene-2,2'-disulfonic acid. Inform. Quim. Anal. 25(5):159-166.

720. Casdorph, H. R. 1970. Treatment of the hyperlipidemic states with special emphasis on the place of cholestyramine in therapy. Angiology 21(10):654-660.

721. Casilli, L., T. Di Lella, and G. Rinaldi. 1958. Contents of riboflavine, calcium pantothenate, pyridoxine, nicotinic acid and vitamin B12 in meat and some components of the "fifth quarter" of buffalo calves reared on buffalo's milk or on cow's milk. Riv. Zootec. 41:478-484.

722. Caspe, S. 1957. Composition for decreasing blood sugar. U. S. Pat. 2,793.977.

723. Caspe, S., B. Davidson, and S. Marsh. 1952. Action of nicotinic acid on carbohydrate metabolism in diabetics. Am. J. Pharm. 124:98-103.

724. Castellano, M. A., J. L. Tortora, N. I. Germino, F. Rama, and C. Ohanian. 1973. The effects of isonicotinic acid hydrazide on the early chick embryo. J. Embryol. Exp. Morphol. 29(1):209-219.

725. Castiello, R. J., and P. J. Lynch. 1972. Pellagra and the carcinoid syndrome. Arch. Dermatol. 105(4):574-577.

726. Castro, J. A., and M. I. Diaz Gomez. 1972. Irreversible binding of carbon-14 tetrachloride to microsomal lipids in rats under varying experimental conditions. Toxicol. Appl. Pharmacol. 23(4):541-552.

727. Cattell, J., et al. 1947. Biological Symposia. Volume XII. Estimation of the vitamins. 531p. Jaques Cattell Press: Lancaster.

728. Causey, K., E. G. Andreassen, M. E. Hausrath, C. Along, P. E. Ramstad, and F. Fenton. 1950. Effect of thawing and cooking methods on palatability and nutritive value of frozen ground meat. I. Pork. II. Beef. III. Lamb. Food Res. 15(3):237-261.

729. Causi, N., A. Romano, and G. Galfano. 1958. Coenzyme A (CoA) in the rat liver during administration of pantothenic acid and nicotinamide. Boll. soc. ital. biol. sper. 34:163-164.

730. Cava, E. E., R. W. P. Achor, K. G. Berge, K. G. Wakim, J. E. Edward, B. F. McKenzie, and N. W. Barker. 1959. Effect of nicotinic acid on experimental atheromatosis of rabbits. Proc. Staff Meet. Mayo Clinic 34(21):502-510.

731. Cavicchi, G. 1951. Detection and differentiation of some derivatives of nicotinic acid. Mikrochemie ver. Mikrochim. Acta 36/37:1015-1019.

732. Cayer, D., and S. Cody. 1948. Urinary excretion of niacin and riboflavin in patients with acute infections and various chronic diseases. Am. J. Med. Sci. 215:273-277.

733. Cazaux, A. V., E. Chombart, and J. P. Lemoine. 1966. Pain relievers containing B vitamins and salicylic acid derivatives. Fr. Pat. M 4492.

734. Cazzullo, C. L. 1941. Determination of nicotinic acid and nicotinamide in cerebrospinal fluid. Boll. Soc. Ital. Bio. Sper. 16:755-757.

735. Cazzullo, C. L. 1943. Nicotinic acid in body fluids: estimation in cerebrospinal fluid. Vitamine u. Hormone 4:274-292.

736. Cazzullo, C. L. 1944. Vitamin PP in the fluids of the organs. Experimental contribution: determination in the cerebrospinal fluid. Vitamin u. Hormone 4:274-292.

737. Ceausi, G., et al. 1968. Physiopathology of the nutritional imbalance caused by deficiency of vitamin PP. Med. Intern. (Bucur) 20:273-278.

738. Cedrangolo, F. 1956. Need of associating methionine with nicotinic acid and nicotinamide when these pyridine compounds are to be administered in high doses. Biochim. Appl. 3:61-68.

739. Cedrangolo, F., and E. Scala. 1959. The need of combining methionine with nicotinic acid and nicotinamide when administering these pyridine compounds in very high doses. Minerva Med. 1959:1299.

740. Cedrangolo, F., and V. Scardi. 1951. Quinolinic acid as the precursor of nicotinic acid. Bull. Soc. Chim. Biol. 33(9): 1286-1291.

741. Cereser, M. 1956. Nicotinamide hypervitaminosis and liver autolysis. Ipervitaminosi (Vitaminologia 11-13:290-306.

742. Cerkes, L. A., N. M. Fil'cagin, and A. A. Dinerman. 1955. Relation of metabolism of nicotinic acid to metabolism of sulphur-containing amino acids. Biohimija 20:140-145.

743. Cerna, J. 1964. Determination of some B-complex vitamins in biological material. Veda Vyzkum Prumyslu Potravinarskem 12: 131-148.

744. Cesa, I. 1947. Action of nicotinic acid on the kinetics of the human Fallopian tube. Arch. Farmacol. Sper. 76:85-97.

745. Chae, D. K. 1963. Complex formation in aqueous solution by caffeine and nicotinamide with lidocaine and saccharin. Yakhak Hoeji 7(1):1-7.

746. Chagovets, R. V., and E. V. Lakhno. 1970. Metabolism of nicotinic acid. Vitam. Eksp. Klin. 1970(2):12-17.

747. Chagovets, R. V., A. G. Khalmuradov, and S. I. Shushevich. 1968. Changes in the activity of liver NADase in response to surplus administration of nicotinic acid, 3-methylpyridine, and nicotinamide. Dokl. Akad. Nauk SSSR 181(1):245-247.

748. Chagovets, R. V., A. G. Khalmuradov, and S. I. Shushevich. 1972. Some problems in regulating nicotinuric acid formation in rat tissue. Dokl. Akad. Nauk SSSR Ser. Biol. 202(6):1447-1450.

749. Chagovets, R. V., E. V. Lakhno, and Ts. M. Shtutman. 1962. Experimental analysis of the principles of vitamin therapy. Mezhdun. Konf. Vitamin., Dokl. Suobsht., Sofia 1960:307-312.

750. Chagovets, R. V., S. I. Shushevich, and A. G. Khalmuradov. 1966. Effect of orotic and nicotinic acids on the incorporation of acetate-1-14C in the total lipids and cholesterol of rat liver. Vopr. Pitaniya 25(2):24-29.

751. Chakrabarti, C. H., and B. Banerjee. 1969. Influence of riboflavine, choline, inositol, and niacin on the hepatic biosynthesis of cholesterol by rats kept on a high-cholesterol diet. J. Vitaminol. (Kyoto) 15(3):204-207.

752. Chakrabarti, J. K., and A. K. Guha. 1956. Separation of pyridine monocarboxylic acids on paper chromatograms. Nature 178:538-539.

753. Chaloupka, M. M. 1957. Interrelationships of diet and certain metabolic components, with particular reference to niacin and tryptophan. Dissertation Absts. 17(3):493-494.

754. Chaloupka, M. M., J. N. Williams Jr., M. S. Reynolds, and C. A. Elvehjem. 1957. Relative roles of niacin and tryptophan in maintaining blood pyridine nucleotides, nitrogen balance and growth in adult rats. J. Nutrition 63(3):361-375.

755. Chamberlain, J. G. 1964. Effects of 6-aminonicotinamide on rat embryogenesis. Dissert. Abst. 24(9):3491.

756. Chamberlain, J. 1966. Development of cleft palate induced by 6-aminonicotinamide late in rat gestation. Anat. Rec. 156(1): 31-35.
Chamberla
757. Chamberlain, J. G. 1967. Effects of acute vitamin replacement therapy on 6-aminonicotinamide induced cleft palate late in rat pregnancy. Proc. Soc. Exp. Biol. Med. 124(3):888-890.

758. Chamberlain, J. G. 1970. Early neurovascular abnormalities underlying 6-aminonicotinamide (6-AN)-induced congenital hydrocephalus in rats. Teratology 3(4):377-388.

759. Chamberlain, J. G. 1972. 6-Aminonicotinamide (6-AN)-induced abnormalities of the developing ependyma and choroid plexus as seen with the scanning electron microscope. Teratology 6(3): 281-286.

760. Chamberlain, J. G., and M. E. Goldyne. 1970. Intraamniotic injection of pyridine nucleotides or adenosine triphosphate as countertherapy for 6-aminonicotinamide (6-AN) teratogenesis. Teratology 3(1):11-16.

761. Chamberlain, J. G., and M. M. Nelson. 1963a. Congenital abnormalities in the rat resulting from single injections of 6-aminonicotinamide during pregnancy. J. Expti. Zool. 153(3):285-300.

762. Chamberlain, J. G., and M. M. Nelson. 1963b. Multiple congenital abnormalities in the rat resulting from acute maternal niacin deficiency during pregnancy. Proc. Soc. Expti. Biol. Med. 112:836-840.

763. Chamberlain, N., T. H. Collins, G. A. H. Elton, D. F. Hollingsworth, D. B. Lisle, and P. R. Payne. 1966. Studies on the composition of food. II. Comparison of the nutrient content of bread made conventionally and by the Chorleywood Bread Process. Brit. J. Nutr. 20(4):747-755.

764. Chambers, H. W., and J. E. Casida. 1967. Protective activity of nicotinic acid derivatives and their 1-alkyl-2 and 1-alkyl-6-pyridones against selected neruotoxic agents. Toxicol. Appl. Pharmacol. 10:105-118.

765. Chambon, P., R. Chambon-Mougenot, and R. Guilluy. 1969. Metabolites containing an N-oxide group. Analysis of N,N-diethylnicotinamide N-oxide (Coramine N-oxide) by mass spectroscopy and nuclear magnetic resonance. C. R. Acad. Sci., Ser. D 269(4):523-526.

766. Chambon-Mougenot, R., M. Riotte, J. Bringuier, and P. Chambon. 1970. In vivo and in vitro study of the intestinal and hepatic N-oxidation of N,N-diethylnicotinamide (Coramine). C. R. Seances Soc. Biol. Filiales 164(4):856-860.

767. Champougny, J., and E. Le Breton. 1947. Nicotinamide, pyridoxine, and pantothenic acid, vitamins of group B, are coenzymes of the higher fat acid dehydrogenase system. Compt. Rend. Soc. Biol. 141:43-45.

768. Chang, A. Y. 1972. On the mechanism for the depression of liver NAD by streptozotocin. Biochim. Biophys. Acta 261(1): 77-84.

769. Chang, M. L. Wu, and B. C. Johnson. 1957. Nicotinic acid metabolism. III. Carbon-14 carboxyl-labeled nicotinamide and nicotinic acid in the chick. J. Biol. Chem. 226:799-804.

770. Chang, M. L. Wu, and B. C. Johnson. 1959. N-Methyl-4-pyridone-5-carboxamide, a new major normal metabolite of nicotinic acid in rat urine. J. Biol. Chem. 234(7):1817-1821.

771. Chang, M. L. Wu, and B. C. Johnson. 1961. N-methyl-4-pyridone-5-carboxamide as a metabolite of nicotinic acid in man and monkey. J. Biol. Chem. 236(7):2096-2098.

772. Chang, M. L., and B. C. Johnson. 1962. Metabolism of C 14-nicotinic acid in pig and sheep. J. Nutr. 76:512-514.

773. Chang, Y. O., T. J. S. Laursen, and J. E. Kirk. 1955. The total nicotinic acid and pyridine nucleotide content of human aortic tissue. J. Gerontol. 19(2):165-169.

774. Chang, Y. T. 1954. Chemotherapy of murien leprosy. III. The effects of nicotinamide and pyrazinamide (aldinamide) on mouse leprosy. Intern. J. Leprosy 22:331-346.

775. Chapman, H. R., J. E. Ford, S. K. Kon, S. Y. Thompson, S. J. Rowland, E. L. Crossley, and J. Rothwell. 1957. The effect of processing on some vitamins of the B complex in milk. J. Dairy Research 24:191-197.

776. Charkey, L. W., E. Dyar, and H. S. Wilgus, Jr. 1947. The nutrient content of high and low quality fresh eggs. II. Vitamins. Poultry Sci. 26(6):632-634.

777. Charlampowicz, Z, and W. Soblech. 1965. Changes in pyridoxine, nicotinic acid, and inositol content during technological processing (canning and freezing) of sweet corn. Zeszyty Probl. Postepow Nauk Rolniczych 53:115-116.

778. Charlampowicz, A. and W. Soblech. 1966. Thiamine, riboflavine, nicotinic acid, pyridoxine, cyanocobalamin, and inositol content of some vegetable and fruit products. Przem. Spozyw. 20(12):812-819.

* 779. Charman, R. C., L. B. Matthews, and C. Braeuler. 1972. Nicotinic acid in the treatment of hypercholesterolemia: A long term study. Angiology 23(1):29-35.

780. Chason, J. L., and A. G. Pearse. 1961. Phenazine methosulphate and nicotinamide in the histochemical demonstration of dehydrogenases in rat brain. J. Neurochem. 6:259-266.

781. Chattopadhyay, D. P., and S. Banerjee. 1959. Site of synthesis of nicotinic acid from tryptophan in rabbits. Indian J. Med. Research 47:428-433.

782. Chattopadhyay, D., N. C. Ghosh, H. Chattopadhyay, and S. Banerjee. 1953. The metabolism of nicotinic acid in rabbits. J. Biol. Chem. 201:529-534.

783. Chauchard, P. 1942. Effects of small doses of vitamins on the nervous system. Bull. Soc. Chim. Biol. 24:182-185.

784. Chauchard, P., and H. Mazoue. 1945. Vitamins antagonizing the action of thyroxine on nerve chronaxia. Compt. Rend. Soc. Biol. 139:594-595.

785. Chauchard, P., H. Mazoue, and R. Lecoq. 1949. Drugs accelerating and inhibiting alcoholic intoxication. Compt. Rend. Soc. Biol. 143(23/24):1550-1553.

786. Chaudhari, P. N., and V. G. Hatwaine. 1971a. Effect of Acacia catechu on niacin, ascorbic acid, and riboflavine status in rats. J. Vitaminol. (Kyoto) 17(2):105-107.

787. Chaudhari, P. N., and V. G. Hatwaine. 1971b. Effect of Acacia catechu on niacin biosynthesis and on niacin requirement in rats. J. Vitaminol. (Kyoto) 17(3):125-127.

788. Chaudhuri, D. K. 1951a. A chemical method for the quantitative estimation of the bound form (B.F.) of nicotinic acid in cereals. Sci. Culture. 17(6):270-271.

789. Chaudhuri, D. K. 1951b. Estimation of nicotinic acid. Indian J. Med. Research 39:491-505.

790. Chaudhuri, K. D. 1952. Estimation of nicotinic acid in urine. Ann. Biochem. and Expti. Med. (India) 12:119-134.

791. Chaudhuri, D. K. 1955. Distribution of the bound nicotinic acid in pure-bred strains of rice. Science and Culture (India) 20:561-562.

792. Chaudhuri, D. K. 1963. Studies on the isolation of bound nicotinic acid from rice-bran. Ann. Biochem. Exp. Med. 23: 277-278.

793. Chaudhuri, D. K., and E. Kodicek. 1960. The availability of bound nicotinic acid to the rat. 4. The effect of treating wheat, rice and barley brans and a purified preparation of bound nicotinic acid with sodium hydroxide. Brit. J. Nutr. 14:35-42.

794. Chaudhuri, S. N., E. Suter, N. S. Shah, and S. P. Martin. 1963. Metabolism in infection; enzymic damage in kidney of guinea pigs infected with Mycobacterium tuberculosis. J. Expti. Med. 117:71-79.

795. Chaykin, S. 1964. The biosynthesis of N-methyl-4-pyridone-3-carboxamide, (metabolite of nicotinamide). Biochim. et Biophys. Acta 82(3):633-634.

796. Chaykin, S. 1969. Assay of nicotinamide deamidase: Determination of ammonia by the indophenol reaction. Anal. Biochem. 31(1-3):375-382.

797. Chaykin, S., L. King, and R. Schindler. 1967. Nicotinamide metabolism in a nicotinamide-requiring yeast Saccharomyces fragilis C351. Arch. Biochem. Biophys. 118(1):97-105.

798. Chaykin, S., M. Dagani, L. Johnson, and M. Samii. 1965. The fate of nicotinamide in the mouse: Urinary metabolites. J. Biol. Chem. 240(2):932-938.

799. Chaykin, S., M. Dagani, L. Johnson, M. Samii, and J. Battaile. 1965. The fate of nicotinamide in the mouse; Tissue metabolites. Biochim. Biophys. Acta 100(2):351-365.

* 800. Chazin, B. J. 1960. Effect of nicotinic acid on blood cholesterol. Geriatrics 15:423-429.

801. Chekmareva, I. B., E. S. Zhdanovich, and N. A. Preobrazhenskii. 1965. Synthesis of pyridine-beta-carboxylic (nicotinic) acid. Zh. Prikl. Khim. 38(1):220-221.

802. Chekmareva, I. B., E. S. Zhdanovich, A. I. Reznik, and N. A. Preobrazhenskii. Synthesis of pyridineca rboxylic acids. III. Quinolinic and nicotinic acids. Zh. Prikl. Khim. 38(3):707-708.

803. Chekmareva, I. B., E. S. Zhdanovich, G. I. Szaonova, and N. A. Preobrazhenskii. 1964. Nicotinamide. U.S.S.R. Pat. 164,601.

804. Cheldelin, V. H., and A. Baich. 1961. Physiological control of nicotinic acid biosynthesis in Aerobacter aerogenes. Biochim. Biophys. Acta 46:607-608.

805. Cheldelin, V. H., and R. J. Williams. 1942. The B vitamin content of foods. Univ. Texas Pub. No. 4237:105-124.

806. Cheldelin, V. H., and R. R. Williams. 1943. Studies of the average American diet. II. Riboflavin, nicotinic acid and pantothenic acid content. J. Nutrition 26:417-430.

807. Chemnitius, K. H., and J. Gebhard. 1963. Pharmacodynamics of vitamins B6 and B12. Z. Vitamin-, Hormon- Fermentforsch. 12:333-349.

* 808. Chen, K. K., C. L. Rose, and E. B. Robbins. 1938. Toxicity of nicotinic acid. Proc. Soc. Exp. Biol. and Med. 38(2):241-245.

809. Chenier, L.-P., and E. Page. 1951. Nicotinic acid and the vestiblar action of streptomycin in the rat. Ann. ACFAS 17: 108-110.

810. Chera, Gh., D. Lacatis, D. Boicu, L. Enescu, I. Pojoga, and I. Nitulescu. 1970. Effect of nicotinic acid the liver damage induced by an unbalanced lipid-protein diet. Stud. Cercet. Embriol. Citol., Ser. Citol. 7(1):3-7.

811. Chera, G., E. Raileanu, L. Raileanu, L. Enescu, C. Haller, and D. Lacatis. 1969. Effect of nicotinic acid on blood sugar in rats. Fiziol. Normala Patol. 15:231-240.

812. Cheraskin, E., and W. M. Ringsdorf, Jr. 1971. Daily phenylalanine consumption and psychologic state. Nutr. Rep. Int. 3(6):377-382.

813. Cherepanova, V. V. 1965. Effect of trace elements and vitamins of the B group on growth and development of suckling piglets. Sb. Nauch. Rab. Stud., Saratov. Zootekh.-Vet. Inst. 3:21-29.

814. Cherkes, G. A. 1952. Metabolism of nicotinic acid in the organism of the guinea pig. Biokhimiya 17:706-710.

815. Cherkes, G. A. 1954. Methylation of nicotinic acid in hypothyroidism. Voprosy Pitaniya 13(1):12-15.

816. Cherkes, G. A. 1958. The sources of methyl groups in the formation of N'-methylnicotinamide in the organism. Biokhimiya (Transl.) 23(3):376-378.

817. Cherkes, L. A., N. M. Fil'chagin, and A. A. Dinerman. 1955. The relation between acid metabolism and the metabolism of sulfur containing amino acids. Biokhimiya 20(2):140-145.

818. Chernov, V. M., L. N. Oskolova, and N. A. Kudryavina. 1946. Antianaphylactic properties of vitamin B1 in large doses. Farmakol. i Toksikol. 9(5):34-39.

819. Chernykh, V. P., H. P. Petyunin, and O. O. Krasnovs'ka. 1972. Synthesis and pharmacologic activity of substituted amides of pyridine-carboxylic acids. Farm. Zh. 27(1):16-18.

820. Chevillard, L., and H. Giono. 1952. Investigations of peripheral vasodilatation in the guinea pig. J. Physiol. (Paris) 44:238-239.

821. Chevillard, L., and H. Giono. 1958. Influence of chronic sympathetic denervation on the action of various vasodilator drugs. Compt. Rend. Soc. Biol. 152:38-40.

822. Chevillard, L., and M. C. Laury. 1960. Inhibition of the vasodilatory effect of sodium nicotinate by structural analogs. Compt. Rend. 250:3746-3748.

823. Chevillard, L., and M. C. Laury. 1963. The action of the sympathetic system and catechol amines on the vasodilatory response to nicotinic acid derivatives. Compt. Rend. 256: 1040-1042.

824. Chevillard, L., R. Charonnat, and H. Giono. 1949. Cutaneous absorption of nicotinic esters. Compt. Rend. Soc. Biol. 143 (13/14):898-900.

825. Chevillard, L., R. Charonnat, and H. Giono. 1950a. Peripheral vasodilatation provoked by rectally administered nicotinic ester in the guinea pig. Variation according to the dose. Compt. Rend. Soc. Biol. 144(3/4):194-196.

826. Chevillard, L., R. Charonnat, and H. Giono. 1950b. Influence of sex in the guinea pig on the hyperemic action of methyl nicotinate administered rectally. Modality of the phenomenon. Compt. Rend. Soc. Biol. 144(3/4):197-199.

827. Chevillard, L., H. Giono, M. Ranson, and M. Cl. Laury. 1960. Peripheral vasomotricity in the guinea pig after administration of vasodilators. I. Tachyphylaxis. II. Inhibition of the vasodilating effect. J. Physiol. (Paris) 52:49-51.

828. Cheymol, J., M. Freyss-Beguin, and J. Bourdais. 1967. Action of some quaternary ammonium derivatives of procaine on the hypoxia resistance and the temperature of the white rat. C. R. Soc. Biol. 161(1):54-57.

829. Chiancone, F. M. 1946. Influence of single massive doses of the vitamin factors of the B complex on growth of rats on a diet deficient in the corresponding factor. Boll. Soc. Ital. Biol. Sper. 21:13-14.

830. Chiancone, F. M. 1962. Endocrine glands and tryptophan - niacin metabolism. Acta Vitaminol. 16:49-60.

831. Chiancone, F. M. 1964. Activities of enzymes of the tryptophan-nicotinic acid pathway in physiopathology. Giorn. Biochim. 13(1):1-31.

832. Chiancone, F. M. 1968. Tryptophan-nicotinic acid metabolism in psychiatric diseases. Acta Vitaminol. Enzymol. 22(3/4): 111-133.

833. Chiang, H.-C., Y. Lin, and Y.-C. Wu. 1969. Polyamide-silica gel thin-layer chromatography of water-soluble vitamins. J. Chromatogr. 45(1):161-162.

834. Chiarini, P., and F. Melani. 1962. Behavior of hepatic diphosphophyridine nucleotide (DPN) in rats after administration of nicotinic acid and of inositol hexanicotinate. Sperimentale 112:74-79.

835. Chick, H. 1951. The causation of pellagra. Nutrition Abst. and Rev. 20(3):523-535.

836. Chick, H., T. F. Macrae, A. J. P. Martin, and C. J. Martin. 1938. Curative action of nicotinic acid on pigs suffering from the effects of a diet consisting largely of maize. Biochem. J. 32:10-12.

837. Childs, G. R., C. W. Carrick, and S. M. Hauge. 1952. The niacin requirement of young chickens. Poultry Sci. 31: 551-558.

838. Chini, V., C. Malaguzzi-Valeri, and G. Conese. 1946. Elimination of nicotinic acid in edema from hunger. Boll. Soc. Ital. Biol. Sper. 22:959-961.

839. Chirico, M. 1951. Serum cholinesterase after methionine or methionine-nicotinamide administration. Osped. Maggiore 39:66-68.

840. Chirico, M. 1954. Stimulatory action of nicotinamide on serum cholinesterase. Arch. Studio Fisiopatol. e Clin. Ricambio 18:188-190.

841. Chitre, R. G., and P. Bhatia. 1959. Studies in nicotinic acid metabolism. I. Excretion of nicotinic acid metabolites in normal and pregnant women. J. Postgrad. Med. (Bombay) 5:1-10.

842. Chitre, R. G., and D. B. Deasi. 1949. A new method for the estimation of available nicotinic acid from food-stuffs. Indian J. Med. Sci. 3(8):479-490.

843. Chitre, R. G., S. D. Ambegaokar, and N. G. Joshi. 1944. Nicotinic acid, riboflavin, ascorbic acid, and glutathione contents of livers of some cancer-susceptible (A and C3H) and cancer-insusceptible (C57) strains of mice. Ann. Biochem. Exptl. Med. 4:87-92.

844. Chitre, R. G., D. B. Deasi, and V. S. Raut. 1955. Nutritive value of purebred strains of cereals and pulses. I. Thiamine, riboflavine, and nicotinic acid contents of 107 purebred strains of cereals and pulses. Indian J. Med. Research 43:575-583.

845. Chiu, G. C. 1961. Mode of action of cholesterol-lowering agents. A critique of facts and theories. Arch. Internal Med. 108:717-732.

846. Chizhova, Z. P. 1964. The use of vitamins of the B group (B1, B2 and B6) and nicotinic acid in acute leukemia in children. In: Collection of scientific papers of the Moscow Children's City Clinical Hospital, Meditsina, Moscow, p. 140-144.

847. Chmelar, M., and M. Chmelarova. 1971a. Interactions of nicotinic acid with hormone-sensitive lipases of different mammalian tissues. Metab. Eff. Nicotinic Acid its Deriv., Pro. 1971:263-281.

848. Chmelarova, M., and M. Chmelar. 1971b. Different interactions of nicotinic acid with tissue lipase stimulated by glucagon or catecholamine. Metab. Eff. Nicotinic Acid its Deriv., Pro. 1971:289-298.

849. Cho, Y. H. 1972. Effects of cycloheximide on the biosynthesis of nicotinamide adenine dinucleotide from nicotinamide in mice. Han'guk Saenghwahakhoe Chi 5(1):1-13.

850. Choi, C., and D. Pak. 1948. The effect of nicotinic acid on dermatitis congelationis. Urol. and Cutaneous Rev. 52: 483-487.

851. Choisy, H., and Potron. 1969. Effect of some sugars and coenzymes on the rate of disappearance of ethanol from rabbit blood. Therapie 24(5):833-851.

852. Christensen, N. A., R. W. Achor, K. G. Berce, and H. L. Mason. 1961. Nicotinic acid treatment of hypercholesteremia. Comparison of plain and sustained-action preparations and report of two cases of jaundice. JAMA 177:546-550.

853. Christie, G. S., and R. N. Le Page. 1962. Liver damage in acute heliotrine poisoning. 2. The effect of nicotinamide on pyridine nucleotide concentrations. Biochem. J. 84:202-212.

854. Christow, C. P. 1971. Experiments on the influence of metabolites and antimetabolites on the model of trichomonas vaginalis. I. Experiments with the Vitamin-B2-complex. Zentralbl. Bakteriol., Parasitenk., Inf 217(3):381-402.

855. Chrusciel, T. 1952. The effect of nicotinic and isonicotinic acids on various levels of medicine in blood and on the secretion of bile. Polska Akad. Umiejtnosci Rozprawy Wydzialu Lekarsk. 12(13):1-27.

856. Chu, H.-I., P.-T. Kuo, and K.-P. Chang. 1942. Blood and urinary nicotinic acid in normal Chinese, pellagra, and various pathological conditions. Chinese Med. J. 61:181-191.

857. Chukichev, E. M. 1959. Antiinflammatory effect of nicotinic acid on aseptic inflammation. Sbornik Nauch. Trudov Permsk. Med. Inst. 29:236-240.

858. Chukichev, E. M. 1966. Combined effect of penicillin, levomycetin, and some water-soluble vitamins on aseptic inflammation and phagocytosis. Antibiotiki 11(5):442-446.

859. Chumakov, Yu. I., P. A. Gangrskii, N. N. Dykhanov, L. A. Rusakova, A. I. Mednikov, R. I. Virnik, E. V. Voronkova, and T. S. Semenovykh. 1957. Nicotinic acid. U.S.S.R. Pat. 109,387.

860. Chunakova, E. P. 1960. On the problem of nicotinic acid metabolism in patients after total gastrectomy. Vop. Pitan. 19:30-35.

861. Chunakova, E. P. 1963a. The possibility of endogenous synthesis of nicotinic acid in patients with total gastric resection. Vopr. Pitaniya 22(6):27-30.

862. Chunakova, E. P. 1963b. Nicotinamide deficiency in patients with achlorhydric gastritis. Vopr. Pitaniya 22(4):61-65.

863. Chung, S. C., and H. Pitot. 1967. Feedback control of rat liver tryptophan pyrrolase. I. End product inhibition of tryptophan pyrrolase activity. J. Biol. Chem. 242(6):1192-1198.

864. Cima, L., G. Fassina, and F. Pozza. 1960. Influence of nicotinamide on the nucleotide pattern of liver cells. Arch. Intern. Pharmacodynamic 124:310-316.

865. Cima, L., I. Mastrogiacomo, and B. Maraschin. 1965. Relation of tissue pyridine coenzymes and vitamin B12 metabolism in the rat. Arch. Ital. Sci. Farmacol. 15(1-2):57-59.

866. Cimino, G. 1948. The action of niacin on thiamine-deficient rats. Boll. Soc. Ital. Biol. Sper. 24:1052-1053.

867. Cimino, G. 1949. Action of nicotinic acid on rats deprived of vitamin B1. Arch. Sci. Biol., Napoli 33:126-130.

868. Ciotti, M. M., J. R. Humphreys, J. M. Venditti, N. O. Kaplan, and A. Goldin. 1960. Antileukemic action of two thiadiazole derivatives. Cancer Research 20:1195-1201.

869. Cirillo, D. 1951. Water-soluble vitamins and serum lysozyme. Acta Paediat. Latina (Parma) 4:69-73.

870. Cislak, F. E., and W. R. Wheeler. 1944. Catalytic oxidation of substituted pyridine bases. Can. Pat. 424,546.

871. Cislak, F. E., and W. R. Wheeler. 1948. Catalytic oxidation of nicotine. U.S. Pat. 2,456,380.

872. Cislak, F. E., and W. R. Wheeler. 1950. Pyridinecarboxylic acids. U.S. Pat. 2,522,163.

873. Ciusa, W. 1950. Simultaneous determination of nicotinic acid and of nicotinamide. Mikrochemie Ver. Mikrochim. Acta 35:20-26.

874. Ciusa, W., and G. Barbiroli. 1963a. Differential determination of 3-pyridylacetic acid, nicotinic acid, and their amides. Ann. Chim. (Rome) 53(10):1248-1258.

875. Ciusa, W., and G. C. Barbiroli. 1963b. Transmethylation processes in the crystalline lens, blood, liver, and kidney of cattle, rabbits, and rats. Acta Vitaminol. 17(4-5): 157-166.

876. Ciusa, W., and G. Barbiroli. 1963c. Crystalline lens and blood as preparations of general application for the study of transmethylation processes. Expti. Eye Res. 2(3):265-267.

877. Ciusa, W., and G. Nebbia. 1952. Metabolism of some derivatives of nicotinic acid. Acta Vitaminol. 6:49-52.

878. Ciusa, W., and W. Pasquali. 1946. The estimation of nicotinic acid in urine. Ann. Chim. Appl. Roma 36:167-178.

879. Ciusa, W., and M. Prato. 1949. Nicotinic acid derivatives in crystalline lens and aqueous humor. Acta Vitaminologica (Milan) 3:168-169.

880. Ciusa, W., G. Barbiroli, and A. Buccelli. 1966. Tryptophan metabolism in the crystalline lens. Ric. Sci. 36(11)1232-1241.

881. Ciusa, W., G. Cristini, and G. Barbiroli. 1964. The transmethylation processes in the aqueous humor and in the lens. Expti. Eye Res. 3(2):169-178.

882. Ciusa, W., C. Rizzoli, and P. Dessi. 1948. The methylation process. Experiments on nicotinic acid and trigonelline with organ slices. Boll. Soc. Ital. Biol. Sperim. 24(5):556-559.

883. Claar, E., and L. Malcangi. 1941. Nicotinic acid in oxalemia. Filia Med. (Naples) 27:649-651.

884. Clark, J. B., and S. Pinder. 1969. Control of the steady-state concentrations of the nicotinamide nucleotides in rat liver. Biochem. J. 114(2):321-330.

885. Clark, J. B., G. M. Ferris, and S. Pinder. 1971. Inhibition of nuclear NAD nucleosidase and poly ADP-ribose polymerase activity from rat liver by nicotinamide and 5'-methylnicotinamide Biochim. Biophys. Acta 238(1):82-85.

886. Clark, T. S. H. 1949. Enrichment composition. U.S. Pat. 2,470,804.

887. Clausen, J., and R. Hustrulid. 1968. Factors affecting recombination of lactate dehydrogenase isozyme subunits. Biochim. Biophys. Acta 167(2):221-226.

888. Claveau, J. 1956. A new method for the microbiological determination of nicotinamide. Inds. Aliment. et Agr. (Paris) 73:3-10.

889. Clayton, C. C., and C. A. Baumann. 1949. Diet and azo dye tumors: effect of diet during a period when the dye is not fed. Cancer Research 9:575-582.

890. Clegg, K. M. 1963. Bound nicotinic acid in dietary wheaten products. Brit. J. Nutr. 17:325-329.

891. Clegg, K. M., E. Kodicek, and S. P. Mistry. 1952. Modified medium for Lactobacillus casei for the assay of B vitamins. Biochem. J. 50:326-331.

892. Clifcorn, L. E. 1944. The nutritive value of canned foods. I. Introduction and sampling procedure. J. Nutrition 28:101-105.

893. Clifford, A. J., R. L. Prior, and W. J. Visek. 1969. Depletion of reduced pyridine nucleotides in liver and blood with ammonia. Am. J. Physiol. 217(5):1269-1272.

894. Clouet, D. H., and M. Ratner. 1964. The effect of altering liver microsomal N-demethylase activity on the development of tolerance to morphine in rats. J. Pharmacol. Expti. Therap. 144(3):362-372.

895. Coates, M. E., J. E. Ford, G. F. Harrison, S. K. Kon, E. E. Shepheard, and F. W. Wilby. 1952. The use of chicks for the biological assay of members of the vitamin B complex. 2. Tests on natural materials and comparison with microbiological and other assays. Brit. J. Nutrition 6(1):75-89.

896. Coelho, J., P. J. Dubash, and D. V. Rege. 1964. Studies on Euglena gracilis assay method for vitamin B12. Bull. Nat. Inst. Sci. India 25:201-209.

897. Cohen, I., I. M. Levinger, and M. Herzberg. 1971. Influence of experimental atherosclerosis and various vasoactive drugs on cerebrospinal fluid pressure in rabbits. Confin. Neurol. 33(6):334-341.

898. Cohen, J. A., B. Goodman, S. L. Yunis, M. F. Levitt, and M. Kahn. 1965. Effects of a pyrogen reaction on urine concentration in the dog. Am. J. Physiol. 209(5):1007-1011.

899. Cohen, P. P., and H. J. Sallach. 1961. Nitrogen metabolism of amino acids. Metabolic Pathways 2:1-78.

900. Coke, E. C. 1944. Wrong use of ascorbic acid (vitamin C) in certain neuropahties and hepatic disease. Clin. Med. 51:12.

901. Colajacomo, A. 1956. Relation between the biosynthesis of pyridine nucleotide, phosphoglucomutase activity, and glycogenolysis in the rat treated with nicotinamide. Boll. Soc. Ital. Biol. Sper. 32:1615-1619.

902. Colajacomo, A., C. Vergnano, and G. Berruto. 1958. Biosynthesis of pyridine nucleotides in Ehrlich solid carcinoma. Boll. Soc. Ital. Biol. Sper. 34:881-882.

903. Colajacomo, A., V. Vallerino, O. Chieffi, and L. Colombo. 1963. Content of DPN-DPNH, TPN-TPNH (oxidized and reduced di- and triphosphopyridine nucleotides), and pyridine compounds in the liver of pregnant rats, and in the fetus and placenta following high doses of nicotinamide. Boll. Soc. Ital. Biol. Sper. 39(7): 424-428.

904. Colborn, L. R. 1957. Vitamins in animal feeding. XXV. Nicotinic acid. Fertiliser Feeding Stuffs J. 46:588-589.

905. Cole, R. A., and B. M. Twarog. 1972. Relaxation of catch in a molluscan smooth muscle: I. Effects of drugs which act on the adenyl cyclase system. Comp. Biochem. Physiol. A. Comp. Physiol. 43(2):321-330.

906. Coleman, H. M. 1951. Mechanism of meat-pigment oxidation. The effect of solutes on the hemoglobin-oxygen equilibrium. Food Research 16:222-229.

907. Coleman, H. M., A. H. Steffen, and E. W. Hopkins. 1951. Improving the color of animal meat and blood. U.S. Pat. 2,541,572.

908. Collazos, Ch. C., H. S. White, R. L. Huenemann, E. Reh, P. L. White, A. Castellanos, R. Benites, Y. Bravo, A. Loo, I. Moscoso, C. Caceres, and A. Dieseldorff. 1954. Dietary surveys in Peru, III. Chacan and Vicos, rural communities in the Peruvian Andes. J. Am. Dietetic Assoc. 30(12):1222-1230.

909. Collier, A., S. Ray, and W. B. Wilson. 1956. Some effects of specific organic compounds on marine organisms. Science 124:220.

910. Collings, A. J. 1968. Lipoid aqueous emulsions for controlling the release rate of depot formulations. S. African Pat. 68 04,234.

* 911. Collins, P. B., and S. Chaykin. 1971. Comparative metabolism of nicotinamide and nicotinic acid in mice. Biochem. J. 125(4):117.

* 912. Collins, P. B., and S. Chaykin. 1972. Management of nicotinamide and nicotinic acid in the mouse. J. Biol. Chem. 247(3): 778-783.

913. Colonna, L, D. Angarano, and D. Rizzi. 1957. Nicotinic acid and oxygen-utilization coefficient in chronic pulmonary heart disease. Clin. Terap. 12:149-160.

914. Comesana, F., A. Nava, B. L. Fishleder, and D. Sodi-Pallares. 1958. The hypocholesterolemic effect of nicotinic acid, phenylethylacetamide, and a combination of both in dogs. Am. Heart J. 55:476-480.

915. Condorelli, L. 1950. Pathologic physiology of the pulmonary arterial circulation. Schweiz. Med. Wochenschr. 80(36):986-993.

916. Condorelli, L. 1954. Nicotinic acid in the cure of cardiorespiratory failure, physiopathologic bases and clinical uses. Therapie 9:674-681.

917. Condorelli, L. 1964. Nicotinic acid in the therapy of the cardiovascular apparatus. In: R. Altschul, Editor. Niacin in Vascular Disorders and Hyperlipemia. C. C. Thomas: Springfield, Illinois. p. 156-207.

918. Conger, T. W., and C. A. Elvehjem. 1941. The biological estimation of pyridoxine (vitamin B6). J. Biol. Chem. 138: 555-561.

919. Consolazio, C. F., H. L. Johnson, H. J. Krzywicki, and N. F. Witt. 1972. Tryptophan-niacin interrelationships during acute fasting and caloric restriction in humans. Am. J. Clin. Nutr. 25(6):572-575.

920. Consolo, F., A. Buda, and G. De Gregorio. 1963. Analysis of the pharmacodynamic action of nicotinic acid on the arterial systemic circulation. Boll. Soc. Ital. Biol. Sper. 39:1072-1074.

921. Conte, G., and M. Orenesu. 1952. Nicotinamide and liver glycogen. Giorn. Biochim. 1:217-222.

922. Coodin, P. 1944. A case of pellagra. Canad. Med. Assoc. J. 50:253.

923. Cook, B. B. 1949. Thiamine, riboflavin, and niacin content of turkey tissues as affected by storage and cooking. Food Research 14:449-458.

924. Cooper, T. P. 1946. Fifty-ninth annual report. Kentucky Agr. Expt. Sta. Ann. Rept. 59:5-68.

925. Cooperman, J. M., and C. A. Elvehjem. 1945. Retention of B vitamins in oatmeal during cooking. J. Am. Dietetic Assoc. 21(3):155-156.

926. Cooperman, J. M., S. H. Rubin, and B. Tabenkin. 1950. Effect of niacin and tryptophane in counteracting toxicity of crystalline borrelidin (an antibiotic from Streptomyces sp.) for rats. Fed. Proc. 9(1):162.

927. Cooperman, J. M., S. H. Rubin, and B. Tabenkin. 1951. Effect of niacin and tryptophan in counteracting toxicity of crystalline borrelidin for rat. Proc. Soc. Expti. Biol. and Med. 76(1):18-20.

928. Coper, H. 1961a. The value of nicotinamide for the anticonvulsive effect of hexachlorocyclohexane) Naunyn Schmiedeberg Arch. Exp. Path. 241:194-195.

929. Coper, H. 1961b. Separation and characterization of the degradation products of diphosphopyridine nucleotide (DPN), reduced DPN (DPNH), and triphosphopyridine nucleotide (TPN) after enzymic hydrolysis by brain homogenates. Arch. Expti. Pathol. Pharmakol. 241:335-345.

930. Coper, H. 1961c. The effect of different drugs on the diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN)-nucleosidase of brain. Arch. Expti. Pathol. Pharmakol. 242:24-33.

931. Coper, H. 1963. The content of NAD, NADP and nicotinamide in the brain of rats subsequent to the action of centrally acting drugs. Arch. Explt. Pathol. u. Pharmakol. 244(5):420-428.

932. Coper, H. 1971. The influence of adrenergic receptor-blocking agents, amphetamine, and 6-aminonicotinamide on thermoregulation. Naunyn-Schmiedeberg's Arch. Pharmakol. 270(4):378-391.

933. Coper, H., and H. Herken. 1963. Damage to the central nervous system by antimetabolites of nicotinic acid amide. A contribution to the molecular pathology of the pyridine nucleotides. Deut. Med. Wochschr. 88(42):2025-2036.

934. Coper, H., G. Deyhle, D. Von Herrath, and J. Veit. 1968. Mechanisms of sleep-extending effect of various drugs. Naunyn-Schmiedeberg's Arch. Pharmakol. Exp. Pathol. 260(4):366-378.

935. Coppi, G., and G. Bonardi. 1970. Urease-inhibiting action of some drugs in vitro and in vivo. Arzneim.-Forsch. 20(3): 384-386.

936. Corda, R. 1952. Thyroid activity and nicotinic acid metabolism. Ann. Ital. Pediat. 5:486-493.

937. Corda, R. 1953. Nicotinic acid content of blood, cerebrospinal fluid, and urine in hydrocephalus. Ann. Ital. Pediat. 6:47-53.

938. Corda, R. 1955. Endocrine system and nicotinic acid metabolism. II. Effect of parathyroid and of thymus on the nicotinic acid content of blood. Ann. Ital. Pediat. 8:146-157.

939. Cording, J., Jr., R. K. Eskew, G. J. Salinard, and J. Sullivan. 1961. Vitamin stability in fortified potato flakes. Food Technol. 15:279-282.

940. Coronato, A., and G. B. J. Glass. 1973. Depression of the intestinal uptake of radio-vitamin B12 by cholestyramine. Proc. Soc. Exp. Biol. Med. 142(4):1341-1344.

941. Corsi, V., et al. 1963. Embolism of the terminal aorta opportunely treated with sodium nicotinate. Boll. Soc. Ital. Cardiol. 8:614-620.

942. Cosi, G. 1968. Separation and determination of nicotinamide, inosine and uridine-5-monophosphate. Farmaco (Prat) 23:331-336.

943. Cote, L., and J. J. Oleson. 1951. Studies on nicotinamide derivatives. J. Bact. 61(4):463-467.

944. Cote, L., J. J. Oleson, and J. H. Williams. 1952. Studies on nicotinamide inhibitors. Proc. Soc. Exptl. Biol. and Med. 80(3):434-436.

945. Cortesi, M. C. 1946. Influence of insulin-shock therapy on protein metabolism and elimination of chlorides in schizophrenia. Rass. Studi Psichiat. 35:79-103.

946. Coryell, M., C. Roderuck, M. E. Harris, S. Miller, M. M. Rutledge, H. H. Williams, and I. G. Macy. 1947. Metabolism of women during the reproductive cycle. XIII. The utilization of niacin during lactation. J. Nutrition 34(2):219-231.

947. Costabile, L., D. Patrono, and E. Gazzerro. 1956. Metabolism of some tryptophan derivatives in human red cells. Biochim. Appl. 3:69-74.

948. Cottini, G. B. 1940. The effect of nicotinic acid on the toxicity of sulfanilamide. Dermatologica 81:83-86.

949. Cotzias, G. C., et al. 1972. Nicotinamide ineffective in parkinsonism. N. Engl. J. Med. 287:147.

950. Cotzias, G. C., L. Tang, J. Z. Ginos, A. R. Nicholson, Jr., and P. S. Papavasiliou. 1971. Block of cerebral actions of L-dopa with methyl receptor substances. Nature (London) 231(5304):533-535.

951. Couch, J. F., and C. F. Krewson. 1948. Nicotinamide from nicotinonitrile. U.S. Pat. 2,453,496.

952. Coulson, R. A., and F. G. Brazda. 1947. Effect of feeding pyridine derivatives to young rats on a high protein diet. Proc. Soc. Expti. Biol. and Med. 65(1):1-5.

953. Coulson, R. A., and P. Ellinger. 1943. Fluorescent derivatives of n-methyl-chloro-nicotinamide. Biochem. J. 37(4):xvii.

954. Coulson, R. A., and C. A. Stewart. 1946. Metabolism of nicotinamide, nicotinic acid, and diethylamide of nicotinic acid (coramine) by newborn and premature infants. Proc. Soc. Expti. Biol. Med. 61:364-369.

955. Coulson, R. A., P. Ellinger, and B. S. Platt. 1942. The comparative effect on the elimination of fluorescent pigments in human urine of nicotinamide and related compounds. Biochem. J. 36:xii-xiii.

956. Covello, M. 1942. Differentiation of nicotinic acid from nicotinamide, beta-aminopyridine and nicotine by ultraviolet spectrography. Quad. Nutrizione 8:259-262.

957. Cover, S., and W. H. Smith, Jr. 1955. Variation in thiamine and niacin content of raw lamb muscle. J. Animal Sci. 14(1): 173-177.

958. Cover, S., and W. H. Smith, Jr. 1956. Effect of moist and dry heat cooking on vitamin retention in meat from beef animals of different levels of fleshing. Food Research 21:209-213.

959. Cover, S., E. M. Dilsaver, and R. M. Hays. 1947a. Variation among lamb carcasses in the B vitamin content of meat. Science 105(2727):364-365.

960. Cover, S., E. M. Dilsaver, and R. M. Hays. 1947b. Retention of the B vitamins in beef and lamb after stewing. IV. Niacin. J. Am. Dietetic Assoc. 23(9):769-772.

961. Cover, S., E. M. Dilsaver, and R. M. Hays. 1947c. Retention of the B vitamins in beef and lamb after stewing. VI. Similarities and differences among the four vitamins. J. Am. Dietetic Assoc. 23(11):962-966.

962. Cover, S., E. M. Dilsaver, and R. M. Hays. 1949. Retention of B vitamins in beef and veal after home stewing and storage. Food Research 14:104-108.

963. Cover, S., E. M. Dilsaver, R. M. Hays, and W. H. Smith. 1949. Retention of B vitamins after large-scale cooking of meat. II. Roasting by two methods. J. Am. Dietetic Assoc. 25:949-951.

964. Cowey, C. B., K. W. Daisley, and G. Parry. 1962. Amino acids, free or as components of protein, and some B vitamins in the tissues of the Atlantic salmon, during spawning migration. Comp. Biochem. Physiol. 7:29-38.

965. Cozzolino, G. 1969. Tryptophan-nicotinic acid metabolism in hyperthyroid subjects and some observations relative to pyridoxine administration. Acta Vitaminol. Enzymol. 23(5): 153-163.

966. Cozzolino, G., and P. Latini. 1968. Metabolism of tryptophan to nicotinic acid in patients with hyperthyroidism before and after treatment with pyridoxine. Ann. Fac. Med. Chir. Univ. Studi Perugia 59(4):733-745.

967. Cozzolino, G. G. Dominici, P. Latini, and U. Milla. 1968. Urinary excretion of some tryptophan metabolites via the nicotinic acid pathway in normal subjects before and after tryptophan loading. Boll. Soc. Ital. Biol. Sper. 44(3): 173-177.

968. Crainz, F. 1941. Action of nicotinamide on the uterus. Boll. Soc. Ital. Biol. Sper. 16:742-743.

969. Cramer, K. 1963. Serum beta-lipoprotein lipids and protein in elderly male survivors of myocardial infarction. Acta Med. Scand. 174(4):421-424.

970. Crandall, L. A., Jr., F. F. Chesly, D. Hansen, and J. Dunbar. 1939. Relationship of the P-P factor to gastrointestinal motility. Proc. Soc. Exptl. Biol. Med. 41:472-474.

971. Cravens, W. W. 1952. Vitamin deficiencies and antagonists. Ann. N.Y. Acad. Sci. 55:188-195.

972. Cravens, W. W., and E. E. Snell. 1949. Effects of desoxy-pyridoxine and vitamin B6 on development of the chick embryo. Proc. Soc. Exptl. Biol. and Med. 71(1):73-76.

973. Cravioto, R. O., J. Guzman G., and M. L. Suarez S. 1955. Increment of niacin content (antipellagra vitamin) during the roasting of coffee and its significance in providing this vitamin in the diet. Ciencia (Mex.) 15:24-26.

974. Cravioto, B., R., E. E. Lockhart, R. K. Anderson, F. de P. Miranda, and R. S. Harris. 1945. Composition of typical Mexican foods. J. Nutrition 29(5):317-329.

975. Cremer, J. E. 1958. The biochemistry of organotin compounds. The conversion of tetraethyltin into triethyltin in mammals. Biochem. J. 68(4):685-692.

976. Crepaldi, G., G. Allegri, A. De Antoni, and M. Muggeo. 1972. Tryptophan metabolism in old subjects. G. Gerontol. 20(12): 1177-1186.

977. Cricchi, M., and A. G. Secchi. 1965. Nicotinic acid inhibition of the degranulation of the mast cells of the isolated guinea pig choroidal membrane during the antigen-antibody reaction. Ann. Ottalmol. Clin. Oculist. 91(6):410-414.

978. Crino, S., and S. Lenzi. 1939. The influence of nicotinic acid on the carbohydrate metabolism and the white blood cell count. Biochim. Terap. Sper. 26:168-170.

979. Crnoevic, V., and M. Gugusevic. 1956. Production of sirup with antipeptic ulcer substance from fresh cabbage. Preliminary communication. Zbornik Rad. Poljopriv. Fak. Univ. Beograd 4(2):231-240.

980. Cronin, E., and R. B. Stoughton. 1962. Percutaneous absorption of nicotinic acid and ethyl nicotinate in human skin. Nature 195(4846):1103-1104.

981. Cronin, E., and R. B. Stoughton. 1963. Nicotinic acid and ethyl nicotinate in excised human skin. Arch. Dermatol. 87:445-449.

982. Crosca, A. 1944. Calcium and potassium in blood serum after nicotinamide injection. Atti reale accad. peloritana 45:199-204

983. Crosca, A., and T. Aversa. 1942. Nicotinamide and glycemic curves from glucose injection. Med. ital. 23:12 p.

984. Cruess-Callaghan, A., and O. FitzGerald. 1966. Mechanism of nicotinic acid induced hyperuricemia. Irish J. Med. Sci. 491:484-487.

985. Cruickshank, E. K. 1952. Dietary neuropathies. Vitamins and Hormones 10:1-45.

986. Crum, L. R., R. G. Harbecke, J. J. Lech, and D. N. Calvert. 1970. Substrate specificity and inhibition characteristics of a fluoride-sensitive tributyrinase. Biochim. Biophys. Acta 198(2):229-235.

987. Cruz-Coke, E., J. M. Calvo, and A. Jadresic. 1950. Effect of tocopherol phosphate on the excretion of N1-methylnicotinamide and of 2,4-dinitrophenol on the excretion of N1-methylnicotinamide and total creatinine in the urine of rats. Bol. Soc. Biol. Santiago, Chile 7:76-81.

988. Cseh, G., and L. Graf. 1971. Lipolytic effect of lipotropic hormone (lipotropin) in vitro. Polypeptide Horm., Proc. Congr. Hung. Soc. 1971:191-196.

989. Cucinotta, D. 1972. Clinical experience with a new pharmacological association in atherosclerosis and dislipidemic diseases. Minerva Med. 63(15):870-885.

990. Cultrera, G., A. Farroni, P. Giarola, and A. Gibelli. 1970. Fibrinogen turnover during treatment with betaine nicotinate, alone and together with aminophylline. Gazz. Int. Med. Chir. 75(14):1050-1057.

991. Cunego, A., and M. Guidi. 1964. Urinary excretion of nicotinic acid metabolites in chronic alcoholics. Arch. "E. Maragliano" Patol. Clin. 20(5):367-371.

992. Cuny, L., and D. Quivy. 1942. Antiheparin action of nicotinic acid in vitro. Compt. Rend. Soc. Biol. 136:707-708.

993. Cuny, L., P. Bouvet, and J. Devillers. 1942. Estimation of nicotinamide in various dried organs. Bull. Soc. Chim. Biol. 24:154-160.

994. Cuny, L., Th. Gayet-Hallion, and D. Quivy. 1940. Effect of injections of nicotinic acid on the circulation of the dog. Compt. Rend. Soc. Biol. 134:416-419.

995. Curt Boeckel, C. R. 1962. Paper chromatography of vitamins B-1 and B-2 and niacin. Sem. Med. (B Air) 120:344-345.

996. Curti, B., and G. Porcellati. 1963. Properties of nicotinamide deamidase of pigeon liver extracts. Giorn. Biochim. 12(1): 13-27.

997. Curzon, G., and A. R. Green. 1969. Rat liver tryptophan pyrrolase activity and brain 5-hydroxytryptamine. Biochem. J. 111(3):15P.

998. Cust, G. 1965. An outbreak of unusual food poisoning after a school meal. Med. Offr. 113(9):124-125.

999. Cutillo, S., V. Ansanelli, and G. Stoppoloni. 1967. Effects of noradrenaline, glucagon, and nicotinic acid on the concentration of plasma nonessential fatty acids (NEFA) and glucose in dystrophic babies. Metabolismo 3(1):37-40, 43-48.

1000. Cutillo, S., V. Ansanelli, G. Stoppoloni, and V. Pacelli. 1968. Effect of nicotinic acid on plasma nonesterified fatty acid levels in children. I. Subjects of various ages. Boll. Soc. Ital. Biol. Sper. 44(1):46-49.

1001. Cymerman-Craig, J., S. D. Rubbo, and B. J. Pierson. 1955. Chemical constitution and antituberculous activity. II. Bases possessing the biphenyl structure. Brit. J. Expti. Pathol. 36:254-260.

1002. Czarski, Z, S. Checinski, and W. Berbec. 1967. A case of poisoning with chlorinated hydrocarbons from the insecticide ditox. Pol. Tyg. Lek. 22(1):27-29.

1003. Czezowska, Z. B. Kowal-Gierczak, and M. Wrzyszcz. 1970. Effect of nicotinic acid amide on urinary excretion of 17-hydroxy steroids in patients with allergic bronchial asthma. Pol. Tyg. Lek. 25(30):116-118.

1004. Dacha, U., and C. Ricci. 1948. Nicotinamide metabolism in dogs. Acta Vitaminol. 2:30-32.

1005. Da Cruz, A. 1945. Effect of oxidation-reduction vitamins on blood glycerophosphatase. Arch. Portugaises Sci. Biol. 7(3 Suppl. 2, Compt. Rend. Soc. Port. Biol.):70-72.

1006. Dadd, R. H., D. L. Krieger, and T. E. Mittler. 1967. The artificial feeding of the aphid Myzus persicae. IV. Requirements for water-soluble vitamins and ascorbic acid. J. Insect. Physiol. 13(2):249-272.

1007. Dagg, C. P., D. A. Karnofsky, C. C. Stock, C. R. Lacon, and J. Roddy. 1955. Effects of certain triazenes on chick embryos and on tumors explanted to the chorioallantois. Proc. Soc. Exptl. Biol. Med. 90:489-494.

1008. Dagianti, A., A. Chiavaro, G. Giordano, A. M. Verde, and P. Angrisani. 1963. The shape of the dye curve during the pharmacological action induced by nicotinic acid. Boll. Soc. Ital. Biol. Sper. 39(24):2101-2104.

1009. D'Agostino, L. 1947. The vascular of erythremic effect of nicotinic acid upon various portions of the body of men in health and various diseases. Acta Vitaminol. (Milan) 1:130-135.

1010. Dahlberg, A. C., and J. K. Loosli. 1948. Nutritive value of commercial ice cream. J. Am. Dietetic Assoc. 24(1):20-22.

1011. Dainow, I. 1944. Clinical studies on anti-allergic properties of nicotinamide. Ztschr. Vitaminforsch. 15:245-250.

1012. Daldorf, G. 1940. Vitamin C: functions and requirements. J. Mt. Sinai Hosp, N. Y. 7:3-15.

1013. Dalton, C. 1967. Antilipemic effect of nicotinamide. Nature 216(5117):825.

1014. Dalton, C., T. C. VanTrabert, and J. X. Dwyer. 1970. Relation of nicotinamide and nicotinic acid to hypolipidemia. Biochem. Pharmacol. 19(9):2609-2619.

1015. Dalton, C., T. C. VanTrabert, and J. X. Dwyer. 1971. Hypolipidemic effects of nicotinamide in the rat arising form its transformation to nicotinic acid. Metab. Eff. Nicotinic Acid its Deriv., Proc. Workshop 1970:65-75.

1016. Dalton, C., C. Kowalski, J. Mallon, and C. Marschhaus. 1968. The cholesterol-lowering mechanism of nicotinic acid and nicotinyl alcohol tartrate. J. Atheroscler. Res. 8(2):265-276.

1017. Dalton, C., J. B. Quinn, H. J. Crowley, and O. N. Miller. 1971. Comparison of the effect of nicotinic acid derivatives on in vitro lipolysis and in vivo lipid lowering. Metab. Eff. Nicotinic Acid its Deriv., Pro 1971:331-339.

1018. Daly, R. J., and F. J. Kane, Jr. 1965. Two severe reactions to benzodiazepine compounds. Am. J. Psychiat. 22(5):577-578.

1019. Damiano, A. 1956. Adrenaline and insulin hypothermia in niacinamide hypervitaminosis. Ipervitaminosi Vitaminologia 11-13:809-814.

1020. Dammann, C. 1969. Experiences with new Cosaldon forms. Med. Klin. 64:344-348.

1021. Danaraj, T. J. 1949. The cerebellar aspect of nutritional spinal ataxia. Trans. Roy. Soc. Trop. Med. Hyg. 43(3):343-344.

1022. Danforth, H. B. 1964. The use of nicotinic acid in myringoplasty surgery. A preliminary report. Laryngoscope 74(11): 1582-1585.

1023. Daniel, L., and L. C. Norris. 1945. The riboflavin, niacin, and thiamine contents of dried leguminous seeds. J. Nutrition 30:31-36.

1024. Daniel, L. J., G. F. Combs, L. C. Norris, and G. F. Heuser. 1947. A new bone deformity in the chick. Proc. Soc. Exptl. Biol. Med. 65:273-275.

1025. Danilova, N. K., R. N. Vilenskaya, S. S. Kanevskaya, and A. N. Kalyuk. 1971. Chemotherapy of limited destructive kidney tuberculosis. Urol. Nefrol. 36(6):13-16.

1026. Dann, W. J. 1937. Nicotinic acid and vitamin B2. Science 86:616-617.

1027. Dann, W. J. 1944. The human requirement for nicotinic acid. Federation Proc. 3:159-161.

1028. Dann, W. J. 1946. Effect of excess nicotinamide on growth of the chicken. Federation Proc. 5(1 Pt. 2):231.

1029. Dann, W. J. 1947. The bioassay for nicotinic acid. In: Biological Symposia, edited by Jaques Cattell, et al. Vol. XII. pp. 181-182.

1030. Dann, W. J., and P. Handler. 1941. The quantitative estimation of nicotinic acid in animal tissues. J. Biol. Chem. 140:201-213

1031. Dann, W. J., and P. Handler. 1942. The nicotinic acid content of meat. J. Nutrition 24(2):153-158.

1032. Dann, W. J., and J. W. Huff. 1946. Metabolism of excess nicotinamide by the chicken. Federation Proc. 5(1 Pt. 2):131.

1033. Dann, W. J., and J. W. Huff. 1947. Dinicotinylornithine: a metabolite of nicotinamide in the chicken. J. Biol. Chem. 168:121-127.

1034. Dann, W. J., H. I. Kohn, and P. Handler. 1940. The effect of pyrazine acids and quinolinic acid on the V-factor content of human blood and upon canine blacktongue. J. Nutrition 20(5): 477-490.

1035. Danilyants, E. I. 1964. The content of vitamin C and nicotinic acid and the orothrombin time in patients with vitiligo treated py psoralen. Med. Zh. Uzbekistana 7:43-46.

1036. Danto, B. L. 1969. Trifluopromazine versus pentylenetetrazol-nicotinic acid for treatment of chronic brain disease on a general-hospital psychiatric service. J. Am. Geriat. Soc. 17:414-420.

1037. Daroga, R. P. 1941. New colorimetric method for determining small quantities of nicotinic acid. J. Soc. Chem. Ind. 60: 263-266.

1038. Das, M. L., and B. C. Guha. 1957. Isolation of niacinogen from wheat bran. Sci. and Culture (Calcutta) 23:156-157.

1039. Das, M. L., and B. C. Guha. 1960. Isolation and chemical characterization of bound niacin (niacinogen) in cereal grains. J. Biol. Chem. 235:2971-2976.

1040. D'Ascenzo, G., and W. W. Wendlandt. 1970. Thermal properties of some metal pyridinecarboxylates. Anal. Chim. Acta 50(1): 79-91.

1041. Daum, K., W. W. Tuttle, R. Kisgen, C. J. Imig, R. Bongey, and C. Martin. 1951. Effect of different types of breakfasts on thiamine and niacin excreted by men. J. Am. Dietetic Assoc. 27(4):298-301.

1042. Davis, G. K., E. B. Hale, and V. A. Freeman. 1943. Response of pigs given large doses of Salmonella choleraesuis to sulfaguanidine, nicotinic acid, thiamine and pyridoxine. J. Animal Sci. 2:138-145.

1043. Davis, M. V., H. G. Oldham, and L. J. Roberts. 1946. Riboflavin excretions of young women on diets containing varying levels of the B vitamins. J. Nutrition 32:143-161.

1044. Dawson, R. F., and H. H. Robson. 1949. Cystine and the stabilization of the microbiological assay for niacin. Am. J. Bot. 36(10):822.

1045. Dawson, R. F., D. R. Christman, and R. U. Byerrum. 1971. Biosynthesis of nicotinic acid in plants and microbes. Methods Enzymol. 18(Pt. B):90-113.

1046. Dawson, R. F., D. R. Christman, A. F. D'Adamo, M. L. Solt, and A. P. Wolf. 1958. Pathway of nicotine biogenesis. Chem. & Ind. (London) 1958:100.

1047. Day, E. J., and B. C. Dilworth. 1966. Effects of supplementing laying rations with certain B-complex vitamins. Brit. Poultry Sci. 7(2):99-103.

1048. Day, P. L., W. C. Langston, and W. J. Darby. 1938. Failure of nicotinic acid to prevent nutritional cytopenia in the monkey. Proc. Soc. Exp. Biol. Med. 38(5):860-863.

1049. Dayton, P. G., A. W. Pruitt, J. L. McNay, and J. Steinhorst. 1972. Studies with triamterene, a substituted pteridine: Unusual brain to plasma ratio in mamals. Neuropharmacology 11(3):435-446.

1050. De, H. N., and K. C. Banerjee. 1948. Nicotinic acid requirements of Indian adult. Indian J. Med. Research 36:335-339.

1051. De, H. N., and S. N. Banerjee. 1949. Mutual influence of nicotinic acid and riboflavin in metabolism. Indian J. Med. Research 37:293-300.

1052. De, H. N., and P. Datta, Jr. 1951. Studies on the biosynthesis of B-vitamins. I. Investigation on the site and mechanism of biosynthesis of nicotinic acid in albino rats on diets containing different amino acids and free from nitrogen. Indian J. Med. Res. 39(1):63-72.

1053. De, H. N., and S. R. Guha. 1951. Studies on the biosynthesis of B-vitamins. IV. Effect of different carbohydrates and some inorganic and organic nitrogenous compounds on the biosynthesis of nicotinic acid in albino rats. Indian J. Med. Res. 39(3): 337-342.

1054. De, H. N., P. Datta, and J. K. Roy. 1951. Studies on the biosynthesis of B-vitamins. VI. Effect of different bactericidal agents on the biosynthesis of nicotinic acid and riboflavin in animals. Indian J. Med. Res. 39(3):353-360.

1055. De, H. N., P. Datta, and P. N. Mankad. 1955. Studies on riboflavin metabolism with typical Indian dietaries. Indian J. Med. Res. 43:501-509.

1056. Dean, P. M., and E. K. Matthews. 1972. Bioelectrical properties of pancreatic islet cells. Effect of diabetogenic agents. Diabetologia 8(3):173-178.

1057. Dean, R. F. A., and W. I. M. Holman. 1948. Nicotinic acid in human blood cells at birth. Nature 161:439.

1058. Dean, R. F. A., and W. I. M. Holman. 1949. Metabolism of nicotinic acid by infants. Nature 163:97.

1059. Dean, R. F. A., and W. I. M. Holman. 1950. Excretion and intake of B vitamins in newborn infants. Arch. Disease Childhood.25:292-296.

1060. Dean, R. T., and V. L. King. 1946. Nicotinic acid. U.S. Pat. 2,409,345.

1061. Debackere, M., and L. Laruelle. 1968. Isolation, detection, and identification of some alkaloids or alkaloid-like substances in biological specimens from horses, with special reference to doping. J. Chromatogr. 35(2):234-247.

1062. Debay, A., J. Marche, and M. Lamotte. 1963. Comparison of the effects exerted by pyridoxine and nicotinamide against the convulsive crises provoked by isoniazid. Therapie 18(1):69-77.

1063. De Bellis, L. 1950. The blood bilirubin curve after administration of nicotinic acid in eclampsia. Boll. Soc. Ital. Biol. Sper. 26:987-990.

1064. Debernardi, G. 1957. Hyperniacinosis and traumatic alveolitis. Vitaminologia (Turin) 15:171-183.

1065. De Caprio, P. 1942. Study regarding the effect of vitamins B and PP upon the test according to Aldrich-McClure. Pediatria 50:105-114.

1066. De Carvalho, L. 1954. Angiopneumography in the study of the pharmacodynamic properties of certain drugs. Diseases of the Chest 25:121-127.

1067. De Carvalho, R. R. 1947. Characterization and determination of nicotinamide. J. Farm. (Lisbon) 6:41-62.

1068. De Chatelet, L. R. 1972. Nicotinamide adenosine dinucleotide glycohydrolase (EC 3.2.2.5) activity in guinea pig polymorphonuclear leukocytes. Infect. Immun. 6(3):302-307.

1069. Decker, K., and E. Rupprecht. 1970. Permeation of NAD from the blood into the liver cells. Hoppe-Seyler's Z. Physiol. Chem. 351(1):15-24.

1070. DeFelice, F. 1949a. New studies on vitamin interrelations. 8. The biological relations between ascorbic acid and nicotinic acid. Fisiol. e Med. (Rome) 17:55-67.

1071. DeFelice, F. 1949b. New studies on vitamin interrelations. 9. The action of synthetic pyridoxin on experimental scurvy. Fisiol. e Med. (Rome) 17:95-106.

1072. De Flora, A., G. A. Calabria, and I. Lorenzoni. 1966. Acute hypervitaminosis PP. I. Effect of adrenalectomy on hepatic glucose 6 phosphate dehydrogenase and 6-phosphogluconic dehydrogenase activities. Boll. Soc. Ital. Biol. Sper. 42(14):897-899.

1073. De Franchis, V., and A. Vianello. 1947. Physico-chemical variations of blood in relationship to variation of blood pressure. Giotn. Clin. Med. 28:6-17.

1074. De Franciscis, G., and F. Marsico. 1953. Behaviour of iron in the serum after intravenous injection of vitamin PP in normal and splenectomised dogs. Boll. Soc. Ital. Biol. Sper. 29:267-269.

1075. Dejica, D., S. Diaconu, N. Raducanu, V. Preda, and O. Craciun. 1960. Influence of the vitamins PP, B12, and E on the regeneration of the liver of rabbits after partial hepatectomy. Spitalul (Bucharest) 73:355-360.

1076. Delachaux, A., and W. Ott. 1943. The metabolism of Fe and the vitamins in the course of physical exercise and training. Schweiz. Med. Wochschr. 73:1026-1028.

1077. De Lacy, P., C. Hooft, J. Timmermans, and J. Snoek. 1964. Biochemical aspects of Hartnup disease. Ann. Paediat. 202(3): 145-160.

1078. De Lacy, C. Hooft, J. Timmermans, and J. Snoeck. 1964. Biochemical aspects of Hartnup disease. II. Some observations on rats about tryptophan metabolism. Ann. Paediat. 202(4): 253-262.

1079. De Langen, C. D., J. C. Boswijk, and C. L. C. van Nieuwenhuizen. Nederland. Tijdschr. Geneeskunde 82:4970-4976.

1080. De la Riega, E., Jr., and C. Burrier. 1960. Studies of blood lipids in relation to atheroslerosis. The effect of nicotinic acid on the electrophoretic lipidogram in atherosclerosis. Dia. Med. 32:2114-2115.

1081. Delgado-Rodriguez, C. A. 1964. Quantitative changes of blood cholesterol due to the effect of nicotinic acid (man). Confed. Med. Panamer. Rev. 11(5):290-294.

1082. Del Guercio, F., and G. Conti. 1963. Considerations on the action of vasodilator drugs by means of microcirculatory data. Study of human bulbar conjunctiva. I. Myolytic drug: Nicotinic acid. Med. Clin. Sperim. 13(4):383-389.

1083. Delindati, G. 1952. The vitamin content of tomatoes and derivvatives. Determination with biological method of vitamin PP. Ind. Conserve Aliment. 27:9-12.

1084. Dell'Omodarme, G., and F. Brunori. 1961. Sorbitol hexanicotinate. Lowering effects on blood cholesterol and lipids. Boll. Chim. Farm. 100:732-744.

1085. Dell'Omodarme, G., and U. Marinari. 1961. Direct action of some substances of biological significance which influence the metabolism of the isolated frog heart. Chronotropic and inotropic effects. Boll. Soc. Ital. Biol. Sper. 37:441-444.

1086. Del Regno, F. 1939. Nicotinic acid content of some foods. Quaderni Nutriz. 6:368-373.

1087. Del Regno, F. 1939. Effect of nicotinic acid on the activity of phosphatase. Boll. Soc. Ital. Biol. Sper. 14:397-398.

1088. Deltombe, J. 1953. Analytical study of the nicotinic acid group. J. Pharm. Belg. 8:59-75.

1089. De Luca, R., and G. Santangelo. 1960. Cortisone derivatives and hyperbilirubinemia due sodium nicotinate. Boll. Soc. Ital. Biol. Sper. 36:704-706.

1090. DeMelo, R. H., A. E. Rakoff, A. Cantarow, and K. E. Paschkis. 1948. Mechanism of inactivation of alpha-estradiol by rat liver "in vitro." Endocrinology 43(2):97-104.

1091. Demichev, A. P. 1960. Effect of nicotinic acid on unconditioned reflectory function of the salivary gland. Fiziol. Zhur. S.S.S.R. 465:561-564, 657-661.

1092. De Nicola, P. 1968. Determination of the antithrombotic effect of vasoactive drugs. Settim. Med. 56(19):1057-1063.

1093. De Nicola, P. 1970. Antifibrinolytic drugs, hemostatic balance and therapy of hemorrhagic and thromboembolic diseases. Proteases Antiproteases Cardioangiol., Int 1970: 73-79.

1094. De Nicola, P., et al. 1963. Activation of fibrinolysis by the prolonged oral administration of a nicotinic derivative in arteriosclerotic subjects. G. Geront. 11:955-972.

1095. De Nicola, P., et al. 1966. Comparative research on the fibrinolytic action of different nicotinic acid derivatives following their prolonged administration into rabbits. Thromb. Diath. Haemorrh. 15:231-237.

1096. De Nicola, P., F. Soardi, and A. Gibelli. 1962. Research on thrombolytic therapy (with natural substances and synthetic compounds). Proc. Intern. Congr. Hematol., 8th, Tokyo, 1960, 3:1594-1598.

1097. Dennis, P. O., and H. G. Rees. 1949. The chemical determination of nicotinic acid in food products. Analyst 74(882):481-484.

* 1098. Denson, R. 1962. Nicotinamide in the treatment of schizophrenia. Dis. Nerv. System 22(3):167-172.

1099. Denton, C. A., W. L. Kellogg, and H. R. Bird. 1946. The effect of diet, age and sex on the nicotinic acid content of the tissues of chickens. Poultry Sci. 25(4):400.

1100. Denton, C. A., W. L. Kellogg, and H. R. Bird. 1947. The effect of diet, age, and sex on the nicotinic acid content of the tissues of chickens. Poultry Sci. 26:299-303.

1101. De Oliveira, J. N., and C. R. da Silva. 1959. B-complex vitamins in Portuguese beers. Anais Fac. Farm. Porto 19:43-69.

1102. De Pra, M., and M. Bruschi. 1963. The urinary elimination of some vitamins in rickets. Arch. Studio Fisiopatol. Clin. Ricambio 27(3):188-194.

1103. De Ritter, E., L. Drekter, J. Scheiner, and S. H. Rubin. 1952. Urinary excretion of hydrazine derivatives of isonicotinic acid in normal humans. Proc. Soc. Exptl. Biol. Med. 79(4):654-658.

1104. Deryagina, G. P. 1964. Effect of drugs widely used in atherosclerosis on the blood clotting system. Kazansk. Med. Zh. 1964(6):26-28.

1105. De Soldati, L. 1964. The effect of large doses of nicotinic acid on blood lipids and on the coagulation of the blood determined by thromboelastography. In: R. Altschul, Editor. Niacin in Vascular Disorders and Hyperlipemia. Charles C. Thomas, Springfield, Illinois. p. 287-294.

1106. De Soldati, L., S. Balassanian, and G. Striztler. 1960. Blood lipide levels in patients with atherosclerosis under treatment with ascorbic acid. Prensa Med. Arg. 47:636-641.

1107. De Soldati, L., G. Stritzler, S. Balassanian, and M. E. Bourguet. 1959. Effect of nicotinic acid on blood lipids in arteriosclerotic patients. Cardiologia 35(2):84-92.

1108. Detrick, L. E., H. C. Upham, R. W. Springsteen, and T. J. Haley. 1963. Increased intestinal elimination of N'-methylnicotinamide in irradiated rats. Internatl. J. Radiation Biol. 7(2):161-166.

1109. Deuel, H. J., Jr., N. Halliday, L. F. Hallman, C. Johnston, and A. J. Miller. 1941. The effect of vitamin A intake on vitamin A content of butterfat. J. Biol. Chem. 139:479-480.

1110. Deutsch, E., and M. Fischer. 1962. Drug-induced fibrinolysis. Proc. Intern. Congr. Hematol., 8th, Tokyo 1960, 3:1718.

1111. Deutsch, E., P. Eisner, and M. Fischer. 1960. Medically induced fibrinolysis. Wien Z. Inn. Med. 41:457-472.

1112. De Valois, J. C., and J. P. C. Peperkamp. 1971. The action of some drugs on the cerebral circulation. Arch. Int. Pharmacodyn. Ther. 189(2):390-391.

1113. Deviatnin, V. A., et al. 1963. Determination of nicotinamide in injection solutions. Med. Promyshl. S.S.S.R. 17:50-51.

1114. Devyatnin, V. A. 1953. Addition of vitamins to food in the case of public nourishment. Voprosy Pitaniya 12(6):79-80.

1115. Dewan, J. G. 1943. An alcohol detoxication mechanism in the central nervous system. Am. J. Psychiatry 99(4):565-568.

1116. De Wulf, H., W. Stalmans, and H. G. Hers. 1970. Effect of glucose and of a treatment by glucocorticoids on the activation in vitro of liver glycogen synthetase. Eur. J. Biochem. 15(1):1-8.

1117. Deysson, G., and M. Delage. 1965. The effect of various B vitamins on the mitoclastic activity of colchicine on onion root cells protective effect of a mixture of nicotinamide and riboflavine. C. R. Acad. Sci. 261(23):5187-5190.

1118. Deysson, G., and A. Delcourt. 1970. Effect of structural analogs of nicotinamide on the mitoclastic activity of colchicine. C. R. Soc. Biol. 164(12):2440-2443.

1119. Dhopeshwarkar, G. A., and N. G. Magar. 1954. Nutritive value of canned foodstuffs. I. Effect of canning procedures on vitamin contents of fruits and vegetables. J. Sci. Ind. Research (India) 13B:849-852.

1120. Dhopeshwarkar, G. A., and N. G. Magar. 1955. Nutritive value of canned foods in India. II. Effect of storage at different temperatures. J. Sci. Ind. Research (India) 14C:27-31.

1121. Dhotel, Y. 1953. Potentiation of adrenocorticotropin (ACTH) given intravenously by association with vitamins. J. Sci. Med. Lille 71:117-129.

1122. Di Castro, G. 1954. Vitamin and essentail biological principal contents of cool-stored fruits and vegetables. Atti 2 Congr. Nazl. Freddo 1953:69-79.

1123. Dickens, F. 1946. The toxic effects of oxygen on brain metabolism and on tissue enzymes. I. Brain metabolism. Biochem. J. 40(1):145-171.

1124. Dietrich, L. S. 1960. Nicotinamide and nicotinic acid uptake by ascites tumor cells. Fed. Proc. 19(1 Pt. 1):413.

1125. Dietrich, L. S. 1963. Augmentation of the anti-tumor activity of 6-aminonicotinamide by estrogens (mouse). In: 54th Annual meeting of the American Association for Cancer Research, Inc., 1963. Proc. Amer. Assoc. Cancer Res. 4(1):16.

1126. Dietrich, L. S. 1964. Augmentation of 6-aminonicotinamide antagonism of tumor growth by compounds with estrogenic activity. Cancer Res. 24(1 Pt. 1):61-63.

* 1127. Dietrich, L. S. 1971. Regulation of nicotinamide metabolism. Am. J. Clin. Nutr. 24(7):800-804.

1128. Dietrich, L. S., and I. M. Friedland. 1960. 6-Aminonicotinamide and 6-amionicotinic acid metabolism in nucleated and nonnucleated erythrocytes. Arch. Biochem. Biophys. 88(2):313-317.

1129. Dietrich. L. S., and O. Muniz. 1972. Inhibition of nicotinamide phosphoribosyltransferase by pyridine nucleotides. Biochemistry 11(9):1691-1695.

1130. Dietrich, L. S., L. Franklin, and B. Farinas. 1970. Effect of hyperphysiological levels of hexestrol on the hepatic metabolism of nicotinate in the mouse. Proc. Soc. Exp. Biol. Med. 133(1):160-163.

1131. Dietrich, L. S., L. Martinez, and L. Franklin. 1968. Role of the liver in systemic pyridine nucleotide metabolism. Naturwissenschaften 55(5):231-232.

1132. Dietrich, L. S., W. J. Monson, and C. A. Elvehjem. 1952a. Folic acid, leucovorin, vitamin B12, and the excretion of N1-methylnicotinamide. J. Biol. Chem. 199(2):765-771.

1133. Dietrich, L. S., W. J. Monson, and C. A. Elvehjem. 1952b. Effect of folic acid and citrovorum factor on N-methylnicotinamide excretion in the rat. Fed. Proc. 11(1):202.

1134. Dietrich, L. S., L. Fuller, I. L. Yero, and L. Martinez. 1966. Nicotinamide mononucleotide pyrophosphorylase activity in animal tissues. J. Biol. Chem. 241(1):188-191.

1135. Dietrich, L. S., O. Muniz, B. Farinas, and L. Franklin. 1968. 6-Aminonicotinamide-14C utilization by the 755 tumor and host liver tissue. Cancer Res. 28(8):1652-1654.

1136. Di Fonzo, M., and A. Sangiorgi. 1953. Action of antibacterial substances on the dehydrogenase of Schardinger. Boll. Soc. Ital. Biol. Sper. 29:1620-1622.

1137. Dimitrova-Ruseva, E., and T. Lilova. 1969. Growth of Mentha piperita and synthesis of essential oil as affected by thiamine (vitamin B1), pyridoxine (vitamin B6), and nicotinic acid (vitamin PP). Rastenievud. Nauki 6(3):73-83.

1138. Dinerman, A. A. 1957. Effect of nicotinic acid on body changes caused by an increase of cystine in the diet. Voprosy Pitaniya 16(1):36-43.

1139. Dioguardi, N., G. Semenza, and E. Mirelli. 1952. Nicotinic acid metabolism. First contribution to the knowledge of amidation. Arch. Studio Fisiopatol. e Clin. Ricambio 16: 241-244.

1140. Dioguardi, N., and L. Martini. 1951. Rate of excretion in the urine of products giving the Huff reaction after administration of nicotinic acid amide in healthy human subjects. Acta Vitaminol. 5:243-245.

1141. Dioguardi, N., L. Contro, and L. Ventura. 1954. Interference of nicotinamide with the excretion of creatine and trigonelline. Atti Soc. Lombarda Sci. Med. e. Biol. 9:211-213.

1142. Di Prima, J. 1951. The action of nicotinic acid upon corneal lesions. Rass. ital. Ottalmol. 19:260-284.

1143. Di Raimondo, F. 1951. In vitro and in vivo antagonism between vitamins and antibiotics. Z. Vitaminforsch. 23:1-12.

1144. Di Raimondo, F., N. Mannino, and L. Trinchese. 1952. Side-effects of antibiotics in the rat: vitamin B complex content of the liver. Internatl. Zeitschr. Vitaminforsch. 24(3): 294-301.

1145. Di Raimondo, F., D. Angarano, N. Mannino, and L. Trinchese. 1952. Side effects of antibiotics on healthy subjects and on patients with special reference to urinary excretion of the vitamin B complex. Intern. Z. Vitaminforsch. 24:302-317.

1146. Dittmann, J. 1967. Separation of some vitamins by thin-layer chromatography on cellulose. Deut. Gesundheitsw. 22(26): 1217-1218.

1147. Dixon, M. 1961. On the nomenclature of nicotinamide nucleotide coenzymes. Biokhimiya 26:563-566.

1148. Dobrescu, D., E. Coeugniet, and P. Anisie. 1969. Effect of certain stimulants of respiration on the analgesic action of fentanyl. Anesth., Analg., Reanim. 26(5):679-684.

1149. Dobrovolskaia-Zavadskaia, N. 1945. Effect of thiamine on growth of spontaneous tumors in mice. Compt. Rend. Soc. Biol. 139:494-495.

1150. Dobry, A. 1941. A new reagent in biological chemistry; Roussin's salt or iron nitrosyl sulfide. Trav. Membres Soc. Chim. Biol. 23:1438-1444.

1151. Dode, M., P. Gavaudan, and H. Poussel. 1946. Narcosis and precipitation of cellular lipides. Compt. Rend. 223:521-523.

1152. Dojphode, N. G., and M. S. Bamji. 1970. Effect of Aureomycin on the nutritional status of the B-vitamins in humans. Int. Z. Vitaminforsch. 40(1):58-63.

1153. Domeniconi, G. 1941. Nicotinamide and carbohydrate metabolism. I. Influence on basal glucemia and on the increase caused by glucose administration and adrenaline. Med. Sper.-Arch. ital. 8:151-160.

1154. Domino, E. F., K. Yamamoto, and A. T. Dren. 1968. Role of cholinergic mechanisms in states of wakefulness and sleep. Progr. Brain Res. 28:113-133.

1155. Donald, E. A., N. C. Esselbaugh, and M. M. Hard. 1962. Nutritional status of selected adolescent children. V. Riboflavin and niacin nutrition assessed by serum level and subclinical symptoms in relation to dietary intake. Am. J. Clin. Nutr. 10:68-78.

1156. Donnasibilla, L. B., and O. Olivi. 1955. Deamination and B complex vitamins in children. IV. Action of niacinamide. Acta Vitaminol. 9:249-252.

1157. Doss, H. H., A. Abd el Hay, and G. Hamel. 1961. The effect of various agents on the blood cholesterol level of the albino rat. J. Pharm. Sci. U. Arab. Rep. 2(1):21-27.

1158. Dotta, F., and C. Campana. 1953. Excretion in the urine of nicotinic acid, nicotinamide and their N1-methylated derivatives in healthy man, and in the rat, treated with isoniazide. Acta Vitaminol. 7:189-193.

1159. Douglas, W. W., and R. P. Rubin. 1961. Mechanism of nicotinic action at the adrenal medulla: Calcium as a link in stimulus-secretion coupling. Nature 192(4807):1087-1089.

1160. Dovgjallo, G. H., G. V. Kulago, and I. F. Mironcik. 1969. Comparison of the effects of vitamins E and A, nicotinic acid and the diet No. 10 on some lipid and protein values in patients with atherosclerosis. Terap. Arkh. 41(11):34-38.

1161. Dovgyallo, G. Kh., and I. S. Gul'ko. 1963. Use of nicotinic acid in atherosclerosis. Terapevt. Arkh. 35(9):279-289.

1162. Dovgyallo, G. Kh., and I. S. Gul'ko. 1971. Interrelation between the shifts of some biochemical and electrophysiological indices during myocardial infarction. Ter. Arkh. 43(7):40-43.

1163. Dovgyallo, G. Kh., G. V. Kulago, and I. F. Mironchik. 1969. Comparative evaluation of the effect of vitamins E and A and nicotinic acid and diet No. 10 on some indices of lipid and protein metabolism in patients with atherosclerosis. Ter. Arkh. 41(11):34-38.

* 1164. Dreizen, S., A. I. Reed, and T. D. Spies. 1951. The nicotinic acid content of saliva and dental caries activity. Internat. Zeitschr. Vitaminforsch. 22(4):396-400.

1165. Dreizen, S., C. N. Spirakis, and R. E. Sloan. 1963. Effect of antimetabolites of selected B vitamins on experimental dental caries in the rat. Intern. Z. Vitaminforsch. 33:321-326.

1166. Drozdowskyj, J. 1961. Studies on Spanish nutrition. XXVII. Study of the nutrition of the people of Madrid during 1958. Anales Bromatol. (Madrid) 13:107-137.

1167. Duchene-Marullaz, P., G. Rispat, J. P. Perriere, J. Hache, and Cl. Labrid. 1971. Pharmacodynamic properties of niaprazine, a new antihistamine. Therapie 26(6):1203-1209.

1168. Duesel, B. F., and H. L. Friedman. 1949. Nicotinamide. U.S. Pat. 2,471,518.

1169. Dulin, W. E., and B. M. Wyse. 1969. Ability of compounds to block the diabetogenic activity of streptozotocin. Diabetes 18(7):459-466.

1170. Dulin, W. E., and B. M. Wyse. 1969. Reversal of streptozotocin diabetes with nicotinamide (rat). Proc. Soc. Exp. Biol. Med. 130(3):992-994.

1171. Duncan, C. H., and M. M. Best. 1959. Lack of nicotinic acid effect on cholesterol metabolism of the rat. J. Lipid Research 2:187.

1172. Duncan, C. H., and M. M. Best. 1960. Lack of nicotinic acid effect on cholesterol metabolism of the rat. J. Lipid Res. 1(2):159-6163.

1173. Duncan, C. H., M. M. Best, and G. L. Robertson. 1965. A comparison of the effects of ethyl chlorophenoxyisobutyrate and nicotinic acid on plasma free fatty acids. Lancet 7378:191-193.

1174. Duncan, M., and H. P. Sarett. 1951. Effect of nicotinic acid and tryptophan on pyridine nucleotides of red blood cells in man. J. Biol. Chem. 193:317-324.

1175. Dunker, C. F., M. Berman, G. G. Snider, and H. S. Tubiash. 1953. Quality and nutritive properties of different types of commercially cured hams. III. Vitamin content, biological value of the protein, and bacteriology. Food Technol. 7:288-291.

1176. Duraiswami, P. K. 1952. Experimental causation of congenital skeletal defects and its significance in orthopaedic surgery. J. Bone and Joint Surg. 34-B(4):646-693.

1177. Durnin, J. V. G. A., E. C. Blake, and J. M. Brockway. 1957. The diets of middle-aged Glasgow housewives and their adult daughters. Brit. J. Nutrition 11(1):94-98.

1178. Dutta, S., A. K. Acharyya, and U. P. Basu. 1969. Utilization of beta-picoline fraction for nicotinic and isonicotinic acid. Indian J. Appl. Chem. 32(4):267-268.

1179. Dzedin, T., L. Lundholm, and N. Svedmyr. 1968. Relation between some metabolic effects of nicotinic acid and catechol amines in the rabbit. Acta Pharmacol. Toxicol. 26(5):446-460.

1180. Dzedin, T., N. Svedmyr, and L. Lundholm. 1971. Effect of nicotinic acid on carbohydrate metabolism. Relation with adrenergic receptors. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1971:747-751.

1181. Eagle, H. 1956. Relative growth-promoting activity in tissue culture of co-factors and the parent vitamins. Proc. Soc. Expti. Biol. Med. 91(3):358-361.

1182. Early, R. G., and B. R. Carlson. 1969. Water-soluble vitamin therapy in the delay of fatigue from physical activity in hot climatic conditions. Internat. Ztschr. Angew. Physiol. Arbeitsphysiol. 27:43-50.

1183. Eaton, R. P. 1963. In vitro inhibition of the fat-mobilizing action of norepinephrine. Proc. Soc. Expti. Biol. Med. 114: 599-600.

1184. Edgington, B. H., W. L. Robison, W. Burroughs, and R. M. Bethke. 1942. Tests with nicotinic acid for the prevention of infectious swine enteritis. J. Am. Vet. Med. Assoc. 101: 103-108.

1185. Edholm, K., and S. Radner. 1948. Intravenous administration of sodium nicotinate for headache ensuing from cord puncture or encephalography. Nord. Med. 40:1997-1999.

1186. Edwards, C. H., L. K. Booker, C. H. Rumm, R. Craven, and S. N. Ganapathy. 1942. Utilization of wheat by adult man: excretion of vitamins and minerals. Am. J. Clin. Nutr. 24(5):547-555.

1187. Efimov, I. S., and V. A. Babosha. 1970. Treatment of injuries to the peripheral arterial vessels in peace-time. Ortop. Travmatol. Prot. 31(7):11-13.

1188. Efremov, V. V., and E. M. Zaburkin. 1972. Characteristics of the pyridoxine and nicotinic acid metabolism in experimental animals after their physical loading by prolonged swimming. Vopr. Pitan. 31(3):39-43.

1189. Efremov, V. V., M. I. Razumov, and A. N. Tikhomirova. 1953. Effect of a diet with deficient content of nicotinic acid, tryptophan, and protein on nicotinic acid metabolism in dogs. Voprosy Pitaniya 12(1):50-59.

1190. Eger, W. 1957. The importance of sulfhydryl, amino, and carboxyl groups of short chain carbon compounds for necrotropic liver protection. Arzneimittel-Forsch. 7:601-606.

1191. Egli, H., and H. Kiensch. 1961. The action of nicotinic acid on fibrinolysis and circulation with special regard to its therapeutic application. Med. Welt 1961:2108-2113.

1192. Egorova, L. N., and V. I. Treshcheva. 1961. Antioxidants and changes in fat in the process of manufacturing fish meal. Rybn. Khoz. 37(11):76-81.

1193. Egurrola, A. F. 1959. Evaluation of vitamin B complex factors and cellulose residue in fruits (cherries, apricots, peaches, and cooked dried peaches). Anales Fac. Quim. y Farm., Univ. Chile 11:50-54.

1194. Eheart, J. F., R. W. Young, and A. H. Allison. 1955. Variety, type, year, and location effects on the chemical composition of peanuts. Food Research 20:497-505.

1195. Ellersen, P., and N. Hobolth. 1959. Treatment of high blood cholesterol with nicotinic acid. Ugeskr. Laeger 121:205-208.

1196. Ellhauer, D., W. Hoefling, G. Reckling, K. H. Meinicke, and P. Fahrig. 1969. Nicotinic and isonicotinic acid. Ger. (East) Pat. 68,229.

1197. Eisen, H. N., M. C. Michaelides, B. J. Underdown, E. P. Schulenburg, and E. S. Simms. 1970. Myeloma proteins with antihapten antibody activity. Fed. Proc., Fed. Am. Soc. Exp. Biol. 29(1):78-84.

1198. Eisen, M. E. 1958. Effect of vitamin A, niacin and riboflavin on vascular lesions. A preliminary report. Am. J. Surg. 95:438-444.

1199. Eissa, A. A. 1949. The effect of nicotinic acid on specific antibody production. Med. Lab. Progr., Egypt 10:27-36.

1200. Ekisenina, N. I., N. B. Shalygina, T. A. Yatsyshina, L. M. Krums, G. A. Fursova, L. M. Ivanova, I. S. Taits, L. K. Lukash, R. I. Chanysheva, and L. P. Myagkova. 1972. Substantiation of a balanced nutrition in chronic enterocolitis. Vopr. Pitan. 31(2):14-20.

1201. Ekstrom-Jodal, B., L. Harthon, E. Haggendal, R. Malmberg, and N. Svedmyr. 1970. Influence of nicotinic acid and pentaerythritol tetranicotinate (Perycit,bofors) on the cardiac output in man. Pharmacol. Clin. 2(2):86-89.

1202. Elektrizitaetswerke, L., and Chemische Fabriken A.-G. 1956. Pyridine carboxylic acids. Brit. Pat. 757,958.

1203. Elinov, N. P., and A. El Sukkari. 1969. Effect of some medicinal substances on Staphylococcus aureus hyaluronidase. Tr. Leningrad. Khim.-Farm. Inst. 1969(27):26-31.

1204. Eller, J. J., and L. A. Diaz. 1943. Vitamins in dermatology. Urol. Cutaneous Rev. 47:234-238.

1205. Ellerbrook, R. C., and M. B. Purdy. 1970. Capacity of stressed humans under mega dosages of nicotinic acid to synthesize methylated compounds. Dis. Nerv. Syst. 31(3):196-197.

1206. Ellinger, P. 1945. Nicotinamide methochloride and its fluorescent derivatives. Nature (London) 155(3933):319-322.

1207. Ellinger, P. 1946. The formation of nicotinamide from nicotinic acid by rat tissues. Biochem. J. 40(3):xxxi-xxxii.

1208. Ellinger, P. 1947. The fate of nicotinamide methochloride and the effect of liver poisons on its elimination rate in the rat. Biochem. J. 41(2):308-314.

1209. Ellinger, P. 1948. The formation of nicotinamide from nicotinic acid by the rat. Biochem. J. 42:175-181.

1210. Ellinger, P., and M. M. Abdel Kader. 1947. Tryptophane as precursor of nicotinamide in mammals. Nature 160:675-676.

1211. Ellinger, P., and M. M. Abdel Kader. 1948. The metabolism of nicotinamide and related compounds in various mammalian species. Biochem. J. 42:xxxiii-xxxiv.

* 1212. Ellinger, P., and M. M. Abdel Kader. 1949a. Nicotinamide metabolism in mammals. Biochem. J. 44:77-87.

1213. Ellinger, P., and M. M. Abdel Kader. 1949b. The effect of various diets on the metabolism of nicotinic acid and nicotinamide in the rabbit. Biochem. J. 44(5):627-631.

1214. Ellinger, P., and M. M. Abdel Kader. 1949c. Tryptophan and the biosynthesis of nicotinamide. Biochem. J. 45(3):276-281.

1215. Ellinger, P., and P. Armitage. 1953. The inheritance in the rat of the capacity to eliminate nicotinamide methochloride. Biochem. J. 53(4):588-596.

1216. Ellinger, P., and R. A. Coulson. 1943. Urinary elimination products following ingestion of nicotinamide (F2 of Najjar and collaborators). Nature 152:383-384.

1217. Ellinger, P., and R. A. Coulson. 1944. The urinary elimination of nicotinamide methochloride by man. Biochem. J. 38:265-270.

1218. Ellinger, P., and S. W. Hardwick. 1947. The nicotinamide saturation test. Brit. Med. J. i:672-676.

1219. Ellinger, P., R. Benesch, and D. P. Greifswald. 1945. Biosynthesis of "Nicotinamide" in the human gut. Lancet 248(6345): 432-434.

1220. Ellinger, P., R. A. Coulson, and R. Benesch. 1944. Production and release of nicotinamide by the intestinal flora in man. Nature (London) 154(3904):270-271.

1221. Ellinger, P., G. Fraenkel, and M. M. Abdel Kader. 1947. The utilization of nicotinamide derivatives and related compounds by mammals, insects and bacteria. Biochem. J. 41(4):559-567.

1222. Ellinger, P., G. E. Glock, and B. S. Platt. 1942. The urinary elimination of fluorescent pigments in animals as a basis for the assay of nicotinamide and related compounds in foodstuffs. Biochem. J. 36(7/8/9):xi-xii.

1223. Elliott, A. M., L. E. Brownell, and J. A. Gross. 1954. Use of Tetrahymena to evaluate the effects of gamma-radiation on essential nutrilites. J. Protozool. 1:193-199.

1224. El-Ridi, M. S., M. M. Abdel Kader, A. Habib, and M. Saadany. 1958. Metabolism of nicotinic acid amide in patients suffering from tuberculosis. Z. Physiol. Chem. 310:275-280.

1225. El-Ridi, M. S., M. M. Abdel Kader, A. Habib, A. Hasaballa, C. Hazzi, M. Zaki, and Y. Riad. 1960. The role of the liver and kidney in the metabolism of nicotinic acid amide in pellagrins and non-pellagrins. Acta Physiol. Hung. 17:429-441.

1226. Elvehjem, C. A. 1939. Nicotinic acid in nutrition. Ann. Internal Med. 13:225-231.

1227. Elvehjem, C. A. 1940. The biological significance of nicotinic acid. Bull. New York Acad. Med. 16(3):173-189.

1228. Elvehjem, C. A. 1944. Symposium on human vitamin requirements. Introduction. Federation Proc. 3:158-159.

1229. Elvehjem, C. A. 1955. The biochemical relation between tryptophan and niacin. Soc. Biol. Chemists, India 1955:54-58.

1230. Elvehjem, C. A., and P. L. Pavcek. 1943. How cooking affects vitamins. Modern Hosp. 61(4):110-115.

1231. Elvehjem, C. A., and L. J. Teply. 1943. The structure and estimation of natural products functionally related to nicotinic acid. Chem. Rev. 33(3):185-208.

1232. Elvehjem, C. A., R. J. Madden, F. M. Strong, and D. M. Woolley. 1937. Relation of nicotinic acid and nicotinic acid amide to canine black tongue. J. Am. Chem. Soc. 59:1767-1768.

1233. Elwood, J. C., D. A. Richert, and W. W. Westerfeld. 1972. A comparison of hypolipidemic drugs in the prevention of an orotic acid fatty liver. Biochem. Pharmacol. 21(8):1127-1134.

1234. Ely, C. M. 1968. Iron salt-antibiotic compositions for controlling nutritional deficiencies in pigs. Brit. Pat. 1,201,423.

1235. Engelhardt, A. W. 1961. Skin reactions to benzyl ester of nicotinic acid and their significance for the differential diagnosis of dermatoses. Hautarzt 12:346-355.

1236. Engelund, A., C. Broen Christensen. 1969. Bufon, a new drug. Ugeskr. Laeger 131(38):1611-1612.

1237. Enikeev, S. G., and V. N. Ozaryanskaya. 1971. Change in the nitrogen and amino acid composition of pea leaves under the action of nicotinic acid. Dokl. Vses. Akad. Sel'skokhoz. Nauk 1971(8):17-19.

1238. Enomoto, Y., C.-T. Kim, K. Nagashima, K. Motonishi, I. Yamakage, and K. Inada. 1959. The pharmacology of 2-methyl-4-amino-5-hydroxymethylpyrimidine. V. The relation between convulsions relieved by 2-methyl-4-amino-5-hydroxymethylpyrimidine, isonicotinic acid hydrazide, and thiamine and the most important substances inhibiting the central nervous system. Bitamin 16:210-214.

1239. Enrique, E. 1943. A case of migraine treated with nicotinic acid. Rev. Clin. Espanola 10:53-54.

1240. Ensign, J. C., and S. C. Rittenberg. 1965. The formation of a blue pigment in the bacterial oxidation of isonicotinic acid. Arch. Mikrobiol. 51:384-392.

1241. Eppright, E., A. L. Marlatt, et al. 1955. Nutrition of 9-, 10- and 11-year-old public school children in Iowa, Kansas and Ohio. I. Dietary findings. Iowa Agric. Expt. Sta. Res. Bull. 434:1-12.

1242. Epshtein, M. M., V. O. Nikonova, Z. I. Spilioti, and I. I. Pavlova. 1966. Effect of certain water-soluble vitamins on the pyridine coenzyme content in animal tissues under hypoxic conditions. Ukr. Biokhim. Zh. 38(5):525-531.

1243. Epshtein, M. M., V. A. Nikonova, Z. I. Spilioti, and N. B. Kakhnover. 1971. Effect of nicotinamide, ascorbic acid, and galascorbin on NAD+ and NADP+ dependent dehydrogenase activities in heart tissues during adrenaline myocarditis. Ukr. Biokhim. Zh. 43(5):572-576.

1244. Epshtein, Ya. A., and U. I. Salakhutdinov. 1967. The role of histamine in the secretion of hydrochloric acid by the gastric mucosa. Dokl. Akad. Nauk Tadzh. SSR 10(3):56-58.

1245. Erbsich, F, and H. D. Cremer. 1972. Malnutrition and peripheral neuropathies. Bibl. Nutr. Dieta 17:46-56.

1246. Erdei, A. 1948. The nicotinic acid tolerance test. Lancet 254:368-369.

1247. Ericson, L. E., and A. E. Harper. 1955. Effect of diet on betaine-homocysteine transmethylase of rat liver. III. B-vitamins other than vitamin B12. Proc. Soc. Exptl. Med. 90(1):298-300.

1248. Erikson, S. E., and R. E. Boyden. 1947. Effect of different methods of cooking on the thiamine, riboflavin, and niacin content of pork. Kentucky Agric. Expt. Sta. Bull. 503 pp.

1249. Eristavi, Z. A. 1968. Thrombogenesis in parturient women with cardiac defects and prophylaxis of thromboses by nicotinic acid. Kardiologiya 8(3):54-58.

1250. Erlich, H. 1962. A rapid semi-quantitative micro-spot plate technique for detecting small amounts of niacin in cultures of M. tuberculosis. Am. Rev. Resp. Dis. 86:587-589.

1251. Ermakov, E. S. 1965. Nicotinic acid metabolism and the gaseous composition of venous blood as indexes of tissue respiration. Pediatriya 1965(4):32-35.

1252. Ermakov, Sh. N. 1949. Influence of ascorbic acid, nicotinic acid, and vitamin B1 on extrasecretory function of pancreas (especially in ailments of the liver and bile passages). Terapevt. Arkh. 21(1):63-69.

1253. Ertel, I. J., and W. A. Newton, Jr. 1969. Therapy in congenital hyperbilirubinemia: phenobarbital and diethylnicotinamide. Pediatrics 44(1):43-48.

1254. Escudero, A., and M. L. Herraiz. 1943. Elimination of nicotinic acid in the urine. Rev. Asoc. Argentina Dietol. 1:182-186.

1255. Escudero, P. 1944. Vitamin requirements of the infant during its first six months of life. Pubs. Inst. Nacl. Nutricion (Buenos Aires) Pubs. Cient. CPa 6:109-117.

1256. Escudero, P., A. Escudero, M. L. Herraiz, and H. G. de Alvarez Herrero. 1942. Thiamine, riboflavin and nicotinic acid of some Argentine citrus fruits. Pubs. Inst. Nacl Nutricion (Buenos Aires) Pubs. Cient CPa5:19-23.

1257. Eser, S. 1948. The action of nicotinic acid amide on the carbohydrate metabolism. Bull. Faculte Med. Istanbul 11:82-96.

1258. Eser, S., S. Tekman, and A. Araz. 1955. In vitro action of nicotinic acid amide on livers of normal and pregnant mice and on livers of normal and alloxan-diabetic rats. Arch. Turk. Acad. Med. 6:107-111.

1259. Eser, I. S., S. Tekman, and A. Araz. 1957. The effect of nicotinic acid amide on the metabolism of ketone bodies in the liver of alloxan diabetic rats. I. Bull. Fac. Med. Istanbul 20:532-536.

1260. Eser, S., S. Tekman, and A. Araz. 1959. Action of nicotinamide on acetoacetate metabolism of liver homogenates of normal and alloxanized rats. Nature 183:184-185.

1261. Esh, G. C., and T. S. De. 1960. Studies on pulse proteins: association with thiamine and nicotinic acid content of pulses. J. Proc. Inst. Chemists (India) 32(Pt. 1):14-16.

1262. Esh, G. C., and T. S. Sutton. 1948a. Effect of tryptophan in the diet on the excretion of niacin and its metabolic products by dairy calves. J. Dairy Sci. 31:675.

1263. Esh, G. C., and T. S. Sutton. 1948b. The nutrition of the newborn dairy calf. 2. Effect of dietary tryptophan on the urinary excretion of niacin and its metabolites by young dairy calves. J. Dairy Sci. 31:909-912.

1264. Esh, G. C., J. M. Som, and M. K. Kar. 1965. Interrelation of dietary protein and vitamins on metabolism. I. Interdependence of the levels of certain B vitamins and dietary protein. Indian J. Biochem. 2(4):267-270.

1265. Esposito, S. 1960. Action of nicotinamide and nicotinic acid on hemopoiesis and hemocatheresis. Changes in concentration of iron and bilirubin in the blood of normal and splenectomized animals. Haematologica (Pavia) 45(8):725-732.

1266. Esposito, S., and L. Buscarini. 1960. The action of nicotinamide and nicotinic acid on hemopoiesis and hemocatheresis. Behavior of the colchicine statmocynetic test and of erythrocyte uptake of Fe59 in animals treated with high doses of nicotinamide. Hepatic and splenic uptake of Fe59 in animals subjected to nicotinic acid load. Haematologica 45:861-876.

1267. Esposito, S., and E. Nicolini. 1962. Sideremia in normal and splenectomized animals on continued treatment with nicotinic acid. Arch. Sci. Med. 114(2):130-137.

1268. Esposito, S., L. Buscarini, and M. Nespoli. 1960a. Action of nicotinamide and nicotinic acid on hemopoiesis and hemocatheresis. Hemopoiesis in animals treated with high doses of nicotinamide; morphological and biochemical findings. Haematologica (Pavia) 45(7):667-688.

1269. Esposito, S., L. Buscarini, and M. Nespoli. 1960b. The action of nicotinamide and of its antagonists on hemopoiesis. Haematologica 45:1235-1379.

1270. Esposito, S., E. Nicolini, and L. Buscarini. 1962. The action of nicotinamide and nicotinic acid on blood coagulation. Riv. Pat. Clin. 17:284-293.

1271. Esposito, S., F. Nigrosini, and L. Petronio. 1959. Nature and prevention of liver steatosis with high doses of nicotinamide and 6-aminonicotinamide. Arch. Sci. Med. 108:857-864.

1272. Estler, C. J. 1969. Indications from the pharmacological viewpoint. Med. Ernaehr. 10(4):87.

1273. Estler, C. J., and H. P. T. Ammon. 1971a. Physical performance of mice treated with nicotinic acid. Metab. Eff. Nicotinic Acid Its Deriv., Pro 1971:1105-1110.

1274. Estler, C. J., and H. P. T. Ammon. 1971b. Effect of various doses of nicotinic acid on oxygen consumption and respiratory quotient in mice. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970:1075-83.

1275. Estler, C. J., and H. P. T. Ammon. 1971c. Thermoregulation of mice treated with nicotinic acid. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1971:1099-1103.

1276. Estler, C. J., H. P. T. Ammon, and B. Lang. 1970. Ineffectiveness of nicotinic acid to impair thermoregulation in cold-exposed mice. Eur. J. Pharmacol. 9(2):257-260.

1277. Evans, W. C., E. T. R. Evans, and L. E. Hughes. 1954. Studies on bracken poisoning in cattle. Brit. Vet. J. 110(8):295-306.

1278. Everson, G. J., and A. H. Smith. 1945. Retention of thiamine, riboflavin and niacin in deep fat cooking. Science 101(2622): 338-339.

1279. Exton, J. H., S. B. Lewis, and C. R. Park. 1971. Examination of in vitro effects of nicotinic acid on basal and hormone-stimulated glycogenolysis, gluconeogenesis, ureogenesis, and ketogenesis in the isolated perfused rat liver. Metab. Eff. Nicotinic Acid its Deriv., Pro. 1971:851-859.

1280. Exton, J. H., G. A. Robison, E. W. Sutherland, and C. R. Park. 1971. Role of adenosine 3',5'-monophosphate in the hepatic actions of glucagon and catechol amines. J. Biol. Chem. 246(20):6166-6177.

1281. Ezaki, C., H. Nakamori, T. Shimamoto, K. Kida, T. Moriyama, and N. Itou. 1968. Alcohol decomposing capacity of the body and regulation of alcohol metabolism. I. Nara Igaku Zasshi 19(4):500-505.

1282. Fabianek, J. 1956a. Influence of the casein and nicotinamide contents of the diet on growth, vascular resistance, and tissue ascorbic acid of the guinea pig. Compt. Rend. Soc. Biol. 150:88-92.

1283. Fabianek, J. 1956b. Treatment with ascorbic acid of scurvy produced by means of synthetic diets. Compt. Rend. Soc. Biol. 150:369-372.

1284. Fabro, S. 1962. Influence of nicotinamide, 3-pyridylacetamide, and guanidineacetic acid on transmethylation in rat liver in vitro. Acta Vitaminol. 16:61-64.

1285. Fachini, G. 1959. Detoxification of tobacco smoke. U.S. Pat. 2,890,973.

1286. Faermark, S. E. 1946. Dynamics of the shift in vegetative reactions from the action of nicotinic acid in cases of open and closed trauma of the skull. Nevropatol. i Psikhiat. 15(5): 39-47.

1287. Fahr, E. 1941. Toxic action of oxygen and reduction-oxidation systems. Klin. Wochschr. 20:763-764.

1288. Fain, J. N. 1967. Adrenergic blockade of hormone-induced lipolysis in isolated fat cells. Ann. N.Y. Acad. Sci. 139(3): 879-890.

1289. Fain, J. N., D. J. Galton, and V. P. Kovacev. 1966. Effect of drugs on the lipolytic action of hormones in isolated fat cells. Mol. Pharmacol. 2(3):237-247.

1290. Fairbanks, B. W., and E. Curzon. 1940. Nicotinic acid and necrotic enteritis in swine. North Am. Vet. 21:536-538.

1291. Famiani, V., and A. Minestrini. 1952. The effect of the administration of nicotinic acid on the arterial pressure of rabbits treated with thyroxine or with ergotamine. Boll. Soc. Ital. Sper. 28:1429-1432.

1292. Fand, I. 1965. The protective influence of substances upon the antimitotic effect of epinephrine and its metabolites in human cell cultures. Arch. Intern. Pharmacodyn. 156(1):201-210.

1293. Fang, V. 1968. Salicylate hypoglycemic action in alloxan-diabetic rats and structural relations. Arch. Int. Pharmacodyn. Ther. 176(1):193-208.

1294. Fang, V. 1969. Correlation between the antilipolytic and hypoglycemic actions of some salicylate structural congeners in normal and alloxan-diabetic rats. Arch. Int. Pharmacodyn. Ther. 178(2):315-323.

1295. Fang, V., W. O. Foye, S. M. Robinson, and H. Jenkins. 1968. Hypoglycemic activity and chemical structure of the salicylates. J. Pharm. Sci. 57(12):2111-2116.

1296. Fantoni, A., G. Leoncini, P. Calissano, C. Cartasegna, and G. Fornaini. 1965. The effect of NADP-glcohydrolase (NADPase) on glucose-6-phosphate dehydrogenase. Enzymol. Biol. Clin. 5(3):161-167.

1297. Farah, A., and M. Frazer. 1961. Studies on the renal tubular secretion of N'-methylnicotinamide. J. Pharmacol. Exptl. Therap. 134(2):245-250.

1298. Farah, A., M. Frazer, and E. Porter. 1959. Studies on the uptake of N'-methylnicotinamide by renal slices of the dog. J. Pharmacol. Exp. Therap. 126:202-211.

1299. Farber, J. E., and D. K. Miller. 1943a. Nutritional studies in tuberculosis. I. Prothrombin deficiency and vitamin K. Am. Rev. Tuberc. 48:406-411.

1300. Farber, J. E., and D. K. Miller. 1943b. Nutritional studies in tuberculosis. II. Niacin (nicotinic acid) and riboflavin deficiency. Am. Rev. Tuberc. 48(6):412-420.

1301. Farkas, T. 1969. Effect of agents modifying the level of cyclic 3',5'-adenosine monophosphate in adipose tissue on mobilization of fats in fish and frogs. Ann. Inst. Biol., Tihany, Hung. 36:163-171.

1302. Farkas, T., R. Vertua, M. M. Usardi, and R. Paoletti. 1964. The mechanism of action of nicotinic acid. Life Sci. 3(8): 821-827.

1303. Fassina, G. 1970. Antagonistic effect of nicotinic acid and phenylisopropyladenosine on catechol amine-stimulated short-circuit current increase in isolated frog skin. Life Sci. 9(22):1281-1287.

1304. Fatterpaker, P., U. Marfatia, and A. Sreenivasan. 1955. Relation between pteroylglutamic acid and nicotinamide metabolism. Biochem. J. 59:470-475.

1305. Feaster, J. F., M. D. Tompkins, and M. Ives. 1948. Retention of vitamins in low acid canned foods. Food Indust. 20(1):14-17.

1306. Fedele, L., F. Tancredi, and I. Riccardi. 1961. Research on the metabolites resulting from the conversion of tryptophan to nicotinic acid in the urine of patients with bladder neoplasms. Minerva Urol. 13:1-3.

1307. Fedorova, G. P. 1965. Effect of nicotinamide on the NAD content in rat tissues during rest and muscular activity. Ukr. Biokhim. Zh. 37(1):91-96.

1308. Fedorovskii, Yu. N., and R. V. Rozhanets. 1967. Problems regarding rheoencephalogram changes when affected by some angiotropic and psychotropic drugs. Nauch. Tr. Aspir. Ord. Pervyi. Mosk. Med. Inst. 436-438.

1309. Feige, A., D. Gross, A. Zureck, and H. R. Schuette. 1970. Biosynthesis of nicotinic acid and quinolinic acid by Mycobacterium bovis strain BCG. Arch. Mikrobiol. 75(1): 80-88.

1310. Feigelson, P., J. N. Williams, Jr., and C. A. Elvehjem. 1951a. Inhibition of diphosphopyridine nucleotide-requiring enzymes by nicotinamide. J. Biol. Chem. 189(1):361-369.

1311. Feigelson, P., J. N. Williams, Jr., and C. A. Elvehjem. 1951b. Comparative effect of tryptophan, niacin, and nicotinamide in forming liver pyridine nucleotides. Proc. Soc. Exptl. Biol. Med. 78(1):34-36.

1312. Feinberg, S. M., A. R. Feinberg, and F. Lee. 1969. Hypersensitivity responses in monkeys. II. Comparison of several indicators in visualization of the immediate skin response to histamine, 48/80, and antigen challenge. J. Allergy 43(2): 65-80.

1313. Feinblatt, T. M., H. M. Feinblatt, and E. A. Ferguson, Jr. 1955. Treatment of arteriosclerosis and vague abdominal distress with niacinamide hydroiodide (without side effects.) Am. J. Digest. Dis. 22(1):5-6.

1314. Feinstein, L. 1945. A quick test for flour enrichment. Science 101(2635):675-676.

1315. Feinstein, R. N., et al. 1963. Effect of nicotinamide on growth of mouse Ehrlich ascites tumor. ANL-6723. U.S. AEC Argonne Nat. Lab. 215.

1316. Feinstein, R. N., and M. E. Volk. 1949. Phosphoprotein phosphatase in mammalian tissues. J. Biol. Chem. 177:339-346.

1317. Feinstone, W. H. 1958. Enrichment of food products. U.S. Pat. 2,829,054.

1318. Fekina, T. V. 1955. The influence of nicotinic acid on the hemoglobin metabolism. Byull. Ekspti. Biol. i Med. 40(8): 42-46.

1319. Feldman, A. M. 1965. Influence of age and diet on vitamin PP metabolism in chickens. Tr. Lab. Biokhim. Fiziol. Zhivotnykh Inst. Biol. Akad. Nauk. Latv. SSR 4:273-284.

1320. Feldman, A. M. 1969. Nicotinamide coenzymes in tissues of chickens on rations with different contents of nicotinic acid and tryptophan. Riga 1969:111-123.

1321. Feldman, E. B. 1964. Nicotinic acid in the management of frank disorders of lipid metabolism. In: R. Altschul, Editor. Niacin in Vascular Disorders and Hyperlipemia. C. C. Thomas, Springfield, Ill. pp. 208-224.

1322. Feldman, E. 1968. Factors modifying cholesterol uptake by intestinal rings. Biochim. Biophys. Acta 150(4):727-729.

1323. Feldmanis, A. 1965. Vitamin PP metabolism in chicks on different rations. Tr. Lab. Biokhim. i Fiziol. Zhivotnykh, Inst. Biol. Akad. Nauk Latv. SSR 4:255-271.

1324. Feldstein, A., and K. K.-K. Wong. 1965. Enzymic conversion of serotonin to 5-hydroxytruptophol. Life Sci. 4(2):183-191.

1325. Feldstein, A., H. Hoagland, and H. Freeman. 1959. Monoamine oxidase, psychoenergizers, and tranquilizers. Science 130:500.

1326. Fellner, M. J. 1970. Side effects caused by isonicotinic acid hydrazide. Hautarzt Z. Dermatol. Venerol. Verw. Geb. 21(7): 320-324.

1327. Fenton, F. 1945. Retention of vitamin values in large-scale food service. Proc. Inst. Food Technologists 1945:35-48.

1328. Fenton, F. 1957. Electronic cooking. J. Home Econ. 49:709-716.

1329. Fenton, F., E. Gleim, and V. M. Chappell. 1947. Vitamin retention and palatability of evaporated apricots. J. Am. Dietetic Assoc. 23(5):423-426.

1330. Fenton, F., M. Albury, K. Visnyei, J. F. Thompson, and E. Gleim. 1945. Effect of quantity preparation procedures on vitamin retention and palatibility of dehydrated potato shreds. J. Am. Dietetic Assoc. 21(8):518-521.

1331. Fenton, F., E. Gleim, M. Albury, J. R. McCartney, and K. Visnyei. 1946. Retention of vitamins and palatability in large-scale food service of unsulfited, dehydrated cabbage. Food Res. 11(6):468-474.

1332. Fenton, F., E. Gleim, M. Albury, K. Visnyei, and J. R. McCartney. 1945. Effect of quantity preparation procedures on vitamin retention: canned peas. J. Am. Dietetic Assoc. 21:700-702.

1333. Fenton, F., E. Gleim, A. Arnason, J. F. Thompson, M. Albury, and M. Phillips. 1946. Retention of vitamins and palatability in large-scale food service of sulfited, dehydrated cabbage. Food Res. 11(6):475-485.

1334. Ferguson, T. M., C. H. Whiteside, C. R. Creger, M. L. Jones, R. L. Atkinson, and J. R. Couch. 1961. B-vitamin deficiency in the mature turkey hen. Poultry Sci. 40:1151-1159.

1335. Ferliga, G. 1968. Improved nicotinic acid effect on lipoprotein normalization in an extemporaneous combination of drugs. G. Gerontol. 15(11):1381-1387.

1336. Ferno, O. B., H. J. Fex, K. B. Hogberg, I. Konyves, and T. O. E. Linderot. 1969. Poly(estriol phosphate)-based pharmaceutical compositions for treatment of menopause symptoms. Fr. Demande Pat. 2,000,281.

1337. Ferrannini, A., and F. Muratori. 1939a. Effect of nicotinic acid on the reticulocytes. Boll. Soc. Ital. Biol. Sper. 14:376-377.

1338. Ferrannini, A., and F. Muratori. 1939b. Action of nicotinic acid on the composition of the blood in some cases of anaemia. Boll. Soc. Ital. Biol. Sper. 14:559-560.

1339. Ferrannini, A., and F. Muratori. 1940. Hematopoietic activity of nicotinamide and gastric juice of anemia. Boll. Soc. Ital. Biol. Sper. 15:294-295.

1340. Ferrari, B. 1963. Evaluation of the results obtained with nicotinic acid in the therapy of pregnancy toxemia. Clin. Ostet. Ginec. 65:165-172.

1341. Ferreira-Marques, J. 1948. The etiology, pathogeny, and therapy of pruriginous diseases. Acta Dermato-Venereol. 28(Suppl. 19):1-68.

1342. Ferrero, S. 1939. Pellegra and nicotinic acid. Arch. Ital. Med. Sper. 4:1033-1048.

1343. Ferrero, S. 1940. Action of nicotinic acid in passive hyperthermia. Riv. Patol. Sper. 24:259-275.

1344. Ferris, G. M., and J. B. Clark. 1971. Nicotinamide nucleotide synthesis in regenerating rat liver. Biochem. J. 121(4):655-662.

1345. Ferris, G. M., and J. B. Clark. 1972. Control of nucleic acid and nicotinamide nucleotide synthesis in regenerating rat liver. Biochem. J. 128(4):869-877.

1346. Ferris, J. P., J. E. Kuder, and A. W. Catalano. 1969. Photochemical evolution of purines and nicotinamide derivatives. Science 166(3906):765-766.

1347. Fex, G., and T. Olivecrona. 1969. Role of uptake and oxidation of plasma free fatty acids by the liver in the development of the ethanol-induced fatty liver. Acta Physiol. Scand. 75(1): 78-81.

1348. Fiala, J., J. Urbancova, and V. Sebestik. 1969. Nicotinamide as an additive to blood preserving solutions. Vnitr. Lek. 15(7):652-656.

1349. Fiala, S. 1941. On the conditions for dry and adhesive growth and the phenomenon of lysis in Pseudomonas pyocyanea. Zentralbl. Bakt. I. Abt. Orig. 148:58-60.

1350. Fichera, G., and S. Vasta. 1941a. The influence of nicotinic acid on the carbohydrate metabolism. Biochim Terap. Sper. 28:97-99.

1351. Fichera, G., and S. Vasta. 1941b. The influence of nicotinic acid on the Ca and K contents of the blood. Biochim. Terap. Sper. 28:100-103.

1352. Fichera, G., and S. Vasta. 1941c. Changes in the total, protein and nonprotein nitrogen brought about by nicotinic acid. Biochim. Terap. Sper. 28:104-107.

1353. Field, H., Jr., and W. D. Robinson. 1940. The absence of reactions following therapeutic doses of nicotinic acid amide. Am. J. Med. Sci. 199:275-276.

1354. Field, H., Jr., C. Parnall, Jr., and W. D. Robinson. 1940. Pellagra in the average population of the northern states. New Engl. J. Med. 223:307-315.

1355. Fields, M. D., C. F. Dunker, and C. E. Swift. 1955. The effect of storage on the composition and nutritive properties of farm-style hams. Food Technol. 9:491-495.

1356. Figdor, S. K., and M. Schach von Wittenau. 1967. Metabolism of 5- 3-pyridyl tetrazole. J. Med. Chem. 10(6):1158-1159.

1357. Filho, R. M. 1954. Pharmacology of the cerebral circulation. Arq. Neuro-Psiquiat. 12(Suppl. 2):5-126.

1358. Fillos, A. M., and W. B. Esselen, Jr. 1946. The vitamin content of canned and cooked fresh mushrooms. J. Am. Dietetic Assoc. 22(9):772-777.

1359. Finck, C., et al. 1968. Liver function test after nicotinic acid loading. I. A clinical study. Acta Hepatospien. (Stuttgart) 15:315-321.

1360. Finholt, P., and T. Higuchi. 1962. Rate studies on the hydrolysis of niacinamide. J. Pharm. Sci. 51:655-661.

1361. Florentino, E., F. Sardella, C. Pietropaolo, and A. Natoli. 1966. Serum lipids during nicotinic acid treatment of a subject with nephrotic syndrome. Gazz. Int. Med. Chir. 71(23 bis):2375-2383.

1362. Firth, J. A. 1955. Quantitative relations between tryptophan and nicotinic acid in the baby pig. Dissertation Abstr. 15:1955.

1363. Firth, J., and B. C. Johnson. 1956. Quantitative relationships of tryptophan and nicotinic acid in the baby pig. J. Nutrition 59:223-234.

1364. Fischer, A. 1942. Intestinal tuberculosis as a cause of pellagra. Deutsch. Tuberkulose-Blatt 16(2):25-31.

1365. Fisher, H., H. M. Scott, and B. C. Johnson. 1955. Liver pyridine nucleotide content as related to dietary tryptophan and nicotinic acid in the chick. Arch. Biochem. Biophys. 56:130-136.

1366. Fitzgerald, O. 1939. Studies of the action of nicotinamide in experimental pellagra in the dog. Ztschr. Vitaminforsch. 9(1/2):62-70.

1367. Fitzgerald, O., R. Mulcahy, J. J. Fennelly, and A. Heffernan. 1960. Serum lipide studies and nicotinic acid therapy. Lancet 1:877-878.

1368. Fitzgerald, O., A. Heffernan, P. Brennan, R. Mulcahy, J. J. Fennelly, and R. McFarlane. 1964. Effect of nicotinic acid on abnormal serum lipids. Brit. Med. J. 5376:157-159.

1369. Fitzpatrick, D. A., O. FitzGerald, and K. F. McGeeney. 1969. Nicotinic acid inhibition of uricase. Ir. J. Med. Sci. 2(11): 531-534.

1370. Fitzpatrick, F. K. 1955. Nicotinamide in murine tuberculosis. Proc. Soc. Exptl. Biol. Med. 88(1):54-56.

1371. Fitzpatrick, J., and S. L. Tompsett. 1950. The daily excretion of riboflavin, biotin, pantothenic acid, and nicotinic acid derivatives by normals. J. Clin. Pathol. 3:69-71.

1372. Flechner, I., A. Amar, and A. Bekierkunst. 1970. NAD biosynthesis in polymorphonuclear leukocytes of guinea pigs. Comparative studies on different NAD precursors in intact cells. Biochim. Biophys. Acta 222(2):320-326.

1373. Flechner, I., A. Amar, and A. Bekierkunst. 1970. NAD biosynthesis in polymorphonuclear leukocytes of guinea pigs. I. Nicotinic acid pathway of NAD synthesis in cell-free preparations. Life Sci. 9(3):153-162.

1374. Fleiderman, G. 1948. Microbiological determination of nicotinic acid and riboflavin in beef, veal, and pork liver produced in Argentina. Rev. Fac. Cienc. Quim. (Univ. Nacl. La Plata) 23:133-136.

1375. Fletcher, A. P., et al. 1964. Abnormal plasminogen-plasmin system activity (fibrinolysis) in patients with hepatic cirrhosis: its cause and consequences. J. Clin. Invest. 43:681-695.

1376. Flinn, B. C., F. J. Pilgrim, H. S. Gregg, and A. E. Axelrod. 1946. Changes produced by starvation in the vitamin content of rat tissues. Proc. Soc. Exptl. Biol. Med. 63:523-528.

1377. Floch, H., and R. Horth. 1952. Nicotinic acid amide therapy in leprosy (intolerance to sulfones and leprotic reactions). Bull. Soc. Path. Exot. 45(2):161-166.

1378. Flockhart, I. R., and J. E. Casida. 1972. Relation of the acylation of membrane esterases and proteins to the teratogenic action of organophosphorus insecticides and eserine in developing hen eggs. Biochem. Pharmacol. 21(19):2591-2603.

1379. Florenskaya, N. K., V. M. Shirokova, and Z. I. Sotnikova. 1966. Preservation of vitamins added to increase the nutritive value of mixed feeds. Tr., Vses. Nauch.-issled. Inst. Zerna Prod. Ego Pererab. 55:169-177.

1380. Florenskaya, N. K., I. I. Zolubas, V. M. Sebekina, and T. I. Fetisova. 1963. Commercial storage of enriched mixed fodder. Tr. Vses. Nauchn.-issled. Inst. Zerna i Produktov ego Pererabotki 1963(44):67-76.

1381. Flynn, L. M., V. B. Williams, B. L. O'dell, and A. G. Hogan. 1951. Medium for assay of vitamins with lactic acid bacteria. Anal. Chem. 23:180-185.

1382. Foa, P. P., N. L. Foa, and H. Field, Jr. 1945. The effect of nicotinic acid and nicotinamide on growth, liver fat, renal hemorrhages and excretion of "trigonelline" in the rat. Arch. Biochem. 6(2):215-224.

1383. Fokina, T. V. 1944. Action of ascorbic acid on experimental anemia. I. Pediatriya 1944(1):37-41.

1384. Fokina, T. V. 1955. The influence of nicotinic acid on the hemoglobin metabolism. Byull. Ekspti. Biol. i Med. 40(8): 42-46.

1385. Fomina, L. G. 1964. Effect of large doses of nicotinic acid on lipid metabolism in atherosclerosis. Materialy Nauchn. Konf. Chelyab. Med. Inst., Chelyabinsk, Sb. 1964:35-36.

1386. Fonda, M. L., and B. M. Anderson. 1967. D-Amino acid oxidase. I. Spectrophotometric studies. J. Biol. Chem. 242(17):3957-3962.

1387. Fondy, T. P., G. S. Ghangas, and M. J. Reza. 1970. Synthesis of 1-halo analogs of DL-glycerol 3-phosphate and their effects on glycerol phosphate dehydrogenase. Biochemistry 9(16):3272-3280.

1388. Fong, C. T. O., L. Silver, and G. Lankau. 1970. Effect of pyridine nucleotide precursors on the permeability of toad bladder in the presence of vasopressin, adenosine 3',5'-cyclic monophosphate, and theophylline. Proc. Nat. Acad. Sci. U.S. 67(3):1221-1224.

1389. Fontaine, L., and S. Gaillot. 1961. A drug for arteriosclerosis. Fr. Pat. M1127.

1390. Fontenot, R., H. Redetzki, and R. Deupree. 1965. Effects of nicotinic acid and nicotinamide on serum cholesterol and erythrocyte nicotinamide adenine dinucleotide levels in rabbits. Proc. Soc. Expti. Biol. Med. 119(4):1053-1055.

1391. Forbes, J. C. 1941. Vitamin B complex and fat metabolism. J. Nutrition 22:359-364.

1392. Forbes, J. C., and G. M. Duncan. 1958. The adrenal response to alcohol intoxication in rats maintained with diets deficient in tryptophan, niacin or lysine. Quart. J. Stud. Alcohol 19(4):553-562.

1393. Forbes, J. C., and G. M. Duncan. 1959. Effect of exposure to cold on the response to alcohol intoxication of rats which are deficient in tryptophan and niacin. Virginia J. Sci. 10(4): 300.

1394. Forbes, J. C., and G. M. Duncan. 1961. Effect of a tryptophan-niacin deficient diet on the adrenal response of rats exposed to cold and alcohol intoxication. Quart. J. Stud. Alcohol 22:254-260.

1395. Ford, J. E., M. E. Gregory, and S. K. Kon. 1956. The B vitamin content of milk in relation to the breed of cow and stage of lactation. 14th Intern. Dairy Congr. Proc., Rome 1956 1(Pt. 11):760-765.

1396. Ford, J. E., M. E. Gregory, and S. Y. Thompson. 1962. The effect of gamma irradiation on the vitamins and proteins of liquid milk. Intern. Dairy Congr. Proc., 16th, Copenhagen 1962(Sect. A):917-923.

1397. Foriano, A. J. 1967. Effect of the component parts of nicotinamide adenine dinucleotide (NAD+) as inhibitors of lactic dehydrogenase. J. Pharm. Sci. 56(6):763-765.

1398. Fornaini, G., and E. Marinello. 1956. Mechanism of hepatic glycogenolysis after large doses of nicotinamide. VI. Formation of an activator of phosphoglucomutase in the liver of animals treated with nicotinamide. Boll. Soc. Ital. Biol. Sper. 32: 1611-1613.

1399. Fornaini, G., and S. Pontremoli. 1960. Biochemical effects of large doses fo vitamin PP. Behavior of the transketolase and transaldolase reactions. Boll. Soc. Ital. Biol. Sper. 36:200-203.

1400. Fornaini, G., G. Segni, and C. Antolini. 1958. Glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase in the liver of rats treated with large doses of nicotinamide. Boll. Soc. Ital. Biol. Sper. 34:1564-1566.

1401. Forni, P. V. 1952. Hypothermia from nicotinic acid and antihistaminics. Acta Vitaminol. 6:3-5.

1402. Forni, P. V., A. Fubini, and F. Ghilardi. 1956. Hypervitaminosis and tissue water content. Ipervitaminosi (Vitaminologia 11-13):89-99.

1403. Fountain, R. B., B. S. Baker, J. W. Hadgraft, and I. Sarkany. 1969. Rate of absorption and duration of action of four different solutions of methyl nicotinate. Brit. J. Dermatol. 81(3):202-206.

1404. Fox, S. H., and L. P. Opferman. 1947. Stable ascorbic acid-nicotinamide vitamin preparations. U.S. Pat. 2,433,688.

1405. Foy, H., and A. Kondi. 1958. Hypochromic anemias of the tropics associated with pyridoxine and nicotinic acid deficiency. Blood, J. Hematol. 13(11):1054-1062.

1406. Fraenkel, G. 1951. Function of nicotinic acid in protein metabolism. Fed. Proc. 10(1):382-383.

1407. Fraenkel, G., and M. Blewett. 1942. Biotin, B1, riboflavin, nicotinic acid, B6 and pantothenic acid as growth factors for insects. Nature 150:177-178.

1408. France, R., R. D. Bates, Jr., W. H. Barker, and E. Matthews. 1938. Two cases of pellagra treated with nicotinic acid. Bull. Johns Hopkins Hosp. 63(1):46-53.

1409. Francescon, M. 1948. Nicotinic acid and pulmonary circulation. Atti Soc. Med.-Chir. Padova 26:51-54.

1410. Frandoli, G. 1962. Effects of nicotinic acid and 3-pyridylacetic acid on mechanisms of haemostasis. Modifications of intensity of haemorrhage. Acta Vitaminol. 16:131-139.

1411. Frank, L., Y. Rapp, L. Biro, and F. S. Glickman. 1964. Inflammation mediators and the inflammatory reaction. Arch. Dermatol. 89:55-67.

1412. Frank, O., H. Baker, S. H. Hutner, and H. Sobotka. 1963. Toxicity to protozoa of thalidomide breakdown products; Counteraction by nicotinic acid and glutamine. Proc. Soc. Exptl. Biol. Med. 114(2):326-328.

1413. Frank, O., A. V. Luisada-Opper, S. Feingold, and H. Baker. 1970. Vitamin binding by human and some animal plasma proteins. Nutr. Rep. Int. 1(3):161-168.

1414. Frank, O., A. Luisada-Opper, M. F. Sorrell, A. D. Thomson, and H. Baker. 1971. Vitamin deficits in severe alcoholic fatty liver of man calculated from multiple reference units. Exp. Mol. Pathol. 15(2):191-197.

1415. Frank, O., H. Baker, H. Ziffer, S. Aaronson, S. H. Hutner, and C. M. Leevy. 1963. Metabolic deficiencies in protozoa induced by thalidomide. Science 139:110-111.

1416. Frankau, I. M. 1943. Acceleration of coordinated muscular effort by nicotinamide. Brit. Med. J. 1943(II):601-603.

1417. Fraser, F. C., M. Goldstein, and M. Feiner. 1961. Teratogenic effects of a two-hour inactivation of nicotinamide activity in the mouse. In: Transactions of the Society for Pediatric Research, Thirty-first Annual Meeting, Atlantic City, New Jersey, May 1961. Am. J. Dis. Children 102(4):532-533.

1418. Frassanito, M., and S. Colonna. 1961. Effects of nicotinic acid on the healing of experimental wounds. Minerva Chir. 16(13):842-845.

1419. Frateschi, T. L. 1969. Glucose content in blood of rabbits parenterally treated with high doses of nicotinamide. Ann. Fac. Med. Vet., Univ. Studi Pisa 21:243-246.

1420. Fratta, I. D. 1969. Nicotinamide deficiency and thalidomide. Potential teratogenic disturbances in Long-Evans rats. Lab. Anim. Care 19(5 Part 2):727-732.

1421. Fratta, I., S. B. Zak, P. Greengard, and E. B. Sigg. 1964. Fetal death from nicotinamide-deficient diet and its prevention by chlorpromazine and imipramine. Science 145(3639): 1429-1430.

1422. Frazier, E. I., T. Porter, and M. J. Humphrey. 1948. The utilization of nicotinic acid by pregnant women. Federation Proc. 7:287.

1423. Frazier, E. I., T. Porter, and M. J. Humphrey. 1949. The utilization of nicotinic acid by pregnant women. J. Nutrition 37:393-410.

1424. Frazier, E. I., M. E. Prather, and E. Hoene. 1955. Nicotinic acid metabolism in humans. I. The urinary excretion of nicotinic acid and its metabolic derivatives on four levels of dietary intake. J. Nutrition 56:501-516.

1425. Frei, R. W., A. Kunz, G. Pataki, T. Prims, and H. Zuercher. 1970. Determination of nicotinic acid and nicotinamide by thin-layer chromatography and in situ fluorometry. Anal. Chim. Acta 49(3):527-534.

1426. Freidman, T. E., and E. I. Frazier. 1945. The use of "tagged" derivatives in the fluorimetric assay of vitamins. Science 102(2639):97-99.

1427. Freifelder, M., and I. W. Sangreiet. 1960. Nicotinamide. U.S. Pat. 2,932,648.

1428. French, F. A., and B. L. Freedlander. 1959. The effect of niacin deficiency, excess nicotinamide, and 3-pyridyl ketones on pulmonary adenomas in strain A mice. Proc. Am. Assoc. Cancer Res. 3(1):21.

1429. Frens, A. M. 1946. Salt drinking water for cows. Tijdschr. Diergeneesk. 71(1):6-11.

1430. Fresia, P., A. Mortari, and G. Sioli. 1963. The vasodilator properties of nicotinic acid at the coronary level. Atti Accad. Med. Lombarda 18(3):658-660.

1431. Freudenthal, R. I., C. E. Cook, R. Rosenfield, and M. E. Wall. 1971. The effect of different incubation systems on the in vitro metabolism of norethynodrel. J. Steroid. Biochem. 2(1):77-82.

1432. Freyss-Beguin, M., and P. Lechat. 1968. Comparative effect of pyridine carboxylic acids and piperidine carboxylic acids on hypercholesterolemia and hyperlipoproteinemia induced in the rat by Triton WR 1339 injection. Therapie 23(6):1343-1355.

1433. Freyss-Beguin, M., E. Van Brussel, and P. Lechat. 1970. Comparative effect of pyridinecarboxylic and piperidinecarboxylic acids on the serum fatty acid content of rats treated with Triton WR-1-339. Therapie 25(5):857-862.

1434. Freyss-Beguin, M., L. Mercier-Parot, P. Lechat, and H. Tuchmann-Duplessis. 1972. Mechanism of embryotoxic and teratogenic action of Triton W. R. 1339 in the rat. C. R. Soc. Biol. 166(1):9-14.

1435. Fried, R., and A. Carvalho da Silva. 1950. Growth depression by ammonium citrate and urea and its reversion by nicotinamide in the rat. Arch. Biochem. 26:161-163.

1436. Fried, R., and A. Carvalho da Silva. 1954a. Some effects of nicotinamide, diammonium citrate, and urea as supplements to low protein diets. Intern. Z. Vitaminforsch. 25:281-294.

1437. Fried, R., and A. Carvalho da Silva. 1954b. Effects of nicotinamide and nitrogen supplements in low protein diets containing sulfonamides. Intern. Z. Vitaminforsch. 25:295-302.

1438. Friedemann, T. E., and C. J. Barborka. 1941. A procedure for the decolorization of acid digestion mixtures for the determination of nicotinic acid. J. Biol. Chem. 138:785-786.

1439. Friedemann, T. E., and E. I. Frazier. 1950. Determination of nicotinic acid. Arch. Biochem. 26:361-374.

1440. Friedland, I. M., L. Fuller, and L. S. Dietrich. 1962. Nicotinic acid and nicotinamide metabolism in ascites cells in vitro. J. Biol. Chem. 237:3829-3831.

1441. Friedman, F. 1955. Effects of vitamins and their analogs upon tumor incidence in Drosophila melanogaster. Trans. N.Y. Acad. Sci. 17:294-300.

1442. Friedman, M. 1960. The effect of nicotinic acid on hypercholesterolaemia. Can. Med. Assoc. J. 83:36.

1443. Friedman, M., and S. O. Byers. 1967. Epinephrine-induced reduction of postprandial lipemia in the rat. Am. J. Physiol. 213(4):829-836.

1444. Friedman, M., S. O. Byers, W. Hayashi, C. Dinoto, and B. Tsai. 1959. Evaluation of nicotinic acid as an hypocholesterolemic and anti-atherogenic substnace. J. Clin. Invest. 38:1328-1333.

1445. Friedmann, N. 1970. Prebiotic synthesis of the aromatic amino acids, hydrocarbons, and nicotinic acid. Diss. Abstr. Int. B 31(8):4542-4543.

1446. Froberg, S. O. 1971. Effects of nicotinic acid on tissue triglycerides in animal and man. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1971:449-456.

1447. Froberg, S. O., J. Boberg, L. A. Carlson, and M. Eriksson. 1971. Effect of nicotinic acid on the diurnal variation of plasma levels of glucose, free fatty acids, triglycerides and cholesterol, and of urinary excretion of catecholamines. Metab. Eff. Nicotinic Acid Its Deriv., Pro 1971:167-181.

1448. Froeberg, S., and L. Oroe. 1963. The effects of nicotinic acid, phentolamine and nethalide on the plasma free fatty acids and the blood pressure in the dog. A comparative study. Acta Med. Scand. 174(5):635-641.

1449. Froebrich, G., and K. Offhaus. 1953. Qualitative vitamin test using Tribolium confusum as test organism. Qualitative determination of vitamins B1, B2, B6, niacin or niacinamide, pantothenic acid, folic aicd, and biotin. Z. Vitamin-, Hormon- u. Fermentforsch. 5:358-369.

1450. Froesch, E. R., M. Waldvogel, and O. Oelz. 1971. Effects of nicotinic acid and structurally related drugs on adipose tissue in vitro and on carbohydrate and lipid metabolism of normal and diabetic rats in vivo. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1971:773-794.

1451. Froesch, E. R., M. Waldvogel, U. A. Meyer, A. Jakob, and A. Labhart. 1967. Effects of 5-methylpyrazole-3-carboxylic acid on adipose tissue. II. Antilipolytic and hypoglycemic effects in vivo. Mol. Pharmacol. 3(5):442-452.

1452. Frola, G. 1942. Action of nicotinamide in various cases of chronic erythroblastosis. Boll. Soc. Ital. Biol. Sper. 17:365-367.

1453. Frol'kis, R. A. 1970. Effect of nicotinamide on the components of tissue respiratory chain of the heart experimental myocardial infarct. Patrol. Fiziol. Eksp. Ter. 14(5):11-15.

1454. Frommel, E., A. Bischler, I. T. Beck, F. Vallette, and M. Favre. 1947. Antihistamine function of nicotinamide and of certain of its derivatives. Intern. Z. Vitaminforsch. 19:193-199.

1455. Frontali, G. 1942. Observations on pellagra. Schweiz. Med. Wochschr. 72:208-217.

1456. Frost, G. M., K. S. Yang, and G. R. Waller. 1967. Nicotinamide adenine dinucleotide as a precursor of nicotine in Nicotiana rusticia. J. Biol. Chem. 242(5):887-888.

1457. Frunder, H., and G. Richter. 1955a. Changes in the DPN plus DPNH concentration in slices of normal and fatty livers during Warburg experiments. Hoppe-Seyler's Zeitschr. Physiol. Chem. 299(1/2):39-47.

1458. Frunder, H., and G. Richter. 1955b. Studies on the splitting of DPN in liver homogenates. Hoppe-Seyler's Zeitschr. Physiol. Chem. 302(1):1-9.

1459. Fruschelli, C., and G. Pompucci. 1965. Quantitative histochemical modifications of liver lipids in rats treated with nicotinamide. Boll. Soc. Ital. Biol. Sper. 41(23):1440-1443.

1460. Fruton, J.S., W. H. Stein, M. A. Stahmann, and C. Golumbic. 1946. Chemical reactions of the nitrogen mustard gases. VI. The reactions of the nitrogen mustard gases with chemical compounds of biological interest. J. Organic Chem. 11(5): 571-580.

1461. Fujii, T., and T. Mizuno. 1965. Failure of nicotinamide to inhibit early carcinogenesis changes in adrenalectomized mice. J. Fac. Sci. Univ. Tokyo Sect. IV 10(3):441-449.

1462. Fujikawa, F., et al. 1969. Chemotherapeutics for Mycobacterium tuberculosis. XXIV. Synthesis and antibacterial activity of 3-methoxy-2-phenoxybenzaldehyde, 3-methoxy-4-(3-methoxyphenoxy)-benzaldehyde and 3-methoxy-4-(4-methoxyphenoxy)benzaldehyde derivatives for Mycobacterium tuberculosis. Yakugaku Zasshi 89(9):1266-1271.

1463. Fujikawa, F., K. Hirai, S. Konishi, F. Kondo, F. Ueda, M. Hayata, Y. Inoue, M. Naito, S. Tsukuma, and N. Mabuchi. 1969. Chemotherapeutics for Mycobacterium tuberculosis. XXIII. Synthesis and antibacterial activity of Mycobacterium tuberculosis of 3-methoxy-4-phenoxybenzaldehyde and 3-hydroxy-4-phenoxy-benzaldehyde derivatives. Yakugaku Zasshi 89(8):1119-1124.

1464. Fujimura, S., S. Hasegawa, Y. Shimizu, and T. Sugimura. 1967. Polymerization of the adenosine 5'-diphosphate-ribose moiety of nicotinamide adenine dinucleotide by nuclear enzyme. I. Enzymic reactions. Biochim. Biophys. Acta 145(2):247-259.

1465. Fukalova, L. A. 1963. The effect of some nicotinic acid preparations on inflammation. Farmakol. i Toksikil. 26(4): 461-465.

1466. Fukumura, M., K. Shimago, K. Hesaka, S. Okanao, and H. Nakatani. 1969. Antidiabetic 3-(hydroxymethyl)-5-methylpyrazole carboxylates. Ger. Offen. Pat. 1,931,061.

1467. Fukushi, S. 1962. Studies on the blood volume of rabbit ocular tissue by means of intravenous injection of 131I-labeled bovine plasma albumin. III. Administration of miscellaneous drugs and application of infrared. Nippon Ganka Gakkei Zasshi 66(5):335-339.

1468. Fulgraff, G., A. Bieg, and K. Wolf. 1970. Renal oxygen consumption after Ouabain and 6-aminonicotinamide. Nauny-Schmiedebims Arch. Pharmakol. 266(1):43-49.

1469. Fuller, L., and L. S. Dietrich. 1971. Comments on the determination of nicotinamide. Anal. Biochem. 39:538-539.

1470. Fumagalli, R. 1971. Pharmacokinetics of nicotinic acid and its derivatives. Metab. Eff. Nicotinic Acid its Deriv., Pro. 1971: 33-49.

1471. Fumaneri, A. E. 1958. Biliary-hepatic protective preparation composed of fluid-extracts. Boll. Chim. Farm. 97:24-27.

1472. Funk, C., and I. C. Funk. 1939. Importance of nicotinic acid and of its amide in nutrition. Z. Vitaminforsch. 8:330-334.

1473. Fussgaenger, R., U. Doid, and H. Holzer. 1967. The influence of Trenimon (2,3,5-tris-ethyleneimino-1,4-benzoquinone) on the content of nicotinic acid and nicotinamide in Ehrlich ascites tumor cells. Z. Krebsforsch. 69(3):275-282.

1474. Fust, B., and A. Studer. 1951. Effect of nicotinamide on tuberculosis of guinea pig. Schweiz Path. u. Bakt. 14(5):523-531.

1475. Furtado, D. 1942. The use of nicotinic acid in cerebral thrombosis. Rev. Clin. 5:193-194.

1476. Gabor, G. 1941. Effect of nicotinic acid on hydrochloric acid production in the stomach. Orvosi Hetilap 85:629-630.

1477. Gabrynowicz, J. W., et al. 1968. A clinical trial of leptazole with nicotinic acid in the management of psycho-geriatric patients. Med. J. Aust. 1:799-802.

1478. Gabuzda, G. J., and C. S. Davidson. 1962. Tryptophan and nicotinic acid metabolism in patients with cirrhosis of the liver. Am. J. Clin. Nutr. 11:502-508.

1479. Gadsden, E. L., C. H. Edwards, and G. A. Edwards. 1960. Paper chromatography of certain vitamins in phenol and butanol-propionic acid-water solvents. Anal. Chem. 32:1415-1417.

1480. Gaebler, O. H., and W. T. Beher. 1951. Studies of antimetabolites. I. Pyridine-3-sulfonic acid and 3-acetylpyridine. J. Biol. Chem. 188(1):343-349.

1481. Gaebler, O. H., and J. C. Mathies. 1946. Further studies on effects of water-soluble vitamins in experimental diabetes. Endocrinology 39:239-246.

1482. Gaenshirt, H., and A. Malzacher. 1960. Separation of several vitamins of the B group and of vitamin C by surface chromatography. Naturwissenschaften 47:279-280.

1483. Gaevyi, M. D., and E. V. Romanova. 1971. Effect of nicotinic acid on the tonus of the intra- and extracranial blood vessels. Vrach. Delo 1971(8):33-35.

1484. Galdenko, A. I. 1966. Interrelation between iron and nicotinic acid metabolism. Vop. Pitan. 25(5):37-41.

1485. Galbraith, P. A., W. F. Perry, and R. E. Beamish. 1959. Effect of nicotinic acid on serum lipides in normal and atherosclerotic subjects. Lancet 1959(I):222-223.

1486. Galeone, A., and A. Romagnolo. 1948. The antidicoumarol action of DL-methionine, vitamins PP and K, and casein hydrolyzate. Minerva Med. 39(1):169-173.

1487. Gall, L. S. 1970. Normal fecal flora of man. Am. J. Clin. Nutr. 23(11):1457-1465.

1488. Gallagher, C. H. 1960a. The effect of precursors of pyridine nucleotides on poisoning by carbon tetrachloride. Australian J. exp. Biol. Med. Sci. 38:251-260.

1489. Gallagher, C. H. 1960b. The effects of nicotinic acid in experimental carbon tetrachloride poisoning of sheep. Australian J. Agr. Research 11:1009-1016.

1490. Gallagher, C. H., J. H. Koch, and D. M. Mann. 1965a. The effect of phenothiazine on the metabolism of liver mitochondria. Biochem. Pharmacol. 14(5):789-797.

1491. Gallagher, C. H., J. H. Koch, and D. M. Mann. 1965b. The effect of phenothiazone on the metabolism of liver mitochondria. Biochem. Pharmacol. 14(5):799-811.

1492. Gallagher, C. H., A. C. Kondos, and W. H. Southcott. 1962. Carbon tetrachloride poisoning in sheep: Effect of administration of nicotinic acid on death rate. Australian Vet. J. 38(8):409-411.

1493. Galletti, C., et al. 1963. Sympathico-nasal reflexes after intramuscular injection of nicotinic acid in subjects with rhinopathy of the allergic type. Otorinolaring. ital. 32:40-45.

1494. Gallo, V. 1948. Leucocytes after sodium nicotinate administration. Acta Vitaminol. 2:127-130.

1495. Gallois, J. 1947a. Vasodilation in chorioretinitis and certain senile cases of retinitis. Bull. Soc. Ophtalmol. Paris 1947:130-132.

1496. Gallois, J. 1947b. A case of progressive choroiditis. Bull. Soc. Ophtalmol. Paris 1947:333-335.

1497. Gallois, J. 1947c. Chronic glaucoma and elective minimal vasodilation. Ann. Oculist. 180:20-28.

1498. Galston, A. W. 1947. Synergism between indoleacetic and nicotinic acids in a plant growth inhibition. J. Biol. Chem. 169(2):465-466.

1499. Galzigna, L. 1970. Complexes between acetylcholine and catechol amines and their tolerance to mental illness. Nature (London) 225(5237):1058-1059.

1500. Gamble, W., and L. D. Wright. 1961. Effect of nicotinic acid and related compounds on incorporation of mevalonic acid into cholesterol. Proc. Expti. Biol. and Med. 107(1):160-162.

1501. Ganelina, I. E. 1948. Action of nicotinic acid on the circulatory system. Klin. Med. (U.S.S.R.) 26(4):51-64.

1502. Gangadharam, P. R., and A. J. Droubi. 1971. A comparison of four different methods for testing the production of niacin by mycobacteria. Am. Rev. Respir. Dis. 104(3):434-437.

1503. Ganguli, N. C., S. Ganguly, and S. C. Roy. 1955. Effect of chloretone on some B-vitamin reserves in the liver tissue of rats. Ann. Biochem. and Expti. Med. 15(2):113-114.

1504. Garattini, S., and A. Bizzi. 1971. Drugs affecting lipolysis. Naunyn-Schmiedebergs Arch. Pharmakol. 269(2-4):372-379.

1505. Garattini, S., and R. Paoletti. 1953. Liberation of hydrogen sulfide by tissues and conditions which favor or inhibit this activity. Atti Soc. Lombarda Sci. Med. Biol. 8:51-54.

1506. Garattini, S., R. Paoletti, L. Bizzi, E. Grossi, and R. Vertua. 1961. Comparative evaluation of hypocholesterolemic drugs with several tests. Drugs Affecting Lipid Metab., Proc. Symp., Milan 1960:144-157.

1507. Garbo, P. W. 1947. Nicotinamide. U.S. Pat. 2,419,831.

1508. Garbo, P. W. 1949. Nicotinamide. U.S. Pat. 2,460,002.

1509. Garbulinski, T., J. Debowy, and I. Dynarowicz. 1971. Cholinergic receptors in regulation of the metabolism of heart high-energy phosphates. Nicotinic receptors. Acta Physiol. Pol. 22(5):617-623.

1510. Garcia-Bunuel, L., D. B. McDougal, Jr., H. B. Burch, E. M. Jones, and E. Touhill. 1962. Oxidized and reduced pyridine nucleotide levels and enzyme activities in brain and liver of niacin-deficient rats. J. Neurochem. 9:589-594.

1511. Gardner, D. A., G. H. Sato, and N. O. Kaplan. 1972. Pyridine nucleotides in normal and nicotinamide depleted adrenal tumor cell cultures. Dev. Biol. 28(1):84-93.

1512. Garsevanishvili, T. I., N. D. Mukeriya, N. N. Grigoryan, and I. N. Chkhartishvili. 1970. Content of B vitamins in the blood and urine of practically healthy under 1 year. Pediatriya 49(6):22-24.

1513. Gassmann, B., and D. Ehrt. 1959. Chemical determination of nicotinic acid in urine. Ernaehrungsforschung 4:72-83.

1514. Gassmann, B., D. Lexow, and V. Erhardt. 1972. Problems and limitations of standardization methods for the determination of vitamins in foods. Nahrung 16(3):245-257.

1515. Gasteiger, E. L., P. C. Haake, and J. A. Gergen. 1960. Investigation of the distribution and function of homarine N-methyl picolinic acid. Ann. N.Y. Acad. Sci. 90(Art. 3): 622-636.

1516. Gaut, Z. N., and H. M. Solomon. 1970a. Inhibition of 7-14C-nicotinic acid metabolism in the human blood platelet by antiinflammatory drugs. Res. Commun. Chem. Pathol. Pharmacol. 1(4): 547-552.

1517. Gaut, Z. N., and H. M. Solomon. 1970b. Uptake and metabolism of nicotinic acid by human blood platelets. Effects of structure analogs and metabolic inhibitors. Biochim. Biophys. Acta 201(2):316-322.

1518. Gaut, Z. N., and H. M. Solomon. 1971a. Inhibition of nicotinate phosphoribosyl transferase by nonsteroidal anti-inflammatory drugs: a possible mechanism of action. J. Pharm. Sci. 60:1887-1888.

1519. Gaut, Z. N., and H. M. Solomon. 1971b. Inhibition of nicotinate phosphoribosyl-transferase in human platelet lysate by nicotinic acid analogs. Biochem. Pharmacol. 20(10): 2903-2906.

1520. Gaut, Z. N., H. M. Solomon, and O. N. Miller. 1971. Effect of antilipemic doses of nicotinic acid on carbohydrate tolerance and plasma insulin levels in man. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1971:923-927.

1521. Gaut, Z. N., R. Pocelinko, H. M. Solomon, and G. B. Thomas. 1971. Oral glucose tolerance, plasma insulin, and uric acid excretion in man during chronic administration of nicotinic acid. Metab. Clin. Exp. 20(11):1031-1035.

1522. Gauthier, J. J. 1971. Metabolism of nicotinic acid. Oxidation of 2,5-dihydroxypyridine by Pseudomonas putida N-9. Diss. Abstr. Int. B 32(1):66.

1523. Gauthier, J. J., and S. C. Rittenberg. 1971. Metabolism of nicotinic acid. I. Purification and properties of 2,5-dihydroxypyridine oxygenase from Pseudomonas putida N-9. J. Biol. Chem. 246(11):3737-3742.

1524. Gautier, J. A. 1944. Microchemical characterization of nicotinic acid and its amide (vitamin PP). Ann. Chim. Anal. 26:89-90.

1525. Gautier, J. A., and P. Cordier. 1947. Contribution on the problem of antivitamines. Bull. Soc. Chim. Biol. 29:514-516.

1526. Gaw, D. W., C. C. Reeck, and J. B. Wray. 1970. Water and electrolyte metabolism in muscle adjacent to a fracture. Clin. Orthop. Relat. Res. 1970(69):245-251.

1527. Gawecka, I., and W. Gumulka. 1965. Mechanism of the hypotensive action of certain monoamine oxidase inhibitors. Acta Physiol. Polon. 16(4):567-577.

1528. Gaylor, J. L. 1960. Biosynthesis of sterols as altered by carcinogens or nicotinic acid. Dissertation Abstr. 21:444-445.

1529. Gaylor, J. L. 1961. Hypocholesterolemic action of nicotinic aicd. New York J. Med. 61:1739-1741.

1530. Gaylor, J. L., R. W. F. Hardy, and C. A. Baumann. 1960. Effects of nicotinic acid and related compounds on sterol metabolism in the chick and rat. J. Nutrition 70:293-301.

1531. Gazzarrini, F., and B. Nagy. 1966. Saturated hydrocarbons in human femoral arterial tissues and plaques. Arch. Biochem. Biophys. 113(1):245-252.

1532. Gebhardt, D. O. E. 1969. Effects of starvation or of treatment with cytotoxic agents on pregnancy in mice. J. Reprod. Fert. 19(3):519-526.

1533. Gebhardt, G. 1955a. The influence of some vitamins on the endogenous and exogenous protein metabolism in growing albino rats. Arch. Tierernaehr. 5:70-124.

1534. Gebhardt, G. 1955b. The influence of some vitamins on the endogenous and exogenous protein metabolism in growing albino rats. II. Arch. Tierernaehr. 5:125-141.

1535. Geer, J. C., H. C. McGill, Jr., and R. L. Holman. 1957. The effect of B vitamins on the incidence of necrotizing arteritis in the dog. Arch. Pathol. 64(6):673-678.

1536. Geiger, E., E. B. Hagerty, and H. D. Gatchell. 1949. Transformation of tryptophan to nicotinic acid investigated with delayed supplementation of tryptophan. Arch. Biochem. 23:315-320.

1537. Geimer, M. 1961. On the treatment of circulatory regulaiton disorders in childhood. Med. Welt 32-33:1624-1627.

1538. Gellenbeck, S. M. 1962. Aerobic respiratory metabolism of Staphylococcus aureus from an infected animal. J. Bacteriol. 83:450-455.

1539. Genin, D. I. 1959. Nicotinic acid as a spermatocide component of chemical contraceptives. Akusherstvo i Ginekol. 35(6): 28-30.

1540. Genski, P., Jr., S. B. Formal, and L. S. Baron. 1971. Identification of two widely separated loci conferring nicotinic acid dependence on wild-type Shigella flexneri 2a. Infec. Immunity 3(3):500-503.

1541. Genthoff, H. 1960. A contribution to improvement in the results of surgery of the sympathetic nervous system (with a study on blood supply of the muscles). Med. Welt 47:2519-2521.

1542. Georg, A., and P. Bachmann. 1943. A simplification of a synthesis of nicotinamide and the reaction of hydrogen peroxide with nitriles. Helv. Chim. Acta 26:358-362.

1543. Gerasimova, I. L. 1962. Effect of nicotinic acid on blood coagulation, on the content of blood heparin, and on the clearing factor in atherosclerotic patients. Materialy Pervogo Soveshch. po Aktual'nym Vopr. Klinich. Biokhim., Rizhsk. Med. Inst. 1962:122-124.

1544. Gerasimova, I. L. 1963. The effect of nicotinic acid on blood clotting, heparin content and on the clarification factor in atherosclerosis. Kardiologiya 3(1):61-64.

1545. Gerber, G. B., and J. Deroo. 1968. Degradation of nicotinamide coenzymes and excretion of their metabolites in irradiated animals. Deut. Ges. Biophys., Oesterr. Ges. Reine Angew, Biophys., Gemeinsame Jahrestag., Tagungsber. 1968:263-266.

1546. Gerber, G. B., and J. Deroo. 1969. Metabolism of nicotinamide coenzymes following whole-body irradiation. I. Catabolism of NAD and excretion of its metabolites. Strahlentherapie 137(6): 724-729.

1547. Gerber, G. B., and J. Deroo. 1970. Metabolism of labeled nicotinamide coenzyme in different organs of mice and rats. Proc. Soc. Exp. Biol. Med. 134(3):689-693.

1548. Gerber, G. B., B. Zicha, and J. Deroo. 1969. Synthesis of NAD and catabolism of nicotinic acid in the isolated perfused liver of normal and x-irradiated rats. Int. J. Radiat. Biol. 15(5):425-434.

1549. Gerlich, N. 1959. Nicotinamide metabolism during cytostatic therapy. Verh. Deutsch. Ges. Inn. Med. 65:208-211.

1550. Gershbein, L. L. 1956. Effect of nicotinic acid and derivatives on rat liver regeneration. Am. J. Physiol. 184(1):47-51.

1551. Gershbein, L. L. 1966. Effect of various agents on liver regeneration and Walker tumor growth in partially hepatectomized rats. Cancer Res. 26(9)(Pt. 1):1905-1908.

1552. Gershbein, L. L. 1967. Effect of transplanted tumor and various agents on liver regeneration during pregnancy. Proc. Soc. Exp. Biol. Med. 126(1):88-92.

1553. Gershenovich, R. S., A. M. Maksudov, and Ts. G. Ioffe. 1940. Nicotinic acid treatment of pellagra in children. Sovet. Med. 1940(13-14):29-32.

1554. Gershoff, S. N., D. M. Hegsted, and M. F. Trulson. 1958. Metabolic studies of mongoloids. Am. J. Clin. Nutrition 6:526-530.

1555. Gersmeyer, E. F., and E. Leicht. 1967. Therapeutic influence on peripheral circulation. Med. Welt 1967(8):426-431.

1556. Gessa, G. L., and G. Clay. 1969. Evidence that hyperthermia produced by d-amphetamine is caused by a peripheral action of the drug. Life Sci. 8(3):135-141.

1557. Gey, K. F., and E. Buehler. 1971. Pilot studies on the release of corticosterone and catecholamines in the rat by nicotinic acid and beta-pyridylcarbinol respectively. Metab. Eff. Nicotinic Acid its Deriv., Pro. 1971:1007-1010.

1558. Gey, K. F., and E. Lorch. 1968. Comparison of nicotinic acids and beta-pyridylcarbinol with respect to lipid metabolism in the rat in vivo. Progr. Biochem. Pharmacol. 4:858-890.

1559. Gey, K. F., K. Von Berlepsch, H. Malanowski, and E. Lorch. 1971. Increase of urea formation by nicotinic acid and beta-pyridylcarbinol in the starved rat. Metab. Eff. Nicotinic Acid its Deriv., Pro. 1971:1035-1044.

* 1560. Gey, K. S., and L. A. Carlson. 1971. Metabolic effects of nicotinic acid and its derivatives. Proceedings of a workshop in Flims, Switzerland, March 23-25, 1970. Hans Huber, Bern, Switzerland, 1261pp.

1561. Gholson, R. K., et al. 1964. The enzymatic conversion of quinolinate to nicotinic acid mononucleotide in mammalian liver. J. Biol. Chem. 239:1208-1214.

1562. Gholson, R. K., G. J. Tritz, T. S. Matney, and A. J. Andreoli. 1969. Mode of nicotinamide adenine (dinucleotide) utilization by Escherichia coli. J. Bacteriol. 99(3):895-896.

1563. Ghosh, N. C. 1941. Stability of nicotinic acid and its urinary excretion. Ann. Biochem. Exptl. Med. 1:235-238.

1564. Ghosh, N. C., N. Nandi, and S. Banerjee. 1951. Studies on the distribution of the bound form of nicotinic acid in fish, tortoise, beef and goat's muscle. Indian J. Med. Res. 39(4): 453-456.

1565. Ghosh, N. C., K. Chatterjee, D. P. Chattopadhyay, and Sachchidananda. 1954. Liver as the site of synthesis of nicotinic acid from tryptophan in rats. Proc. Soc. Exptl. Biol. Med. 86:346-347.

1566. Giannini, A., and P. P. Ognibene. 1959. On a case of Jolliffe's encephalopathy in alcoholism. Riv. Pat. Nerv. Ment. 80:463-467.

1567. Gibb, J. W., and T. M. Brody. 1967. The protective effect of nicotinamide on carbon tetrachloride-induced hepatotoxicity. Biochem. Pharmacol. 16(10):2047-2049.

1568. Gibelli,.A., and G. Sacchetti. 1962. The amide group in nicotinamide and 3-pyridineacetamide, in relation to some of their biological actions. Action of 3-pyridineacetamide and 3-pyridine acetic acid on euglobulin fibrinolysis in man. Acta Vitaminol 16(3/4):127-129.

1569. Gibelli, A., G. Sacchetti, L. Mainieri, and F. Soardi. 1962. Activation of fibrinolysis by 3-pyridineacetic acid and nicotinic acid in man. Acta Vitaminol. 16:107-119.

1570. Giger, K. 1963. Glycolysis by subcellular melanoma fractions and the effects of insulin, endotoxin, and testosterone. Ann. N.Y. Acad. Sci. 100(Pt. 2):866-875.

1571. Gigon, P. L., and M. H. Bickel. 1971. N-Demethylation and N-oxidation of imipramine by rat and pig liver microsomes. Biochem. Pharmacol. 20(8):1921-1931.

1572. Gigon, P. L., T. E. Gram, and J. Gillette. 1969. Rate of reduction of hepatic microsomal cytochrome P-450 by reduced nicotinamide adenine dinucleotide phosphate effect of drug substrates. Mol. Pharmacol. 5(2):109-122.

1573. Gigon, P. L., T. E. Gram, and J. R. Gillette. 1968. Effect of drug substrates on the reduction of hepatic microsomal cytochrome P-450 by NADPH. Biochem. Biophys. Res. Commun. 31(4):558-562.

1574. Gilbert, A. J., and F. Goldman. 1940. Effect of aminophyllin, histaminase, and nicotinic acid on histamine-poisoned puppy bronchioles. Proc. Soc. Exp. Biol. and Med. 44(2):458-459.

1575. Gillard, R. D., and S. H. Laurie. 1971. Adducts of coordination compounds. VIII. Two unusual adducts of bis(picolinato)copper (II). J. Inorg. Nucl. Chem. 33(4):947-951.

1576. Gilunova, N. I. 1965. Metabolism of pyridoxine and nicotinic acid in patients with chronic glomerulonephritis. Klinich. Med. 43(6):43-49.

1577. Ginoulhiac, E., L. T. Tenconi, and F. M. Chiancone. 1962. 3-Pyridineacetic acid and nicotinic acid: blood levels, urinary elimination and excretion of nicotinic acid derivatives in man. Nature 193:948-949.

1578. Ginoulhiac, E., and L. T. Tenconi. 1960. 3-Pyridineacetic acid: pharmacokinetics and relation to nicotinic acid metabolism. Minerva med. 51:1166-1169.

1579. Giordano, G., A. M. Verde, F. Cosentino, L. Perroni, and A. Daglanti. 1966. The hemodynamic effects of nicotinic acid and its higher homolog (3-pyridylacetic acid) in normal subjects. II. Behavior of the pulse rate, arterial pressure, cardiac output, and the oscillographic index. Boll. Soc. Ital. Cardiol. 11(2):224-228.

1580. Giordano, G., A. M. Verde, P. Angrisani, M. Crispo, G. Spano, and A. Daglanti. 1966. The respiratory effects of nicotinic acid and its higher homolog (3-pyridylacetic acid) in normal subjects. II. Behavior of pulmonary diffusion. Boll. Soc. Ital. Cardiol. 11(2):245-249.

1581. Giorgio, G., and V. Diomede-Fresa. 1942. Nicotinamide and formation of antibodies. Boll. Soc. Ital. Microbiol. 14:22-26.

1582. Giovannelli, G., and F. M. De Luca. 1966. Action of nicotinic acid and noradrenaline on plasma nonesterified fatty acids in diabetes mellitus and simple obesity. Metabolismo 2(5): 365-377.

1583. Giovannini, M., A. Calleri, and S. Terzoli. 1964. Metabolic investigations in a group of infants with mental debility. Urinary elimination of amino acids, carbohydrates, metabolites of tryptophan, and anomalous metabolites. Minerva Pediat. 16(10):337-341.

1584. Giri, K. V. 1942. The anti-pellagra factor. Indian Med. Gaz. 77:98-107.

1585. Giri, K. V., and B. Naganna. 1941a. An adsorption method for the estimation of nicotinic acid content of foodstuffs. Indian J. Med. Res. 29(1):125-132.

1586. Giri, K. V., and B. Naganna. 1941b. An adsorption method for the estimation of nicotinic acid content of animal tissues and blood. Indian J. Med. Res. 29(3):585-590.

1587. Guidicelli, Y., R. Nordmann, and J. Nordmann. 1972. Metabolic effects of acetaldehyde on rat adipose tissue in vitro. Biochim. Biophys. Acta 280(3):393-407.

1588. Giudicelli, Y., J. Nordmann, and R. Nordmann. 1972. Influence of certain effectors of cyclic AMP metabolism on the action of acetaldehyde, ethanol, and acetate on lipolysis in vitro. C. R. Acad. Sci., Ser. D. 274(25):3626-3629.

1589. Gjerstad, G. 1965. Intermediary metabolism of ergot. XII. Comparative metabolism of nicotinic, mevalonic, acetic, citric, and formic acids, proline, methionine, and tryptophan. Quart. J. Crude Drug Res. 5(3):735-738.

1590. Glazer, H. S., B. Fichter, J. F. Mueller, and R. W. Vilter. 1951. The effect of pyridoxine deficiency induced by desoxypyridoxine in human subjects upon the excretion of N1-methylnicotinamide after tryptophan administration. Arch. Biochem. Biophys. 32(3): 424-427.

1591. Gleim, E., M. Albury, K. Visnyei, J. R. McCartney, and F. Fenton. 1946a. Effect of quantity preparation procedures on vitamin retention: Canned tomatoes. J. Am. Dietetic Assoc. 22(1):29-31.

1592. Gleim, E., M. Albury, K. Visnyei, J. R. McCartney, and F. Fenton. 1946b. Retention of carotene, thiamine, riboflavin, and niacin during large-scale food service of dehydrated carrots. Food Res. 11(1):61-68.

1593. Gnudi, A., N. M. Schulman, and G. Galansino. 1965. Acute metabolic effects of nicotinic acid in alloxan diabetic dogs. Proc. Soc. Exp. Biol. Med. 119(3):830-831.

1594. Goch, H., A. Szyszko, and J. Wozniak. 1958. Vitamin value of some canned products. Przemyst. Spozywczy. 12:300-303.

1595. Goebell, O. 1940a. The regulation of cozymase action by adrenaline and insulin. I. The effect of insulin on the action of nicotinic acid amide on the carbohydrate metabolism. Klin. Wochschr. 19:710-712.

1596. Goebell, O. 1940b. The regulation of cozymase action by adrenaline and insulin. II. The action of adrenaline on the function of the codehydrogenases. Klin. Wochschr. 19:830-833.

1597. Goebell, O. 1941. The function of nicotinic acid amide in carbohydrate metabolism. Zeitschr. Ges. Exptl. Med. 109(1): 96-124.

1598. Goebell, O, and B. Krause. 1941. Effects of substances on the content of ascorbic acid in blood. Klin. Wochenschr. 20:342-344.

1599. Goebell, O., and H. Lang. 1942. Action of nicotinamide on polycythemia provoked by Co sulfate in rabbits. Arch. Exptl. Path. Pharmakol. 189:70-73.

1600. Goedde, H. W., W. Schloot, and A. Valesky. 1967. Individual different response to drugs characterization of an INH-acetylating system in Rhesus monkeys. Biochem. Pharmacol. 16(9):1793-1799.

1601. Goetz, F., L. Vary, and Z. Kelemen. 1969. Electrolyte excretion of patients with kidney stones. Z. Urol. Nephrol. 62(1):23-28.

1602. Goksel, F. M. 1952. Circulatory effects of pyridine derivatives: niacin, niacinamide, nikethamide and ronicol. Acta Cardiol. 7(6):630-662.

1603. Golberg, L., and J. M. Thorp. 1942. Nicotinic acid excretion in normal men and in Vincent's gingivitis. S. African J. Med. Sci. 7:85-94.

1604. Goldberg, L., J. M. Thorp, and S. Sussman. 1945. B vitamins in African fermented foods. Nature (London) 156:364.

1605. Golbers, L. 1956. Role of some vitamins in prophylaxis and treatment of initial forms of hypertonia and atherosclerosis. Latvijas PSR Zinatnu Akad. Vestis 1956(4):73-82.

1606. Golden, P., L. Baird, W. J. Malaisse, F. Malaisse-Lagae, and M. M. Walker. 1971. Effect of streptozotocin on glucose-induced insulin secretion by isolated islets of Langerhans. Diabetes 20(8):513-518.

1607. Goldman, P. 1967. The inhibition of the biosynthesis of long-chain fatty acids by salicylate and nicotinate. Biochem. Pharmacol. 16(1):47-52.

1608. Goldner, B., and L. Goldner. 1970. Niacin deficiency in tuberculous patients treated with izoniazid. Plucne Bolesti Tuberk. 22(1):38-42.

1609. Goldner, M. G., and M. M. Mahl. 1964. Clinical experiences with large doses of nicotinic acid in the treatment of hypercholesterolemia. In: R. Altschul, Editor. Niacin in Vascular Disorders and Hyperlipemia. C. C. Thomas, Springfield, Ill. pp. 225-233.

1610. Goldner, M. G., and L. E. Vallan. 1958. Marked and sustained blood-cholesterol lowering effect by medication with niacin and pyridoxine. Am. J. Med. Sci. 236:341-352.

1611. Goldsborough, C. E. 1960. Nicotinic acid in the treatment of ischaemic heart-disease. Lancet 1970(ii):675-677.

1612. Gol'dshtein, V. D. 1960a. On the problem of the effect of therapeutic administration of phthivazide on vitamin B6 and nicotinic acid in patients with tuberculosis of the lungs. Suvr. Med. (Sofia) 11(6):3-10.

1613. Gol'dshtein, V. D. 1960b. Influence of cycloserine therapy on the metabolism of vitamin B6 and nicotinic acid. Problemy Tuberkuleza 1960(3):46-52.

1614. Gol'dshtein, V. D. 1960c. Status of metabolism of nicotinic acid in patients with tuberculosis of the lungs and its changes during chemotherapy. Terap. Arkh. 32(7):66-72.

1615. Gol'dshtein, V. D. 1962. State of pyridoxine and nicotinic acid metabolism in pulmonary tuberculosis patients undergoing chemotherapy. Nauchn. Raboty Aspirantov i Klinich. Ordinatorov, Tsentr. Inst. Usoversh. Vrachei 1962(7):91-102.

1616. Gol'dshtein, V. D. 1963. Pyridoxine and nicotinic acid metabolism in patients with pulmonary tuberculosis during chemotherapy. Terap. Arkh. 13(12):128.

1617. Goldsmith, G. A. 1942. Evaluation of nicotinic acid nutrition by studies of urinary excretion. Proc. Soc. Expti. Biol. Med. 51:42-43.

1618. Goldsmith, G. A. 1943. The vasodilating effects of nicotinic acid. (Relation to metabolic rate and body temperature.) Am. J. Med. Sci. 205:204-208.

1619. Goldsmith, G. A. 1944. Urinary excretion of nicotinic acid and its derivatives. Arch. Internal Med. 73:410-414.

* 1620. Goldsmith, G. A. 1958. Niacin-tryptophan relations in man and niacin requirement. Am. J. Clin. Nutrition 6:479-486.

* 1621. Goldsmith, G. A. 1965. Niacin: antipellagara factor, hypocholesterolemic agent. Model of nutrition research yesterday and today. J. Am. Med. Assoc. 194(2):167-173.

1622. Goldsmith, G. A. 1960. Lowering of serum lipide concentrations. Mechanisms used by unsaturated fats, nicotinic acid, and neomycin: excretion of sterols and bile acids. A. M. A. Arch. Internal Med. 105:512-517.

1623. Goldsmith, G. A., J. Gibbens, W. G. Unglaub, and O. N. Miller. 1956. Niacin requirement in man. III. Comparative effects of diets containing lime-treated and untreated corn in the production of experimental pellagra. Am. J. Clin. Nutrition 4:151-160.

1624. Goldsmith, G. A., O. N. Miller, W. G. Unglaub, and K. Kercheval. 1959. Human studies of biologic availability of niacin in coffee. Proc. Soc. Biol. Med. 102:579-580.

1625. Goldsmith, G. A., H. L. Rosenthal, J. Gibbens, and W. G. Unglaub. 1955. Studies of niacin requirement in man. II. Requirement on wheat and corn diets low in tryptophan. J. Nutrition 56(3):371-386.

1626. Goldsmith, G. A., H. P. Sarett, U. D. Register, and J. Gibbens. 1951. Niacin depletion and requirement in man. Fed. Proc. 10(1):383.

1627. Goldsmith, G. A., H. P. Sarett, U. D. Register, and J. Gibbens. 1952. Niacin requirement in man. I. Experimental pellagra in subjects on corn diets low in niacin and tryptophan. J. Clin. Invest. 31:533-542.

1628. Goldsmith, M. 1949. Metabolic changes under thiopentone anesthesia. Anesthesia 4:22-29.

1629. Goldstein, A. C. 1962. Niacin deficiency and behavioral effects in albino rats. In: 70th Annual convention of the American Psychological Association, 1962. Am. Psychol. 17(6):394.

* 1630. Goldstein, M., M. F. Pinsky, and F. C. Fraser. 1963. Genetically determined organ specific responses to the teratogenic action of 6-aminonicotinamide in the mouse. Genet. Res. 4(2):258-265.

1631. Goldthorpe, H. C., and D. Tippit. 1947. The estimation of nicotinic acid in tissues. Federation Proc. 6:255.

1632. Goldthorpe, H. C., and D. Tippit. 1951. Estimation of nicotinic acid in tissues by the cyanogen bromide reaction. Anal. Chem. 23:484-487.

1633. Golubev, T. I. 1960. New aminophospholipid preparation for parenteral feeding. Vopr. Pitaniya 19(1):35-38.

1634. Golubev, T. I. 1961. Nutrient and biological value of corn oil as well as possibilities of its use in bread bakeries. Vopr. Pitaniya 20(4):72-73.

1635. Gomez, F. J. I. 1944. Pharmacological actions of vitamin C and nicotinamide on the intestine and relation to acetylcholine and adrenaline. Farmacoterap. Actual (Madrid) 1(6):25-31.

1636. Gomez, F. J. I., and F. T. Sanchez. 1949. Vitamin administration into the ventricle. Farmacoterap. Actual (Madrid) 6:131-134.

1637. Gomez, F. J. I., and S. T. Sanchez. 1956. Effect of various vitamins upon respiration in dogs. Arch. Inst. Farmacol. Exptl. (Madrid) 8:164-171.

1638. Goncharova, D. N. 1972. Biosynthesis of corticosteroids by adrenal glands of dogs with experimental myocardial infarct during their treatment with glucose and nicotinamide. Gipertonicheskaya Bolezn, Ateroskler. Koro 4:152-153.

1639. Goncharova, L. A., A. V. Starkov, and I. A. Rubstov. 1972. Synthesis of some N-substituted amides of nicotinic acid. Khim.-Farm. Zh. 6(3):21-22.

1640. Goncharova, V. N. 1966. Detection of nicotinamide in the fraction of polar steroids in the adrenal blood of dogs. Probl. Endokrinol. i Gormonoterap. 12(3):78-81.

1641. Gonick, H. C., G. Goldberg, and D. Mulcare. 1968. Reexamination of the acid-ash content of several diets. Am. J. Clin. Nutr. 21(9):898-903.

1642. Gonzales, C. T. O. 1971. Studies on the effects of niacin on the digestive tract of domestic fowl. Acta Vet. Acad. Sci. Hung. 21(2/3):333-340.

1643. Gonzalez-Ojeda, D., and C. Casas-Campillo. 1960. The microbiological estimation of vitamins in food yeasts grown on the wastes of the pineapple canning industry. Rev. Latinoam. Microbiol. 3:51-65.

1644. Goodyear, J. M., and H. W. Murphy. 1944. Direct quantitative determination of nicotinamide in pharmaceutical preparations. J. Am. Pharm. Assoc. 33:129-134.

1645. Goor, R. S., A. M. Pappenheimer, Jr., and E. Ames. 1967. Studies on the mode of action of diptheria toxin. V. Inhibition of peptide bond formation by toxin and NAD in cell-free systems and its reversal by nicotinamide. J. Exp. Med. 126(5):923-939.

1646. Goossens, N. 1967. Fibrinolysis activation in vitro and in vivo by nicotinic acid, heparin, and their mixtures. Med. Welt 1967(14):899-903.

1647. Gopalan, C. 1970. Pathogenesis of pellagra. Ann. Indian Acad. Med. Sci. 4(4):207-213.

1648. Gorbunova, V. I., S. Y. Osetrova, A. A. Anisova, and I.D. Rebrikova. 1971. Study of the urinary excretion of B group vitamins in workers engaged in the production of streptomycin. Vopr. Pitan. 30(4):48-51.

1649. Gordon, B. G. 1962. Influence of various compounds on the ammonia and glutamine content of rat brain during the carbon tetrachloride intoxication. Tr. Inst. Fiziol. 10: 294-302.

1650. Gorham, P. R. 1948. Canadian Wiltshire bacon. XXIX. Changes in the thiamine, riboflavin, and niacin contents produced by curing, storage, and cooking. Can. J. Res. Sec. F. Technol. 26(1):8-13.

1651. Gorin, N., and G. P. Schuetz. 1970. Comparison of a microbiological and a spectrophotometric method for the determination of nicotinic acid in fresh meat. J. Sci. Food Agric. 21:423-425.

1652. Gormsen, J., and B. Laursen. 1967. Fibrinogen breakdown products and clotting parameters. Thromb. Diath. Haemorrh. 17(3-4):467-481.

1653. Gorin, N., E. J. S. Meulenhoff, and D. Yarrow. 1970. Determination of niacin in orange juice with lyophilized Lactobacillus arabinosus ATCC 8014. Appl. Microbiol. 20: 641-642.

1654. Gornig, H. 1966. A rare drug-induced burn of the eye by Nicodan-percutan. Derm. Wschr. 152:531-534.

1655. Gortner, W. A., and R. W. Leeper. 1969. Relation of chemical structure to plant growth-regulator activity in the pineapple plant. V. Postharvest delay of senescence of pineapple fruit. Bot. Gaz. (Chicago) 130(2):87-97.

1656. Gorvat, V. F. 1961. Some aspects of nicotinic acid metabolism during the treatment of pregnant subjects with early toxicoses. Akush Ginek. 37:57-61.

1657. Gorvat, V. F. 1966. The vitamin PP content in human milk. Vop. Okhr. Materin. Dets. 11:71-73.

1658. Gorvat, V. F. 1967. The remote results of the nicotinic acid treatment of patients with toxicosis of pregnancy. In: Information on the 6th scientific session of the All-Union Scientific Research Institute of Vitaminology, 1967. Moscow. 117 pp.

1659. Goto, M. 1955. Useful components in natural sources. I. Crude drugs and oriental crude drug preparations by bioassay. 1. Citrovorum factor in crude drugs and oriental crude drug preparations. J. Pharm. Soc. Japan 75:1180-1183.

1660. Goto, M. 1957. Useful components in natural sources. XIII. Crude drugs and oriental crude drug preparations by bioassay. 9. Niacin in crude drugs and oriental crude drug preparations. Yakugaku Zasshi 77:467-470.

1661. Gottlieb, B. 1944. Acute nicotinic acid deficiency (aniacinosis). Brit. Med. J. 1944(I):392-393.

1662. Gottstein, U., A. Bernsmeier, and K. Steiner. 1962. Effect of nicotinic acid on cerebral circulation and cerebral metabolism in man. Studies with Ronicol (nicotinamide) and Complamin (3-(methoxyethylamino)-2-hydroxypropyltheophylline nicotinate). Klin. Wochenschr. 40:772-778.

1663. Gougeon, J., et al. 1968. Clinical assay of niflumic acid in rheumatology. Therapie 23:951-960.

1664. Goulon, M., R. Escourolle, S. Grosbuis, R. Caldera, F. Nouailhat, and A. Barois. 1969. Endogenous pellagra, without amino-aciduria. Rev. Neurol. (Paris) 120(3):149-158.

1665. Gounelle, H., M. Mitrovic, and M. Demarne. 1961. Vitamin B-complex content of the hair of normal and pellagrous subjects. Am. J. Clin. Nutrition 9:746-751.

1666. Gounelle, H., Y. Raoul, and J. Marche. 1945a. Nicotinamide content of human liver. Compt. Rend. Soc. Biol. 139:30-31.

1667. Gounelle, H., Y. Raoul, and J. Marche. 1945b. The content of pellagra-preventing vitamin in the blood and liver of man. Compt. Rend. Soc. Biol. 139:144-145.

1668. Gounelle, H., A. Vallette, and Y. Raoul. 1945a. The daily requirements of the pellagra-preventing vitamin. Relation between amount ingested and blood leve. C.R. Soc. Biol. 139:16-17.

1669. Gounelle, H., A. Vallette, and Y. Raoul. 1945b. Blood nicotinic acid of patients with serous tuberculosis. Compt. Rend. Soc. Biol. 139:449-451.

1670. Gounelle, H., M. Demarchi, H. Rabli, R. Rashid, S. Findakly, H. F. Selloumi, and S. Cofman. 1956. Nutritional inquest in the Middle East on young adults. Bull. Soc. Sci. Hyg. Aliment. 44:269-278.

1671. Govier, W. M. 1944. Rationale for use of vitamins in the therapy of shock and anoxia. J. Am. Med. Assoc. 126:749-750.

1672. Govil, K. K., D. Mitra, and K. C. Pant. 1953. Dietary habits of school boys in Uttar Pradesh. Indian Med. Gaz. 88(7): 357-363.

1673. Goyal, R. K., and S. Rattan. 1973. Mechanism of the lower esophageal sphincter relaxation: Action of prostaglandin E1 and theophylline. J. Clin. Invest. 52(2):337-341.

1674. Grafnetter, D., and T. Zemplenyi. 1967. Effect of some drugs and cold exposure on heart lipolytic activity in rats. Progr. Biochem. Pharmacol. 3:381-386.

1675. Graham, R. K., G. R. Skurray, and P. Caiger. 1970. Nutritional studies on yeasts during batch and continuous fermentation: I. Changes in vitamin concentrations. J. Inst. Brew. 76(4): 366-371.

1676. Granados, H., J. Glavind, and H. Dam. 1949. Experimental dental caries. VI. Effect of two levels of B vitamins given in three different ways. Intern. Z. Vitaminforsch. 21:52-61.

1677. Grande, F. 1964. Nicotinic acid and serum cholesterol in normal and in thyroid ectomized dogs. In: 48th Annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1964. Fed. Proc. 23(2 Pt. 1):145.

1678. Grande, F. 1966. Effect of nicotinic acid on the serum lipids of normal and of thyroidectomized dogs. Metabolism 15:661-671.

1679. Grande, F., and D. S. Amatuzio. 1960. Nicotinic acid and serum cholesterol in the dog. Fed. Proc. 19(1 Pt. 1):237.

1680. Grande, G. T., and E. Dal Flume. 1961. Tonographic variations after retrobulbar injections of nicotinic acid. Ann. Ottal. 87:1-7.

1681. Grande Covian, F. 1942. Estimation of nicotinic acid in foods. Rev. Clin. Espanola 7:127-133.

1682. Grant, J. M., E. Zschiesche, and T. D. Spies. 1938. Effect of nicotinic acid on pellagrins maintained on a pellagra-producing diet. Lancet 234:939-941.

1683. Gray, M. E., and J. M. Merrill. 1964. Correlation of hepatic morphology with biochemical alterations induced by nicotinic acid. In: 48th Annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1964. Fed. Proc. 23(2 Pt. 1):579.

1684. Greaves, A. V. 1944. Amblyopia due to a vitamin deficiency. Lancet 247(6311):227-228.

1685. Grebennik, L. I., T. V. Gnevkovskaia, and G. A. Velikodvorskaia. 1960. Comparative data on the metabolism of nicotinic and isonicotinic acids in the rat organism. Farmakol. Toksikol. 23:436-439.

1686. Grebennik, L. I., E. Ya. Levashova, and N. G. Shakhnazarova. 1962. Effects of nicotinic and isonicotinic acids on hypercholesterolemia and atherosclerosis in rabbits. Farmakol. i Toksikol. 25:590-596.

1687. Greco, D. 1939. Effect of nicotinic acid on blood sugar. Boll. Soc. ital. Biol. Sper. 14:403-405.

1688. Green, S., and A. Dobrjansky. 1972. Nicotinamide adenine dinucleotide glycohydrolases from Ehrlich ascites tumor cell nuclei. Isolation, partial purification, and properties. Biochemistry 11(22):4108-4113.

1689. Greenberg, J., and Q. N. LaHam. 1970. Reversal of malathion-induced teratisms and its biochemical implications in the developing chick. Can. J. Zool. 48(5):1047-1053.

1690. Greenberg, L. D. 1957. II. Biotin, pyridoxine group, nicotinamide, ascorbic acid. Ann. Rev. Biochem. 26:209-242.

1691. Greenberg, L. D., U. J. P. Hoessly, R. Brooks, and J. F. Rinehart. 1952. Electrophoretic studies on serum and plasma of control and vitamin deficient monkeys. Proc. Soc. Exptl. Biol. and Med. 49(3):425-430.

1692. Greenberg, S. I. 1941. Urinary excretion of nicotinic acid in various dermatoses. J. Investigative Dermatol. 5:139-141.

1693. Greene, R. D., A. Black, and F. O. Howland. 1943. Microbiological and chemical assay of nicotinic acid in B complex products. Analyt. Ed. Indust. and Engineer. Chem. 15(1):77-78.

1694. Greengard, P., and G. P. Quinn. 1962. Metabolic effects of tranquilizers and hypophysectomy. Ann. N.Y. Acad. Sci. 96:179-184.

1695. Greengard, P., H. Kalinsky, and B. Petrack. 1961. Effect of hypophysectomy on liver diphosphopyridine nucleotide (DPN): role of nicotinamide. Biochim. et Biophys. Acta 52:408-409.

1696. Greengard, P., B. Petrack, and H. Kalinsky. 1967. Effect of hypophysectomy on pyridine nucleotide metabolism: The role of nicotinamide. J. Biol. Chem. 242(1):152-154.

1697. Greengard, P., B. Petrack, and H. J. Kalinsky. 1969. Identification of hormonally controlled endogenous inhibitor of liver nicotinamide deamidase. Biochim. Biophys. Acta 184(1):148-153.

1698. Greengard, P., H. Kalinsky, T. J. Manning, and S. B. Zak. 1968. Prevention and remission by adrenocortical steroids of nicotinamide deficiency disease. II. A study of the mechanism. J. Biol. Chem. 243(16):4216-4221.

1699. Greengard, P., E. B. Sigg, I. Fratta, and S. B. Zak. 1966. Prevention and remission by adrenocortical steroids of nicotinamide deficiency disorders and of 6-aminonicotinamide toxicity in rats and dogs. J. Pharmacol. Exp. Therap. 154(3): 624-631.

1700. Greengard, P., G. P. Quinn, M. B. Reid, and M. A. Landrau. 1962. Hormonal effects on the response of liver DPN to nicotinamide administration. In: 46th Annual Meeting, Atlantic City, New Jersey, April 1962. Fed. Proc. 21(2):241.

1701. Greenwood, D. A., H. R. Kraybill, J. F. Feaster, and J. M. Jackson. 1944. Vitamin retention in processed meat. Effect of thermal processing. Indust. and Engineer. Chem., Indust. Ed. 36(10):922-927.

* 1702. Gregory, I. 1955. The role of nicotinic acid (niacin) in mental health and disease. J. Mental Sci. 101:85-109.

1703. Greig, M. E. 1944. Shock induced by hemorrhage. VII. Destruction of cozymase and alloxazine adenine dinucleotide in tissues during shock. J. Pharmacol. 81:164-173.

1704. Greimer, M. S. 1964. The effect of antibacterial therapy on nicotinic acid metabolism in tubercular adolsscents. In: Problems of the clinical physiology and functional diagnosis and therapy in tuberculosis. Meditsina (Moscow) 350-353.

1705. Greksakova, O., and J. Celechovsky. 1970. Spectral study of pyridinecarboxylic acid amides and hydrazides. Cesk. Farm. 19(7):259-263.

1706. Greville, G. D., D. Richter, J. H. Quastel, and R. Benesch. 1945. Biochemistry and psychiatry. Proc. Roy. Soc. Med. 38:671-680.

1707. Gries, C. L., and M. L. Scott. 1972. The pathology of thiamin, riboflavin, pantothenic acid and niacin deficiencies in the chick. J. Nutr. 102(10):1269-1285.

1708. Griffith, G. D., T. Griffith, and R. U. Byerrum. 1960. Nicotinic acid as a metabolite of nicotine in Nicotiana rustica. J. Biol. Chem. 235:3536-3538.

1709. Griffith, W. H., and D. J. Mulford. 1941. Choline deficiency in rats. VII. Some dietary factors affecting the incidence and severity of hemorrhagic degeneration in young rats. J. Nutrition 21:633-646.

1710. Grigor'ev, Yu. G. 1956. Clinical application of nicotinic acid in the treatment of complications arising from radiation therapy. Med. Radiol. 1(4):67-70.

1711. Grigorovich, Yu. A. 1970. Effect of cordiamine on NAD-glucohydrolase in rabbit heart muscle. Vop. Med. Khim. 16(1): 90-94.

1712. Grigorovich, Yu. A. 1971. Effects of cordiamine on NADH-oxidase activity of Keilin-Hurtrey preparation from bovine heart. Vopr. Med. Khim. 17(6):578-582.

1713. Grintsevich, G. V. 1967. Extent of the renal glomerular filtration affected by electrophoresis of nicotinic acid during renal diseases. In: Information of the 8th conference of pediatricians in Estonian S.S.S.R.)Tallin 157-158.

1714. Griswold, R. M., L. M. Jans, and E. G. Halliday. 1947. The effect of cooking on the thiamine, riboflavin, and niacin content of sweetbreads. J. Am. Dietetic Assoc. 23(7):600-603.

1715. Griswold, R. M., L. M. Jans, and E. G. Halliday. 1949. Retention of thiamine, riboflavin, and niacin in pork heart and beef kidneys. J. Am. Dietetic Assoc. 25:866-870.

1716. Gritsyna, V. A. 1971. Metabolism of vitamins B1, PP, B6 in patients with infantile cerebral paralysis in the course of complex treatment. Vrach. Delo. 5:121-123.

1717. Groen, J., P. L. Hoogland, A. E. Willebrands, J. Bastiaans, and E. G. Godfried. 1947. The vitamin and nitrogen metabolism in typhoid fever patients. Voeding 8:1-26.

1718. Groot, E. H. 1962. Bound nicotinic acid in grain products. Voeding 23:441-446.

1719. Gropp, J., V. Schulz, G. Sauerwein, and J. Tiews. 1972. Studies on the nicotinic acid activity of 3-pyridine nitrile and contribution to determination of the nicotinic acid requirement of the Japanese quail. Int. J. Vitam. Nutr. Res. 42(2):205-213.

1720. Groschke, A. C., and G. M. Briggs. 1946. Inhibitory action of certain amino acids on chicks receiving nicotinic acid-low diets. J. Biol. Chem. 165(2):739-740.

1721. Grosman, J. S. 1963. Anti-inflammatory properties of Na-nicotinic acid (NaNA) and 4-antipyrilamide of nicotinic acid NAAP). In: 2nd International Pharmacological Meeting, Prague, 1962. Biochem. Pharmacol. 12(Suppl.):175.

1722. Grosman, Yu. S., and E. M. Chukichev. 1966. The effect of some water-soluble vitamins on the development of aseptic inflammation. Patol. Fiziol. Eksp. Ter. 10(1):65-68.

1723. Grosman, Yu. S., and Yu. K. Kozyr. 1954. Characteristic effects of ascorbic acid and some vitamins of the B complex in rabbits treated with medinal. Farmakol. i Toksikol. 17(2):26-30.

1724. Grosman, Yu. S., and Z. A. Nazarova. 1957. Effects of vitamins C, PP, and B2 on acute omicron-nitrochlorobenzene poisoning. Farmakol. i. Toksikol. 20(3):82-86.

1725. Grosman, Yu. S., and Z. A. Nazarova. 1959. Influence of vitamins C and B complex on the effect of poisons of oxidative phosphorylation (2,4-dinitrophenol). Sbornik Nauch. Trudov Permsk. Med. Inst. 1959(29):215-221.

1726. Grosman, Yu. S., A. S. Zaks, L. G. Zil'bermints, and I. U. M. Rabotnikov. 1969. Effect of vitamins and their combination with cholinolytics on the course of acute poisoning with some phosphoorganic compounds. Farmakol. Toksik. 32:102-105.

1727. Gross, D. 1966. Biosynthesis of nicotinic acid in Mycobacterium tuberculosis. Abh. Deut. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol. 1966(3):151-155.

1728. Gross, E. S., Y. Sasaki, and T. D. Spies. 1938. Effect of nicotinic acid on increased porphyrinuria occurring in seven painters. Proc. Soc. Exp. Biol. and Med. 38(2):289-292.

1729. Gross, H. J., and D. Wildenauer. 1972. Enzymic methylations. I. Isonicotinic acid hydrazide, an inhibitor of tRNA and protein methylation. Biochem. Biophys. Res. Commun. 47(5): 1215-1220.

1730. Gross, R. C., and L. A. Carlson. 1968. Metabolic effects of nicotinic acid in acute insulin deficiency in the rat. Diabetes 17(6):353-361.

1731. Grossman, L., and N. O. Kaplan. 1958. Nicotinamide riboside phosphorylase from human erythrocytes. I. Phosphorolytic activity, II. Nicotinamide sensitivity. J. Biol. Chem. 231(2): 717-726.

1732. Grossowicz, N., and E. Sherstinsky. 1947. An improved microbiological method for the determination of nicotinic acid based on the use of Proteus HX19. J. Biol. Chem. 167: 101-105.

1733. Grote, W. 1972. Experimental production and prophylaxis of malformations in rabbits. Z. Morphol. Antrhopol. 63(3):261-305.

1734. Grote, W., U. Claussen, and D. Heinz. 1971. Inducing and preventing development anomalies in rabbits by administration of 6-aminonicotinic acid amide and nicotinic acid amide. Arzneim.-Forsch. 21(6):825-828.

1735. Gruenthal, E. 1939. Vitamins and the nervous system. Z. Vitaminforsch. 9:255-280.

1736. Grumbach, F. 1961. The therapeutic effect of increasing doses of isoniazid combined with decreasing doses of ethionamide(3-ethylisothionicotinamide). In: XV th international tuberculosis conference, Canada 1961. Excerpta Med. Internati. Cong. Ser. 41:97-98.

1737. Grunberg, E., and R. J. Schnitzer. 1952. The effect of hydrazine derivatives of isonicotinic acid on the infection of mice with M. tuberculosis var. bovis. Yale J. Biol. Med. 24(5):359-365.

1738. Grunicke, H. 1966. Effect of alkylating cytostatic agents on the metabolism of nicotinamide. B. Vitamine, Klin. Physiol. Chem. Probl., Symp., Berlin 1965, 265-274.

1739. Grunicke, H., J. Keller, and M. Liersch. 1971. Effect of nicotinic acid on the intracellular pyridine nucleotide cycle in perfused rat liver. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970, 123-131.

1740. Grunicke, H., M. Liersch, M. Hinz, B. Puschendorf, E. Richter, and H. Holzer. 1966. The role of nicotinamide in the synthesis of NAD in Ehrlich ascites tumor cells. Biochim. Biophys. Acta 121(2):228-240.

1741. Guelmezoglu, E., and N. H. Fisek. 1956. Riboflavine, nicotinic acid, and biotin content of yoghurt. Turk. Bull. Hyg. Expti. Biol. 16:222-227.

1742. Guerdoux, J. L. 1969. High frequency of reversion of a nicotinic acid gene in Coprinus radiatus. Mol. Gen. Genet. 105(4):334-343.

1743. Guerrant, N. B., and M. B. O'Hara. 1953. Vitamin retention in peas and Lima beans after blanching, freezing, processing in tin and in glass, after storage, and after cooking. Food Technol. 7:473-477.

1744. Guerrant, N. B., M. G. Vavich, and O. B. Fardig. 1945. Nutritive value of canned foods. Comparison of vitamin values obtained by different methods of assay. Indust. Engineer. Chem., Analyt. Ed. 17(11):710-713.

1745. Guerrant, N. B., O. B. Fardig, M. C. Vavich, and H. A. Ellenberger. 1948. Nutritive value of canned food. Influence of temperature and time of storage on vitamin content. Ind. Eng. Chem. 40:2258-2263.

1746. Guggenheim, K., and E. J. Diamant. 1958. Effects of 3-acetylpyridine on metabolism of nicotinic acid in rats. Biochem. J. 69:56-59.

1747. Guha, B. C., and M. L. Das. 1957. Isolation of the bound form of nicotinic acid. Nature 180:1285.

1748. Guidi, J. C. 1946. Metabolism of nicotinic acid and nicotinamide in normal and cardiac subjects. Rev. Facultad. Cienc. Quim. 21:47-54.

1749. Guidotti, P. L., R. Martinez, and L. Di Guglielmo. 1953. Influence of nicotinamide and sodium nicotinate on the oxygen saturation of arterial and venous blood in normal subjects. Il Policlinico (Rome) Sez. Prat. 60:1792-1795.

1750. Guidotti, P. L., R. Martinez, and L. Di Guglielmo. 1954. Influence of sodium nicotinate on the oxygen saturation of arterial and venous blood in subjects with cardiorespiratory insufficiency. Folia Cardiol. 12 Suppl., Atti Soc. Ital. Cardiol. 15th Congr. 317.

1751. Guilhon, J., and G. Jolivet. 1962. Anthelminthic action of the hydroxymethylamide of nicotinic acid on the small liver fluke. Bull. Acad. Vet. Ecole France 35(6):215-217.

1752. Gulati, S. M., J. R. Talwar, and B. M. L. Kapur. 1969. Large doses of nicotinic acid therapy in frostbite in monkeys. Indian J. Med. Res. 57:1579-1586.

1753. Gulbaran, R. 1960. Niacin test in the differentiation of various types of tubercle bacillus. Tip. Fak. Mec. (Istanbul) 23:530-537.

1754. Gumaa, K. A., and P. McLean. 1969. Effect of oxamate, pyruvate, nicotinamide, and streptozotocin on the pentose phosphate pathway intermediates in ascites tumor cells. Biochem. Biophys. Res. Commun. 35(1):86-93.

1755. Gundersen, K., and H. V. Demissianos. 1969. Effects of 5-methylpyrazole-3-carboxylic and (U-19,425) and nicotinic acid (NA) on free fatty acids (FFA), triglycerides (TG), and cholesterol in man. Advan. Exp. Med. Biol. 4:213-226.

1756. Gunter, M. J., K. S. Kim, D. F. Magee, H. Ralston, and A. C. Ivy. 1950. Choleretic potencies of some synthetic compounds. J. Pharmacol. Exptl. Therap. 99(4, Part I):465-478.

1757. Gurian, H., and D. Adlersberg. 1959. Effect of large doses of nicotinic acid on circulating lipides and carbohydrate tolerance. Am J. Med. Sci. 237:12-22.

1758. Gurnani, S. U., U. S. Kumta, and M. B. Sahasrabudhe. 1956. Effects of total body X-ray irradiation on the levels of tryptophane and nicotinic acid in liver and kidney of rats. Current Sci. 25(3):90-91.

1759. Gutierrez-Lopez, A., and A. Nava-Rivera. 1965. Modification of acetylcholine response in isolated rabbit aorta by some pyridines. Ciencia 23(6):240-242.

1760. Gutina, M. A. 1954. Vascular reactions of rabbit ears to nicotinic acid in pain spasms. Farmakol. i Toksikol. 17(2): 19-22.

1761. Gutmanis, K., and B. Lazdane. 1969. Chemical composition of some Brassica species and potatoes. Vop. Biol. Mater. Konf. 1968, 101-106.

1762. Gutmann, H. R., B. J. Jandorf, and O. Bodansky. 1947. Pyridine nucleotides in the reduction of methemoglobin. J. Biol. Chem. 169:145-152.

1763. Guttman, D. E., and D. Brooke. 1963. Solution phase interaction of nicotinamide with ascrobic acid. J. Pharm. Sci. 52(10):941-945.

1764. Guven, K. C., and S. Kanber. 1969. Stability of nikethamide solutions. Eczacilik Bul. 11(11):170-174.

1765. Guyer, R. B., and J. W. Holmquist. 1955. Enzyme regeneration in high temperature-short time sterilized canned food. Food Technol. Australia 7:199,201,203,207.

1766. Gydell, K. 1958a. The hyperbilirubinemic and hyperferricemic action of nicotinic acid. Scand. J. Clin. Lab. Invest. 10:115.

1767. Gydell, K. 1958b. On the hyperbilirubinemic and hypersideremic action of nicotinic acid on normal subjects and on patients with some hematological disorders. Acta Med. Scand. 162:9-27.

1768. Gydell, K. 1959. Nicotinic acid induced hyperbilirubinemia and hypersideremia. 1. Observations in hemolytic disease and allied conditions. 2. Observations in anemia and polycythemia. Acta Med. Scand. 164:305-320.

1769. Gydell, K. 1960a. Nicotinic acid-induced hyperbilirubinemia and hypersideremia. II. Observations in anemia and polycythemia. Acta Med. Scand. 166:55-67.

1770. Gydell, K. 1960b. Hyperbilirubinemia and hypersideremia following intravenous injection of stored blood, nicotinic acid, and hemoglobin solution. Acta Med. Scand. 166:433-443.

1771. Gydell, K. 1960c. Transient effect of nicotinic acid on bilirubin metabolism and formation of carbon monoxide. Acta Med. Scand. 167:431-441.

1772. Gyulkhasyan, A. A. 1971a. Efficacy of a number of medicinal drugs used for the reduction of the experimental ototoxic effect of some antibiotics and saluside. Vestn. Otorinolaringol. 33(2): 26-29.

1773. Gyulkhasyan, A. A. 1971b. Effectiveness of a series of medicinal preparations used for decreasing the ototoxic effect of some antibiotics and saluzid in an experiment. Zh. Eksp. Klin. Med. 11(1):8-12.

1774. Hackbart, W., and H. Weiss. 1967. Multivitamin tablets. East German Pat. 54,769.

1775. Hadnagy, C., K. Kinda, and I. Szabo. 1961. Hemolytic shock. II. Serological investigations. Z. Immunitaetsforsch. 121:1-11.

1776. Haeger, K. 1968. Treatment of peripheral occlusive arterial disease with alpha-tocopherol as compared with vasodilator agents and antiprothrombin (dicoumarol). Vasc. Dis. 5(4):199-213.

1777. Haenel, H. 1956. Microbiological investigation of the factors of the B complex in foods and feeding stuff. Ernaehrungsforschung 1:533-540.

1778. Haenel, H. and W. Mueller-Beuthow. 1956. Microbial analysis with fungi (Neurospora, Phycomyces). Ernaehrungsforschung 1:541-552.

1779. Haenel, H., R. Wegner, and W. Mueller-Beuthow. 1956. The content of microbiologically measurable amounts of vitamins in "vitamine-free" casein. Pharmazie 11:470-472.

1780. Haeseler, G., A. M. Herbst, and F. Just. 1957. Determination of vitamins of the B complex in various vinegars. Branntweinwirtschaft 79:156-157.

1781. Haff, R. F., and H. E. Swim. 1957. Minimal vitamin requirements of rabbit fibroblasts, strain RM3-73. Proc. Soc. Expt. Biol. Med. 94(4):779-782.

1782. Hagino, Y., S. J. Lan, C. Y. Ng, and L. M. Henderson. 1968. Metabolism of pyridinium precursors of pyridine nucleotides in perfused rat liver. J. Biol. Chem. 243(19):4980-4986.

1783. Hahn, H. J., and R. Michael. 1972. Influence of nicotinic acid on insulin release in vitro. Acta Diabetol. Lat. 9(1):87-96.

1784. Hahn, K. J., and E. Weber. 1972. Effect of cholestyramine on the resorption of drugs in humans. Verh. Deut. Ges. Inn. Med. 78:1567-1570.

1785. Hallman, H. F. 1944. The effect of vitamins of the B complex on the resistance of the organism to anoxia. Am J. Physiol. 141:176-186.

1786. Haining, C.GG. 1963. Effects of antirheumatic compounds and pyridine derivatives on the cutaneous response to thurfyl nicotinate in the guinea pig. Brit. J. Pharmacol. 21(1):104-112.

1787. Hale, E. B., G. K. Davis, and H. R. Baldwin. 1942a. The distribution of nicotinic acid in feeds. J. Biol. Chem. 146:565-570.

1788. Hale, E. B., G. K. Davis, and H. R. Baldwin. 1942b. The chemical determination of nicotinic acid in plant materials. J. Biol. Chem. 146:553-563.

1789. Halevy, S., E. J. Diamant, and K. Guggneheim. 1955. The effect of antibiotics on the metabolism of nicotinic acid, biotin and folic acid in rats. Brit. J. Nutrition (1):57-62.

1790. Hallay, L. I. 1957. Experiences with nicotinic acid in diabetes mellitus. Virginia Med. Monthly 84(8):403-405.

1791. Haller, H., and S. E. Strauzenberg. 1957. Influence of nicotinic acid on carbohydrate metabolism. 12:954-956.

1792. Halmuradov, A. G., R. V. Cagovec, S. I. Susevic, and A. I. Fomenko. 1970. Activation of NADase in liver of rats by giving precursors of NAD biosynthesis. Vop. Pitan. 29(6): 7-13.

1793. Halpern, B. N., and I. Dalenow. 1944a. Anaphylaxis and nicotinamide. Z. Vitaminforsch. 15:217-173.

1794. Halpern, B. N., and I. Dalenow. 1944b. Experimental studies of a new pharmacodynamic property of nicotinamide. Antagonistic action to certain effects of histamine. Z. Vitaminforsch. 15: 250-259.

1795. Halpern, B. N., and I. Dalenow. 1944c. The antagonism of nicotinamide and histamine on isolated organs with smooth muscles. Z. Vitaminforsch. 15:260-267.

1796. Halpern, R. M., S. Chaney, B. C. Halpern, and R. A. Smith. 1971. Nicotinamide natural inhibitor of TRNA methylase. Biochem. Biophys. Res. Commun. 42(4):602-607.

1797. Ham, W. E., and K. W. Scott. 1953. Intestinal synthesis of biotin in the rat. Effect of deficiencies of certain B vitamins and of sulfasuxadine and Terramycin. J. Nutrition 51(3):423-433.

1798. Hamamoto, H. 1970. Induction of tyrosine transaminase by administration of a large dose of vitamin B6. Vitamins (Kyoto) 42(3):141-149.

1799. Hamil, B. M., M. Coryell, C. Roderuck, M. Kaucher, E. Z. Moyer, M. E. Harris, and H. H. Williams. 1947. Thiamine, riboflavin, nicotinic acid, pantothenic acid, and biotin in the urine of newborn infants. Am. J. Diseases Children 74:434-436.

1800. Hamly, C., G. D. Trasler, and F. C. Fraser. 1970. Reduction of 6-aminonicotinamide teratogenicity in mide by etherization. Teratology 3(4):293-294.

1801. Hancock, R. C. G. 1942. Nicotinic acid in the treatment of Stuttgart disease. Vet. Rec. 54:115.

* 1802. Handler, P. 1944. The effect of excessive nicotinamide feeding on rabbits and guinea pigs. J. Biol. Chem. 154:203-206.

1803. Handler, P. 1946. Factors affecting the occurrence of hemorrhagic kidneys due to choline deficiency. J. Nutrition 31(5): 621-633.

1804. Handler. P. 1948. The present status of nicotinic acid. Int. Ztsch. Vitaminforsch. 19:393-451.

1805. Handler. P. 1959. Metabolism of nicotinic acid and the pyridine nucleotides. Proc. Intern. Congr. Biochem. 4th Congr., Vienna, 1958 11:39-53.

1806. Handler, P., and W. J. Dann. 1942. The inhibition of rat growth by nicotinamide. J. Biol. Chem. 146(2):357-368.

1807. Handler, P., and I. N. Dubin. 1946. The significance of fatty infiltration in the development of hepatic cirrhosis due to choline deficiency. J. Nutrition 31(2):141-158.

1808. Handler, P., and W. P. Featherston. 1943. Biochemical defect in nicotinic acid deficiency. II. The nature of the anemia. J. Biol. Chem. 151:395-404.

1809. Handler, P., and H. I. Kohn. 1943. The mechanism of cozymase synthesis in the human erythrocyte: A comparison of the roles of nicotinic acid and nicotinamide. J. Biol. Chem. 150:447-452.

1810. Handler, P., W. J. Dann, W. S. Branning, P. Gray, and B. M. Morrison. 1942. Biochemical defect in nicotinic acid deficiency. J. Biol. Chem. 145:145-153.

1811. Hankes, L. V., R. L. Lyman, and C. A. Elvehjem. 1950. Effect of niacin precursors on growth of rats fed tryptophan-low rations. J. Biol. Chem. 187(2):547-555.

1812. Hankes, L. V., J. E. Leklem, R. R. Brown, and R. C. Mekel. 1971. Tryptophan metabolism in patients with pellagra. Problem of vitamin B6 enzyme activity and feedback control of tryptophan pyrolase enzyme. Am. J. Clin. Nutr. 24(6):730-739.

1813. Hansen, F., E. Brandt, and E. Hoff-Jorgensen. 1957. Investigations about the composition and the food value of Danish potatoes. Tidsskr. Planteavl. 61:292-376.

1814. Hansen-Pruss, O. C. 1943. Pellagra developing in a patient receiving liver extract parenterally for sprue. Southern Med. J. 36:440-442.

1815. Hanson, P. G., R. E. Johnson, and G. Engel. 1965. Plasma free fatty acid changes in man during acute cold exposure and nicotinic acid ingestion. Aerospace Med. 36(11):1054-1058.

1816. Hanson, R. W., and Z. Z. Ziporin. 1966. Factors influencing the utilization of ketone bodies by mouse adipose tissue. J. Lipid Res. 7(1):56-61.

1817. Hanson, R. W., and Z. Ziporin. 1967. Pyridine nucleotide synthesis by rat adipose tissue in vitro. J. Lipid Res. 8(1):30-37.

1818. Haque, M., F. R. Chughtai, and M. I. D. Chughtai. 1969. Semi-quantitative determination of water-soluble vitamins by circular thin-lay chromatography. Mikrochim. Acta 5:951-955.

1819. Harako, I. 1961a. Skin diseases and nicotinic acid metabolism. I. Nicotinic acid metabolism in healthy subjects. Jap. J. Derm. 71:285-292.

1820. Harako, I. 1961b. Metabolism of nicotinic acid in skin diseases. Report II. Nicotinic acid metabolism in patients with pigmentary disturbances. Jap. J. Dermatol. 71(3):293-299.

1821. Harako, I. 1961c. Metabolism of nicotinic acid in skin diseases. Report III. Nicotinic acid metabolism in patients with riboflavin deficiency and reactive skin diseases. Jap. J. Dermatol. 71(3):300-312.

1822. Harary, I. 1957. Bacterial fermentation of nicotinic acid. I. End products. J. Biol. Chem. 227:815-822.

1823. Hardman, R. 1967. Extraction of steroidal saponins and sapogenins from vegetable materials. Brit. Pat. 1,239,555.

1824. Hardy, R. W., J. L. Gaylor, and C. A. Baumann: 1960. Biosynthesis of sterols and fatty acids as affected by nicotinic acid and related compounds. J. Nutr. 71:159-167.

1825. Harmon, B. G., D. E. Becker, A. H. Jensen, and D. H. Baker. 1969. Nicotinic acid-tryptophan relationship in the nutrition of the weanling pig. J. Animal Sci. 28:848-852.

1826. Harmon, B. G., D. E. Becker, A. H. Jensen, and D. H. Baker. 1970. Nicotinic acid-tryptophan nutrition and immunologic implications in young swine. J. Animal Sci. 31(2):339-342.

1827. Harper, A. E., et al. 1970. Effects of ingestion of disproportionate amounts of amino acids. Physiol. Rev. 50: 428-558.

1828. Harris, L. E., and B. I. Duis. 1943. Determination of nicotinic acid and sodium nicotinate. J. Am. Pharm. Assoc. 32:31-32.

1829. Harris, L. J. 1938. The vitamin B2 complex. VIII. Further notes on "monkey pellagra" and its cure with nicotinic acid. Biochem. J. 32:1479-1481.

1830. Harris, L. J., and W. D. Raymond. 1939. Assessment of the level of nutrition. A method for the estimation of nicotinic acid in urine. Biochem. J. 33(12):2037-2051.

1831. Harris, R. S., F. K. C. Wang, Y. H. Wu, C. S. Tsao, and L. Y. S. Loe. 1949. The composition of Chinese foods. J. Am. Diet. Assoc. 25(1):28-38.

1832. Harrison, R. J., and M. Feiwel. 1956. Pellagra caused by isoniazid. Brit. Med. J. 1956(4997):852-854.

1833. Harthon, L., R. Brattsand, and L. Lundholm. 1971. Dose-response relationship of nicotinic acid inhibition of lipolysis and secondary potentiation. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970, 313-322.

1834. Harthon, L., R. Brattsand, and L. Lundholm. 1971. Effect of nicotinic acid derivatives on NAD+ levels of blood, liver, adipose tissue, and aorta during hyperlipemic conditions. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 115-122.

1835. Hartmann, G. 1971. Effect of beta-pyridylcarbinol on the nitrogen balance in the starving man. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop.1970, 1047-1051.

1836. Hartog, M., R. J. Havel, G. Copinschi, J. M. Earll, and B. C. Ritchie. 1967. The relation between changes in serum levels of growth hormone and mobilization of fat during exercise in man. Quart. J. Exp. Physiol. 52(1):86-96.

1837. Hartzler, E., W. Ross, and E. L. Willett. 1949. Thiamine, riboflavin, and niacin content of raw and cooked pork and grain-fed and garbage-fed pigs. Food Res. 14:15-24.

1838. Hashmi, M. H., F. R. Chughtai, and M. I. D. Chughtai. 1969. Semiquantitative determination of water-soluble vitamins by circular thin-layer chromatography. Mikrochim. Acta 951-956.

1839. Hasselblatt, A., U. Panten, and W. Poser. 1971a. Effects of antilipolytic compounds on hepatic and renal gluconeogenesis in the rat. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 879-894.

1840. Hasselblatt, A., U. Panten, and W. Poser. 1971b. Effect of antilipolysis on adrenal cortical function in the rat. Metab. Eff. Nicotinic Acid its Deriv., Proc. 1003-1006.

1841. Hasselblatt, A., U. Panten, and W. Poser. 1971c. Stimulatory effect of antilipolytic compounds on amino acid metabolism and urea synthesis in the rat. Metab. Eff. Nicotinic Acid its Deriv., Pro. 1023-1034.

1842. Hata, S., M. Yamakawa, S. Tomioka, and J. Sano. 1965. Quantum chemical considerations on the stabolity of aqueous solution of an electron acceptor such as menadione. Chem. Pharm. Bull. (Tokyo) 13(1):96-99.

1843. Hatem, S. 1960. Nicotinamide and carcinogenic substances. Compt. Rend. 250:4479-4482.

1844. Hatem-Champy. S. 1962. Affinity of the imidazole ring for carcinogenic substances. Arch. Maladies Profess. Med. Trav. Securite Sociale 23(7-8):461-473.

1845. Hatano, A. 1969. Ascorbic acid and its complexes. II. Effect of magnesium ions on an ascorbic acid monostearate-nicotinamide complex. Bitamin 39(6):399-401.

1846. Haubrich, M. 1969. On the so-called "parasite folly". Pol. Tyg. Lek. 24(33):1284-1286.

1847. Hausman, E., L. Rosner, and H. J. Cannon. 1943. The preparation and decolorization of cereal extracts for nicotinic acid determination. Cereal Chem., 20:82-86.

1848. Havas, H. F., L. J. Berry, and D. S. Smythe. 1964. Effect of endotoxin on liver carbohydrate of mice bearing transplantable tumors, sarcoma 37 and Krebs-2 carcinoma. Cancer Res. 26:1666-1671.

1849. Havel, R. J. 1965. Some influences of the sympathetic nervous system and insulin on mobilization of fat from adipose tissue. Turnover rates of free fatty acids and glycerol. Ann. N.Y. Acad. Sci. 131(1):91-101.

1850. Havel, R. J., and L. A. Carlson. 1963. Comparative turnover rates of free fatty acids and glycerol in blood of dogs under various conditions. Life Sci. 2(9):651-658.

1851. Havel, R. J., L. A. Carlson, L. G. Ekelund, and A. Holmgren. 1964. Relation between mobilization of free fatty acids and energy metabolism in man; effects of norepinephrine and nicotinic acid. Metab., Clin. Exptl. 13(12):1402-1412.

1852. Hawker, R.W. 1946a. The effect of nicotinic acid on the growth of the testes and seminal vesicles in immature male rats. Australian J. Exptl. Biol. Med. Sci. 24:251-252.

1853. Hawker, R.W. 1946b. Studies in nicotinic acid. Med. J. Austral. I:872-876.

1854. Hawkinson, A. T., and A. A. Elston. 1944. Nicotinic acid. U.S. Pat. 2,347,410.

1855. Hawkinson, A. T., and A. A. Elston. 1945. Quinolinic acid. U.S. Pat. 2,371,691.

1856. Hawthorne, G. A. 1941. Nutritional diseases of swine. N. Amer. Vet. 22:147-155.

1857. Hayaishi, O. 1966. Metabolism of nicotinamide adenine dinucleotide. U.S. Govt. Res. Develop. Rept. 41(18):23.

1858. Hayano, K., F. Ito, and Y. Yamamura. 1965. Fatty liver induced by 2-ethylthioisonicotinamide (Ethionamide). J. Biochem. 58(1): 34-38.

1859. Hayashi, M., S. Ohguri, and A. Okugi. 1969. Tryptophan metabolism. VII. Hissu Amino-san Kenkyu (41):25-27.

1860. Hayashi, M., and S. Ohguri. 1969. Tryptophan metabolism. VIII. Hissu Amino-san Kenkyu (44):4-6.

1861. Hayashishi, O., I. Hamao, and A. Ichiyama. 1968. Studies on the biosynthesis of NAD by a direct method of tracing metabolism in vivo. Advan. Enzyme. Regul. 1967:59-22.

1862. Hayes, B. W., G. E. Mitchell, Jr., and C. O. Little. 1967. Factors affecting concentrations of B vitamins in ruminal fluid in vitro. Int. Z. Vitaminforsch. 37(3):348-353.

1863. Hedbom, C., E. Helgstrand, A. Misiorny, N. E. Stjernstrom, and G. Westin. 1972. Potential hypolipidemic agents: II. Preparation of 5-halo-3-pyridylmethanols. Acta Pharm. Suec. 9(3):259-260.

1864. Heffernan, A., N. Hickey, R. Mulcahy, and O. Fitzgerald. 1969. The chemotherapy of hypercholesterolaemia. Acta Cardiol. 24(1): 47-55.

1865. Helberg, A. 1969. Nicotinyl alcohol as a cholesterol-lowering agent. Nord. Med. 81:698-700.

1866. Heidelberger, C., E. P. Abraham, and S. Lepkovsky. 1948. Concerning the mechanism of the mammalian conversion of tryptophan into nicotinic acid. J. Biol. Chem. 176:1461-1462.

1867. Heidermanns, C., and I. Kirchner-Kuehn. 1956. Urea synthesis in the rat liver from various physiological substances and their influence in vitro. Zool. Jahrb. Abt. allg. Zool. u. Physiol. Tiere 66(2/3):295-354.

1868. Heinrich, P., and H. J. Foerster. 1971. The intraoperative measurement of the peripheric resistance in arterial circulatory disturbances, and the effect of acetylcholine and nicotinic acid. Z. Exp. Chir. 4(3):148-151.

1869. Hekker, J. E., and M. S. Sipalov. 1956. Commercial production of vitamin A and E concentrates by the molecular distillation method. In Vitamins 2. Isolation and purification of vitamins; physiology and biochemistry of vitamins. Academy of Sciences, Kiev., pp. 5-13.

1870. Hellman. L., and J. J. Burns. 1958. Metabolism of L-ascorbic acid-1-C14 in man. J. Biol. Chem. 230(2):923-930.

1871. Henderson, L. M., T. Deodhar, W. A. Krehl, and C. A. Elvehjem. 1947. Factors affecting the growth of rats receiving niacin-tryptophane deficient diets. J. Biol. Chem. 170(1):261-268.

1872. Henderson, L. M., R. E. Koski, and F. D'Angeli. 1955. The role of riboflavin and vitamin B6 in tryptophan metabolism. J. Biol. Chem. 215(1):369-376.

* 1873. Heninger, G. R., and M. B. Bowers. 1968. Adverse effects of niacin in emergent psychosis. J. Am. Med. Assoc. 204:1010-1011.

1874. Heninger, G. R., and J. B. Bowers, Jr. 1969. Adverse effects of niacin in emergent psychosis. J. Am. Med. Assoc. 207:1355.

1875. Hennessy, D. J., A. M. Steinberg, G. S. Wilson, and W. P. Keaveney. 1960. Fluorometric determination of added pyridoxine in enriched white flour and in bread baked from it. J. Assoc. Offic. Agr. Chem. 43:765-768.

1876. Hepburn, F. N. 1971. Nutrient composition of selected wheats and wheat products. VII. Total and free niacin. Cereal Chem. 48(4):369-372.

1877. Hepp, K. D., G. Dietze, and O. Wieland. 1971. Antilipolytic action of nicotinic acid. Possible role of nicotinic acid on cyclic AMP metabolism in adipose cells and liver. Metab. Eff. Nicotinic Acid Its. Deriv., Pro. 357-366.

1878. Hepp, W. 1941. Vitamin-tolerance experiments. Klin. Wochschr. 20:1098-1101.

1879. Herd, C. W. 1942. The determination of vitamins in cereals. I. Vitamin B1. 2. Riboflavin. 3. Nicotinic acid and vitamin E. Food 11:283-288, 298-300, 328-330.

1880. Herken, H. 1965. Pharmacological investigations into the problem of selective vulnerability of the brain. Arzneimittel-Forsch. 15(7):707-718.

1881. Herken, H. 1968. Biosynthesis and action of dinucleotides containing 6-aminonicotinamide on membrane transport processes. Arzneim.-Forsch. 18(10):1235-1245.

1882. Herken, H., and K. Lange. 1969. Blocking the pentose phosphate pathway in the brain of rats by 6-aminonicotinamide. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 263(3):496-499.

1883. Herken, H., K. Lange, and H. Kolbe. 1969. Brain disorders induced by pharmacological blockade of the pentose phosphate pathway. Biochem. Biophys. Res. Commun. 36(1):93-100.

1884. Herraiz, M. L., and H. G. de Alvarez Herrero. 1943. Vitamin content of dehydrated eggs. Rev. Asoc. Argentina Dietol. 1(1): 46-48.

1885. Hermann, B., et al. 1967. Treatment of arteriosclerosis with permanently administered large doses of nicotinic acid. Z. Aerztl. Fortbild (Jena) 61:77-81.

1886. Herrero, H. G. D. A., J. C. Cecchetti, and J. D. Sala. 1961. Riboflavine and niacin in meat. Rev. Asoc. Arg. Nutr. Dietol. 19(73-76):47-48.

1887. Herrmann, G. R., and A. Samawi. 1962. Effects of various serum cholesterol-lowering procedures and agents in patients with coronary artery disease. Texas Rept. Biol. Med. 20:599-614.

1888. Herrmann, K.,1968. Effect of storage, processing, and preservation on the vitamin content of vegetables. Ernaehr.-Umsch. 15(3):81-83.

1889. Herrmann, K. 1969. Fruit and vegetables, particularly spinach, as foods for babies. Deut. Apoth.-Ztg. 109(6):201-203.

1890. Hertelendy, F., and D. M. Kipnis. 1973. Studies on growth hormone secretion: V. Influence of plasma free fatty acid levels. Endocrinology 92(2):402-410.

1891. Hertz, R. 1946. Biotin and the avidin-biotin complex. Physiol. Rev. 26(4):479-494.

1892. Herz, A. 1968. Actions of cholinergic and anticholinergic drugs on reactive behavior. Progr. Brain Res. 28:73-85.

1893. Herzfeld, U., and H. Erbe. 1971. Control of the cerebral cirulation time under long-term therapy with Wallerox: A measuring with external scintillation counters. Med. Welt. 48:1933-1935.

1894. Hess, R., and W. Bencze. 1968. Hypolipidemic properties of a new tetralin derivative CIBA 13,437-SU. Experientia 24(5):418-419.

1895. Heuser, G. F., and M. L. Scott. 1953. Studies in duck nutrition. 5. Bowed legs in ducks, a nutritional disorder. Poultry Sci. 32:137-142.

1896. Heyck, H. 1962a. Effect of drugs on cerebral blood supply and metabolism results of quantitative determinations in man. Arquiv. Neuro-Psiquiat. 20:77-88.

1897. Heyck, H. 1962b. Influence of nicotinic acid on blood circulation of the brain and its metabolism in cerebral sclerosis and other diffuse cirulatory disturbances of the brain. Schweiz. Med. Wochschr. 92:226-231.

1898. Heyman, J. J. 1964. Nicotinamide metabolism in schizophrenics, drug addicts, and normals: the effect of psychotropic drugs and hormones. Trans. N.Y. Acad. Sci. 26(3):354-360.

1899. Heyman, J. J., S. Halpern, and S. Merlis. 1964. The use of nicotinamide test dose in the assessment of psychotropic drugs in schizophrenic patients. J. Neuropsychiat. 5(4):221-224.

1900. Heyns, K. 1939. Estimation of vitamin B1 by menas of a yeast test. Z. Physiol. Chem. 258:219-237.

1901. Heyrovsky, J. 1953. The use of oscillographic polarography in pharmacy. Ceskoslov. Farm. 2:403-406.

1902. Hibbs, J. W., and W. E. Krauss. 1947. The effect of supplementary vitamins on blood composition, liver storage, and incidence of scours in calves. J. Dairy Sci. 30(2):115-120.

1903. Hicks, S. P. 1955. Pathologic effects of antimetabolites. 1. Acute lesions in the hypothalamus, peripheral ganglia, and adrenal medulla caused by 3-acetylpyridine and prevented by nicotinamide. Am. J. Pathol. 31:189-199.

1904. Hild, R., T. Brecht, H. Zolg, and B. Hess. 1961. The pharmacologic influence of circulation and metabolism in angiopathies. Metab. Parietis Vasorum, Papers Intern. Cong. Angiol. 5th, Prague, pp. 1024-1028.

1905. Hill, J. A. 1956. Halogenated lower-alkanal adducts with nicotinamide. U.S. Pat. 2,755,283.

1906. Hill, W. H. 1941. Separation of acids such as benzoic acid, quinolinic acid, picolinic acid, phthalamic acid, phthalic acid, nicotinic acid, and alpha-hydroxyisobutyric acid from crude oxidation mixtures containing them. U.S. Pat. 2,283,991.

1907. Hilz, H., and H. Berndt. 1964. Protective action of nicotinamide against radiation-induced injury of deoxyribonucleic acid (DNA) synthesis as a cell population problem. Z. Krebsforsch. 66(2):155-164.

1908. Hilz, H., M. von Gossler, M. Oldekop, and M. Scholz. 1961. Effects of x-ray irradiation in ascites tumor cells: partial restoration of diphosphopyridine nucleotide (DPN) content and deoxyribonucleic acid (DNA) synthesis by nicotinamide. Biochem. Biophys. Res. Communs. 6:379-384.

1909. Hinz, M., N. Katsilambros, V. Maier, H. Schatz, and E. F. Pfeiffer. 1973. Significance of streptozotocin induced nicotinamide-adenine-dinucleotide (NAD) degradation in mouse pancreatic islets. Fed. Eur. Biochem. Soc. Lett. 30(2):225-228.

1910. Hirata, Y., T. Kawachi, and Sugimura. 1967. Fatty liver induced by injection of L-tryptophan. Biochim. Biophys. Acta 144(2):233-241.

1911. Hiremath, R. V. 1972. Amino acid and vitamin requirements of a mycoparasite Cephalosporium chrococcum var. uredinicola. Mysore J. Agric. Sci. 6(3):268-271.

1912. Hirsch, W., et al. 1967. Therapy of cerebral vascular insufficiency. Ther. Gegenw. 106:1186-1187.

1913. Hirschberg, E. 1963. Cancer chemotherapy screening data. XXI. Patterns of response of animal tumors to anticancer agents. A systematic analysis of the literature in experimental cancer chemotherapy - 1945-1958. Cancer Res. Suppl. 23(5 Part 2): 521-980.

1914. Hirschberg, R., and J. C. Ensign. 1972. Oxidation of nicotinic acid by a Bacillus species: Regulation of nicotinic acid and 6-hydroxynicotinic acid hydroxylases. J. Bacteriol. 112(1): 392-397.

1915. Hirschhorn, K., and W. Seegers. 1964. Nicotinic acid and hyperlipemia. Experiences and a hypothesis. In: R. Altschul, Ed. Niacin in Vascular Disorders and Hyperlipemia. Charles C. Thomas: Springfield, Ill., pp. 234-244.

1916. Hiszpanska, C., J. Zaleski, E. Rutczynska-Skonieczna, B. Chojnicka, and I. Ardyn. 1956. Nutritional values of canned green peas. I. Energetic and mineral constituents. Reczniki Panstowowega Zakladu Hig. 7:43-53.

1917. Hitachi, M. 1965. The effect of nicotinamide on the adrenal cortex in methylcholanthrene-treated mice. J. Fac. Sci. Univ. Tokyo Sect. IV 10(3):459-465.

1918. Hjarde, W., H. Lieck, and H. Sondergaard. 1961. Content of B and E vitamins in feeds. Dansk Pelsdyravl. 24:143-148.

1919. Hladovec, J. 1970. Cement substance and platelet adhesion to the endothelial surface. Influence of several groups of drugs. Physiol. Bohemoslov. 19(5):425-430.

1920. Hmaladze, A. G., and N. T. K. Kartozija. 1968. Conditions and duration of supplying riboflavine and nicotinic acid to schoolchildren. Pediatrija. (8):69.

1921. Ho, C. K., and S. A. Hashim. 1972. Pyridine nucleotide depletion in pancreatic islets associated with streptozotocin-induced diabetes. Diabetes 21(7):789-793.

1922. Ho, R. J., and B. Jeanrenaud. 1967. Insulin-like action of Ouabain. I. Effect on carbohydrate metabolism. Biochim. Biophys. Acta 144(1):61-73.

1923. Hoagland, C. L., and R. E. Shank. 1942. Studies on the synthesis of total coenzyme from the oral and parenteral administration of nicotinic acid and nicotinamide. J. Clin. Invest. 21:622.

1924. Hoagland, C. L., S. M. Ward, and R. E. Shank. 1943. Synthesis of coenzyme and factor V in erythrocytes, and the excretion of nicotinic acid derivatives in the urine following the ingestion of nicotinic acid and nicotinamide. J. Biol. Chem. 151(2):369-375.

1925. Hodak, K. 1961. Plate assay of nicotinic acid using Proteus vulgaris OX-19. Spisy Prirodovedecke Fak. Univ. Brno (419): 1-57.

1926. Hodson, A. Z. 1945. The nicotinic acid, pantothenic acid, choline and biotin content of fresh, irradiated evaporated and dry milk. J. Nutr. 29(2):137-142.

1927. Hoeck, K. 1953. Influence of nicotinic acid on the heart and circulation. Z. Ges. Inn. Med. u. Grenzgebiete 8:106-111.

1928. Hoefling, W., H. D. Eilhauer, G. Krautschik, and R. Mohrhauer. 1967. Separation of nicotinic and isonicotinic acid. East Ger. Pat. 58,090.

1929. Hoefike, H. 1953. The riboflavine, nicotinic acid, pantothenic acid, and biotin content of Dutch market milks, determined by the microbiological method. Neth. Milk Dairy J. 7:227-39.

1930. Hoegberg, B., F. Schlenk, and H. von Euler. 1942. Reactions for the investigation of cozymase and its fission products. Arkiv. Kemi, Mineral. Geol. A 15(18):9pp.

1931. Hoelzel, F., and H. Maass. 1962. Biochemical investigations on ascites tumor cells under the action of Trenimon. Deut. Med. Wochschr. 87:1663-1665.

1932. Hoelzel, F., H. Maass, and H. A. Kuenkel. 1961. Effect of nicotinamide and 2,3,5-tris(ethylenimmo)-para-benzoquinone on the incorporation of C14-glycine into protein of Yoshida-ascites-sarcoma cells. Naturwissenschaften 48:627.

1933. Hoffer, A. 1956. Effect of niacin and nicotinamide on leucocytes and some urinary constituents. Can. Med. Assoc. J. 74:448-451.

1934. Hoffer, A. 1961. The relationship of nicotinic acid to cholesterol metabolism. J. Clin. Exptl. Psychopathol. Quart. Rev. Psychiat. Neurol. 22(3):165-179.

1935. Hoffer, A. 1963. Nicotinic acid: an adjunct in the treatment of schizophrenia. Am. J. Psychiat. 120:171-173.

1936. Hoffer, A. 1965. Treatment of organic psychosis with nicotinic acid. (A single case). Dis. Nerv. Syst. 26(6):358-361.

* 1937. Hoffer, A. 1967. Biochemistry of nicotinic acid and nicotinamide. Psychosomatics. 8(2):95-100.

1938. Hoffer, A. 1969a. Adverse effects of niacin in emergent psychosis. J. Am. Med. Assoc. 207:1355.

* 1939. Hoffer, A. 1969b. Safety, side effects, and relative lack of toxicity of nicotinic acid and nicotinamide. Schizophrenia 1(2):78-87.

* 1940. Hoffer, A. 1971. Vitamin B3 dependent child. Schizophrenia 3(2):107-113.

* 1941. Hoffer, A. 1973. Schizophrenia: an evolutionary advance. J. Orthomolecular Psych. 2(1 & 2):39-65.

* 1942. Hoffer, A. 1973. An examination of the double-blind method as it has been applied to megavitamin therapy. J. Orthomolecular Psych. 2(3):107-114.

1943. Hoffer, A., and M. J. Callbeck. 1959. Effect of nicotinic acid on liver function and leukocytes. Can. Med. Assoc. J. 80:736-737.

1944. Hoffer, A., and H. Osmond. 1964. Treatment of schizophrenia with nicotinic acid: A ten year follow-up. Acta Psychiat. Scand. 40(2):171-189.

1945. Hoffer, A., P. O. O'Reilly, and M. J. Callbeck. 1959. Specificity of the hypocholesterolemic activity of nicotinic acid. Dis. Nerv. System 20(7):286-288.

1946. Hoffer, A., H. Osmond, M. J. Callbeck, and I. Kahan. 1957. Treatment of schizophrenia with nicotinic acid and nicotinamide. J. Clin. Expti. Psychopath. Quart. Rev. Psychiatry Neurol. 18(2):131-158.

1947. Hoff-Jorgensen, E., J. Moustgaard, and P. Moeller. 1952. The content of B vitamins in some ordinary Danish feedstuffs: the application of an improved medium for vitamin determinations with Lactobacillus casei. Acta Agr. Scand. 2:305-311.

1948. Hoffmann, B., P. Humburg, and R. P. Martin. 1968. Isolation of crystalline nicotinamide from bovine blood. Proc. Soc. Exp. Biol. Med. 128(4):967-970.

1949. Hoffmann-La Roche, F., and Co. 1968. Vitamin-enriched grains. Fr. Pat. 1,530,248.

1950. Hogan, A. G., G. T. Gillespie, O. Koctuerk, B. L. O'Dell, and L. M. Flynn. 1955. The percentage of protein in corn and its nutritional properties. J. Nutr. 57(2):225-240.

1951. Holcenberg, J. S., and E. R. Stadtman. 1969. Nicotinic acid metabolism. III. Purification and properties of a nicotinic acid hydroxylase. J. Biol. Chem. 244(5):1194-1203.

1952. Holcenberg, J. S., and L. Tsai. 1969. Nicotinic acid metabolism. IV. Ferredoxin-dependent reduction of 6-hydroxynicotinic acid to 6-oxo-1,4,5,6-tetrahydronicotinic acid. J. Biol. Chem. 244(5):1204-1211.

1953. Holden, J. T., and N. M. Utech. 1967. Effect of biotin, pantothenic acid and nicotinic acid deficiencies on amino acid transport in Lactobacillus plantarum. Biochim. Biophys. Acta 135(3):517-531.

1954. Holecek, V., and V. Kulich. 1962. Influence of human erythrocytes on the synthesis of nicotinamide mononucleotide in vitro. Clin. Chim. Acta 7(5):652-656.

1955. Holemans, R., D. McConnell, and J. G. Johnston. 1966a. Hageman factor and fibrinolysis. Am. J. Med. Sci. 251(5):557-562.

1956. Holemans, R., D. McConnell, and J. G. Johnston. 1966b. Urokinase levels in urine after nicotinic acid injection. Thorrom. Diath. Haemorrh. 15(1/2):192-204.

1957. Holland, G. F., and J. N. Pereira. 1967a. 5-(3-Pyridyl)tetrazole, a potent and long-acting lipolysis inhibitor. Experientia 23(2):88-89.

1958. Holland, G. F., and J. Pereira. 1967b. Heterocyclic tetrazoles, a new class ofilipolysis inhibitors. J. Med. Chem. 20(2): 149-154.

1959. Hollander, W., and A. V. Chobanian. 1961. The comparative effects of triparanol, D-thyroxin, and nicotinic acid on body cholesterol metabolism in man. Fed. Proc. 20(1 Pt. 1):174.

1960. Hollmann, M., H. Ketti, and K. F. Weinges. 1970. Inhibition of lipolysis by nicotinic acid in isolated rat fat cells. Verh. Deut. Ges. Inn. Med. 76:843-847.

1961. Hollmann, M., H. Ketti, and K. F. Weinges. 1971. Influence of nicotinic acid on lipolysis in isolated fat cells of rats. Horm. Metab. Res. 3(2):103-109.

1962. Hollobaugh, S. L., F. A. Kruger, and G. J. Hamwi. 1967. The effect of a pyrazole derivative on plasma free fatty acids in man. Met. Clin. Exp. 16(11):996-1000.

1963. Holloman, J. L. S., C. C. Davis, and L. C. Leeper. 1962. Nicotinic acid levels as a index of aluminum nicotinate activity in the treatment of hyperlipemia. J. Am. Geriat. Soc. 10(10): 903-905.

1964. Holly, R. G. 1951. Megaloblastic anemia in pregnancy. Remissions following combined therapy with ascorbic acid and vitamin B12. Proc. Soc. Expt. Biol. Med. 78:238-241.

1965. Holm, G. C., D. F. Eveleth, and W. E. Dinusson. 1953. Trichloreothylene soybean meal poisoning in sheep. J. Am. Vet. Med. Assoc. 122(14):380-382.

1966. Holman, W. I. M. 1954. A colorimetric method for the determination of the principal metabolites of nicotinic acid in human urine. Biochem. J. 56(3):513-520.

1967. Holman, W. I. M., and D. J. De Lange. 1949. Methods for the determination of N-methyl-2-pyridone-5-carboxylamide and of N-methyl-2-pyridone-3-carboxylamide in human urine. Biochem. J. 45(5):559-563.

1968. Holman, W. I. M., and D. J. De Lange. 1950a. The determination of N-methyl-2-pyridone-5-carboxylic acid in human urine. Biochem. J. 46(1):47-49.

1969. Holman, W. I. M., and D. J. de Lange. 1950b. Metabolism of nicotinic acid and related compounds by humans. Nature (London) 165(4198):604-605.

1970. Holman, W. I. M., and D. J. de Lange. 1950c. Role of tryptophan and other amino acids in the metabolism of nicotinic acid by human subjects. Nature 166:468-469.

1971. Holman, W. I. M., and C. Wiegand. 1948. The chemical conversion of nicotinic acid and nicotinamide to derivatives of N-methyl-2-pyridone by methylation and oxidation. Biochem. J. 43(3):423-426.

1972. Holtzman, J. L. 1970. Effect of 4,4-dideuteration of reduced nicotinamide-adenine dinucleotide phosphate on the mixed function oxidases of hepatic microsomes. Biochemistry 9(4):995-1001.

1973. Holzer, H., and H. J. Boltze. 1961. On the effect of nicotinic acid amide on the inhibition of glycolysis in ascites tumor cells by ethylene imine compounds. Z. Krebsforsch. 64:113-121.

1974. Holzer, H., and H. Kroeger. 1958. Mechanism of action of B518 (Endoxan-ASTA) on Jensen sarcoma and the inhibition of tumor chemotherapy by the vitamin nicotin amide. Klin. Wochschr. 36:677-678.

1975. Holzer, H., W. Duntze, and S. Frank. 1958. Carcinostatic mechanisms of ethylenimine compounds. Alkylation of nicotinamide in pyridine-nitrogen. Angew. Chem. 70:746.

1976. Holzer, H., G. Friedrich, and H. Grisebach. 1961. The action of nicotinic acid and nicotine acid amide on the biosynthesis of DPN in ascites tumor cells. Biochim. Biophys. Acta 51(3): 600-601.

1977. Homb, T., T. Matre, and E. Nordrum. 1968. Niacin-supplementation of a barley-soybean-herringmeal ration for growing-finishing pigs. Z. Tier. Physiol. Tierernaehr. Futtermittelk 24(3):133-136.

1978. Hopkins, R. H. 1945. Biochemistry applied to brewing. Chem. Indust. (London) (17):134.

1979. Hopkins, R. H. 1945. Vitamins in top fermentation brewing materials and beer. Wallerstein Lab. Communic. 8(24):110-117.

1980. Hopper, J. H., and B. C. Johnson. 1955. The production and study of an acute nicotinic acid deficiency in the calf. J. Nutr. 56(2):303-310.

* 1981. Horger, L. M., and E. B. Gerheim. 1958. Effects of excess dietary methionine and niacinamide in the rat. Proc. Soc. Exptl. Biol. Med. 97(2):444-446.

1982. Horlick, L. 1959. Regulation of serum cholesterol levels in man; the effects of corn oil, ethyl stearate, hydrogenated soybean oil, and nicotinic acid when added to a very low-fat basal diet. Lab. Invest. 8:723-735.

1983. Horlick, L. 1971. Mechanism of action of drugs used in the treatment of hyperlipidemia. Pap. Symp. Metab. Dis. pp 43-49.

1984. Horst, H. G. 1941. Nicotinamide and carbohydrate metabolism. Vitamine u. Hormone 1:269-272.

1985. Horvath, J. et al. 1969. Results of nifluril therapy for degenerative cervical changes with or without cervical syndrome in a double blind experiment. Praxis 58:1342-1345.

1986. Horwitt, M. K. 1959. Water-soluble vitamins, Part I, thiamine, riboflavin, pantothenic acid, nicotinamide, lipoic acid (thioctic acid). Ann. Rev. Biochem. 28:411-438.

1987. Horwitt, M. K., C. C. Harvey, W. S. Rothwell, J. L. Cutler, and D. Haffron. 1956. Tryptophan-niacin relationships in man. Studies with diets deficient in ribofavin and niacin together with observations on the excretion of nitrogen and niacin metabolites. J. Nutr. 60 (Suppl. 1):1-43.

1988. Hosoya, Y., H. S. Fang, and M. T. Peng. 1950. The effect of nicotinic acid amide on dark adaptation. A preliminary report. Tohoku J. Expt. Med. 53:103-108.

1989. Hou, H. C. 1939. Pellagra and its treatment with nicotinic acid. Chines Med. J. 55(6):528-536.

1990. Hou, H. C., and M.-Y. Dju. 1942. Urinary excretion of nicotinic acid among normal Chinese, pellagrins, and other patients. Chinese Med. J. 61:192-198.

1991. Howard, F. D., J. H. Mac Gillivray, and M. Yamaguchi. 1962. Nutrient composition of fresh California-grown vegetables. Calif. Univ. Agr. Expt. Sta. Bull. 788, 44 pp.

1992. Hrubes, V., and V. Benes. 1968. The time course of nicotinic acid on stress-induced changes in serum nonesterified fatty acids in rats. Activ. Nerv. Super. 10(1):45-48.

1993. Huang, T. F. 1959. Effect of niacinamide on cardiac output, cardiac excitability and membrane action potential of single cardiac muscle fibers. Am. J. Physiol. 196(4):735-737.

1994. Huang, T. F. 1961. The effect of niacinamide and sodium nicotinate on the cardiac output both in normal and in the coronary ligated cats. Tohoku J. Exp. Med. 75:10-16.

1995. Huang, T. F., and C. C. Chao. 1960. Effect of nicotinamide on cerebral circulation. Proc. Soc. Exptl. Biol. Med. 105:551-553.

1996. Huber, F. C. 1949. Recovery of nicotinic acid. U.S. Pat. 2,487,874.

1997. Hudgins, A. P. 1952. Niacin for dysmenorrhea. Am. Practitioner 3(11):892-893.

1998. Huebner, C. 1951. Paper chromatography of pyridine derivatives. Nature 167:119-120.

1999. Huellstrung, H., and F. Steitz. 1941. Nicotinamide metabolism in normal man. Klin. Wochenschr. 20:612-616.

2000. Huff, J. W. 1947. The fluorescent condensation product of N1-methylnicotinamide and acetone. I. Synthesis and properties. J. Biol. Chem. 167(1):151-156.

2001. Huff, J. W., and W. A. Perlzweig. 1947. The fluorescent condensation product of N1-methylnicotinamide and acetone. II. A senstivie method for the deteramination of N1-methylnicotinamide in urine. J. Biol. Chem. 167(1):157-167.

2002. Huff, J. W., P. B. Pearson, and W. A. Perlzweig. 1946. Further studies on the metabolism of nicotinic acid and related compounds in the horse. Arch. Biochem. 9(1):99-104.

2003. Huff, J. W., W. A. Perlzweig, and D. G. Sharp. 1943. N1-methylnicotinamide, a metabolite of nicotinic acid in the urine. J. Biol. Chem. 150(2):395-400.

2004. Huff, J. W., W. A. Perlzweig, R. Forth, and F. Spilman. 1942. Nicotinic acid metabolism. III. Metabolism and synthesis of nicotinic acid in the rat. J. Biol. Chem. 142:401-416.

2005. Hughes, D. E. 1949. A modified chemical estimation of nicotinic acid. Biochem. J. 45(5):xxxiv-xxxv.

2006. Hughes, E. H. 1943. The minimum requirement of nicotinic acid for the growing pig. J. Animal Sci. 2:23-26.

2007. Hugues, F. C., and J. Marche. 1970. Nicotinic acid and adrenaline-induced hyperglycemia in rats. Therapie 25(6): 1017-1024.

2008. Huidobro, F., E. Contreras, and R. Croxatto. 1963. Morphine. III. Action of metabolic precursors to serotonin and nor-adrenaline and related substances on the abstinence syndrome to morphine in white mice. Arch. Intern. Pharmacodyn. 146(3-4): 444-454.

2009. Hummler, H. 1971. The antitoxic effects of beta-pyridyl-carbinol and nicotinic acid in the rat liver damaged by CCl4. Arzneim. Forsch. 21(3):360-362.

2010. Humphreys, S. R., J. M. Venditti, C. J. Ciotti, I. Kline, A. Goldin, and N. O. Kaplan. 1962. Toxicity and antileukemic effectiveness of pyridine derivatives and 1,3,4-thiadiazole derivatives in mice. Relationship to nicotinamide antagonism. In: Cancer chemotherapy screening data XV. Cancer Res. 22(5 Pt. 2):483-550.

2011. Hundley, J. M. 1947. Production of niacin deficiency in rats. J. Nutr. 34(3):253-262.

2012. Hunt, C. H., L. D. Rodriguez, and R. M. Bethke. 1950. The niacin and pantothenic acid content of normal and moldy corn. Cereal Chem. 27:342-343.

2013. Hunt, R., and R. R. Renshaw. 1929. Action of certain heterocyclic compounds on the autonomic nervous system. J. Pharmacol. 35:75-98.

2014. Hunter, J. D. 1962. Nicotinic acid therapy in coronary disease. Am. Heart J. 63:143-145.

2015. Hunter, S. F., and P. Handler. 1952. Metabolism of methyl-nicotinamide by the livers of rats, rabbits and guinea pigs in vitro. Arch. Biochem. Biophys. 35(2):377-383.

2016. Husain, S. M. 1948. Therapeutic uses of nicotinic acid. Antiseptic 45:12-17.

2017. Hyma, A. M. 1945. Synthetic medium for microbiological assay of riboflavin, pantothenic acid, biotin, nicotinic acid, pyridoxine, and folic acid. Microfilm Abs. 6(2):10-11.

2018. Iachello, I. 1954. Diphasic action of sodium nicotinate on the isolated heart. Bol. Soc. Ital. Biol. Sper. 30:656-657.

2019. Ibragimov, I. I. 1972. Effect of glutamate, methionine, and cofactors of their metabolism on the distribution of the regional fund of biogenetic amines in the brain and blood. Soobshch. Akad. Nauk. Gruz. S.S.R. 68(3):721-724.

2020. Ibragimov, V. K., and A. S. Udovichenko. 1962. On the treatment of alcoholism with nicotinic acid (vitamin PP). Zdravookhr Kazakh. 22(3):30-33.

2021. Ibragimova, Z. G. 1968. Capacity of yellow-pigment bacteria of the Promyxobacterium genus, separated from hydroponically grown tomato roots, to synthesize B-group vitamins. Tr. Azerb. Nauch.-Issled. Inst. Zemled. 14:295-298.

2022. Ichikawa, A., E. Nakajima, and M. Hirose. 1966. Polypropylene fibers with good dyeability. Jap. Pat. 69 28,873.

2023. Ichise, Y. 1961. Effect of vitamins B on urease. I. Effect of thiamine on urease. Eiyo to Shokuryo 13(6):355-359.

2024. Ichise, Y., and T. Baba. 1958. Effect of B vitamins and sodium chloride on the oxidation of vitamin C. VI. Effect of nicotinic acid and sodium chloride on the oxidation of vitamin C. Nagasaki Daigaku Gakugeigakubu Shizen Kagaku Kenkyu Hokoku 7:37-41.

2025. Ichiyama, T. 1963. Effects of various drugs on the blood flow of the perfused cat brain. Okayama Igakkai Zasshi 75(4-5-6):355-366.

2026. Iengar, N. G. C., B. R. Sen, and S. Nagarajan. 1962. Estimation of nicotinic acid in foods of vegetable origin. Defence Sci. J. 12(2):170-179.

2027. Igic, R., J. Jelicic, and P. Stern. 1969. Effect of xanthinol nicotinate (Complamin) on vitamin B1 avitaminosis in animals. Bull. Sci., Cons. Acad. Sci. Arts R.S.F. Yougoslavie, Sect. A 14(3-4):75-76.

2028. Iijima, Y. 1972. Studies on the mechanism of 2 types of clonic convulsions and increasing of brain gamma-amino butyric acid caused by hydrazine 2 HCl in mice. Nichidai Igaku Zasshi 31(2):95-104.

2029. Ijichi, H., A. Ichiyama, and O. Hayaishi. 1966. Studies on the biosynthesis of nicotinamide adenine dinucleotide. III. Comparative in vivo studies on nicotinic acid, nicotinamide, and quinolinic acid as precursors of nicotinamide adenine dinucleotide. J. Biol. Chem. 241(16):3701-3707.

2030. Iliescu, M., et al. 1964. Prolonged treatment with large doses of nicotinic acid in coronary arteriosclerosis. Med. Intern. (Bucur.) 16:301-310.

2031. Iliescu, C. C., M. Iliescu, G. Domocos, P. Iacobini, S. Constantinescu, and S. Nitu. 1964. Essential hyperlipemia associated with atherosclerosis (effects of nicotinic acid). Viata Med. 11(1):9-17.

2032. Iliescu, C. C., M. Iliescu, L. Roman, P. Iacobini, S. Constantinescu, and S. Nutu. 1963. The effect of nicotinic acid on blood lipids in atherosclerosis. Med. Intern. (Bucur.) 15:39-49.

2033. Imhof, P., M. Imhof, E. Eichenberger, and H. Lauener. 1959. Activation of fibrinolysis by administration of nicotinic acid. Schweiz. Med. Wochenschr. 89:736-740.

2034. Indovina, I., and N. Causi. 1952. The metabolism of nicotinamide in man. I. The effect of administration intravenously in normal subjects. Boll. Soc. Ital. Biol. Sper. 28:1514-1516.

2035. Inesi, G., and A. Garagnani. 1958. Cardiovascular changes in animals intoxicated by 6-aminonicotinamide. Sperimentale 108(5):411-418.

2036. Ingelfinger, F. J. 1945. The parenteral use of vitamin preparations. New Eng. J. Med. 233:379-385, 409-417.

2037. Ingram, R. L. 1962. Maintenance of organized adult liver tissue in vitro. Exptl. Cell Res. 28:370-380.

2038. Inoue, G., and K. Takahashi. 1965. Pyridinecarboxamides. Jap. Pat. 70 06,021.

2039. Inouye, K., and S. Omori. 1942. Protein metabolism and vitamin B2 complex. Bull. Inst. Phys. Chem. Res. (Tokyo) 21:489-492.

2040. Instytut Chemii Ogolnej. 1965. Preparation of nicotinic acids. Brit. Pat. 979,761.

2041. Intengan, C. L., I. del Rosario, V. L. Arzaga, I. Concepcion, R. D. Salud, and J. D. Manalo. 1954. Nutritional evaluation of meals served in government institutions by chemical methods. Philippine J. Sci. 83(2):177-186.

2042. Investigations Scientifiques Pharmaceutigues S.A. 1967. Pharmaceutical compositions for treating hyperlipidemia and atheromatosis. Fr. Pat. 6622.

2043. Ippen, H. 1970. Drug induced alopecia. Deutsch Med. Wschr. 95:1411-1416.

2044. Irie, M., T. Tsushima, and M. Sakuma. 1970. Effect of nicotinic acid administration on plasma HGH, FFA and glucose in obese subjects and in hypopitultary patients. Meta. Clin. Exp. 19(11): 972-979.

2045. Irie, M., M. Sakuma, T. Tsushima, K. Shizume, and K. Nakao. 1967. Effect of nicotinic acid administration on plasma growth hormone concentrations. Proc. Soc. Expt. Biol. Med. 126(3): 708-711.

2046. Irkov, F. Y. 1957. Nicotinic acid. U.S.S.R. Pat. 106,959.

2047. Isa-Zade, G. M., and S. A. Tagiyeva. 1956. The effect of niacin on cholesterol metabolism in hypertensive disease. Sb. Trudov. Azerb. Med. Inst. (2):43-47.

2048. Isbell, E. R., H. K. Mitchell, A. Taylor, and R. J. Williams. Univ. Texas Pub. (4237):81-83.

2049. Isbell, H. 1942. Effect of p-aminobenzoic acid on the microbiological assay for nicotinic acid. J. Biol. Chem. 144(2): 567-568.

2050. Isbell, H. 1945. The use of charcoal-treated peptone in microbiological assays. Science 102:671-672.

2051. Isbell, H., J. G. Wooley, R. E. Butler, and W. H. Sebrell. 1941. A bacterial assay method for nicotinamide and related substances in blood, urine, and spinal fluid. J. Biol. Chem. 139:499-510.

2052. Isbenjian, H. 1957. Oxidation of methyl pyridines. U.S. Pat. 2,818,378.

2053. Isberto, A. R., A. P. Bautista, C. C. Gervasio, and L. B. Dimaunahan. 1964. The effect of various cooking procedures on cooking losses and retention of B-vitamins in pork and beef. Philippine J. Sci. 93(3):343-354.

2054. Ishigami, R., S. Shiotani, A. Yoshida, T. Kawata, H. Natori, Y. Akiyama, J. Omoto, and H. Okada. 1965. Drug diabetes. IV. Abnormal carbohydrate metabolism induced by nicotinic acid. Bitamin 32(2):232-239.

2055. Ishikawa, A. 1964. Effects of adrenalectomy and cortisol administration on nicotinamide adenine dinucleotide (NAD) concentration in the mouse liver. J. Fac. Sci. Univ. Tokyo, Sect. IV 10 (Pt. 2):323-327.

2056. Ishikawa, J. 1970. Studies on the regulation mechanism of nicotinamide-adenine dinucleotide phosphate synthesis in rat liver. J. Fac. Sci. Univ. Tokyo Sect. IV Zool. 11(4): 589-598.

2057. Ismailov, N. I., M. S. Tursunkhodzhaeva, D. A. Kanazahrova, and Y. A. Karimova. 1959. Vitamin status of healthy and sick people in Uzbekistan. Izvest. Akad. Nauk Uzbek. S.S.R., Ser. Med. (5):63-69.

2058. Isselkutz, B., Jr., and Paul. 1968. Intramuscular energy sources in exercising normal and pancreatectomized dogs. Am. J. Physiol. 215(1):197-204.

2059. Itami, J. 1958. Disturbance of biological oxidation and niacin metabolism in hypertension and its treatment. I. Biological oxidation in hypertension. Osaka Daigaku Igaku Zasshi 10:1899-1904.

2060. Ito, H., and Y. Takeda. 1961. Effects of artificial sweetening in relation to the quantity of salivation. Kaseigaku Zasshi 12:201-205.

2061. Ito, R., T. Suga, M. Shimura, K. Tanaka, G. Ishizuka, Y. Miyauchi, T. Saiki, K. Ohkubo, K. Kamei, et al. 1971. Pharmacology of complamex, a molecular compound of methoxylin and nicotinic acid. Toho Igakkai Zasshi 18(2):325-247.

2062. Ito, S., and A. Kuroshima. 1970. Adaptation ot cold (IV) basal metabolism and blood lipids. Hokkaido J. Med. Sci, 45(5):1-11.

2063. Ito, T. 1971. Studies on nicotinamide deamidation in rat stomach. Bull. Osaka Med. Sch. 17(1):1-10.

2064. Ito, Y. 1955. Hemolysis on paper. I. Detection of hemolysis with the use of filter paper chromatograms. Acta Schol. Med., Univ. Kito 33:81-85.

2065. Ivanchenko, F. T. 1967. Comparative evaluation of the effectiveness of nicatole and nicotinic acid treatment of patients with coronary atherosclerosis. Vrach. Delo 1:76-80.

2066. Ivanov, N., and Y. Profirov. 1972. Nicotinamide coenzyme concentration in the liver of chicks as affected by nicotinic acid, nicotinamide, and tryptophan. Zhivotnovud. Nauki 9(1): 47-54.

2067. Ivanova, A. 1960. Studies on the participation of the nervous system in the mechanism of spermatorrheic reaction to prolan in frogs. Nauch. Tr. Vlash. Med. Inst. Sofia 39(2):145-153.

2068. Ivanova, R. A., G. I. Mil'shtein, L. B. Smirnova, and N. D. Fanchenko. 1964. Effect of nicotin acid on the experimental psychosis induced by lysergic acid diethylamide. Zh. Nevropatol. Psikhiat. im S. S. Korsakova 64(8):1172-1176.

2069. Ivanova, V. D. 1964. Disorders of tryptophan metabolism in leukemia. Acta, Unio Intern. Contra Cancrum 20(4-5):1085-1086.

2070. Ivanovskaya, T. V. 1959. Effect of vitamin C and vitamin B complex on the sensitivity to some analeptics in deep hexanol narcosis. Ekspti. Issledovan. po Fiziol., Biokhimii i Farmakol., Perm, Sbornik (1):141-144.

* 2071. Iversen, M. 1942. Nicotinic acid and its therapeutic use. Nord. Med. 16:3052-3053.

2072. Ives, M., M. Zepplin, S. R. Ames, F. M. Strong, and C. A. Elvehjem. 1945. The nutritive value of canned foods. X. Further studies on riboflavin, niacin and pantothenic acid. J. Am. Dietetic Assoc. 21(6):357-359.

2073. Ivleva, A. Y., S. I. Zolotukhin. 1971. Activation of the body fibrinolytic system with pharmacological agents of a nonenzymic nature. Farmakol. Toksikol. 34(6):749-755.

2074. Ivy, A. C., E. Karvinen, T. M. Lin, C. R. Prasad, and C. S. Setty. 1959. Cholesterol metabolism: comparative study of the effect of the addition of various fats, stearic acid and niacin to the diet on serum cholesterol, liver and arterial lipids and atheromatosis in the chocken. U.S.A.F. Office Sci. Res. A.F.O.S.R. Tr. 59-79:1-57.

2075. Iwaguchi, T., and Y. Sakurai. 1972. Chemical modification of cell membrane of Yoshida sarcoma cells by 6,6'-dithiodinicotinic and its effect on sensitivity to nitrogen mustard. Gann Jap. J. Cancer Res. 63(6):757-764.

2076. Iwai, K., and H. Yokomizo. 1968. The distribution of B-vitamins in rice grain. Eiyo to Shokuryo 20(6):495-499.

2077. Iwata, H., and Inoue. 1968. Antagonism between nicotine and thiamine derivatives on the isolated atrium of the guinea pig. Nippon Yakurigaku Zasshi 64(2):46-51.

2078. Iwatsubo, M., M. Ishibashi, T. Takashina, K. Ibaraki, and H. Kashida. 1954. Mode of combination of the substrate and diphosphopyridine nucleotide in the glutamic dehydrogenase system. Symposia on Enzyme Chem. 10:135-141.

2079. Jackson, S. H., A. Crook, V. Malone, and T. G. H. Drake. 1945. The retention of thiamine, riboflavin and niacin in cooling pork and in processing bacon. J. Nutr. 29(6):391-403.

2080. Jacobs, R. S., M. S. Grebner, and D. L. Cook. 1965. Effect of nicotinic acid on serum triglyceride, cholesterol, and chylomicrons in rats. Proc. Soc. Expti. Biol. Med. 119(4):1117-1120.

2081. Jacobsen, E. 1944. The role of vitamins in tissue metabolism. Dansk Tids. Farm. 18:112-132.

2082. Jacobsohn, K. P., and J. M. Cruz. 1945. Effect of some oxidation-reduction vitamins urease. Arch. Portugaises Sci. Biol. 7(3) (Suppl. 2, Compt. Rend. Soc. Port. Biol.):73-75.

2083. Jacobsohn, K. P., and M. Deodata de Azevedo. 1953. The activation of thiaminase. Compt. Rend. Soc. Biol. 147:1822-1824.

2084. Jacobson, K. B., and N. O. Kaplan. 1957. Pyridine coenzymes of subcellular tissue fractions. J. Biol. Chem. 226(2): 603-613.

2085. Jacquot, R., and T. Terroine. 1949. Physiological relations between tryptophan and nicotinic acid. Bull. Soc. Chim. Biol. 31(1):7-10.

2086. Jacquot, R., and T. Terroine. 1951. Some new intermetabolic relations and their significance. J. Recherches Centre Natl. Recherche Sci., Labs. Bellevue (Paris) 17:54-65.

2087. Jacquot, R., T. Terroine, J. Creveaux, F. Charconnet, J. Adrain, and M. A. Quievreux. 1950. Corn and tryptophane-niacin interrelationships. Arch. Sci. Physiol. 4(2):115-143.

2088. Jadhav, M. G., and N. G. Magar. 1970. Preservation of fish by freezing, and glazing. III. Effect of freezing, glazing, and frozen storage on the B-vitamins and essential minerals present in the fish flesh. Fish. Technol. 7(2):158-163.

2089. Jaehnchen, E., J. Kriegistein, and Kuschinsky. 1969. Significance of the benzene rings in the protein binding of promazine and chlorpromazine. Naunyn-Schmiedebergs Arch. Pharmakol. E 263(2):375-386.

2090. Jaennes, J. 1950. Studies on the nicotinic and pantothenic acid content in the blood, urine and feces of man and on the appearance of these vitamins in intestinal diseases. Acta Med. Scand. (Suppl.) 249:1-71.

2091. Jaffe, E. R. 1964. Influence of the age of mammalian erythrocytes on the incorporation of nicotinic acid and nicotinamide into pyridine nucleotides. Proc. Congr. Intern. Soc. Hematol., 9th, Mexico, D.F. 1962(3):257-259.

2092. Jaffe, E. R., and E. E. Gordon. 1963. The incorporation of nicotinic acid and of nicotinamide into the pyridine nucleotides of erythrocytes and reticulocytes of rabbits in vitro. J. Clin. Invest. 42(7):1017-1024.

2093. Jaffe, E. R., and G. Neumann. 1965. The synthesis of pyridine nucleotides in fresh and stored human erythrocytes. Transfusion 5(5):412-420.

2094. Jaffe, E. R., and G. Neumann. 1970. Effect of diazooxonorleucine and N-ethyl maleimide on the incorporation of nicotinic acid and nicotinamide into the pyridine nucleotides of human erythrocytes in vitro. Haematologia 4(1):5-14.

2095. James, D. P. 1952. Nicotinic acid, pantothenic acid, and biotin in fruits, vegetables, and nuts. Brit. J. Nutr. 6:341-356.

2096. James, E. M., F. W. Norris, and F. Wokes. 1947. The chemical estimation of nicotinic acid in cereals and other foods. Analyst 72:327-336.

2097. Janes, R. G. 1950. Comparative study of the ketogenic activity of certain niacin compounds. Proc. Soc. Exptl. Biol. Med. 75(1):246-250.

2098. Janes, R. G. 1953. Certain metabolic effects of niacin and Priscoline. Am. J. Physiol. 174:46-48.

2099. Janes, R. G., and L. S. Boeke. 1952. Influence of niacin and Priscoline on ketonuria, liver glycogen and liver lipid. Proc. Soc. Exptl. Biol. Med. 80(4):591-594.

2100. Janes, R. G., and J. Brady. 1949. Ketogenic action of niacin in the normal fasted rat. Am. J. Physiol. 159:547-550.

2101. Janes, R. G., and L. Myers. 1946. Production of ketosis in alloxan diabetic rats with nicotinic acid. Proc. Soc. Exptl. Biol. Med. 63(2):410-414.

2102. Janes, R. G., and F. W. Schueler. 1955. Protection against the diabetogenic action of alloxan. Proc. Soc. Exptl. Biol. Med. 89:582-584.

2103. Janicki, J., D. Olejnik, and E. Kaminski. 1967. Modification of the cyanobromide method for vitamin PP determination in cereal and cereal products. Rocz. Wyzsz. Szk. Roln. Poznaniu 35:87-97.

2104. Jansen, H. 1955. Toxicology of antihistamines. Pharm. Weekblad. 90:609-614.

2105. Jaennes, J. 1950. Studies on the nicotinic and pantothenic acid content in the blood, urine, and feces of man and on the appearance of these vitamins in intestinal diseases. Acta Med. Scand. 139(Suppl. 249):71 pp.

2106. Janni, A. 1961. Nicotinic acid and insensible perspiration. Boll. Soc. Ital. Biol. Sper. 37:81-84.

2107. Janovsky, R. C. 1968. Diabetogenic effects of nicotinic acid. Case reports and discussions. Ohio Med. J. 64:1139-1142.

2108. Jaramillo, E. B. 1963. Effects of the vitamin PP on the odontogenic process. Arch. Inst. Farmacol. Exptl. 15(2): 191-208.

2109. Jefcoate, C. R. E., J. L. Gaylor, and R. L. Calabrese. 1969. Ligand interactions with cytochrome P-450. I. Binding of primary amines. Biochemistry 8(8):3455-3463.

2110. Jeffman, I. 1968. Determination of vitamin B6, niacin, and biotin in food products. Eng. Quim. 20(5):4-6.

2111. Jeffrey, R. N., and T. C. Tso. 1955. Qualitative differences in the alkaloid fraction of cured tobaccos. J. Agr. Food Chem. 3:680-682.

2112. Jeffus, M. T., and C. T. Kenner. 1969. Determination of niacinamide in pharmaceutical preparations. J. Pharm. Sci. 58:749-752.

2113. Jelinek, V., and E. Zikmund. 1948. Variation in the vascular action of nicotinic acid according to sex. Compt. Rend. Soc. Biol. 142:1044-1047.

2114. Jemmali, M., L. Carre, A. Buquet, and P. Manchon. 1970. Microbiological characteristics of bread preserved with ethylene oxide. Aliment. Vie 58(4-5-6):97-100.

2115. Jenkins, A. J. D. 1965. Effects of nicotinic acid on carbohydrate and fat metabolism during exercise. Lancet I(7399):1307-1308.

2116. Jequier, R., C. Plotka, and M. Peterfalvi. 1949. Parallelism of action, on the (frog) heart, of acetylcholine and of intermediate products of carbohydrate metabolism. Compt. Rend. Soc. Biol. 143:32-34.

2117. Jimenez Vargas, J. 1945. Comparative effects of nicotinic acid, sodium nicotinate, and nicotinamide. Rev. Espanola Fisiol. 1:127-149.

2118. Jitariu, P., and N. Topala. 1953. The study of nicotinic acid effect on the excitability of the sciatic nerve of the frog. Acad. Rep. Populare Romane, Filiala Iasi, Studii Cercetari Stiint. 4(1/4):385-388.

2119. Johnson, B. B., A. H. Lieberman, and P. J. Mulrow. 1957. Aldosterone excretion in normal subjects depleted of sodium and potassium. J. Clin. Invest. 36(6):757-766.

2120. Johnson, B. C. 1945. The microbiological determination of nicotinic acid, nicotinamide, and nicotinuric acid. J. Biol. Chem. 159(1):227-230.

2121. Johnson, B. C., and P. H. Lin. 1951. Metabolism of radioactive nicotinic acid and nicotinamide in the rat. Fed. Proc. 10:203.

2122. Johnson, B. C., and P. H. Lin. 1953. Nicotinic acid metabolism. 1. The use of paper chromatography in the study of nicotinic acid metabolism. J. Am. Chem. Soc. 75:2791-2973.

2123. Johnson, B. C., J. Firth, and S. P. Mistry. 1955. Vitamin B12 and choline synthesis from glycine in vivo. Arch. Biochem. and Biophys. 54:467-473.

2124. Johnson, B. C., T. S. Hamilton, and H. H. Mitchell. 1945. The excretion of nicotinic acid, nicotinamide, nicotinuric acid, and N1-methylnicotinamide by normal individuals. J. Biol. Chem. 159:231-236.

2125. Johnson, B. C., A. C. Wiese, H. H. Mitchell, and W. B. Nevens. 1947. The metabolism of nicotinic acid and its role in the nutrition of the calf. J. Biol. Chem. 167(3):729-736.

2126. Johnson, H. H., Jr., and G. W. Binkley. 1950. Nicotinic acid therapy of dermatitis herpetiformis. J. Invest. Dermatol. 14:233-238.

2127. Johnson, H. J. 1967. Multivitamin food enrichment composition. U.S. Pat. 3,536,494.

2128. Johnson, R. E., C. Henderson, P. F. Robinson, and F. C. Consolazio. Comparative merits of fasting specimens, random specimens, and oral loading tests in field nutritional surveys. J. Nutr. 30:89-98.

2129. Johnson, W. J., and L. Kanics. 1969. Stimulation of adrenocortical secretion by nicotinic acid and certain of its derivatives and analogues. Biochem. Med. 2(6):438-447.

2130. Johnston, P. M., and E. M. Weitz. 1952. The effect of niacin deficiency on the appearance of the Golgi apparatus in the columnar absorbing cells of the duodenum of the albino rat. J. Morphol. 91(1):79-109.

2131. Jokay, I., and B. Toth. 1964. The effect of pyridine derivatives on the activity of crystalline ribonuclease. Biochim. Biophys. Acta 87(2):181-187.

2132. Jolley, R. L., and C. D. Scott. 1970. Preliminary results from high-resolution analyses of ultraviolet-absorbing and carbohydrate constituents in several pathologic body fluids. Clin. Chem. 16(8):687-696.

2133. Jollifee, N., and T. C. Tung. 1956. Nutrition status survey of the civilian population of Formosa. Metabolism 5(3):309-327.

2134. Jones, A., M. P. Taylor, and D. N. Gore. 1954. The detection of the vitamins of the B group by means of small circular chromatograms. Chem. Indust. 1954(16):461-462.

2135. Jones, K. M. 1959. A chromatographic method for the estimation of nicotinuric acid and nicotinamide. Biochem. J. 73:719-723.

2136. Jones, L. D., D. G. Fairchild, and W. C. Morse. 1971. The induction of pulmonary neoplasms in mice by isonicotinic acid hydrazide. Am. Rev. Resp. Dis. 103(5):612-617.

2137. Jones, M. V., and D. E. Hughes. 1972. The oxidation of nicotinic acid by Pseudomonas ovalis Chester: The terminal oxidase. Biochem J. 129(3):755-761.

2138. Jones, W. S. 1941. Photoelectric determination of nicotinic acid. J. Am. Pharm. Assoc. 30:272-275.

2139. Jordahl, D., R. Des Prez, K. Deuschle, C. Muschenheim, and W. McDermott. 1961. Ineffectiveness of nicotinamide and isoniazid in the treatment of pulmonary tuberculosis. Am. Rev. Resp. Dis. 83:899-900.

2140. Jorgensen, P. S. 1940. Report on nicotinic acid. J. Assoc. Off. Agric. Chem. 23:765-767.

2141. Josem, S. 1944. Nicotinic acid content of Argentine flour. An. Asoc. Quimica Argentina 32(168):185-194.

2142. Joubert, C. P., and D. J. de Lange. 1962. Modification of the method for the determination of 5-carbamoyl-N-methyl-2-pyridone in human urine and its application in evaluation of nicotinic acid studies. Proc. Nutr. Soc. S. Africa 3:60-65.

2143. Jourdan, F., and G. Faucon. 1959. Inequality of vasodilator effect of nicotinic acid. Therapie 14:364-375.

2144. Jovanovic, U. J. 1968. Prevention of side effects in electroshock therapy. Arzneim-Forsch. 18(4):417-424.

2145. Jovet-Lavergne, P. 1941. Effect of vitamin-B2 (lactoflavin) on utilisation of glucose by the living cell in course of respiration. C. R. Acad. Sci. 213:406-407.

2146. Juergens, J. 1960. New methods of fibrinolytic treatment. Proc. Intern. Congr. Hematol., 8th, Tokyo, 1960 3:1613-1618.

2147. Juergens, R. 1948. The effect of vitamins on experimental hypoprothrombinemia. Intern. Z. Vitaminforsch. 19:342-361.

2148. Juhlin, L., and G. Michaelsson. 1971. Abnormal cutaneous reactions to a nicotinic acid ester. Acta Derm. Venereol. 51(6):448-452.

2149. Jung, A. 1945. Nicotinic acid, nicotinamide, and their clinical importance. Arztl. Monatsh. 1(1):7-15.

2150. Jungert, S. 1964. Histilos (Dilligan) in Neniere's disease. A clinical trial. Svensk. Lakartidn. 61:553-566.

2151. Junod, A., A. E. Lambert, W. Stauffacher, and A. E. Renold. 1969. Diabetogenic action of streptozotocin: relation of dose to metabolic response. J. Clin. Invest. 48(11):2129-2139.

2152. Junqueira, P. B., and B. S. Schweigert. 1948. Urinary excretion of nicotinic acid and N1-methylnicotinamide by rats fed tryptophan and diets deficient in various B vitamins. J. Biol. Chem. 175:535-546.

2153. Kabarity, A., and W. Frote. 1972. Disturbed embryonic mitosis in the rabbit following administration of 6-aminonicotinamide. Arzneim.-Forsch. 22(2):435-438.

2154. Kabelitz, G. 1941. Action of liver-extract preparations on blood catalase. Z. Ges. Exptl. Med. 108:700-707.

2155. Kachurina, N. A., and T. P. Novozhilova. 1961. Blood content and excretion of riboflavine and nicotinic acid in pyodermia. Tr. V-go (Pryatogo) Sezda Dermatol.-Venerol., Leningrad, pp. 271-272.

2156. Kaganovich, V. I. 1967. Use of a model of rat liver fat dystrophy as a functional load in a toxicological experiment. Mater. Nauch.-Prakt. Konf. Molodykh Gig. Sanit. Vrachei, 11th, pp. 151-153.

2157. Kagedal, S. Laurell, and G. Rooth. 1970. Effect of variation of lipolysis after nicotinic acid and acetylsalicylate on blood concentrations of 3-hydroxybutyrate and acetoacetate in starving subjects. Scand. J. Clin. Lab. Invest. 25(4):317-323.

2158. Kagedal, B., S. Laurell, C. Rerup, and J. Thorell. 1973. Effect of nicotinic-acid-induced variation in plasma free fatty acids on some hormones in starving subjects. Scand. J. Clin. Lab. Invest. 31(3):331-336.

2159. Kahn, V., and J. J. Blum. 1968. Studies of nicotinic acid metabolism in Astasia longa: I. Incorporation of nicotinic acid into pyridine derivatives in exponentially growing and in synchronized cultures. J. Biol. Chem. 243(7):1441-1447.

2160. Kaiser, W., and N. Zoellner. 1971. Effect of nicotinic acid and beta-pyridylcarbinol on cholesterol biosynthesis in the rat liver. Metab. Eff. Nicotinic Acid its Deriv., Proc. Workshop 1970, pp. 621-624.

2161. Kaiser, W., and N. Zoellner. 1972. Regulation cholesterol synthesis in the rat liver using serum cholesterol-lowering drugs. Verh. Deut. Des. Inn. Med. 78:1307-1310.

2162. Kajtor, F. 1950. The spasm-preventing effect of histamine and nicotinic acid on experimental human convulsions. Kiserletes Orvostudomany 2:206-217.

2163. Kakac, B., and Z. J. Vejdelek. 1961. Photometric determination of some substances of the vitamin B group. Cesk. Farm. 10(10): 522-540.

2164. Kakemi, K., H. Sezaki, M. Nakano, K. Ohsuga, and T. Mitsunaga. 1969. Hydrolytic and associative behavior of aromatic amides in aqueous solution. Chem. Pharm. Bull. (Tokyo) 17(5):901-905.

2165. Kakhidze, N. T., and G. A. Medvedeva. 1956. Study of secretion of vitamins by organs of a flower by the technique of indicator cultures. Fiziol. Rastenii 3(5):435-439.

2166. Kakimoto, D., and A. Kanazawa. 1956-1957. The B-vitamins in the pyloric ceca of skipjack. I. Thiamine, nicotinic acid, folic acid, biotin, and pantothenic acid. Nippon Suisan Gakkaishi 22:574-576.

2167. Kalantaevskaia, K. A., and A. P. Vashchenkova. 1962. Reflex vascular reactions of the skin in children following the administration of adrenalin, histamine and nicotinic acid. Vestn. Derm. Vener. 36:19-23.

2168. Kalashnikov, A. P. 1964a. Advisability of use of nicotinic acid in patients with carcinoma of the stomach. In: Proceedings of the Fourth Conference of Young Scientists of Moldavis, 1964. Section of physiology and medicine. Kishinev., pp. 187-190.

2169. Kalashnikov, A. P. 1964b. Concentration and excretion of nicotinic acid derivatives in patients with stomach and lung cancer. Vop. Onkol. 10(12):32-34.

2170. Kalashnikova, V. P. 1958. Changes of nicotinic acid metabolism in irradiated rats receiving different diets. Voprosy Pitaniya 17(4):15-19.

2171. Kalashnikova, V. P. 1963. Nicotinic acid metabolism in the irradiated organism. Fed. Proc. 22:1202-1203.

2172. Kalashnikova, V. P. 1967. Vitamin metabolism in experimentally induced radiation sickness. Med. Radiol. 12(4):89-91.

2173. Kalenderov, S. 1969. The need of nicotinic acid additives to basic standard rations for pig fattening. Zhivotnovod Nauki 6(6):41-48.

2174. Kalliomaki, J.L., and T. K. Markkanen. 1962. Riboflavine and nicotinic acid content of blood in rheumatoid arthritis. Arch. Interam. Rheumatol. 5:81-89.

2175. Kalliomaki, J. L., V. A. I. Laine, and T. K. Markkanen. 1960. Urinary excretion of thiamine, riboflavine, nicotinic acid, and pantothenic acid in patients with rheumatoid arthritis. Acta Med. Scand. 166:275-279.

2176. Kalopissis, G. 1969. Antiseborrheic shampoos. German Offen. Pat. 1,904,159.

2177. Kaludina, T. 1970. Effect of nicotinic acid on the absorption and accumulation of vitamin E. Dokl. Akad. Sel'skokhoz. Nauk Bolg. 3(4):381-384.

2178. Kaludina, T. 1971. Effect of nicotinic acid on the absorption and accumulation of vitamin A and carotene. Vet.-Med. Nauki 8(4):85-89.

2179. Kalvoda, R., and J. Zyka. 1952. Polarographic determination of the effective compounds of Nicofer lozenges. Farmacia 21:45-47.

2180. Kalyanpur, S. G., S. R. Naik, and U. K. Sheth. 1968. Some factors affecting pentobarbital sleeping time. Arch. Int. Pharmacodyn. Ther. 173(1):1-10.

2181. Kamala, B. 1943. Combined estimation of thiamin and nicotinic acid in foodstuffs by chemical methods. Indian Jour. Med. Res. 31(2):145-153.

2182. Kamei, S. 1958. The effect of the prolonged and repeated carbon monoxide inhalation on the riboflavin and nicotinic acid metabolism of the rats. Med. J. Shinshu Univ. 3(4):281-288.

2183. Kamei, T. 1927. The behavior of pyridine, quinoline and nicotinic acid in the Eck-fistula dog. J. Biochem. (Japan) 7:197-201.

2184. Kamenkovich, V. M. 1969. Influence of phenatine on the thresholds of color discrimination in man. Zh. Vyssh. Nerv. Deyatel. im. I. P. Pavlova 19(4):716-718.

2185. Kamimura, M. 1969. Effect of alpha-tocopheryl nicotinate on microcirculation in acrocyanosis. Bitamin 40(4):204-244.

2186. Kamiya, T., and T. Takahashi. 1961. Mechanism of cell division. I. Changes in pyridine nucleotide and reduced diphosphopyridine nucleotide (DPNH) cytochrome c reductase in Tetrahymena pyriformis during the course of synchronous culture. J. Biochem. 50:277-283.

2187. Kanatini, H. 1962. Effects of nicotinamide on growth and mitotic activity in regenerating planaria and bean root tips. J. Fac. Sci. Tokyo Univ. Sec. IV Zool. 9(3):387-395.

2188. Kang, S. H., and T. J. Choi. 1962. The influence of nicotinamide and folic acid on the regeneration of rhodopsin. J. Korean Chem. Soc. 6:32-35.

2189. Kanig, K. 1970. Biochemical action mechanism of nicotinic acid, nicotinamide, methionine, and D-penicillamine in the treatment of psychoses. Arzneim.-Forsch. 20(7):909-911.

2190. Kanig, K., and W. Oesterle. 1967. The effects of niacin, niacinamide, and pantothenic acid on poisoning with 3-acetylpyridine, thiamine, and d-tubocurarine. Neuro-Psycho-Pharmacol., Proc. Int. Congr. Coll. Int. Neuro-Psycho-Pharmacol., 5th, Washington, D.C. 1966, 1219-1223.

2191. Kaplan, N. O. 1961. Metabolic pathways involving niacin and its derivatives. In: D. M. Greenberg, Ed. Metabolic Pathways, Vol. II, Academic Press, New York, pp. 627-672.

2192. Kaplan, N. O. 1969. Regulation of pyridine nucleotide coenzymes. J. Vitaminol. (Kyoto). 14(Suppl.):103-113.

2193. Kaplan, N.O., M. M. Ciotti, J. Van Eyes, and R. M. Burton. 1959. Effect of pyridine derivatives on animal tissue diphosphopyridine nucleotidases. J. Biol. Chem. 234(1): 134-138.

2194. Kaplan, N. O., A. Goldin, S. R. Humphreys, and F. E. Stolzenbach. 1957. Pyridine precursors of mouse liver diphosphopyridine nucleotide. J. Biol. Chem. 226(1): 365-371.

2195. Kaplan, N. O., A. Goldin, S. R. Humphreys, M. M. Ciotti, and F. E. Stolzenbach. 1956. Pyridine nucleotide synthesis in the mouse. J. Biol. Chem. 219:287-298.

2196. Kaptereva, Y. V., and I. V. Aseeva. 1969. Effect of vitamins and amino acids on the biosynthesis of L-valine by Bacterium fimbriatum. Mikrobiologiya 37(1):62-68.

2197. Karabinos, J. V., and D. M. Dicken. 1944. The isolation of nicotinic acid from milk and its role as an essential growth factor for Acetobacter suboxydans. Arch. Biochem. 4(2): 211-215.

2198. Karamyshev, V. A. 1971. Effect of neomycin, monomycin, and nicotinic acid on the concentration of sulfapyridazine in the blood of sheep. Sb. Rab., Leningrad Vet. Inst. 32:219-223.

2199. Karasek, F., and J. Heller. 1960. Effect of nicotinic acid and ethiacin on water diuresis. Cesk Fysiol. 9:241-242.

2200. Karasek, F., O. Poupa, and V. Jelinek. 1948. Potential toxicity of nicotinic acid. Minerva Med. 39:28-29.

2201. Karasek, M. 1965. Electron-microscopic cytological examination of white rat pineal gland after reserpine and nicotinamide administration. Endokrynol. Polska 16(5):447-456.

2202. Kariyone, T., and Y. Hashimoto. 1951. Paper-partition chromatography of some organic bases by the method of N-methylation. Nature 116:739.

2203. Karkun, J. N., and S. P. De. 1952. Cylinder-plate method of microbiological assay of nicotinic acid. Indian J. Med. Res. 40(2):257-263.

2204. Karlin, R. 1959. On the level of nicotinic acid in human whole blood. Compt. Rend. Soc. Biol. 153:1044-1046.

2205. Karlin, R., S. Guerillot-Vinet, A. M. LeClerc, and J. Adrian. 1966. Vitamins. Ann. Nutr. Aliment. 20(2): 221-233.

2206. Karlin, R., and J. Viallier. 1959. Effect of combined antibiotic therapy in pulmonary tuberculosis on the nicotinic acid and pantothenic acid content of the blood. Ann. Biol. Clin. (Paris) 17:440-448.

2207. Karmas, G. 1969. 2,3-Dialkyl-4-arylcyclohexenemethanols and esters as parenteral contraceptives. German Pat. 1,920,865.

2208. Karpenko, M. K. 1959. Metabolism of nicotinic acid and content of diphosphopyridinenucleotide in cells of "active" and "slightly active" cultures of race "Mz" of Saccharomyces cerevisiae. Mikrobiol Zh. (Kiev) 21(5):18-24.

2209. Karrer, P. 1947. Vitamins as building stones of ferments. Chimia 1:3-12.

2210. Karrer, P., and F. Blumer. 1957. Crystallized N-Methyl-p-dihydro-nicotinamide. Helvitica Chim. Acta 30(5):1157.

2211. Karrer, P., and H. Keller. 1938a. Colorimetric determination of nicotinic acid amide. Helv. Chim. Acta, 21:463-469.

2212. Karrer, P., and H. Keller. 1938b. Determination of nicotinamide in animal organs. Helv. Chim. Acta 21:1170-1171.

2213. Karrer, P., and H. Keller. 1939. Determination of nicotinamide in animal organs. Helv. Chim. Acta 22:1292-1293.

2214. Karrick, N. L., W. Clegg, and M. E. Stansby. 1957. Vitamin content of fishery by-products. III. Riboflavine, nicotinic acid, vitamin B12, moisture, oil, ash, and protein content of commercial fish meals. Com. Fisheries Rev. 19(5a):14-23.

2215. Kasahara, A. 1968. Steroids. X. Pharmacological Studies. 4. Conversion of beta-hydroxy-5alpha-androstano 2,3-C furazan into 17-oxo compound by rat liver in vitro. Chem. Pharm. Bull. 16(8):1460-1465.

2216. Kasarov, L. B., and A. G. Moat. 1972. Convenient method for enzymic synthesis of (14C)-nicotinamide riboside. Anal. Biochem. 46(1):181-186.

2217. Kashai, D., and B. Mate. 1961. The effect of nicotinic acid on the temperature of the skin of patients with schizophrenia in different states. Zh. Nevropat Psikhiat Korasakov 61:1688-1698.

2218. Kashiwada, K., and S. Teshima. 1966. Production of B vitamins by intestinal bacteria of fish. I. Nicotinic acid, pantothenic acid, and vitamin B12 in carp. Nippon Suisan Gakkaishi 32(11): 961-966.

2219. Kassai, D., and V. Mate. 1961. Utilization of the vascular reaction to nicotinic acid for a study of changes in the function of the nervous system in psyciatry. Zh. Nevropat. Psikhiat. Korsakov 61:1232-1240.

2220. Kassay, G., and V. Mathe-Kassay, 1960. Sleep and the vascular action of nicotinic acid. Confin. Neurol. 20:355-365.

2221. Kassay, G., and V. Mathe-Kassay. 1962. The use of a conditioned reflex built up on the vascular reaction to nicotinic acid in studies of nervous activities of mental patients. Acta Neuroveg. (Wien) 23:490-498.

2222. Kasuya, R., H. Ikehata, T. Miyamoto, and K. Murata. 1967. The content of the vitamin B group in natto and tempeh. Kaseigaku Zasshi 18(6):362-364.

2223. Katchen, B., S. Buxbaum, J. Meyer, and J. Ning. 1973. Metabolism and pharmacokinetics of a new nonsteroid, anti-inflammatory agent, 2-(3-cholor-o-toludino) nicotinic acid (clonixin) in rats, dogs, and monkeys. J. Pharmacol. Exp. Ther. 184(2):453-464.

2224. Kating, H. 1968. The antipellagra vitamin, nicotinic acid-nicotinamide (biosynthesis, metabolism, antivitamin substances, pharmacology, therapeutic application). Pharm. Ztg. 113(23): 810-818.

2225. Kato, M. 1953. A simple method for the detection of niacin derivatives. Kagaku (Science) 23:478-479.

2226. Kating, H., and G. Drephal. 1966. Effect of nicotinic acid amide on growth, N utilization and fat synthesis in Endomycopsis vernalis and Torulopsis utilis. Arch. Mikrobiol. 53(2): 163-172.

2227. Kato, M., and H. Shimizu. 1951. Flurometric determination of nicotinamide by use of synthetic ion-exchange resins. Science 114:12-14.

2228. Kato, T., H. Yamanaka, and J. Kawamata. 1969. Ketene and its derivatives. XXXII. Reactions of alpha,beta-unsaturated acid anhydrides with beta-aminocrotonamide and related compounds. Chem. Pharm. Bull. 17(12):2411-2416.

2229. Katunuma, N., and O. Mitsuko. 1966. Regulation of the urea cycle and tricarboxylic acid cycle by ammonia. Advan. Enzyme Regulation 4:317-335.

2230. Katzenelbogen, E., A. E. Axelrod, and C. A. Elvehjem. 1941. The coenzyme I content of rat tissues in experimental hyperthyroidism. J. Biol. Chem. 141(2):611-617.

2231. Katzenellenbogen, I. 1939. Nicotinic acid in endemic glossitis. Lancet 236(6040):1260-1262.

2232. Kawanabe, K. 1956. Influence of agents in vitamin B2-complex on the metabolism of carbohydrate. I. Influence upon the blood sugar content of normal fasting rabbit. Kansai Ika-daigaku Zasshi 8:7-17.

2233. Kawasaki, C., T. Kishi, and T. Nishihara. 1970. Relation between thiamine and pyridoxine on Saccharomyces carlsbergensis 4228. X. Indirect inhibition of biosynthesis of nicotinic acid by thiamine. Bitamin 41(2):107-112.

2234. Kawashima, K. 1948. Method of quantitative determination of nicotinic acid in animal and vegetable tissues. Kitasato Arch. Exp. Med. 21:109-112.

2235. Kawashima, M. 1954. Synthesizing activity of pancreatic lipase. I. Influence of bile acids and amino acids. II. Influence of vitamins and antibiotics. Hiroshima J. Med. 3:145-152.

2236. Kawashima, T. 1963. Cytochemical studies on ascites tumor. II. Effects of nitrogen mustard N-oxide, colchicine, sarkomycin, and mitomycin C on oxidative enzymes in Ehrlich ascites tumor cells. Okayama Igakkai Zasshi 75(1,2,3):189-199.

2237. Kazantsev, A. P. 1963. Influence of some vitamins on skin vessel resistance in scarlet fever patients. Vopr. Pitaniya 22(4): 56-58.

2238. Kedra, M., M. Markiewicz, H. Miturzynska, and Z. Stazka. 1964. The effect of nicotinic acidoon blood lipids, especially cholesterol in atheromatic patients. Pol. Tyg. Lek. 19(37): 1937-1400.

2239. Keining, E., and F. Oldach. 1941. Results with nicotinamide in the treatment of erythema multiforme. Dermatol. Wochschr. 112:285-293.

2240. Kelada, F. S., G. A. Abdel-Tawab, M. H. Moustafa, and A. A. Konbar. 1972. Comparative studies on the in vivo effects of tartar emetic, vitamin B6, and the chelating agent 2,3-dimercaptopropanol (BAL) on the functional capacity of the tryptophan-niacin pathway in patients with schistosomiasis. Metab. Clin. Exp. 21(12):1105-1112.

2241. Kel'giubaeva, L. V. 1961. Coamide in the treatment of eye diseases. Materialy II-oi (Vtoroi) Vses. Konf. Oftal'mologov, Tbilisi, Resp. Nauchn. Obshchestvo Oftal'mologov Gruz. S.S.R., 303-304.

2242. Keller, E. B., Jr. 1942. Biotin and skin sensitivity. J. Allergy 14:87-88.

2243. Keller, J., M. Liersch, and H. Grunicke. 1971. Studies on the biosynthesis of NAD from nicotinamide and on the intracellular pyridine nucleotide cycle in isolated perfused rat liver. Eur. J. Biochem. 22(2):263-270.

2244. Kelley, M. T., R. T. Aexel, B. L. Herndon, and H. Nicholas. 1969. Biosynthesis of squalene and cholesterol by cell-free extracts of adult rat brain. J. Lipid Res. 10(2):166-174.

2245. Kelsay, J., L. T. Miller, and H. Linkswiler. 1968. Effect of protein intake on the excretion of quinolinic acid and niacin metabolites by men during vitamin B6 depletion. J. Nutr. 94(1):27-31.

2246. Kenawy, M. R., and G. Barsoum. 1944. The effect of nicotinic acid on the circulation. J. Roy. Egypt. Med. Assoc. 28:43-49.

2247. Kende, H. 1960. Biosynthesis and significance of trigonelline in Coffea arabica. Ber. Schweiz. Botan. Ges. 70:232-267.

2248. Kendrick, J. L., and B. M. Watts. 1969. Nicotinamide and nicotinic acid in color preservation of fresh meat. J. Food Sci. 34(3):292-294.

2249. Kennedy, B. L., and Ellis. 1969. Dissociation of catechol amine-induced calorigenesis from lipolysis and glycogenolysis in intact animals. J. Pharmacol. Exp. Ther. 168(1):137-145.

2250. Kennedy, T. S., and F. J. Ley. 1971. Combined effect of gamma radiation and cooking on the nutritional value of fish. J. Sci. Food Agr. 22(3):146-148.

2251. Kent-Jones, D. W., and M. Melklejohn. 1944. Some experiences with microbiological assays of riboflavin, nicotinic acid and other nutrient factors. Analyst 69:330-336.

2252. Kent-Jones, D. W., A. J. Amos, and G. B. Thackray. 1958. Vitamin contents of animal feedingstuffs. Analyst 83:479-480.

2253. Kepp, R. K. 1942. Treatment of X-ray sickness with nicotinamide. Med. Klin. 38:1070-1072.

2254. Keresztesy, J. C., D. Laszlo, and C. Leuchtenberger. 1946. Neutralization of inhibition of tumor growth. Cancer Res. 6:128-130.

2255. Kernen, R., and R. Brun. 1953. Experiments on transpiration. Dermatologica 106:1-13.

2256. Kerpel, S., and P. Laudat. 1967. Effect of nicotinic acid and vitamin D2 on rat adipose tissue lipases in vivo. C. R. Acad. Sci., Ser. D (Paris) 265(1):52-54.

2257. Kershaw, P. W. 1967. Blood thiamine and nicotinic acid levels in alcoholism and confusional states. Brit. J. Psychiat. 113 (497):387-393.

2258. Keys, A., and A. F. Henschel. 1941. High vitamin supplementation (B1, nicotinic acid and C) and the response to intensive exercise in U.S. Army infantrymen. Amer. J. Physiol. 133:350-351.

2259. Keys, A., A. Henschel, H. L. Taylor, O. Mickelsen, and J. Brozek. 1945. Experimental studies on man with a restricted intake of the B vitamins. Am. J. Physiol. 144(1):5-42.

2260. Khachatryan, S. S., and R. G. Avetisyan. 1972. Content of vitamin B in table grapes and hybrid grape seedlings. Prikl. Biokhim. Mikrobiol. 8(1):117-121.

2261. Khaes, S. I. 1954. Changes in blood sugar and glycogen after dosage with insulin or adrenaline along with nicotinic acid. Farmakol. i.Toksikol. 17(4):58-59.

2262. Khaes, S. I. 1955. Mechanism of action of nicotinic acid. Voprosy Pitaniya 14(2):13-16.

2263. Khaes, S. I. 1959. Physiological mechanism of the activity of nicotinic acid. Vitamins (Akad. Nauk Ukrainsk. S.S.R., Kiev) 4:144-147.

2264. Khakimov, K. K., M. A. Azozov, K. M. Kantsepol'skaya, and A. D. Khamraev. 1969. Determination of the structure of complexes of cobalt and manganese with N,N-diethylnicotinamide by an infrared spectroscopic method. Zh. Strukt. Khim. 10(6): 1036-1040.

2265. Khaimuradov, A. G. 1963. Changes in the content of nicotinamide adenine dinucleotides in the tissues of rats and pigeons on introduction of beta-picoline. Ukr. Biokhim. Zh. 35(3):401-409.

2266. Khaimuradov, A. G. 1965. Some data on the metabolism and utilization of beta-picoline in the synthesis of coenzymes in various animals. Sb. Rab. Molodykh Uchen. Aspir. Sel. Khoz. 1:461-462.

2267. Khaimuradov, A. G., and S. I. Shushevich. 1970. Biochemical evolution of pyridine coenzymes. Vitaminy 5:29-46.

2268. Khaimuradov, A. G., R. V. Chagovets, and G. V. Donchenko. 1969. Effect of 3-methylpyridine on the pyridine coenzymes and ubiquinone content in tissues of normal rats and rats with niacin-avitaminosis. Vop. Pitan. 28(3):40-43.

2269. Khaimuradov, A. G., S. I. Shushevich, and R. V. Chagovets. 1970. Separation and identification of nicotinic acid metabolism products in rat liver. Ukr. Biokhim. Zh. 42(6):779-785.

2270. Khaimuradov, A. G., S. I. Shushevich, and R. V. Chagovets. 1971. NAD biosynthesis in rat liver under the effect of surplus nicotinic acid. Ukr. Biokhim. Zh. 43(2):204-209.

2271. Khaimuradov, A. H., S. I. Shushevich, and A. I. Fomenko. 1971. Formation of nicotinamide from nicotinic acid in rat liver. Ukr. Biokhim. Zh. 43(5):566-571.

2272. Khaimuradov, A. G., S. I. Shushevich, and A. I. Fomenko. 1972. Synthesis of nicotinamide adenine dinucleotide phosphate and its regulation in rat tissues on administration of nicotinic acid. Ukr. Biokhim. Zh. 44(3):275-282.

2273. Khaimuradov, A. G., R. V. Chagovets, V. N. Mironova, and S. I. Shushevich. 1969. Role of nicotinic acid and chloramphenicol in the synthesis of pyridine coenzymes in rat liver. Ukr. Biokhim. Zh. 41(1):47-51.

2274. Khaimuradov, A. G., R. V. Chagovets, S. I. Shushevich, and A. I. Fomenko. 1970. Activation of the rat liver NADase following administration of NAD biosynthesis precursors. Vop. Pitan. 29(6):7013.

2275. Khaimuradov, A. G., R. V. Chagovets, S. I. Shushevich, and G. F. Stepanova. 1971. Formation of nicotinuric acid as a means of regulating nicotinic acid metabolism in vivo in tissues. Dokl. Akad. Nauk. S.S.S.R. 200(4):993-995.

2276. Khaimuradov, A. G., R. V. Chagovets, S. I. Shushevich, I. S. Khazbievich, and T. I. Glushchenko. 1972. Conversions of 3-methylpyridine to biologically active derivatives and its compartmentation in rat liver. Biokhimiya 37(4):797-806.

2277. Khan, N. 1951. Cerebral malaria. Indian Med. Gaz. 86(3):91-94.

2278. Khanna, P., and S. C. Jain. 1972. Effect of nicotinic acid on growth and production of trigonelline by Trigonella foenum-graecum L. tissue cultures. Indian J. Exp. Biol. 10(3):248-249.

2279. Khil, G. N. 1968. Vitamin composition of the preparation Biovit. Pishch. Prom. (Kiev) 7:43-48.

2280. Khomyakov, V. G., N. A. Dzbanovskii, and L. D. Borkhi. 1966. Electrosynthesis of nicotinic acid from quinoline. Tr., Vses. Nauch. Issled. Inst. Khim. Reaktivov Osobo Chist. Khim. Veshchestv. 29:304-311.

2281. Khusainova, G. K., and K. S. Daribaeva. 1972. Effect of illumination and nicotinamide treatment on content of growth substances in wheat shoots. Izv. Akad. Nauk. Kaz. S.S.R. Ser. Biol. 2:20-23.

2282. Khusanov, K. K. 1954. Treatment of some dermatoses by intramuscular injection of nicotinic acid. Vestnik. Venerol. i Dermatol. (6):8-11.

2283. Kies, C., and H. M. Fox. 1972. Interrelationships of leucine with lysine, tryptophan, and niacin as they influence protein value of cereal grains for humans. Cereal Chem. 49(2):223-231.

2284. Kik, M. C. 1955. Influence of processing on nutritive value of milled rice. J. Agr. Food Chem. 3:600-603.

2285. Kik, M. C., and F. B. Van Landingham. 1943. Riboflavin in products of commercial rice milling and thiamin and riboflavin in rice varieties. The influence of processing on the thiamin, riboflavin, and niacin content of rice. Cereal Chem. 20:563-569, 569-572.

2286. Kikkawa, T. 1971. Prognostic observation of chloroquine retinopathy. Ophthalmology (Tokyo) 13:726-736.

2287. Kilburn, J. O., et al. 1968. Reagent-impregnated paper strips for detection of niacin. Am. J. Clin. Path. 50:530-532.

2288. Kim, H. C. 1962. Effect of ginseng and niacin on lipid metabolism of rabbits fed cholesterol. Korea J. Med. 5:21-48.

2289. Kimmerling, H. W. 1962. Concepts, theory and treatment of atherosclerosis. J. Am. Geriat. Soc. 10:865-878.

2290. Kimura, K. 1960. Biosynthesis of pyridine nucleotide by human erythrocytes in vitro. Nagoya J. Med. Sci. 23:119-135.

2291. Kinetzel, H. W., and G. K. Hinkel. 1969. Nikethamide effect on serum bilirubin level of prematurely born infants. Monatsschr. Kinderheilk. 117(3):84-87.

2292. King, D. S. 1950. Tuberculosis. New Eng. J. Med. 243:530-536, 565-572.

2293. King, J. D. 1940. Vincent's disease treated with nicotinic acid. Lancet II:32-35.

2294. King, J. D. 1943. Nutritional and other factors in "trench mouth" with special reference to the nicotinic acid component of the vitamin B2 complex. Brit. Dental J. 74:113-122.

2295. Kinsey, V. E., E. Camacho, G. A. Cavanaugh, M. Constant, and D. A. McGinty. 1955. Dependence of intraocular pressure-lowering effect of acetazoleamide on salt. Arch. Ophthalmol. (Chicago) 53:680-685.

2296. Kirakosova, A. S. 1967. Biosynthesis of nicotinic acid in rhesus macaque monkeys species. Vop. Pitan. 26(4):21-23.

2297. Kirchner, J. 1966. Metabolism of nicotinamide. Dissertation Abstr. 26(8):4212-4213.

2298. Kirk, J. E. 1957. Enzyme activities and coenzyme concentration of human arterial tissue and their relation to age. Congr. Intern. Assoc. Gerontol., 4th, Merano, Italy 1:288-291.

2299. Kirk, J. E., and M. Chieffi. 1950. Vitamin studies in middle-aged and old individuals. IV. Clinical studies in hypo-vitaminemia B1. J. Gerontol. 5(3):236-240.

2300. Kiroshka, V. S. 1972. Nucleic acid level in tissues during the chemotherapy of experimental tuberculosis. Sovrem. Vop. Tuberk. 273-277.

2301. Kiseleva, L. N., and G. K. Romanenko. 1966. Changes in the blood coagulation and anticoagulation systems from the effects of nicotinic acid. Klin. Med. 44(1):48-50.

2302. Kitulescu, I., and V. Baluta. 1960. Effect of nicotinamide on the production of acetylphosphate by normal and cancerous blood. Acad. Rep. Populare Romine, Inst. Biochim. Studii Cercetari Biochim. 3(1):53-58.

2303. Kitulescu, I., and V. Baluta. 1960. Influence of glucose and nicotinamide on the capacity of synthesis of acetylphosphate. Rev. Sci. Med. (Bucur.) 5:57-60.

2304. Klizes, G., and C. A. Elvehjem. 1944. Vitamin content of prepared cereal foods. J. Am. Med. Assoc. 126(2):100-101.

2305. Klatzkin, C., F. W. Norris, and F. Wokes. 1949. The chemical estimation of nicotinic acid, using p-aminopropiophenone. Analyst 74(881):447-454.

2306. Klaudianos, S. 1972. Slow-release alginate tablets. Effect of technological factors on the release of active material. Pharm. Ind. 34(12):976-982.

2307. Klaushofer, H. 1957. Vitamin contents of Austrian beers. IV. Nicotinic acid contents. Mitt. Veruchssta. Gaerungsgewerbe Inst. Angew. Mikrobiol. 11:56-58.

2308. Klebanov, B. M. 1963. Pharmacological studies on the preparation "nicatol." Farm. Zh. (Kiev) 18:48-51.

2309. Klebanov, B. M. 1968. Effect of some antiatheromatous substances on tissue respiration of the vascular wall in normal rabbits and those with atherosclerosis. Farmakol. Toksikol. (Kiev) (4):53-56.

2310. Kleber, H. D., and R. W. Manthei. 1961. Influence of nicotinic acid and nicotinamide on insulin hypoglycemia. Proc. Soc. Exp. Biol. Med. 107:975-977.

2311. Kleiber, H. D., and R. W. Manthei. 1961. Influence of nicotinic acid and nicotinamide on insulin hypoglycemia. Proc. Soc. Exptl. Biol. Med. 107:975-977.

2312. Klein, E. E. 1952. Oxidative deamination of L-glutamic acid in brain homogenates. Soobshcheniya Akad. Nauk Gruzin. S.S.R. 13:273-280.

2313. Klein, J. R., W. A. Perlzweig, and P. Handler. 1942. Determination of nicotinic acid in blood cells and plasma. J. Biol. Chem. 145:27-34.

2314. Kleinschmidt, W. J., D. H. Holmes, and O. K. Behrens. 1956. Vitamin content of purified typhus rickettsiae, tobacco mosaic virus, and celiphage T6. Biochim. Biophys. Acta 22:277-283.

2315. Kleinwichs, C. J. 1964. Antiseptic lotion for the treatment of scalp affections. Fr. Pat. M3203.

2316. Kleinzeller, A., and M. Kuenstlinger. 1951. A single medium applicable to the microbiological assay of several vitamins of the B group. Chem. Listy 45:268-272.

2317. Kligler, I. J., and N. Grossowicz. 1941. The function of nicotinic acid in bacterial metabolism. J. Bact. 42(2):173-192.

2318. Kline, O. L. 1944. Report on (the determination of) vitamin B1. J. Assoc. Official Agr. Chem. 27:534-537.

2319. Kline, O. L., C. D. Tolle, and E. M. Nelson. 1938. Basal diets for vitamin B1 determination. Science 88:508.

2320. Klinskaya, T. P. 1962. Effect of adrenaline and nicotinic acid on skin permeability and diffusion properties of lipase. Nauchn. Zap Uzhgorodsk. Univ. 47:154-156.

2321. Kloster, J. H. 1961. Long-term treatment of hypercholesterolemia with nicotinic acid. Ugeskr. Laeg. 123:1169-1171.

2322. Klotz, L., and W. Poethke. 1964a. Separation and determination of vitamin B complex by means of synthetic ion-exchange resins. II. Studies on vitamin B6, nicotinamide and panthenol. Pharm. Zentralhalle 103:1-9.

2323. Klotz, L., and W. Poethke. 1964b. Separation and estimation of vitamins of the B-complex with synthetic ion-exchange resins. 4. Separation of the B-complex into its components. Pharm. Zentralhalle 103:255-260.

2324. Klumpp, E. 1961. Milk aid. Ger. Pat. 1,214,519.

2325. Knizshko, P. O., A. I. Zakin, and V. A. Grizo. 1956. Microcrystalline reactions for nicotinic acid, nikethamide, quinacrine, and procaine. Nekotorye Voprosy Farmatsii, Sbornik Nauch. Trudov. Vyssh. Farm. Ucheb. Zavednii Ukr. S.S.R. 66-68.

2326. Knox, W. E., and W. I. Grossman. 1946. A new metabolite of nicotinamide. J. Biol. Chem. 166(1):391-392.

2327. Ko, J. 1965. A histopathological study on peripheral nervous tissues of experimental deficiences of thiamine, riboflavine and niacin. Bitamin 31(1):53-64.

2328. Koch, R. 1950. Influence of vitamins B1 and B2 upon the glycogen content of rat liver, also a comparison with the action of ascorbic acid, niacinamide, and pantothenic acid. Intern. Z. Vitaminforsch. 22:136-145.

2329. Koch, R. 1963. The protective action of nicotinamide. In: 1st Scientific meeting of the Association of Radiobiolotists of the Euratom Countries, Rapallo, Italy, 1961. Int. J. Radiation Biol. 6(4):400.

2330. Koch, R., and J. Braeutigam. 1950. The influence of nicotinamide on glycogen formation and postmortem glycogenolysis. Klin. Wochschr. 28:308-310.

2331. Koch, R., and S. Klemm. 1962. On the problem of radiation protection with nicotinamide. Nuclearmedizin 2:272-276.

2332. Koch, R., and I. Seiter. 1961. Effect of nicotinamide on the sensitivity to radiation of tumor cells and of x-ray whole body-irradiated mice. Naturwissenschaften 48:626-627.

2333. Koch, R., and I. Seiter. 1964. Chemical influence on irradiation sensitivity of various experimental neoplasms. Arzneimittel-Forsch. 19(4):1018-1021.

2334. Koch, W. 1947. A rapid method for the evaluation of microbiologic tests. Am. J. Clin. Path. 17:897-903.

2335. Kochakian, D. C., V. Raut, and D. M. Nall. 1957. Metabolism of testosterone by guinea pig liver and kidney homogenates. Am. J. Physiol. 189(1):78-82.

2336. Kochhar, B. D. 1940. The quantitative estimation of nicotinic acid in blood and other body fluids. Indian J. Med. Res. 28(2):385-396.

2337. Kochhar, B. D. 1941a. Nicotinic acid in blood. Indian J. Med. Res. 29:133-136.

2338. Kochhar, B. D. 1941b. Nicotinic acid in blood and in urine. Indian J. Med. Res. 29:341-350.

2339. Kochhar, B. D. 1941c. Nicotinic acid in blood cells. Ann. Biochem. Expti. Med. 1(4):285-292.

2340. Koda, A., H. Azuma, M. Hiramatsu, and Y. Yoshida. 1971. Effect of nicotinic acid derivatives on cerebral blood circulation. Oyo Yakuri 5(2):239-246.

2341. Kodama, R. 1957. Microbiological determination of niacinamide. Bull. Agr. Chem. Soc. Japan 21:173-176.

2342. Kodicek, E. 1940. Estimation of nicotinic acid in animal tissues, blood and certain foodstuffs. I. Method. Biochem. J. 34(5):712-723.

2343. Kodicek, E. 1942. Minimal requirements of nicotinic acid. Lancet 242:380-81.

2344. Kodicek, E. 1960. The availability of bound nicotinic acid to the rat. 2. The effect of treating maize and other materials with sodium hydroxide. Brit. J. Nutr. 14:13-24.

* 2345. Kodicek, E. 1962. Nicotinic acid and the pellagra problem. Bibliotheca "Nutr. Dieta" 4(4):109-127.

2346. Kodicek, E. 1966. Antivitamins of nicotinic acid and of biotin. In: Proceedings of the Symposium of the Institute of Nutrition Research: Antivitamins, 19-21 Oct. 1964. Bibl. Nutr. Dieta 8:159.

2347. Kodicek, E., and D. K. Chandhuri. 1949. A fluorometric method for the determination of the nicotinamide. Bull. Soc. Chim. Biol. 31(2):249-256.

2348. Kodicek, E., and C. R. Pepper. 1948a. A critical study of factors influencing the microbiological assay of nicotinic acid. J. Gen. Microbiol. 2:292-305.

2349. Kodicek, E., and C. R. Pepper. 1948b. The microbiological estimation of nicotinic acid and comparison with a chemical method. J. Gen. Microbiol. 2:306-314.

2350. Kodicek, E., and Y. L. Wang. 1941. New method for the estimation of Trigonelline in urine and foodstuffs. Nature (London) 148(3740):23-24.

2351. Kodicek, E., R. Braude, Konsk, and K. G. Mitchell. 1959. The availability to pigs of nicotinic acid in tortilla baked from maize treated with lime-water. Brit. J. Nutr. 13:363-384.

2352. Koethe, M., and G. A. Schoger. 1954. Influence of nicotinic acid on peripheral circulation. Deut. Med. Wochschr. 32:503-505.

2353. Kohn, H. I. 1938. The concentration of coenzyme-like substance in blood following the administration of nicotinic acid to normal individuals and pellagrins. Biochem. J. 32(12): 2075-2083.

2354. Kohn, H. I., and J. R. Klein. 1939. The synthesis of cozymase and of factor V from nicotinic acid by the human erythrocyte in vitro and in vivo. J. Biol. Chem. 130(1):1-11.

2355. Kohn, H. I., and J. R. Klein. 1940. Synthesis of factor V (pyridine nucleotides) from nicotinic acid in vitro by human erythrocytes. J. Biol. Chem. 135(2):685-689.

2356. Kohn, R. N., and M. Montes. 1969. Hepatic fibrosis following long-acting nicotinic acid therapy: a case report. Am. J. Med. Sci. 258:94-99.

2357. Kojima, H., Y. Matsuya, H. Ozawa, M. Konno, and T. Uemura. 1958. Microbiological assay of vitamins and amino acids by the pulp disc method. I. Assay of several B vitamins. 1. Nippon Nogei Kagaku Kaishi 32:33-37.

2358. Kokovikhina, K. I. 1946. Spectrophotometric and colorimetric determination of nicotinic acid and its derivatives in urine. Biokhimiya 11:63-70.

2359. Kolaszynski, J. 1965. Effect of reserpine and nicotinamide on the cytological and hisothcemical patterns of the anterior pituitary lobe in rats. Endokrynol. Polska 16(5):475-483.

2360. Kolesnikova, I. S., and M. D. Shkol'nikova. 1959. Characteristics of unconditioned and conditioned reflex reactions to nicotinic acid in tuberculous patients. Probl. Tuberk. 37(5):83-88.

2361. Kolla, V. E., and Z. G. Zubova. 1966. The anti-ulcer action of the 4-antipyrilamide nicotinic acid (nikofezon). Sb. Nauch. Tr. Perm. Med. Inst. 63:32-36.

2362. Kon, T. Y., and K. R. Bharucha. 1967. Stable orally active heparinoid complexes. U.S. Pat. 3,506,642.

2363. Kondra, P. A., J. L. Sell, and J. A. McKirdy. 1968. Effect of thalidomide on embryonic and post-embryonic development of the chick. Can J. Anim. Sci. 48(3):285-292.

2364. Kondrashova, A. A., L. O. Shnaidman, S. V. Balatsenko, and E. S. Zhdanovich. 1960. Nicotinic acid. U.S.S.R. Pat. 132,225.

2365. Konno, K., R. Kurzmann, K. T. Bird, and A. Sbarra. 1958. Differentiation of human tubercle bacilli from atypical acid-fast bacilli. I. Niacin production of human tubercle bacilli and atypical acid-fast bacilli. Am. Rev. Tuberc. Pulm. Dis. 77:669-674.

2366. Kono, T. 1959. Absorption of calcium chloride and magnesium sulfate from rabbit intestine. Nippon Yakurigaku Zasshi 55:1089-1114.

2367. Kontsevaya, N. G., A. A. Konstantinov, S. E. Shapiro, and G. S. Koval'skii. 1970. Protein metabolism and vitamin balance in persons with Far East hemorrhagic fever with kidney syndrome. Vop. Med. Khim. 16(4):376-381.

2368. Konttinen, K., E. Oyra, and H. Suomalainen. 1967. Influence of short-term alcohol consumption on the excretion of some components of the vitamin B group in the urine of rats. Ann. Med. Exp. Biol. Fenn. 45(1):63-67.

2369. Kooij, R. 1964. Sardoidosis or leprosy? Brit. J. Dermatol. 76(5):203-210.

2370. Kopidakis, M., and E. J. Lazaro. 1966. Role of the B-complex vitamins on intestinal activity in dogs. Can. J. Surg. 9(2): 184-192.

2371. Kormano, M., M. Harkonen, and E. Kontinen. 1964. Effect of experimental cryptorchidism on the histochemically demonstrable dehydrogenases of the rat testis. Endocrinology 74(1):44-51.

2372. Kornfeld, M., L. M. Geller, D. Cowen, A. Wolf, and F. Altmann. 1970. Pathologic changes in the inner ear of audiogenic seizure-susceptible mice treated with 6-aminonicotinamide. Exp. Neurol. 26(1):17-35.

2373. Korotchenko, N. I., and A. A. Balabanova. 1961. Vitamins in fodder yeasts. Gidvoiz. i Lesokhim. Prom. 14(4):3-4.

2374. Korycki, S. 1970. Concentration of nicotinic acid in blood serum of cow in different stages of the reproductive cycle. Pol. Arch. Wet. 13(3):67-74.

2375. Kowalewski, K., and V. Conrad. 1950. Action of nicotinic acid on cutaneous temperature and gastric secretion. Acta Gastro-Enterol. Belgica 13(2):156-160.

2376. Koser, S. A., and G. J. Kasai. 1947. The effect of large amounts of nicotinic acid and nicotinamide on bacterial growth. J. Bact. 53:743-753.

2377. Koser, S. A., and G. J. Kasai. 1948. The growth response of Leuconostoc to nicotinic acid, nicotinamide, and some related compounds. J. Infect. Dis. 83(3):271-278.

2378. Kost, A. N., P. B. Terent'ev, L. A. Golovleva, and A. A. Stolyarchuk. 1967. The synthesis and properties of substituted pyridine-carboxylic acids. Khim.-Farm. Zh. 1(5):3-10.

2379. Kotake, Y. 1949. Biochemistry of kynurenine. The formation of ommochrome, kynurenic acid, xanthurenic acid, nicotinic acid, anthranilic acid, and 3- and 5-hydroxyanthranilic acid, and their physiological significances. J. Japan. Biochem. Soc. 21:155-164.

2380. Kotake, Y., M. Tsuji, and N. Hasegawa. 1960. Fluorometric determination of nicotinamide and N'-methylnicotinamide and their urinary excretion in man. J. Vitamin 6:271-277.

2381. Kotaki, A., T. Sakurai, A. Kobayashi, and K. Yagi. 1968. Myo-inositol. IV. Effect of myoinositol on the cholesterol metabolism of rats with experimental fatty liver. J. Vitaminol. 14(2):87-94.

2382. Kotaki, A., K. Kato, T. Sakurai, O. Terada, and K. Yagi. 1969a. Riboflavine tetranicotinate. III. Incorporation of the nicotinic acid moiety of orally administered riboflavine tetranicotinate into blood and tissue NAD. Bitamin 39(6):382-385.

2383. Kotaki, A., K. Kato, T. Sakurai, O. Terada, and K. Yagi. 1969b. Studies on riboflavin-tetranicotinate: VIII. Incorporation of the nicotinic acid moiety of orally administered riboflavin-tetranicotinate into blood stream and tissue NAD. Vitamins (Kyoto) 39(6):382-385.

2384. Kotschevar, L. H. 1955. B-vitamin retention in frozen meat. J. Am. Dietet. Assoc. 31:589-596.

2385. Kottke, B. A. 1965. Cholesterol metabolism as modified by nicotinic acid and its analogs, triparanol, and dietary fat: effects on cholesterol synthesis, bile acid formation, and atherosclerosis. Dissertation Abstr. 25(7):4187-4188.

2386. Kottke, B. A., J. L. Bollman, and J. L. Juergens. 1962a. Comparison of effect of nicotinic acid on two different types of hypercholesteremia. Circulat. Res. 11:108-114.

2387. Kottke, B. A., J. L. Bollman, and J. L. Juergens. 1962b. A syndrome of dehydration produced by hypocholesteremic agents. Proc. Mayo Clin. 37:1-6.

2388. Kowalewski, K., and V. Conard. 1950. Effect of nicotinic acid on skin temperature and gastric secretion. Acta Gastro-Enterol. Belg. 13:156-160.

2389. Kowaloff, I. 1941. Lead encephalopathy. Two cases with a hypothesis of the biochemical pathogenesis. Am. J. Dis. Children 61:547-556.

2390. Koyama, Y., and H. Iizuka. 1960. Royal jelly. I. The vitamin content in royal jelly. J. Japan. Soc. Food Nutrition 13(2): 50-52.

2391. Koyanagi, T., and S. Hareyama. 1961. Test dose experiments of thamine and riboflavin on undernourished children. J. Vitaminol., Japan 7:137-140.

2392. Koyanagi, T., and S. Yamada. 1967. Effect of content of niacin and protein in diet on the gastric acidity and vitamin B12 binding capacity in rats. Vitamins (Kyoto) 36(2):126-129.

2393. Koyanagi, T., and S. Yamada. 1968. Effects of dietary niacin concentration and protein content on gastric acidity and vitamin B binding capacity of gastric mucosa in rats. Tohoku J. Exp. Med. 94(1):63-68.

2394. Koyanagi, T., J. Suwa, and Ishiguro. 1968. Effect of riboflavine, pyridoxine, and other vitamins on the urinary corticoids and tryptophan metabolism inc hildren. Tohoku J. Exp. Med. 94:275-279.

2395. Koyanagi, T., S. Hareyama, R. Kikuchi, T. Takanohashi, K. Oikawa, and N. Akazawa. 1969. Effect of administration of thiamine, riboflavin, ascorbic acid and vitamin A to students on their pantothenic acid contents in serum and urine. Tohoku J. Exp. Med. 98:357-362.

2396. Krakoff, I. H., C. R. Lacon, and D. A. Karnofsky. 1960. Teratogenic, uricogenic and protective effects of nicotinamide antagonists and substitutes in the chick embryo. Fed. Proc. 19(1 Pt. 1): 411.

2397. Krammer, F. 1963. The significance of percutaneous treatment in the course of the therapy of rheumatic diseases. Wien. Med. Wschr. 113:134-136.

2398. Krane, S. M., and R. J. Crane. 1961. Alterations in pyridine nucleotides of dividing marine eggs. Ann. Symp. Soc. Gen. Physiologists, 8th., Woods Hole, Mass. 157-166.

2399. Krasnova, N. S. 1961a. The content of di- and triphosphopyridine nucleotides in the blood and of N'-methylnicotinamide in the urine in infectious hepatitis. Sovet. Med. 25(11): 85-87.

2400. Krasnova, N. S. 1961b. Relation of nicotinic acid metabolism to some therapeutic methods in Botkin's disease. Zdravookhr. Beloruss. 7:27-30.

2401. Krasnova, N. S. 1963. Nicotinic acid metabolism in epidemic hepatitis. 1963. Materialy 2-go (Vtorogo) Soveshch. po Klinich. Biokhim. Infekts. Boleznei i Simpoziuma po Klinich. Biokhim. Boleznei Pecheni, Riga, pp. 171-172.

2402. Kraupp, O. 1961. Cholesterol metabolism during atherosclerosis and pharmacodynamic influences. Fette, Seifen, Anstrichmittel 63:819-827.

2403. Kraupp, O., and E. Schnetz. 1959a. Influence of heparin on the hypocholesterolemic action of nicotinic acid. Arch. Exptl. Pathol. Pharmakol. 235:103-112.

2404. Kraupp, O., and E. Schnetz. 1959b. Influence of heparin on the hypocholesterolemic effect of nicotinic acid. Arch. Exptl. Pathol. Pharmakol. 236:75-76.

2405. Kraupp, O., and E. Schnetz. 1961. The effect of nicotinic acid and other vasodilatory substances in the elimination of Congo red. Naunyn Schmiedeberg Arch. Exp. Path. 240:408-421.

2406. Kraupp, O., E. Schentz, and H. Stormann. 1958. Investigations of the mechanism of the hypocholesteremic action of nicotinic acid. Zeitschr. ges. Exptl. Med. 129(6():601-614.

2407. Krause, E. 1969. Occurrence of estrogenic substances in forage plants. Arch. Exp. Veterinaermed. 23(3):481-487.

2408. Krehl, W. A. 1949. Niacin in amino acid metabolism. Vitamins and Hormones 7:111-146.

2409. Krehl, W. A., and G. R. Cowgill. 1955. Nutrient content of cane- and beet-sugar products. Food Res. 20:449-468.

2410. Krehl, W. A., and C. A. Elvehjem. 1945. The importance of "folic acid" in rations low in nicotinic acid. J. Biol. Chem. 158(1): 173-179.

2411. Krehl, W. A., J. De La Huerga, and C. A. Elvehjem. 1946. Tryptophane studies. 1. The effect of niacin on the utilization of tryptophane. J. Biol. Chem. 164(2):551-561.

2412. Krehl, W. A., P. S. Sarma, and C. A. Elvehjem. 1946. The effect of protein on the nicotinic acid and tryptophane requirement of the growing rat. J. Biol. Chem. 162:403-411.

2413. Krehl, W. A., F. M. Strong, and C. A. Elvehjem. 1943. Determination of nicotinic acid. Modifications in the microbiological method. Indust. Eng. Chem. Analyt. Ed. 15(7):471-475.

2414. Krehl, W. A., L. J. Teply, and C. A. Elvehjem. 1945. Effect of corn grits on nicotinic acid requirements of the dog. Proc. Soc. Exptl. Biol. Med. 58:334-337.

2415. Krewson, C. F. 1943. A method for the determination of nicotinamide. Am. J. Pharm. 115:122-125.

2416. Krewson, C. F., and J. F. Couch. 1943. Hydrolysis of nicotinonitrile by ammonia. J. Am. Chem. Soc. 65:2256-2257.

2417. Kringstad, H., and T. Naess. 1938. Colorimetric determination of nicotinic acid and nicotinamide. Naturwissen. 26:709.

2418. Kringstad, H., and T. Naess. 1939. A colorimetric method for the estimation of nicotinic acid and its amide in foodstuffs. Z. Physiol. Chem. 260:108-118.

2419. Krishchuk, A. A. 1965. The therapeutic significance of vitamin B12 and nicotinic acid in cerebral atherosclerosis. Zdorov'ya (Kiev. 168-171.

2420. Krishnaswamy, K., and P. S. V. R. Murthy. 1970. Mental changes and platelet serotonin in pellagrins. Clin. Chim. Acta 27(2): 301-304.

2421. Kritchevsky, D. 1968. The use of pharmacologic agents in atherosclerosis therapy. Ann. N.Y. Acad. Sci. 149:1058-1068.

2422. Kritchevsky, D. 1971a. Lipid metabolism. Blood cholesterol-lowering agent. Drill's Pharmacol. Med., 4th Ed. 1315-1332.

2423. Kritchevsky, D. 1971b. Effect of nicotinic acid and its derivatives on cholesterol metabolism. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 541-556.

2424. Kritchevsky, D., and S. A. Tepper. 1962. Influence of nicotinic acid homologs on oxidation of cholesterol-26-C14 by rat liver mitochondria. Arch. Intern. Pharmacodyn. 138:349-353.

2425. Kritchevsky, D., and S. A. Tepper. 1964a. Oxidation of cholesterol-26-C14 by rat liver mitochondria: Effect of compounds related to nicotinic acid and nicotinamide. Arch. Int. Pharmacodyn. Therap. 147(3/4):564-568.

2426. Kritchevsky, D., and S. A. Tepper. 1964b. Influence of nicotinic, picolinic, and pyridine-3-sulfonic acids on cholesterol metabolism in the rat. J. Nutr. 82(1):157-161.

2427. Kritchevsky, D., M. W. Whitehouse, and E. Staple. 1960. Oxidation of cholesterol-26-C14 by rat liver mitochondria: Effect of nicotinic acid. J. Lipid Res. 1(2):154-158.

2428. Kritchevsky, D., M. Kitagawa, S. A. Tepper, and L. M. Davidson. 1971. Effect of nicotinic acid and its derivatives on oxidation of cholesterol by rat liver mitochondria. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 585-595.

2429. Krivoruchenko, I. V. 1965. Characteristics of lipid metabolism in essential hyperlipemia and xanthomatosis. Vopr. Pitaniya 24(1):60-66.

2430. Kroeger, I., H. Werchau, and H. Kroeger. 1966. The metabolism of pyridine nucleotides in the rat liver during carcinogenesis. Z. Krebsforsch. 68(2):156-163.

2431. Krolikowska-Prasal, I. 1967. Histochemical investigations of hydrolytic enzymes in the liver of the Syrian hamster (Mesocricetus auratus). Ann. Univ. Mariae Curie-Sklodowska, Sect. D 1966, 21:89-93.

2432. Kronberg, S. 1968. Infrared photography and nicotinic acid determination. Farm. Revy 67(21-22):481-484.

2433. Kronfeld, D. S., and F. Raggi. 1964. Nicotinamide coenzyme concentrations in liver of normal, starved and alloxan-diabetic rats. Biochem. J. 93(3):517-520.

2434. Kronfeld, D. S., and F. Raggi. 1966. Decreases in concentrations of the nicotinamide coenzymes in the livers of fasting pregnant sheep and of field cases of pregnancy toxaemia. Res. Vet. Sci. 7(4):499-503.

2435. Krulich, L. 1952. Influence of nicotinic acid on the circulation. Cas. Lek. Ces. 91:1401-1404.

2436. Krulich, L., J. Heller, and J. Stepan. 1955. Pharmacology of products of choline and nicotinic acid. Naunyn-Schmiedebergs Arch. Exptl. Pathol. Pharmakol. 226:328-334.

2437. Kubasta, M., V. Jezdinska, H. Vaverkova, J. Vrana, A. Zmeskal, and J. Niznik. 1970. Effect of nicotinic acid on steatosis of the liver. Ces. Gastroenterol. Vyz. 24:200-205.

2438. Kubasta, M., J. Niznik, P. Vrublovsky, A. Zmeskal, H. Vaverkova, and J. Vrana. 1970. Effect of nicotinic acid on serum lipids in patients with ischemic heart disease. Vnitr. Lek. 16(9):877-886.

2439. Kubo, A., H. Furukawa, A. Okamura, S. Yukita, and S. Sakuyama. 1960. Correlation of vitamin B complex in vivo with special reference to the relation of choline to thiamine, riboflavine, and nicotinic acid contents in the blood. Hirosaki Igaku 12(2):358-361.

2440. Kuchino, Y. 1971. Identification of tRNA methylase inhibitors in rat liver. Fukuoka Acta Med. 62(10):874-880.

2441. Kuchino, Y. and H. Endo. 1972. Nicotinamide and its methyltransferase as apparent inhibitors of tRNA methylase. J. Biochem. (Tokyo) 71(4):719-723.

2442. Kuck, H. 1954. Increase in blood flow in kidneys under the influence of nicotinic acid. Med. Klin. 49:371-374.

2443. Kuechmeister, H. 1947. Influence of nicotinamide on methanol poisoning in rats. Arch. Exptl. Path. Pharmakol. 204:555-557.

2444. Kuehnau, W. W. 1939. Retention of nicotinic acid in the body fluids of pellagra patients and healthy subjects. Klin. Wochschr. 18:1333-1334.

2445. Kuhns, K. 1950. Investigations on new vasodilatory substances (Preparation 7337 Ciba) as well as the nicotinic acid preparations Niconacid, Ronicol, and Trafuril. Helvetia Med. Acta 17(3):215-230.

2446. Kuipers, F. C. 1943. Cerebral impairment due to nicotinic acid amide deficiency. Nederland Tijdschr. Geneeskunde 87:929-934.

2447. Kulagin, V. K. 1966. Pathogenic principles of traumatic shock prophylaxis. Tr. Kishinev. Med. Inst. 26:25-33.

2448. Kulp, K., O. C. Golosinec, C. W. Shank, and W. B. Bradley. 1956. Current practices in bread enrichment. Nutritive content of enriched bread. J. Am. Dietet. Assoc. 32:331-334.

2449. Kulwick, R., L. Struglia, and P. B. Pearson. 1953. The effect of coprophagy on the excretion of B vitamins by the rabbit. J. Nutr. 49(4):639-645.

2450. Kumasaka, B. 1954. Quinoline dehydrogenase substrate specificity of various tetrabasic halogen-alkyl compounds of quinoline, nicotinic acid, and nicotinamide. Nichidai Igaku Zasshi 13:491-506.

2451. Kumsars, K., A. Velena, G. Duburs, J. Uldrikis, and A. Zidermane. 1971. Action of various 1,4-dihydropyridine and 1,6-dihydropyrimidine derivatives on the energy metabolism of normal and tumor cells. Biokhimiya 36(6):1204-1209.

2452. Kung, H.-F., and T. C. Stadtman. 1971. Nicotinic acid metabolism. VI. Purification and properties of alpha-methylene-glutarate mutase (B12-dependent) and methylitaconate isomerase. J. Biol. Chem. 246(10):3378-3388.

2453. Kunzman, G., and J. Stingl. 1970. Prophylaxis of thrombosis in cardiac insufficiency with Solvosal-Heparin. Med. Welt. 31/32: 1388-1390.

2454. Kupiecki, F. P., and N. B. Marshall. 1968. Effects of 5-methyl-pyrazole-3-carboxylic acid U-19425 and nicotinic acid on lipolysis in vitro and in vivo and on cyclic-3',5'-AMP phosphodiesterase. J. Pharmacol. Exp. Ther. 160(1):166-170.

2455. Kupiecki, F. P., and D. I. Schneider. 1970. Stimulation of lipolysis in adipose tissue in vitro by inhibitors of lipid mobilization. J. Lipid Res. 11(1):38-41.

2456. Kupka, E., and K. Neuhold. 1954. Effect of B vitamins on experimental diphtheria toxicosis in golden hamsters. Z. Vitamin-, Hormun-u. Fermentforsch. 6:406-421.

2457. Kuriyama, K. 1962. Effect of nicotine derivatives on brain metabolism in vitro. Kyoto Furitsu Ika Daigaku Zasshi 71: 185-189.

2458. Kuroda, T. 1955. The influence of various substances on the absorption of iron in the large intestine. Folia Pharmacol. Japon. 51:443-475.

2459. Kurskii, M. D., A. N. Fedorov, A. G. Khlamuradov, and V. T. Tugai. 1970. The effect of serotonin on the content of nicotinamide coenzymes in the brain and liver tissues of rabbits. Izv. Akad. Nauk. S.S.S.R. Ser. Biol. 6:921-925.

2460. Kurtar, M. K., and H. Daginstanli. 1962. The niacin test and its importance for the identification of tubercle bacilli of the human type. Beitr. Klin. Tuberk. 125:178-184.

2461. Kushnir, V. E. 1967. Use of nicatol in the treatment of patients with atherosclerosis. Vrech. Delo. (5):76-79.

2462. Kuss, E. 1966. Identification of the intermediate product in the biosynthesis of nicotinic acid from 3-hydroxyanthranilic acid. Hoppe Seyler's Z. Physiol. Chem. 345(2/3):195-196.

2463. Kuss, E. 1967. Identification of the acyclic intermediate of nicotinic acid biosynthesis. II. Synthesis of the diastereoisomers of epsilon-hydroxy-beta-carboxynorleucine. Hoppe-Seyler's Z. Physiol. Chem. 348(12):1589-1595.

2464. Kusui, K. 1931. Studies in comparative biochemistry. VIII. Bheavior of some heterocyclic compounds in the frog organism. J. Biochem. (Japan) 13:343-350.

2465. Kutschera, E. 1961. Clinical experiences with iodo-niacin. Klin. Mbl. Augenheilk 138:102-104.

2466. Kuzel, N. R., and F. W. Kavanagh. 1971. Automated system for analytical microbiology: II. Construction of system and evaluation of antibiotics and vitamins. J. Pharm. Sci. 60(5):767-773.

2467. Kuzhman, M. I. 1955. The effect of procaine on the activity of the cerebral dehydrogenase. Trudy Chkalov. Med. Inst. (4):65-73.

2468. Kuznetsov, L. S. 1965. Experimental alcoholic gastropathy. Arkhiv. Patol. 27(12):41-46.

2469. Kvam, D. C. 1965. Effect of beta-adrenergic blockade or nicotinic acid on norepinephrine-induced increases in plasma free fatty acids and total cholesterol in the dog. Life Sci. 4(4):479-485.

2470. Kvasnykov, Y. I., D. M. Isakova, V. I. Sudenko, and H. S. Yelisyeyeva. 1972. Vitamin synthesis by the yeast Candida tropicalis K-41 and variants obtained under the effect of mutagenic factors. Mikrobiol. Zh. (Kiev) 34(2):160-164.

2471. Kwon, C. K. 1965. The effects of various anticholesterol agents on fat metabolism in patients with atherosclerosis. II. The effects of niacin on hypercholesterolemia. Taehan Naekwahak Hoe Chapchi 8(5):291-294.

2472. Laakso, P. V., and J. R. Mellberg. 1963. Dietary fluoride and vitamin preparation. U.S. Pat. 3,306,824.

2473. Labadan, M. M. 1969. Effects of various treatments and additives on the feeding value of ipil-ipil leaf meal in poultry. Philipp. Agr. 53(7):392-401.

2474. Labbe, R. F., J. Nutter, M. L. Cowger, and L. D. Nielsen. 1970. Control of heme biosynthesis. Effect of nicotinamide adenine dinucleotide on the induction of delta-aminolevulinate synthetase. Biochem. Med. 3(6):465-474.

2475. Laboratorio Atral, Lim. 1960. Salts of antibiotics and vitamins. Brit. Pat. 852,334.

2476. Lachs, A. 1948. Treatment of pellagrous diarrhoea ("pellagra sine pellagra") with nicotinamide. Nord. Med. 39:1507-1509.

2477. Lafourcade, S. 1956. Determination of nicotinamide in Bordeaux wines. Inds. Aliment. et Agr. 11:779-786.

2478. Lagnado, J. R., and T. L. Sourkes. 1958. Further observations on the enzymatic reduction of tetrazolium salts by monoamines. Can. J. Biochem. Physiol. 36(6):587-594.

2479. Laguna, J. 1961. Nicotinic acid and cholesterolemia. Gac. Med. Mex. 91:1047-1049.

2480. Lagunas, R., P. McLean, and A. L. Greenbaum. 1970. The effect of raising the NAD+ content on the pathways of carbohydrate metabolism and lipogenesis in rat liver. European J. Biochem. 15:179-190.

2481. Lakin, K. M., A. P. Gavrilov, and A. I. Maiskii. 1968. Effect of some pyridine derivatives on the fibrinolytic activity of the blood. Teor. Klin. Vop. Probl. Svertyvaniya Krovi 108-111.

2482. Lal, S. 1972. Primary xanthoma tuberosum: A case report. Indian J. Dermatol. 17(2):45-46.

2483. Lamb, F. C., A. Pressley, and T. Zuch. 1947. Nutritive value of canned foods. XXI. Retention of nutrients during commercial production of various canned fruits and vegetables. Food Res. 12(4):273-287.

2484. Lamb, F. W. 1943. Direct quantitative determination of nicotinamide in vitamin mixtures. Indust. Engineer. Chem. Analyt. Ed. 15(5):352-355.

2485. Lami, G. 1940. Action of intradermal application of nicotinic acid, similar to that of histamine. Rass. Fisiopat. Clin. Terap. 12:43-46.

2486. Lammers, W., P. Siderius, and J. H. Gaarenstroom. 1950. Effect of nicotinic acid on the blood-sugar level. Acta Physiol. et Pharmacol. Neerland. 1:193-197.

2487. Lan, S. J., and L. M. Henderson. 1968. Uptake of nicotinic acid and nicotinamide by rat erythrocytes. J. Biol. Chem. 243(12):3388-3394.

2488. Landauer, W. 1948. Effect of nicotinamide and alpha-ketoglutaric acid on the teratogenic action of insulin. J. Exptl. Zool. 109:283-290.

2489. Landauer, W. 1957. Niacin antagonists and chick development. J. Exp. Zool. 136(3):509-530.

2490. Landauer, W., et al. 1964. Teratogenic risks of drug synergism. Nature (London) 203:527-528.

2491. Landauer, W., et al. 1972. Aspects of dimethyl sulfoxide as solvent for teratogens. Dev. Biol. 28:35-46.

2492. Landureau, J. C. 1969. Requirements of an insect cell line. (EPa strain). II. Water-soluble vitamins. Exp. Cell Res. 54(3):399-402.

2493. Lanfranchi, F. 1941. Action of hippurase on nicotinuric acid. Atti Accad. Italia, Rend. (7) 3:103-112.

2494. Lang, E., and J. Koehler. 1969. Effect of xanthinol nicotinate on heart and cirulation. Arzneim.-Forsch. 19(11):1870-1873.

2495. Lange, G. 1967. Different stimulation of the microsomal N- and P-hydroxylation of aniline and N-ethylaniline in rabbits. Naunyn-Schmiedebergs Arch. Pharmakol. E. 257(2):230-256.

2496. Lange, K., et al. 1963. A long term study of the effect of nicotinic acid medication on hypercholesteremia. Am. J. Med. Sci. 246:673-677.

2497. Lange, K., H. Kolbe, K. Keller, and H. Herken. 1970. The carbohydrate metabolism of the brain after inhibition of the pentose phosphate pathway by 6-aminonicotinamide. Hoppe-Seyler's Z. Physiol. Chem. 351(10):1241-1252.

2498. Langer, T., and R. I. Levy. 1971. Effect of nicotinic acid on the turnover of low density lipoproteins in Type II hyper-lipoproteinemia. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970, 641-647.

2499. Lapin, I. P. 1972. Interaction of kynurenine and its metabolites with tryptamine, serotonin and its precurosrs, and oxotremorine. Psychopharmacologia 26(3):237-247.

2500. Laquer, F. 1938. Vitamins of the B group according to the present status of research. Z. Vitaminforsch. 7:334-367.

2501. Lardy, H. A. 1948. Vitamins and carbohydrate metabolism. J. Chem. Educ. 25(5):262-267.

2502. Larina, V. S. 1966. The nicotinic acid treatment of patients with coronary atherosclerosis. In: Information on the 4th Volga conference of physiologists, pharmacologists, and biochemists, with the participation of morphologists and clinicians, 1966. Saratov. 2:52-53.

2503. La Rosa Bazalar, D. 1953. Effect of nicotinamide on the hyperglycaemia of alloxan diabetes. An. Fac. Farm. Bioquim., Lima 4:245-255.

2504. Larsh, J. E., Jr. 1952. The effect of a blacktongue-producing diet on experimental amebiasis in dogs. Am. J. Trop. Med. Hyg. 1(6):970-979.

2505. Lassers, B. W., et al. 1972. Effect of nicotinic acid on myocardial metabolism in man at rest and during exercise. J. Appl. Physiol. 33:72-80.

2506. Lassers, B. W., L. Wahlqvist, L. Kaijser, and L. A. Carlson. 1971. Relationship in man between plasma free fatty acids and myocardial metabolism of carbohydrate substrates. Lancet 2(7722):448-450.

2507. Laszt, L. 1941. Skin disease of adrenalectomized rats caused by lack of nicotinamide. Z. Vitaminforsch. 11:76-87.

2508. Latenko, Y. P., and E. F. Shamrai. 1970. The effect of galascorbin on some links in nitrogen metabolism in patients with infectious hepatitis (Botkin's disease). Vitam. Eksp. Klin. Resp. Mezhved. Sb. 2:183-188.

2509. Lattanzi, A. 1948. The influence of vitamin PP on the absorption of iron. Boll. Soc. Ital. Biol. Sper. 24:561-563.

2510. Lattanzi, A. 1949. Vitamins and iron metabolism. Intern. Z. Vitaminforsch. 21:307-312.

2511. Laubinger, G. 1968. The significance of Clofibratt in the treatment of defects of fat metabolism. Med. Kin. 63(4):139-142.

2512. Laug, E. P., A. Mikalis, H. M. Bolliner, and J. M. Dimitroff. 1963. Total diet study. Strontium-90 and cesium-137 content. J. Assoc. Offic. Agr. Chemists 46(4):752-758.

2513. Laurell, C.-B. 1952. Influence of nicotinic acid on the intermediary metabolism of iron and bilirubin. Acta Pharmacol. Toxicol. 9(1):86-92.

2514. Laurens, A., P. Mandel, and O. Thomas. 1944. Influence of thiamine, riboflavin, and nicotinic acid on endogenous nitrogen metabolism. Compt. Rend. Soc. Biol. 138:672-673.

2515. Laurnagaray, R. 1945. Nicotinic acid content of commercial flours. An. Asoc. Quimica Argentina 33(172):120-134.

2516. Laursen, B., and J. Gormsen. 1969. Pharmacological enhancement and short-term stimulation of blood fibrinolytic activity. Scand. J. Haematol. 6(6):402-408.

2517. Laursen, B., and J. Gormsen. 1970. Fibrinolytic activity in normal persons and patients with atherosclerotic vascular disease after physical activity and injections of nicotinic acid. Angiology 21(7):486-492.

2518. Lawler, J. V. 1947. Recent developments in vitamin therapy. Australasian J. Pharm. 28:199-202.

2519. Lawrence, J. M., B. L. Herrington, and L. A. Maynard. 1946. The nicotinic acid, biotin, and pantothenic acid content of cow milk. J. Nutr. 32:73-91.

2520. Leal, A. M., M. J. da Silva, and J. Costa Santos. 1952a. A colorimetric method for determining nicotinamide and coramine. Anais Azevedos (Lisbon) 4:196-205.

2521. Leal, A. M., M. J. M. da Silva, and J. Costa Santos. 1952b. Colorimetric assay of a galenical preparation of nicotinamide and nikethamide by reaction with copper sulfate. Congr. Luso-Espan. Farm., II Cong., 2., Ia. Sec. 202-211.

2522. Leanderson, R., and L. Levi. 1967. Biochemical and behavioral studies of psychotropic drugs during experimentally induced emotional stress and during basal conditions. Report on methodology. Antidepressant Drugs, Proc. Int. Symp., 1st, Milan 1966, 75-79.

2523. Lease, E. J. 1953. Corn meal enrichment. J. Am. Dietet. Assoc. 29:866-872.

2524. Le Breton, E., and J. Champougny-Clement. 1948. Desaturase of higher fat acids. Arch. Sci. Physiol. 2:243-255.

2525. Lechat, P., M. Freyss-Beguin, E. Van Brussel, and N. Mathieu-Levy. 1971.SStudy of the hypolipemic effect of some thiophenic acids in rats treated with Triton WR-1339. Therapie 26(4):831-838.

2526. Lechat, P., M. Freyss-Beguin, A. Boime, N. Mathieu-Levy, and E. Van Brussel. 1971. Comparison of the hypolipemic effect of nicotinic acid and some substituted thiazole acids. Study on rat serum treated with Triton WR-1339. Therapie 26(3):497-509.

2527. Le Clerc, A. M., and P. Douzou. 1953. Spectrophotometric estimation of nicotinic acid and nicotinamide. C. R. Acad. Sci. 236:2006-2008.

2528. Lecoq, R. 1951a. Disturbance of alcohol and pyruvic acid metabolism and the appearance of the alcoholic syndrome. Bull. Acad. Natl. Med. 135:271-277.

2529. Lecoq, R. 1951b. Pyruvic acid and the metabolism of ethyl alcohol. Compt. Rend. 232:1017-1019.

2530. Lecoq, R. 1958. Salts of calcium and acid-base equilibrium. Observations concerning the effects of several new salts of calcium on the alkaline reserve of the blood. J. Physiol. (Paris) 50:359-361.

2531. Lecoq, R., P. Chauchard, and H. Mazoue. 1944. Comparative studies in pigeon and rat of the modifications of neuromuscular excitability during total or partially compensated avitaminosis B. Compt. Rend. 218:946-947.

2532. Lecoq, R., P. Chauchard, and H. Mazoue. 1945. Role of adenine and pantothenic acid in the correction of the neuromuscular disorder produced by total B-complex avitaminosis partially compensated by addition of thiamine, riboflavin, and nicotinamide. Compt. Rend. Soc. Biol. 139:623-624.

2533. Lecoq, R., P. Chauchard, and H. Mazoue. 1946a. Suppression of neuromuscular manifestations of experimental chronic alcoholism by injection or ingestion if vitamins B3 and B4. Compt. Rend. Acad. Sci. (Paris) 222:414-416.

2534. Lecoq, R., P. Chauchard, and H. Mazoue. 1946b. Antagonism between sulfanilamide and certain vitamins with respect to the nervous system of the rat. Compt. Rend. Soc. Biol. 140:279-280.

2535. Lecoq, R., P. Chauchard, and H. Mazoue. 1947a. Disturbances of neuromuscular excitability during alimentary imbalance and avitaminoses. XX. Relation between vitamin needs and certain amino acids. Bull. Soc. Chim. Biol. 29:705-716.

2536. Lecoq, R., P. Chauchard, and H. Mazoue. 1947b. Role of lipides in modifying certain vitamin requirements. Compt. Rend. Soc. Biol. 141:1196-1197.

2537. Lecoq, R., P. Chauchard, and H. Mazoue. 1948a. Disturbances of neuromuscular excitability during alimentary imbalance and avitaminoses. XXV. Vitamin requirements linked with metabolism of lipides and cholesterol. Bull. Soc. Chim. Biol. 30:296-305.

2538. Lecoq, R., P. Chauchard, and H. Mazoue. 1948b. Vitamins necessary for the utilization of amino acids. Compt. Rend. 226:130-132.

2539. Lecoq, R., P. Chauchard, and H. Mazoue. 1948c.Vitamins antagonizing the action of histamine on the nerves and in anaphylactic shock. Compt. Rend. 227:1264-1266.

2540. Lecoq, R., P. Chauchard, and H. Mazoue. 1951. Influence of substances producing acidosis or alkalosis on the effect of vitamins. Ann. Pharm. Franc. 9:711-718.

2541. Lecoq, R., P. Chauchard, and H. Mazoue. 1959. Chronaximetric determination of the inhibiting action of adenine, guanine, and some other substances on the effects of benzopyrene, dibenzanthracene, methylcholanthrene, aminoazotoluene, and dimentylaminoazobenzene on the nervous system. Ann. Pharm. Franc. 17:498-515.

2542. Le Douarin, G. 1964. Action of hormones and vitamins on the growth and differentiation of bone cultures in vitro. Annee Biol. (4) 3(5/6):233-260.

2543. Ledrut, J. 1940. Metabolism of glucides. I. Action of yeast extract. II. Action of nicotinic acid. Bull. Soc. Chim. Biol. 22:321-328.

2544. Lee, F. A., and J. Whitcombe. 1945. Effect of freezing preservation and cooking on vitamin content of green soybeans and soybean sprouts. J. Am. Dietetic Assoc. 21(10):696-697.

2545. Lee, H. M., R. M. Ellis, and M. V. Sigal, Jr. 1961. Some insulin-like effects of nicotinic acid observed with isolated rat epididymal adipose tissue. Biochim. Biophys. Acta 49:408-410.

* 2546. Lee, K. W., D. M. Abelson, and Y. O. Kwon. 1968. Nicotinic acid-6-14C metabolism in man. Am. J. Clin. Nutr. 21(3):223-225.

2547. Lee, T.-L., and T.-F. Huang. 1957. The effects of niacinamide, pyridine, and acetone on the contraction of the striated muscles of the toad. Tai-wan i-hsuech-hui tsa-chih 56:235-239.

* 2548. Lee, Y. C. 1971. Metabolism of nicotinic acid and nicotinamide in rats. Diss. Abstr. Int. B 31(8):4554.

2549. Lee, Y. C., J. L. R. Chandler, and R. K. Gholson. 1971. Quantitative studies on the excretory metabolites of nicotinic acid and nicotinamide in normal, hypohysectomized, and germ-free rats. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970, 133-147.

* 2550. Lee, Y. C., R. K. Gholson, and N. Raica. 1969. Isolation and identification of two new nicotinamide metabolites. J. Biol. Chem. 244(12):3277-3282.

2551. Lee, Y. C., R. M. McKenzie, R. K. Gholson, and N. Raica. 1972. A comparative study of the metabolism of nicotinamide and nicotinic acid in normal and germ-free rats. Biochim. Biophys. Acta 264(1):59-64.

2552. Leekley, J. R., R. G. Landgraf, Jr., J. E. Bjork, and W. A. Hagevig. 1952. Salmon cannery waste for mink feed. U.S. Fish Wildlife Service, Fishery Leaflet 405, 31 pp.

2553. Leemann, W. 1954. Nicotinic acid content of blood in healthy and in sick horses. Schweiz. Arch. Tierheilk. 95:228-238.

2554. Leffertstra, L. J. 1962. Results of early treatment in a case of spasm of the central retinal artery. Ophthalmologica (Basel) 144:433-437.

2555. Legros, J., I. Rosner, C. Berger, and H. Khalili-Varasteh. 1972. Protective effects of xylitol pentanicotinate in hypoxia and asphyxic anoxia. Therapie 27(6):1107-1117.

2556. Lehmann, C. et al. 1972. Treatment of rheumatoid arthritis with niflumic acid. Rev. Med. Chil. 100:515-519.

2557. Lehmann, G., and H. G. Hahn. 1968. Polyamide method for quantitative estimation of nicotinic acid. Ztschr. Anal. Chem. 243:554-559.

2558. Lehmann, H. E., and T. A. Ban. 1967. Comparative pharmacotherapy of the aging psychotic patient. Laval Med. 38(6):588-595.

2559. Lehnartz, E. 1948. Physiological and pathological chemistry including nutrition. Fiat Rev. German Sci. 1939-1946 (Wiesbaden), 348 pp.

2560. Leifer, E., J. R. Hogness, L. J. Roth, and W. Langham. 1948. Utilization of nicotinic acid and its amide by the human erythrocyte in vitro. J. Am. Chem. Soc. 70:2908-2910.

* 2561. Leifer, E., L. J. Roth, D. S. Hogness, and M. H. Corson. 1951. The metabolism of radioactive nicotinic acid and nicotinamide. J. Biol. Chem. 190(2):595-602.

2562. Leifer, P., and R. C. Batterman. 1955. Local cutaneous response of nicotinic acid and its esters as diagnostic aid for rheumatoid arthritis. Am. J. Med. Sci. 230:657-659.

2563. Leinweber, W., H. Becker, W. Prassek, and E. Boehle. 1969. Clinical experimental investigations on the effect of nicotinic acid and tolbutamide on fat and carbohydrate metabolism. Med. Ernaehr. 10(6):118-120.

2564. Leiter, J. 1962. Cancer chemotherapy screening data. XV. Cancer Res. (Suppl. 22, Pt. 2):363-557.

2565. Leitner, Z. A. 1943. Untoward effects of vitamin B1. Lancet II: 474-475.

2566. Lekberg, R. D., R. A. Jensen, and W. Buiter. 1964. Preparation of nicotinic acid. U.S. Pat. 3,313,821.

2567. Le Mer, G. 1961. Results obtained with an anti-smoking agent on a group of 45 smokers. Clinique (Paris) 56:643.

2568. Lemke, P. 1965. Electrophysiological studies on the reflex preparation 6-amino-nicotinamide poisoned rats. In: Proceedings of the German Pharmacological Society, 28th Session, Bad Neuheim, 5-8 October, 1964. Arch. Exp. Pathol. Pharmakol. (Naunyn Schmiedebergs) 250(2):271.

2569. Leonardi, G., and F. Campus. 1949. Action of vitamin PP and insulin on enzymic destruction of penicillin in vitro. Boll. Soc. Ital. Biol. Sper. 25:151-152.

2570. Leonian, L. H., and V. G. Lilly. 1945. The comparative value of different test organisms in the microbiological assay of B vitamins. West Virginia Agr. Expt. Sta. Bull. 319, 35 pp.

2571. Leontovich, V. A., and N. N. Abezgauz. 1964. Assessment of some substrates and coenzymes of the carbohydrate-phosphorus metabolism for prolonging leukocyte life during preservation. Probl. Gematol. i Pereliv. Krovi 9(10):36-42.

2572. LePage, G. A. 1948. Phosphorylated intermediates in tumor glycolysis. 1. Analysis of tumors. Cancer Res. 8:193-196.

2573. Lepkovsky, S. 1940. The water-soluble vitamins. Ann. Rev. Biochem. 9:383-422.

2574. Lepp, A., P. R. Moore, C. A. Elvehjem, and E. B. Hart. 1947. Effect of vitamin C on hemoglobin production in chicks. Poultry Sci. 26:594-597.

2575. Lequime, J., P. Cammaerts, F. Goksel, and L. Jonnart. 1950. Circulatory changes following intravenous injection of nicotinic acid in man. Acta Clin. Belg. 5:466-476.

2576. Lessin, A. W., and R. J. Kramer. 1969. Bronchodilator action of analeptics. J. Pharm. Pharmacol. 21(5): 309-313.

2577. Leszczynska, D. 1970. Effect of some herbicides on yeast from the rhizosphere of cultivated plants. Meded. Fac. Land-Bouwwetensch., Rijksuniv. Gent 35(2):637-645.

2578. Le Talaer, J. Y., J. B. le Pecq, B. Festy, and C. Paoletti. 1964. Effect of substrate concentration on the kinetics of neutral pancreatic deoxyribonuclease. Compt. Rend. 258(9): 2698-2701.

2579. Leuthardt, F., and J. Mauron. 1948. Effect of calcium and of nicotinamide on fumarate oxidation in liver homogenates. Helv. Physiol. Pharm. Acta 6:836-841.

2580. Leuts'kii, K. M. 1953. The study of the role of nicotinic acid and vitamin A in food metabolism. Vitaminy, Akad. Nauk Ukr. S.S.R. 1:239-252.

2581. Leuts'kii, K. M., and N. G. Kitovchenko. 1958. Deficiency and excessive dosages of sodium and chloride in diets and their effect on in vitro synthesis of nicotinic acid from L-tryptophan by the liver. Ukrain. Biokhim. Zhur. 30:487-492.

2582. Levaditi, C., and A. Valsman. 1952. Effects of nicotinamide in tuberculosis. 1952. Compt. Rend. 234:1588-1590.

2583. Levenson, S. M., R. W. Green, F. H. L. Taylor, P. Robinson, R. C. Page, R. E. Johnson, and C. C. Lund. 1946. Ascorbic acid, riboflavin, thiamine, and nicotinic acid in relation to sever injury, hemorrhage, and infection in the human. Ann. Surg. 124:840-856.

2584. Levitas, N., J. Robinson, F. Rosen, J. W. Huff, and W. A. Perlzweig. 1947. The fluorescent condensation product of N1-m thylnicotinamide and acetone. III. A rapid fluorometric method for the determination of the total pyridine nucleotides in the red blood cells. J. Biol. Chem. 167(1):169-175.

2585. Levoshin, V. V. 1954. Action of nicotinic acid on the vascular system in rabbits. Farmakol. i Toksikol. 17(2):16-19.

2586. Levoshin, V. V. 1959. Effect of nicotinic acid on respiration and on vessels of an isolated kidney connected with the central nervous system. Trudy Blagoveshch. Med. Inst. 4:102-105.

2587. Lewis, L. R., and C. C. Cheng. 1972. Antineoplastic activity of 6-dimethylaminonicotinamide. J. Med. Chem. 15(8):849-850.

2588. Leyden, A. F., E. Pomerantz, and E. F. Bouchard. 1956. Pharmaceutical aspects of reserpine. J. Am. Pharm. Assoc. 45:771-775.

2589. Lhuissier, M., and B. Potteau. 1971. The influence of thermopolymerized soy and linseed oils on the liver content of thiamine, riboflavin, vitamin B6, and niacin (in the rat). Ann. Nutr. Aliment. 25(5):215-221.

2590. Liaci, L. 1940a. The influence of nicotinamide on the staining of vital tissues and on the diffusion of the coloring matters through the peritoneal membrane. Arch. Farmacol. Sper. 69:186-193.

2591. Liaci, L. 1940b. Action of nicotinic amide, nicotinic acid and sodium nicotinate on the movements of the isolated uterus, stomach and intestine and on the vibrating cilia. Arch. Farmacol. e Sci. Aff. 69(6):200-211.

2592. Liaci, L. 1940c. Experimental results on the influence of nicotinamide on salt and water exchanges. Boll. Soc. Ital. Biol. Sper. 15:787-789.

2593. Liberman, T. Y. 1963. Effects produced by certain pharmacological agents employed for elimination of cephalalgia in hypertonic patients on the tone of cerebral vessels. Farmakol. i Toksikol. 26(5):573-578.

2594. Lichtin, J. L., and L. E. Harris. 1951. Preparation and toxicity of some new organic gold compounds. J. Am. Pharm. Assoc. 40:215-217.

2595. Lieck, H. 1954. Studies at the State Vitamin Laboratory of the nicotinic acid content of Danish foods. Statens Husholdningsrads Faglige Medd. (10-12):41-46.

2596. Liener, I. E., and M. O. Schultze. 1952. The excretion of N1-methylnicotinamide and creatinine as influenced by vitamin B12 and various methyl donors. J. Nutr. 46(2):223-237.

2597. Liesch, E., and M. Bassi. 1931. The plethysmographic, pressor and rhythmic changes of the heart and the vasomotor skin reactions after nicotinic acid injection in nonpellagrous persons. Sperimentale 94(10-11):R36-37.

2598. Liggio, F. 1970. Diet deficient in animal protein and atypical neuropsychiatric disturbances of the Hartnup disease type characterized by a few similar symptoms. Acta Neurol. (Naples) 25(3):404-410.

2599. Lin, P.-H., and B. C. Johnson. 1952. Nicotinic acid metabolite excreted by rats given radioactive nicotinic acid or nicotinamide. Fed. Proc. 11(1):448.

2600. Lin, P.-H., and B. C. Johnson. 1953. Nicotinic acid metabolism. II. The metabolism of radioactive nicotinic acid and nicitinamide in the rat. J. Am. Chem. Soc. 75:2974-2977.

2601. Linari, G. 1969. Nicotinoylglycolic acid: a new ester of nicotinic acid. Studies on its spectrophotometric behavior, chemical hydrolysis in vitro and toxicity. Farmaco (Prat.) 24:649-654.

2602. Linari, G. 1970. Observations on the synthesis, chemical hydrolysis in vitro and toxicty of a new ester of nicotinic acid: the mesoinosito pentanicotinate. Arzneimittelforschung 20:723-724.

2603. Lindberg, N. O. 1970. Preparation of effervescent tablets containg nicotinic acid and sodium bicarbonate. Acta Pharm. Suecica 7(1):23-28.

2604. Lindenblad, G. E., M. Kaihara, and J. M. Price. 1956. The occurrence of N-methyl-2-pyridone-5-carboxylic acid and its glycine conjugate in normal human urine. J. Biol. Chem. 219(2): 893-901.

2605. Lindholm. H. 1938. A consideration of the B-vitamins. Arch. Pharm. Chem. 45:637-648.

2606. Ling, C.-T., D. M. Hegsted, and F. J. Stare. 1948. The effect of pyridoxine deficiency on the tryptophan-niacin transformation in rats. J. Biol. Chem. 174(3):803-812.

2607. Lingane, J. J., and O. L. Davis. 1941. Polarographic determination of riboflavin (vitamin B2) and other vitamin B factors. J. Biol. Chem. 137(2):567-574.

2608. Linko, P. 1971. Vitamin and mineral contents of Finnish rolled oats with special reference to infant nutrition. Suom. Kemistilehti B 44(2):83-86.

* 2609. Lipkan, G. N. 1972. Toxicity of some vitamin preparations in experiments. Farmakol. Toksikol. (Kiev) 7:128-131.

2610. Lipson, M. J., and S. Naimi. 1971. Effect of free fatty acid mobilization on the electrophoretic mobility of alpha-lipoproteins in the dog. J. Lipid Res. 12(3):294-305.

2611. Lipson, M. J., S. Naimi, and S. Proger. 1971a E. Effect of a combination of propranolol and nicotinic acid on the inhibition of norepinephrine-induced elevations of serum triglyceride, serum glycerol, and plasma free fatty acids in the dog. Metab., Clin. Exp. 20(6):580-589.

2612. Lipson, M. J., S. Naimi, and S. Proger. 1971b. Synergistic effect of propranolol and nicotinic acid on the inhibition of plasma free fatty acid release in the dog. Circ. Res. 28(2):270-276.

2613. Lipton, P., and J. G. Michels. 1962. Effect of nicotinic acid on the concentration of cholesterol in the serum, liver, heart, and aorta of the hypercholesteremic rabbit. In: American Heart Association Council on Arteriosclerosis, annual meeting, 1962. Circulation 26(4 Pt. 2):661.

2614. Lipton, P., and J. G. Michels. 1965. Effects of nicotinic acid on rabbit hypercholesterolemia and atherogenesis. Geriatrics 20(5):379-387.

2615. Lis, A. W., R. Bijan, E. W. Lis, and K. F. De Hackbeil. 1968. Ultraviolet-absorbing urinary components of mentally retarded children and schizophrenic adults. Clin. Chem. 14(5):391-402.

2616. Lisan, P., W. Oaks, and S. Basch. 1961. Determination of the minimum dose of nicotinic acid for maximum serum cholesterol depression. Fed. Proc. 20(1 Pt. 1):91.

2617. Lisan, P., W. Oaks, and S. Basch. 1962. Use of small doses of sustained-acting nicotinic acid for cholesterol lowering. In: American Heart Association 35th scientific sessions, 1962. Circulation 26(4 Pt. 2):752.

2618. Lison, H. 1970. Differentiation of the functional disturbances of the central nervous system produced by 5-aminonicotinamide, an antimetabolite of nicotinamide. Naunyn. Schmiedebergs Arch. Pharmakol. 267(2):155-169.

2619. Litter, M. 1944. Pharmacological action of nicotinic acid and its amide. Rev. Inst. Bacteriol. "Carlos G. Malbran" 12:149-178.

2620. Little, P. A., J. J. Oleson, and Y. SubbaRow. 1948. Effect of nutrition on the tumor response in Rous chicken sarcoma. J. Lab. Clin. Med. 33:1139-1143.

2621. Litwack, G., L. V. Hankes, and C. A. Elvehjem. 1952. Effect of factors other than choline on liver fat deposition. Proc. Soc. Expti. Biol. Med. 81(2):441-445.

2622. Livesco, M. 1939. Treatment of pellagra with nicotinic acid amide. Bull. Acad. Med. Roumanie 4:439-441.

2623. Livshits, M. I. 1946. Microbiological estimation of vitamins. Vitamin Research News (U.S.S.R.) 1:102-105.

2624. Livshits-Vorob'eva, P. G. 1959. The influence of nicotinic acid on the motor activity of the stomach and on saliva secretion. In: Problems of morphology, physiology and pathology of the digestive organs. Medgiz (Moscow) 103-138.

2625. Ljunggren, H., J. Grissler, and F. Probst. 1961. Nicotinic acid treatment in hypercholesterolemia and atheromatosis. Svensk Lakartidn 58:653-658.

2626. Lockhart, W. C., R. L. Bryant, and D. W. Bolin. 1966a. The effects of B-vitamin deprivation on subsequent energy metabolism. Poultry Sci. 45(3):520-523.

2627. Lockhart, W. C., R. L. Bryant, and D. W. Bolin. 1966b. The effects of B-vitamin deficiencies on the efficiency of metabolizable energy and protein utilization. Poultry Sci. 45(5):939-945.

2628. Loddo, B., G. L. Gessa, M. L. Schivo, A. Spanedda, G. Brotzu, and W. Ferrari. 1966. Antagonism of the guanidine interference with poliovirus replication by simple methylated and ethylated compounds. Virology 28(4):707-712.

2629. Loeffler, G. L., and C. Ahrendt. 1971. Effect of nicotinic acid on the triglyceride lipase of adipose tissue. Metab. Eff. Nicotinic Acid Its Deriv., Pro., 283-288.

2630. Loeffler, G., and I. Trautschold. 1971. Effect of nicotinic acid on insulin secretion in vivo and in vitro. Metab. Eff. Nicotinic Acid Its Deriv., Pro., 933-937.

2631. Loevendahl, H. 1940. Pellagra and insanity. Nord. Med. 8:2269-2272.

2632. Loehr, G. W., and H. D. Waller. 1959. Cell metabolism and cell aging. Klin. Wochschr. 37:833-843.

2633. Loewenstein, E. 1940. Vitamin determination. An analysis describing fluorometric and colorimetric methods. Am. Wine Liquor J. 8(3):27-28, 30.

2634. Loginov, E. N. 1971. Anatomopathological data on healing of destructive tuberculosis of the lungs treated with antibacterial agents. Probl. Tuberk. 49(9):77-81.

2635. Loh, H. H., and C. P. Berg. 1971. Conversion of D-tryptophan to nicotinic acid in the rat. J. Nutr. 101(12):1601-1606.

2636. Lohmann, E., G. Feige, G. Loeffler, and I. Trautschold. 1968. Glucagon effect on insulin secretion. Symp. Deut. Ges. Endokrinol. (14):282-285.

2637. Loibman, G. I. 1952. The influence of thiamine and nicotinic acid on the cholesterol in the blood of rabbits. Ukrain. Biokhim. Zhur. 24:19-24.

2638. Lojkin, M. E. 1956. Effect of ovariectomy and administration of ovarian hormones and testosterone on nicotinic acid metabolism of rats. J. Nutrition 59(4):443-457.

2639. Lojkin, M. E. 1962. Tryptophan-niacin metabolism. I. Pregnancy, ovarian hormones and levels of tryptophan intake as factors affecting the tryptophan-niacin metabolism of the rat. J. Nutrition 78(3):287-294.

2640. Lojkin, M. E., A. W. Wertz, and C. G. Dietz. 1952. Metabolism of nicotinic acid in pregnancy. J. Nutrition 46(3):335-352.

2641. Loman, J., M. Rinkel, and A. Myerson. 1941. The intracranial and peripheral vascular effects of nicotinic acid. Amer. J. Med. Sci. 202:211-216.

2642. Longenecker, H. E., H. H. Fricke, and C. G. King. 1940. The effect of organic compounds upon vitamin C synthesis in the rat. J. Biol. Chem. 135(2):497-510.

2643. Lopez-Matas, A., and C. R. Fellers. 1948. Composition and nutritive value of fresh, cooked, and processed swordfish. Food Research 13:387-396.

2644. Lopez, A. G., M. L. Jimenez, and A. N. Rivera. 1963. Action of some pyridines upon the response to noradrenaline in the aorta of rabbits. Ciencia (Mex.) 22(3):54-58.

2645. Lorch, E., and K. F. Gey. 1971. Insulin response of blood glucose and glucose tolerance in rats and dogs treated with antilipolytic agents. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 735-746.

2646. Lorenzini, R., and A. Benedetti. 1953. Content of niacin, ascorbic acid, and N'-substituted pyridine derivatives in transudates and exudates. Acta Vitaminol. 7:213-216.

2647. Lorenzoni, I., G. A. Calabria, and A. De Flora. 1966. Acute hypervitaminosis PP. II. Effect of adrenalectomy on hepatic transketolase and transaldolase activities and hexose content. Boll. Soc. Ital. Biol. Sper. 42(14):899-902.

2648. Lorian, V. 1962. Standardization of the niacin test. Amer. Rev. Respiratory Dis. 86(6):929-931.

2649. Lossy, F. T., G. A. Goldsmith, and H. P. Sarett. 1951. A study of test-dose excretion of five B complex vitamins in man. J. Nutrition 45:213-224.

2650. Lotmar, R. 1958. Effect of various pharmacological chemicals on the ionic permeability of skin. Arch. Physik. Therapie 10: 392-399.

2651. Louw, M. E. J., J. P. Du Plessis, A. S. Van den Berg, and S. A. Fellingham. 1969. Intercorrelation study of dietary and biochemical data from schoolchildren in the Pretoria area. S. Afr. J. Nutr. 5(4):1516-1527.

2652. Lovesey, A. C. 1969. Potential coenzyme inhibitors. III. Some reactions of substituted nicotinamide and dihydronicotinamide derivatives. J. Med. Chem. 12(6):1018-1023.

2653. Lovkova, M. Y., and N. I. Klimenteva. 1970. Nicotine biosynthesis in Nicotiana tabacum shoots. Prikl. Biokhim. Mikrobiol. 6(5):615-616.

2654. Loy, H. W. 1958. Revision of microbiological methods for the B vitamins. J. Assoc. Offic. Agr. Chemists 41:587-588.

2655. Loy, H. W. 1959. Revision of microbiological methods for the B vitamins. J. Assoc. Offic. Agr. Chemists 42:529-532.

2656. Loy, H. W.,Jr., W. P. Parrish, and S. S. Schiaffino. 1956. Use of turbidity measurements in microbiological methods for vitamins. J. Assoc. Offic. Agr. Chemists 39:172-179.

2657. Luckey, T. D., J. R. Pleasants, M. Wagner, H. A. Gordon, and J. A. Reyniers. 1955. Some observations on vitamin metabolism in germ-free rats. J. Nutrition 57(2):169-182.

2658. Ludovici, P. P. 1951. Circulating antibodies in vitamin-deficiency states. Pteroylglutamic acid, niacin-tryptophan, vitamin B12, A, and D deficiencies. Proc. Soc. Expti. Biol. Med. 77(3):526-530.

2659. Ludwig, H. 1970. Anticoagulants in pregnancy and puerperium. Geburtshilfe Frauenheilk 30:337-347.

2660. Luecke, R. W. 1952. Role of B vitamins in the nutrition of the pig. Natl. Vitamin Foundation, Nutrition Symposium Ser. 5:112-120.

2661. Lueders, D. 1964. Exeprimental studies of bilirubin solubility. I. Acceleration of the diazo reaction of indirect serum bilirubin by Decholin and other substances. Z. Kinderheilk. 91(3):254-64.

2662. Luedy-Tenger, F. 1951. Microchemical tests for identifying nicotylamide and nicotinic acid. Microchemie ver Mikrochim. Acta 38:460-465.

2663. Luedy-Tenger, F. 1953. Microchemical identification of some pyridine derivatives. Pharm. Acta Helv. 28:22-26.

2664. Lugol, P., and M. Plissier. 1968. Use of nicotinamide for treating gingival and buccal lesions. French Patent No. 7217.

2665. Lukes, R., J. Jizba, and V. Galik. 1961. Some methylpyridine-carboxylic acids and pyridinedicarboxylic acids. Collection Czechoslov. Chem. Communs. 26:3044-3050.

2666. Lukjan, H., M. Bielawiec, and K. Buluk. 1972. Behavior of kininogenic blood systems during activation of fibrinolysis by pharmacologic agents and during operations. Ann. Med. Sect. Pol. Acad. Sci. 17(2):159-166.

2667. Luk'yanchikova, G. I., V. N. Bernshtein, and S. N. Stepanyuk. 1969. Use of the polymethine dye formation reaction in the analysis of some pyridine derivatives. Farm. Zh. (Kiev) 24(5): 66-70.

2668. Lund, C. C., S. M. Levenson, R. W. Green, R. W. Paige, P. E. Robinson, M. A. Adams, A. H. McDonald, F. H. L. Taylor, and R. E. Johnson. 1947. Ascorbic acid, thiamine, riboflavin, and nicotinic acid in relation to acute burns in man. Arch. Surgery 55:557-583.

2669. Lupien, P. J., and C. M. McCay. 1960. Thermic contraction and elasticity in the chinchilla tendon fiber as influenced by age. Gerontologia 4:90-103.

2670. Lushbough, C. H. 1958. Water-soluble vitamins. II. Ascorbic acid, biotin, nicotinamide, vitamin B6. Ann. Rev. Biochem. 27:313-338.

2671. Lustig, B., and H. Wachtel. 1936. Studies in the chemotherapy of cancer. Bull. Assoc. Franc. Etude Cancer 25:542-588.

2672. Lustig, O. 1956. Preparation of nicotinamide. U.S. Patent 2,752,355.

2673. Luthman, J., and G. Jonson. 1971. The effect of cyclic adenosine 3', 5' monophosphate, methyl xanthines and nicotinic acid on plasma nonesterified fatty acids in sheep. Acta Vet. Scand. 12(4):536-550.

2674. Luthman, J., G. Jonson, and P. Holtenius. 1970. Preventive effect of nicotinic acid on carbon tetrachloride toxicity in sheep. Acta. Vet. Scand. 11(2):254-267.

2675. Luthman, J., G. Jonson, and J. Persson. 1972. Studies on norepinephrine-induced hypocalcemia in sheep before and after thyroidectomy. Acta Vet. Scand. 13(1):20-30.

2676. Luyckx, A., and P. Lefebvre. 1970. Factors influencing the secretion of pancreatic and extrapancreatic glucagon. Acta Isotop. 10(3-4):269-284.

2677. Lwoff, A., and M. Morel, 1942. Secretion of nicotinamide in (human) colostrum and milk. Compt. Rend. Soc. Biol. 136: 379-380.

2678. Lwoff, A., and A. Querido. 1938. Method of estimating nicotinic acid amide by the Proteus growth test. Compt. Rend. Soc. Biol 129:1039-1043.

2679. Lwoff, A., L. Digonnet, and H. Dusi. 1942. Enrichment of breast milk in the P-P factor after ingestion of nicotinamide. Compt. Rend. 214:39-40.

2680. Lwoff, A., A. Querido, L. Digonnet, and Garnier. 1939. Nicotinamide of the blood of pregnant women. Compt. Rend. Soc. Biol. 131:900-903.

2681. Lykke, A. W. J., and E. R. Kosche. 1966. The effect of traumatic shock on metabolism of ethyl alcohol in mice. III. The interaction of treatments by nicotinamide, diphosphorpyridine nucleotide, and traumatic shock on the rate of whole-body metabolism of ethyl alcohol. Australian J. Exptl. Biol. Med. Sci. 44(5):601-604.

2682. Lyndian, K. H. 1961. The diagnostic value of the nicotinic acid ester reaction in allergic diseases. Allergie Asthmaforsch. 4: 398-401.

2683. Lyukova, L. A. 1958. Effect of nicotinic acid on the growth and the yield of some vegetable plants. Fiziol. Rastenii, Akad. Nauk S.S.S.R. 5:24-30.

2684. Maass, H., F. Hoelzel, and H. A. Kuenkel. 1960. The influence of 2,3,5-tris(ethylenimino)-rho-benzoquinone on the incorporation of amino acids-C14 into the protein of tumor cells. Naturwissenschaften 47:449.

2685. Maayan, M. L. 1964. NAD-glycohydrolase of thyroid homogenates. Nature 204(4964):1169-1170.

2686. Maayan, M. L. 1965. Effect of injection of nicotinamide, nicotinic acid and L-tryptophan upon deiodination of diiodotyrosine by thyroid and liver homogenates of normal and hypophysectomized rats. Endocrinology 77(1):32-36.

2687. Maayan, M. L., and I. N. Rosenberg. 1968. Pyridine nucleotides in the thyroid gland. II. Effect of nicotinamide, nicotinic acid, and L-tryptophan administration. Endocrinology 82(2):209-217.

2688. Macabies, J., A. Sassine, and J. M. Bourgeois. 1970. Study of a mechanism of the hyperglycemiating action of nicotinamide. C. R. Seances Soc. Biol. Filiiales 164(7):1570-1572.

2689. Maccacaro, G. A., and A. M. Lugli. 1954. Microbiological determination of amino acids and vitamins according to a new criterion. III. Determination of three amino acids and three vitamins. Arch. Sci. Biol. (Italy) 38:437-448.

2690. Macchioro, G. 1947. Research in vivo and in vitro on the action of vitamins K, C, and PP in the agglutination of red cells. Minerva Med. 38(II):339-340.

2691. Machlin, L. J., C. A. Denton, and H. R. Bird. 1951. Effect of vitamin B12 and folic acid on glycine toxicity in the chick. Fed. Proc. 10(1):388.

2692. Mackaness, G. B. 1956. The intracellular activation of pyrazinamide and nicotinamide. Am. Rev. Tuberc. Pulmonary Diseases 75:718-728.

2693. Mackay, I. F. S., S. J. Patrick, D. M. Stafford, and F. W. Cleveland, Jr. 1956. The influence of vitamin B12 and Aureomycin upon the growth of protein deficient children. J. Nutr. 59(1):155-170.

2694. MacWillie, J. 1944. The vitamins. II. Biol. Human Affairs 10:33-40.

2695. Madison, L. C., R. C. Miller, and T. B. Keith. 1939. Nicotinic acid in swine nutrition. Science 89:490-491.

2696. Madison, R. R., M. Fish, and O. Frick. 1938. Effects of nicotinic acid on specific antibody production. Proc. Soc. Exp. Biol. Med. 39(3):438-439.

2697. Magyar, I., and G. Gabor. 1949. Imbalance of vitamins. Intern. Z. Vitaminforsch. 21:1-5.

2698. Magyar, I., G. Gabor, and Z. Eoelloes. 1949. Exhaustion of the phosphorylation. Acta Med. Scand. 135(2):142-146.

2699. Mahl, M., and K. Lange. 1963. A long term study of the effect of nicotinic acid medication on hypercholesteremia. Am. J. Med. Sci. 246:673-677.

2700. Mahler, R. J., and Szabo. 1970. Mechanism of carbohydrate intolerance produced by fasting. Metab., Clin. Exp. 19(4): 271-279.

2701. Mainardi, L. 1949. Nicotinic acid and its amide in biliary secretion, examined by means of fistula in rats. Boll. Ital. Biol. Sper. 25:1228-1230.

2702. Mainardi, L. 1960. The metabolism of nicotinic acid and of its higher homologue, 3-pyridine acetic acid, supplied by a large dose in man. I. Tests with nicotinic acid. Acta Vitaminol. 14(6):261-267.

2703. Mainardi, L. 1961. Observations on the metabolism of nicotinic acid and of its higher homologue, 3-pyridylacetic acid, administered in massive doses in humans. II. Experiments with 3-pyridylacetic acid. Acta Vitamin. (Milano) 15:209-213.

2704. Mainardi, L. 1967. Niacin, niacinamide and blood sugar. Acta Vitamin. (Milano) 21:139-159.

2705. Mainardi, L., and L. T. Tenconi. 1967. Effect of high doses of nicotinic acid and its derivatives on blood sugar in rats. Acta Vitaminol. Enzymol. 21(1/2):31-35.

2706. Mainardi, L., A. Bissanti, and L. T. Tenconi. 1967. Effects of high doses of nicotinic acid and its derivatives on free fatty acids in rats. Acta Vitaminol. Enzymol. 21(3):87-92.

2707. Maisin, J., Y. Pourbaix, and J. Camerman. 1939. Prevention of cancer by benzopyrine: Action of high doses of vitamin B1, nicotinamide. A phosphorolytic system. Compt. Rend. Soc. Biol. 132(23):87-90.

2708. Maiwald, L., and H. Maske. 1956. The detection of pyridoxine, pyridoxamine, nicotinic acid and nicotinamide by means of paper chromatography. Hoppe-Seyler's Zeitsch. Physiol. Chem. 306(2/3): 143-144.

2709. Maiwald, L., and K. Wyrwoll. 1971. Effect of steroid treatment in combination with vitamin B12, folic acid, nicotinic acid, and vitamin C on the course of carbon tetrachloride-induced cirrhosis. Experimental study in animals. Med. Welt (6):223-228.

2710. Majumdar, A. C. 1950. Role of thyroid and nicotinic acid on hemopoiesis. Indian J. Physiol. 4:50-60.

2711. Majupuria, K. C., L. C. Gupta, and S. B. Agarwal. 1968. Nitrogen mustard in operable bronchogenic carcinoma. Indian J. Radiol. 22(1):33-34.

2712. Majupuria, K. C., S. R. Gupta, and L. C. Gupta. 1968. Radiation sickness treatment with nicotinic acid and sodium chloride (human). Indian J. Radiol. 22(1):66-67.

2713. Maksimovich, Ya. B. 1960a. Influence of nicotinic acid on the organism. Sovremennye Dannye po Lechebnomu Primeneniyu Vitaminov, 4-oe (Chetvertoe) Vsesoyuz. Soveshchanie po Vitaminam, Moscow 1957:226-232.

2714. Maksimovich, Ya. B. 1960b. The basic mechanisms of the pharmacodynamic effect of nicotinic acid in animals and man. Akad. Med. Nauk S.S.S.R. (Moscow): 1959.

2715. Maksimovich, Ya. B., and O. V. Maksiutinskaia. 1961. An objective test for the determination of human vitamin PP supply. Vop. Pitan. 20:82-88.

2716. Maksimovich, Ya. B., and A. I. Gaidenko. 1963. Changes in metabolism and distribution of vitamins PP and C under the effect of cobalt. Vopr. Pitan. 22(5):50-55.

2717. Maksimovich, Ya. B., O. P. Kalashnikov, and O. V. Tsibul's'ka. 1966. Nicotinic acid and tumor growth. Ukr. Biokhim. Zh. 28(4):436-439.

2718. Maksimovich, Ya. B., M. B. Maksimovich, and K. A. Maksimovich. 1968. Disturbance of the resistance of mice to latent ectromelia in vitamin PP hypervitaminosis. Mikrobiol. Zh. (Kiev) 30(6):557-560.

2719. Maksimovich, Ya. B., V. Y. Yurchenko, and A. P. Kalashnikov. 1970. State of nicotinic acid metabolism in thermal burns. Vrach. Delo 11:48-52.

2720. Maksimovich, Ya. B., L. G. Reznichenko, E. A. Legeda, and L. E. Gorbatova. 1964. Some aspects of vitamin C, vitamin P, vitamin B2, and vitamin PP metabolism in experimental atherosclerosis. Materialy X V-oi (Pyatnadtsatoi) Nauchn. Sessii Inst. Pitaniya, Akad. Med. Nauk S.S.S.R., Moscow, Sb. (1):52-54.

2721. Maksiutinskaia, O. V. 1959. On the effect of increase in the quantity of proteins in food on the PP-vitamin level in senior-age creche children. Vop. Pitan. 18:24-28.

2722. Malaguzzi-Valeri, C. 1939. Some therapeutic actions of nicotinic acid. Boll. Soc. Ital. Biol. Sper. 14:556-557.

2723. Malaguzzi-Valeri, C., and P. Paterno. 1939. Effect of nicotinic acid and nicotinamide on gastric secretion. Gazz. Ospedali Clin. 60:925-928.

2724. Malaguzzi-Valeri, C., G. Conese, and D. Angarano. 1950. Action of thiamine and niacin on basal metabolism. Intern. Z. Vitaminforsch. 22:174-179.

2725. Malanova, N. L. 1956. Penetration of streptomycin after various methods of its administration and the effect of nicotinic acid on its activity in the organism. Vestnik. Oftalmol. 69(4):10-12.

2726. Malanova, N. L. 1958. Use of nicotinic acid in the treatment of tuberculous chorio-retinitis with streptomycin. Vestn. Oftalmol. (5):39-41.

2727. Maleki, M., and S. Daghir. 1967. Effect of baking on retention of thiamine, riboflavine, and niacin in Arabic bread. Cereal Chem. 44(5):483-487.

2728. Malesani, L. 1952. Italian contribution to the study of the relation of the PP vitamin to tuberculosis. Acta Vitaminol. 6:119-123.

2729. Malkin, Z. I., S. I. Shcherbatenko, and L. A. Lushnikova. 1948. Pharmacodynamic and therapeutic action of nicotinic acid. Terapevt. Arkhiv. 20(6):62-74.

2730. Malone, T. E. 1960. Effects of x-irradiation on the development of copora lutea in the albino rat. Am J. Anat. 107(2):117-191.

2731. Mameesh, M. S., G. Boge, H. Mueklestad, and O. R. Braekkan. 1965. Radiation preservation of fish. The effect on certain vitamins in fresh cod and dogfish fillets and in smoked cod and herring fillets. Fiskeridirektorat. Skrifter, Ser. Teknol. Undersoek. 4(10):1-10.

2732. Mameesh, M. S., V. C. Metta, P. V. Rama Rao, and B. C. Johnson. 1962. Vitamin K deficiency in male rats fed irradiated beef and the production of vitamin K deficiency using an amino acid synthetic diet. J. Nutr. 77(2):165-170.

2733. Mancini, F. 1940. Action of sodium nicotinate and nicotin amide on arterial pressure in man. Quaderni Nutriz. 7:119-125.

2734. Mandel, P., M. Revel, and S. Dreyfus. 1962. Effect of nicotinamide on the metabolism of nuclear ribonucleic acid (RNA) in rat kidney. Compt. Rend. 255:406-408.

2735. Mandel, P., M. Revel, J. D. Weill, S. Busch, and P. Chambon. 1962. Biosynthesis of ribonucleic acid in rat- and chicken-cell nuclei. Biochem. J. 84:88.

2736. Mangay, A. S., W. N. Pearson, and W. J. Darby. 1957. Millet (Setaria italica): Its amino acid and niacin content and supplementary nutritive value for corn (maize). J. Nutr. 62(3):377-393.

2737. Mankovsky, N., and A. Mints. 1972. Cerebral atherosclerosis in senile age: Drug therapy. G. Gerontol. 20(1):42-49.

2738. Mann, G. V., S. S. Kahn, and F. J. Stare. 1949. A study of the influence of DL-tryptophan upon blood sugar levels. Am. J. Physiol. 158(1):38-44.

2739. Mann, P. J. G., and J. H. Quastel. 1941. Nicotinamide, cozymase and tissue metabolism. Biochem. J. 35:502-517.

2740. Manoukas, A. G., R. C. Ringrose, and A. E. Teeri. 1968. Availability of niacin in corn, soybean meal, and wheat middlings for the hen. Poultry Sci. 47(6):1836-1842.

2741. Mansoor-Ul-Hassan, and A. L. Lehninger. 1956. Enzymic formation of ascorbic acid in rat-liver extracts. J. Biol. Chem. 223:132-138.

2742. Marakulin, V. S. 1963. Test for "spotty" hyperemia of the skin after injection of nicotinic acid in some categories of nervous disorders. Zh. Nevropatol. Psikhiat. Im. S. S. Korsakova 63(12):1823-1827.

2743. Marche, J. 1950. Metabolism of vitamin A, carotene, vitamin C, and vitamin PP. Laval Med. 15:202-225.

2744. Marche, J., and F. Delbarre. 1943. Action of nicotinic acid and amide on blood sugar in man. C. R. Soc. Biol. 137:153-154.

2745. Marchetti, M., V. Ottani, and P. Puddu. 1970. Azaserine-induced fatty liver in the rat. Proc. Soc. Exp. Biol. Med. 133(1):30-33.

2746. Marenzi, A. D., and J. L. Moglia. 1944. Distribution of free and combined nicotinic acid. Anales Farm. Bioquim. 15:8-25.

2747. Marfori, L., M. Stefanini, and P. Bramante. 1946a. Modifications of blood bilirubin after nicotinic acid-tolerance test. Boll. Soc. Ital. Biol. Sper. 22:160-162.

2748. Marfori, L., M. Stefanini, and P. Bramante. 1946b. Modifications of bilirubinemia after administration of nicotinic acid. II. Mechanism of hyperbilirubinemia. Boll. Soc. Ital. Biol. Sper. 22:707-709.

2749. Marfori, L., M. Stefanini, and P. Bramante. 1946c. Modifications of bilirubinemia after administration of nicotinic acid. III. Behavior of bilirubinemia and bilirubinuria. Boll. Soc. Ital. Biol. Sper. 22:709-711.

2750. Marfori, L., M. Stefanini, and P. Bramante. 1946d. The biliary secretion of malarial livers under the effect of nicotinic acid. Riv. Malariol. 25(5):169-179.

2751. Marfori, L., M. Stefanini, and P. Bramante. 1947. Clinical significance of hyperbilirubinemia due to nicotinic acid. Am. J. Med. Sci. 213:150-152.

2752. Margolina, L. T. 1945. Determination of ascorbic acid in blood plasma in C-hypovitaminosis. Klin. Med. 23(7-8):64-65.

2753. Margolis, L. H., G. Margolis, and S. G. Smith. 1939. Secondary deficiency of vitamin B1 and riboflavin in the blacktongue producing diet. J. Nutr. 17(1):63-76.

2754. Mariani, A. P. 1969a. Electrophoretic study of serum proteins in rabbits parenterally treated with massive doses of nicotinamide. Ann. Fac. Med. Vet., Univ. Studi Pisa 21:247-253.

2755. Mariani, A. P. 1969b. Glutamic oxaloacetic transaminase (GOT) in blood serum of rabbits given large parenteral doses of nicotinamide. Ann. Fac. Med. Vet., Pisa, 1968 21:254-256.

2756. Mariani, A. P. 1971. Free reducing total corticoids in plasma in rabbits parenterally treated with high doses of nicotinamide. Ann. Fac. Med. Vet., Univ. Studi Pisa 1970 23:26-29.

2757. Mariani, B., G. De Simoni, and G. Boccitto. 1961. The treatment of liver disease during tuberculosis with vitamins B12, C, PP and folic acid. Panminerva Med. 3:369-372.

2758. Marinelli, L. 1950. Hyperbilirubinemia from nicotinic acid. Arch. Studio Fisiopatol. e Clin. Ricambio 14:57-72.

2759. Marinelli, L., and C. Tramontana. 1950. Variations in the iron content of blood by nicotinic acid. Giorn. Clin. Med. 31:152-157.

2760. Marinello, E. 1960. Purification of an activator of phosphoglucomutase from the liver of rats given a large dose of nicotinamide. Ricerca Sci. 30:1221-1224.

2761. Marinello, E., and V. Pallini. 1960a. Pyruvate oxidation by liver homogenates from nicotinamide treated rats. In: Proceedings of the Fifth Latin International Biochemical Meeting. Rev. Espanola Fisiol. 16(Suppl. 2):287-292.

2762. Marinello, E., and V. Pallini. 1960b. Pyruvate oxidation in the liver homogenates of rats treated with nicotinamide. Ricerca Sci. 30(9):1379-1383.

2763. Marinello, E., G. Pompucci, and V. Pallini. 1961. Behavior of pyridine coenzyme dehydrogenases of rat liver treated with large doses of nicotinamide. Boll. Soc. Ital. Biol. Sper. 37:11-12.

2764. Marinello, E., V. Pallini, G. Pompucci, and C. Ricci. 1960. Content of diphosphopyridine nucleotide (DPN) and reduced diphosphopyridine nucleotide (DPNH) in the liver of rats on a normal diet and fasting, treated with strong doses of nicotinamide. Boll. Soc. Ital. Biol. Sper. 36:2001-2004.

2765. Markacheva, T. M., and G. N. Lebedeva. 1950. Preparation of nicotinic acid from the heavy bases of coal tar. J. Applied Chem. 23:299-305.

2766. Markkanen. T. 1962a. Riboflavin, nicotinic acid and pantothenic acid contents of blood after partial gastrectomy. Ann. Med. Intern. Fenn. 51(2):111-117.

2767. Markkanen, T. 1962b. Nicotinic acid and pantothenic acid content of blood in carriers of fish tapeworm. Ann. Med. Intern. Fenniae 51:118-123.

2768. Markkanen, T. K., and R. Lahesmaa. 1961. Effect of oral administration of neomycin and oxytetracycline on urinary excretion of thiamine, riboflavine, nicotinic acid, pantothenic acid, and biotin in man. Ann. Med. Exptl. Biol. Fenniae (Helsinki) 39:394-399.

2769. Marrazza, P., and S. Luca. 1960. Fibrinolytic action of nicotinic acid. Acta Vitamin. (Milano) 14:207-209.

2770. Martelli, P., et al. 1966. Nicotinamide deamidase during development of the chick embryo. Boll. Soc. Ital. Biol. Sper. 42:1187-1189.

2771. Martelli, P., and C. Ricci. 1964. In vivo NAD biosynthesis. Giorn. Biochim. 13(5):288-299.

2772. Martin, C. 1968. Action of paraminobenzenesulfamide and of nicotinamide on the development of the embryos of the Leghorn and Creeper chickens. C. R. Hebd. Seances Acad. Sci. Ser. D Sci. Natur. (Paris) 266(12):1320-1322.

2773. Martin, G. J., and M. R. Thompson. 1944. Detoxicants. Brit. Pat. 564,154.

2774. Martin, G. J., M. R. Thompson, and J. de Carvaijal-Forero. 1941. The influence of inositol and other B complex factors upon the motility of the gastro-intestinal tract. Am. J. Digest Dis. 8(8):290-295.

2775. Martin, H., and C. E. Koop. 1942. The precancerous mouth lesions of avitaminosis B. Am. J. Surg. 57:195.

2776. Martin, N., and W. J. Oosterveld. 1970. The vestibular effects of meclizine hydrochloride-niacin combination (Antivert). Acta Oto-Laryngol. 70(1):6-9.

2777. Martinek, R. G., E. R. Kirch, and G. L. Webster. 1943. Determination of nicotinic acid. J. Biol. Chem. 149(1):245-249.

2778. Martinez, R. 1954. Oxygen saturation of arterial and venous blood after sodium nicotinate administration ot normal subjects. Folia Cardiol. 12(Suppl., Atti Soc. Ital. Cardiol. 15th Congr.): 316.

2779. Martinez-Fresneda, C. G. 1958. Idiopathic hyperlipemia with secondary xanthomatosis; treatment with large doses of nicotinic acid. Actas Dermo-Sifiliograficas 49:372-375.

2780. Martynenko, A. G., L. A. Kartasheva, M. I. Golkhberg, and I. A. Klimenko. 1972. Tryptophan metabolism disturbances in cancer of the urinary bladder. Vopr. Onkol. 18(5):23-26.

2781. Martz, D. M. 1965. Acute brain syndrome (man) secondary to niacin deficiency. Am. J. Psychiat. 122(2):215-216.

2782. Marx, R. 1969. Fibrinolytic states. Haematol. Lat. 12:609-621.

2783. Maruyama, M. 1960. Studies on themode of action of RC-4, a new anticancer agent containing ethylenimino ring. II. On the inverse relation between inhibitor activity on anaerobic glycolysis and anticancer effect of RC-4 on Ehrlich ascites tumor cells. Gann 51:285-300.

2784. Marzat, J. 1955. Incompatibilities of vitamin PP (nicotinamide). Bull. Soc. Pharm. Bordeaux 94:138-144.

2785. Masahito, P. 1959. The effect of nicotinamide on prolactin-induced mitosis of crop-sac epithelium in the pigeon. J. Fac. Sci. Tokyo Univ. Sect. IV. Zool. 8(3):412-417.

2786. Maschette, D. S., W. F. Hinman, and E. G. Halliday. 1947. Effect of time and temperature of storage on vitamin content of commercially canned fruits and fruit juices (stored 12 months). Indust. Engineer. Chem. Indust. Ed. 39(8):994-999.

2787. Mascitelli-Coriandoli, E. 1959. Action of nicotinamide on coenzyme A in normal and tumor tissue. Naturwissenschaften 46:561.

2788. Masek, J. 1946. Studies on intragastric temperature and modifying factors. Arch. Mal. Appar. Digest 35(6/7):215-223.

2789. Mashkovskii, M. D. 1940. Vitamin B1. Sovet. Med. (19):43-44.

2790. Maslenikova, E. M., and S. A. Kosenko. 1962. Excretion of riboflavin in children from 3 to 7 years old. Vop. Pitan. 21(5): 31-36.

2791. Mason, J. B., et al. 1971. The fate of dietary bound nicotinic acid in the nicotinic acid-deficient and -supplemented rat. Biochem. J. 125:118.

2792. Mason, J. B., and E. Kodicek. 1968. The metabolism of niacytin in the rat. Biochem. J. 107(4):23-24.

2793. Mason, J. B., and E. Kodicek. 1970a. The metabolism of niacytin in the rat. Studies of the excretion of nicotinic acid metabolites. Biochem. J. 120(3):509-513.

2794. Mason, J. B., and E. Kodicek. 1970b. The metabolism of niacytin in the rat. Trigonelline as a major metabolite of niacytin in the urine. Biochem. J. 120(3):515-521.

2795. Massieu, H., Guilermo, and B. G. Orgega. 1959. Antagonistic action of 3-acetylpyridine and niacinamide on glycemia. An. Inst. Biol. Univ. Mexico 30(1/2):3-8.

2796. Massieu, H., O. Y. Cravioto, R. O. Cravioto, J. Guzman, and M. de L. Suarez Soto. 1956. New data about the effect of corn and the tortilla on the growth of rats fed on diets low in tryptophan and niacin. Ciencia (Mex.) 16:24-30.

2797. Matakbaev, N. M., I. P. Zinov'ev, and R. I. Zhuklina. 1970. Some data on the inactivation of isonicotinic acid hydrazine in patients with pulmonary tuberculosis. Zdravookhr. Kaz. 10:30.

2798. Matei-Vladescu, C. 1971. Insulin anorexia in chickens. Rev. Roum. Biol., Ser. Zool. 16(6):383-388.

2799. Matsko, S. N., and E. V. Zavadovskaya. 1951. Effect of carotene, vitamin C, and nicotinic acid on the development of D-hypervitaminosis. Fiziol Zhur. S.S.S.R. 37:233-239.

2800. Matsukawa, Matsushita, S., and F. Ibuki, 1965. Antioxidative and prooxidative abilities of some biological substances and physiologically active substances on the oxidation of unsaturated fatty acids. Agr. Biol. Chem. 29(9):297-795.

2801. Matsuyama, M., and T. Nagayo. 1960. Influence of nicotinamide and diphosphopyridine nucleotide on azo-dye and methylcholanthrene carcinogenesis. Gann 51:265-271.

2802. Matsuyama, M., A. Maekawa, and T. Nagayo. 1961. Inhibiting effect of nicotinamide and diphosphopyridine nucleotide on the methylcholanthrene sarcoma in rats. Nature (Lond.) 189:673-674.

2803. Mattei, C. 1946. Bilirubinemia accompanying the administration of nicotinic acid to normal and hepatic patients. Minerva Med. 37:308-313.

2804. Mattila, M., and P. Torsti. 1966. Effect of monoamine oxidase inhibitors and some related compounds on lipid metabolism in rat. Ann. Med. Exp. Biol. Fenn. 44(3):397-400.

2805. Mattocks, A. R., and N. H. White. 1971. Conversion of pyrrolizidine alkaloids to N-oxides and to dihydropyrrolizine derivatives by rat-liver microsomes in vitro. Chem.-Biol. Interactions 3(5):383-391.

2806. Maurina, H. 1969. Variation of the content of B group vitamins depending on plan sexualization. Fiziol. Rast. 16(1):132-135.

2807. Maurina, H., R. Varna, and S. K. Kondratovich. 1969. Effect of growth conditions on the level of B vitamins in the generative organs of corn during flowering. Vop. Biol. Mater. Kong. 1968 61-69.

2808. Mawson, E. H., and S. Y. Thompson. 1948. A note on the estimation of vitamin B1 in urine. Biochem. J. 43(1):2-5.

2809. May, C. D., B. B. Levine, and G. Weissmann. 1970. Effects of compounds which inhibit antigenic release of histamine and phagocytic release of lysosomal enzyme on glucose utilization byleukocytes in humans. Proc. Soc. Exp. Biol. Med. 133(3): 758-763.

2810. May, D. G., and M. K. Carter. 1970. Effect of vasoactive agents on urine and electrolyte excretion in the chicken. Am. J. Physiol. 218(2):417-422.

2811. Mayfield, H. L., and M. T. Hedrick. 1949. Thiamine and riboflavin retention in beef during roasting, canning, and corning. J. Am. Dietetic Assoc. 25:1024-1027.

2812. Maymone, B., and A. Battaglini. 1955. Digestibility and nutritive value of carob-seed embryo. Ann. Ist. Sper. Zootec. Rome 5:217-224.

2813. Mayor, D. V., and D. H. Williamson. 1967. Effects of nicotinic acid on the acetoacetate and 3-hydroxybutyrate concentrations of rat blood and liver. Biochem. J. 104(3):57.

2814. Mazza, L., and H. Gandolfi. 1960. Histopathological aspects of chronic poisoning with 6-aminonicotinamide. Biol. Lat. (Milano) 13:361-368.

2815. Mazzetti, G. M. 1959. Research on renal pharmacodynamics. Influence of nicotinic acid on renal function, studied by the depuration test. Minerva Nefrol. 74-79.

2816. McCay, J. B. 1946. Nutritive value of the U.S. food supply. J. Home Econ. 38(6):333-337.

2817. McCoy, T. A., and J. Q. Snyder. 1950. The use of Streptococcus faecalis, A.T.C.C. No. 6057, as a test organism in a microbiological assay. Proc. Okla. Acad. Sci. 31:100-104.

2818. McCusker, K., K. Y. Ota, W. W. Michaux, and A. A. Kurland. 1962. N-(2,5-dimethyl-1-pyrrolyl)isonicotinamide in the treatment of the inactive chronically psychotic patient. J. New Drugs 2(4):232-238.

2819. McElvain, S. M., and M. A. Goese. 1941. Preparation of nicotinic acid from pyridine. J. Am. Chem. Soc. 63:2283-2284.

2820. McGowan, J. P. 1939. Nicotinic acid, pentose-nucleotides and anaemia. Nature 144:244-245.

2821. McGraw, J. Y. 1959. Regulation of capillary resistance. IV. Influence of vitamins and hormones on the growth and capillary resistance of the guinea pig. Laval. Med. 27:660-710.

2822. McIlwain, H. 1942. The biochemical specificity of sulfanilamide and of other antibacterial agents. Science 95:509-511.

2823. McIlwain, H. 1955. Mediation of metabolic response in cerebral tissues to electrical impulses. Congr. Intern. Biochim., Resumes Communs., 3d Congr., Brussels 80.

2824. McIlwain, H. 1956. Anaerobic glycolysis of cerebral tissues and a second, electrically-induced, metabolic defect. Biochem. J. 63(2):257-263.

2825. McIlwain, H., and I. Grinyer. 1950. Concentration or exclusion of some heterocyclic compounds by brain cortex, in relation to their effects on carbohydrate metabolism. Biochem. J. 46(5):620-628.

2826. McIlwain, H., and M. A. Tresize. 1957. The speed of several cerebral reactions involving the nicotinamide coenzymes. Biochem. J. 65(2):288-296.

2827. McIlwain, H., J. Thomas, and J. L. Bell. 1956. The composition of isolated cerebral tissues: Ascorbic acid and cozymase. Biochem. J. 64(2):332-335.

2828. McIntire, J. M., H. A. Waisman, L. M. Henderson, and C. A. Elvehjem. 1941. Nicotinic acid content of meat and meat products. J. Nutr. 22(5):535-540.

2829. McMillen, W. N., R. W. Luecke, and F. Thorp, Jr. 1949. The effect of liberal B-vitamin supplementation on growth of weanling pigs fed rations containing a variety of feedstuffs. J. Animal Sci. 8:518-523.

2830. McVicar, R. W., and G. H. Berryman. 1942. Nicotinic acid in foods. J. Nutr. 24(3):235-243.

2831. Meade, R. J., L. E. Hanson, H. E. Hanke, K. P. Miller, J. W. Rust, R. S. Grant, and M. E. Tumbleson. 1969. B-vitamin supplementation of conventional diets for growing swine. Minn. Agr. Exp. Sta. Tech. Bull. 263:3-15.

2832. Meani, A. 1970. Influence of various steroids on tryptophan-nicotinic acid metabolism. Acta Vitaminol. Enzymol. 24(3):81-103.

2833. Meani, A., and G. Cartei. 1970. Comparison of variations of tryptophan-nicotinic acid metabolism and of the blood levels of ceruloplasmin and transferrin during pregnancy and treatment with contraceptives or estrogens. Acta Vitaminol. Enzymol. 24(6): 231-235.

2834. Mears, A. R. R. 1942. Pellagrin's progress. S. African Med. J. 16:147-148.

2835. Meckel, R. B., and G. Anderson. 1945. Thiamine retention and composition of U.S. Army bread. Cereal Chem. 22(5):429-437.

2836. Medini, G. 1943. The determination of nicotinic acid in blood. Boll. Soc. Ital. Biol. Sperim. 18(5):149-150.

2837. Medisan, A. 1968. Compositions for topical treatment of muscular pains. Brit. Pat. 1,106,580.

2838. Medlicott, R. W. 1945. Nicotinic acid in the treatment of some psychiatric syndromes. N.Z. Med. J. 44:28-33.

2839. Medveczky, E. 1960. A micromethod for testing for niacin. Nature (London) 186:332.

2840. Mehlhorn, C. 1970. Contact eczeme from beta-pyridylcarbinol (Radecol comp.). Allerg. Asthma (Leipzig) 16:75-80.

2841. Mehler, A. H., K. Yano, and E. L. May. 1964. Nicotinic acid biosynthesis. Control by an enzyme that competes with a spontaneous reaction. Science 145(3634):817-819.

2842. Mehta, S. M. 1957. Metabolic aspects of vitamins. Discussion held at the 44th session, Indian Sci. Congr.,Calcutta, 1957. Proc. Indian Sci. Congr. 1957(4):60-64.

2843. Mehta, S. K., S. Kaur, G. Avasthi, N. N. Wig, and P. N. Chhuttani. 1972. Small intestinal deficit in pellagra. Am. J. Clin. Nutr. 25(6):545-549.

2844. Melloni, G. F., and D. Franzini. 1946. Vitamin PP and hepatic function. Boll. Soc. Ital. Biol. Sper. 21:155-156.

2845. Melnick, D. 1942. Collaborative study of the applicability of microbiological and chemical methods to the determination of niacin (nicotinic acid) in cereal products. Cereal Chem. 19(5):553-567.

2846. Melnick, D., and H. Field, Jr. 1940a. Determination of nicotinic acid in biological materials by means of photoelectric colorimetry. J. Biol. Chem. 134(1):1-16.

2847. Melnick, D., and H. Field, Jr. 1940bb. Chemical determination of nicotinic acid: inhibitory effect of cyanogen bromide upon the aniline side reactions. J. Biol. Chem. 135:53-58.

2848. Melnick, D., and B. L. Oser. 1943. Chemical differentiation between niacinamide and niacin in pharmaceutical products. Indust. Eng. Chem. Anal. Ed. 15:355-356.

2849. Melnick, D., B. L. Oser, and S. Siegel. 1941. Chemical determination of nicotinic acid content of flour and bread. Indust. Eng. Chem. Anal. Ed. 13:879-883.

2850. Meneghini, P., and F. Piccinini. 1958. Fibrinolytic activation of blood by nicotinic alcohol and acid. Arch. "E. Maragliano" Patol. e Clin. 14:69-74.

2851. Mera, A. F. 1945. Nicotinic acid and pellagra. Rev. Med. Vet. Buenos Aires 27:209-225.

* 2852. Merck and Co., Inc. 1968. The Merck Index. An encyclopedia of chemicals and drugs. Merck and Co., Inc., Rahway, N.J.

2853. Meredeith, P., and R. W. Cawley. 1971. Nutritional value of wheats, flour, and breads. Food Technol. N.Z. 6(6):22-23.

2854. Meric, N., and K. Ozkan. 1968. Comparison of the effects of Atromid-S, niacin, and cholemine on serum cholesterol, total lipid, and triglyceride levels. Ankara Univ. Tip Fak. Mecm. 21(4): 1063-1071.

2855. Merinello, E., P. Martelli, and C. Ricci. 1961. Behavior of glucose-6-phosphate dehydrogenase and transketolase during the hepatic biosynthesis of cozymase from nicotinamide by the fasting rat. Boll. Soc. Ital. Biol. Sper. 37:682-683.

2856. Merlo, P. 1946. The influence of nicotinamide on the uric acid balance in liver disease. Vitaminologica (Milan) 3-13.

2857. Merrill, J. M. 1958. Effect of nicotinic acid on the incorporation of radiocarbon into cholesterol. Circ. Res. 6(4):482-484.

2858. Merrill, J. M. 1963. The effect of nicotinic acid on rat liver triglycerides. In: 47th Annual meeting of the Federation of American Societies for Experimental Biology, 1963. Fed. Proc. 22(2 Pt. 1):517.

2859. Merrill, J. M. 1964. Fatty acid composition of the "fatty liver" induced by nicotinic acid. In: 48th Annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1964. Fed. Proc. 23(2 Pt. 1):243.

2860. Merrill, J. M. 1967. The effect of nicotinic acid on lipoprotein synthesis and triglyceride secretion by the liver. In: 2nd International Symposium on drugs affecting lipid metabolism, 1965, Milan, Italy, Part 1. Progr. Biochem. Pharmacol. 2:412-418.

2861. Merrill, J. M., and J. Lemley-Stone. 1957. Effects of nicotinic acid on serum and tissue cholesterol in rabbits. Circ. Res. 5: 617-619.

2862. Messina, R. 1948. Influence of vitamin PP on the creatine and creatinine metabolism in some diseases. I. In liver disease. Arch. Sci. Med. 85:263-270.

2863. Mestres, R. 1962a. Fluorimetric estimation of niacinamide. In: Societe de Pharmacie de Montpellier, Seance du 19 Feb. 1962. Ann. Pharmaceut. Franc. 20(12):944.

2864. Mestres, R. 1962b. Fluorimetric determination of nicotinamide. Trav. Soc. Pharm. Montpellier 22(1):46-48.

2865. Meszaros, J. 1948. Production of foods containing ascorbic acid. Magyar Chemiai Folyoirat, 1945-1947 51-53:42-45.

2866. Metlitskii, L. V., and V. M. Trekhomskaya. 1955. Peculiarities of chemical composition of citrus fruit of Georgian S.S.R. Biokhim. Plodov i Oveshehei. Akad. Nauk S.S.S.R. Inst. Biokhim. Shernik 3:163-175.

2867. Mettler, F. A., and H. M. S. Smith. 1966. Administration of the antimetabolite 6AN(6-aminonicotinamide) to horses. Cornell Vet. 56(1):123-128.

2868. Metys, J., N. Wagner, J. Metysova, and A. Herz. 1969. Central antinociceptive action of cholinomimetic agents. Int. J. Neuropharmacol. 8(5):413-425.

2869. Meyer, B. H., W. F. Hinman, and E. G. Holliday. 1947. Retention of some vitamins of the B-complex in beef during cooking. Food Res. 12(3):203-211.

2870. Meyer, B., M. Mysinger, and R. Buckley. 1963. The effect of three years of freezer storage on the thiamine, riboflavine, and niacin content of ripened and unripened beef. J. Agr. Food Chem. 11(6):525-527.

2871. Meyer, J., R. Sartory, J. Malgras, and P. Bischhausen. 1956. The influence of therapy with antibiotics upon niacinemia in tuberculosis. Bull. Assoc. Diplomes Microbiol. Fac. Pharm. Nancy (64):34-38.

2872. Meyer, W. C. 1941. On the use of nicotinic acid for chronic diarrhea from anacidity of the stomach. Munchener Med. Wochenschr. 88(25):707-708.

2873. Mgaloblishvili, B. I. 1971. Rheoencephalographic study of vascular responses in schizophrenia. Soobshch. Akad. Nauk Gruz S.S.R. 64(2):485-488.

2874. Michaelis, D., H. J. Hahn, R. Michael, S. Knospe, H. Schaefer, E. Jutzi, and P. Wulfert. 1970. Effects of the intravenous infusion of nicotinic acid on blood concentrations of substrates, metabolites, and hormones in juvenile-onset diabetes. Diabetologia 6(6):550-557.

2875. Micheli, H., and L. A. Carlson. 1971. Study on isolated adpiose tissue of the nicotinic acid-induced free fatty acid rebound phenomenon with a comparison with prostaglandin E1. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970, 323-328.

2876. Michkel, M. A., and W. F. Webb. 1967. Mechanisms underlying the hypolipemic effects of atromid S, nicotinic acid and benzmalecene-I. Metabolism of free fatty acid-albumin complex by the isolated perfused liver. Biochem. Pharmacol. 16:897-905.

2877. Mickelsen, O., and L. L. Erickson. 1945. F2 (fluorescent substance) excretion of normal men on different levels of niacin intake. Proc. Soc. Exptl. Biol. Med. 58:33-36.

2878. Mickelsen, O., and A. Keys. 1943. Composition of sweat, with special reference to the vitamins. J. Biol. Chem. 149:479-490.

2879. Mickus, R. R. 1955. Seals enriching additives on white rice. Food Eng. 27(11):91-93.

2880. Middleton, E., Jr., and A. Devi. 1963. Effect of nicotinamide on in vitro histamine release and slow-reacting substance formation in anaphylactically sensitized lung and its relation to acid-soluble nucleotides. J. Allergy. 34:331-336.

2881. Mielsch, M., H. Grimberg, U. Dold, and H. Holzer. 1962. Influence of nicotinamide on the concentration of diphosphopyridine nucleotide, glycolysis and viability of ascites tumor cells following treatment with carcinostatic ethyleneimine compounds. Biochim. Biophys. Acta 62(3):519-524.

2882. Miettinen, T. A. 1968. Effect of nicotinic acid on catabolism and synthesis of cholesterol in man. Clin. Chim. Acta 20(1): 43-51.

2883. Miettinen, T. A. 1970. Drugs affecting bile acid and cholesterol excretion. Atheroscler., Proc. Int. Symp., 2nd 508-515.

2884. Miettinen, T. A. 1971a. Effects of nicotinic acid on cholesterol synthesis in man. Metab. Eff. Nicotinic Acid Its. Deriv., Pro. 649-658.

2885. Miettinen, T. A. 1971ba. Effect of nicotinic acid on the fecal excretion of neutral sterols and bile acids. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 677-686.

2886. Miettinen, T. A. 1971c. Effect of nicotinic acid on glucuronidation capacity in man. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1111-1113.

2887. Miettinen, T., M. R. Taskinen, R. Pelkonen, and E. A. Nikkila. 1969. Glucose tolerance and plasma insulin in man during acute and chronic administration of nicotinic acid. Acta Med. Scand. 186(4):247-253.

2888. Mihel'son, D. A. 1969. Effects of thiamin and niacin on biochemical processes in animals exposed to vibration. Vop. Pitan. 28(6):54-58.

2889. Mikes, A., and V. Dratil-Stevanovic. 1961. Effect of nicotinic acid on sideremia, bilirubinemia and total iron-binding capacity of the blood (TIBC). Srpski Arh. Celok. Lek. 9:981-989.

2890. Mikhalevskaya, L. A. 1970. The use of nicotinic acid in the treatment of patients with toxoplasmosis. Vrach. Delo 3:147-149.

2891. Mikhalevskaya, L. A., M. K. Mikhalyuk, and V. Y. Mironov. 1970. The effect of pyrimethamine and sulfademezine on the co-enzymatic forms of nicotinic acid in the blood and organs of white rats. Farmakol. Toksikol. 33(6):701-702.

2892. Mikhel'son, D. A. 1969. Effect of vitamin B1 and niacin on the course of biochemical processes in organisms exposed to the action of vibration. Vop. Pitan. 28(6):54-58.

2893. Mikhlin, S. Y., M. F. Nesterin, and N. P. Bochkov. 1964. Secretion of intestinal enzymes in experimental niacin insufficiency induced by administration of beta-acetylpyridine. Vrachebnoe Delo (9):40-43.

2894. Mikkelsen, V. H. 1939. Nicotinic amide and nicotinic acid. Arch. Pharm. Chem. 46:479-497.

2895. Mile, J. P. 1965. Aluminum nicotinate: a hypocholesteremic agent. Current. Therap. Res. 7:392-400.

2896. Mileikovskii, Y. A. 1966. The effect of nicotinic acid on the blood supply to the brain. Tr. Pervogo Mosk. Med. Inst. 47:329-334.

2897. Milhorat, A. T. 1944. A color reaction of ascorbic acid with derivatives of pyridine, piperidine, quinoline and isoquinoline. Proc. Soc. Exptl. Biol. 55:52-55.

2898. Miller, D. E., and C. R. Gilmore. 1968. Titanium dioxide-whitened comestible compositions. U.S. Pat. 3,579,356.

2899. Miller, E. C., and C. A. Baumann. 1944. The maintenance of adult rats on diets low in certain B vitamins. J. Nutr. 27:319-328.

2900. Miller, J., and R. P. Abernathy. 1965. Metabolic patterns in preadolescent children. XIV. Excretion of niacin or tryptophan metabolites by girls fed controlled diets supplemented with nicotinamide. J. Nutr. 86(3):309-312.

2901. Miller, O. N., J. G. Hamilton, and G. A. Goldsmith. 1960. Investigation of the mechanism of action of nicotinic acid on serum lipid levels in man. Am. J. Clin. Nutr. 8(4):480-490.

2902. Miller, O. N., J. G. Hamilton, and G. A. Goldsmith. 1962. On the mechanism of action of nicotinic acid in lowering serum lipids. Am J. Clin. Nutr. 10(4):285-296.

2903. Miller, O. N., M. Gutierrez, A. Sullivan, and J. G. Hamilton. 1971. Effect of nicotinic acid and ring-substituted analogs on the in vivo biosynthesis of cholesterol and fatty acids in rat liver. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 609-620.

2904. Mills, L. C. 1958. Comparison of the therapeutic effectiveness of desiccated thyroid with and without added nutritional supplements in the treatment of hypothyroidism. Antibiot. Med. Clin. Ther. 5(2):114-119.

2905. Mima, H. 1955. Vitamin-enriched artificial cereal grains. Jap. Pat. 8125.

2906. Minestrini, A. 1952a. Effects of giving vitamin PP. 1. Vitamin PP and arterial pressure. Boll. Soc. Ital. Biol. Sper. 28:476-477.

2907. Minestrini, A. 1952b. Effects of giving vitamin PP. 2. Effect on the arterial blood pressure of giving vitamin PP at the same time as acetylcholine or adrenaline. Boll. Soc. Ital. Biol. Sper. 28:1181-1182.

2908. Minkh. A. A. 1963. Highly ionized air as a factor in enhancing physical work capacity. Vestn. Akad. Med. Nauk S.S.S.R. 18(2): 33-38.

2909. Minoru, I. 1968. Metabolic regulation of human growth hormone secretion. Nippon Naibunpi Gakkai Zasshi 44(9):977-986.

2910. Mirsky, I. A., G. Perisutti, and R. Jinks. 1957. The hypoglycemic action of metabolic derivatives of L-tryptophan by mouth. Endocrinology 60(2):318-324.

2911. Misaki, M. 1971. Hypnotic intoxication with reference to quantitative charges of vitamins in various organs. Nichidai Igaku Zasshi 30(8):661-677.

2912. Mischel, W. 1956. Chemical composition of the human placenta. Zentr. Gynaekol. 78:1089-1099.

2913. Mishkel, M. A., and W. F. Webb. 1967. The mechanisms underlying the hypolipidemic effects of atromid S, nicotinic acid, and benzmalecene, I. The metabolism of free fatty acid-albumin complex by the isolated perfused liver. Biochem. Pharmacol. 16(5):897-905.

2914. Missale, G., C. Dalla Valle, and L. Luzzatto. 1957. Decrease in the ascrobic acid of the adrenal by a strong dose of nicotinamide. Boll. Soc. Ital. Biol. Sper. 33:562-564.

2915. Mitani, F., A. P. Alvares, S. Sassa, and A. Kappas. 1971. Preparation and properties of a solubilized form of cytochrome P-450 from chick embryo liver microsomes. Mol. Pharmacol. 7(3):280-292.

2916. Mitchell, H. K., and E. R. Isbell. 1942. The B vitamin content of normal rat tissues. Univ. Texas Pub. 4237:37-40.

2917. Mitchell, H. K., J. F. Nyc, and R. D. Owen. 1948. Utilization by the rat of 3-hydroxyanthranilic acid as a substitute for nicotinamide. J. Biol. Chem. 175(1):433-438.

2918. Mitev, I. P., N. A. Nikolov, G. B. Kosturkov, T. G. Tashev, and D. C. Panitsa. 1962. Effect of nicotinic acid on the serum proteins and on the cardiovascular, respiratory, autonomic, and central nervous system. Mezhdun. Konf. Vitamin., Dokl. Suobsht., Sofia 1960 185-196.

2919. Mitolo, M., and D. Ruccia. 1960. On the correlations between four vitamin factors in the guinea pig (ascorbic acid, thiamine, nicotinamide, and meso-inositol; or ascorbic acid, rho-aminobenzoate, biotin, and riboflavine). Boll. Soc. Ital. Biol. Sper. 36:97-99.

2920. Mitra, B. R., and D. K. Chaudhuri. 1957. Effect of cooking on the bound nicotinic acid of some purebred strains of rice. Ann. Biochem. Exptl. Med. (Calcutta) 17:49-52.

2921. Miura, S., L. Burzio, and S. S. Koide. 1972. Studies on deoxyribonucleic acid synthesis in uteri of immature mouse. Horm. Metab. Res. 4(4):273-277.

2922. Miyamoto, H., A. Ichikawa, K. Takahashi, and O. Fujita. 1967. Chlorinated polypropylenes. Jap. Pat 71 22,208.

2923. Miyamoto, T., and T. Hagiwara. 1953. Assay of nicotinic acid in foods by using Lactobacillus casei. Repts. Sci. Living Osaka City Univ. (3), 1:8-13.

2924. Miyamoto, T., H. Morita, and M. Itami. 1956. Loss of nicotinic acid by cooking. J. Japanese Soc. Food Nutr. 9(3):143-145.

2925. Miyazaki, M. 1966. Measurement of cerebral blood flow by the ultrasonic Doppler technique. Effects of several vasodilators on cerebral circulation, with special reference to aminophylline, nicotinic acid, and papaverine. Jap. Circ. J. 30(9):1203-1209.

2926. Mizuno, S., T. Taniguchi, H., Araki, and K. Hamada. 1971. Influence of harvest date on the storage of Satsuma oranges. Kobe Daigaku Nogakubu Kenkyu Kokoku 9(1-2):6-10.

2927. Mizuno, T., and H. I. H. P. Masahito. 1961. The effect of nicotinamide on epidermal mitotic activity in normal and adrenalectomized mice. J. Fac. Sci. Tokyo Univ. Sect. IV Zool. 9(2):213-222.

2928. Mjos, O. D. 1971. Effect of inhibition of lipolysis on myocardial oxygen consumption in the presence of isoproterenol. J. Clin. Invest. 50(9):1869-1873.

2929. Mjos, O. D., and S. Akre. 1971. Effect of catecholamines on blood flow, oxygen consumption, and release/uptake of free fatty acids in adipose tissue. Scand. J. Clin. Lab. Invest. 27(3):221-225.

2930. Mjos, O. D., B. Bugge-Asperheim, and F. Kiil. 1972. Factors determining myocardial oxygen consumption (MVO2) during elevation of aortic blood pressure. 2. Relation between MVO2 and free fatty acids. Cardiovasc. Res. 6(1):23-27.

2931. Miodecka, J., and B. Sekowska. 1968. Detection of nicotinic acid and its amide in nicotinonitrile, and isonicotinic acid and its amide in isonicotinonitrile by thin-layer chromatography. Chem. Anal. (Warsaw) 13(1):159-167.

2932. Mndzhoyan, A. L., G. L. Papayan, L. D. Zhurull, S. G. Karagezyan, L. S. Galstyan, and V. G. Sarafyan. 1969. Indole derivatives. Synthesis and a biological study of hydrazido-hydrazones of indole aldehydes and ketones series. Arm. Khim. Zh. 22(8):707-713.

2933. Modestov, V. K., and A. B. Sokolov. 1964. Distribution and excretion of nicotinic-14C acid in rats. Tr. Tsentr. Inst. Usoversh. Vrachei 71:194-200.

2934. Moerman, P. C. 1963. The effect of nicotinic acid and nicotinamide on the color of raw ground meat. Conserva (Hague) 12(1):9-12.

2935. Moers, A. M., and G. J. den Ottolander. 1962. Various trials on the effect of nicotinic acid and Complamin on fibrinolysis. Med. T. Geneesk. 106:1221-1225.

2936. Moglia, J. L. 1943. Study on the metabolism of nicotinic acid. An. Farm. y Bioquim. (Buenos Aires) 14(2):53-76.

2937. Mohan, V.S., B. L. Reid, and J. R. Couch. 1959. Chemical method for estimation of niacin in poultry feeds and premixes. J. Agric. Food Chem. 7:42-44.

2938. Mohran, Y. Z. 1967a. A new method for estimating nicotinamide intakes. Proc. Int. Congr., Nutr., 7th 1966 5:573-576.

2939. Mohran, Y. Z. 1967b. A new method for estimating nicotinamide intakes. Nutr. Dieta 9(3):177-182.

2940. Moiseeva, I. G. 1963. Chemical composition of chicken eggs and their nutritional and biological significance for humans. Tr. Inst. Genet. (Moskva) 30:357-375.

2941. Molitor, H. 1942. Vitamins as pharmacological agents. Fed. Proc. 1:309-315.

* 2942. Molnar, G. D., K. G. Berge, J. W. Rosevear, W. F. McGuckin, and R. W. P. Achor. 1964. The effect of nicotinic acid in diabetes mellitus. Metab., Clin. Exptl. 13(2):181-190.

2943. Molner, G. D., K. G. Berge, J. W. Rosevear, W. F. McGuckin, and R. W. P. Achor. 1964. The effect of nicotinic acid in diabetes mellitus. Metab. Clin. Expt. 13(2):181-190.

2944. Molotkov, V. I. 1966. Effect of a complex of vitamins on the degree of vitamin B1 and vitamin B2 saturation of the organism in elderly and senile individuals. Vrach. Delo (1): 68-70.

2945. Monche, J., J. Jimenez-Vargas, and M. Ferrer-Arenillas. 1955. Several factors of phosphatasemia apparent in blood serum. Rev. Espan. Fisiol. 11:219-223.

2946. Mondain-Monval-Gerondeau, M., J. Diot, and A. R. Ratsimamanga. 1967. Effects of dietary testosterone on body weight gain and skeletal and muscle development of the normal and vitamin-deficient prepuberal male rat. C. R. Acad Sci., Ser. D 265(7):548-552.

2947. Monroe, R. A., and C. W. Turner. 1949. The metabolism of thyroxine. Missouri Agr. Expt. Sta., Res. Bull No. 446, 76 pp.

2948. Montanaro, L., and S. Sperti. 1968. Effect of adenine and nicotinamide on amino acid incorporation of cell-free systems inhibited by diphtheria toxin and NAD. Arch. Sci. Biol. (Bologna) 52(2):159-166.

2949. Moore, E. L., E. Wiederhold, and D. Atkins. 1944. Changes occurring in orange and grapefruit juices during commerical processing and subsequent storage of the glass and tin packed products. Fruit Prod. J. 23(9):270-275.

2950. Moore, J. M. 1969. Polarographic assay of niacinamide in pharmaceutical preparations. J. Pharm. Sci. 58:1117-1120.

2951. Moore, M. T. 1940. Treatment of multiple sclerosis with nicotinic acid and vitamin B1. Arch. Internal Med. 65:1-20.

2952. Morandini, G., and G. D'yala Valva. 1961. Sphygmic activity of the upper extremity. Pharmacodynamic investigations by intraarterial administration of drugs and iontophoresis in subjects with Raynaud's disease. II. Effect of muscle-relaxant drugs and histamine. Rass. Neurol. Veg. 15:403-419.

2953. Morczek, A., and D. Muecke. 1957. Effect of ionizing radiation on the biological effect of B-complex vitamins. Strahlen-therapie 102:535-538.

2954. Morel, M. 1941. Decomposition of nicotin amide by Proteus vulgaris. Ann. Inst. Pasteur (Paris) 67:285-298.

2955. Morel, M., and J. Baratte. 1943. The nicotinamide content of cow's milk. Lait 23:147-149.

2956. Morell, T. 1939. The vitamin nature of nicotinic acid amide. Deut. Med. Wochschr. 65:1126-1127.

2957. Morelli, A., and S. Di Lauro. 1944. Influence of nicotinic acid and nicotinamide on hepatic function. Boll. Soc. Ital. Biol. Sper. 19:32-34.

2958. Morelli, A., and D. Greco. 1939. On the nature of hyperglycemia due to nicotinic acid. Arch. Sci. Biol. (Naples) 25(6):506-509.

2959. Morelli, A., and F. P. Oliva. 1942. Nature of hyperglucemia after nicotinic acid; influence of nicotinic acid on the blood-sugar curve following administration of adrenaline, insulin and thyroxine. Arch. Sci. Biol. (Italy) 28:279-284.

2960. Moretti, A., C. Ciceri, and G. Suchowsky. 1969. Effect of a combination of B-complex vitamins and ascorbic acid on liver lipid content in rats intoxicated with ethyl alcohol. Arzneim.-Forsch. 19(10):1742-1743.

2961. Morgan, A. F. 1941. The effect of imbalance in the "filtrate fraction" of the vitamin B complex in dogs. Science 93:261-262.

2962. Morgan, A. F., G. MacKinney, and R. Cailleau. 1945. Losses of ascorbic acid and four B vitamins in vegetables as a result of dehydration, storage and cooking. Food Res. 10(1):5-15.

2963. Morgan, A. F., L. E. Kidder, M. Hunner, B. K. Sharokh, and R. M. Chesbro. 1949. The thiamine, riboflavin and niacin content of chicken tissues as affected by cooking and frozen storage. Food Res. 14(5):439-448.

2964. Morgan, A. F., B. C. Carl, M. C. Hunner, L. E. Kidder, M. Hummel, and J. M. Peat. 1944. Vitamin losses in commercially produced dehydrated vegetables, cabbage, potatoes, carrots and onions. Fruit Prod. J. 23(7):207-211.

* 2965. Morgan, Z. R. 1955. A newer method of nicotinic acid therapy in headache of the vasoconstrictive type. J. Am. Geriat. Soc. 3(8):545-551.

2966. Moriwaki, T. 1958a. The urinary content of ketone bodies and its significance in the treatment of diabetes mellitus. I. Urinary excretion of ketone bodies and its relation to the types of diabetes mellitus and to the complications. Nippon Naibunpi Gakkai Zasshi 33:983-988.

2967. Moriwaki, T. 1958b. Significance of ketone bodies in management of diabetes mellitus. III. Influence of various types of treatment on the metabolism of ketone bodies in alloxan-diabetic rats. Nippon Naibunpi Gakkai Zasshi 34:583-588.

2968. Moriwaki, T. 1958c. Beta-hydroxybutyric acid dehydrogenase activity in alloxan diabetic animals. Nippon Naibunpi Gakkai Zasshi 34:904-909.

2969. Moriwaki, T., T. Amemori, and M. Wada. 1960. Beta-hydroxybutyric dehydrogenase activity in alloxan diabetic animals. Med. J. Osaka Univ. 10:507-511.

2970. Moriwaki, T., Y. Shigeta, M. Wada, K. Oji, and T. Yoshida. 1958. Quantitative study of urinary excretion of ketone bodies and its significance in the management of diabetes mellitus. Med. J. Osaka Univ. 8(2/3):455-464.

2971. Morley, A., P. Quesenberry, M. Garrity, and F. J. Stohlman. 1971. Inhibition of marrow growth by cyclic AMP. Proc. Soc. Exp. Biol. Med. 138(1):57-59.

2972. Morley, N. H., and C. A. Storvick. 1957. Oxidized pyridine nucleotides in various fractions of the blood and niacin and tryptophan metabolites in the urine of women on a controlled adequate dietary. J. Nutr. 63(4):539-554.

2973. Morley, N. H., C. A. Storvick, F. Duryee, M. Edwards, and I. Irgens-Moller. 1957. Oxidized pyridine nucleotides in various fractions of the blood and niacin and tryptophan metabolites in the urine of women on a controlled adequate diet. J. Nutr. 63:539-554.

2974. Mormone, V. 1957. Use of nicotinamide in deficient lactation. Pediatria, Naples 65:818-835.

2975. Morris, G. 1948. Hemicrania. Can. Med. Assoc. J. 59:565-567.

2976. Morris, S., and A. Jones. 1953. Plate-assay technique for biotin, nicotinic acid, and pantothenic acid. Analyst 78:15-20.

2977. Morrison, M. A. 1960. Amino acid balance and imbalance. IV. Specificity of threonine in producing an imbalance in diets deficient in niacin and tryptophan. J. Nutr. 71(3):296-302.

2978. Morrison, M. A., and A. E. Harper. 1960a. Effect of dietary level of niacin and tryptophan on blood and liver pyridine nucleotide concentrations. Fed. Proc. 19(1 Pt. 1):415.

2979. Morrison, M. A., and A. E. Harper. 1960b. Amino acid balance and imbalance. IV. Specificity of threonine in producing an imbalance in diets deficient in niacin and tryptophan. J. Nutr. 71:296-302.

2980. Morrison, M. A., M. S. Reynolds, and A. E. Harper. 1960. Amino acid balance and imbalance. V. Effect of an amino acid imbalance involving niacin on liver pyridine nucleotide concentration in the rat. J. Nutr. 72:302-308.

2981. Morselli, P. L., H. H. Ong. E. R. Bowman, and H. McKennis, Jr. 1967. Metabolism of -cotinine-2-14C in the rat. J. Med. Chem. 10(6):1033-1036.

2982. Morsiani, M., and A. Califano. 1960. Aspects of experimental treatment combined with 6-aminonicotinamide and diphosphopyridine nucleotide (DPN) in the mouse. Boll. Soc. Ital. Biol. Sper. 36(23):1391-1392.

2983. Moruzzi, G., C. A. Rossi, and A. Rabbi. 1949. Sodium 2-methyl-4-dimethylaminophenylphosphinite, a probable methyl donor. Science 110(2868):657-658.

2984. Moses, C. 1962. Pharmacology of drugs used in the control of hypercholesterolemia. Angiol. 13:59-68.

* 2985. Mosher, L. R. 1970. Nicotinic acid side effects and toxicity: A review. Am. J. Psychiat. 126(9):1290-1296.

2986. Mosonyi, J. 1954. Influence of vitamin C on hematopoiesis. Zentr. Allgem. Pathol. u. Pathol. Anat. 92:48-52.

2987. Mosso, H. E. 1960. Action of nicotinic acid on cholesterol and lipoproteins in atherosclerosis. Sem. Med. Buenos Aires 117:39-43.

2988. Mota, I., W. Dias da Silva, and J. F. Fernandes. 1960. The inhibition of mast cell damage and histamine release in anaphylaxis by pyridine and diphosphopyridine nucleotidase inhibitors. Comparison with compound 48/80. Brit. J. Pharmacol. Chemoth. 15:406-409.

2989. Motegi, T. 1960. Nicotinic acid metabolism in various eye diseases. Japan. J. Ophthalmol. 4(2):128-137.

2990. Mothes, E. 1964. A deficiency of zinc and biosynthesis of nicotinic acid by Mycobacterium tuberculosis (strain BCG). Z. Allgem. Mikrobiol. 4(1):42-58.

2991. Mothes, E., D. Gross, H. R. Schuette, and K. Mothes. 1961. Biosynthesis of nicotinic acid with Mycobacterium tuberculosis. Naturwissenschaften 48:623.

2992. Motoyoshi, K., A. Fujii, and M. Suzuki. 1968. Experimental edema of the mouse hind paw in response to local cold exposure. Nippon Yakurigaku Zasshi 64(3):301-313.

2993. Mouriquand, G., V. Edel, and R. Chighizola. 1948. Nicotinic acid, nicotinamide, and vestibular chronaxia. Compt. Rend. Soc. Biol. 142:1134-1135.

2994. Moussatche, H., and M. V. Dias. 1939. The action of nicotinic acid on the respiratory movement in monkeys (M. rhesus). The absence of suffocation caused by the nicotinic acid. Mem. Inst. Oswaldo Cruz 34:615-618.

2995. Moussatche, H., and A. Prouvost-Danon. 1961. Inhibition by nicotinamide and nicotinic acid of the histamine release in the anaphylactic reation in vitro. Influence of some metabolites. Anais Acad. Brasil. Cienc. 33:173-178.

2996. Moutafis, C. D., and N. B. Myant. 1971. Effects of nicotinic acid, alone or in combination with cholestyramine, on cholesterol metabolism in patients suffering from familial hyperbetalipoproteinemia in the homozygous form. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 659-676.

2997. Mowli, A. C. 1944. Nicotinic acid therapy. Antiseptic 41:456-458.

2998. Moyer, J. H. 1967. A current appraisal of drug therapy of atherosclerosis. Arch. Environ. Health 14(2):337-347.

2999. Moynihan, I. W., and R. Gwatkin. 1944. The effect of various diets on growing pigs. Sci. Agric. (Ottawa) 24(10):443-450.

3000. Mozgov, I. E., and V. V. Sobolev. 1964. Toxicity of nicotinic acid and its amide. Materialy IX-oi (Devyatoi) Nauchn. Konf. po Farmakol., Moscow, Sb. 38-39.

3001. Mozgov, I. E., S. M. Krylov, and F. M. Yushkin. 1964. Stimulating effect of nicotinic acid. Mater. Nauch. Konf. Farmakol., 9th, Moscow 34-37.

3002. Mrsulja, B. B. 1971. The influence of serotonine on the glycogen concentration in the rat brain in vitro. Iugosl. Physiol. Pharmacol. Acta 7(1):131-134.

3003. Mrsulja, B. B., and L. M. Rakic. 1972. Effect of biogenic amines on glycogen concentration in the rat brain. Iugoslav. Physiol. Pharmacol. Acta 8(1):1-8.

3004. Mueller, A., and S. H. Fox. 1947. Chemical determination of niacin. J. Biol. Chem. 167(1):291-292.

3005. Mueller, A., and S. H. Fox. 1951. Determination of nicotinic acid in pharmaceutical products. J. Am. Pharm. Assoc. Sci. Ed. 41(10):513-516.

3006. Mueller, P. B., and H. Moor. 1949. Vitamin determination in foods by chemical methods. Mitt. Lebensm. Hyg. 40:358-415.

3007. Mueller, R., and A. Knapp. 1961. On the transformation of tryptophan into nicotinic acid in vitamin B-6 deficient rats. Ernaehrungsforsch. 6:44-53.

3008. Muggeo, M., G. Allegri, A. De Antoni, U. Dusi, and G. Crepaldi. 1968. Effect of nicotinamide on urinary elimination of tryptophan metabolites in Hodgkin's disease. Acta Med. Patavina 28(4): 697-708.

3009. Muggeo, M., A. De Antoni, G. Allegri, C. Costa, and G. Crepaldi. 1970. Influence of nicotinamide on the urinary excretion of tryptophan metabolites in Hodgkin's disease. Clin. Chim. Acta 30(3):779-785.

3010. Mukherjee, S. L., and S. P. Sen. 1957. Stability of vitamin B12. Protetion by iron salts against destruction by vitamin B1 and nicotinamide. J. Pharm. Pharmacol. 9:759-762.

3011. Mullick, P., and U. N. Chatterji. 1969. Niacin inhibition of germination and early growth of certain common cereals of Rajasthan (India). Curr. Sci. 38(21):523-524.

3012. Mul'menko, A. M. 1966. The effect of vitamins B1 and PP on the nervous system in chronic trinitrotoluene poisoning. Tr. Perm. Med. Inst. 72:66-73.

3013. Mul'menko, A. M., and E. L. Pidemskii. 1966. The effect of vitamin B1 and PP on some variables of liver function in chronic trinitrotoluene poisoning. Tr. Perm. Med. Inst. 72:118-122.

3014. Munsell, H. E., L. P. Guild, C. B. Troescher, G. Nightingale, and R. S. Harris. 1948. Retention of thiamine, riboflavin, and niacin in cooked, enriched farina. J. Am. Dietetic Assoc. 24(4): 314-316.

3015. Munsell, H. E., F. Streightoff, B. Bendor, M. L. Orr, M. E. Richardson, and F. G. Koch. 1949. Effect of large-scale methods of preparation on the vitamin content of food. III. Cabbage. J. Am. Dietetic Assoc. 25:420-426.

3016. Murashige, K., D. McDaniel, and S. Chaykin. 1966. N-methylnicotinamide oxidation in hog liver. Biochem. Biophys. Acta 118(3): 556-565.

3017. Murata, K., H. Ikehata, M. Kato, and Y. Kamata. 1967. Relation between protein nutrition and B-vitamins: III. Urinary excretion of B-vitamins and their retention in liver of rats on amino acid devoid diets. Vitamins (Kyoto) 36(1):13-20.

3018. Murata, K., H. Ikehata, H. Kono, and K. Nakagawa. 1967. Relation between protein nutrition and B vitamins. I. Retention of B vitamins in organs of fasting rats or of rats on a protein-free diet. Bitamins 36(1):1-8.

3019. Muratori. F. 1940. The action of nicotinic acid and nicotinic amide on glucemia in normal persons. Gazz. Ospedali Clin. 61:290-292.

3020. Murea, L., A. Iacob, and I. Calafeteanu. 1958. The determination of nicotinic acid and of nicotinamide in pharmaceutical preparations by means of physicochemical methods. Farmacia (Bucharest) 6:333-349.

3021. Murphy, R. A., Jr., J. N. McClure, Jr., F. W. Cooper, Jr., and L. G. Crowley. 1950. The effect of Priscoline, papaverine, and nicotinic acid on blood flow in the lower extremity of man. A comparative study. Surgery 27:655-663.

3022. Murthy, M. R. V., and D. A. Rappaport. 1963. Biochemistry of the developing rat brain. IV. Effect of nicotinamide on brain and liver mitochondria. Biochim. Biophys. Acta 48(1):71-76.

3023. Murthy, P. S. V. R., and B. V. R. Sastri. 1968. Use of dehydrated meat protein hydrolyzate in the microbiological assay of some B-complex vitamins. Indian J. Med. Res. 56(11):1740-1742.

3024. Musakin, A. P., V. G. Pal'mskii, and E. N. Ivanova. 1969. Separation of some pyridinecarboxylic acids by paper electrophoresis. Zh. Anal. Khim. 24(9):1412-1414.

3025. Mushin, W. W., and H. M. Wood. 1944. Effect of nicotinic acid on post-operative vomiting. Brit. Med. J. I:719-720.

3026. Mustafaev, M. A. 1969. The effect of nicotinic acid on the urea-forming function of the experimentally disordered liver. Uch. Zap. Azerb. Sel'skokhoz Inst. Ser. Vet. 4:39-41.

3027. Myasnikov, A. L. 1950. Influence of certain vitamins on cholesterolemia and the development of experimental atherosclerosis. Klin. Med. U.S.S.R. 28(2):3-10.

3028. Myburgh, S. J., and J. W. Groenewald. 1953. The influence of enrichment of maize meal on the growth of rats. Onderstepoort J. Vet. Res. 26(2):235-240.

3029. Myers, D. K., D. E. DeWolfe, and K. Araki. 1962. Effects of X-irradiation and of metabolic inhibitors on rat thymocytes in vitro. Can. J. Biochem. Physiol. 40:1535-1552.

3030. Myers, G. S., N. L. Petrakis, and M. Lee. 1967. Effect of 6-aminonicotinamide and added vitamin A on fusion of embryonic rat palates in vitro. J. Nutr. 93(3):252-262.

3031. Naber, E. C., and E. J. Largent. 1965. Thalidomide teratogenesis in the developing chick embryo and its relation to vitamin metabolism. Poultry Sci. 44(6):1583-1591.

3032. Nadkarni, B. Y. 1965. A modified cyanogen bromide method for the determination of nicotinic acid in vegetable foodstuffs. Mikrochim. Ichnoanal. Acta 5:880-887.

3033. Nagagawa, I., T. Takahashi, T. Suzuki, and Y. Masana. 1969. Effect in man of the addition of tryptophan or niacin to the diet on the excretion of their metabolites. J. Nutr. 99(3):325-330.

3034. Nagayama, H. 1961. Studies on nicotinic acid synthesis in mycobacteria. II. Nicotinic acid production of human tubercle bacilli under various culture conditions. Sci. Rep. Res. Inst. Tohoku Univ. (Med.) 10:157-166.

3035. Nagayama, K., and A. Fujita. 1957. The synthesis of vitamins by intestinal bacteria in man and the effect of cellulose. V. Synthesis of niacin. J. Vitaminol. 3(1):24-29.

3036. Naguib, K. 1960. Growth and metabolism of Penicillium lilacinum Thom. with reference to the effects of riboflavin and nicotinic acid. Arch. Mikrobiol. 35(3):296-302.

3037. Naik, S. R., S. V. Gokhale, and S. M. Chittal. 1969. Effect of analeptics on brain pentobarbital levels and sleeping time in mice. Biochem. Pharmacol. 18(8):2038-2040.

3038. Naik, S. R., E. N. Rupawalla, and U. K. Sheth. 1970. Anti-inflammatory activity of thiamine and nicotinic acid. Biochem. Pharmacol. 19(11):2867-2873.

3039. Naito, S., and M. Mizutani. 1969. Absorption and excretion of drugs. XXXV. Biopharmaceutical studies on guaiacol glycerol ether and related compounds. 2. Hypocholesteremic action. Chem. Pharm. Bull. (Tokyo) 17(4):822-826.

3040. Naito, S., M. Mizutani, K. Kitao, and Nishimura. 1969. Absorption and excretion of drugs. XXXVI. Biopharmaceutical studies on guaiacol glycerol ether and related compounds. 3. Metabolites of guaiacol glycerol ether and its mononicotinate. Chem. Pharm. Bull. 17(9):1794-1798.

3041. Naito, S., K. Nakane, A. Nishimura, Y. Nishihata, and S. Ogata. 1966. Absorption and excretion of drugs. XXXII. Effects of mephenesin and niacin on plasma and organ cholesterol levels in rabbits. Yakuzaigaku 26(3):219-226.

3042. Naito, S., M. Mizutani, S. Osumi, K. Umetsu, T. Mikawa, Y. Nishimura, and N. Yamamoto. 1970. Absorption and excretion of drugs. XXXIX. Biopharmaceutical studies on guaiacol glycerol ether and related compounds. IV. Drug in blood and bile. J. Pharm. Sci. 59(12):1742-1745.

3043. Najjar, V. A. 1944. The laboratory diagnosis of nicotinic acid deficiency. An improved procedure for the determination of F2 (N-methylnicotinamide derivative) in urine. Bull. Johns Hopkins Hosp. 74(6):392-399.

3044. Najjar, V. A., and I. A. Ratcliffe. 1947. The lipotropic effect of N1-methylnicotinamide. Bull. Johns Hopkins Hosp. 80(2):142-148.

3045. Najjar, V. A., and V. White. 1944a. Identification of the fluorescent substance F2. Science 99(2571):284-285.

3046. Najjar, V. A., and V. White. 1944b. F2 and N1-methylnicotinamide. Science 100(2594):247-248.

3047. Najjar, V. A., R. S. Hall, and C. C. Deal. 1945. The methylation of nicotinamide. A simple and practical test for liver function. Bull. Johns Hopkins Hosp. 76(2):83-91.

3048. Najjar, V. A., V. White, and D. B. M. Scott. 1944. On the isolation and properties of the fluorescent factor F2 from human urine. Bull. Johns Hopkins Hosp. 74(6):378-391.

3049. Najjar, V. A., H. J. Stein, L. E. Holt, Jr., and C. V. Kabler. 1942. The excretion of specific fluorescent substances in the urine in experimental nicotinic acid deficiency. J. Clin. Invest. 21:263-267.

3050. Najjar, V. A., M. M. Hammond, M. A. English, M. B. Wooden, and C. C. Deal. 1944. The anti-black tongue activity of N-methylnicotinamide chloride. Bull. Johns Hopkins Hosp. 74(6):406-414.

3051. Nakada, H. 1953. Biological studies on isonicotinoyl hydrazide. II. Acute toxicity of isonicotinoyl hydrazide and its active groupings. Chemotherapy (Japan) 2:109-111.

3052. Nakagawa, I. et al. 1964. Amino acid requirements of children: Nitrogen balance at the minimal level of essential amino acids. J. Nutr. 83:115-118.

3053. Nakagawa, I., and Y. Masana. 1969. Assessment of nutritional status: protein. Koshu Eiseiin Kenkyu Hokoku 17(4):293-301.

3054. Nakagawa, I., and K. Tomabechi, 1955. Effect of vitamins on angular stomatitis. Vitamins (Japan) 8:41-44.

3055. Nakagawa, I., T. Takahashi, T. Suzuki, and Y. Masana. 1969. Effect in man of the addition of tryptophan or niacin to the diet on the excretion of their metabolites. J. Nutr. 99(3): 325-330.

3056. Nakamura, K., Y. Masuda, and H. Nakamura. 1967. Response of hepatic and small intestinal biosynthesis of cholesterol to nicotinic acid and anabolic steroids in rats. J. Atheroscler. Res. 7(2):253-256.

3057. Nakano, J. 1970. Effects of nicotinic acid on hormone-, theophylline- and dibutyryl cyclic AMP-induced lipolysis and on cyclic AMP-phosphodiesterase. Res. Commun. Chem. Pathol. Pharmacol. 1(6):769-779.

3058. Nakazawa, K., K. Ueda, T. Honjo, K. Yoshihara, Y. Nishizuka, and O. Hayai. 1968. Nicotinamide-adenine dinucleotide glycohydrolases and polyadenosine diphosphate ribose synthesis in rat liver. Biochem. Biophys. Res. Commun. 32(2):143-149.

3059. Nambaru, S. 1970. Action of pyridazine-3-carboxamide, an analog of nicotinamide, on bacteria. Bitamin 41(1):5-9.

3060. Nani, S. 1957. Urinary elimination of riboflavine, the vitamin B6 group, and vitamin PP in rats treated with prednisone. Acta Vitaminol. 11:163-168.

3061. Naranjo, R. 1962. Metabolism of labeled nicotinamide in mammary adenocarcinoma. Use Radioisotopes Animal Biol. Med. Sci., Proc. Conf., Mexico City, 1961 1:125-131.

3062. Narsinghani, V. G., and S. Kumar. 1970. Modifying effect of antibiotics and vitamins on chromosomal aberrations induced by EMS in pisum sativum. Labdev, Part B 8(4):248-251.

3063. Naruke, T., and Irikura. 1969. New nicotinic acid ester derivatives. 6. Serum cholesterol level lowering effect of 2,2,6,6-tetrakis-nicotinoyloxymethyl cyclohexanol K-31. J. Atheroscler. Res. 10(3):391-401.

3064. Narurkar, M. V., U. S. Kumita, and M. B. Sahasrabudhe. 1957. Pyridine nucleotide synthesis in host tissues of tumor-bearing animals. Brit. J. Cancer 11:482-486.

3065. Nasio, J. 1944. Action of algunas vitamins on experimental peptic ucer cincofenica. Vitamins: A, B1, nicotinic acid and nicotinamide, C, D2, and K. Rev. Med. Rosario 34(12):1238-1239.

3066. Nasio, J. 1946. Influence of some vitamins and hormones in the prevention of experimental cinchophen peptic ulcer. Rev. Gastroenterol. 13(3):195-204.

3067. Nasu, H., and G. L. Viale. 1961. On the use of nicotinic acid amide in the histochemical demonstration of pyridine nucleotide-bound enzymes in brain tissue. Histochemie 2: 322-331.

3068. Nath, M. C., and C. H. Chakrabarti. 1953. Effect of aceto-acetate and beta-hydroxy butyrate on riboflavin and nicotinic acid. Proc. Soc. Expti. Biol. and Med. 82(1): 5-7.

3069. Nath, M. C., and N. V. Shastri. 1969. Effect of aceto-acetate on urinary excretion of xanthurenic acid and other tryptophan metabolites in rats. Brit. J. Nutr. 23(1):153-155.

3070. Nath, M.C., N. V. Shastri, and S. G. Nayudu. 1969. Effect of acetoacetate on biosynthesis of niacin in vitro. Indian J. Exp. Biol. 7(2):130-131.

3071. Nath, N., A. E. Harper, and C. A. Elvehjem. 1959. Diet and cholesteremia. IV. Effects of carbohydrate and nicotinic acid. Proc. Soc. Expti. Biol. and Med. 102(3):571-574.

3072. Nava, A., F. Comesana, F. Lozano, B. L. Fishleder, and D. Sodi-Palleres (with A. Cuellar). 1958. The effect of nicotinic acid, phenyl-ethyl-acetamide, and a combination of both drugs on hypercholesterolemic dogs and human beings. Amer. Heart J. 56:598-606.

3073. Nava, G., and C. De Bac. 1952. Gastric reactivity to pharmacological stimuli. Arch. "E. Maragliano" Patol. e Clin 7: 691-712.

3074. Navab, E., and A. M. Asatoor. 1970. Studies on intestinal absorption of amino acids and a dipeptide in a case of Hartnup disease. Gut 11(5):373-379.

3075. Nava Rivers, A. 1962. Hypocholesterolemic action of nicotinic acid and analagous substances. Prensa Med. Mex. 27:55-7.

3076. Nava-Rivera, A., L. Bernal-Diaz, and M. Avendano-Olvera. 1964a. Relations between the metabolism of cholesterol and carbohydrates. II. Antagonism of nicotinic acid and D-thyroxine in euthyroid rats. Bol. Inst. Estud. Med. Biol. (Mexico) 12(3):415-421.

3077. Nava-Rivera, A., L. Bernal-Diaz, and M. Avendano-Olvera. 1964b. Relations between metabolism of cholesterol and carbohydrates. I. Antagonism of nicotinic acid and D-thyroxine to insulin in hypothyroid rats. Bol. Inst. Estud. Med. Biol. (Mexico) 22(2):323-330.

3078. Nava-Rivera, A., F. Rodriguez-Trujillo, and L. Bernal-Diaz. 1963. Hormone interrelations of the salivary glands. The salivary glands and the thyroid. I. Protection of the effects of methylthiouracil for some pyridines. Bol. Inst. Estud. Med. Biol. 21(1):25-38.

3079. Nava-Rivera, A., B. Williams, and G. Uruchurtu. 1962. The hypocholesterolemic effect of nicotinic acid in hypercholesterolemia induced with methylthiouracil. Bol. Inst. Estud. Med. Biol. (Mexico) 20:79-103.

3080. Nechay, B. R., and L. M. Pardee, Jr. 1965. Inhibition of N'-methylnicotinamide secretion by ouabain in the chicken kidney. J. Pharmacol. Exp. Therap. 147(2):270-276.

3081. Neeter, R., and N. M. M. Nibbering. 1971. Mass spectrometry of pyridine compounds. II. Hydrogen exchange in the molecular ions of isonicotinic and nicotinic acid as a function of internal energy. Org. Mass Spectrom. 5(6):735-742.

3082. Negishi, T., and A. Ichiyama. 1969. Metabolism of nicotinamide adenine dinucleotide. Bitamin 40(1):38-45.

3083. Neikes, K. 1960. Nicotinic acid in the treatment of vascular diseases. Med. Welt 38:1977-1984.

3084. Neilands, J. B., F. M. Strong, and C. A. Elvehjem. 1947. The nutritive value of canned foods. XXV. Vitamin content of canned fish products. J. Nutrition 34(6):633-643.

3085. Neimeister, R. P. 1969. Preliminary report on the technique of extracting niacin from Mycobacterium tuberculosis cultured on 7H10 agar. Amer. Rev. Resp. Dis. 100(3):401-402.

3086. Nelson, G. H., and J. I. Abbenhaus. 1957. Ethanol metabolism in vitamin deficiencies. I. Niacin. Proc. Soc. Exptl. Biol. and Med. 96(1):5-7.

3087. Nelson, R. A. 1961. The sorption of water, sodium and potassium in the small bowel of dogs during nicotinic acid deficiency. Dissertation Absts. 22(2):615-616.

3088. Nelson, R. A., C. F. Code, and A. L. Brown Jr. 1962. Sorption of water and electrolytes, and mucosal strucure, in niacin deficiency. Gastroenterology 42(1):26-35.

3089. Nemir, P., Jr., et al. 1967. Tolerance to denatured globin hemochromogen. An experimental study. Ann. Surg. 166:919-929.

3090. Neraal, L. 1960. Additive for meat and meat products. Norw. Pat. 98,023.

3091. Nerio, H., S. Pawlak, and W. Czarnecki. 1969. Separation of vitamins in poly B vitamin injections and yeast by ion-exchange column chromatography. Acta Pol. Pharm. 26(2):173-176.

3092. Nerurkar, M. K., and M. B. Sahasrabudhe. 1960. Synthesis of N'-methylnicotinamide in X-irradiated rats. Intl. J. Rad. Biol. 2(2):210-217.

3093. Nestel, P. J. 1964. Plasma triglyceride concentration and plasma free fatty acid changes in response to norepinephrine in man. J. Clin. Invest. 43(1):77-82.

3094. Nesterin, M. F., and S. Ya. Mikhlin. 1963. Enzyme secretion in the principal digestive glands in some conditions of experimental vitamin deficiency. Vopr. Pitaniya 22(5):19-22.

3095. Nesterin, M. F., and S. Ya. Mikhlin. 1964a. Effect of some B vitamin deficiencies on the exocrine activity of the pancreas. Byul. Eksperim. Biol. i Med. 57(1):41-44.

3096. Nesterin, M. F. and S. Ya. Mikhlin. 1964b. Secretory activity of the dog's digestive tract in deficiency of nicotinic acid. Vop. Pitan. 23(3):53-58.

3097. Nesterova, E. A. 1967. Methods of estimating vitamins in feeds. Izdat. "Kolos", Moscow, 224 pp.

3098. Neiter, K. J., and K. Bodenschatz. 1967. Inhibition of histamine N-methylation by some antihistamines. Biochem. Pharmacol. 16(8):1627-1631.

3099. Neugebauer, A., F. K. Splinter, D. Haefke, R. Kober, H. Shirlitz, and Klinger. 1969. Kinetic study of the enzymic hydroxylation of phenazone, oxidative O-demethylation of codeine, and N-demethylation of aminophenazone by rat liver microsomes. Biochem. Pharmacol. 18(7):1559-1576.

3100. Neuhann, W. 1970. Therapy of defective retinal circulation. Therap. Gegenwart 109(10):1465-1472.

3101. Neujahr, H. Y., and Z. Varga. 1966. Transport of B-vitamins in microorganisms. VII. The uptake of C14-niacinamide by non-proliferating cells and by protoplasis of Streptococcus faecalis. Acta Chem. Scand. 20(6):1529-1534.

3102. Neumann, H. H. 1971. B-complex and enriched flour as causes of atopic dermatitis. J. Am. Med. Assoc. 217:477.

3103. Neuwahl, F. J. 1943. Action of nicotinic acid on carbohydrate metabolism. Lancet 245(6264):348-351.

3104. Neuweiler, N. 1944. The supply of the fetal organism with nicotinic acid. Z. Vitaminforsch. 15:76-82.

3105. Neuweiler, W. 1944. The nicotinic acid content of human milk, and its relation to the amount supplied. Ztschr. Vitaminforsch. 15:193-197.

3106. Neuweiler, W. 1945. The influence of water-soluble vitamins (C, B1, B2, nicotinic acid, and pantothenic acid) on the iron and copper levels in the serum. Z. Vitaminforsch. 16:1-11.

3107. Neville, J. N., J. A. Eagles, G. Samson, and R. E. Olson. 1968. Nutritional status of alcoholics. Amer. J. Clin. Nutr. 21(11):1329-1340.

3108. Nevin, T. A., M. D. Appleman, and H. M. Kurtz. 1958. Availability of certain streptococcal growth factors in human saliva. J. Dental Research 37:527-531.

* 3109. Newbold, H. L., and L. R. Mosher. 1970. Niacin and the schizophrenic patient. Amer. J. Psychiat. 127:535-536.

3110. Nichele, G. 1943. Studies of the metabolism of nicotinic acid. Arch. Ital. Pediat. Puericolt. 10:233-258.

3111. Nichele, G. 1951. Nicotinic acid and trigonelline in urine after administration of nicotinic acid. Arch. Ital. Pediat. Puericult. 15:77-98.

3112. Nichele, G., and V. Boccardelli. 1951. Urinary excretion of nicotinic acid, nicotinuric acid, and trigonelline after administration of nicotinic acid and nicotinamide. Arch. Ital. Pediat. Puericult. 15:99-121.

3113. Nicolaysen, R., and P. Laland. 1938. The curative effect of nicotinic acid and of liver in the canine blacktongue disease. Skand. Arch. Physiol. 79:299-302.

3114. Nicoletti, F., A. M. Grasso, and G. Gasso. 1965. Use of radionuclides for studying blood-spinal fluid dynamics. Alterations induced by administration of pyrogenic and vasodilator substances. Acta Neurol. (Naples) 20(3):322-341.

3115. Nicrosini, F., and O. Piccinelli. 1960. Various drugs acting on the serum lipid pattern of atherosclerosis. Therapeutic significance of an extractive heparinoid. Drugs Affecting Lipid Metab., Proc. Symp., Milan pp. 508-511.

3116. Nielsen, W. 1958. Detection and determination of pyridine and its derivatives. Chemiker-Ztg. 82:137-138.

3117. Niemeijer, J. A. 1946a. Observations on nicotinic acid in the blood. Nederland. Tijdschr. Geneesk. 90:493-495.

3118. Niemeyer, J. A. 1946b. Presence of nicotinic acid (free and combined) in blood. Rec. Trav. Chim. 65(2):84.

3119. Nieschulz, O. 1970. Pharmacology of the active substances in betel. 3. Experiments with arecaidine. Arzneimittelforschung 20:218-229.

3120. Nigeon-Dureuil, M., M. Rabinowicz, and A. R. Ratsimamanga. 1956. The action of nicotinic acid, ascorbic acid, and nicoscorbine on the fate of the suprarenal corticosteroids and the evolution of scurvy in the guinea pig. J. Physiol. (Paris) 48:674-676.

3121. Nikki, P. 1969. Arecoline and halothane shivering in thryroxine-treated mice. Ann. Med. Exp. Biol. Fenn. 47(3):191-196.

3122. Nikkila, E. A. 1969. Effect of nicotinic acid on glucose metabolism. Diabetes, Proc. Congr. Int. Diabetes Fed., 6th 1967, 360-362.

3123. Nikkila, E. A. 1971a. Effect of nicotinic acid on hepatic lipogenesis and triglyceride synthesis and release. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 471-477.

3124. Nikkila, E. A. 1971b. Effect of nicotinic acid on adipose tissue lipoprotein lipase and removal rat of plasma triglycerides. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 487-496.

3125. Nikkila, E. A., and T. A. Miettinen. 1971. Nicotinic acid and gluconeogenesis in man. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 753-755.

3126. Nikkila, E. A., and O. Pykalisto. 1968. Induction of adipose tissue lipoprotein lipase by nicotinic acid. Biochim. Biophys. Acta 152(2):421-423.

3127. Nikkila, E. A., and O. Pykalisto. 1969. Influence of lipolytic and antilipolytic agents on synthesis of adipose tissue lipoprotein lipase. Advan. Exp. Med. Biol. 4:239-248.

3128. Nikl, J., and T. Lehky. 1961. Metabolism of heteroplasma. III. Influence of simultaneous administration of biologically active substances on the body weight of rats. Ceskoslov. Gastroenterol. Vyziva 15:107-111.

3129. Nikolaev, A. I., and A. K. Akhmadieva. 1959. Effect of koamid on certain blood indexes of irradiated mice, and on the survival of the latter. Med. Zhur. Uzbekistana (8):16-20.

3130. Nikolaev, A. I., and R. A. Alimov. 1964. Influence of some stimulators of hemopoiesis on the antitumor activity of sarcolysine. Vopr. Onkol. 10(10):78-81.

3131. Nikolaev, A. I., A. K. Akhmadieva, and T. G. Pankratova. 1959. Effect of coamide on the dehydrogenase activity of organs of white mice in acute radiation disease. Med. Zhur. Uzbekistana (7):53-60.

3132. Nikolaev, A. I., S. M. Khalifaev, and K. R. Mukhammadzhanov. 1966. Influence of complex compounds of trace elements on the intensity of glycine-14C inclusion into gamma-globulin and antibodies of irradiated and nonirradiated rats. Radiobiologiya 6(6):802-803.

3133. Nikolaev, A. I., K. R. Mukhamedzhanov, and S. M. Khalifaev. 1965. The effect of some complex trace element compounds on the phagocytic activity of leukocytes and agglutinin formation in nonirradiated and irradiated rabbits. Zh. Mikrobiol., Epidemiol. i Immunobiol. 42(2):90-95.

3134. Nikolics, I. K. 1962. Microcrystalloscopy in rapid informatory tests. Acta Pharm. Hung. 32:211-220.

3135. Nikolov, N. A. 1962a. Effect of nicotinic acid and its amide on higher nervous activity. Vop. Pitan. 21(2):64-68.

3136. Nikolov, N. A. 1962b. Effects of nicotinic acid and its amide on higher nervous activity. Activatis Nervosa Super. 4(3-4):411-415.

3137. Nilson, K. 1966. How does nicotinic acid influence lipids in humans? Farm. Revy 65(17):421-431.

3138. Nilson, K. M., F. G. Owen, and C. E. Georgi. 1967. Effect of abrupt ration change on rumen microorganisms and the niacin and vitamin B6 content of rumen fluid and milk. J. Dairy Sci. 50(7): 1172-1176.

3139. Nilsson, A., et al. 1967. Absorption and metabolism of lecithin and lysolecithin by intestinal slices. Biochim. Biophys. Acta 137:240-254.

3140. Nishino, H. 1957. Metabolism of niacin of Mycobacterium avium. Nagoya J. Med. Sci. 29:119-138.

3141. Nitulescu, I., L. Wasserman, and E. Copal. 1952. The action of nicotinic acid on thyroid and hypophyseal changes produced in cabbage goiter of rabbits. Acad. Rep. Populare Romane Filiala Iasi, Studii Cercetari Stiint. 3:254-270.

3142. Nitulescu, I., L. Wasserman, and D. Klingher-Wasserman. 1956. Effect of nicotinic acid on the evolution of avitaminosis of the rat. Acad. Rep. Populare Romine, Bul. Stiint. Sect. Stiint. Med. 8(1):49-61.

3143. Nitzescu, I. I., and C. Stoicescu. 1960-1961. Effect of vitamin PP (nicotinamide) on anaphylactic shock. Z. Vitamin. Hormon. Fermentforsch. 11:360-363.

3144. Nitzulescou, J., and L. Wasserman. 1958. Studies on the protective action of vitamin PP in syndromes of toxicity or deficiency. Sem. Hop. 34. Sem. Therap. (6):616-620.

3145. Niven, C. F., Jr., M. R. Washburn, and G. A. Sperling. 1946. Growth retardation and corneal vascularization with tyrosine and phenylalanine in a purified diet. Proc. Soc. Exptl. Biol. Med. 63(1):106-108.

3146. Niwa, S. 1955. Influence of calcium salts on riboflavine used for the enrichment of foodstuffs. Vitamins (Japan) 8:157-158.

3147. Nizhegorodov, V. M., and I. T. Kalinin. 1967a. Effect of long-term action of small concentrations of ammonia on the content of vitamins A, B1, B2, PP, and ascorbic acid in animals. Gig. Sanit. 32(2):102-104.

3148. Nizhegorodov, V. M., and I. T. Kalinin. 1967b. Effect of prolonged exposure to low concentrations of carbon monoxide and nitrogen oxides on the level of vitamin PP in the animal organism. Zdravookhr. Beloruss. 13(1):42-43.

3149. Nizhegorodov, V. M., and I. T. Kalinin. 1968. The effect of chlorophos on the content of certain vitamins in rat tissue. Vop. Pitan. 27:80-81.

3150. Nizhegorodov, V. M., I. T. Kalinin, and A. P. Voronin. 1971. Adequate supply of vitamins B2, B6, C, and PP to animals chronically and simultaneously exposed to carbon monoxide, nitrogen pentoxide, and ammonia. Biokhim. Patokhimiya Obmena Veshchestv. Mek. 133-138.

3151. Nizhegorodov, V. M., I. T. Kalinin, A. P. Voronin, N. G. Tsae, and I. Markhotski. 1969. The effect of prolonged, combined exposure to carbon monoxide, nitric oxide and ammonia on the supply and demand of the human organism in relation to vitamins A, B1, B2, B6, PP and C. Gig. Tr. Prof. Zabol. 13: 43-45.

3152. Njaa, L. R., F. Utne, G. Boge, and O. R. Braekkan. 1968. Amino acid composition and the protein value of four selected fish meals for the young chick. Fiskeridir. (Norway) Skr., Ser. Teknol. Unders. 5(5):12 pp.

3153. Noesen, R., and M. Mosinger. 1971. Magnesium-vitamin-pyroshock treatment. Prot. Vitae 16(3):111-112.

3154. Nojiri, T., and F. Tanaka. 1971. Phosphotransacetylase of lactic acid bacteria. V. Effects of some medium constituents on the phosphotransacetylase levels of Lactobacillus fermenti. Yakugaku Zasshi 91(5):525-533.

3155. Noll, C. I., and O. G. Jensen. 1941. The chemical determination of nicotinic acid in milk and milk derivatives. J. Biol. Chem. 140:755-762.

3156. Norcia, L. N., H. J. Brown, and R. H. Furman. 1959. Nonhypocholesterolemic action of nicotinic acid in dogs. Lancet 1255.

3157. Nordoey, A., and E. Gjone. 1970. Treatment of essential hypercholesterolemia with clofibrate and nicotinic acid. Acta Med. Scand. 188(6):487-490.

3158. Nordoey, A., and J. M. Roedset. 1971. Platelet function and platelet phospholipids in patients with hyperbetalipoproteinemia. Effect of nicotinic acid and clofibrate. Acta Med. Scand. 189(5):385-389.

3159. Norris, F. W. 1948. Vitamins in brewing materials and beer. Brewers Digest 23(8):45-48.

3160. Norris, L. C., and G. F. Heuser. 1945. Water-soluble vitamins. Ann. Rev. Biochem. 14:469-524.

3161. Nose, Y. 1949. Human tolerance tests on nicotinic acid. Eiyo to Shokuryo 2:116-118.

3162. Notario, A., and S. Esposito. 1960. Influence of nicotinamide and of 6-aminonicotinamide on the enzymatic activities and respiration of the erythrocytes and lymphatic tissues. Haematologica 45:1137-1154.

3163. Noto, T. 1969. Tissue transformations caused by nicotinamide and riboflavine in the isolated ectoderm of the early chick blastoderm. Miyazaki Daigaku Kybiku Gakubu Kiyo, Shizenkagaku (25):13.

3164. Noto, T., M. Sawada, K. Ando, and K. Koyama. 1969. Biological properties of mycophenolic acid. J. Antibiot. (Tokyo) 22(4): 165-169.

3165. Novakovskaya, A. A., and A. N. Tikhomirova. 1959. Effect of the content in the diet of protein and nicotinic acid on the metabolism of nicotinic acid in patients with dysentery. Znachenie Belka v Pitanii Zdorovogo i Bol'nogo Cheloveka, Sb. Tr. Inst. Pitaniya Akad. Med Nauk S.S.S.R. 166-190.

3166. Nozawa, R., S. Natori, M. Obinata, and D. Mizuno. 1968. DNA synthesis during niacin starvation in niacin requiring Escherichia coli. Biochem. Biophys. Res. Commun. 32(4):602-609.

3167. Nunn, S. L., W. N. Tauze, and J. L. Juergens. 1961. Effect of nicotinic acid on human cholesterol biosynthesis. Circulation 24(4 Pt. 2):1099.

3168. Nuvolone, U, and F. Gatti. 1950. A hematocirculatory change immediately following the intravenous administration of nicotinic acid. Acta Vitaminol. 4:219-222.

3169. Nye, E. R., and H. Buchanan. 1969. Short-term effect of nicotinic acid on plasma level and turnover of free fatty acids. J. Lipid Res. 10(2):193-196.

3170. Nymon, M. C., and W. A. Gortner. 1947. Niacin, riboflavin, and thiamin studies on dehydrated pork loaves. Food Res. 12(1):77-86.

3171. Obrecht, P., and N. E. Fusenig. 1966. The effect of vincaleukoblastine on glycolysis of tumor cells. European J. Cancer 2(2):109-115.

3172. O'Brien, J. R. 1934. Vitamin B3. Biochem. J. 28:926-932.

3173. O'Brochta, J. 1959. 8-Hydroxyquinoline and nicotinic acid. U.S. Pat. 2,999,094.

3174. Oda, A. 1961. The reactions of pyridils and related compounds with alkali. I. 2,2'-Pyridil and phenyl 2-pyridyl diketone. Nippon Kagaku Zasshi 82:478-480.

3175. Odello, V. 1959. Stimulation of vascular reactions in normal pregnancy and in toxicosis. Pathologica 51:569-572.

3176. Odland, L. M., R. L. Mason, and A. I. Alexeff. 1972. Bone density and dietary findings of 409 Tennessee subjects: II. Dietary considerations. Am. J. Clin. Nutr. 25(9):908-911.

3177. Oeriu, S., and I. Soimu. 1962. Biochemistry of biologic aging processes. I. Electrophoretic studies on serum protein fractions of the rat in relation to age and during treatment with vitamins. Z. Alternsforsch. 15:303-307.

3178. Oest, C. R. 1960. Treatment with nicotinic acid of patients with arteriosclerosis and abnormal serum lipid patterns. Nord. Med. 64:1380-1383.

3179. Oesterling, M. J., and W. C. Rose. 1952. Tryptophan requirement for growth and the utilization of its optical isomers. J. Biol. Chem. 196:33-43.

3180. Oettgen, H. F., J. A. Reppert, V. Coley, and J. H. Burchenal. 1960a. Effects of nicotinamide and related compounds on the antileukemic activity of 2-amino-1,3,4-thiadiazole. Cancer Res. 20:1597-1601.

3181. Oettgen, H. F., J. A. Reppert, V. Coley, and J. H. Burchenal. 1960b. Effects of nicotinamide and related compounds on the antileukemic activity of 2-amino-1,3,4-thiadiazole. Fed. Proc. 19(1 Pt. 1):416.

3182. Oettgen, H. F., J. R. Purple, V. C. Coley, I. H. Krakoff, and J. H. Burchenal. 1964. Potentiation of the antileukemic effects of 2-aminothiadiazole by isonicotinamide and derivatives. Cancer Res. 24(4):689-692.

3183. Ofori-Nkansah, N., and F. Von Bruchhausen. 1972a. The impairment of glycogen metabolism in adipose tissue by 6-aminonicotinamide as influenced by the inhibition of phosphofructokinase. Naunyn-schmeidebergs Archiv. Pharmacol. 272(2):143-155.

3184. Ofori-Nkansah, N., and F. Von Bruchhausen. 1972b. Metabolic alterations in Yoshida ascites tumour cells caused by 6-amino-nicotinamide and prevented by nicotinamide. Naunyn-Schmeidebergs Archiv. Pharmacol. 272(2):156-168.

3185. Ogawa, T., E. Hatanaka, and S. Nishimura. 1968. Niacin test for differentiation of Mycobacterium tuberculosis var. hominis from other acid-fast bacilli: XII. Clinical and bacteriogical examination of 2 cases with pulmonary tuberculosis var. hominis for a long period: III. Animal inoculation of the detected acid-fast bacilli. Kitasato Arch. Exp. Med. 41(3/4):23-36.

3186. Ogawa, T., E. Hatanaka, S. Nishimura, and K. Saito. 1968a. Niacin test for differentiation of Mycobacterium tuberculosis var. hominis from other acid-fast bacilli. XI. Clinical and bacteriological examination of the 2 cases with pulmonary tuberculosis which had excreted niacin test negative Mycobacterium tuberculosis var. hominis for a long period: II. Some properties of the acid-fast bacilli detected. Kitasato Arch. Exp. Med. 41(3/4):13-22.

3187. Ogawa, T., E. Hatanaka, S. Nishimura, and K. Saito. 1968b. Niacin test for differentiation of Mycobacterium tuberculosis var. hominis from other acid-fast bacilli: X. Clinical and bacteriological examination of the 2 cases with pulmonary tuberculosis which had excreted niacin test negative Mycobacterium tuberculosis var. hominis for a long period: I. Clinical observation. Kitasato Arch. Exp. Med. 41(3/4):1-11.

3188. Ogden, H. D., and C. L. Ching. 1962. Clinical study of headache relief with a niacin-containing compound. Headache 1:21-29.

3189. Ogino, S. 1951. Metabolism of ascorbic acid in the incubated hen egg. Igaku to Seibutsugaku (Med. and Biol.) 20:234-237.

3190. Ognivenko, V. M., and V. I. Yakubovskaya. 1970. Niamide (nicotinamide) action on cholesterol metabolism against the background of an atherogenic diet. Farmakol. Toksikol. (Moscow) 33(1):31-34.

3191. Ogunmodede, B. K., and V. A. Oyenuga. 1969. Vitamin B content of cowpeas (Vigna unguiculata Walp.) Pt. 1: thiamine, riboflavin and niacin. J. Sci. Fd. Agric. 20:101-103.

3192. Ohashi, T., and N. Ando. 1967. Water-holding capacity of meat. I. Determination of water-holding capacity of meat and the effects of various food additives on the water-holding capacity of meat. Miyazaki Daigaku Nogakubu, Kenkyu Jiho 14(2):381-389.

3193. Ohnishi, T. 1961. Changes in diphosphopyridine nucleotide contents of sea urchin eggs after fertilization and during mitotic phases, with special reference to the effect of nicotinamide. J. Fac. Sci. Tokyo Univ. Sect. IV Zool. 9(2):205-211.

3194. Oi, S., and Y. Satomura. 1967. Substrate specificity, mode of action, and of inhibition by organic acids of purified acetylesterase from Sclerotinia fungus. Agr. Biol. Chem. (Tokyo) 31(5):561-568.

3195. Oide, H. 1959. Effect of transplanted tumor on the pyridine nucleotide synthesis in the mouse liver. Gann 50:177-183.

3196. Oivin, I. A., and V. P. Baluda. 1962. The role of the fibrinolytic system of blood. Byul. Eksperim. Biol. i Med. 54(9):35-39.

3197. Oivin, I. A., V. I. Oivin, and V. P. Baluda. 1962. The role of fibrin in the mechanism of vascular permeability. Byul. Eksperim. Biol. i Med. 54(10):45-47.

3198. Oivin, I. A., M. A. Kir'yakov, L. V. Koroleva, L. L. Romanovskaya, A. A. Sveshnikov, O. Y. Tokarev, and L. I. Uklonskaya. 1965. Radiometric study of problems of pathogenesis and experimental therapy of inflammatory edema. Vestn. Akad. Med. Nauk S.S.S.R. 20(9):87-93.

3199. Oji, N. 1963. The inactivation of cortisol in experimental diabetic animals. Med. J. Osaka Univ. 13(2/3):293-298.

3200. Oka, H., and J. B. Field. 1967. Pyridine nucleotides in the thyroid gland. VIII. Effect of thyroid-stimulating hormone on nicotinic acid-14C incorporation into NAD, NADP, and NADPH. Endocrinology 81(6):1291-1296.

3201. Okada, K., and Y. Namba. 1972. Growth-inhibition of baker's yeast by cationic surface-active agents. IV. Inhibition against logarithmically growing cells and effects of some additives containing vitamins. Vitamins 45(6):333-339.

3202. Okamoto, Y., T. Tsuji, and T. Ueda. 1969. Synthesis of 2-substituted-6-amino-4,5-dihydropyrimidine. Chem. Pharm. Bull. 17(11): 2273-2278.

3203. Okano, T., and K. Tsuji, 1969. Electronic properties of N-heteroaromatics. XXXI. Interaction of the carcinogen 4-nitroquinoline 1-oxide with nicotinamide. Yakugaku Zasshi 89(3):297-301.

3204. Okayama, T. 1972. Factors which regulate growth hormone secretion. II. Influence of exogenous ATP on the secretion of human growth hormone. Med. J. Shinshu Univ. 17(1):13-19.

3205. Oko, O. L. 1966. Nutritive value of mushrooms. W. Afr. Pharm. 8(3):51-54.

3206. Okuda, Y. 1959. Studies on the methylation of pyridine compounds in animal organism. IV. Paperchromatographic examination for the behavior of nicotinic acid in rabbit organism. J. Biochem. (Tokyo) 46(8):1057-1059.

3207. Okuda, Y. 1960. Studies on the methylation of pyridine compounds in animal organisms. V. Comparison with the behaviour of nicotinic acid in some vertebrate animals. J. Biochem. (Tokyo) 48(1):13-17.

3208. Okumura, K., H. Sezaki, and K. Kakemi. 1972. Absorption of drugs from the skeletal muscle of the rats: IV. Absorption of cationic drugs from the muscle. Chem. Pharm. Bull. (Tokyo) 20(8):1609-1611.

3209. Oldham, H. G., M. V. Davis, and L. Roberts. 1946. Thiamine excretions and blood levels of young women on diets containing varying levels of the B vitamins, with some observations on niacin and pantothenic acid. J. Nutr. 32:163-180.

3210. Oliva, G., and A. Magrini. 1941. The distribution of nicotinic acid and nicotinic acid amide between plasma and blood corpuscles under normal conditions and in loading. Boll. Soc. Ital. Biol. Sper. 16:245-246.

3211. Olivo, O., and C. Rizzolil. 1960. Studies on growth factors in vitro: the action of vitamin PP antimetabolites and iodine. Riv. Biol. (Perugia) 52(1):3-26.

3212. Ooi, N. 1956. Urinary output of amino acids in children with nutritional dystrophy and the effect of riboflavine and nicotinamide upon these. Vitamins (Kyoto) 10:407-411.

3213. Ooi, N. 1957. Urinary output of amino acid nitrogen of children with nutritional dystrophy and the effect of riboflavine or nicotinamide upon it. Studies on the nutrition of children in Hirosaeki area. Tohoku J. Exptl. Med. 66(1):7-16.

3214. Opanashchenko, G. A. 1970. The effect of radiation therapy on the metabolism of vitamin PP and the possibility of its use in combined treatment of patients with carcinoma of the larynx. Sovrem. Probl. Otorinolaringol. Resp. Mezhved. Sb. 1:346-351.

3215. Oparin, A. G. 1971. Pathogenetic substantiation of the use of vitamin PP and B1 in ulcers. Kazan. Med. Zh. 4:22-24.

3216. Opitz, K., and Chu. 1968. Calorigenic action of catechol amines. Naunyn-schmiedebergs Arch. Pharmakol. 259(4):329-333.

3217. Oppel, T. W. 1942. Studies of biotin metabolism in man. J. Clin. Invest. 21(5):630.

3218. Orabona, M. L. 1954. Comparative action of thiamine and cocarboxylase on beri beri complicated by disturbances in vitamin equilibrium. Internatl. Zeitschr. Vitaminforsch. 25(2):170-175.

3219. Orange, R. P., and K. F. Austen. 1968. Pharmacologic dissociation of immunologic release of histamine and slow-reacting substance of anaphylaxis in rats. Proc. Soc. Exp. Biol. Med. 129(3): 836-841.

3220. O'Reilly, P. O. 1955. Nicotinic acid therapy and the chronic schizophrenic. Dis. Nerv. System. 16(3):67-72.

* 3221. O'Reilly, P. O. 1958. Some clinical aspects of nicotinic acid therapy in hypercholesterolaemia. Canad. Med. Assoc. J. 78:402-405.

3222. O'Reilly, P. O., and R. P. Keogh. 1958. Effect of niacin on the electroencephalogram of psychosis with cerebral arteriosclerosis. Dis. Nerv. System 19(3):100-103.

3223. O'Reilly, P. O., M. J. Callbeck, and A. Hoffer. 1959. Sustained-release nicotinic acid (Nicospan). Effect on cholesterol levels and leucocytes. Can. Med. Assoc. J. 80:359-362.

3224. O'Reilly, P. O., M. Demay, and K. Kotlowski. 1957. Cholesteremia and nicotinic acid. A.M.A. Arch. Internal Med. 100:797-780.

3225. Orent-Keiles, E., E. M. Hewston, and L. Butler. 1946. Effects of different methods of dehydration on vitamin and mineral value of meat. Food Res. 11(6):486-493.

3226. Oreshnikova, N. A., M. A. Novikova, and G. L. Zhdanov. 1965. Respiration and oxidative phosphorylation in mitochondria of regenerating liver. Vopr. Med. Khim. 11(3):67-72.

3227. Orru, A. 1939a. Effect of nicotinic acid, sodium nicotinate, nicotinic amide and trigonelline on blood pressure. Arch. Sci. Biol. (Naples) 25(5):487-492.

3228. Orru, A. 1939b. Action of nicotinamide on the erythrocytes and leucocytes of the blood of normal animals. Atti. Accad. Italia, Rend. Classe Sci. Fis., Mat. Nat. (7) 1:74-79.

3229. Orru, A. 1939c. Action of nicotinic acid on the erythrocytes and leucocytes of blood in normal animals. Atti. Accad. Lincei, Classe Sci. Fis., Mat. Nat. 29:333-343.

3230. Orskov, S. L. 1943. The effect of antipernicious-anemia substances, several vitamins and fe on the permeability of red blood cells of normal men. Chem. Zentr. 11:833-834.

3231. Orunesu, M., and G. Fornaini. 1952a. The mechanism of hepatic glycogenolysis by strong doses of nicotinamide. I. The behavior of glucose-6-phosphate phosphatase. Boll. Soc. Ital. Biol. Sper. 31:985-986.

3232. Orunesu, M., and G. Fornaini. 1955b. The mechanism of glycogenolysis with strong doses of nicotinamide. III. The behavior of some reactions of the oxidative metabolism of glucose. Boll. Soc. Ital. Biol. Sper. 31:1476-1478.

3233. Orunesu, M., and G. Fornaini. 1956. The mechanism of the hepatic glycogenolysis of strong doses of nicotinamide. IV. Behavior of the hepatic polysaccharide phosphorylase. Boll. Soc. Ital. Biol. Sper. 32:763-765.

3234. Orunesu, M., G. Fornaini, and L. Sacerdote. 1956. Mechanism of hepatic glycogenolysis with strong doses of nicotinamide. V. Behavior of the hepatic phosphoglucomutase. Boll. Soc. Ital. Biol. Sper. 32:1151-1153.

* 3235. Osmond, H., and A. Hoffer. 1962. Massive niacin treatment in schizophrenia. Review of a nine-year study. Lancet 1:316-319.

3236. Ota, S. 1955. The influence of various substances on the absorption of histamine in the large intestine and the mechanism of the absorption. Folia Pharmacol. Japon. 51:692-714.

3237. Otway, S., D. S. Robinson, M. P. Rogers, and D. R. Wing. 1971. Effects of nicotinic acid and of glucose on adipose tissue and heart clearing factor lipase activities and free fatty acid concentrations in the starved rat. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 497-514.

3238. Overman, D. O. 1971. Early biochemical changes in the embryonic rat heart after teratogen treatment. Teratology 4(2):183-190.

3239. Overman, D. O., R. E. Seegmiller, and M. N. Runner. 1972. Coenzyme competition and precursor specificity during teratogenesis induced by 6-aminonicotinamide. Develop. Biol. 28(4):573-582.

3240. Ozaki, A., Y. Inoue, and N. Hashiguchi. 1965. Compound alteration of diazepam. Yakuzaigaku 25(2):157-160.

3241. Ozols, R. F. 1971. Nicotinamide adenine dinucleotide stimulation of liquid phosphorylation in rat liver microsomes. Cytosol. 182pp.

3242. Paczek, K., and H. Wardynska. 1971. Assays of B-complex vitamins in pharmaceuticals by means of chromatographic separation. Part II. Assays of vitamins B1, B2, and PP (nicotinamide) in multivitamin dragees. Acta Pol. Pharm. 28(1):71-74.

3243. Paes, E., F. Grande Covian, and J. C. Oya. 1947-1948. Effect of nicotinamide on carbohydrate metabolism. Arch. Portugaises Sci. Biol. 9(1):20-22.

3244. Page, E., and F. M. Hanning. 1963. Vitamin B6 and niacin in potatoes. Retention after storage and cooking. J. Am. Diet. Assoc. 42:42-45.

3245. Page, H. M., E. S. Erwin, and G. E. Nelms. 1959. Effect of heat and solar radiation on vitamin A utilization by the bovine animal. Am. J. Physiol. 196:917-918.

3246. Page, R. C. 1967. Experimental lathyrism: a molecular disease of connective and vascular tissues. Diss. Abstr. B 28(5):1832.

3247. Pai, M. L. 1956. Urinary excretion of nicotinic acid in toxemia of pregnancy. J. Animal Morphol. Physiol. 3(2):79-86.

3248. Pai, M. L. 1958. Influence of cooking on the nutritional value of foods. IV. Thiamine, riboflavine, and nicotinic acid content of cooked foods. Indian J. Med. Res. 46:609-612.

3249. Pai, M. L. 1964. Levels of vitamin B complex, thiamine, riboflavine, and nicotinic acid in toxemias of pregnancy. Bull. Nat. Inst. Sci. India (25):171-175.

3250. Pai, M. L. 1965. Vitamin metabolism: Levels of thiamine, riboflavin and nicotinic acid in eclampsias. J. Anim. Morphol. Physiol. 12(1):104-106.

3251. Pai, M. L., and T. V. Patel. 1958. Some observations on the causative relationship between the thiamine, riboflavin and nicotinic acid deficiency and occurrence of toxaemias of pregnancy. Indian J. Med. Res. 46(5):722-726.

3252. Paladino, T., and G. Sanfilippo. 1946. The action of vitamin PP on the motility of the isolated uterus of guinea pigs. Boll. Soc. Ital. Biol. Sperim. 22(4):295-296.

3253. Palafox, A. L., and M. M. Rosenberg. 1956. Niacin content of molasses produced in different localities. Poultry Sci. 35:1127-1128.

3254. Palamarchuk, E. S., P. V. Khomenko, and E. F. Dovgan. 1970. Treatment of barbiturate coma with consideration of the cellular metabolism. Farm. Zh. (Kiev) 25(6):63-66.

3255. Paliev, K., D. Mircheva, and S. Kalenderov. 1970. Effect of the addition of vitamins B2, B3, B5, and B6 to low-value ration of vegetable feeds on the fattening of gilts. Zhivotnovud. Nauki 7(2):35-40.

3256. Palit, N. 1950. Meyer's synthesis of pyridines from acrylonitriles. Verification in the light of Gastaldi's objections. J. Indian Chem. Soc. 27:71-76.

3257. Pallini, V., and G. Pompucci. 1960. Codehydrogenases in liver of rats treated with nicotinamide. Boll. Soc. Ital. Biol. Sper. 36:515-517.

3258. Pallini, V., and C. Ricci. 1965. Formation of nicotinic acid nucleotides in the liver of nicotinamide-treated cats. Arch. Biochem. Biophys. 112(2):282-287.

3259. Pallini, V., G. Pompucci, and C. Ricci. 1962. Behavior of ADPR (adenosinediphosphoribose) and ATPR (adenosinetriphoribose) in the liver of normal and nicotinamide-treated rats. Boll. Soc. Ital. Biol. Sper. 38:399-400.

3260. Pallini, V., C. Ricci, and P. Martelli. 1965. Nicotinamide deamidase and synthesis of nicotinamide of adenine dinucleotide in the avian liver. Giorn. Biochim. 14(6):710-714.

3261. Pallini, V., C. Vasconetto, and C. Ricci. 1965. Induction of tryptophan pyrrolase in the liver of the rat treated with nicotinamide. Giorn. Biochim. 14(6):743-748.

3262. Pallotta, M. A., and R. F. Krause. 1963. Effect of vitamin A on certain blood constituents of geriatric subjects. Am. J. Clin. Nutr. 13:201-208.

3263. Pallucchini, M. 1960. Effect of nicotinic acid on experimental atheromatosis. Arch. Pat. Clin. Med. 37:98-106.

3264. Palumbo, E., G. Benvenuto, and Marcacci. 1968. Variations in the peripheral platelet and leukocyte count of rabbits treated with a combination of myeloid-stimulating and hepatoprotective substances. Boll. Soc. Ital. Biol. Sper. 64(18):1513-1517.

3265. Pancrazio, G., M. Vitali, and E. Marchese. 1957. Vitamin A. I. Lyophilization of vitamin A. Farmaco (Pavia), Ed. Prat. 12:417-424.

3266. Panosyan, A. K., and L. P. Puchinyan. 1971. Vitamin B synthesis by certain microorganisms of the peach rhizosphere. Dokl. Akad. Nauk Arm. SSR. 53(2):115-117.

3267. Panov, A. N. 1968. Effect of corticosteroid hormones on mitochondrial metabolism in rat brain and heart. Ukr. Biokhim. Zh. 40(1):3-6.

3268. Pant, K. C., Q. R. Rogers, and A. E. Harper. 1972a. Growth and food intake of rats fed tryptophan-imbalanced diets with or without niacin. J. Nutr. 102(1):117-130.

3269. Pant, K. C., Q. R. Rogers, and A. E. Harper. 1972b. Food selection studies of rats fed tryptophan-imbalanced diets with or without niacin. J. Nutr. 102(1):131-142.

3270. Pantyukhova, O. N. 1956. Nicotinic acid in the neurological clinic. Zhur. Nevropatal. i Psikhiatrii im. Korsakova 56:323-324.

3271. Panuccio, P., F. Cresci, and M. M. Brunori. 1959. Effects of nicotinic acid on the hemodynamics of the lesser circulation, on the saturation of the blood and on respiratory function. G. Geront. 7:743-754.

3272. Paolantonio, G., and U. Paolantonio. 1959. Action of nicotinic acid on the respiratory function of patients with pulmonary tuberculosis and with stress of the lesser circulation. Gass. Inter. Med. e Chir. 64:227-235.

3273. Paolantonio, U., and G. Sulli. 1948. Relationships between antibiotic substances and vitamin metabolism. 1. Action of penicillin on urinary excretion of nicotinic acid. 2. Action of penicillin on vitamin B1. Fisiol. e Med. Rome 16:215-217; 219-229.

3274. Paoletti, R. 1962. Comparative studies on hypocholestermic agents. Am. J. Clin. Nutr. 10:277-284.

3275. Paoletti, R., and R. Fumagalli. 1971. Effects of drugs on structure, biosynthesis and catabolism of nucleic acids, proteins, carbohydrates and lipids. Drugs acting on blood lipids. Fundam. Biochem. Pharmacol. 557-570.

3276. Paoletti, R., R. L. Lentati, and Z. Korolkiewicz. 1967. Pharmacological investigations on the prostaglandin E1 effect on lipolysis. Prostaglandins, Proc. Nobel Symp., 2nd, Stockholm 1966 147-159.

3277. Papa, S., K. S. Cheah, H. N. Rasmussen, I.-Y. Lee, and B. Chance. 1970. Mechanism of malate utilization in Ascaris muscle mitochondria. Eur. J. Biochem. 12(3):540-543.

3278. Pappalardo, P. 1946. Action of nicotinic acid and nicotinamide on the glucose content of human blood. Acta Neurol. (Naples) 1:102-110.

3279. Pappalardo, P., and G. Ottaviano. 1946. Calcium and potassium variations in human blood serum after injection of nicotinic acid. Acta Neurol. (Naples) 1:451-454.

3280. Pappas, P. W. 1972. Hymenolepis diminuta. Absorption of nicotinamide. Exp. Parasitol. 32(3):403-406.

3281. Paracchi, P., and N. Paracchi. 1946. Determination of vitamin PP (nicotinic acid) in the blood and urine of patients with carcinomas of the female genital tract under treatment by radium and by Roentgen irradiation. Vitaminologica (Milan) 112-122.

3282. Pardue, W. O. 1961. Severe liver dysfunction during nicotinic acid therapy. J. Am. Med. Assoc. 175:137-138.

3283. Parli, C. J., and G. J. Mannering. 1971. Inhibition of microsomal mixed-function oxidase activity with nicotinamide. Biochem. Pharmacol. 20(8):2118-2121.

3284. Parsons, W. B., Jr. 1960a. Production of fibrinolysin following administration of nicotinic acid to humans. Circulation 22(4 Pt. 2):795.

3285. Parsons, W. B., Jr. 1960b. Activation of peptic ulcer by nicotinic acid: report of five cases. J. Am. Med. Assoc. 173:1466-1470.

3286. Parsons, W. B., Jr. 1960c. The effect of nicotinic acid on serum lipids. Am. J. Clin. Nutr. 8(4):471-479.

3287. Parsons, W. B., Jr. 1961a. The effect of nicotinic acid on serum lipids. Am. Practit. 12:247-248.

3288. Parsons, W. B., Jr. 1961b. Treatment of hypercholestermia by nicotinic acid. Progress report with review of studies regarding mechanism of action. Arch. Intern. Med. (Chicago) 107:639-652.

3289. Parsons, W. B., Jr. 1961c. Treatment of hypercholesteremia by nicotinic acid. Progress report with review of studies regarding mechanism of action. Arch. Intern. Med. (Chicago) 107:639-652.

3290. Parsons, W. B., Jr. 1961d. Studies of nicotinic acid use in hypercholesteremia. Changes in hepatic function, carbohydrate tolerance, and uric acid metabolism. Arch. Intern. Med. (Chicago) 107:653-667.

3291. Parsons, W. B., Jr. 1962a. Evidence for temporary hepatic dysfunction, not damage, during nicotinic acid therapy in hypercholesteremic patients. In: American Heart Association Council on Arteriosclerosis, annual meeting, 1962. Circulation 26(4 Pt. 2):666.

3292. Parsons, W. B., Jr. 1962b. Use of nicotinic acid to reduce serum lipid levels. J. Am. Geriat. Soc. 10(10):850-864.

3293. Parsons, W. B., Jr. 1963a. Comparison of the effects of nicotinic acid and aluminum nicotinate in hypercholesteremic patients. In: 17th Annual meeting of the American Heart Association Council on Arteriosclerosis, 1963. Circulation 28(4 Pt. 2):668.

3294. Parsons, W. B., Jr. 1963b. Pharmacologic agents and lipid metabolism. Geriatrics 18:31-38.

* 3295. Parsons, W. B., Jr. 1963c. Use of nicotinic acid to reduce serum cholesterol and remove tissue cholesterol. Southern Med. J. 56:427-433.

3296. Parsons, W. B., Jr. 1964a. Reduction of serum lipids by nicotinic acid: Summary of eight years' experience. In: 13th Annual meeting, American College of Cardiology, New Orleans, 1964. Am. J. Cardiol. 13(1):126.

3297. Parsons, W. B., Jr. 1964b. The effect of nicotinic acid on the liver. Evidence favoring functional alternation of enzymatic reactions without hepatocellular damage. In: R. Altschul, Ed. Niacin in Vascular Disorders and Hyperlipemia. Charles C. Thomas: Springfield, Illinois, p. 263-286.

3298. Parsons, W. B., Jr. 1971. Treatment of hyperlipidemia: The rationale for combinations of lipid-lowering drugs. Clin. Med. 78(11):15-20.

* 3299. Parsons, W. B., Jr., and J. H. Flinn. 1957. Reduction in elevated blood cholesterol levels by large doses of nicotinic acid. J. Am. Med. Assoc. 165:234-238.

3300. Parsons, W. B., Jr., and J. H. Flinn. 1959. Reduction of serum cholesterol levels and beta-lipoprotein levels by nicotinic acid. Arch. A.M.A. Intern. Med. 103:783-790.

3301. Parsons, W. B., Jr., R. W. P. Achor, K. G. Berge, B. F. McKenzie, and N. W. Barker. 1956. Changes in concentration of blood lipides following prolonged administration of nicotinic acid to persons with hypercholesterolemia: preliminary observations. Proc. Staff Meetings Mayo Clinic 31:377-390.

3302. Parteni, L., M. Corneanu, and C. Popescu. 1954. Anticholinesterase effect of some compounds. Comun. Acad. Rep. Populare Romane 4:161-166.

3303. Parteshko, V. G., M. S. Pavlovskaya, and A. A. Lesyuis. 1973. Effect of exogenous lipoperoxides on the level of vitamin B in the liver of animals. Byull. Eksp. Biol. Med. 75(4):52-53.

3304. Parups, E. V., and I. Hoffman. 1967. Induced alkaloid levels in potato tubers. Am. Potato J. 44(8):277-280.

3305. Pascher, G., and H. Roecki. 1960. Quantitative determination of some water-soluble vitamins in the human epidermis of healthy-skinned subjects. Arch. Klin. u. Exptl. Dermatol. 210: 485-495.

3306. Pashovkin, V. G. 1956. Content of vitamins B1 and B2, and niacin in basic types of bread. Vitaminizatsiya Pishchevykh Produktov (Moscow) Sbornik 1956, 25-30.

3307. Pasquariello, G. 1964. Tryptophan-nicotinic acid pathway in diabetes mellitus. Acta Vitaminol. 18(5):225-234.

3308. Pasquariello, G. 1966. Effect of ACTH and cortisones on the conversion of tryptophan to nicotinic acid in humans. Reumatismo, Suppl. (5):482-486.

3309. Pasquariello, G., and L. Mainardi. 1970. Effect of corticosteroid treatment repeated at short intervals on the tryptophan-nicotinic acid pathway in man. Acta Vitaminol. Enzymol. 24(1-2):11-14.

3310. Pasquariello, G., and L. T. Tenconi. 1963. Alteration of the tryptophan-to-nicotinic acid conversion in rheumatoid arthritis. Reumatismo 15(3):266-272.

3311. Pasquariello, G., and L. T. Tenconi. 1964. Urinary excretion of nicotinic acid derivatives in rheumatoid arthritis. Lancet 7334: 675-676.

3312. Pasquariello, G., and L. T. Tenconi. 1967. Influence of ACTH on the tryptophan-nicotinic acid pathway in healthy subjects and in patients suffering from rheumatoid arthritis. Acta Vitaminol. Enzymol. 21(1):21-23.

3313. Pasquariello, G., A. Quadri, and L. T. Tenconi. 1964. Tryptophan-nicotinic acid metabolism in chronic alcoholics. Acta Vitaminol. 10:3-6.

3314. Pasricha, W. 1969. Effect of curdling on the thiamine, riboflavine, and nicotinic acid contents of milk. J. Nutr. Diet. 6(3):196-199.

3315. Pastan, I., et al. 1964. Nicotinic acid metabolism. I. Distribution of isotope in fermentation products of labelled nicotinic acid. J. Biol. Chem. 239:902-906.

3316. Patterson, E. B., J. R. Hunt, P. Vohra, L. G. Blaylock, and J. McGinnis. 1956. The niacin and tryptophan requirements of chicks. Poultry Sci. 35(3):499-504.

3317. Paulet, A. C., P. Barjon, and B. Descomps. 1967. Effects of beta-pyridyl carbinol on the plasma free fatty acids in normal man. Progr. Biochem. Pharmacol. 3:256-269.

3318. Pavlova, O. N., and L. M. Mirochnik. 1962. Acute arsine poisoning. Vopr. Neotlozhn. Diagnostiki i Terapii Sb. 103-119.

3319. Pavlovic, S., et al. 1967. The anti-pellagra factor and energy metabolism. Z. Ernaehrungswiss 8:215-222.

3320. Pawan, G. L. S. 1968a. The effect of vitamin supplements and various sugars on the rate of metabolism of ethanol in man. Biochem. J. 107(4):25p-26p.

3321. Pawan, G. L. S. 1968b. Vitamins, sugars, and ethanol metabolism in man. Nature (London) 220(5165):374-376.

3322. Payne, I. R., and M. M. Hudson. 1972. Dietary intakes of mental patients. Am. J. Pub. Health 62(9):1210-1215.

3323. Pearlman, W. H., E. Cerceo, and M. Thomas. 1954. The conversion of delta-5-pregnen-3-beta-ol-20-one to progesterone by homogenates of human placental tissue. J. Biol. Chem. 208(1):231-239.

3324. Pearson, P. B. 1940. Metabolism and dispensibility of nicotinic acid in sheep. Proc. Amer. Soc. Animal Prod. 323-325.

3325. Pearson, P. B., and R. W. Luecke. 1945. Studies on the metabolism of nicotinic acid in the horse. Arch. Biochem. 6:63-68.

3326. Pearson, P. B., and A. H. Winegar. 1940. Excretion of nicotinic acid by rabbits as affected by the amount ingested. Z. Vitaminforsch. 10:238-244.

3327. Pearson, P. B., W. A. Perlzweig, and F. Rosen. 1949. The metabolism of niacin in ruminants (sheep, goats and calves). Arch. Biochem. 22(2):191-194.

3328. Pearson, P. B., L. Struglia, and I. L. Lindahl. 1953. The fecal and urinary excretion of certain B vitamins by sheep fed hay and semisynthetic rations. J. Animal Sci. 12:213-218.

3329. Pearson, W. N., J. S. Valenzuela, and J. Van Eys. 1958. The influence of dietary fat on the niacin requirement of the mouse. J. Nutr. 66:277-290.

3330. Pearson, P. B., A. H. Winegar, and H. Schmidt. 1940. Studies on the metabolism of nicotinic acid in the sheep. J. Nutr. 20(6):551-563.

3331. Pearson, W. N., J. P. Owens, G. W. Hudson, and W. J. Darby. 1953. Effect of whole-body x-irradiation on urinary B-vitamin excretion of rats. Am. J. Physiol. 173:120-124.

3332. Pearson, W. N., S. J. Stempfel, J. S. Valenzuela, M. J. Utley, and W. J. Darby. 1957. The influence of cooked vs. raw maize on the growth of rats receiving a 9% casein ration. J. Nutr. 62(3): 445-463.

3333. Pecora, L., A. Silvestroni, and A. Brancaccio. 1966. Relations between the prophyrin metabolism and the nicotinic acid metabolism in saturnine poisoning. Panminerva Med. 8(7-8):284-288.

3334. Pecorella, F. 1940. Influence of nicotinic acid on the complementary power of blood serum. Boll. Ist. Sieroterap. Milan. 19:282-285.

3335. Peczon, J. D., W. M. Grant, and B. W. Lambert. 1971. Systemic vasodilators, intraocular pressure, and chamber depth in glaucoma. Am. J. Ophthalmol. 72(1):74-78.

3336. Pedrazzi, F., M. Loli Piccolomini, and L. L. Barbieri. 1959. Effect of riboflavin and its monophosphate ester on nitrogen metabolism in the rat. Acta Vitaminol. 13:61-64.

3337. Peguin, J. S. 1952. Nicotinic acid and burning feet. Lancet 263:536.

3338. Pelletier, O. 1968. Chemical determination of niacinamide in multivitamin preparations. J. Assoc. Off. Anal. Chem. 51:828-834.

3339. Pelletier, O., and J. A. Campbell. 1961. Direct determination of niacinamide in multivitamin preparations. J. Pharm. Sci. 50:926-928.

3340. Pelletier, O., and J. A. Campbell. 1962. A rapid method for the determination of N'-methylnicotinamide in urine. Analyt. Biochem. 3(1):60-67.

3341. Pelner, L. 1947. Anaphylaxis to the injection of nicotinic acid (niacin); successful treatment with adrenaline. Ann. Intern. Med. 26:290-294.

3342. Pelosio, C. 1947. Contribution to the knowledge of the action of nicoting acid on glucose metabolism and on vegetative nervous system. Fisiol. e Med. (Rome) 15:481-495.

3343. Pen'kova, A. F. 1966. The effectiveness of various cobalt compounds in sheep nutrition. Vestn. Sel'skokhoz. Nauki (Moscow) 11(11):69-71.

3344. Pennington, J., and B. Yeomans. 1961. Pyridinecarboxylic acids. Distiller's Co. Ltd. Fr. Pat. 1,327,679.

3345. Pereira, J. N. 1967. The plasma free fatty acid rebound induced by nicotinic acid. J. Lipid Res. 8:239-244.

3346. Pereira, J. N., and G. F. Holland. 1966. The effect of nicotinamide adenine dinucleotide on lipolysis in adipose tissue in vitro. Experientia 22(10):658-659.

3347. Pereira, J. N., and G. F. Holland. 1967. The development of resistance to a potent lipolysis inhibitor, 3-methylisoxazole-5-carboxylic acid. J. Pharmacol. Exp. Ther. 157(2):381-387.

3348. Pereira, J. N., and G. A. Mears. 1971. Biphasic effect of nicotinic acid on plasma FFA (free fatty acid) levels. Life Sci. 1(1)(Pt. 1):1-8.

3349. Pereira, J. N., G. F. Holland, F. A. Hochstein, S. Gilgore, S. Defelice, and Pinson. 1968. The pharmacology of 5- 3-pyridyl tetrazole, a nypocholesteremic lipolysis inhibitor. J. Pharmacol. Exp. Ther. 162(1):148-154.

3350. Perla, P. 1946. Modifications of the autohemoglycolytic power in diabetes mellitus under the action of water-soluble vitamins. Boll. Soc. Ital. Biol. Sper. 22:1031-1033.

3351. Perlman, L., and A. F. Morgan. 1945. Stability of the B vitamins in grape-juices and wines. Food Res. 10(4):334-341.

3352. Perlzweig, W. A. 1947. The chemical methods of determination of nicotinic acid and derivatives. In: Biological Symposia, ed. by J. Cattell, et al. Vol. XII pp. 204-212.

3353. Perlzweig, W. A., and J. W. Huff. 1944. F2 and N1-methylnicotinamide. Science 100(2585):28-29.

3354. Perlzweig, W. A., and J. W. Huff. 1945. The fate of N-methylnicotinamide in man. J. Biol. Chem. 161(1):417-418.

3355. Perlzweig, W. A., M. L. C. Bernheim, and F. Bernheim. 1943. The methylation of nicotinamide by rat liver in vitro. J. Biol. Chem. 150(2):401-406.

3356. Perlzweig, W. A., J. W. Huff, and I. Gue. 1944. The excretion of thiamin, riboflavin and nicotinic acid by fasting men. Fed. Proc. 3:62.

3357. Perlzweig, W. A., E. D. Levy, and H. Sarett. 1940a. On the quantitative determination of nicotinic acid and its derivatives in urine. J. Biol. Chem. 133:lxxiv-lxxv.

3358. Perlzweig, W. A., E. D. Levy, and H. P. Sarett. 1940b. Nicotinic acid derivatives in human urine and their determination. J. Biol. Chem. 136(3):729-745.

3359. Perlzweig, W. A., P. B. Pearson, and F. Rosen. 1950. Comparative studies in niacin metabolism. The fate of niacin in man, rat, dog, pig, rabbit, guinea pig, goat, sheep and calf. J. Nutr. 40(3):453-469.

* 3360. Perlzweig, W. A., F. Rosen, and P. B. Pearson. 1950. Comparative studies in niacin metabolism. The fate of niacin in man, rat, dog, pig, rabbit, guinea pig, goat, sheep and calf. J. Nutr. 40(3):453-469.

3361. Perlzweig, W. A., H. P. Sarett, and L. H. Margolis. 1942. Studies in nicotinic acid metabolism. V. A test for nicotinic acid deficiency in man. J. Am. Med. Assoc. 118:28-30.

3362. Perlzweig, W. A., F. Rosen, N. Levitas, and J. Robinson. 1947. The excretion of nicotinic acid derivatives after ingestion of tryptophane by man. J. Biol. Chem. 167(2):511-514.

3363. Perlzweig, W. A., F. Rosen, I. G. Leder, S. Hunter, and P. B. Pearson. 1949. Comparative studies in niacin metabolism. Fed. Proc. 8:236.

3364. Perlzweig, W. A.,, F. Rosen, P. B. Pearson, B. J. Peck, and P. Sparks. Comparative studies in niacin metabolism. The fate of niacin man, rat, dog, pig, rabbit, guinea pig, goat, sheep, and calf. J. Nutr. 40:453-569.

3365. Permyakov, F. K. 1943. Effect of nicotinic acid on the acidity and digestive capacity of digestive juice. Klin. Med. (U.S.S.R.) 21(9):63-69.

3366. Pernow, B., and B. Saltin. 1971. Availability of substrates and capacity for prolonged heavy exercise in man. J. Appl. Physiol. 31(3):416-422.

3367. Pernow, B. B., R. J. Havel, and D. B. Jennings. 1967. The second wind phenomenon in McArdle's syndrome. Acta Med. Scand. Suppl. 472:294-307.

3368. Pero, C. 1946. Subarachnoid treatment of some subacute nervous diseases with nicotinic acid. Acta Neurol. (Naples) 1:81-87.

3369. Perrin, A., R. Loire, M. C. Couchat, M. C. Bourdillon, J. Gras, M. T. Rameaux, and A. Rameaux. 1968. Atheroma of rabbits and its prevention by certain lipolytic agents. Rev. Lyon Med. 17(17): 727-740.

3370. Perry, W. F. 1960. Effect of nicotinic acid and nicotinamide on incorporation of acetate into cholesterol, fatty acids and carbon dioxide by rat liver slices. Metabolism 9:686-698.

3371. Persson, B., J. C. H. Gentz, J. Hakkarainen, and M. Kellum. 1971. Catechol amine-induced lipolysis and its relation to oxygen consumption in the newborn piglet. Pediat. Res. 5(9):435-445.

3372. Peruzzi, P. 1947. Bioregulators and chemical mediators. Boll. Soc. Ital. Biol. Sper. 23:236-238.

3373. Peruzzi, P. 1950. Chemical mediators for mammalian heart in relation to certain bioregulators. Arch. Fisiol. 49:12-23.

3374. Petelina, V. V. 1966. Complex chemical activity during acute radiation sickness. Tr. Inst. Eksp. Med. Akad. Med. Nauk S.S.S.R. 9(2):103-105.

3375. Peters, J. H., and H. R. Gutmann. 1955. Stimulation of hydroxylation and protein binding of the carcinogen 2-acetamidofluorene in rat-liver homogenates. Arch. Biochem. Biophys. 62:234-236.

3376. Peters, J. H., A. H. Randall, Jr., J. Mendeloff, R. Peace, J. C. Coberly, and M. B. Hurley. 1958. Jaundice during administration of methylestrenolone. J. Clin. Endocrinol. Metab. 18(1):114-115.

3377. Peters, R. A., and J. R. O'Brien. 1938. The vitamin B group. Ann. Rev. Biochem. 7:305-324.

3378. Peterson, M. J., C. C. Hillman, and J. Ashmore. 1968. Nicotinic acid: Studies on the mechanism of ita antilipolytic action. Mol. Pharmacol. 4(1):1-9.

3379. Peterson, M. J., C. Patterson, and J. Ashmore. 1968. Effects of antilipolytic agents on dibutyryl cyclic AMP induced lipolysis in adipose tissue. Life Sci. (Oxford) 7(9 Pt. 1):551-560.

3380. Petrack, B., E. A. Craston, and P. Greengard. 1963. Nicotinamide deamidation by rat liver. In: 47th Annual meeting of the Federation of American Societies for Experimental Biology, 1963.

3381. Petrack, B., P. Greengard, and H. Kalinsky. 1966. The relative efficacy of nicotinamide and nicotinic acid as precursors of nicotinamide adenine dinucleotide. J. Biol. Chem. 241(20):2367-2372.

3382. Petri, S. 1969. The significance of the stomach for the antipernicious principle in the liver of pigs: V. Acta Med. Scand. 185(4):339-340.

3383. Petri, S., F. Norgaard, and E. Bandier. 1938. Studies on the effect of nicotinic acid upon experimental gastroprival pellagra. Acta Med. Scand. 98(1/2):117-127.

3384. Petri, S., F. Norgaard, and E. Bandier. 1940. Studies on the causation of experimental gastroprival pellagra. Acta Med. Scand. 103:584-606.

3385. Petri, S., O. Bang, W. Kiaer, and A. K. Nielsen. 1944. Experimental studies on the significance of the various regions of the stomach for the content of antipernicious anemia principle in the liver in swine. II. Countereffect of nicotinic acid on the disappearance of antipernicious anemia principle in the liver following resection of the fundus of the stomach. Acta Med. Scand. 116:273-287.

3386. Petrova, T. R. 1967. Relation of some indices of the lipid exchange with heparin and heparinocytes of the blood in patients with coronary atherosclerosis. Vrach. Delo (3):37-41.

3387. Petrovic, D., V. Jovic, B. Djivanovic, S. Jevtic, and M. Stankovic. 1963. Metabolism of nucleic acids in pellagrous children. Hrana Ishrana 4(2):69-76.

3388. Petrovic, D., B. Djivanovic, M. Stankovic, V. Jovic, and V. Ljubinkovic. 1967. Mechanism of the PP factor effect on protein synthesis in pellagrous children. Proc. Int. Congr. Nutr., 7th, 1966(5):576-578.

3389. Petrun'kina, A. M. 1959. Determination of nicotinic acid in small quantities of the blood with the aid of a quartz spectrophotometer SF-4. Tr. Inst. Fiziol. Pavlov 8:549-555.

3390. Petrun'kina, A. M. 1963. On the determination of small quantities of nicotinic acid in the blood (second report). Lab. Delo 9(2):31-34.

3391. Petrun'kina, A. M., and S. A. Dmitrieva. 1953. The elimination of nicotinic acid by patients with neuroses and by normal controls. Zhur. Nevropatol. i I'sikhiatrii im. Korsakova 53:796-798.

3392. Petrun'kina, A. M., S. A. Dmitrieva, and L. I. Silina. 1957. The optimum ratio between some B vitamins. Pediatriya 35(7): 88-92.

3393. Pfeiffer, C., and I. Arnove. 1937. Glycerol toxicity and hemoglobinuria in relation to vitamin C. Proc. Soc. Exptl. Biol. Med. 37:467-469.

3394. Philiips, A. M., Jr., and D. R. Brockway. 1947. The niacin and biotin requirement of trout. Trans. Am. Fisheries Soc. 77:152-159.

3395. Phillips, P. H., N. S. Lundquist, and P. D. Boyer. 1941. The effect of vitamin A and certain members of the B-complex upon calf scours. J. Dairy Sci. 24:977-982.

3396. Piana, G., and G. Piva. 1968. Determining the dietary source of nonprotein nitrogen. Conditions for tryptophan synthesis by rumen microorganisms. Ann. Fac. Agr., Univ. Catt. Sacro Cuore 8(1):189-199.

3397. Piazza, M., F. Tancredi, and E. Quagliariello. 1961. Blockage of transformation of tryptophan to nicotinic acid by experimental hepatitis in mice. Nature (London) 19:601.

3398. Piccinelli, O. 1960. On the hypolipemizing action of nicotinic acid. Farmaco (Prat.) 15:259-267.

3399. Piccinelli, O., F. Nicrosini, and A. Del Favero. 1961. Modifications induced by nicotinic acid on the blood lipid picture in atherosclerotic patients. Farmaco (Sci.) 16:32-38.

3400. Pidemskii, E. L., R. P. Cherednichenko, and E. M. Chukichev. 1969. Effect of some antiinflammatory drugs on phagocytosis in experimental hepatitis. Zh. Mikrobiol., Epidemiol. Immunobiol. 46(7):59-61.

3401. Pidemskii, E. L., E. M. Chukichev, and A. M. Mul'Menko. 1968. Effect of vitamin PP on phagocytosis in chronic trinitrotoluene poisoning. Farmakol. Toksikol. 31(3):365-366.

3402. Pietrogrande, V., and L. Emanuele. 1952. Vitamin D in bones. Ortoped. e Traumatol. App. Motore 20:45-51.

3403. Piette, Y. 1950. Motor, respiratory, cardiovacular, and blood-sugar changes during electric shock. Ann. Soc. Roy. Sci. Med. et Nat. Bruxelles 3:5-71.

3404. Pike, R. L. 1951. Congenital cataract in albino rats fed different amounts of tryptophan and niacin. J. Nutr. 44:191-204.

3405. Pimenta de Mello, R. 1951. Effect of folic acid, vitamin B12, and nicotinamide on urinary coproporphyrin excretion in photosensitized rabbits. Proc. Soc. Exptl. Biol. Med. 77(4):744-747.

3406. Pinelli, A., and L. Favalli. 1972a. Antilipaemic and antiporphyric activity of nicotinic acid in allylisopropylacetamide-treated rats. Biochim. Biophys. Acta 279(2):316-319.

3407. Pinelli, A., and L. Favalli. 1972b. Chemically induced porphyria. Protection by treatment with nicotinic acid. Eur. J. Pharmacol. 20(1):136-138.

3408. Pinelli, A., and L. Favalli. 1972c. Hypertriglyceridemia associated with low levels of plasma free fatty acids in allylisopropylacetamide-treated rats: Effects of nicotinic acid treatment. Pharmacol. Res. Commun. 4(3):179-184.

3409. Pinelli, A., L. Favalli, N. Ferrario, and N. Zucal. 1972. Hypertriglyceridemia associated with low levels of plasma free fatty acids in allylisopropylacetamide-treated rats. Effects of nicotinic acid treatment. Pharmacol. Res. Commun. 4(3):179-184.

3410. Pinsky, L., and F. C. Fraser. 1960. Congenital malformations after a two-hour inactivation of nicotinamide in pregnant mice. Brit. Med. J. 5193:195-197.

3411. Pinter, E. J., and C. J. Pattee. 1967. Biphasic nature of blood glucose and free fatty acid changes following intravenous nicotinic acid in man. J. Clin. Endocrinol. Metab. 27(3):440-443.

3412. Pinter, E. J., C. J. Pattee, G. Peterfy, and J. M. Cleghorn. 1967. Metabolic effects of autonomic blockage. Lancet II(7506):101-102.

3413. Pinto de Barros, J. 1970. Lipolytic activities in adipose tissue. Arg. Port. Bioquim. 11(304):300-325.

3414. Pittera, A. 1956. Influence of nicotinamide on the bilirubin level of blood. Arch. Studio Fisiopatol. e Clin. Ricambio 20:594-604.

3415. Pittnerova, A., P. Kovacs, and A. Jindra. 1969. Carboxylase activity in the tobacco plant. Acta Fac. Pharm. Univ. Comeniana 17:147-162.

3416. Piva, S. 1959. On the clinical use of a combination of adenosine-triphosphoric acid, (A.T.P.), cocarboxylase, vitamin B12 and nicotinamide (vitamin PP) in the therapy of neuralgia and neuritis. Gazz. Med. Ital. 118:269-273.

3417. Piva, S. 1960. Clinical use of a combination of adenosine triphosphoric acid (ATP), cocarboxylase, vitamin B12 and nicotinamide (PP) in the therapy of neuralgia and neuritis. Scalpel (Brux.) 113:454-457.

3418. Plastunov, A. B. 1949. Treatment of threatened abortion with nicotinic acid (vitamin PP). Akuserstvo Ginekol. (1):39-42.

3419. Platt, B. S., and G. E. Glock. 1942. The effect of autolysis and of freezing on the "total nicotinic acid" content of skeletal muscle. Biochem. J. 36(7/8/9):xv.

3420. Plessas, C. T. 1972. Physicochemical study of protein binding of drugs. Example of nicotinic acid. Genike Ekdosis 37(1):8-9.

3421. Pleticha, R. 1958. Polarographic investigation of several vitamins of the B complex. Pharmazie 13:622-627.

3422. Plotnikova, M. N. 1962. Effect of levomycetin, vitamin B6 and vitamin PP on dysenterial infection in experimental conditions. Antibiotiki 7:56-58.

3423. Plough, I. C., and C. F. Consolazio. 1959. The use of casual urine specimens in the evaluation of the excretion rates of thiamine, riboflavin, and N1-methylnicotinamide. J. Nutr. 69(4): 365-370.

3424. Podgorskii, V. S. 1969. Effect of B group vitamins on the growth of lactic acid bacilli isolated from the rumen of cattle. Mikrobiol. Zh. (Kiev) 31(4):407-409.

3425. Podorozhnyi, P. H., and Y. I. Tomashevs'kyi. 1971. Methods for determining the content of nicotinic acid derivatives in biological material. Ukr. Biokhim. Zh. 43(4):467-470.

3426. Pojer, J., and J. Tovarek. 1960. Urine citric acid in internal diseases. Vnitrni Lekarstvi 6:121-128.

3427. Pokora, J. 1965. Effect of reserpine, nicotinamide, and Deseril upon the diurnal urinary excretion of 5-hydroxyindoleacetic acid and the ceruloplasmin activity in human serum. Polski Tygod. Lekar. 20(1):1-4.

3428. Pokotilenko, G. M. 1967. Pyridine coenzyme content in rat tissues in hyperthyreosis. Ukr. Biokhim. Zh. 39(2):215-219.

3429. Pokotilenko, G. M. 1970. Level of ascorbic acid and nicotinamide-containing coenzymes in animal tissues when the thyroid gland was in various functional states. Vitam. Eksp. Klin. 1970(2): 54-61.

3430. Polak, E., and D. Horgas. 1967. Mineral substances and vitamins in carrots (Daucus carota) during various stages of plant development. Poljopr. Znan. Smotra 24(Pt. 6):3-20.

3431. Poli, G. 1949. Glycemia in children after administration of adrenaline. Minerva Pediat. 1:55-58.

3432. Polimbetova, F. A., E. I. Omarova, and E. D. Bogdanova. 1969. Effect of nicotinic acid and its analogs on the physiological characteristics and productivity of spring wheat. Fiziol. Rast. 16(4):726-729.

3433. Pollard, A. A., and L. Beck. 1971. Distinct nature of the sustained dilator system. Evidence against the pseudotransmitter hypothesis. J. Pharmacol. Exp. Ther. 179(1):132-143.

3434. Polli, E. 1952. Action of nicotinamide on the intermediate metabolism of acetone bodies. Arch. Studio Fisiopatol. e Clin. Ricambio 16:252-254.

3435. Pollock, L. J., and I. Finkelman. 1942. The action of pyridine and some of its derivatives in preventing experimental convulsions in animals. J. Nervous Mental Disease 96:424-434.

3436. Pollock, L. J., I. Finkelman, and E. L. Tigay. 1941. The action of pyridine, some of its derivatives, and phenylcinchoninic acid in preventing convulsions produced by metrazole. Trans. Am. Neurol. Assoc. 67:6-10.

3437. Polonia, J., and F. Martinez. 1962. Determination of nicotinamide in an injection of the B complex. An. Fac. Farm. Porto. 22:43-50.

3438. Polumbrik, O. M., G. F. Dvorko, and O. M. Grishin. 1969a. Mechanism of dehydrogenation of dihydropyridines by triphenylverdazyl cation. Dopov. Akad. Nauk Ukr. R.S.R., Ser. B 21(9):812-815.

3439. Polumbrik, O. M., G. F. Dvorko, and O. M. Grishin. 1969b. Reaction of triphenylverdazyl with N-benzyl-1,4-dihydronicotinamide. Ukr. Khim. Zh. 35(10):1046-1052.

3440. Polyakova, M. A. 1969. Effect of phenamine and phenatine on plasma cholinesterase activity of rabbits poisoned with tetraethylpyrophosphate. Farmakol. Tsent. Kholinolitikov Drugikh Neirotropnykh Sredstv 1969:255-256.

3441. Polyanskaya, L. A. 1967. Vitamin dynamics in the ontogenesis of early- and late-ripening cotton plants. Tr. Konf. Biokhim. Respub. Srednei Azii Kaz., 1st, Alma-Ata 1966:175-179.

3442. Polyanskaya, L. A., and M. K. Kuvadov. 1971. Results of practical investigations of the effect of nicotinic acid on cotton. Izv. Akad. Nauk Trukm. S.S.R., Ser. Biol. Nauk 1971(1):8-13.

3443. Pomeranz, Y., P. Halton, and F. G. Peers. 1956. The effects on flour dough and bread quality of molds grown in wheat and those added to flour in the form of specific cultures. Cereal Chem. 33:157-169.

3444. Pompucci, G., L. Corsi, and C. Ricci. 1966. Regulation of NAD synthesis in rat liver. Boll. Soc. Ital. Biol. Sper. 42(18):1189-1191.

3445. Pompucci, G., V. Pallini, P. Martelli, and C. Ricci. 1962. Variations in the pool of acid-soluble nucleotides in the livers of rats treated with nicotinamide. Boll. Soc. Ital. Biol. Sper. 38(24):1734-1735.

3446. Pongratz, A., and K. Zirm. 1963. para-Acetamidophenol esters. Austrian Pat. 243,263.

3447. Ponomarev, G. A. 1945. Colorimetric determination of nicotinic acid (and amide) in blood. Farmakol. i Toksikol. 8(5):31-33.

3448. Ponomarev, G. A. 1947. Influence of nicotinic acid on rates of absorption and elimination of some sulfonamides. Farmakol. i Toksikol. 10(3):16-20.

3449. Pontremoli, S., and G. Ivaldi. 1953. Dehydrogenase of higher fatty acids in the isolated liver of the normal and depancreatized animal. Boll. Soc. Ital. Biol. Sper. 29:529-530.

3450. Popa, I. 1961. The use of nicotinic acid in patients with coronary insuffieiency. Ter. Arkh. 33:49-54.

3451. Popkin, R. J. 1939. Nicotinic acid: its action on the peripheral vascular system. Am. Heart J. 18:697-704.

3452. Popov, G. D., M. I. Taranenko, and L. V. Luchinskaya. 1970. Pyridoxine and nicotinic acid in the complex treatment of patients with lung tuberculosis. Probl. Tuberk. 48(9):29-33.

3453. Poppe, W., and P. Fehlow. 1969. Sporadic pellagra psychosis. Deutsch. Gesundheitswesen 24:1256-1259.

3454. Popper, A., A. Vass, A. Elekes, and A. Firez. 1965. Effect of nicotinic acid on carbohydrate metabolism in diabetics. Med. Interna 17(10):1241-1244.

3455. Popper, A., S. Vass, S. Elekes, S. Firez, and G. Ferenczy. 1969. Effect of nicotinic acid on carbohydrate metabolism in diabetics. Magy. Belorv. Arch. 22(3):130-133.

3456. Porcellati, G. 1954. Biological synthesis and hydrolysis of nicotinamide. Giorn. Biochim. 3:231-250.

3457. Porcellati, G., and G. Quagliariello. 1955. Some aspects of the metabolism of nicotinamide in vitro. Bol. Soc. Ital. Biol. Sper. 31:1330-1334.

3458. Porje, I. G. 1939. A method to determine nicotinic acid in urine. Nordisk Med. 2(15):1108-1110.

3459. Porte, D., Jr. 1967a. Beta-adrenergic stimulation of insulin release in man. Diabetes 16(3):150-155.

3460. Porte, D., Jr. 1967b. A receptor mechanism for the inhibition of insulin release by epinephrine in man. J. Clin. Invest. 46(1):86-94.

3461. Portig, J., W. Koransky, and D. Wahner-Roedler. 1972. Biotransformation of nikethamide in the rat and its acceleration by hexachlorocyclohexane. Naunyn-Schmiedeberg's Arch. Pharmacol. 274(2):154-170.

3462. Pozza, F. 1960. The radioprotective action of nicotinamide. II. Mice irradiated with a LD99. Quaderni Radiol. 25(2):189-192.

3463. Praag, H., and B. Leijnse. 1966. Some aspects of the metabolism of glucose and of the nonesterified fatty acids in depressive patients. Psychopharmacologia 9:220-233.

3464. Prane, L. 1972. Changes in marrow hemopoiesis in rats with sarcoma M-1 treated with beta-(5-nitro-2-furyl)acrolein N,N-bis(2-chloroethyl)hydrazone (IF-202) and B-group vitamins. Protivoopukholevye Soedin. 5-Nitrofuranovo 1972:197-208.

3465. Prane, L., A. A. Nozhenko, and A. Sternberga. 1972. Effect of beta-(5-nitro-2-furyl)acrolein N,N-bis(2-chloroethyl)hydrazone (IF-202) and B group vitamins on the amount of RNA and DNA in the bone marrow of rats with sarcoma M-1. Protivoopukholevye Soedin. 5-Nitrofuranovo 1972:209-217.

3466. Prasad, B. G., Y. P. Gupta, T. D. Biswas, and N. B. Das. 1953. Chemical method for the estimation of nicotinic acid in wheat. Sci. Culture 18(9):439.

3467. Prasad, M. 1972. Comparative studies on the effect of vitamins on sporulation in Fusarium oxysporum Schlecht. ex. Fr. and Fusarium moniliforme v. subglutinans Wr. et Rg. Mycopathol. Mycol. Appl. 46(4):367-372.

3468. Pratesi, F., M. Tesi, S. Brunetti, L. Caramelli, and R. P. Dabizzi. 1968. Pharmacological effects on the fibrinolytic potential in human blood vessles. Settim. Med. 56(19):1065-1073.

3469. Preiss, J., and P. Handler. 1957. Enzymatic synthesis of nicotinamide mononucleotide. J. Biol. Chem. 225(2):759-770.

3470. Prescott, B. 1963. Detoxification of some toxic chemotherapeutically active drugs. Atti Accad. Med. Lombarda 18(4):856-860.

3471. Prescott, B., G. Kauffman, and W. D. James. 1957. Means of increasing the tolerated dose of isoniazid in mide. III. Certain vitamins. Proc. Soc. Exptl. Biol. Med. 95(4):705-708.

3472. Prescott, B., G. Kauffmann, and H. J. Stone. 1960. Means of increasing the tolerated dose of isoniazid-streptomycin mixtures in mice. II. Certain vitamins. Antibiotics Chemotherapy 10:163-168.

3473. Prescott, B., G. Kauffmann, W. D. James, and H. J. Stone. 1959. Means of increasing the tolerated dose of streptomycin in mice. II. Certain vitamins. Antibiotics & Chemotherapy 9:369-375.

* 3474. Press, E., and L. Yeager. 1962. Food "poisoning" due to sodium nicotinate: Report of an outbreak and review of the literature. Amer. J. Pub. Health 52:1720-1728.

3475. Preuss, H. G. 1968. Pyridine nucleotides in renal ammonia metabolism. J. Lab. Clin. Med. 72(3):370-382.

3476. Preziosi, P., B. Loscalzo, E. Marmo, and E. Miele. 1961a. Decrease of blood cholesterol and lipids by components with a pyridine core: Relations between structure and activity and between dosage and effectiveness. Arch. Ital. Sci. Farmacol. 11:386-389.

3477. Preziosi, P., B. Loscalzo, E. Marmo, and E. Miele. 1961b. Apropos of the hypocholesterolemic effects of nicotinic acid. Experimental investigations of such a compound and of inositol hexanicotinate. Clin. Ter. (Roma) 21:231-272.

3478. Price, J. M., R. R. Brown, and N. Yess. 1965. Testing the functional capacity of the tryptophanniacin pathway in man by analysis of urinary metabolites. Advances in Metabol. Dis. 2:159-225.

3479. Prigge, W. F., and F. Grande. 1971. Effects of glucagon, epinephrine, and insulin on in vitro lipolysis of adipose tissue from mammals and birds. Comp. Biochem. Physiol. B 39(1):69-82.

3480. Prina, C., B. Magrassi, and G. Roveta. 1962. Complexes of 3,4-benzopyrine and various substances in aqueous solution. Action in vitro and in vivo on Ehrlich ascites cancer cells. Boll. Soc. Ital. Biol. Sper. 38:1183-1184.

3481. Proctor, B. E., and S. A. Goldblith. 1948. Effect of high-voltage x-rays and cathode rays on vitamins (niacin). Neucleonics 3(2):32-43.

3482. Proctor, B. E., and S. E. Goldblith. 1949. The effect of soft x-rays on vitamins (niacin, riboflavin, and ascorbic acid). Nucleonics 5(3):56-62.

3483. Proenca da Cunha, O. R., and A. Proenca da Cunha. 1965. Separation and determination of vitamins by paper electrophoresis. Bol. Escola Farm., Univ. Coimbra, Ed. Cient. (25):54-67.

3484. Prosiegel, R. 1955. The influence of liver protective substances on the content of Pyridincoferments (DPN/ DPNH2) in the liver of the rat injured by carbontetrachloride. Zeitschr. Ges. EXptl. Med. 125(4):323-330.

* 3485. Prosser, A. R., and A. J. Sheppard. 1968. Gas-liquid chromatography of niacin and niacinamide. J. Pharm. Sci. 57(6): 1004-1006.

3486. Provenzale, L. 1947. Action of hormones and vitamins on the proliferation of connective tissue. Fisiol. e Med. (Rome) 15:19-63.

3487. Puddu, P., C. M. Calderera, and M. Marchetti. 1967. Ethionine-induced fatty liver. Biochem. J. 102:163-167.

3488. Pudlik-Pankiewicz, K., B. Secomska, and A. Szczygiel. 1962. Diagnostic value of a morbid complex in the oral cavity partially attributed to niacin deficiency. Pediat. Pol. 37:481-488.

3489. Pueschner, H., and R. Fankhauser. 1969. Neuropathological findings in experimental Vioform poisoning of mice. Schweiz. Arch. Tierheilk. 111(7):371-379.

3490. Pugliese, F., G. Marri, and P. Calandra. 1961. Changes in bilirubinemia caused by nicotinic acid in normal and pathological conditions. Boll. Soc. Ital. Biol. Sper. 37:771-773.

3491. Pulatov, R. P., A. T. Artykov, and B. Sadritdinov. 1968. Mechanism of the hypotensive action of a complex compound of cobaltous chloride with nicotinic acid and nicotinamide. Med. Zh. Uzb. 1:37-39.

3492. Pushkarenko, G. D. 1961. Vasculo-cutaneous reaction to nicotinic acid in normal children and those affected by epileptic seizures. Tr. Kharkov Inst. 50:213-219.

3493. Pushkina, N. N. 1957. Nicotinic acid in food products of Tatar Autonomous S.S.R. and Modavian Autonomous S.S.R. Sbornik Nauch. Rabot Kazan. Gosudarst. Med. Inst. 1:85-90.

3494. Pushinka, N. N. 1968. On the mechnism of disturbance of vitamin metabolism under the effect of various factors of the external environment. Gig. Sanit. 33:23-26.

3495. Pushinka, N. N., and N. N. Skvortsova. 1970. Alteration in the levels of some vitamins in albino-rat organs and urine during chronic exposure to 3,4-benzpyrene and sulfur dioxide. Byull. Eksp. Biol. Med. 70(12):45-47.

3496. Pushkinskaya, O. I., and L. S. Kutseva. 1955. Microbiological method for determination of nicotinic acid (vitamin PP). Vitaminnye Resursy i Ikh Ispol'zovanie, Akad. Nauk S.S.S.R., Inst. Biokhim. im. A. N. Bakha, Sbornik 3:133-144.

3497. Pusztai, Z., and I. Joo. 1967. Influence of nicotinic acid on the antigenic structure of Bordetella pertussis. Ann. Immunol. Hung. 10:63-67.

3498. Putowa, A., L. Samochowiec, and J. Wojcicki. 1967. Experimental administration of certain drugs in carbon disulfide poisoning. Med. Pracy 18(2):128-131.

3499. Pyatnitskii, N. P., and M. N. Selyukova. 1958. The effect of nicotinic acid on the gastric secretion of pepsin and HCl. Vopr. Pitaniya 17(4):20-24.

3500. Quabbe, H.-J., H.-J. Bratzke, U. Siegers, and K. Elban. 1972. Studies on the relationship between plasma free fatty acids and growth hormone secretion in man. J. Clin. Invest. 51(9):2388-2398.

3501. Quadbeck, G., W. Sachsse, and O. Hess. 1961. On the anticonvulsive effect of nicotinic acid in animal experiments. Klin. Wschr. 39:599.

3502. Quadri, G., and R. Spitali. 1963. Administration of nicotinamide and the behavior of some pyridine dehydrogenases in rat fetal livers. Boll. Soc. Ital. Biol. Sper. 39:282-285.

3503. Quagliariello, E. 1963. The metabolism of tryptophan-nicotinic acid; considerations of the biochemical lesions caused in this metabolic path. Giorn. Biochim. 12(2):65-129.

3504. Quagliariello, E., and S. Auricchio. 1954. The transformation of 3-hydroxyanthranilic acid to quinolinic acid in the presence of homogenate of chick embryo. Boll. Soc. Ital. Biol. Sper. 30:1421-1423.

3505. Quagliariello, E., G. Della Pietra, and R. Piazza. 1952. Microbiological method of estimating nicotinic acid and tryptophan in hen's eggs. Boll. Soc. Ital. Biol. Sper. 28:687-690.

3506. Quagliariello, E., L. Fedele, and F. Tancredi. 1960. Possibility of diagnosis of tumors of the bladder by chromatagraphic revelation of metabolites of the tryptophan-nicotinic acid interrelation. Boll. Soc. Ital. Biol. Sper. 36:722-724.

3507. Quagliariello, E., F. Tancredi, L. Fedele, and C. Saccone. 1961. Tryptophan-nicotinic acid metabolism in patients with tumours of the bladder. Changes in the excretory products after treatment with nicotinamide and vitamin B6. Brit. J. Cancer 15(2):367-372.

3508. Quagliariello, E., F. Tancredi, C. Saccone, and M. Piazza. 1962. Interrelation between tryptophan and nicotinic acid in human viral hepatitis. Nature 194(4832):977-979.

3509. Quagliariello, G., D. Guerritore, and G. Porcellati. 1952. Synthesis and hydrolysis of nicotinamide. Boll. Soc. Ital. Biol. Sper. 28:685-687.

3510. Quastel, J. H. 1946. Role of members of the vitamin B complex in enzyme systems. Proc. Nutrition Soc. (Cambridge) 4(2): 92-106.

3511. Quastel, J. H., and L. J. Zatman. 1953. Effects of extracts of normal tissues and of tumours on yeast fermentation. Estimations of relative diphosphopyridine nucleosidase activities. Biochim. et Biophys. Acta 10(2):256-267.

3512. Queguiner, G., and P. Pastour. 1969. Synthesis in the pyridine series. V. Study of the reduction of ethyl pyridinedicaroxylates. Bull. Soc. Chim. Fr. 10:3678-3683.

3513. Querido, A., L. Lwoff, and C. Lataste. 1039. Estimation of nicotinamide in blood. Compt. Red. Soc. Biol. 130:1580-1584.

3514. Quinn, G., P., M. B. Reid, and P. Greengard. 1962. Effect of tranquilizers and hypophysectomy on the response of liver DPN to nicotinamide administration In: 46th Annual Meeting, Atlantic City, New Jersey, April 1962. Fed. Proc. 21(2):419.

3515. Rachinskii, F. Yu., Ya. M. Slobodin, and I. N. Shokhor. 1946. Colorimetric determination of nicotinic acid. J. Applied Chem. (U.S.S.R.) 19:176-179.

3516. Rachmiliwetz, M., and K. Braun. 1945. Electrocardiographic changes and the effect of niacin in pellagra. British Heart J. 7(2)71-80.

3517. Racker, E., and I. Krimsky. 1945. Effect of nicotinic acid amide and sodium on glycolysis and oxygen uptake in brain homgenates. J. Biol. Chem. 161(2):453-461.

3518. Radhakrishnamurty, R., and P. S. Sarma. 1953. Paper chromatographic separation of B-group vitamins. Current Sci. (India) 22:209-210.

3519. Radkevich, R. A. 1960. Nicotinic acid metabolism in children with osteoarthritic tuberculosis treated with antibiotics. Sovremen. Dannye po Lechebn. Primenen. Vitaminov Sbornik 1960: 108-113.

3520. Raffaele, C., and M. Ricciuti. 1943. Influence of nicotinic acid on the blood picture and bone marrow of rats. Arch. Sci. Med. 75:354-365.

3521. Rafsky, H. A., and B. Newman. 1942. Porphyrinuria in the aged. Am. J. Digestive Diseases 9:43-45.

3522. Rafsky, H. A., and B. Newman. 1943. Relationship of Niacin (nicotinic acid) to porphyrinuria in the aged. Amer. J. Med. Sci. 205:209-213.

3523. Raghuramulu, N., B. S. Narasinga Rao, and C. Gopalan. 1965. Amino acid imbalance and tryptophan-niacin metabolism. I. Effect of excess leucine on the urinary excretion of tryptophan-niacin metabolites in rats. J. Nutr. 86(1):100-106.

3524. Ragno, I., and R. Pinto 1961. Tryptophan-nicotinic acid metabolism in human hepatic cirrhosis. Boll. Soc. Ital. Biol. Sper. 37: 1296-1297.

3525. Raimondo, F. Di, N. Mannino, and M. L. Orabona. 1953. Inhibition of antibiosis by vitamins through metabolic antagonism. Research in vitro on Micrococcus pyogenes var. aureus with Terramycin and tyrothricin. Boll. Ist. Sieroterap. Milan. 32:45-51.

3526. Rajagopalan, K. V., T. K. Sundaram, and P. S. Sarma. 1958. Biological deamidation of nicotinamide in vertebrates. Nature 182:51-52.

3527. Rajagopalan, K. V., T. K. Sundaram, and P. S. Sarma. 1960. Metabolism of nicotinamide and nicotinic acid in Corcyra cephalonica St. Biochem. J. 74(2):355-359.

3528. Rajalakshmi, R., K. Nanavaty, and A. Gumashta. 1964. Effect of cooking procedures on the free and total niacin content of certain foods. J. Nutr. Dietet. (Coimbatore, India) 1(4):276-280.

3529. Rajka, E. 1962. The mechanism of urea pustule formation. IV. Influence of several drugs on urea pustule formation in human skin. Hautarzt 13(10):449-459.

3530. Rajka, E., S. Korossy, and M. Gozony. 1956. The pathogenesis of urticarial pruritus. III. Quantitative evaluation of the effects of various drugs on morphine-induced pruritus. Dermatologica 112:81-107.

3531. Rakieten, N., D. A. Cooney, and R. D. Davis. 1968. Use of nicotinamide for modifying the diabetogenic and hepatotoxic action of streptozotocin, lot no. 6742-DEG-30-5. U.S. Clearinghouse Fed. Sci. Tech. Inform., PB Rep. 1968, PB-180002, 159 pp.

3532. Rakieten, N., B. S. Gordon, A. Beaty, D. A. Cooney, R. D. Davis, and P. S. Schein. 1971. Pancreatic islet cell tumors produced by the combined action of streptozotocin and nicotinamide. Proc. Soc. Exp. Biol. Med. 137(1):280-283.

3533. Ralli, E. P. 1949. The relations of vitamins to the adrenal cortex. Conf. on Adrenal Cortex, Trans. 1:159-189.

3534. Ramanamurthy, P. S. V., and S. G. Strikantia. 1970. Effects of leucine on brain serotonin. J. Neurcochem. 17(1):27-32.

3535. Ramanuja, M. N., T. S. Satyanarayana Rao, P. D. Vaidya, M. V. R. Koteswara Rao, N. A. N. Rao, and P. K. Vijayaraghavan. 1969. Vitamin content of some processed military rations. J. Nutr. Diet. 6(4):295-300.

3536. Ramos, L., and O. Ramos. 1968. Fall in the intraocular pressure produced by ethanol in the rabbit and the influence of nikethamide or pentylenetetrazole (intraocular pressure, ethanol, and analeptic drugs). Rev. Brasil. Pesqui. Med. Biol. 1(1):9-15.

3537. Ramsay, R. A., T. A. Ban, H. E. Lehmann, B. M. Saxena, and J. Bennett. 1970. Nicotinic acid as adjuvant therapy in newly admitted schizophrenic patients. Can. Med. Assoc. J. 102(2): 939-942.

3538. Randall, L. O., N. Atkinson, and V. Iliev. 1960. The effect of psychostimulants and psychodepressants on diphospho-pyridine nucleotide synthesis in the liver. Arch. Intern. Pharmacodynamie 129:434-437.

3539. Randoin, L., and J. Causeret. 1946. Favorable action of nicotinamide administered to young rats completely deprived of all vitamins of the B group. Compt. Rend. Soc. Biol. 140: 493-496.

3540. Raudoin, L., and J. Causeret. 1948. Physiopathologic effects of large doses of niacinamide on the young rat. Compt. Rend. 227: 367-369.

3541. Randoin, L., and J. Causeret. 1949a. Can methionine supplementation prevent growth inhibition in the rat caused by an excess of nicotinamide in diet? Compt. Rend. Acad. Sci. (Paris) 228(6):504-506.

3542. Randoin, L., and J. Causeret. 1949b. The influence of certain factors of the vitamin B complex on the development of PP hypervitaminosis in the rat. Compt. Rend. Acad. Sci. 229: 855-856.

3543. Randoin, L., and J. Causeret. 1949c. Hepervitaminosis PP and deficiency of pantothenic acid. Relations between the metabolism of nicotinamide and pantothenic acid. J. Physiol. Paris 1949:259A-260A.

3544. Randoin, L., O. Guerillot, and A. Perroteau. 1953. The vitamin value of beer. The vitamin B complex content of various French beers. Comparison with English beers. Inds. Agr. et Aliment. (Paris) 70:31-40.

3545. Ranke, B., E. Ranke, and B. F. Chow. 1962. Methylation of nicotinamide in vitamin B12- and vitamin B6-deficient rats. J. Nutrition 76(4):441-446.

3546. Rao, P. S., and B. V. Ramasastri. 1969a. Nutritive value of some Indica, Japonica, and hybrid varieties of rice. J. Nutr. Diet. 6(3):204-208.

3547. Rao, P. S., and B. V. Ramasastri. 1969b. Riboflavine and nicotinic acid content of some foods of plant origin. J. Nutr. Diet. 6(3):218-223.

3548. Rao, P. Srinivasa, C. M. Jacob, and B. V. Ramasastri. 1969. Nutritive value of bamboo seeds. J. Nutr. Diet. 6(3):192-195.

3549. Rao, T. N. Ramachandra, and D. S. Johar. 1956. Nutritive value of yeast-fortified drinks. Bull. Central Food Technol. Research Inst., Mysore (India) 5:353-354.

3550. Rao, V. 1941. Influence of nicotinic acid on the reticulocytogenic power of the gastric juice. Riv. Patol. Sper. 26: 49-58.

3551. Raoul, Y. 1943a. Determination of nicotinic acid in urine and tissue. Ann. Pharm. Franc. 1:17-20.

3552. Raoul, Y. 1943b. Biochemical study of avitaminoses of the pellagra group. I. Estimation of excretion of subtances with a blue fluorescence during treatment with nicotinic acid. Bull. Soc. Chim. Biol. 25:266-271.

3553. Raoul, Y., and O. Crepy. 1941. A chemical method for determining nicotinic acid in blood. Bull. Soc. Chim. Biol. 23: 362-375.

3554. Raoul, Y., and C. Marnay. 1945. Biochemical study of avitaminoses of the pellagra group. VIII. Relation of pyridoxine, nicotinic acid, and pantothenic acid to cutaneous excretion of porphyrin by rats. Bull. Soc. Chim. Biol. 17:111-117.

3555. Raoul, Y., and C. Marnay. 1948. Double deficiency of nicotinic acid and tryptophan in the rat. Bull. Soc. Chim. biol. 30: 450-454.

3556. Raoul, Y., A. Vallette, and J. Marche, 1942. Nicotinic acid content of blood of normal subjects. Compt. Rend. Soc. Biol. 136:740-741.

3557. Rapp, M. S. 1968. Use and abuse of drugs. Canad. Med. Assoc. J. 98:922.

3558. Rappe, A. 1969. Qualitative microbiological determination of B vitamins. Application to the analysis of drugs, dietetic preparations, and foods. J. Pharm. Belg. 24(3-4):186-194.

3559. Rappoport, D. A., R. R. Fritz, and W. Yarger. 1964. Guanosine metabolism and corticosterone synthesis by rat adrenal homogenates. Texas Rept. Biol. Med. 22(4):722-730.

3560. Raskin, I. M. O. 1961. Man's requirement of nicotinic acid. Vop. Pitan. 20(5):79-84.

3561. Rastogi, S. K. 1972. Serum cholesterol reducing agents. Curr. Med. Pract. 16(8):333-335, 339.

3562. Ravazzoni, C., and G. Brunetto. 1939/40. The action of substances with the properties of the antipellagra vitamin on some phosphatases and catalases. Rend. ist. Lombardo Sci. Classe Sci. Mat. Nat. 3(73):481-491.

3563. Ray, S. N., W. C. Weir, A. L. Pope, and P. H. Phillips. 1947. The concentration of some B vitamins in the blood of normal and cobalt-deficient sheep. J. Nutrition 34:595-599.

3564. Razdolskii, I. Ya. 1945. Avitaminotic ailments of the nervous system in besieged Leningrad. Klin. Med. (U.S.S.R) 23(7-8):14-19.

3565. Reboucas, G., and K. J. Isselbacher. 1961. Pathogenesis of ethanol-induced fatty liver. I. Synthesis and oxidation of fatty acid by the liver. J. Clin. Invest. 40:1355-1362.

3566. Reddi, K. K. 1952. Estimation of the bound form of nicotinic acid. Nature 170:745-746.

* 3567. Reddi, K. K., and E. Kodicek. 1953. Metabolism of nicotinic acid and related compounds in man and rat. Biochem. J. 53(2): 286-294.

3568. Redetzki, H. M., and F. Alvarez-O'Bourke. 1962. 6-amino-nicotinamide a central nervous system depressant. In: 46th Annual Meeting, Atlantic City, New Jersey, April 1962.

3569. Redetzki, H. M., F. A. O'Bourke, and A. Ruskin. 1961. Effect of nicotinamide and nicotinic acid on DPN synthesis. Fed. Proc. 20(1 Pt. 1): 448.

3570. Redetzki, H. M., F. A. O'Bourke, and M. Schneider. 1961. Influence of nicotinic acid and nicotinamide on diphospho-pyridine nucleotide (DNP) synthesis in asceites tumor cells. Biochem. Pharmacol. 8(3):335-336.

3571. Redetzki, H. M., F. A. O'Bourke, and L. Tucker. 1963. Pharm-acological and biochemical activities of 6-amino-nicotinamide (antitumor agent in mice with Ehrlich ascites tumor). In: 2nd International Pharmacological Meeting, Prague, 1962.

3572. Rege, A. B. 1971. Synthesis of certain 1,2-disubstituted cyclobutane derivatives related to acetylcholine. 78pp. Diss. Abstr. Int. B 32(3):1473.

3573. Regoeczi, E., and P. Walton. 1967. Metabolism of 125I-fibrinogen in normal monkeys and in those with pharmacologically induced plasminogen activator release. Clin. Sci. 33(3):559-568.

3574. Rehbinder, D., and W. Deckers. 1968. Metabolic effects of Catapresan (2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride). Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 261(2):162-175.

3575. Reid, M. E. 1961. Nutritional studies with the guinea pig. VII. Niacin. J. Nutrition 75(3):279-286.

3576. Reid, M. E., and L. Von Sallmann. 1960. Nutritional studies with the guinea pig. VI. Tryptophan (with ample dietary niacin.) J. Nutrition 70(3):329-336.

3577. Reid, J. T., C. F. Huffman, and C. W. Duncan. 1946. The therapeutic effect of yeast and pyridoxine on poikilocytosis in dairy cattle. J. Nutrition 30(6):413-423.

3578. Reimann, E. M., M. L. Sunde, and W. G. Hoekstra. 1971. Effect of chloroquine and certain amines, vitamines, and arthritis-influencing agents on the zinc-deficient chick. Proc. Soc. Exp. Biol. Med. 137(2):473-479.

3579. Reitano, U., and M. Gaglio. 1952a. Modifications of the prothrombin activity of the arterial and venous blood in load tests with nicotinic acid. Boll. Soc. Ital. Biol. Sper. 28:23-26.

3580. Reitano, U., and M. Gaglio. 1952b. The utilisation of prothrombin and the thromboplastic activity of arterial and venous blood. Boll. Soc. Ital. Biol. Sper. 28:186-189.

3581. Reitano, U., and S. Ricceri. 1952. Effect of intravenous injection of nicotinic acid on the amount of iron in arterial and venous blood. Boll. Soc. Ital. Biol. Sper. 28:46-48.

3582. Reith, J. F., A. Gorter, and M. van Eekelen. 1949. Nutritive value of bread. II. Calculations of the importance of different types of bread in the Netherlands diet. Voeding 10: 206-220.

3583. Rengo, F., G. Migliau, D. Artese, V. Dolce, and M. Ferro-Luzzi. 1967. Further contribution to the study of the Raynaud's syndrome. Med. Clin. Speri. 17(5):509-524.

3584. Rentschler, H. 1963. Importance of fruit and vegetable juices and the beverages prepared from them in supplying the population with vitamins and minerals. Qualitas Plant. Mater. Vegetables 10(1-4):208-220.

3585. Rerat, A., H. Le Bars, and J. Molle. 1958. A perfusion method for demonstrating the absorption of B vitamins in normally fed sheep. Compt Rend. 246:1920-1922.

3586. Reshef, L., and R. W. Hanson. 1972. Interaction of catechol amines and adrenal corticosteroids in the induction of phosphopyruvate carboxylase in rat liver and adipose tissue. Biochem. J. 127(5):809-818.

3587. Resources Committee, Prime Minister's Office, Japanese Government. 1954. Nutritional standards for Japanese. J. Japanese Soc. Food and Nutrition 6(6):243-257.

3588. Reusser, F. 1968. Mode of action of melinacidin, an inhibitor of nicotinic acid biosynthesis. J. Bacteriol. 96(4):1285-1290.

3589. Reusser, F. 1969. Mode of action of albocycline, an inhibitor of nicotinate biosynthesis. J. Bacteriol. 100(1):11-13.

3590. Revel, M., and P. Mandel. 1962. Effect of an induced synthesis of pyridine nucleotides in vivo on the metabolism of ribonucleic acid. Cancer Res. 22:456-462.

3591. Revel, M., J. Navech, and J. P. Vives. 1963. Action of tertiary nitrogen bases on several phosphoric acid chlorides. Bull. Soc. Chim. France 10:2327-2331.

3592. Revel, M., L. Mandel, M. Wintzerith, N. Klein, and P. Mandel. 1961. Regulation of the biosynthesis of ribonucleic acids (RNA). Action of nicotinamide. Bull. Soc. Chim. Biol. 43:91-101.

3593. Revelli, M. 1968. Group B vitamins and iron content of rice and rice food products. Minerva Dietol. 8(2):70-85.

3594. Reynard, A. M. 1968. N1-Methylnicotinamide uptake by rat kidney slices; reversible and irreversible inhibition. Brit. J. Pharmacol. 34(1):190P-191P.

3595. Ricci, C. 1953. Possible relation between nucleic acids and pyridine nucleotides. Arch. "E. Maragliano" Patol. e Clin. 8:1345-1350.

3596. Ricci, C. 1971. The physiological effects of nicotinamide. Acta Vitaminol. Enzymol. 25(1/2):65-80.

3597. Ricci, C., and A. Grassellini. 1958. Incorporation of phosophorus-32 in the various phosphoric fractions of rat liver during the biosynthesis of diphosphopyridine nucleotide (DPN). Boll. Soc. Ital. Biol. Sper. 34:767-768.

3598. Ricci, C., and G. Ivaldi. 1954. Separation of cytoplasmic fractions from the liver of the rat by the use of nicotinamide. Boll. Soc. Ital. Biol. Sper. 30:1043-1044.

3599. Ricci, C., and G. Ivaldi. 1958. Adenylpolyphosphate content and liver biosynthesis of diphosphopyridine nucleotide (DPN). Boll. Soc. Ital. Biol. Sper. 34:765-767.

3600. Ricci, C., and E. Marre. 1954. Coenzyme activity on plant dehydrogenase systems of the pyridine nucleotide synthesised in the liver of animals treated with nicotinamide. Boll. Soc. Ital. Biol. Sper. 30:1041-1043.

3601. Ricci, C., and V. Pallini. 1964. Occurrence of free nicotinic acid in the liver of nicotinamide-injected rats. Biochem. Biophys. Res. Commun. 17(1):34-38.

3602. Ricci, C., E. Marinello, and G. Quadri. 1961. Glycogen content and coenzyme biosynthesis in the liver of guinea pigs treated with high doses of nicotinamide. Boll. Soc. Ital. Biol. Sper. 37:680-681.

3603. Ricci, C., V. Pallini, and M. Bari. 1965. Comparative investigation of the biosynthesis of nicotinamide adenine dinucleotide. Giorn. Biochim. 14(6):715-721.

3604. Ricci, C., V. Pallini, and P. Martelli. 1965. Stero-specificity of the enzymic NAD synthesis. Biochem. Biophys. Res. Commun. 19(3):296-299.

3605. Ricci, C., V. Pallini, and G. Pompucci. 1960a. Acid-soluble nucleotides of the liver of rats treated with nicotinamide. Boll. Soc. Ital. Biol. Sper. 36:1020-1023.

3606. Ricci, C., V. Pallini, and G. Pompucci. 1960b. On the DPN/DPNH relation in liver of rats treated with strong doses of nicotinamide. In: Proceedings of fifth Latin International Biochemical Meeting. Rev. Espanola Fisiol. 16(Suppl. 2): 241-244.

3607. Riccitelli, L., and N. Lolli. 1940. Further studies on the function of nervous vegetative centers with direct vitamin innoculation: D and PP factors. With a digest on the relations between nervous system and vitamins. Riv. Biol. 30: 21-56.

3608. Rice, E. E., J. F. Beuk, and J. F. Fried. 1947. Effect of commercial curing, smoking, storage, and cooking operations upon vitamin content of pork hams. Food Res. 12(3):239-246.

3609. Rice, E. E., E. M. Squires, and J. F. Fried. 1948. Effect of storage and microbial action on vitamin content of meat. II. Food Res. 13(3):195-202.

3610. Rice, E. E., E. J. Strandine, E. M. Squires, and B. Lyddon. 1946. The distribution and comparative content of certain B-complex vitamins in chicken muscles. Arch. Biochem. 10(2):251-260.

3611. Richert, D. A., R. Amberg, and M. Wilson. 1962. Metabolism of glycine by avian liver. J. Biol. Chem. 237:99-103.

3612. Richet, C., and F. Delbarre. 1949. Antinutrition factors. Rev. Path. Comparee et Hyg. Gen. 49:566-574.

3613. Richter, C. P., and C. D. Hawkes. 1941. The dependence of the carbohydrate, fat and protein appetite of rats on the various components of the vitamin B complex. Amer. J. Physiol. 131(3):639-649.

3614. Riedl, O. 1949. Pharmacodynamic effects of nicotinic acid and its derivatives upon the blood sugar. Casopis Lekaru Ceskych 88:411-414.

3615. Rigdon, R. H. 1948. A consideration of the use of blood and oxygen in the treatment of maleria. Am. J. Clin. Path. 18:485-490.

3616. Rigdon, R. H. 1966. Effect of niacin on the spontaneously occurring myopathy in the duck. Tex. Rep. Biol. Med. 24(4): 655-658.

3617. Riggio Bevilacqua, L. 1951. On the different behaviour of N1-methylnicotinamide in the guinea pig and rat. Boll. Soc. Ital. Biol. Sper. 27:1223-1225.

3618. Riggs, J. K. 1940. Length of time required for depletion of vitamin A reserves in range cattle. J. Nutrition 20:491-500.

3619. Rikans, L. L., D. Arata, and D. C. Cederquist. 1964. Fatty livers produced in albino rats by excess niacin in high fat diets. I. Alterations in enzyme and coenzyme systems induced by supplementing 40% fat diets with 0.1% of niacin. J. Nutr. 82(1):83-87.

3620. Rikans, L. L., D. Arata, and D. C. Cederquist. 1965. Fatty livers produced in albino rats by excess niacin in high-fat diets. II. Effect of choline supplements. J. Nutr. 85(1): 107-112.

3621. Rindani, T. H., and S. N. N. Rao. 1950. Studies of the urinary excretion of nicotinic acid in diabetic patients. Indian Med. Gaz. 85(11):488-490.

3622. Rindi, G. 1953. Influence of sulfur dioxide upon preserves with respect to their thiamine, riboflavin, niacin, folic acid, and ascorbic acid content, and palatability. Intern. Z. Vitaminforsch. 24:430-441.

3623. Ringrose, R. C., A. G. Manoukas, R. Hinkson, and A. E. Teeri. 1965. The niacin requirement of the hen. Poultry Sci. 44:1053-1065.

3624. Rink, M., and R. Lux. 1961. Determination of organic bases and alkali salts of organic acids with a solution of perchloric acid in glacial acetic acid in a water-free medium. Deut. Apotheker-Ztg. 101:911-918.

3625. Ritsert, K. 1939. The determination of nicotinic acid and its amide in urine, tissues and blood. Klin. Wochschr. 18:934-936.

3626. Ritsner, M. S., and V. S. Aleshko. 1971. Certain disturbances in tryptophan metabolism in oligophrenia. Vopr. Okhr. Materin. Det. 16(5):85.

3627. Rivin, A. U. 1959. Jaundice occurring during nicotinic acid therapy for hypercholesteremia. J. Amer. Med. Assoc. 170:2088-2089.

* 3628. Rivin, A. U. 1962. Hypercholesterolemia. Use of niacin and niacin combinations in therapy. California Med. 96(4):267-269.

3629. Rizzo, A., et al. 1964. Action of nicotinic acid on capacity of alveolo-capillary diffusion in subjects with chronic pulmonary heart disease. Riforma Med. 78:33-35.

3630. Rizzo, E. 1956. Quantitative and qualitative changes induced by nicotinic acid on the milk secretion of hypogalactic nursing mothers. Riv. Pediat. Siciliana 11:71-80.

3631. Robb, J. S. 1962. Effect of nerve stimulation and of drugs on nucleic acid fragments in N, N-dimethylformamide extracts of dog hearts. J. Pharmacol. Exptl. Therap. 135:323-334.

3632. Robb, J. S., and I. C. L. Chang. 1957. Studies of vitamin B depletion in perfused hearts. Circulation Res. 5(3):315-318.

3633. Robert, P. 1951. Blood chemical investigations in various skin diseases with special reference to vitiligo. Dermatologica 102:253-277.

3634. Robert, P., and H. Zuercher. 1950. Investigations on the formation of pigment. I. The influence of heavy metal compounds, hemin, vitamins, amino acids, bacteriotoxins and other materials on the formation of dopa melanin in vitro and the formation of pigment in vivo. Dermatologica (Basel) 100(4/6):217-241.

3635. Roberts, E. C., and E. E. Snell. 1946. An improved medium for microbiological assays with Lactobacillus casei. J. Biol. Chem. 163:499-509.

3636. Roberts, W. M., and L. F. Blanton. 1954. Observations on cold milk separation. Southern Dairy Prod. J. 55(4):91-92, 98-100, 106, 108.

3637. Robertson, B. R. 1971. On thrombosis, thrombolysis and fibrinolysis: I. Thrombolytic therapy of deep venous thrombosis: II Assay of individual fibronolytic response. Acta Chir. Scand. Suppl. 421:5-51.

3638. Robinson, F. A. 1945. The vitamins. Progress in 1944. Food Manufacture 20(3):97-100.

3639. Robinson, I. F. A. 1955. The vitamins--recent research. Mfg. Chemist 26:262-264.

3640. Roblin, R. O. Jr. 1946. Metabolic antagonists. Chem. Rev. 38(2):255-377.

3641. Roccuzzo, M. 1949. Action of nicotinic acid on agglutinating power and on leucocyte characteristics of rabbits during antityphoid immunization. Boll. Soc. Ital. Biol. Sper. 25:984-986.

3642. Roccuzzo, M. 1953. Iron of blood in children after nicotinic acid treatment. Riv. Pediat. Siciliana 8:215-223.

3643. Roche, J., A. Laurens, P. Mandel, and O. Thomas. 1944. Action of riboflavin associated with nicotinamide on replacement of important losses of nitrogen. Compt. Rend. Soc. Biol. 138:937-938.

3644. Roche, J., A. Laurens, P. Mandel, and O. Thomas. 1948. Restoration of large nitrogen losses and filling of nutritional protein requirements. IV. The action of riboflavin and nicotinamide on the restoration of protein losses in adults. Rec. Trav. Inst. Nation. Hyg. (Paris) 3(2):603-619.

3645. Rock, G. C. 1969. Sterol and water-soluble vitamin requirements for larvae for the red-banded leaf roller, Argyrotaenia velutinana. Ann. Entomol. Soc. Amer. 62(3):611-613.

3646. Rodeck, H. 1967. Effect of ADH-stimulating drugs on the neurosecretory system. Med. Welt. 9:508-509.

3647. Rodeck, H., and R. Braukmann. 1966. Effect of nicotinic acid on the neurosecretory system. Z. Zellforschung Mikroskop. Anat. 75(1):83-95.

3648. Rodrigues, J. A. R. 1966. Control of vitamins in food products. Rev. Brasil. Quim. (Sao Paulo) 61(364):265-272.

3649. Rodrigues, L. D., and J. A. da Silva. 1955. Separation and identification in pharmaceutical products of the principal vitamins of the B complex with chromatographic paper. Rev. Port. Ferm. 5:75-88.

3650. Rodriguez Cristobal, J., and C. L. De Cuenca Esteban. 1969. Microbiological methods for the determination of B-complex vitamins. Am. Inst. Invest. Vet., Madrid, pp 18-19, 141-152.

3651. Roesch, W., J. Brater, and M. Classen. 1972. Influence of xanthinol nicotinate on gastric acid secretion. Med. Klin. (Munich) 67(52):1723-1727.

3652. Roger, J. C., H. Chambers, and J. E. Casida. 1964. Nicotinic acid analogs--effects on response of chick embryos and hens to organophosphate toxicants. Science 144(3618):539-540.

3653. Roger, J. C., D. G. Upshall, and J. E. Casida. 1969. Structure-activity and metabolism studies on organophosphate teratogens and their alleviating agents in developing hen eggs with special emphasis on Bidrin. Biochem. Pharmacol. 18(2):373-392.

3654. Rogers, D., and M. N. Mickelson. 1948. Vitamin B contents of sugar beets and by-products. Ind. Eng. Chem. 40:597-599.

3655. Rogers, K. S., J. C. Forbes, and N. A. Nakonecz. 1969. Arthritogenic properties of lipophilic, aryl molecules. Proc. Soc. Exp. Biol. Med. 131(2):670-672.

3656. Roggen, J. C. 1942. Estimation of nicotinic acid in human blood. I. Rec. Trav. Chim. 61:616-626.

3657. Roggen, J. C. 1943. Determination of nicotinic acid, etc., in human urine and feces. II. Rec. Trav. Chim. 62:137-147.

3658. Roggen, J. C. 1946. Note on a precursor of niacin. Rec. Trav. Chim. Pays-Bas 65(10/11):682.

3659. Rogosa, M. 1943. Nicotinic acid requirements of certain yeasts. J. Bacteriol. 46:435-440.

3660. Rogozinski, R. 1963. Effect of certain B vitamins and of cocarboxylase on the glucose-tolerance test in juvenile diabetes. Polski Tygod. Lekar. 18(32):1169-1172.

3661. Rogozkin, V. A., and Ya. Afar. 1965. Effect of experimental training on induced synthesis of NAD in the rat. Ukr. Biokhim. Zh. 37(4):558-564.

3662. Rogozkin, V. A., and L. V. Maksimova. 1965. Effect of nicotinamide on the level of NAD and NAD-glycohydrolase activity in skeletal muscles and liver. Ukr. Biokhim Zh. 37(3):379-385.

3663. Rohrbach, P., and C. Leprince. 1966. Nicotinic acid and various derivatives as hypolipemia-producing compounds. Therapie 21(4):1063-1073.

3664. Rohrlich, M. 1950. Synthesis of nicotinic acid and nicotinamide. Arch. Pharm. 283:122-127.

3665. Roitt, I. M. 1956. Inhibition of carbohydrate metabolism in ascites-tumor cells by ethylenimines. Biochem. J. 63:300-307.

* 3666. Rook, H. C. 1944. Nicotinic acid in angina pectoris. Lancet 247(6331):864.

3667. Roos, C. J. 1939. The estimation of nicotinic acid (amide). Acta Brevia Neerland. 9(6):156.

3668. Root, M. A., and J. Ashmore. 1964. The hypoglycemic activity of nicotinic acid in rats. Arch. Exptl. Pathol. Pharmakol. 248(2):117-123.

3669. Rosa, G. 1962. Modifications of the curarelike activity of succinylcholine due to administration of other drugs. Minerva Anestesiol. 28(9):367-371.

3670. Rosa, L., and G. Marzocchi. 1949. Bilirubin and nicotinic acid. Bull. Sci. Med. 121:293-298.

3671. Rose, A. H. 1960. Excretion of nicotinic acid and nicotinic acid adenine dinucleotide by Biotin-deficient yeast. Nature 186(4719):139-140.

3672. Rose, D. P., and F. McGinty. 1968. The influence of adrenocortical hormones and vitamins upon tryptophan metabolism in man. Clin. Sci. 35(1):1-9.

3673. Rose, D., and R. Peterson. 1948. Canadian Wiltshire bacon. XXX. Effects of curing and cooking on the thiamine, riboflavin, and niacin contents of longissimus dorsi muscles. Canadian J. Res. Sect. F. Technol. 26(2):66-75.

3674. Rosen, F. 1955. Effect of isonicotinic acid hydrazide on niacin and pyridoxine metabolism in rats. Proc. Soc. Exptl. Biol. and Med. 88(2):243-246.

3675. Rosen, H., S. Feldman, and M. Madorsky. 1953. Effect of a combined administration of auromycin and nicotinic acid in ozena. Ann. Otol. Rhinol. Laryngol. 62:161-168.

3676. Rosen, S. 1953. The importance of biotin, niacin, and pantothenic acid in cucumber fermentation. Dissertation Abstracts 13:6.

3677. Rosenberg, P., and J. M. Coon. 1960. Nikethamide, nicotinamide and some related compounds in anticholinesterase poisoning. J. Pharmacol. and Exptl. Therap. 128(3):289-298.

3678. Rosenblum, L. A., and N. Jolliffe. 1940. Application to urine of Bandier and Hald's method for determination of nicotinic acid. J. Biol. Chem. 134(1):137-141.

3679. Rosenthal, C. 1967. Chemical composition and importance of pollen. Apicultura (Bucharest) 20(1):11-15.

3680. Rosenthal, H. L., G. A. Goldsmith, and H. P. Sarett. 1953. Excretion of N'-methylnicotinamide and the 6-pyridone of N'-methylnicotinamide in urine of human subjects. Proc. Soc. Exptl. Biol. and Med. 84(1):208-211.

3681. Ross, C., and A. Farah. 1966. p-Aminohippurate and N-methylnicotinamide transport in dog renal slices: An evaluation of the counter-transport hypothesis. J. Pharmacol. Exp. Therap. 151(2):159-167.

3682. Ross, S. G. 1950. Pellagra in Fiji. Amer. J. Trop. Med. 30(6):921-928.

3683. Ross, V. 1957. Nicotinamide in adenocarcinoma 755 and in the milk of mice carrying the "agent" of spontaneous mammary tumor. Experientia 13(12):497.

3684. Ross, W. C. J. 1967. Some 6-substituted nicotinamides: synthesis and antineoplastic activities. Biochem. Pharmacol. 16(4):675-680.

3685. Rossi, C. A. 1947. Course of nicotinamide and trigonelline elimination following vitamin PP administration. Boll. Soc. Ital. Sper. 23(7):833-835.

3686. Rossi, L., V. Laghi, and A. Cavallaro. 1968. Liver-protective effect of L-amino acids involved in the Krebs-Henseleit cycle associated with vitamins. Minerva Med. 59(75):3919-3930.

3687. Rossi-Espagnet, A., and G. Toriontano. 1955. Temperature and state of vasodilatation of the stomach. Response to nicotinic acid and to adrenaline and relation to rectal and skin temperature. Boll. Soc. Ital. Biol. Sper. 31:1458-1460.

3688. Rossini, G. 1947. Vitamin PP, salicylate intoxication and metabolism, of sodium salicylate. Acta Vitaminol. 1:8-11.

3689. Roth, J. S., and J. Bukovsky. 1961. N-Demethylating system in rat liver microsomes. J. Pharmacol. Exptl. Therap. 131: 275-281.

3690. Roth, L. J., E. Leifer, J. R. Hogness, and W. H. Langham. 1948. Studies on the metabolism of radioactive nicotinic acid and nicotinamide in mice. J. Biol. Chem. 176(1):249-257.

3691. Rottini, E., G. Cozzolino, G. Dominici, and L. Scianaro. 1967. Trytophan-nicotinic acid metabolism in acute and chronic liver diseases. Ann. Fac. Med. Chir. Univ. Studi. Perugia 59(1): 79-89.

3692. Rotzsch, W., and H. Aurich. 1961. Behavior of several B vitamins in the skeletal musculature as affected by thyroid hormones. Wiss. Z. Karl-Marx-Univ., Leipzig, Math.-Naturw. Reihe 10:615-620.

3693. Rouir, E. V. 1948. Factory control of the vitamins. Rev. Fermentations et Inds. Aliment. 3:47-53.

3694. Rovira, A. D., and J. R. Harris. 1961. Root excretions in relation to the rhizosphere effect. V. The exudation of B vitamins. Plant and Soil 14:199-214.

3695. Rowe, D. M., G. J. Mountney, and I. Prudent. 1963. Effect of freeze-drying on the thiamine, riboflavine, and niacin content of chicken muscle. Food Technol. 17(11):111-112.

3696. Roy, B. R. 1964. Effect of nutritional deficiency of niacin and riboflavin at the mitochondrial level. Indian J. Exp. Biol. 2(3): 135-137.

3697. Royer, M., and P. A. Mazure. 1951. Transit through the normal human intestine. Pharmacologic actions. Rev. Soc. Argentina Biol. 27(5/6):210-219.

3698. Royer, M., and P. A. Mazure. 1952. Pharmacology of the normal intestine. Medicina (Buenos Aires) 12(5):308-318.

3699. Rozanov, A. Ya., and A. M. Torbinskii. 1969. Effect of some vitamins and cortisone on the oxidation of pyruvate in Walker-256 carcinoma implanted into rat lung tissue. Vop. Med. Khim. 15(2):147-150.

3700. Rozanov, A. Ya., and Vu-Van-An. 1970. Effect of pantothenate, riboflavine, and nicotinate on the deposition of thiamine-35S in rats. Ukr. Biokhim. Zh. 42(1):8-11.

3701. Rozanov, A. Ya., V. P. Voitenko, and S. V. Bogush. 1966. Nicotinic acid metabolism in rats of various ages. Vitaminy Preduprezhdenii Lech. Prezhdevremennogo Stareniya, Inst. Gerontol. Akad. Med. Nauk S.S.S.R. pp. 229-233.

3702. Rozanov, A. Ya., L. G. Savluchinskaya, E. S. Zhdanovich, and V. Kopelevich. 1970. Biosynthesis of coenzyme A from pantothenate derivatives in rats. Biokhimiya 35(1):58-63.

3703. Rozenberg, M. A. 1953. Effect of vitamin B1 and niacin on the cardiac blood system and respiration of normal and anaphylacticized animals. Med. Zhur., Akad. Nauk Ukr. R.S.R. 23(5):36-41.

3704. Rubchinskaya, K. I. 1968. Effect of cardiac stimulants on carbohydrate-phosphorus metabolism of rat myocardium under hypoxia. Farmakol. Toksikol. (Kiev) 4:20-23.

3705. Rubenchyk, B. L., and H. P. Horban. 1970. Mechanochemical changes and nicotinamide coenzyme contents in rat liver mitochondria during carcinogenesis. Ukr. Biokhim. Zh. 42(4): 464-468.

3706. Rudenko, A. T. 1970. The vitamin provision in patients with face and jaw injuries. Vestn. Khir. im I. I. Grekova 104(7): 54-57.

3707. Rudenko, O. M. 1968. The effectiveness of Campolon in the therapy of chronic hepatitis of children. Pediat. Akush. Hinekol. 30(5):12-14.

3708. Ruderman, N. B., and V. Lauris. 1968. Effect of acute insulin deprivation on rat liver glucokinase. Diabetes 17(10):611-616.

3709. Rudy, A., and R. Hoffman. 1942. Skin disturbances in diabetes mellitus: their relation to vitamin deficiencies. New England J. Med. 227(24):893-900.

3710. Ruetgerswerke und Teerverwertung A.-G. 1968. Nicotinic acid and isonicotinic acid. Brit. Pat. 1,132,746.

3711. Ruf, K. B. 1968. Blockade of ovulation in the rat initiated by an antimetabolite. Experientia 24(12):1256-1257.

3712. Ruffin, J. M. 1939. The treatment of pellagra. J. S. Carolina Med. Assoc. 35(4):107-108.

3713. Ruffin, J. M., and D. T. Smith. 1939. Treatment of pellagra with special reference to the use of nicotinic acid. Southern Med. J. 32(1):40-47.

3714. Ruffin, J. M., G. Margolis, L. H. Margolis, S. G. Smith, and D. T. Smith. 1938. The effect of nicotinic acid on pellagra and experimental canine black tongue. J. Clin. Invest. 17:529.

3715. Ruffo, A. 1940. Determination of nicotinic acid. Boll. Soc. Ital. Biol. Sper. 15:1130-1132.

3716. Ruffo, A., and A. Vescia. 1940. Determination of nicotinic acid in biological material. Quaderni Nutriz. 7:230-240.

3717. Ruffo, A., and A. Vescia. 1942. Importance of nicotinic acid for rats. Quad. Nutriz. 8:97-107.

3718. Rufli, T., and H. Stahelin. 1972. Xanthomatoses and hyperlipemia: Cutaneous manifestations of 3 patients with hyperlipemia. Dermatologica (Basel) 144(5):270-282.

3719. Ruggieri, G., L. Smilari, and P. Bellia. 1955. Changes of the pancreas lipase activity induced by thiamine, pyridoxine and nicotinamide. Boll. Soc. Med. Chir. Catania 23: 149-173.

3720. Ruiter, M., and L. Meyler. 1960. Skin changes after therapeutic administration of nicotinic acid in large doses. Dermatologica (Basel) 120:139-144.

3721. Ruiter, M., and L. Meyler. 1960. Skin changes after the therapeutic use of high doses of nicotinic acid. Ned. T. Geneesk. 104:1114-1116.

3722. Rumyantsev, G. I., and D. A. Mekhelson. 1971. Effect of the noise-vibration factor on sailors under complex conditions. Gig. Sanit. 36(9):25-27.

3723. Runova, M. F. 1961. Effects of some cobalt salt complexes with B group vitamins on peripheral blood in experimental radiation sickness. Farmikol. i Toksikol. 24:121-127.

3724. Runova, M. F. 1964. Effects of some cobalt, manganese, and copper salt complexes on the blood in induced anemia. Farmikol. i Toksikol. 27(2):196-199.

3725. Russell, D. W. 1972. Low circulating levels of acid-labile hydrazones after oral administration of isonicotinic acid hydrazide. Clin. Chim. Acta 41:163-168.

3726. Rus'yanova, N. D., L. P. Yurkina, and N. S. Popova. 1969. Nicotinic acid from coke chemical quinoline. Koks Khim. 5:41-46.

3727. Rus'yanova, N. D., N. V. Malysheva, L. P. Yurkina, and V. K. Kondratov. 1967. Nicotinic acid. U.S.S.R. Pat. 191,562.

3728. Rutter, L. 1966. Transaminase deficiency in alcoholics and cases of peptic ulcer. Nature 210(5035):538.

3729. Ruzyllo, E., W. B. Szostak., and W. Olszak. 1968. The influence of intravenous injection of heparin and nicotinic acid on plasma glyceride-glycerol (GG) and free fatty acids (FFA) level. Pol. Med. Sci. Hist. Bull. 11(2):52-53.

3730. Ryan, C. F., W. F. Bousquet, and T. S. Miya. 1967. Stress and the maintenance of nicotinamide-induced hepatic nicotinamide adenine dinucleotide elevation by chlorpromazine (mouse, rat). Biochem. Pharmacol. 16(12):2454-2457.

3731. Ryan, F. J., and K. Kiritani. 1959. Effect of temperature on natural mutation in Escherichia coli. J. Gen. Microbiol. 20(3):644-653.

3732. Rybalko, L. I. 1967. The improvement of the external respiratory function by some drugs. Nauch Tr. Irkutsk Med. Inst. 80:86-87.

3733. Rybina, A. O., and Yu. V. Lakhno. 1961. On the distribution and storage of thiamine and nicotinic acid introduced into the organism. Ukr. Biokhim. Zh. 33:46-56.

3734. Rybkina, G. V. 1968. Effect of respiration inhibitors and stimulants on water metabolism in plant cells. Fiziol. Vodoobmena Ustoich. Rast. 1:90-96.

3735. Rydstrom, J., A. T. da Cruz, and L. Ernster. 1971. Steady-state kinetics of mitochondrial nicotinamide nucleotide transhydrogenase: 2. The energy-linked reaction. Eur. J. Biochem. 23(2):212-219.

3736. Ryrie, I. J., and K. J. Scott. 1969. Nicotinate, quinolinate, and nicotinamide as precursors in the biosynthesis of nicotinamide adenine dinucleotide in barley. Biochem. J. 115(4): 679-685.

3737. Ryss, S. M. 1940. The vitamins of the B group and their significance for internal pathology. Sovet. Vrachebnyi Zh. 44: 725-732.

3738. Ryss, S. M. 1950. The antivitamins and the role of the sulfonamides in vitamin metabolism. Klin. Med. (U.S.S.R.) 28(4): 3-12.

3739. Rzaev, N. M., and D. D. Zakirdzhaev. 1967. Pathogenesis of the "ricochet effect" of anticoagulant treatment. Dokl. Akad. Nauk Azerb. S.S.R. 23(1):80-83.

3740. Saakyants, E. M. 1959. The effect of vitamin PP on the chemotherapeutic activity in experimental tuberculosis of white rats. Probl. Tuberk. 1:94-97.

3741. Sablosky, L. 1965. Combination therapy in hypertension. Western Med. 6(1):7-8.

3742. Sabri, M. I., and V. K. M. Rao. 1965. Stabilization of vitamins in pharmaceutical preparations. IX. Stability of thiamine. Indian J. Technol. 3(1):28-32.

3743. Sacca, M. 1946. Vitamin PP and mineral metabolism in infancy. Dosage of potassium and calcium following administration of nicotinamide. Boll. Soc. Ital. Biol. Sper. 22(5):477-478.

3744. Sacchetti, G. 1962. The amide group in nicotinamide and 3-pyridineacetamide in relation to some of their biological actions. Studies on hypercholesterolemia in man. Acta Vitaminol. 16(3/4):121-126.

3745. Sacchetti, G., M. Giovannini, and L. T. Tenconi. 1963. Nicotinic acid in children suffering from mongoloid idiocy. Acta Vitaminol. 17(3):107-112.

3746. Saccone, C., F. Tancredi, L. Fedele, and E. Quagliariellos. 1960. Studies on the metabolic conversion of tryptophan into nicotinic acid in individuals with tumors of the bladder. Modifications in the urinary excretory picture after the administration of nicotinamide and vitamin B6. Boll. Soc. Ital. Biol. Sper. 36:1942-1943.

3747. Sagar, P., and J. Kara. 1966. Activation of deoxycytidylate deaminase from certain embryonal and tumor tissues by 6-aza-2'-deoxycytidine 5'-monophosphate and 2'-deoxycytidine 5'-triphosphate. Folia Biol. (Prague) 12(1):75-79.

3748. Saglimbene, F. 1961. Changes of blood lipid levels during the administration of large doses of nicotinic acid in hypercholesterolemic patients. Gazz. Intern. Med. e Chir. 66: 1200-1205.

3749. Saha, K. C. 1941. Nicotinic acid content of fish. Ann. Biochem. Exp. Med. 1:75-78.

3750. Said, F., M. M. Amer, and K. N. Girgis. 1970. Stability of some pharmaceutical formulations. III. Stability of dihydrostreptomycin sulfate in syrupy solutions with some vitamin B factors. Bull. Fac. Pharm., Cairo Univ. 1969 8(1):31-36.

3751. Sailer, S. 1960. On the mechanism of action of nicotinic acid on blood coagulation and fibrinolysis. Wien Z. Inn. Med. 41:307-316.

3752. Sailer, S., and O. Eber. 1960. On thrombolysis studies on the rabbit with combined nicotinic acid-heparin therapy. Klin. Wschr. 38:548-551.

3753. Saitgaleeva, M. Sh., and V. R. Klyachko. 1966. Serum lipoproteins in patients with myxedema during triiodothyronine therapy. Kazan. Med. Zh. 4:45-47.

3754. Saito, S., Y. Tokunaga, Y. Takagi, M. Torizuka, and K. Fukushima. 1970. Acute toxicity of CL 65562(4-(alpha, alpha, alpha-trifluoro-m-toluidinonicotinic acid)). Nippon Univ. J. Med. 12(1-2):21-26.

3755. Saito, T. 1972. Pharmacological studies on riboflavine derivatives. 2. Effects on various blood vessels. Vitamins 46(5):227-231.

3756. Sakakibara, S., H. Hiratsuka, Y. Ota, H. Gomi, M. Yokoyama, T. Akimoto, and K. Kishik. 1967. An elevation of ventricular fibrillation threshold after surgical resection of infarcted myocardium (dog). Amer. Heart J. 74(3):381-386.

3757. Sakakida, H. 1956. Niacin metabolism. I. Critical studies on the method of niacin loading test and some experiments with nicotinamide. Vitamins 10:337-343.

3758. Sakakida, H. 1957. Niacin metabolism. VIII. Nicotinamide loading test in dogs with experimental jaundice caused by ligation of common bile duct. Naika Hokan 4:23-24.

3759. Sakate, M., and A. O. Ramos. 1965. Phenylheptylamide of the nicotinic acid: Its effect on smooth muscles and blood pressure. Folia Clin. Biol. 34(2):92-100.

3760. Saksena, C., and S. Petri. 1971. Studies on vitamin requirements of the cockroach, Periplaneta americana Linn. Labdev. J. Sci. Technol. Part B, Life Sci. 9B(2):126-131.

3761. Sakuma, R., T. Shimazaki, and J. Kitamura. 1968. Microbiological assay of vitamins in a sample containing kanamycin with resistant strain of lactobacilli. Bitamin 37(5):504-508.

3762. Sakuma, R., T. Shimazaki, J. Kitamura, and K. Takatori. 1968. Assay of pantothenic acid, nicotinic acid, and folic acid using leucomycin-resistant lactic acid bacteria. Bitamin 37(5):498-503.

3763. Sakuyama, S. 1961. Studies on the concentration of nicotinic acid in whole blood. Hirosaki Med. J. 13(1):198-208.

3764. Salam, E. A., and W. S. Elyahky. 1968. Evaluation of prognosis and treatment in Bell's palsy in children. Acta Paediat. Scand. 57(6); 468-472.

3765. Salamon, T. 1960. On the variability of blood nicotinic acid levels in pellagra during the course of its therapy. Srpski Arhiv. Celok Lek' 88:887-891.

3766. Sales Vazquez, M. 1943. Antitoxic value of nicotinic acid. Rev. Clin. Espanola 10:40-43.

3767. Salmon, W. D. 1947a. The tryptophane-sparing action of nicotinic acid. Federation Proc. 6:287.

3768. Salmon, W. D. 1947b. Relation of corn to the requirement of the rat for dietary nicotinic acid. J. Nutrition 33(2): 169-175.

3769. Salter, W. T. 1942. Medical progress. The chemical measurement and control of clinical vitamin deficiency. New Engl. J. Med. 226:649-656, 688-694.

3770. Saltykov, I. I., and V. M. Malishenko. 1970. Effect of vitamins on the physiological characteristics and productivity of sugar beets. Zroshuvane Zemlerobstvo 10:79-82.

3771. Salvador, R. A., and R. M. Burton. 1965. Inhibition of the methylation of nicotinamide by chlorpromazine. Biochem. Pharmacol. 14(8):1185-1196.

3772. Salvi, A., G. B. Rancati, and P. Marrama. 1957. The metabolism of vitamin PP and the level of beta-carotene and vitamin A during antiboitic therapy. Acta Vitaminol. 11:57-62.

3773. Salvi, P., and G. Di Chiro. 1947. Vitamin inhibitors of cholinesterase. II. Action of vitamin K on serum cholinesterase in vitro and in vivo. Acta Neurol. (Naples) 2:485-488.

3774. Salvini, M. 1947. Pharmacological effect of nicotinic acid administered intravenously. Boll. Soc. Ital. Biol. Sper. 23:907-908.

3775. Salvini, M., and C. Dal Palu. 1948. Hemodynamic compensation of the peripheral vasodilation by sodium nicotinate. Boll. Soc. Ital. Biol. Sper. 24:986-988.

3776. Salvini, M., and A. Fracasso. 1947. Spleen reduction by nicotinic acid. Atti Soc. Med.-Chir. Padova 25:277-282.

3777. Salvini, M., F. S. Ferugilo, and G. Barufaldo. 1948. Vitamin PP in the healing of bone fractures. Boll. Soc. Ital. Biol. Sper. 24:982-984.

3778. Salvioli, G. F., L. Marani, and R. Zandomeneghi. 1966. Lipemic syndrome in diabetic ketosis. Action of nicotinic acid. Acta Vitaminol. (Milan) 20(5):181-187.

3779. Sanchez, F. S., and E. Castella Betran. 1950. Action of some organic compounds on acid phosphomonoesterase of dog liver. Anales Facultiad Vet. Univ. Madrid y Inst. Invest. Vet. 2: 70-78.

3780. Sanchez, F. T. 1951. Intraventricular (cranial) route in pharmacology. Arch. Inst. Farmacol. Exptl.(Med.) (Madrid) 3:208-228.

3781. Sandritter, W., W. Benstz, G. Schlueter, and A. K. Kleinschmidt. 1962. Animal experiment studies. Med. Welt 31:1613-1619.

3782. Saneblidze, M. G. 1963. Effect of nicotinic acid on the secretory function of the stomach. Soobshch Akad. Nauk Gruzinsk SSR. 30(2):233-240.

3783. Sangiorgi, M., D. Cannata, and B. Moscatello. 1971. Preventive action of sodium nitrite, nicotinic acid, papaverine, and aminophylline on angina of effort. Comparative pharmacodynamic study. Cor. Vasa. 13(4):244-250.

3784. Sangiorgi, M., B. Moscatello, A. Malarbi, L. Pierangeli, G. Mastroberardino, and D. Cannata. 1970. Pharmacological study of the stenocardia of effort: III. Effect of nicotinic acid. Boll. Soc. Ital. Cardiol. 15(3):226-247.

3785. Sanitskii, V. I. 1970. Dyanmics of vitamin PP metabolism in elderly and senile patients with pulmonary tuberculosis. Vrach Delo. 7:90-92.

3786. Sanitskii, V. I. 1971. Vitamin PP deficiency and allowances in elderly pulmonary tuberculous patients. Probl. Tuberk. 49(7): 56-58.

3787. Santararo, R. 1954. Action of some nicotinic acid derivatives on tissue respiration in vitro. Arch. Ital. Sci. Farmacol. 3(4): 322-323.

3788. Sanwal, B. D. 1969. Regularotry mechanisms involving nicotinamide adenine nucleotides as allosteric effectors. J. Biol. Chem. 244(7):1831-1832.

3789. Sanz, A. B. 1962. Pyridinecarboxylic acids. Span. Pat. 272,411.

3790. Sapezhinskaya, N. V. 1947. Nicotinic acid and spasmodic poisons. Farmacol. i Toksikol. 10(3):11-14.

3791. Saphir, W. 1941. Xerostomia successfully treated with nicotinic acid. 1941. Am. J. Orthodontics Oral Surg. 27:106-108.

3792. Sardal, J., et al. 1971. Comparative study of the ulcerogenic action of various oral non-steroid anti-inflammatory drugs in the rat. Therapie 27:483-489.

3793. Sarett, H. P. 1942. Studies in nicotinic acid metabolism. II. The fate of nicotinic acid in normal and blacktongue dogs. J. Nutrition 23(1):35-45.

3794. Sarett, H. P. 1948. Indoleacetic acid studies in man. Proc. Soc. Exptl. Biol. and Med. 69(3):494-499.

3795. Sarett, H. P. 1950. The effect of pyridoxine upon the conversion of tryptophan to nicotinic acid compounds in man. J. Biol. Chem. 182(2):691-697.

3796. Sarett, H. P., and V. H. Cheldelin. 1945. Thiamine, riboflavin and nicotinic acid retention in preparation of overseas hams and bacons. J. Nutrition 30(1):25-30.

3797. Sarett, H. P., and G. A. Goldsmith. 1947. Further observations on the relationship of tryptophane and nicotinic acid metabolism in humans. Federation Proc. 6:288.

3798. Sarett, H. P., and G. A. Goldsmith. 1948. Effects of gelatin, glycine and pyridoxine on tryptophane and nicotinic acid metabolism in humans. Federation Proc. 7:298.

3799. Sarett, H. P., and G. A. Goldsmith. 1949. Tryptophan and nicotinic acid studies in man. J. Biol. Chem. 177:461-475.

3800. Sarett, H. P., and G. A. Goldsmith. 1950. Metabolism of L- and DL-tryptophan in normal man and in pellagrins. J. Biol. Chem. 182(2):679-690.

* 3801. Sarett, H. P., J. W. Huff, and W. A. Perlzweig. 1942. Studies in nicotinic acid metabolism. I. The fate of nicotinic acid in man. J. Nutrition 23(1):23-34.

3802. Sarett, H. P., R. L. Pederson, and V. H. Cheldelin. 1945. Microbiological assay methods for nicotinic acid. Arch. Biochem. 7:77-85.

3803. Sarett, H. P., M. J. Bennett, T. R. Riggs, and V. H. Cheldelin. 1946. Thiamine, riboflavin, nicotinic acid, pantothenic acid and ascorbic acid content of restaurant foods. J. Nutrition 31(6):755-763.

3804. Sarin, J. P. S., R. B. Chakravarty, and G. K. Ray. 1964. Estimation of nicotinamide in pharmaceutical preparations. Indian J. Pharm. 26:165-167.

3805. Sarma, D. S. R., S. Rajalakshmi, and P. S. Sarma. 1961. Deamidation of nicotinamide and nicotinamide mononucleotide (NMN). Biochem. Biophys. Research Communs. 6:389-393.

3806. Sarma, D. S. R., S. Rajalakshmi, and P. S. Sarma. 1962. Metabolism of nicotinic acid and nicotinamide in Aspergillus niger. Enzymologia 24(3):148-154.

3807. Sarma, D. S. R., S. Rajalakshmi, and P. S. Sarma. 1963. Reaction between nicotinamide and iodoacetic acid. Biochim. Biophys. Acta 78(4):733-736.

3808. Sarma, R. H., and R. J. Mynott. 1972. Complete analysis of fast Fourier transformed 100 MHz proton magnetic resonance spectra of oxidized and reduced pyridine mononucleotides. J. Chem. Soc., Chem. Commun. 17:975-977.

3809. Sarma, R. H., M. Moore, N. O. Kaplan. 1970. Investigation of the configuration oand conformation of N-methyl-N-ethylnicotinamide-adenine dinucleotide by nuclear magnetic resonance spectroscopy. Biochemistry 9(3):549-556.

3810. Sarukhanyan, F. G., R. S. Karimyan, and R. M. Akhinyan. 1966. Effect of different concentrations of vitamins and cultural medium extracts on yeast growth. Vop. Mikrobiol., Akad. Nauk Arm. SSR. 3:111-126.

3811. Sarnecki, W., A. Nuerrenbach, and W. Reif. 1962. Axerophthylidenes. Ger. Pat. 1,158,505.

3812. Sasame, H. A., and J. R. Gillette. 1970. Studies on the inhibitory effects of various substances on drug metabolism by liver microsomes: The effect of nicotinamide in altering the apparent mechanism of inhibition. Biochem. Pharmacol. 19: 1025-1041.

3813. Sassi, L. 1956. Chemical estimation of nicotinic acid in blood. Arch. Inst. Pasteur Tunis 33:127-136.

3814. Sassine, A., J. M. Bourgeois, and J. Macabies. 1972. The positive inotropic cardiac effect of insulin: Inhibition of this effect by two hyperglycemia-inducing amides: Study on the right atrium of the rabbit in vitro. C. R. Seances Soc. Biol Fil. 166(1):172-175.

3815. Sassiene, A., E. Rechencq, and J. M. Bourgeois. 1970. Hyperglycemic effect of nicotinamide. J. Physiol. (Paris), Suppl. 62(2):315.

3816. Sastry, S. D., and Waller, G. R. 1972. Biosynthesis of N-methyl-5-carboxamide-2-pyridone from Trewia nudiflora. Phytochemistry 11(7):2241-2245.

3817. Sato, S., and Y. Miura. 1967. Analysis of niacin-positive substances produced in mycobacteria, in particular in those of fish origin. Application of the niacin test in classification of mycobacteria. Sci. Rep. Res. Inst., Tohoku Univ., Ser. C 14(3-4):107-113.

3818. Sato, S., M. Motomiya, T. Amizuka, and H. Funakoshi. 1957. Binding of streptomycin, para-aminosalicylic acid and isonicotinic acid to serum protein. Sci. Repts. Res. Inst. Tohoku Univ., Ser. C. (Med.) 8(1):111-135.

3819. Satyanarayana, M. N., and S. B. Kadkol. 1963. Carotene, riboflavin and nicotinic acid content of some Indian foodstuffs. Indian J. Med. Res. 51(4):764-767.

3820. Sauter, H., and J. Jenny. 1954. Action of quinine on the human uterus. Schweiz. Med. Wochschr. 84:1341-1342.

3821. Savage, J. R. 1965. Nutritional factors influencing the conversion of tryptophan to niacin. Dissert. Absts. 23(9): 3346-3347.

3822. Savel'ev, A. A., and M. G. Shershevskii. 1965. Effect of the parenteral administration of nicotinic acid on the state of the cardiovascular system in patients with atherosclerosis. Klin. Med. 43(8):80-84.

3823. Savenkov, P. M. 1967. Treatment by cetamiphen and nicotinic acid in patients with coronary atherosclerosis. Kardiologiya 7(4):50-53.

3824. Savitskaya, A. B. 1964. Experience in the use of nicotinic acid in schizophrenic patients with speech disorders. In: Problems of the clinical aspects, pathogenesis, and treatment of schizophrenia. Moscow 1:123-125.

3825. Savitskaya, L. G. 1971. Effect of nicotinic acid on some indexes of the experimental reactivity of an organism. Mikroelem. Med. 2: 97-99.

3826. Savitskii, I. V., and V. G. Zelinskii. 1967. Effect of some radiomimetics on nicotinamide methylation in albino rat liver slices. Vop. Med. Khim. 13(3):291-295.

3827. Savulescu, O. T., and V. Tudosescu. 1968. Effect of some vitamins on spore germination and growth of some phytopathogenic fungi. Agr. Ital. (Pisa) 68(6):272-277.

3828. Savini, R. 1948a. The action of nicotinic acid and its amide on the normal isolated intestine of rabbits and on atropinized or ergotaminized intestine or intestine with blocked autonomic system. Boll. Soc. Ital. Biol. Sper 24:819-821.

3829. Savini, R. 1948b. Inversion of the vagus effect of nicotinic acid. Boll. Soc. Ital. Biol. Sper. 24:821-822.

3830. Savini, R. 1948c. Influence of nicotinic acid and riboflavin on the threshold of excitation of the cerebral cortex. Boll. Soc. Ital Biol. Sper. 24:822-823.

3831. Savini, R. 1950. Vagal excitability and nicotinic acid. Fisiol. e Med. (Rome) 17:191-197.

3832. Sbragia, S. 1960. Nicotinic acid-streptomycin combination in the therapy of pulmonary tuberculosis. Riforma Med. 74:637-642.

3833. Scaffidi, V., Jr. 1939. Action of nicotinic acid on isolated musculature of stomach and intestine. Riv. Patol. Sper. 22: 443-450.

3834. Scaffidi, V., Jr., and L. D'Agostino. 1939. Action of nicotinic acid on coronary circulation. Studies on isolated heart. Riv. Patol Sper. 22:437-442.

3835. Scaffidi, V., and N. Molino. 1940. Action of pyridine and other substances containing the pyridine radical on intestinal peristalsis. Experiments to explain the pharmacological mechanism of nicotinic acid. Riv. Patol. Sper. 25:147-154.

3836. Scaffidi, V., and N. Molino. 1941. Action of nicotinic acid on motility of the uterus in vivo. Boll. Soc. Ital. Biol. Sper. 16:284-287.

3837. Scalfe, J. F. 1963. Effect of ionizing radiation on the pyridine nucleotides of thymocytes. Can. J. Biochem. Physiol. 41:1469-1481.

3838. Scala, E. 1955. Need of associating methionine with nicotinic acid and nicotinamide when administered at high doses. Biochim. Appl. 2:159-166.

3839. Scala, J., D. E. McOsker, and H. H. Reller. 1968. The percutaneous absorption of ionic surfactants. J. Invest. Dermatol. 50(5):371-379.

3840. Scanu, A., and M. Mancini. 1955. Inhibiting action on hyposideremia from histamine shock in guinea pigs, by low doses of vitamin B12, vitamin PP, histidine-HCl, and cortisone. Folia Allergol. (Rome) 2:206-208.

3841. Scardigli, G., A. Tesi, G. Guidi, and V. Lombardi. 1959. Effects of nicotinic acid on blood coagulation and on the fibrinolytic activity of the plasma. (Dynamic loading and prolonged treatment). G. Geront. 7:769-782.

3842. Scarselli, E., and U. Becattini. 1959. Dynamic effects of nicotinic acid on the circulation of the extemities and cranium. Rheographic, plethysmographic, venous pressure and cerebrospinal fluid pressure observations. G. Geront. 7:755-768.

3843. Scartozzi, C. 1940. Effect of nicotinic acid (Vitamin PP) on repair of experimental fractures and on the reticulo-endothelial system. Med. Sper. Arch. Ital. 6(10):609-628.

3844. Schaaf, F. 1948. Nicotinamide in cosmetic emulsions. U.S. Pat. 2,437,561.

3845. Schaaf, F., and F. Gross. 1959. Cosmetics for the treatment of the skin. Ger. Pat. 972,443.

3846. Schacht, U., G. Schultz, and G. Senft. 1964. Disturbances in adrenal catechol amine metabolism after administration of 6-aminonicotinic acid amide. In: Proceedings of the German Pharmacological Soc. 28th Session, Bad Nauheim, 5-8 Oct., 1944. Arch. Exp. Pathol. Pharmakol. (Naunyn Schmiedebergs) 250(2): 281-282.

3847. Schacht, U., G. Schultz, and G. Senft. 1966. Catecholamine and ATP content of the adrenal gland after injection of 6-aminonicotinamide. Naunyn-Schmiedebergs Arch. Expt. Pathol. Pharmakol. 253(3):355-363.

3848. Schade, H., and P. Saltman. 1959. Influence of nicotinic acid on hepatic cholesterol synthesis in rabbits. Proc. Soc. Exptl. Biol. and Med. 102(2):265-267.

3849. Schardein, J. L., et al. 1967. Congenital malformations induced by 6-aminonicotinamide in rabbit kits. Exp. Molec. Path. 6: 335-346.

3850. Scharrer, I., and K. Breddin. 1969. Role of platelet aggregation and its inhibition in vascular diseases. Platelets Vessel Wall-Fibrin Deposition, Symp. pp. 171-175.

3851. Scheff, G. J. 1945. Biochemical and immunological properties of Histoplasma capsulatum No. 650. Yale J. Biol. and Med. 18(1): 41-54.

3852. Schein, P. 1969a. 1-methyl-1-nitrosourea and dialkylnitrosamine depression of nicotinamide adenine dinucleotide. Cancer Res. 6: 1226-1232.

3853. Schein, P. 1969b. 1-methyl-nitrosourea depression of brain nicotinamide adenine dinucleotide in the production of neurologic toxicity. Proc. Soc. Exp. Biol. Med. 131(2):517-520.

3854. Schein, P., and R. W. Bates. 1968. Plasma glucose levels in normal and adrenalectomized mice treated with streptozotocin and nicotinamide. Diabetes 17(12):760-765.

3855. Schein, P. S., and S. Loftus. 1968. Streptozotocin: depression of mouse liver pyridine nucleotides. Cancer Res. 28(8):1501-1506.

3856. Schein, P. S., K. G. M. M. Alberti, and D. H. Williamson. 1971. Effects of streptozotocin on carbohydrate and lipid metabolism in the rat. Endocrinology 89(3):827-834.

3857. Schein, P. S., D. A. Cooney, and M. L. Vernon. 1967. The use of nicotinamide to modify the toxicity of streptozotocin diabetes without loss of antitumor activity (Streptomyces achromogenes). Cancer Res. 27(12 Pt. 1):2324-2332.

3858. Schein, P. S., N. Rakieten, D. A. Cooney, R. Davis, and M. L. Vernon. 1973. Streptozotocin diabetes in monkeys and dogs, and its prevention by nicotinamide. Proc. Soc. Exp. Biol. Med. 143(2):514-518.

3859. Scheinberg, P. 1950. The effect of nicotinic acid on the cerebral circulation, with observations on extracerebral contamination of cerebral venous blood in the nitrous oxide procedure for cerebral blood flow. Circulation 1(5):1152-1154.

3860. Schenkman, J. B. 1970. Nature of the type I and II spectral changes in liver microsomes. Biochemistry 9(10):2081-2091.

3861. Schenkman, J. B., J. A. Ball, and R. W. Estabrook. 1967. On the use of nicotinamide in assays for (rat liver) microsomal mixed-function oxidase activity. Biochem. Pharmacol. 16(6):1071-1081.

3862. Scherer, B., and W. Kraemer. 1972. Influence of niacinamide administration on brain 5-hydrozytryptamine 5-HT and a possible mode of action. Life Sci. 11(4 Pt. 1):189-195.

3863. Schertel, M.E., and A. J. Sheppard. 1971. Cathode ray polarography of riboflavin, thiamine hydrochloride, and niacinamide content of pharmaceutical preparations. J. Pharm. Sci. 60(7):1070-1074.

3864. Scheunert, A., and H. Haenel. 1956a. The partition of the B-complex vitamins in the fruit juice and residue of fruits. Ernaehrungsforsch. 1:520-525.

3865. Scheunert, A., and H. Haenel. 1956b. B-vitamin content of fruit juice. Fruchtsaft-Ind. 1:115-118.

3866. Schievelbein, H. 1965. Metabolism of thrombocytes and the release of 5-hydroxytryptamine. Acta Haematol. 33(2):110-117.

3867. Schillinger, A., and G. Zimmermann. 1964. The stability of various vitamins in enriched confectionery. Zucker-Suesswarenwirtsch. 17(1):12-14, 16, 25-27.

3868. Schleinzer, R. 1953. B vitamins and allergic reactions. Allergie 2:19-20.

3869. Schlenk, F. 1945. Enzymatic reactions involving nicotinamide and its related compounds. Advances Enzymol. 5:207-236.

3870. Schlenk, F., and H. von Euler. 1941. Nicotinic acid amide nucleoside. Arkiv Kemi, Min. och Geol. 14A:paper no. 13.

3871. Schleyer, W. L., and R. J. Schnitzer. 1948. The inhibition of the anti-trypanosomal activity of arsenoso compounds and acridines by esters and amides of organic acids. J. Immunol., Virus-Res. Exptl., Chemother. 60(2):265-276.

3872. Schmaehl, D., and S. Von Stackelberg. 1968. Effect of lactoflavine, nicotinamide, or dipyridamole on the carcinogenic activity of diethylnitrosamine in rats. Arzneim.-Forsch. 18(3):318-319.

3873. Schmid, J., and P. Keller. 1971. Influence of vasoactive agents on the placental function. Schweiz. Z. Gynaekol. Geburtsh. 2(4-6): 453-455.

3874. Schmid, J., and P. J. Keller. 1972. Isoxsuprinum, dipyridamol and nicotinic-acid-preparations as treatment of fetal malnutrition. Arch. Gynaekol. 212(1):68-74.

3875. Schmidt, W., and J. Pape. 1961. Experiences in the treatment of concomitant rheumatic disorders in tuberculotics. Med. Welt 38: 1942-1945.

3876. Schmidt-Hebbel, H., M. A. Jara, E. D. Barra, D. K. Moll, C. M. Pereira, I. O. Bollmann, O. O. Bollmann, and A. Passalacqua. 1941. Evaluation of hydrosoluble vitamins in various popular diets. Bol. Soc. Quim. Peru 7:12-20.

3877. Schneider, H., et al. 1968. Morphological findings in the central nervous system of the rat after poisoning with antimetabolites of nicotinamide (6-aminonicotinamide and 3-acetylpyridine) and a quinoline derivative (5-nitro-8-hydroxyquinoline). Arch. Psychiat. Nervenkr. 211:138-154.

3878. Schoen, G. 1953. Paper chromatographic analysis of vitamins. Acta Vitaminol. 7:151-167.

3879. Schoen, H. 1958. Effect of nicotinic acid on the cholesterol contents of rat livers. Nature 182:534.

3880. Scholler, J., J. J. Bittner, and F. S. Philips. 1957. Chemotherapeutic studies with transplants of spontaneous mammary tumors of mice growing in various hosts. Cancer Res. 17:605-608.

3881. Scholz, H. 1967. Vitamins. Properties, occurrence, and detection of vitamins. Mikrokosmos 56(7):206-207.

3882. Schormueller, J., and W. Grosch. 1967. Nucleosides and heterocyclic bases of peas (Pisum sativum) and possible changes during the enzymic phase of cooking. Z. Lebensm.-Unters.-Forsch. 134(3): 162-173.

3883. Schultz, G., G. Senft, W. Losert, and U. Schacht. 1966. Mechanism of aminonicotinamide hyperglycemia. Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol. 253(3):345-354.

3884. Schuphan, W., M. Kling, and G. Overbeck. 1968. Effect of genetic and environmental factors on the content of vitamin B1, vitamin B2, and nicotinic acid in winter and summer wheat. Qual. Plant. Mater. Veg. 15(3):177-214.

3885. Schreiber, F. K. 1961. Contribution to the therapy of cerebral circulation disorders. Med. Welt 23:1262-1267.

3886. Schreiber, F. K. 1964. Side effects of nicotinic acid. Klin. Wochenschr. 42:1070-1073.

3887. Schreiber, F. K. 1970. Blood pressure after large doses of nicotinic acid. 1. Clinical and experimental studies. Muench. Med. Wochenschr. 112:970-972.

3888. Schrumpf, E. 1967. Allergicologic toxicologic studies of a topical drug containing a surface anesthetic. Wien. Med. Wschr. 117:721-723.

3889. Schurr, P. E., J. R. Schultz, and T. M. Parkinson. 1972. Triton-induced hyperlipidemia in rats as an animal model for screening hypolipidemic drugs. Lipids 7(1):68-74.

3890. Schwabe, U. 1971. Effect of nicotinic acid on 3',5'-AMP-phosphodiesterase activity in adipose tissue. Metab. Eff. Nicotinic Acid Its Deriv., Pr. 367-369.

3891. Schwandt, P., T. Hartmann, and H. J. Karl. 1967. Effect of nicotinic acid and propranolol on the lipolytic activity of catechol amines and peptide hormones in vitro. Z. Gesamte Exp. Med. 143(1): 79-84.

3892. Schwandt, P., R. Lindlbauer, and M. Knedel. 1969. Effect of ouabain, nicotinic acid, and potassium-free incubation media on ACTH-induced lipolysis of free fatty acids. Clin. Chim. Acta 24(2): 267-274.

3893. Schwartzman, J., and L. Grossman. 1941. Vincent's ulceromembranous gingivostomatitis. Arch. Pediatrics 58:515-520.

3894. Schwarz, I., and A. Koch. 1962. The Tribolium test as a quantitative assay for eight B vitamins. Z. Vitamin-, Hormon-Fermentforsch. 12:291-306.

3895. Schwarz, I., and A. Koch. 1963. The Tribolium test as quantitative method of estimation of eight B-vitamins. Z. Vitamin-, Hormon-Fermentforsch. 13(1):16-21.

3896. Schwarz, W., and V. Schulz. 1971. Hepatic blood-flow measurement in rats with the krypton-85 clearance method after infusion of Norfenefrin and the sodium salt of nicotinic acid. Z. Gesamte Exp. Med. 155(3):225-233.

3897. Schweigert, B. S. 1947. Effect of indole on the determination of N'-methylnicotinamide. Science 106(2761):522-523.

3898. Schweigert, B. S., and P. B. Pearson. 1948. Studies on the metabolism of tryptophan and nicotinic acid by the rat and other animals. J. Biol. Chem. 172:485-493.

3899. Schweigert, B. S., P. B. Pearson, and M. C. Wilkening. 1947. The metabolic conversion of tryptophan to nicotinic acid and to N'-methylnicotinamide. Arch. Biochem. 12(1):139-145.

3900. Schwimmer, S., and D. G. Guadagni. 1968. Kinetics of the enzymic development of pyruvic acid and odor in frozen onions treated with cystein C-S lyase. J. Food Sci. 33(2):193-196.

3901. Sciacca, F. 1952. Nicotinic acid and hemoglobin metabolism. Riv. Pediat. Siciliana 7:105-110.

3902. Sciagra, A., and A. Nuti. 1959. Research on the action of vaso-active drugs on cerebral circulation in patients suffering from apoplectic strokes. II. Action of nicotinic acid. Riv. Crit. Clin. Med. 59:309-316.

3903. Scott, M. L. 1953. Prevention of the enlarged hock disorder in turkeys with niacin and vitamin E. Poultry Sci. 32:670-677.

3904. Scott, M. L., E. R. Holm, and R. E. Reynolds. 1959. Studies on the niacin, riboflavin, choline, manganese and zinc requirements of young Ringnecked pheasants for growth, feathering and prevention of leg disorders. Poultry Sci. 38(6):1344-1350.

3905. Scott, M. L., and G. F. Heuser. 1952. Studies in duck nutrition. 4. Bowed legs in ducks caused by niacin deficiency. Poultry Sci. 31:752-754.

3906. Scott, T. A. 1967. A method for the degradation of radioactive nicotinic acid. Biochem. J. 102:87-93.

3907. Scott, T. A. 1971. Degradation of nicotinic acid and related compounds. Methods Enzymol. 18(Pt. B):71-90.

3908. Scott, T. A., and J. P. Glynn. 1967. The incorporation of nicotinic-2,3,7-14C acid into nicotinic by Nicotiana tabacum. Phytochemistry 6(4):505-510.

3909. Scott, T. A., and M. Mattey. 1968. The incorporation of formate into nicotinic acid by Clostridium butylicum. Biochem. J. 107(4): 606-607.

3910. Scott, T. A., E. Bellion, and M. Mattey. 1969. Conversion of N-formyl-L-aspartate into nicotinic acid by extracts of Clostridium butylicum. Eur. J. Biochem. 10(2):318-323.

3911. Scotti, G. 1942. The action of nicotinic acid on arterial pressure. Rass. Clin. Terap. Sci. Affini 41:119-123.

3912. Scriabine, A., S. Bellet, A. Kershbaum, and L. J. Feinberg. 1968. Effect of dihydroergotamine on plasma free fatty acids (FFA) in dogs. Life Sci. (Oxford) 7(9 Pt. 1):453-463.

3913. Scuderi, G. 1950. Vitamin P2, vitamin C, and nicotinic acid in the eye hemorrhagic allergy. Ann. Ottalmol. e Clin. Oculist. 76:275-288.

3914. Scudi, J. V. 1946. On the fluorometric determination of nicotinamide. Science 103(2679):567-568.

3915. Seakins, J. W. T., and R. S. Ersser. 1967. Effects of amino acid loads on a healthy infant with the biochemical features of Hartnup disease. Arch. Dis. Child. 42(226):682-688.

3916. Sebrell, W. H., and R. E. Butler. 1938. Riboflavin deficiency in man. A preliminary note. U.S. Publ. Health Repts. 53(52):2282-2284.

3917. Sebrell, W. H., R. H. Onstott, H. F. Fraser, and F. S. Daft. 1938. Nicotinic acid in the prevention of blacktongue of dogs. J. Nutr. 16:355-362.

3918. Secomska, B. 1965. Excretion of nicotinic acid, N'-methylnicotinamide and riboflavine in young women with different amounts of nicotinic acid and riboflavine in diet. Rocz. Panstwowego Zakt. Hig. 16:529-539.

3919. Sedlakova, A., E. Misurova, E. Ahlersova, I. Ahlers, and M. Praslicka. 1971. Concentration of lipoperoxides and deoxyribonucleoprotein in liver, kidneys and heart muscle of continuously irradiated rats. Biologia (Bratisl.) 26(12):915-919.

3920. Seegmiller, R. E., D. O. Overman, and M. N. Runner. 1972. Histological and fine structural changes during chondrogenesis in micromelia induced by 6-aminonicotinamide. Dev. Biol. 28(4):555-572.

3921. Seidel, G., et al. 1972. Kinin liberation by xantinol nicotinate? Arzneim. Forsch. 22:1012-1013.

3922. Seidel, M. C., K. L. Viste, and R. Y. Yih. 1969. N-Aryl-2-pyridones. Ger. Pat. 1,900,947.

3923. Seifart, K. H., and W. Hansel. 1968. Some characteristics and optimum incubation conditions of in vitro progesterone synthesis by bovine corpora lutea. Endocrinology 82(2):232-240.

3924. Seifullin, F. Kh. 1966. Effect of cobalt preparations on healing of skin wounds in irradiated animals. Med. Zh. Uzb. (10):34-35.

3925. Segre, G. 1950. Diphosphopyridinenucleotidase and the relation of oxidized to reduced cozymase in homogenates. Acta Vitaminol. 4:6-9.

3926. Seki, S. 1963. Effects of nicotinamide, isonicotinic acid hydrazide, and 3-acetylpyridine on the growth and nicotinamide adenine dinucleotide content of L cells. Acta Med. Okayama 17(3):153-173.

3927. Selinus, R., G. Awalom, and A. Gobezie. 1971. Dietary studies in Ethiopia: II. Dietary pattern in two rural communities in N. Ethiopia: A study with special attention to the situation in young children. Acta Soc. Med. Upsal. 76(1/2):17-38.

3928. Selivanova, V. M., N. P. Dobronravova, and L. M. Chelnokova. 1970. Level of ascorbic acid in blood and urine and resistance of skin capillaries in persons engaged in streptomycin production. Antibiotiki 15(2):181-185.

3929. Sellin, D. 1965. The potentiation of fibrinolytic activity of nicotinic acid by adrenoxyl. Mater. Med. Nordmark. 17(13):582-593.

3930. Semenov, A. D., G. I. Vavilin, V. M. Migulina, and T. I. Zlatkina. 1970. Use of vitamins in the treatment of experimentally-induced tuberculosis in white mice receiving tubazid. Probl. Tuberk. 48(4):82-84.

3931. Sen, S. C., and S. Sen. 1954. Effect of niacin on the calcium level of blood. Indian J. Med. Res. 42:605-612.

3932. Sen, S. C., and S. Sen. 1956. Niacin and coagulability of blood. Indian J. Med. Res. 44:67-70.

3933. Senker, D. I. 1963. Metabolism of vitamin B1 and nicotinic acid by healthy subjects in Taskent. Vop. Pitan. 22(4):59-61.

3934. Senyukov, M. V. 1971. Effectiveness in the treatment of patients with an auditory function disorder associated with streptomycin therapy. Vestn. Otorinolaringol. 33(4):22-27.

3935. Serkov, S., N. Lalov, and S. Stanev. 1970. Effect of balanced and unbalanced rations with supplements of vitamins and Biofuran 3 in preventing coccidiosis in chickens. Vet.-Med. Nauki 7(8): 71-81.

3936. Serpa dos Santos, M. 1958. Detection of water-soluble vitamins in pharmaceutical specialties. Bol. Escola Farm., Univ. Coimbra 18:103-129.

3937. Serra, C., R. Logoluso, and L. Municchi. 1961. Action of monoamine oxidase inhibitors in the electroencephalogram of epileptics. Boll. Soc. Ital. Biol. Sper. 37:817-819.

3938. Serrano, M., and M. Medir. 1967. Significance of nicotinic acid and nicotinamide in the viability of seeds with high carbohydrate contents. Farmacognosia (Madrid) 27(12):9-11.

3939. Sesame, H. A., and J. R. Gillette. 1970. Inhibitory effects of various substances on drug metabolism by liver microsomes: effect of nicotinamide in altering the apparent mechanism of inhibition. Biochem. Pharmacol. 19(March):1025-1041.

3940. Sessa, T., and M. D'Anzi. 1960. The action of nicotinic acid on respiratory function in bronchitis and emphysema patients. Poumon. Coeur 16:629-640.

3941. Sessa, T., and C. Vecchione. 1960. The effect of the nicotinic acid on both arterial and venous oxygen content in normal subjects and in patients affected by chronic bronchitis and emphysema, and by silicosis. Lavoro Umano 12:349-368.

3942. Sessa, T., F. Turco, and M. D'Anzi. 1959. Action of nicotinic acid on the respiratory function in silicosis. Folia Med. (Naples) 42:89-101.

3943. Setty, C. S. N. 1960. Effect of sodium dehydrocholate and niacin on cholesterol absorption. Fed. Proc. 19(1 Pt. 1):184.

3944. Severin, S. E. 1970. Formation and conversion of nicotinamide coenzymes and thiamine pyrophosphate during experimental myocarditis and denervation of the skeletal muscles. Probl. Med. Enzimol., Mater., Vses. Simp., 1st 1969:85-97.

3945. Severin, S. E., and L. A. Tseitlin. 1964. Enzymic degradation of diphosphopyridine nucleotide in heart muscle homogenates in experimental myocarditis. Vopr. Med. Khim. 10(3):300-305.

3946. Severin, S. E., and L. A. Tseitlin. 1967. Effect of nicotinamide on the content of high energy phosphates in the heart muscle normally and during myocarditis. Vop. Med. Khim. 13(5):498-502.

3947. Severin, S. E., V. I. Telepneva, and L. A. Tseitlin. 1970. Isolation, purification, and properties of NAD kinase from heart muscle. Biokhimya 35(2):329-335.

3948. Severin, S. E., L. A. Tseitlin, and V. I. Telepneva. 1965. Peculiarities of glycolysis in heart and skeletal muscles in normal and pathological conditions, dependent on enzymic changes of NAD. Materialy Vses. Konf. po Probl. "Khim. i Obmen Uglevodov", 3rd, Mowcow 1963:236-243.

3949. Seydel, J. K., E. Wempe, and H. J. Nestler. 1968. The hypothesis that isoniazid acts via isonicotinic acid. Arzneim.-Forsch. 18(3): 362-367.

3950. Shadani, K. M., I. L. Hathaway, and P. L. Kelley. 1962. B-complex vitamin content of cheese. II. Niacin, pantothenic acid, pyridoxine, biotin, and folic acid. J. Dairy Sci. 45:833-841.

3951. Shafrir, E. 1971. Effect of nicotinic acid on the various lipolytic activities in tissues. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 249-262.

3952. Shafrir, E., and Y. Bieale. 1971. Lipoprotein lipase activity in rat tissues as influenced by various metabolic situations and by nicotinic acid. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 515-523.

3953. Shafrir, E., M. Orevi, and A. Gutman. 1971. Effect of nicotinic acid on carbohydrate metabolism in adipose tissue. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 763-771.

3954. Shah, N. S., and S. P. Martin. 1967. Isocitric dehydrogenase in experimental tuberculosis influence of isoniazid on metabolic damage. Amer. Rev. Resp. Dis. 95(6):1026-1035.

3955. Shamov, I. A. 1972. Effect of liver preparations and vitamin B12 on the development of experimental amyloidosis. Vop. Pitan. 30(1):67-70.

3956. Shamrai, E. F., and T. V. Fetisova. 1960. The functional interaction of vitamins C, P, and B1. Byull. Ekspti. Biol. i Med. 49(1):70-74.

3957. Shank, R. E. 1958. Revised recommended dietary allowances - 1958. J. Am. Dietetic Assoc. 34(9):909-913.

3958. Shankaran, R., and T. A. Venkitasubramanian. 1970. Effect of cord factor on carbohydrate metabolism in mice. Am. Rev. Resp. Dis. 101(3):401-407.

3959. Shapiro, D. M., L. S. Dietrich, and M. E. Shils. 1957. Quantitative biochemical differences between tumor and host as a basis for cancer chemotherapy. V. Niacin and 6-aminonicotinamide. Cancer Res. 17(6):600-604.

* 3960. Shapiro, D. M., R. A. Fugmann, and L. S. Dietrich. 1957. Partial regression of a "solid" tumor with multi-compound chemotherapy. Cancer Res. 17(11):1067-1070.

3961. Shapiro, D. M., M. E. Shils, R. A. Fugmann, and I. M. Friedland. 1957. Quantitative biochemical differences between tumor and host as a basis for cancer chemotherapy. IV. Niacin and 2-ethylamino-1,3,4-thiadiazole. Cancer Res. 17:29-33.

3962. Shaposhnikov, O. K. 1963. Oxidation processes in the skin in some dermatoses. Vestn. Dermatol. i Venerol. 37(11):8-14.

3963. Sharma, P. L. 1969. Effect of xanthinol nicotinate on the survival rate of dogs subjected to acute blood loss. Quart. J. Exp. Physiol. 54:385-393.

3964. Shastri, N. V., S. G. Nayudu, and M. C. Nath. 1968. Effect of high fat and high fat-high protein diets on biosynthesis of niacin from tryptophan in rats. J. Vitaminol. Osaka 14(3):198-202.

3965. Shaw, G. E., and C. A. Macdonald. 1938. Colorimetric estimation of nicotinic acid as applied to commercial liver extracts. Quart. J. Pharm. Pharmacol. 11:380-390.

3966. Shaw, J. C. 1946. Studies on ketosis in dairy cattle. VII. The efficacy of B vitamins and methionine in the treatment of ketosis. J. Dairy Sci. 29(3):131-139.

3967. Shaw, R. C., M. E. Holzer, D. Venzon, R. Ullman, and H. R. Butcher, Jr. 1966. A bioassay of treatment of hemorrhagic shock. III. Effects of a saline solution, ascorbic acid, and nicotinamide upon the toxicity of endotoxin for rats. Arch. Surg. 93(4):562-566.

3968. Sheehan, D., and J. S. Labate. 1942. The effect of nicotine on uterine responses to hypogastric nerve stimulation. Am. J. Physiol. 137(2):456-458.

3969. Sheen, T. N., E. H. Tiffany, Jr., and F. N. Berger. 1965. Anti-inflammatory compositions of aspirin and niacin. U.S. Pat. 3,312,593.

3970. Sheft, B. B., R. M. Griswold, E. Tarlowsky, and E. G. Halliday. 1949. Nutritive value of canned foods. Effect of time and temperature of storage on vitamin content of commercially canned fruits and fruit juices (stored 18 and 24 months). Indust. Engineer. Chem. 41(1):144-145.

3971. Sheleketina, I. I. 1969. Sorbitol and xylitol action on glycogen and vitamin levels in the liver. Vop. Pitan. 28(6):44-47.

3972. Shell, L. C., J. A. Burdick, and K. Wilson. 1968. Effects of medication on respiration pattern of tranquilized mice. Proc. Iowa Acad. Sci. 1967 74:218-221.

3973. Shenker, D. I. 1963. The status of vitamin B1 and nicotinic acid metabolism in the body of healthy humans under conditions of Tashkent. Vopr. Pitaniya 22(4):59-61.

3974. Sherman, H. C. 1941. Some relations of food chemistry to the time of aging and the length of life. News Ed. (Am. Chem. Soc.) 19:1081-1082.

3975. Sherman, I. W. 1966. In vitro studies of factors affecting penetration of duck erythrocytes by avian malaria plasmodium lophurae. J. Parasitol. 52(1):17-22.

3976. Shershevskii, M. G. 1963a. Effect of nicotinic acid on fibrinolytic activity of the blood in atherosclerosis. Fed. Proc. (Transl. Suppl.) 22:1154-1156.

3977. Shershevskii, M. G. 1963b. The influence of nicotinic acid on the fibrinolytic activity of the blood in atherosclerosis. Kardiologiya 3(1):64-68.

3978. Shevchuk, L. G., V. S. Zhikharev, and N. A. Vysotskaya. 1969. Kinetics of the reaction of hydroxyl radicals with benzene and pyridine derivatives. Zh. Org. Khim. 5(9):1655-1658.

3979. Shiba, S., et al. 1964. Studies on the tryptophan metabolism in tumor-bearing animals. Gann 55:41-47.

3980. Shibata, Y., and K. Ohira. 1971. 5-Hydroxyindole-acetic acid. Doshisha Joshi Daigaku Gakujutsu Kenkyu Ne 22:515-529.

3981. Shikina, A. P. 1970a. Effect of zinc and Nicosan on carbohydrate and phosphorus metabolism of potatoes. Tr. Inst. Bot., Akad. Nauk Kaz. S.S.R. 28:63-75.

3982. Shikina, A. P. 1970b. Effect of trace elements and nicosan on the phosphorus metabolism of the potato. Izv. Akad. Nauk Kaz. S.S.R., Ser. Biol 8(3):15-21.

3983. Shikina, A. P. 1971. Effect of trace elements and nicosan on the yield and starch content of potato tubers. Izv. Akad. Nauk Kaz. S.S.R., Ser. Biol. 9(2):26-33.

3984. Shikina, A. P., and O. F. Ovsyannikova. 1971. Effect of nicotinic acid on the phosphorus metabolism of wheat. Tr. Inst. Bot., Akad. Nauk Kaz. S.S.R. 29:13-28.

3985. Shimoyama, M., M. Ohota, K. Kakehi, and I. Ueda. 1970. Increase of NAD glycohydrolase activity and decrease of NAD concentration in rat liver during fasting. Biochim. Biophys. Acta 215(1): 207-209.

3986. Shimoyama, M., Y. Tanigawa, T. Ito, R. Murashima, I. Ueda, and T. Tomoda. 1971. Nicotinamide deamidation by microorganisms in rat stomach. J. Bacteriol. 108(1):191-195.

3987. Shinagawa, T., T. Baba, and Y. Takeuchi. 1957. The effect of the overdoses of thiamine and thiamine allyl disulfide on the urinary excretion of riboflavin and niacin. J. Vitaminol. 3(2): 135-142.

3988. Shkapina, V. A. 1961. Certain data on experimental vitamin therapy and prophylaxis of acute radiation illness. II. Tr. Smolenskogo Med. Inst. 13:397-411.

3989. Shkapina, V. A. 1962a. Effect of vitamins of the B group on the course of radiation illness. III. Tr. Smolenskogo Med. Inst. 14:177-183.

3990. Shkapina, V. A. 1962b. Effect on carbohydrate metabolism of administration of adrenaline and insulin to animals which had been subjected to ionizing radiation and vitamin treatment. IV. Tr. Smolenskogo Med. Inst. 14:184-194.

3991. Shkol'nik, M. I. 1956. Effect of copper and manganese on the content of ascorbic and nicotinic acids in different functional states of the central nervous system. Mikroelementy v Sel'sk. Khoz. i Med. (Riga) Sbornik 543-552.

3992. Shlykov, I. P. 1962. Effect of vitamin PP on reparative processes in the thyroid gland. Materialy Simpoziuma po Kletochn. Deleniyu i Regeneratsii Zhelez Vnutri Sekretsii, Moscow, Sb. 35-36.

3993. Shmat'ko, T. M. 1968. Change in the content of some free amino acids in the liver of white rats when affected by nicotinamide. Ukr. Biokhim. Zh. 40(6):568-571.

3994. Shmat'ko, T. M., and R. V. Chagovets. 1969. Changes in methionine-35S metabolism in rat liver in the presence of nicotinic acid and nicotinamide, and features of nicotinamide methylation. Ukr. Biokhim. Zh. 41(1):41-46.

3995. Shnitser, J. S. 1949. Effect of B vitamins on stomach acidity. Klin. Med. (U.S.S.R.) 27(2):77-81.

3996. Shock, N. W., and W. H. Sebrell. 1944. The effect of vitamins of the B complex on the work output of perfused frog muscles. Am. J. Physiol. 142(2):265-273.

3997. Shock, N. W., and W. H. Sebrell. 1946a. The effect of different concentrations of nicotinic acid amide on the work output of perfused frog muscles. Am. J. Physiol. 146:52-55.

3998. Shock, N. W., and W. H. Sebrell. 1946b. Effect of riboflavin and other B complex vitamins on work of perfused frog muscles. Proc. Soc. Exptl. Biol. Med. 63:290-293.

3999. Shokova, R. I., and A. V. Paravyan. 1969. Effect of nicotinic acid on the levels of chlorophyll, total nitrogen, and solasodine in leaves of the lobed nightshade (Solanum lalciniatum) under mineral nutrition conditions. Tr. Vot. Sadov, Akad. Nauk Kaz. S.S.R. 11:18-25.

4000. Shourie, K. L. 1941. Dental caries in Indian children. Indian J. Med. Res. 29(4):709-722.

4001. Shourie, K. L., and A. R. Sundararajan. 1942. The effect of milling on the vitamin B1 (thiamins) and nicotinic acid content of Indian wheat products. Indian J. Med. Res. 30:51-64.

4002. Shpak, V. M., and R. I. Karshenbaum. 1954. Intravenous niacin therapy in some of the psychoses. Zhur. Nevropatol. i Psikhiatrii im. Korsakova 54:671-676.

4003. Shteinberg, M. A. 1960. The significance of porphyrinuria and vitamin PP deficiency in experimental and clinical skin pathology. Vestn. Derm. Vener. 34:15-20.

4004. Shukla, D. S. 1972. Growth and sporulation of colletotrichum gloeosporioides in relation to vitamins. Indian Phytopathol. 25(2):300-302.

4005. Shushevich, S. I., and R. V. Chagovets. 1965. Effect of nicotinic acid on incorporation of acetate-1-14C by cholesterol and animal liver proteins. Ukr. Biokhim. Zh. 37(6):895-901.

4006. Shushevich, S. I., and R. V. Chagovets. 1966. Effect of starvation and loading with nicotinic acid on the incorporation of radioactive acetate into liver and serum cholesterol of animals. Ukr. Biokhim. Zh. 38(2):176-181.

4007. Shushevich, S. I., and M. P. Kuz'mins'kii. 1966. Influence of chronic administration of excess nicotinic acid to rabbits on the inclusion of radioactive acetate in cholesterol and on the tissue microstructure. Ukr. Biokhim. Zh. 38(1):33-38.

4008. Shuster, L., and A. Goldin. 1958. The incorporation of C14-glucose and C14-ribose into mouse liver diphosphopyridine nucleotide. J. Biol. Chem. 230(2):873-881.

4009. Shuster, L., and A. Goldin. 1959. The effect of nicotinamide on incorporation in vivo of formate-C14. J. Biol. Chem. 234(1):129-133.

4010. Shuster, L., and R. V. Hannam. 1964. The indirect inhibition of protein synthesis in vivo by chloropromazine. J. Biol. Chem. 239 (10):3401-3416.

4011. Sidor, V. 1956. Anemia in young pigs and its control by the compounds of iron and copper. Pol'nohospodarstvo 3:478-496.

4012. Sidorov, N. V. 1963. Nicotinic acid metabolism in patients with ophthalmologic conditions under treatment with this vitamin. Vopr. Pitaniya 22(3):83-84.

4013. Siedek, H., and L. Reuss. 1939. Action of nicotinamide in disturbances of fat absorption. Wien. Klin. Wochschr. 52:432-433.

4014. Siess, M. 1971. Effects of nicotinic acid and derivatives on performance and metabolism of spontaneously beating isolated atria. Metab. Eff. Nicotinic Acid its Deriv., Proc. Workshop 1970 819-849.

4015. Sikharulidze, A. I., A. Zurabashvili, R. G. Meskhi, and N. P. Macharashvili. 1970. Effect of some psychotropic drugs on physicochemical and neurodynamic indexes in acute experimental conditions. Aktual. Vop. Psikhofarmakologii, Mater. Vs 434-435.

4016. Silli, U. 1969. Clinical experience of the antipyretic and analgesic effects of an association of a new pyrazolone (methylniphenazine) and aminopyrine in children. Minerva Pediat. 21(50): 2364-2372.

4017. Silverman, M., J. C. Keresztesy, and G. J. Koval. 1954. Isolation of N-10-formylfolic acid. J. Biol. Chem. 211(1):53-61.

4018. Silvestri, U., and P. Grifa. 1951. Glucose of blood in nicotinamide-treated patients with skin tuberculosis. Arch. Ital. Dermatol. Sifilog. e Venereol. 24:260-266.

4019. Silvestroni, A., and A. Balletta. 1964. The biosynthesis of nicotinamide nucleotides in the erythrocytes after experimental lead intoxication. Biochim. Appl. 11(6):250-257.

4020. Silvestroni, A., and R. Fimiani. 1970. Microcirculation in chronic experimental intoxication with carbon disulfide. Effects of nicotinic acid. Folia Med. (Naples) 53(1):1-26.

4021. Simicnescu, S., A. Bordeianu, C. Stancu, B. Daniel-Slavescu, and V. Pintilescu. 1972. Influence of the nonspecific pharmacodynamic action of certain vitamins with a metabolizing role (group B) on the reactivity of the genital tract and evolution of the sexual cycle. Fiziol. Norm. Patol. 18(1):13-19.

4022. Simek, J., A. Husakova, K. Lejsek, J. Kanta, and M. Pospisil. 1967. The effect of nicotinic acid on the development of liver regenerating activity in rats with partial hepatectomy. Naturwissenschaften 54:251-252.

4023. Simek, J., V. Chmelar, J. Melka, J. Pazderka, Z. Charvat, and M. Pospisil. 1967. Regenerative activity of liver tissue after administration of nicotinic acid to rats partial hepatectomy. Phys. Bohemoslov. 16(4):324-329.

4024. Simon, I. B. 1965. Prospective synthetic substances promoting a decrease in cholesterol in the organism. Farmakol. Serd.-Sosud. Veshchestv, Sb. (Kiev) 183-188.

4025. Simon, I. 1966a. A new class of drugs. Hypotensive-anticoagulants. Gazz. Med. Ital. 125(4):89-107.

4026. Simon, I. 1966b. A new class of drugs: the hypotensive antithrombics. Minerva Med. 57(44):2023-2027.

4027. Simonelli, M. 1941. Quantitative investigation of the nicotinic acid content of various tissues and fluids of the eye. Chem. Zentr. I:558.

4028. Simonelli, M. 1948. Permeability of the blood-aqueous barrier. G. Ital. Oftal. 1:317-325.

4029. Sinclair, D. C. 1948. Observations on sensory paralysis produced by compression of a human limb. J. Neurophysiol. 11(1): 75-92.

4030. Singal, S. A., V. P. Sydenstricker, and J. M. Littlejohn. 1947. The effect of some amino acids on the growth and nicotinic acid storage of rats on low casein diets. J. Biol. Chem. 171(1):203-207.

4031. Singal, S. A., V. P. Sydenstricker, and J. M. Littlejohn. 1948. Further studies on the effect of some amino acids on the growth and nicotinic acid storage of rats on low casein diets. J. Biol. Chem. 176(3):1063-1068.

4032. Singh, I., and S. Singh. 1946. Effects of some metals (compounds), vitamins, anesthetics, and other substances on unstriated muscle. Proc. Indian Acad. Sci. 23B:301-311.

4033. Singh, J., and R. S. Chopra. 1969. Influence of calcium pantothenate and nicotinamide on fat formation by Penicillium aurantiobrunneum. Res. Bull. Panjab Univ. Sci. 20(1/2):15-17.

4034. Singh, R. 1971. Effects of nicotinic acid, cyclospasmol, and ronicol on the electrocortical activity and automatic movement of the rat. Curr. Mod. Biol. 3(4):323-331.

4035. Singh, R. A. 1972a. Effect of D-thyroxine and nicotinic acid on cholesterol metabolism of laying hens. Indian J. Anim. Sci. 42(6):433-435.

4036. Singh, R. 1972b. Some observations on the autocorrelation and Fourier analyses of the rat electroencephalogram. Indian J. Exp. Biol. 10(5):337-340.

4037. Singh, R., and C. P. Merilan. 1957. Influence of temperature on vitamin levels in bovine blood-a study of B vitamins and vitamin C levels in the blood of Brahman, Santa Gertrudis, and shorthorn heifers reared under different environmental temperature conditions. Missouri, Univ. Agr. Expt. Sta., Res. Bull. No. 639, 40 pp.

4038. Singh, S. P., and E. O. Essary. 1971. Vitamin content of broiler meat as affected by age, sex, thawing, and cooking. Poultry Sci. 50(4):1150-1155.

4039. Sinkovics, M. 1965. The role of vitamins B in the heterosis phenomenon. Novenytermeles 14(2):173-180.

4040. Siro-Brigiani, G., and E. Antoncecchi. 1967. Analysis of the ganglionic action of nikethamide. Accad. Pugliese Sci., Atti Relaz., Parte 2 25(Pt. 2):741-748.

4041. Siver, P. Ya., L. N. Zamanskii, and A. I. Lopushanskii. 1955. The effect of some vitamins on the absorption of iodine-131 by the thyroid gland. Byull. Ekspti. Biologii i Med. 39(6): 43-45.

4042. Sivieri, L. 1958. Nicotinic acid and milk secretion in women. Lattante 29:193-207.

4043. Sjunjakova, Z. M., and I. N. Karpova. 1966. Comparison of the effects of gamma-rays and heat sterilisation on thiamine, riboflavine, nicotinic acid and tocopherol in beef. Vop. Pitan. 25(2):52-55.

4044. Skerman, K. D., and L. G. Newton. 1952. Bracken fern poisoning in cattle. Queensland Agric. J. 74(3):163-167.

4045. Skidmore, I. F., D. Kritchevsky, and P. Schoenhoefer. 1971. Effect of nicotinic acid and nicotinic acid homologs on lipolysis, phosphodiesterase activity, adenyl cyclase activity, and cyclic AMP synthesis in fat cells. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970 371-377.

4046. Skidmore, I. F., P. S. Schoenhoefer, and D. Kritchevsky. 1971. Effects of nicotinic acid and some of its homologs on lipolysis, adenyl cyclase, phosphodiesterase, and cyclic AMP accumulation in isolated fat cells. Pharmacology 6(6):330-338.

4047. Skryabin, G. K., L. A. Golovleva, and B. I. Krupyanko. 1959. Microbiological transformation of pyridine compounds. Izv. Akad. Nauk S.S.S.R., Ser. Biol. (5):660-669.

4048. Skurski, A., E. Lapinska, and Z. Wieczorek. 1957. The behavior of various BCG strains in regard to in vitro phagocytosis. Arch. Immunologii i Terapii Doswiadczalnej 5:21-35.

4049. Sladek, N. E. 1971. Cyclophosphamide metabolism. I. Metabolism of cyclophosphamide by rat hepatic microsomes. Cancer Res. 31(6): 901-908.

4050. Slater, T. F. 1967. Oxidized and reduced nicotinamide adenine dinucleotide phosphate in tissue suspensions of rat liver. Biochem. J. 104:833-842.

4051. Slavicek, J. 1963. Effect of nicotinic acid on the isolated frog heart. Sb. Lekar. 65:164-168.

4052. Slovohotnova, I. I. 1969. Role of some vitamins of the B group in prevention of dental caries. Vop. Pitan. 28(2):27-31.

4053. Slowik, S. 1969. Role of nicotinic acid and its derivatives in the etiopathogenesis of (human) schizophrenia. Psychiat. Pol. 3(1):89-95.

4054. Slutzky, L. 1963. Concomitance of hyperglycemia with the use of large doses of nicotinic acid in diabetics. Semana Med. (Buenos Aires) 123(47):1846-1850.

4055. Slyusarev, F. M. 1966. Content of nicotinic acid and its derivatives in blood, urine, and spinal fluid of patients suffering from disorders of the nervous system. Zh. Nevropatol. i Psikhiatr. 66(1):57-60.

4056. Slyusarev, F. M., and A. G. Buchinskii. 1966. Effect of vitamin PP (niacin) on the indices of electric excitability of the neuromuscular apparatus in patients with neurological disturbances. Zh. Nevropatol. Psikhiat. im. S.S. Korsakova 66(6):854-857.

4057. Smalii, V. T., O. I. Levchenko, and M. N. Boyarskaya. 1971. Accumulation of group B vitamins during the transformation of caustobioliths by microorganisms of humic substances. Mikrobiol. Zh. (Kiev) 33(4):423-427.

4058. Smat'ko, T. M., and R. V. Cagovec. 1969. Changes of methionine-35S metabolism in liver of albino rats induced by nicotinic acid and nicotinamide and peculiarities of nicotinamide methylation. Ukrajin. Biohim. Z. 41:41-46.

4059. Smirnova, T. T., and S. A. Pavlov. 1967. Crosslinking of liquid rubbers (oligomers) with organic peroxides. Nauch.-Issled. Tr. Vses. Nauch.-Issled. Inst. Plenoch. Mater. Iskusstv. Kozhi (18):168-174.

4060. Smith, C. M., A. Hoffer, M. Dantow, and S. McIntyre. 1963. Nicotinic acid therapy in old age. The placebo effect and other factors in the collection of valid data. J. Am. Geriat. Soc. 11(6):580-585.

4061. Smith, D. H., and E. Gaman. 1960. Comparative effects of MK-135 (anion exchange resin) and nicotinic acid on cholesterol levels of hypercholesterolemic humans. Fed. Proc. 19(1 Pt. 1):236.

4062. Smith, E. L. 1958. Solubilization of ostreogrycin antibiotics. Brit. Pat. 875,702.

4063. Smith, I. M., A. Lopez, J. Gell, and P. Tarr. 1970. Amino acid metabolism in murine lethal staphylococcal infection. Progr. Antimicrob. Anticancer Chemother. Proc. Int. Congr. Chemother., 6th 1969 1:260-265.

4064. Smith, J. M., N. Morgenstern, and L. Peters. 1967. Inhibition of the renal tubular transport and excretion of tetraethylammonium and N-methylnicotinamide by nonnitrogenous onium compounds. J. Pharmacol. Exp. Ther. 158(3):451-459.

4065. Smith, J. M. B., R. D. Jolly, L. K. Georg, and M. D. Connole. 1968. Trichophyton equinum var. autotrophicum; its characteristics and geographical distribution. Sabouraudia 6(4):296-304.

4066. Smith, Q. T., and R. S. Allen. 1954. Vitamin levels in the blood of young dairy calves fed on a milk replacement diet with and without Aureomycin. J. Dairy Sci. 37(10):1190-1197.

4067. Smith, R. G. 1945. Developments in drug manufacture in Australia. Research and production by Nicholas Pty. Ltd., Melbourne. Australasian J. Pharm. 26:326-330.

4068. Smith, S. G., R. Curry, and H. Hawfield. 1943. Nicotinic acid storage in the dog at different dose levels of the vitamin. J. Nutrition 25(4):341-348.

4069. Smith, S. G., G. Margolis, and L. H. Margolis. 1938. Effect of autoclaving on the vitamin potency of nicotinic acid. Proc. Soc. Exp. Biol. and Med. 38(2):251-254.

4070. Smithberg, M., and M. N. Runner. 1963. Teratogenic effects of hypoglycemic treatments in inbred strains of mice. Am. J. Anat. 113(3):479-489.

4071. Snell, E. E. 1947. The microbiological determination of nicotinic acid. In: Biological Symposia, ed. J. Catell et al. Vol XII pp. 183-203.

4072. Snell, E. E. 1953. Metabolic significance of B-vitamins. Summary of known metabolic functions of nicotinic acid, riboflavine, and vitamin B6. Physiol. Revs. 33:509-525.

4073. Snell, E. E., and D. E. Metzler. 1956. II. Vitamin B6, nicotinic acid, biotin, ascorbic acid. Ann. Rev. Biochem. 25:435-462.

4074. Snell, E. E., and E. Quarles. 1941. Effect of incubation on the vitamin content of eggs. J. Nutrition 22:483-489.

4075. Snell, E. E., and L. D. Wright. 1941a. A microbiological assay for nicotinic acid. J. Biol. Chem. 139(2):675-686.

4076. Snell, E. E., and L. D. Wright. 1941b. A microbiological assay for nicotinic acid. J. Biol. Chem. 140:cxix-cxx.

4077. Snell, E. E., and L. D. Wright. 1950. The water-soluble vitamins. Ann. Rev. Biochem. 19:277-318.

4078. Snow, G. A., and S. S. Zilva. 1943. A critical examination of Lugg's method for the determination of l-ascorbic acid. Biochem. J. 37:630-640.

4079. Snyderman, S. E., K. C. Ketron, R. Carretero, and L. E. Holt Jr. 1949. Site of conversion of tryptophan into nicotinic acid in man. Proc. Soc. Exp. Biol. Med. 70:569-571.

4080. Sobrinho Simoes, M., and J. Pinto de Barros. 1968. Variations in the blood fatty acid level provoked by nicotinic acid. Arq. Port. Bioquim. 10(4):483-489.

4081. Societe Amilloise de Produits Chimiques. 1971. Hypocholesterolemic medicaments based on nicotinic acid N-oxides. French Pat. 2,036,939.

4082. Sodhi, H. S., B. J. Kudchodkar, and L. Horlick. 1973. Hypocholesterolemic agents and mobilization of tissue cholesterol in man. Atherosclerosis 17(1):1-19.

4083. Soeling, H. D., B. Willms, G. Janson, and H. Peters. 1970. Effects of nicotinic acid on the action of glucagon in the isolated perfused rat liver. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970. pp. 861-867.

4084. Sohr, H. 1944. Lactoflavin and nicotinic acid as constituents of the vitamin B group and their role in ophthalmology. Klin. Monatsbl. Augenheilk. 110:385-392.

4085. Soibel, B. I. 1962. Some effects of nicotinic acid during the treatment of patients with impaired coronary blood flow. Sb. Nauchn. Tr., Andizhansk. Gos. Med. Inst. 3:272-289.

4086. Soibel, B. I. 1966. Use of nicotinic acid in cases of myocardial infarction. Klin. Med. 44(8):60-65.

4087. Soibel, B. I., L. L. Dymshits, and S. Yu. Tursunov. 1964. The use of nicotinic acid in the treatment of patients with coronary atherosclerosis with disturbances of the coronary circulation. In: Information on the 15th scientific session of the Institute of Nutrition of the Academy of Medical Sciences of the U.S.S.R., Moscow 1:25.

4088. Sokolov, A. B., and V. V. Nikolkov. 1967. Experimental data on the effect produced by some pharmacological agents on the permeability of the blood-brain barrier. Farmakol. Toksikol. 30(1):15-18.

4089. Sokolova, G. A. 1971. Effect of sodium sulfapyridazine and nicotinic acid on stomach secretion by chickens. Sb. Rab., Leningrad Vet. Inst. 32:275-279.

4090. Sokolova, T. F. 1966. Characteristics of nicotinic acid excretion in persons of advanced and senile age. Vop. Pitan. 25(4):48-51.

4091. Sokolova, V. E. 1956. The effect of ascorbic acid on the activity of adenosinetriphosphatase of the heart and skeletal muscles of guinea pigs. Biokhimiya 21:465-468.

4092. Solarino, G. 1957. Vitamins and immune reactions of the organism. Intern. Z. Vitaminforsch. 27:373-381.

4093. Solarino, G. 1960. Power of organic defense and vitamins. Arch. De Vecchi Anat. Pat. 32:913-921.

4094. Solarino, G., and V. Rizza. 1941. Nicotinic acid in the healing of experimental fractures. Med. Sper.-Arch. Ital. 8:193-216.

4095. Soliman, M. A. 1964. Some toxicological studies on carbon tetrachloride. Vet. Med. J. (Giza) 10:57-78.

4096. Soliman, M. A., H. A. Hondt., and A. M. Elwi. 1969. Vitamin E, nicotinic acid, vitamin C., and total beladonna alkaloids as liver cell regenerators. Pharmacology 2(6):352-360.

4097. Solla, E., and F. Manca. 1956. Quantitative changes of milk cells and cetrifuged lipides following vitamin PP injections in the first days of puerperium. Minerva Nipiol. 6:92-96.

4098. Solomko, G. I. 1966. Characteristics of nicotinic acid metabolism in experimental animals. Vitaminy Preduprezhdenii Lech. Prezhdevremennogo Stareniya, Inst. Gerontol. Akad. Med. Nauk S.S.S.R. 245-251.

4099. Solomko, G. I. 1971. Certain characteristics of endogenous synthesis of nicotinic acid in elderly and senile people. Vrach. Delo 4:124-125.

4100. Solomko, G. I., I. P. Barchenko, and Y. G. Grigorov. 1970. Quantitatively differing nutrition and vitamin PP allowances for the aged. Vop. Pitan. 29(5):25-30.

4101. Solyom, A., and L. Puglisi. 1966. Effect in vitro of nicotinic acid on triglyceride synthesis in rat adipose tissue. Biochem. Pharmacol. 15(1):41-48.

4102. Solyom, A., and L. Puglisi. 1968. On the effect of norepinephrine and nicotinic acid on free fatty acid transport and incorporation in tissue lipids. Progr. Biochem. Pharmacol. 4:371-372.

4103. Sommariva, V., and L. M. Rapisarda. 1958. Modifications of the electrophoretic picture of zonal arterial and venous serum lipo- and glycoproteins in arteriopathic subjects after treatment with a pharmacological cocktail. Riv. Patol. e Clin. 13:41-62.

4104. Sommer, H. 1965. Nicotinic acid levels in the blood and fibrinolysis under the influence of the hexanicotinic acid ester of myo-inositol. Arzneim.-Forsch. 15(11):1337-1339.

4105. Somodi, E. 1966. Vitamin made of poison. Termeszettud. Kozl. 97(12):545-546.

4106. Sopin, E. F. 1961. Effect of vitamin B1 and niacin on cholesterol metabolism in radiation lesions. Visn. Kiivs'k. Univ., Ser. Biol. 4(1):114-119.

4107. Sopin, E. F., and V. M. Haidai. 1961. Effect of vitamins B1 and PP on the metabolism of citric and furamic acids in radiation injury. Ukr. Biokhim. Zh. 33:57-63.

4108. Sorce, G., M. Pelliconi, and V. Pallini. 1966. The biosynthesis of NAD in rat reticulocytes and erythrocytes. Boll. Soc. Ital. Biol. Sper. 42(18):1230-1231.

4109. Sorman, L., and R. Uherova. 1966. Canned foods as sources of vitamin B. Vyziva Zdravie 11(8):179-180.

4110. Sorrell, M. F., O. Frank, H. Aquino, A. D. Thomson, and H. Baker. 1971. In vivo and in vitro penetration of vitamins into human red blood cells. Amer. J. Clin. Nutr. 24(8):924-929.

4111. Sotgiu, G., and L. Romaro. 1939. Some effects of nicotinic acid. Atti Soc. Med. Chir. Padova 17:214-218.

4112. Sozanskii, A. M. 1958. The content of sugar, chlorides, and nicotinic acid in amniotic fluid and in the blood of parturient women in pathologic pregnancy. Akusherstvo i Ginekologiya 5:21-23.

4113. Spacek, M. 1955. Physiological investigations on the excretion of kynurenine in humans. Canadian J. Biochem. Physiol. 33(1): 14-20.

4114. Spano, G., A. Saponaro, G. Giordano, A. M. Verde, F. Cosentino, and A. Dagianti. 1967. Pharmacodynamic study of nicotinic acid and its homolog, 3-pyridylacetic acid, in obliterative arteriopathies of the limbs. Boll. Soc. Ital. Cardiol. 12(2):148-153.

4115. Sparthan, M., and S. Chaykin. 1969. Determination of nicotinamide N-oxide: A human excretory product. Anal. Biochem. 31(1-3):286-295.

4116. Spatz, M. 1961. Carcinoid syndrome in tryptophan- and niacin-deficient guinea pigs. Univ. Mich. Med. Bull. 27:289-292.

4117. Spector, H. 1948. The metabolic interrelationship between tryptophan, pyridoxine, and nicotinic acid; forced feeding studies in rats. J. Biol. Chem. 173(2):659-676.

4118. Spies, T. D. 1938. The response of pellagrins to nicotinic acid. Lancet I:252-253.

4119. Spies, T. D. 1939. Review of nicotinic acid as a therapeutic agent. Med. Woman's J. 46(4):97-100.

4120. Spies, T. D. 1940. Vitamin B deficiencies. Trans. & Studies Coll. Physicians Phila. 8:12-26.

4121. Spies, T. D. 1948. Clinical aspects of vitamins. Ann. Rev. Biochem. 17:449-470.

4122. Spies, T. D. 1951. Recent advances in diagnosis and treatment of deficiency diseases. J. Amer. Med. Assoc. 145(2):66-72.

4123. Spies, T. D. 1962. Niacinamide malnutrition and pellagra. In: Clinical Nutrition, N. Jolliffe, Ed., Harper and Brothers, New York pp. 622-634.

4124. Spies, T. D., and A. W. Mann. 1944. Effect of synthetic niacinamide, synthetic thiamine, and synthetic riboflavin on infants and young children with deficiency diseases. Arch. Pediat. 61:517-531.

4125. Spies, T. D., W. B. Bean, and W. F. Ashe. 1939. Recent advances in the treatment of pellagra and associated deficiencies. Ann. Internal Med. 12(11):1830-1844.

4126. Spies, T. D., W. B. Bean, and R. E. Stone. 1938. The treatment of subclinical and classic pellagra. Use of nicotinic acid, nicotinic acid amide and sodium nicotinate, with special reference to the vasodilator action and the effect on mental symptoms. J. Am. Med. Assoc. 111:584-592.

* 4127. Spies, T. D., E. S. Gross, and Y. Sasaki. 1938. Effect of yeast and nicotinic acid on porphyrinuria. Proc. Soc. Exptl. Biol. Med. 38:178-181.

4128. Spies, T. D., R. W. Vilter, and S. P. Vilter. 1939. Fresh work on pellagra and nicotinic acid. Lancet 236(6021):170.

4129. Spindler, F. 1947. Chemical estimation of nicotinic acid in kefir powder. Milchwissenschaft 2:133-137.

4130. Spira, L. 1950. Fluorine and vitamin B. Eptl. Med. Surg. 8:361-370.

4131. Spirtes, M. A., and C. Alper. 1961. The effect of niacin-deficient, tryptophan-low and protein-deficient diets on the DPN/DPNH ratio in mouse liver. J. Nutrition 73(4): 374-378.

4132. Spisni, D. 1965. Metabolism of tryptophan and nicotinic acid in different animals. Veterinaria (Milan) 14(3):211-229.

4133. Spisni, D., and A. P. Mariani. 1963. Xanthurenic acid in the urine of rabbits treated parenterally with high doses of nicotinamide. Ann. Fac. Med. Vet. Univ. Pisa 16:1-7.

4134. Spisni, D., and A. P. Mariani. 1968. Pyridoxine in urine of rabbits given large parenteral doses of nicotinamide. Ann. Fac. Med. Vet. Pisa 21:238-242.

4135. Spisni, D., and A. P. Mariani. 1970. Pyridoxine and xanthurenic acid in the urine of rabbits given parenterally high doses of nicotinamide. Boll. Soc. Ital. Biol. Aper. 46(4):206-207.

4136. Spitali, R., and G. Quadri. 1963. The effect of nicotinamide on the placental content of pyridine coenzymes in the rat. Boll. Soc. Ital. Biol. Sper. 39:285-287.

4137. Spitzer, J. J., and J. Scott. 1970. Effects of diazoxide on myocardial free fatty acid metabolism and hemodynamics in the dog. Arch. Int. Pharmacodyn. Ther. 184(2):405-414.

4138. Spoetti, F., and F. Holzknecht. 1970. The influence of inhibitors of plasmin and plasminogen activation on the streptokinase-induced fibrinolytic state. Thromb. Diath. Haemorrh. 24(1):100-112.

4139. Sporn, E. M., and E. J. Schantz. 1950. Niacin, biotin and folic acid in nutrition of the mouse. Fed. Proc. 9(1):372.

4140. Sporn, E. M., M. A. Mehlman, E. W. Somberg, C. Dalton, and J. Quinn. 1969. Effect of theophyline on serum and liver lipid composition and rate of lipolysis from adipose tissue cells of cold-exposed rats. Bull., N. J. Acad. Sci. (Spec. Issue): 104-109.

4141. Sprince, H. 1970. Metabolic aspects and interrelationships of methionine and tryptophan: Behavioral implications. Nutr. Rep. Int. 1(4):243-261.

4142. Sprince, H., C. M. Parker, D. Jameson, and J. A. Josephs Jr. 1965. Effect of methionine on nicotinic acid and indoleacetic acid pathways of tryptophan metabolism in vivo. Proc. Soc. Exp. Biol. Med. 119(4):942-946.

4143. Sprince, H., C. M. Parker, D. Jameson, and J. A. Josephs Jr. 1969. Experimental alteration of tryptophan metabolism by methionine: neuropharmacologic implications. Int. J. Neuropharmacol. 8(6):615-626.

4144. Squadrito, G. 1955. Prothrombin of blood after administration of nicotinic acid and its amide. Gazz. Intern. Med. e Chir. 60:208-215.

4145. Srivastava, S. K., S. B. Maini, and C. V. Ramakrishnan. 1969. Regulation of pyridine nucleotide level in normal and tumor tissues of Rumex acetosa cultivated in vitro. Indian J. Biochem. 6(4):214-215.

4146. Srivastava, S. K., S. B. Maini, B. I. Naik, and C. V. Ramakrishnan. 1971. Early effects of nicotinamide, 2,4-dichlorophenoxy acetic acid and actinomycin D on the synthesis of nicotinamide amidohydrolase in Rumex acetosa tumor tissue. Indian J. Biochem. Biophys. 8(2):118-119.

4147. Sruoginyte, A. 1965. Influence of riboflavine and nicotinic acid on the activity of carbonic anhydrase in animals and plants. Lietuvos T.S.R. Aukstuju Mokyklu Mokslo Darbai, Biol. 5:9-18.

4148. Stainier, C. 1965. The analysis of complex mixtures of medicaments. Boll. Chim. Farm. 104:70-85.

4149. Stakhovskaya, E. K., V. K. Kondrat'eva, and A. N. Usova. 1953. A study of the effect of nicotinic acid on the oak silk worm. Uchenye Zapiski Gosudarst. Pedagog. Inst. 77(7):81-91.

4150. Stalmans, W., H. DeWulf., B. Lederer, and H. G. Hers. 1970. Effect of glucose and of a treatment by glucocorticoids on the inactivation in vitro of liver glycogen phosphorylase. Eur. J. Biochem. 15(1):9-12.

4151. Stalmans, W., H. De Wulf, and H. G. Hers. 1971. Control of liver glycogen synthetase phosphatase by phosphorylase. Eur. J. Biochem. 18(4):582-587.

4152. Stanbury, J. B. 1957. The requirement of monoiodotyrosine deiodinase for triphosphopyridine nucleotide. J. Biol. Chem. 228(2):801-811.

4153. Stanbury, J. B., A. A. H. Kassenaar, J. W. A. Meijer, and J. Terpstra. 1955. The occurrence of mono- and di-iodotyrosine in the blood of a patient with congenital goiter. J. Clin. Endocrinol. and Metab. 15(10):1216-1227.

4154. Starcher, B. 1969. Effect of pyridoxine deficiency on aortic elastin biosynthesis. Proc. Soc. Exp. Biol. Med. 132(1):379-382.

4155. Starshov, P. D. 1962a. On the fluorimetric determination of thiamine, riboflavin, 4-pyridoxic acid, and N1-methylnicotinamide in urine. Lab. Delo 8(6):37-42.

4156. Starshov, P. D. 1962b. Thiamine, riboflavin, nicotinic acid and pyridoxine urinary excretion in infectious hepatitis during treatment with hormonal preparations. Voprosy Med. Khim. 7(2):169-176.

4157. Starshov, P. D. 1963. Effect of certain B vitamins on experimental toxic hepatitis. Materialy 2-go(Vtorogo) Soveshch. po Klinich. Biokhim. Infekts. Boleznei i Simpoziuma po Klinich. Biokhim. Boleznei Pecheni, Riga, Sb. pp. 182-185.

4158. Starshov, P. D. 1967a. The effect of glucocorticoids on the metabolism of riboflavin and nicotinic acid in acute liver disease. In: Information on the 6th scientific session of the All-Union Scientific Research Institute of Vitaminology 1967. pp. 100-101.

4159. Starshov, P. D. 1967b. The influence of certain vitamins of the B group on the course of virus hepatitis in white mice. Byull. Eksp. Biol. Med. 63(1):35-37.

4160. Starshov, P. D., and A. S. Ostapenko. 1969. Nicotinic acid metabolism in acute respiratory diseases. Klin. Med. (Moscow) 47(11):138-142.

4161. Stauffacher, W., I. Burr, D. Cameron, M. Amherdt, and L. Orci. 1971. Effects of nicotinamide and of nicotinic acid on the pancreas in experimental diabetes. Metab. Eff. Nicotinic Acid Its Deriv. Proc. Workshop 1970 pp. 939-954.

4162. Stauffacher, W., I. Burr, A. Gutzeit, D. Beaven, J. Veleminsky, and A. E. Renold. 1970. Streptozotocin diabetes: time course of irreversible B-cell damage; further observations on prevention by nicotinamide. Proc. Soc. Exp. Biol. Med. 133(1):194-200.

4163. Steele, H. K. 1945. Report of the 1944-45 committee on niacin (nicotinic acid) assay. Cereal Chem. 22(5):448-454.

4164. Stefanescu, D., D. Moraru, I. Predescu, P. Barza, T. Stanciu, and F. Coman. 1969. Preparation of a pyridine derivative from methane, ammonia, and water by high frequency electric discharge. Farmacia (Bucharest) 17(2):115-120.

4165. Stefanini, M. 1949. The hyperbilirubinemic effect of sodium nicotinate. J. Lab. Clin. Med. 34(8):1039-1048.

4166. Stefanini, M. 1950. The cholagogic and choleretic effect of sodium nicotinate. Am. J. Digestive Dis. 17:337-339.

4167. Stefanini, M., and M. Petrillo. 1947. Influence of nicotinic acid and nicotinimide on blood clotting. Progresso Med. 3:5-9.

4168. Stein, A. M. 1971. Preparation and properties of nicotinamide guanine dinucleotide. Fed. Eur. Biochem. Soc. Lett. 19(3):270-272.

4169. Steinbach, M. 1970. The effect of vascunicol on circulatory defects of the brain. Med. Klin. 65(24):1175-1177.

4170. Stepanova, E. N. 1963. Colorimetric method of estimating nicotinic acid in foods and biological materials. Vop. Pitan. 22(4):66-70.

4171. Stepanyan, N. O., and L. S. Tseitlin. 1968. Effect of cordiamine on the titer of pyridine nucleotides in the rabbit myocardium. Byull. Eksp. Biol. Med. 66(7):51-53.

4172. Stepp, W. 1956. Recent progress in the realm of vitamin research and therapy. Intern. Z. Vitaminforsch. 26:360-376.

4173. Sterescu, M., M. Dobrovici, and S. Negritescu. 1955. The determination of vitamins A, B1, B2, C, and PP in polyvitamins by physicochemical methods. Rev. Chim. (Bucharest) 6:356-360.

4174. Sternberg, S. S., and F. S. Philips. 1958. 6-Aminonicotinamide and acute degenerative changes in the central nervous system. Science 127:644-646.

4175. Stich, W. 1949. Significance of B2 vitamins for the dual function of porphyrine and the formation of haem-protein compounds. Deutsch. Med. Wochenschr. 75:1217-1220.

4176. Stock, K., and E. Westermann. 1965. Effects of adrenergic blockade and nicotinic acid on the mobilization of free fatty acids. Life Sci. 4(11):1115-1124.

4177. Stock, K., and E. Westermann. 1966. Inhibition of lipase by alpha- and beta-sympatholytic agents, nicotinic acid, and prostaglandin E1. Arch. Pharmakol. Exptl. Pathol. 254(4):334-354.

4178. Stoeger, R. 1941. Blood sugar and vitamin C. Wien. Med. Wochschr. 54:271-274.

4179. Stokes, W. 1944. Nicotinic acid in the treatment of angina pectoris. Brit. Heart J. 6:157-160.

4180. Stokstad, E. L. R. 1962. The biochemistry of the water-soluble vitamins. Ann. Rev. Biochem. 31:451-490.

4181. Stokstad, E. L. R., and T. H. Jukes. 1949. Water-soluble vitamins. Ann. Rev. Biochem. 18:435-486.

4182. Stotz, E. 1941. A clinical method for the determination of nicotinic acid in blood and urine. J. Lab. Clin. Med. 26: 1042-1046.

4183. Stoughton, R. B., W. E. Clendenning, and D. Kruse. 1960. Percutaneous absorption of nicotinic acid and derivatives. J. Invest. Derm. 35:337-341.

4184. Stowers, J. M., P. D. Bewsher, J. M. Stein, and J. Mowat. 1971a. Effects of nicotinic acid given orally or intravenously on oral and intravenous glucose tolerance in man. Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop 1970 723-731.

4185. Stowers, J. M., P. D. Bewsher, J. M. Stein, and J. Mowat. 1971b. Effect of nicotinic acid or derivatives on plasma insulin in man. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 913-921.

4186. Strangway, A. K. 1956. Food and nutrition in Angola. J. Canad. Dietetic Assoc. 18(4):21-27.

4187. Street, H. R., and G. R. Cowgill. 1937. The cure of canine blacktongue with nicotinic acid. Proc. Soc. Exptl. Biol. Med. 37:547-548.

4188. Streffer, C., and J. Benes. 1971. Nicotinamide mononucleotide. Determination of its enzymic formation in vitro and its physiological role for the biosynthesis of nicotinamide-adenine dinucleotide in mice. Eur. J. Biochem. 21(3):357-362.

4189. Streffer, C., W. Brauer, and J. Benes. 1971. Levels of pyridine nucleotides after repeated applications of nicotinic acid in animal tissues. Metab. Eff. Nicotinic Acid its Deriv., Pro. 97-114.

4190. Streightoff, F. 1963. Inhibition of bacteria by 4-fluoronicotinic acid and other analogs of nicotinic acid. J. Bacteriol. 85:42-48.

4191. Stroganova, L. A. 1965. Some indices of nicotinic acid metabolism in early childhood. Pediatriya 44(3):10-16.

4192. Stubbs, J. J., W. M. Noble, and J. C. Lewis. 1944. Fruit juices yield food yeast. Food Industries 16(9):68-70.

4193. Studnicin, A. A., and L. D. Tiscenko. 1969. Vitamins in dermatology. Izdat. "Medicina" (Moscow) pp. 166.

4194. Stuttgen, G., J. Fuerst, and E. Hoffmann. 1969. The capillary-microscopic picture of the nail wall and lip during the intravenous infusion of nicotinic acid derivatives. Med. Welt. 30: 1654-1658.

4195. Su, S., L. Albizati, and S. Chaykin. 1969. Nicotinamide deamidase from rabbit liver: II. Purification and properties. J. Biol. Chem. 244(11):2956-2965.

4196. Subrahmanyan, V., M. N. Rao, and M. Swaminathan. 1956. Nutritive value of rice and rice diets. I. Nutritive value of husked, undermilled, and milled raw rice. Ann. Biochem. Exptl. Med. (Calcutta) 16:81-88.

4197. Sugahara, T. 1958. Microbial degradation of nicotinic acid and nicotinamide. Bitamin 14:245-248.

4198. Sugenoya, T. 1962. The vascular effect of nicotinic acid and nicotinamide. Nagoya Igakkai Zasshi 85(1/6):269-277.

4199. Sugihara, A., M. Kakei, and S. Mitsuno. 1970. Nicotinamide. Jap. Pat. 73 03,625.

4200. Sugimoto, I. 1968. Studies on complexes: XII. Effect of complex formation on drug absorption from alimentary tract: 4. Chem. Pharm. Bull. 16(8):1527-1532.

4201. Sugimoto, I. 1969a. Complexes. XIV. Effect of complex formation on drug absorption from alimentary tract. 5. Enhancing the absorption of certain drugs by complex formation. Chem. Pharm. Bull. (Tokyo) 17(5):994-998.

4202. Sugimoto, I. 1969b. Complexes, XVI. Effect of complex formation on drug absorption from the alimentary tract. 6. Factors affecting complex absorption. Chem. Pharm. Bull. 17(7):1377-1382.

4203. Sugimoto, I. 1970. Complexes, XX. Effect of complex formation on drug absorption from alimentary tract. 7. Chem. Pharm. Bull. 18(3):515-526.

4204. Sugimoto, I., and M. Samejima. 1968. Complexes. XI. Effect of complex formation on drug absorption from the alimentary tract. 2. Yakugaku Zasshi 88(6):690-694.

4205. Sukhorukova, L. I., and I. S. Yakobson. 1965. Changes in the central nervous system of dogs after chronic alcohol intoxication. Zh. Nevropatol. i Psikhiatr. 65(3):423-430.

4206. Sullivan, R. A., E. Bloom, and J. Jarnol. 1943. The value of dairy products in nutrition. III. The riboflavin, pantothenic acid, nicotinic acid and biotin content of several varieties of cheese. J. Nutr. 25:463-470.

4207. Sullivan, W. T., and L. M. Strong. 1958. Behavioral changes in rats and guinea pigs induced by the administration of indole 3-acetic acid and 6-aminonicotinamide. J. Nutr. 65(2):199-210.

4208. Sundaram, T. K., and P. S. Sarma. 1956. Metabolism of nicotinic acid under normal conditions and in pantothenate deficiency, studied in the rat. Biochim. Biophys. Acta 22(3):547-549.

4209. Sundaram, T. K., N. R. Moudgal, and P. S. Sarma. 1956. Influence of thyroid hormone on nicotinamide metabolism in the rat. Biochim. Biophys. Acta 20:413-414.

4210. Sunde, M. L., and H. R. Bird. 1957. The niacin requirement of the young ringneck pheasant. Poultry Sci. 36(1):34-42.

4211. Sung, S.-C., and T.-C. Tung. 1950. Conversion of monomethyl-L-tryptophan to niacin and N1-methylnicotinamide by the rat. J. Biol. Chem. 186(7):637-640.

4212. Suomalainen, H., E. Oura, and T. Linnahalme. 1965. Extractability of vitamin and nucleotide compounds from dried yeast and vitaminized dried yeast. J. Inst. Brewing 71(4):330-336.

4213. Suomalainen, H., A. Bjoerklund, K. Vihervaara, and E. Oura. 1965. Nicotinic acid and nicotinamide adenine dinucleotide contents of baker's yeast in changing culture conditions. J. Inst. Brewing 71(May/Jun)221-226.

4214. Suomalainen, H., T. Nurminen, K. Vihervaara, and E. Oura. 1965. Effect of aeration on the synthesis of nicotinic acid and nicotinamide adenine dinucleotide by baker's yeast. J. Inst. Brewing 71(May/June)227-231.

4215. Supniewski, J. V., and J. Hano. 1937. The pharmacological action of some nicotinic acid derivatives. Bull. Intern. Acad. Polon. Sci., Classe Med. 9:925-934.

4216. Supniewski, J. V., J. Hano, and E. Taschner. 1936. The pharmacological action of nicotinic acid amide. Bull. Intern. Acad. Polon. Sci., Classe Med. 85-97.

4217. Sure, B., and F. Romans. 1948. Influence of the concentration of mixtures of various components of the vitamin B complex on biological value of casein and on economy of food utilization. J. Nutr. 36:727-737.

4218. Sure, B., L. Easterling, and S. Jeu. 1952. The specific effect of niacin on growth. J. Nutr. 46(1):55-60.

4219. Suslavicius, B., and P. Bluzmanas. 1969. Effect of some vitamins and succinic acid on the growth of the seedlings of winter crops. Liet. T.S.R. Aukst. Mokyklu Mokslo Darb., Biol. 9:155-162.

4220. Suvorov, B. V., et al. 1966. Nicotinic acid. U.S.S.R. Pat. 235,764.

4221. Suzuki, Y. 1961. Studies on the vitamin effect of baker's yeast. III. The secretion type of nicotinic acid by biotin-dependent baker's yeast. Agric. Biol. Chem. 25(12):A97.

4222. Svec, G. A. 1967. Effect of level and pattern of dietary essential amino acids on nitrogen retention and on niacin metabolism in men. Diss. Abstr. B 28(3):979-980.

4223. Svechnikova, N. V., and R. Lisitskaya. 1970. Effect of polyvitamins on the adrenal cortex. Vrach. Delo (5):44-47.

4224. Svedmyr, N. 1966. The mechanism for the calorigenic effect of adrenaline in man. Acta Physiol. Scand. 68(1):84-95.

4225. Svedmyr, N., et al. 1971. Arteriosclerosis-nicotinic acid therapy. 5. Acute effects in man. Lakartidningen 68:1753-1757.

4226. Svedmyr, N., and L. Harthon. 1970. Comparison between the absorption of nicotinic acid and pentaerythritol tetranicotinate (Perycit) from ordinary and enterocoated tablets. Acta Pharmacol. Toxicol. 28(1):66-74.

4227. Svedmyr, N., L. Harthon, and L. Lundholm. 1969a. Relation between the plasma concentration of free nicotinic acid and some of its pharmacologic effects in man. Clin. Pharmacol. Ther. 10(4):559-570.

4228. Svedmyr, N., L. Harthon, and L. Lundholm. 1969b. Relation between the plasma concentration of free nicotinic acid and some of its pharmacologic effects in man. Clin. Pharmacol. Ther. 10(4):859-870.

4229. Svedmyr, N., L. Harthon, and L. Lundholm. 1969c. Acute pharmacodynamic effects of pentaerythritoltetranicotinate perycit in man. Pharmacol. Clin. 2(1):13-18.

4230. Svedmyr, N., L. Harthon, and L. Lundholm. 1971. Dose-response relation between concentration of free nicotinic acid concentration of plasma and metabolic and circulatory effects after administration of nicotinic acid and pentaerythritoltetranicotinate in man. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 1085-1098.

4231. Svetlova, A. K., and V. N. Nemchaninov. 1966. Vitamin PP (nicotinamide) deficiency in children with recurrent and chronic pneumonia. Pediatriya 45(11):23-27.

4232. Svetocheva, Z. F. 1964. Study of the effect of nicotinic acid on the caliber of retinal vessels. Oftal. Zh. 19:109-113.

4233. Swaminathan, M. 1938a. A chemical method for the estimation of nicotinic acid in biological materials. Indian J. Med. Res. 26(2):427-434.

4234. Swaminathan, M. 1938b. A colorimetric method for the estimation of nicotinic acid in foodstuffs. Nature 141:830.

4235. Swaminathan, M. 1939. The urinary excretion of nicotinic acid. Indian J. Med. Res. 27:417-428.

4236. Swaminathan, M. 1941. Further studies on the cyanogen bromide method of estimating nicotinic acid in biological materials. Indian J. Med. Res. 29(2):325-340.

4237. Swaminathan, M. 1942a. A simple procedure for estimating nicotinic acid in biological materials using the cyanogen bromide-aniline reagent. Indian J. Med. Res. 30:397-401.

4238. Swaminathan, M. 1942b. The application of the cyanogen bromide test to a study of the metabolism of nicotinic acid in rabbits. Indian J. Med. Res. 30(4):537-552.

4239. Swaminathan, M. 1946. Improvements in the cyanogen bromide method for the determination of nicotinic acid in urine. Ann. Biochem. Exptl. Med. (Calcutta) 6(2):69-74.

4240. Swash, M., A. H. Roberts, and D. J. Murnaghan. 1972. Reversible pellagra-like encephalopathy with ethionamide and cycloserine. Tubercle 53(2):132-136.

4241. Sweat, M. L., and L. T. Samuels. 1948. Diphosphopyridine nucleotide as an essential factor in the metabolism of testosterone by the liver. J. Biol. Chem. 173:433-434.

4242. Sweeney, J. P. 1951. Report on a chemical method for nicotinic acid. J. Assoc. Offic. Agr. Chem. 34:380-387.

4243. Sweeney, J. P. 1952. Report on a chemical method for nicotinic acid. J. Assoc. Offic. Agr. Chem. 35:721-722.

4244. Sweeney, J. P., and W. L. Hall. 1953. The use of ion exchange resin in the quantitative chemical differentiation between nicotinic acid and nicotinamide. J. Assoc. Offic. Agric. Chem. 36(3):1018-1022.

4245. Sweeney, J. P., and W. P. Parrish. 1954. Extraction of nicotinic acid from naturally occurring materials. J. Assoc. Offic. Agric. Chem. 37:771-777.

4246. Swendseid, M. E., D. Barense, and F. H. Bethell. 1951. Methylation of nicotinamide in patients with pernicious anemia. Proc. Soc. Exp. Biol. Med. 78:230-231.

4247. Sydenstricker, V. P. 1941a. The clinical manifestations of nicotinic acid and riboflavin deficiency (pellagra). Ann. Int. Med. 14:1499-1517.

4248. Sydenstricker, V. P. 1941b. The present status of nicotinic acid. Arch. Intern. Med. 67:746-754.

* 4249. Sydenstricker, V. P., and H. M. Cleckley. 1941. The effect of nicotinic acid in stupor, lethargy and various other psychiatric disorders. Am. J. Psychiat. 98:83-92.

4250. Syhalov, D. L. 1970. Role of blood indicators of the respiratory function in rationalizing the form of treatment of acute pneumonia in children. Pediat. Akush. Hinekol. 32(2):10-11.

4251. Syllanco, C. Y. L., and C. P. Berg. 1959. The effect of riboflavin-deficiency upon the metabolism of tryptophan by liver and kidney tissue. J. Biol. Chem. 234(4):912-917.

4252. Syunyakova, Z. M., and I. N. Karpova. 1966. The effect of gamma-rays and thermal sterilization on the content of thiamine, riboflavine, nicotinic acid, and tocopherol in beef. Vopr. Pitan. 25(2):52-55.

4253. Szabo, M. M., and M. Goldstein. 1969. Effect of guanine derivatives on palmitate-1-14C incorporation into rat epididymal adipose tissue. Proc. Soc. Exp. Biol. Med. 131(3):1055-1059.

4254. Szeberenyi, S., K. S. Szalay, and S. Garattini. 1969. Removal of plasma metyrapone in rats submitted to previous pharmacological treatment. J. Pharm. Pharmacol. 21(3):201-202.

4255. Szegedi, G., et al. 1963. Prolonged treatment of atherosclerosis obliterans with large doses of nicotinic acid. Orv. Hetil. 104:2462-2464.

4256. Szember, A., and M. Malka. 1967. Influence of vitamins in the culture medium on the production of antibiotics by some strains of milk bacteria. Ann. Univ. Mariae Curie-Sklodowska, Sect. E 1966 21:245-251.

4257. Szirmai, E. 1968. Experimental tests with maphylinol, a new linoleic acid-magnesium-theophylline salt. Punjab Med. J. 17(12):527-530.

4258. Szwarcberg, R., et al. 1970. An exceptional cause of fetal death "in utero": material massive digestive hemorrhage. Bull. Fed. Soc. Gynecol. Obstet. Lang Fr. 22:257-258.

4259. Tabachnick, I., and F. E. Roth. 1962. Potentiation of antihistamines 2-(rho-chloro-alpha-(dimethylaminoethoxy)benzyl)pyridine and 5-(N-methyl-4-piperidylidene)dibenzo(a,e)cycloheptatriene. U.S. Pat. 3,126,319.

4260. Tabaqchali, S., and C. Pallis. 1970. Reversible nicotinamide-deficiency encephalopathy in a patient with jejunal diverticulosis. Gut 11:1024-1028.

4261. Tada, T. 1958. Disturbance of the metabolism of nicotinic acid and its clinical significance in liver damage. I. Influence of nicotinamide and diphosphopyridine nucleotide on the disturbance of biological oxidation in experimental liver damage. Osaka Daigaku Igaku Zasshi 10:2125-2129.

4262. Tada, K., T. Morikawa, and T. Arakawa. 1966. Tryptophan load and uptake of tryptophan by leukocytes in Hartnup disease. Tohoku J. Exp. Med. 90(4):337-346.

4263. Taeufel, K., and F. Dahle. 1943. Decolorizing test solutions for the determination of nicotinic acid and nicotinamide. Z. Untersuch. Lebensm. 85:414-423.

4264. Tagg, J., and Mitoma. 1968. Microsomal drug-metabolizing enzyme system. Effect of isooctane and pyridine nucleotides. Biochem. Pharmacol. 17(12):2471-2479.

4265. Takakuwa, M., and T. Oda. 1968. Effect of nicotinamide during preparation of NAD from bakers' yeasts. Ehime Daigaku Kiyo, Dai-6-Bu 13(1):15-24.

4266. Take, T. 1969. Production of B vitamins by various microorganisms. I. Production of B vitamins by Escherichia coli. Niigata Igakkai Zasshi 83(3):142-147.

4267. Take, T. 1970. Production of vitamins B group by various microorganisms. 6. Production of vitamin B group by intestinal bacteria of infants with reference to their health and the influence of antibiotics. Niigata Igakkai Zasshi 84(11):787-798.

4268. Takenouchi, K., et al. 1963. Participation of ascorbic acid in the formation of tyrosine melanin. Bitamin 28:501-507.

4269. Talafant, E., and J. Tovarek. 1959. The influence of the derivatives of nicotinic acid on the conjugation of bilirubin. Scripta Med. Fac. Med. Univ. Brunensis et Olomucencis 32:161-170.

4270. Talke, H. 1968. Effect of nicotinamide on metabolites of fat and carbohydrate metabolism in rat blood and liver. Verh. Deut. Ges. Inn. Med. 74:946-950.

4271. Talke, H., and M. Kersten. 1972. Experimental animal investigations on the action of reduced offerings of unesterified fatty acids on carbohydrate metabolism of the liver during nutritional benefits. Verh. Deut. Ges. Inn. Med. 78:1367-1371.

4272. Talke, H., J. Keller, and F. W. Schmahl. 1970. Effect of nicotinamide on the regulation of carbohydrate metabolism in rat liver. Horm. Metab. Res. 2(3):147-152.

4273. Talke, H., F. W. Schmahl, and J. Keller. 1969. Effect of nicotinamide on the level of unesterified fatty acids, acetoacetate, lactate, pyruvate, and glucose in rat blood or plasma. Z. Gesamte Exp. Med. 151(3):232-240.

4274. Tamasi, G., and J. Borsy. 1969. Effect of free fatty acid-lowering compounds on rats with alloxan diabetes. Kiseri. Orvostud. 21(3):259-263.

4275. Tamasi, G., J. Borsy, and Gyenge. 1970. Changes in serum triglyceride and cholesterol levels independent of free fatty acid after lipolysis inhibitors. Biochem. Pharmacol. 19(5):1826-1830.

4276. Tamasi, G., J. Borsy, and A. Patthy. 1968. Comparison of the antilipemic effect of nicotinic acid (NA) and 3-methylpyrazole-5-carboxylic acid (MPC) in rats. Biochem. Pharmacol. 17(9):1789-1794.

4277. Tamburino, G. 1952. Effect of nicotinic acid on blood volume and blood components. Riforma Med. 66:1151-1154.

4278. Tamburro, C., O. Frank, A. D. Thomson, M. F. Sorrell, and H. Baker. 1971. Interactions of folate, nicotinate, and riboflavin deficiencies in rats. Nutr. Rep. Intl. 4(4):185-189.

4279. Tamura, M., and S. Takano. 1971. Comparison between antituberculous activity of alpha-ethyl-thioisonicotinamide (1314TH) and alpha-N-propylthioisonicotinamide (1321TH) in vitro. Kekkaku 46(5):137-152.

4280. Tamura, T. 1957. Rapid spectrophotometric determination of isonicotinic acid and nicotinic acid mixtures. Tokyo Daigaku Rikogaku Kenkyushu Hokoku 11:57-61.

4281. Tanigawa, Y., M. Shimoyama, J. Asamizu, and I. Ueda. 1971. Subcellular localization of nicotinamide deamidase in rat liver. Biochim. Biophys. Acta 230(3):510-517.

4282. Tanner, E. 1951. A new drug therapy of bronchial tuberculosis. Helvetica Med. Acta 18(4/5):456-460.

4283. Tantengco, V. O., B. D. Canlas, L. C. Somera, and E. Credo. 1966. Effects of nicotinic acid, ascorbic acid, and L-triiodothyronine on serum and liver cholesterol levels. Acta Med. Philippina 3(1):1-12.

4284. Tantengco, V. O., L. C. Somera, and E. Credo. 1966. Effects of L-triiodothyronine, nicotinic acid, and ascorbic acid on the electrophoretic pattern of serum lipoproteins in cockerels. Acta Med. Philippina 3(1):13-19.

4285. Tapadinhas, J. 1944. Vitamins of oxidation-reductions and cholinesterase. Arch. Portugaises Sci. Biol. 7(Suppl. 1):1-3.

4286. Tappan, D. V., U. J. Lewis, U. D. Register, and C. A. Elvehjem. 1952. Niacin deficiency in the rhesus monkey. J. Nutr. 46(1): 75-85.

4287. Tarasashvili, K. M., and Yu. M. Nadimov. 1966. Vitamin contents in some varieties of potato. Fiziol. Drev. Rast., Akad. Nauk Gruz. S.S.R., Inst. Bot. (2):64-70.

4288. Tardif, R. 1961. Differential spectrophotometric titration of vitamins and drugs in pharmaceutical preparations. J. Pharm. Sci. 50:693-703.

4289. Tarshis, M. S. 1966. A Tween plasma niacin test medium for the rapid and eugonic cultivation of Mycobacterial and the rapid determination of their niacin content. Can. J. Microbiol. 12(4): 870-871.

4290. Tarsitano, A. 1940. Action of nicotinic acid on azotemia. Boll. Soc. Ital. Biol. Sper. 15:1139-1142.

4291. Tarutin, P. P., and M. Ya. Zitserman. 1961. Vitaminization of flour in mills. Soobshch. i Ref. Vses. Nauchn.-Issled. Inst. Zerna i Produktov ego Pererabotki (5):4-13.

4292. Tatarenko, L. M. 1961. Nicotinic acid content of blood and skin in patients with eczema. Vestnik Dematol. i Venerol. 35(11):24-27.

4293. Tatarskii, V. V. 1953. Nicotinic acid metabolism during cancer. Voprosy Med. Khim. 6:157-165.

4294. Tatarskii, V. V. 1955. Methylation of nicotinamide in the liver of cancerous rat. Voprosy Onkologii 1(6):101-103.

4295. Taub, D., C. H. Kuo, and N. L. Wendler. 1967. Transformations in the 1,2,5,6-tetrahydropyridine series. J. Chem. Soc., C (16):1558-1564.

4296. Taylor, A., H. K. Mitchell, and M. A. Pollack. 1941. Modification of "B vitamin" content during embryological development. Univ. Texas Pub. (4137):67-80.

* 4297. Taylor, A., M, A. Pollack, M. J. Hofer, and R. J. Williams. 1942. B vitamins in cancerous tissues. II. Nicotinic acid. Cancer Res. 2(11):744-747.

4298. Taylor, W. 1954. The metabolism of progesterone by animal tissues in vitro. 1. Factors influencing the metabolism of progesterone by rat liver and the investigation of the products of metabolism. Biochem. J. 56(3):463-470.

4299. Taylor, W. 1955. The metabolism of progesterone by animal tissue in vitro. 2. Factors influencing the metabolism of progesterone by rabbit liver and the investigation of the products of metabolism. Biochem. J. 60(3):380-388.

4300. Taylor, W. J. R. 1969. Inhibition of nikethamide by nicotinamide. Int. Z. Klin. Pharmakol. Ther. Toxikol. 2(1):38-43.

4301. Taylor, W. J. R., and C. R. Woolf. 1967. Comparative evaluation of nikethamide, prethcamide, and caffeine as respiratory stimulants in patients with chronic chest disease, mostly emphysema. Int. Z. Klin. Pharmakol. Ther. Toxikol. (2):92-100.

4302. Teas, H. J., and A. C. Newton. 1951. Tryptophan, niacin, and indoleacetic acid in several endosperm mutants and standard lines of maize. Plant Physiol. 26(3):494-501.

4303. Teas, H. J., E. G. Anderson, and J. W. Cameron. 1955. Roles of embryo and endosperm in determining niacin content of starchy and sugary maize endosperms. Plant Physiol. 30:334-337.

4304. Tecce, R., and P. Visconti. 1941a. Influence of nicotinic acid on the index of immunity. Boll. Soc. Ital. Biol. Sper. 16:182-184.

4305. Tecce, R., and P. Visconti. 1941b. Blood variations due to nicotinic acid. Boll. Soc. Ital. Biol. Sper. 16:184-185.

4306. Teeri, A. E. 1948. Thiamine and the cyanogen bromide reaction. J. Biol. Chem. 173(2):503-505.

4307. Teeri, A. E., and S. R. Shimer. 1944. A colorimetric determination of nicotinic acid. J. Biol. Chem. 153(1):307-311.

4308. Teeri, A. E., M. E. Loughlin, and D. Josselyn. 1957. Nutritive value of fish. I. Nicotinic acid, riboflavine, vitamin B12, and amino acids of various salt-water species. Food Res. 22:145-150.

4309. Teeri, A. E., M. Leavitt, D. Josselyn, N. F. Colovos, and H. A. Keener. 1950. The effect of sulfathalidine on the excretion of vitamin B by ruminants. J. Biol. Chem. 182:509-514.

4310. Teggia, L. 1950. Action of niacin on the induced excretion of hippuric acid in normal persons and patients with liver disease. Boll. Ist. Aliment. Dietol. 1:70-83.

4311. Teixeira Da Cruz, A., J. Rydstrom, and L. Ernster. 1971. Steady-state kinetics of mitochondrial nicotinamide nucleotide transhydrogenase: 1. The nonenergy-linked reaction. Eur. J. Biochem. 23(2):203-211.

4312. Tekeli, S. T. 1954. The essential amino acids and nicotinic acid content of the predominant planted corn varieties in Turkey. 10th Cong. Intern. Ind. Agr. y Aliment., Madrid 989-994.

4313. Telepneva, V. I., and I. V. Isaeva. 1967. Effect of nicotinamide upon content and enzymic degradation of NAD in skeletal muscle of the normal rabbit and after denervation. Vop. Med. Khim. 13(2): 182-187.

4314. Temime, P., P. Saint-Andre, and F. Chastel. 1964. Pseudo-peladic study of epilatory (hair-removing) folliculitis (niacin, inflammation, man). In: Meetings of the French Society of Dermatology and Syphilography, Feb., Mar., and May, 1964. Bull. Soc. Franc. Dermatol. Syphiligr. 71(3):401-402.

4315. Tenconi, L. T. 1964. Urinary elimination of metabolites of tryptophan - nicotinic acid pathway in pancreatectomy diabetes in the rat. Acta Vitaminol. 18(4):193-204.

4316. Tenconi, L. T., and G. Acocella. 1966. Chemotherapy of experimental lead poisoning. I. Effects of lead poisoning on the metabolism of tryptophan and nicotinic acid in the rat. Acta Vitaminol. 20(5):189-194.

4317. Tenconi, L. T., and G. Pasquariello. 1967. Elimination of metabolites of the tryptophan - nicotinic acid pathway after hydrocortisone treatment in the rat. Acta Vitaminol. Enzymol. 21(1): 17-20.

4318. Tensho, A., I. Shimizu, T. Takenawa, H. Kikuchi, and T. Rokujo. 1972. Acutely-induced dietary hypercholesterolemia in the rat. Yakugaku Zasshi 92(7):879-885.

4319. Teply, L. J. 1958. Nutritional study of instant-coffee powder. Food Technol. 12:485-486.

4320. Teply, L. J., and R. F. Prier. 1957. Nutritional evaluation of coffee, including niacin bioassay. J. Agr. Food Chem. 5:375-377.

4321. Teply, L. J., W. A. Krehl, and C. A. Elvehjem. 1945. Studies on the nicotinic acid content of coffee. Arch. Biochem. 6:139-149.

4322. Teply, L. J., W. A. Krehl, and C. A. Elvehjem. 1945b. Biological activity of N-methylnicotinamide and nipecotic acid. Proc. Soc. Exp. Biol. Med. 58(2):169-171.

4323. Teply, L. J., F. M. Strong, and C. A. Elvehjem. 1942. The distribution of nicotinic acid in foods. J. Nutr. 23(4):417-423.

4324. Teply, L. J., P. H. Derse, C. H. Krieger, and C. A. Elvehjem. 1953. Nutritive value of canned foods. Vitamin B6, folic acid, beta-carotene, ascorbic acid, thiamine, riboflavine, and niacin content, and proximate composition. J. Agr. Food Chem. 1:1204-1207.

4325. Terho, T., and Hartiala. 1967. Hydroxylation of cinchophen by microsomal enzymes. Biochem. Pharmacol. 16(3):598-600.

4326. Terroine, T., and J. Adrian. 1950. Vitamin interrelationships. Pyridoxine deficiency and tissue content of riboflavin, niacin, and pantothenic acid. Arch. Sci. Physiol. 4(4):435-444.

4327. Tesi, M. 1967. Nicotinic acid and fibrinolysis in humans. I. Regional fibrinolysis (cerebral, of the upper extremity and of the lower extremity) caused by "arterial" administration of nicotinic acid. Riv. Crit. Clin. Med. 67:465-483.

4328. Tesi, M., S. Brunetti, L. Caramelli, and R. P. Dabizzi. 1968. Variations of the cerebral fibrinolytic potential due to the intracarotid injection of nicotinic acid (the nicotinic acid-fibrinolytic test) in subjects with progressive cerebral infarct. Settim. Med. 56(17):927-930.

4329. Thakur, S. S., and K. R. Karandikar. 1951. Estimation of fat, oil, thiamin and nicotinic acid in Sciaenoides brunneus, Day (Sciaenidae). J. Univ. Bombay 19(5 Sec. B):64-68.

4330. Therriault, D. G., and V. G. Winters. 1970. Effect of nicotinic acid on cyclic nucleotide phosphodiesterase activity in rat heart and adipose tissue. Life Sci. 9(8 Pt. 1):421-428.

4331. Thiers, H. 1950. The effect of P.A.S. in disturbances of the keratinization. J. Med. Lyon 31(735):699-700.

4332. Thiers, H., and J. Fayolle. 1961. High doses of nicotinamide in therapeutics. J. Med. Lyon 42:2049-2054.

4333. Thiers, H., and J. Fayolle. 1962. Strong doses of nicotinamide in therapy (pellagra excepted). Gaz. Med. France 69:1365-1368.

4334. Thomas, B., and L. Tunger. 1966. Approximate values for the vitamin and mineral content of bread flour as a function of the degree of milling. Nahrung 10(2):185-194.

4335. Thomas, M. H., and D. E. Sherman. 1969. Effect of freeze-thaw cycling on the vitamin content of the ready-to-eat, individual meal. U.S. CLearinghouse Fed. Sci. Techn. Inform., AD-695642 37 pp.

4336. Thomas, M. H., S. Brenner, A. Heaton, and V. Craig. 1949. Effect of electronic cooking on nutritive value of foods. J. Am. Dietetic. Assoc. 25(1):39-45.

4337. Thomas, R. G., and W. G. Wysor, Jr. 1967. Alteration of serotonin metabolism in rats deficient in niacin and tryptophan. Proc. Soc. Exp. Biol. Med. 126(2):374-377.

4338. Thompson, S. Y., and L. Ascarelli. 1962. Utilization of carotene by the cow. Intern. Dairy Congr. Proc., 16th, Copenhagen Sect. A 81-88.

4339. Thomson, W. B., J. Green, and I. L. Evans. 1964. The effect of some physiological stimuli on fibrinolytic activity in man measured by the heparin fractionation method. J. Clin. Pathol. 17(3):341-344.

4340. Thoyer-Rozat, J., O. Blanpin, and R. Pierre. 1962. Riboflavin in muscular cramp in pregnancy. Experimental and clinical study. Sem. Hop. 38(Sen Therap. 7):Th652-Th653.

4341. Threlfall, C. J. 1959. Synthesis of diphosphopyridine nucleotide from nicotinamide by slices of liver. Nature 184(4679):60-61.

4342. Tiberi, G. F. 1959. Nicotinic acid associated with streptomycin in the treatment of experimental ocular tuberculosis. Boll. Oculist. 38:525-538.

4343. Tikhanovich, G. S. 1949. Employment of nicotinic acid in cases of hepatitis. Klin. Med., Mosk. 27(6):67-78.

4344. Tikhomirova, A. N., and E. A. Beiul. 1960. Studies on nicotinic acid metabolism in patients with chronic colitis. Vop. Pitan. 19:48-52.

4345. Tikhomirova, G. P. 1959. Applications of the polarographic method in food industry. Tr., Ukr. Nauchn.-Issled. Inst., Pishchevoi Prom. (2):135-140.

4346. Tikhomirova, G. P., and A. I. Ermakova. 1960. Polarographic method of estimating nicotinic acid in monovitamin dragees. Vop. Pitan. 19:61-63.

4347. Tikhomirova, G. P., S. L. Belen'kaya, R. G. Madievskaya, and O. A. Kurochkina. 1965. Polarographic determination of vitamins B1, B2, nicotinic acid, and nicotinamide when there is increased vitamin C content. Vop. Pitan. 24(2):32-37.

4348. Timofeeva, T. V. 1959. Effect of biomycin on Pasteurella pestis in vitro in the presence of some vitamins. Trudy Gosudarst. Nauch.-Issledovatel. Inst. Mikrobiol. i Epidemiol. Yugo-Vostoch. S.S.S.R. (3):117-118.

4349. Timokhina, V. I., and V. G. Lappo. 1972. Use of a model of hepatic adipose dystrophy in a sanitary-toxicological experiment. Gig. Sanit. (10):67-70.

4350. Tinao, M. M., and J. L. Mateos. 1951. Stimulation of gastric acidity with pharmaceuticals. Variations of acidity with splanchnic block. Arch. Inst. Farmacol. Exptl. (Med.) (Madrid) 3:229-237.

4351. Tinao, M. M., F. I. Gomez, and F. T. Sanchez. 1954. Pharmacology of adrenaline and acetylcholine tested on the ureter and its reaction to vitamin C and PP. Arch. Inst. Exptl. (Madrid) 6:140-149.

4352. Ting, S.-M., and Y.-N. Wu. 1968. Biochemistry of the development of duck embryo: 3. Pantothenic acid, coenzyme A, and nicotinic acid in the developing liver. J. Formosan Med. Ass. 67(1):14-17.

4353. Tiselius, A. 1940. Electrophoretic analysis and the constitution of native fluids. Harvey Lectures 35:37-70.

4354. Tisna-Amidjaja, D. A. 1958. Effects of acetylcholine, alloxan, nadisan, Aristamid, nicotinamide, and rho-aminobenzoic acid on the growth of chick embryos. Arch. Entwicklungsmech. Organ. 150: 655-658.

4355. Titova, N. N., and I. S. Badyugin. 1970. Acute chlorophos poisoning. Kazan Med. Zh. 1:37-40.

4356. Titova, T. S., B. F. Ustavshchikov, M. I. Farberov, and E. V. Degtyarev. 1969. Practical synthesis of 2,5-pyridinedicarboxylic and nicotinic acids by the oxidation of alkylpyridines with dilute nitric acid. Zh. Prikl. Khim. (Leningrad) 42(4):910-920.

4357. Tjutina, E. M. 1970. Effect of a complex of B vitamins and vitamin C on the content of free amino acids in the blood and urine of women with late pregnancy toxaemia. Vop. Ohrany Mater. Det. 15(11):89-90.

4358. Todorutiu, C., and J. Mustea. 1965. The protective effect of stimulation of certain oxido-reductase cofactors during experimental hepatic cancer. Bull. Assoc. Franc. Etude Cancer 52(2):185-191.

4359. Toida, I., F. Ando, and S. Yamamoto. 1968. Biochemical study on the host response to tuberculous infection. IV. Influences of isoniazid, streptomycin, nicotinamide, and cortisone. Am. Rev. Resp. Dis. 98(3):424-428.

4360. Toivanen, A., T. Markkanen, R. Mantyjarvi, and P. Toivanen. 1964. Microbiologically determined pantothenic acid and nicotinic acid content of chick embryos after treatment with thalidomide and of rat fetuses, newborns, and placentas from mothers treated with thalidomide. Biochem. Pharmacol. 13(11):1489-1497.

4361. Toland, W. G., Jr. 1954. Aliphatic, aromatic, and heterocyclic carboxylic acids. Ger. Pat. 1,109,683.

4362. Toleikis, A., A. Praskevicius, and A. Smits. 1969. Effect of biostimulants of reparative processes in the heart muscle on oxidative phosphorylation during experimental myocardial infarct. Latv. P.S.R. Zinat. Akad. Vestis (3):133-136.

4363. Tolone, S. 1947. Blood lysozyme and nicotinic acid. Acta Neurol. (Naples) 2:296-305.

4364. Tomabechi, K. 1955. The conversion of L- and D-tryptophan to niacin in human body. J. Vitaminol. 1(2):18-23.

4365. Tompkins, P. C., and C. L. A. Schmidt. 1942. A polarographic characterization of nicotinic acid and related compounds. I. Pyridine and nicotinic acid. J. Biol. Chem. 143:643-653.

4366. Tompkins, P. C., and C. L. A. Schmidt. 1943. A polarographic characterization of nicotinic acid and related compounds. II. Methyl pyridinium hydroxide and trigonelline. III. Picolinic acid and isonicotinic acid. IV. Homarine and isonicotinic acid chloromethylate. V. Nicotinic acid amide and nicotinic acid amide chloromethylate. Univ. Calif. Publ. Physiol. 8(16):221-256.

4367. Tondii, L. D. 1963. An electrocardiographic study of the changes following the administration of a complex of drugs (reserpine, nicotinic acid beta-phenylisopropylamide, rutin, and vitamin B12) in hypertensive patients. Sb. Nauch. Rabot. Ukr. Inst. Usoversh. Vrachei. 2:78-81.

4368. Tonge, W. L. 1953. Nicotinic acid in the treatment of depression. Ann. Int. Med. 38(3):551-553.

4369. Tonkova-Yampolskaja, R. V. 1960. Effect of different doses of nicotinic acid on excitability of the cerebral cortex of children in the third year of life. Vop. Pitan. 19(6):26-30.

4370. Toone, E. C., and J. L. Berkley. 1939. The therapeutic effects of nicotinic acid in pellagra and related conditions. Virginia Med. Monthly 66:282-288.

4371. Toporek, M., E. Gizis, and L. M. Meyer. 1971. Effect of human serum B12 binders on uptake of vitamin B12 by isolated perfused rat liver. Proc. Soc. Exp. Biol. Med. 136(4):1119-1121.

4372. Torben, K. 1946. Do carotene and the A-active carotenoids act as provitamin A or do they develop their biological action in the organism without previous transformation into vitamin A? Z. Vitaminforsch. 17:88-97.

4373. Torizuka, K., K. Hamamoto, R. Morita, T. Mukai, T. Kosaka, J. Handa, and H. Nishitani. 1971. Regional cerebral blood flow measurement with xenon 133 and the scinticamera. Am. J. Roentgenol. Radium Ther. Nucl. Med. 112(4):691-700.

4374. Toth, B. 1972. Tumorigenesis studies with 1,2-dimethylhydrazine dihydrochloride, hydrazine sulfate, and isonicotinic acid in golden hamsters. Cancer Res. 32(4):804-807.

4375. Touchard, P., et al. 1969. Drug cytopenia with active antibodies in the presence of acetyl-salicylic acid and niflumic acid. Rev. Franc. Transfus. 12(Suppl 4):15-19.

4376. Toury, J. 1970. Current estimates of mineral and vitamin requirements. Med. Afr. Noire 17(6):507-509.

4377. Travia, L., and S. Calamaro. 1941. Nicotinic acid and mineral metabolism. II. Influence of nicotinic acid on serum calcium. Boll. Soc. Ital. Biol. Sper. 16:157.

4378. Travia, L., C. Pelosio, and M. Gattini. 1949. Elimination of some group B group vitamins in diabetes. Acta Vitaminol. 3:193-195.

4379. Travia, L., C. Pelosio, and G. Tecce. 1949. Antagonism among some components of the B complex. Acta Vitaminol. 3:4-11.

4380. Treshchinskii, A. I., E. S. Vakhnovan, and Z. N. Miroshichenko. 1970. Tissue respiration in barbiturate poisoning. Progr. Anaesthesiol., Proc. World Congr. Anaesthesiol., 4th 1968 716-722.

4381. Trevelyan, W. E., and J. S. Harrison. 1956. Yeast metabolism. V. The trehalose content of bakers' yeast during anaerobic fermentation. Biochem. J. 62:177-183.

4382. Trofimova, Z. G. 1964. The effect of riboflavin, nicotinic and ascorbic acids, and testosterone propionate on experimentally induced toxic myocarditis. Byul. Eksp. Biol. Med. 57(2):53-58.

4383. Tromovitch, T. A., P. H. Jacobs, and S. Kern. 1964. Acanthosis nigricans-like lesions from nicotinic acid. Arch. Dermatol. 89(2): 222-223.

4384. Trout, D. L., H. L. Bitter, and W. W. Lackey. 1967. Effects of nicotinic acid on the choice of substrates utilized during fasting. Biochem. Pharmacol. 16(6):971-978.

4385. Trubnikov, V. I., V. V. Petrov, E. S. Zhdanovich, and N. A. Preobrazhenskii. 1969. Pyridinecarboxylic acids. IV. Synthesis of nicotinic acid and its amide by vapor-phase oxidative ammonolysis of quinoline. Khim.-Farm. Zh. 3(9):49-52.

4386. Trufanov, A. V. 1943. Water-soluble vitamins and their interrelations with the enzymes. Uspekhi Khim. 12:452-471.

4387. Trufanov, A. V. 1958. The dietary importance of rho-aminobenzoic acid. Vop. Pitan. 17(2):66-68.

4388. Truswell, A. S. 1963. The role of maize in the pathogenesis of pellagra. Effect of leucine on N'-methylnicotinamide excretion in human adults. S. African Med. J. 37(10):253-256.

4389. Tscherkes, L. A., and E. L. Rosenfeld. 1941. The influence of nicotinic acid on the blood sugar level and on adrenaline hyperglycaemia. Biochimia 6(1):58-66.

4390. Tschumi, R. 1946. On the physiology of sperm motility and the influence of vitamins and hormones. Gynaecologia 121(4):169-203.

4391. Tseitlin, L. A. 1969. Effect of nicotinamide on the level of energy-rich phosphorus compounds in cardiac muscle under normal conditions and during (experimental) myocarditis. Khim. Biokhim. Uglevodov, Mater. Vses. Konf., 4th 1967 260-262.

4392. Tsilikov, V. V. 1969. Effect of the sodium salt of 2,4-D, carbothion, trichlorometaphos, nicotine, and arecoline on the adrenal cortex. Farmakol. Tsent. Kholinolitikov Drugikh Neirotropnykh Sredstv. 186-188.

4393. Tsiltiklis, C., and T. Christides. 1970. The effects of the tuberculostatic drugs upon the incidence of Candida albicans in the intestine. Ann. Sclavo 12(2):211-216.

4394. Tsiomik, V. A., N. M. Razumnaya, N. P. Kuz'minskii, L. N. Garkusha, and N. I. Kovaleva. 1972. Effect of a complex of water-soluble vitamins on energy processes in tissues and on the development of experimental atherosclerosis. Gipertonicheskaya Bolezn, Ateroskler. Koro 4:94-99.

4395. Tso, T. C., and R. N. Jeffrey. 1953. Paper chromatography of alkaloids and their transformation products in Maryland tobacco. Arch. Biochem. Biophys. 43(2):269-285.

4396. Tsuji, M., and S. Sakamoto. 1960. The fluorometric determination of niacinamide and N-methylniacinamide and their urinary excretion in man. Bitamin (Kyoto) 19(3):433-437.

4397. Tsukamura, M. 1965. Combined effect of chromomycin A3 on mycobacterium smegmatis with 8-azaguanine or dihydrostreptomycin. J. Antibiot., Ser. A. 18(3):137.

4398. Tsushima, T., M. Sakuma, and M. Irie. 1971. Effect of changes in plasma free fatty acids level on secretion of human growth hormone. Endocrinol. Jap. 17(5):369-377.

4399. Tucker, R. E., C. L. Brine, and M. S. Wallace. 1958. Nutritive intake of older institutionalized persons. I. Variations of food intake. J. Am. Dietetic Assoc. 34(8):819-822.

4400. Tudoranu, G., I. Foni, P. Toporas, G. Creteanu, and C. Pavelescu. 1950. Chemical anticoagulating agents. Le Song 21:511-514.

4401. Tudoriu, C. D., C. Ionica, S. Cambir, G. Moldovan, and P. Iul. 1962/1963. Studies on strain typing of tubercle bacilli isolated from animals. Lucr. Stiint. Inst. Pathol. ig Anim. 12:39-55.

4402. Tuennerhoff, F. K., and H. K. Schwabe. 1955. The action of derivatives of nicotinic acid on normal inbred mice. Arzneimittel-Forsch. 5:277-282.

4403. Tulpule, P. G. 1960. Studies on pyridine nucleotide metabolism. IV. Effect of protein deficiency on ribosyl nicotinamide synthesis by rat liver preparations. Indian J. Med. Res. 48(1):96-102.

4404. Tulpule, P. G. 1961. Effect of pyridoxine deficiency on the utilization of nicotinamide and tryptophan as precursors of pyridine nucleotides in vivo. Indian J. Med. Res. 49(3):479-484.

4405. Tuomainen, L. 1950. Effect of nicotinic acid feed on the blood of the cow and the nicotinic acid percentage of the milk. A preliminary report. Suomen Kemist. 23B(7/8):69-70.

4406. Turazza, G., P. L. Spreafico, and G. Frandoli. 1973. Comparative investigations on the effect of nicotinic acid alone and in association with a synthetic, heparinlike sulfated polyanion on fibrinolysis, platelet aggregation and lipidic fractions. Long-term prophylactic treatment under double-blind conditions. Arzneim.-Forsch. 23(5):654-657.

4407. Turchetti, A. 1952. Nicotinic acid in vascular therapy. Riforma Med. 66:729-731.

4408. Turcu, G., V. Vasilescu, A. Ciuses, and A. S. Aleu. 1965. Cytochemical and cytospectrophotometric studies on leukocytes in rats irradiated internally with phosphorus-32. III. Use of a vitamin complex as a radioprotective agent. Stud. Cercet. Biochim. 8(2):235-246.

4409. Turetskaya, E. S., and N. N. Sakhnovskaya. 1969. Effect of nicotinic acid on the thyroid gland. Faktory Vnesh. Sredy Ikh. Znachenie Zdorov'ya Naseleniya (1):87-92.

4410. Turpeinen, O. 1952. Nutrition among lower income classes in Finland. II. (Continuation from Ann. Med. Intern. Fenniae 41:233. 1952.) Ann. Med. Intern. Fenniae 41:305-315.

4411. Turpeinen, O. 1953. Nutrition among lower income classes in Finland. III. Ann. Med. Fennicae 42(1):75-85.

4412. Turpini, R., P. L. Cipolli, and P. Barello. 1961. Cerebral infarct: new pathogenetic and therapeutic concepts in the light of 419 cases. G. Geront. 9:151-160.

4413. Tyner, E. P., H. B. Lewis, and H. C. Eckstein. 1950. Niacin and the ability of cystine to augment deposition of liver fat. J. Biol. Chem. 187(2):651-654.

4414. Tytgat, G., D. Collen, R. De Vreker, and M. Verstraete. 1968. Investigations on the fibrinolytic system in liver cirrhosis. Acta Haematol. (Basel) 40(5):265-274.

4415. Tyupalo, N. F., V. A. Yakobi, L. A. Kozorez, P. A. Gangrskii, and A. A. Nikiforov. 1969. Nicotinic acid. U.S.S.R. Pat. 306,848.

4416. Udalov, Y. F., and I. N. Chernyakov. 1965. Influence of calcium pangamate on the organism in hypoxic conditions. Vitamin B15 (Pangamovaya Kislota), Svoistva, Funktsii i Primenenie, Akad. Nauk S.S.S.R., Inst. Biokhim. 64-72.

4417. Udalov, Y. F., and N. A. Gaidamakin. 1971. Evaluation of the effectiveness of prolonged vitamin enrichment of the diet (effect on total morbidity). Vop. Pitan. 30(4):43-47.

4418. Ueda, Y. 1972. Nicotinamide adenine dinucleotide metabolism in damaged mice liver, especially in the NAD biosynthesis. J. Kyoto Prefect Univ. Med. 81(1):7-20.

4419. Ulasevich, I. I. 1965. Influence of the water-soluble analog of vitamin K (vicasol) on changes in the sarcoplasmic proteins of muscles developing in vitamin E deficiency. Byul. Eksperim. Biol. i Med. 59(7):54-56.

4420. Umetov, A. 1969. Effect of some vitamins on the growth of rhizosphere microorganisms. Tr. Kirg. Nauch.-issled. Inst. Pochvoved. (2):153-157.

4421. Unger, H. 1959. On the problem of effects of nicotinic acid on the carbohydrate metabolism. Reply to the paper by Haller and Strauzenberg. Z. Ges. Inn. Med. 14:924-926.

4422. Unna, K. 1938. The toxicity and pharmacology of nicotinic acid. Am. J. Physiol. 123:206-207.

* 4423. Unna, K. 1939. Studies on the toxicity and pharmacology of nicotinic acid. J. Pharmacol. Exp. Therap. 65(1):95-103.

4424. Upshall, D. G., J. C. Roger, and J. E. Casida. 1968. Biochemical studies on the teratogenic action of Bidrin and other neuroactive agents in developing hen eggs. Biochem. Pharmacol. 17(8):1529-1542.

4425. Urbaniuk, K. G. 1962. Nicotinic acid in the diagnosis of prethrombotic conditions. Vop. Med. Khim. 8:298-304.

4426. Urbaniuk, K. G. 1965. Blood clotting in hypertension. Belki v Med. i Nar. Khoz., Akad. Nauk Ukr. S.S.R. 111-114.

4427. Utsugi, K. 1965. The effects of nicotinamide on mitosis in regenerating rat liver. J. Fac. Sci. Univ. Tokyo Sect. IV 10(3):451-457.

4428. Utsumi, I., M. Samejima, and H. Kurita. 1961. Chemical determination of nicotinic acid and nicotinamide. J. Vitaminol. 7(3): 209-214.

4429. Utsumi, I., T. Watanabe, K. Kohno, and I. Daira. 1967. Pyridoxal esters. Ger. Pat. 1,811,054.

4430. Uzabekov, M. G. 1962. Controlled changes of biochemical processes in brain. Sb. Nauchn. Tr., Ryazansk. Med. Inst. 15:137-140.

4431. Uzienko, A. B., O. M. Grishin, and A. A. Yasnikov. 1969. Reaction of 1-benzyl-1,4-dihydronicotinamide with nucleophilic agents. Reakts. Sposobnost Org. Soedin 6(3):810-821.

4432. Vaccari, L., and G. Conte. 1951. Insulin and biosynthesis of cozymase. Boll. Soc. Ital. Biol. Sper. 27:1249-1250.

4433. Vacher, M., and O. Tounichon. 1949. Spectrophotometric study of the action of cyanogen bromide on some derivatives of pyridine. Application to the identification and determination of nicotinic acid and amide in a complex mixture. Bull. Soc. Chim. Biol. 31: 1430-1438.

4434. Vaidyanathan, E. P. 1961. Trial of a vasodilator on trophic ulcers. Leprosy Rev. 32:144-149.

4435. Vaishwanar, I., G. G. Jiddewar, R. D. Shukla, and C. N. Kowale. 1972. Effect of nicotinic acid on serum and hepatic lipids in experimentally induced fatty liver. Indian J. Exp. Biol. 20(6): 428-430.

4436. Vajic, B., S. Sibalic, and N. Radej. 1956. Nicotinic acid content of the blood in pellagrins. Intern. Z. Vitaminforsch. 27: 174-181.

4437. Valdivia Alvarez, J., R. S. Mendez, and M. E. Font. 1971. Mycobacterium habana: A probable new species among the unclassified mycobacteria. Bol. Hig. Epidemiol. 9(1):65-73.

4438. Valenzuela, F., and F. Huidobro. 1948. Action of pyridine and some derivative of pyridine-3-carboxylic acid on neuromuscular transmission. J. Pharmacol. Expti. Therap. 92:1-14.

4439. Valeri, C. M. 1943. Relationship between nicotinic acid and thiamine. Klin. Wochenschr. 22:391-392.

4440. Valeri, C. M., and P. Paterno. 1939. Nicotinic acid and gastric chemistry. Boll. Soc. Ital. Biol. Sper. 14:377-378.

4441. Valeri, C. M., G. Conese, and D. Angarano. 1950. Effect of vitamin B1 and nicotinic acid on basal metabolism. Internat. Ztschr. Vitaminforsch. 22:174-179.

4442. Val'ter, L. Y., S. M. Nemets, and Z. M. Sinyakova. 1952. Content of vitamins in canned fish. Rybnoe Khoz. (5):56-59.

4443. Van Beurden, A. J. R. E., and S. Van Beurden. 1940. Treatment of acrodynia with nicotinic acid: the pathogenesis of this disease. Nederland. Tijdschr. Geneesk. 84:4793-4800.

4444. Van Eys, J. 1955. Metabolism of nicotinic acid. Univ. Microfilms 12, 1975, 149pp; Diss. Abstr. 15:1494.

4445. Van Heerden, P. D. R., R. Grieve, and J. Metz. 1966. Fat absorption in pellagrins with observations on the effect of induced diarrhoea. Trans. Roy. Soc. Trop. Med. Hyg. 60(2):241-244.

4446. Van Itallie, P. H. 1967. Hypercholesterolemia and coronary heart disease. Hosp. Pharm. 2:23-25.

4447. Van Nueten, J. M. 1969. Comparative bioassay of vasoactive drugs using isolated perfused rabbit arteries. Eur. J. Pharmacol. 6(3):286-293.

4448. Van Praag, H. M., and B. Leijnse. 1966. Some aspects of the metabolism of glucose and of the nonesterified fatty acids in depressive patients. Psychopharmacologia 9:220-233.

4449. Van Reen, R., and M. Quesada. 1966. Bone nicotinamide adenine dinucleotide levels in response to nicotinamide and parathyroid extract injections. Biochem. Biophys. Res. Commun. 24(1):56-60.

4450. Van Reen, R., and F. E. Stolzenbach. 1957. Pyridine derivatives as growth factors in the duckling. J. Biol. Chem. 226:373-380.

4451. Van Veen, A. G., and R. S. Dhanoedibroto. 1940. Nicotinic acid determinations in the blood of nutritional edema patients in central Java. Geneeskund. Tijdschr. Nederland. Indiee 80:1622-1637.

4452. Varagic, V. M., and M. Zugic. 1971. Interactions of xanthine derivatives, catechol amines, and glucose 6-phosphate on the isolated phrenic nerve diaphragm preparation of the rat. Pharmacology 5(5):275-286.

4453. Varagic, V. M., M. Zugic, and B. B. Mrsulja. 1972. Effect of cyclic N-2-O-dibutyryladenosine 3',5'-monophosphate on neuromuscular transmission and concentration of glycogen in the isolated nerve-diaphragm preparation of the rat. Experientia 28(3):305-306.

4454. Vargas, J. J. 1945. Comparative effect of nicotinic acid, sodium nicotinate, and nicotinamide on isolated rabbit hearts. Rev. Espan. Fisiol. 1:127-149.

4455. Vargas Gomez, E. 1957. Estimation of nicotinic acid in urine of apparently healthy children in Lima. An. Fac. Farm. Bioquim., Lima 8:391.

4456. Vasantha, L. 1970. Histidine, urocanic acid and histidine alpha-deaminase in the stratum corneum in pellagrins. Indian J. Med. Res. 58(8):1079-1084.

4457. Vaschuk, V. V. 1963. Effects of diet and certain drugs on pancreatic juice secretion through a pancreatic fistula. Klinich. Med. 41(7):57-63.

4458. Vasile, N. 1940a. The hemopoietic action of nicotinic acid. Minerva Med. (25):544.

4459. Vasile, B. 1940b. Hematpoietic action of nicotinic acid; experimental study. Pediatria (Riv.) 48:243-259.

4460. Vasko, J., et al. 1963. Anti-atherogenic effects of aluminum nicotinate in the hypercholesterolemic canine. Surg. Forum 14:308-309.

4461. Vasyutochkin, V. M., A. V. Drobintseva, O. N. Borovikova, Z. N. Lebedeva, and O. A. Goryacheva. 1956. Biochemistry of experimental gastritis in light of corticovisceral connections. Fiziol. Zhur. S.S.S.R. 42:192-202.

4462. Vaughan, D. A., and L. N. Vaughan. 1959. The effect of a low environmental temperature on the weight and food consumption of riboflavin-deficient rats. J. Nutr. 68:485-493.

4463. Vaz Pinto, A., and F. Santos. 1969. Ferrous sulphate and ascorbic acid in the treatment of iron-deficiency anaemia. Hospital, Rio de Janeiro 76:2201-2205.

4464. Veghelyi, P., and E. Sass-Kortsak. 1949. Nicotinic acid tolerance test in infants. Orvosi Hetilap, 90:249-251.

4465. Venturi, V. M. 1949. Sulfoconjugation of resorcinol in animals treated with vit. C and the B-vitamins. Arch. Internat. Pharmacodyn. et Ther. 78(4):499-511.

4466. Verdeaux, G., and R. Marty. 1954. Effect on the electroencephalogram of pharmacodynamic substances of clinical interest. Rev. Neurol. 91:405-427.

4467. Vergara Uribe, A. 1954. Fish meal for human consumption; acceptability tests. Arch. Venezolanos Nutricion 5(2):365-375.

4468. Verkhovskaya, P. B., and N. I. Chumakova. 1969. Determination of adenine nucleotides in blood erythrocytes by low-voltage paper electrophoresis. Lab.. Delo (12):729-732.

4469. Verrotti, I. 1940. The effect of vitamin B complex on the morphology of the blood of healthy infants. Pediatrica (Riv.) 48:735-750.

4470. Verrotti, I. 1942. Blood level and the requirement of nicotinic acid in newborn infants. Pediatria (Riv.) 50:20-34.

4471. Verrusio, A. C., D. R. Pollard, and F. C. Fraser. 1968. A cytoplasmically transmitted, diet-dependent difference in response to the teratogenic effects of 6-aminonicotinamide. Science 160(3824):206-207.

4472. Vertua, R., M. M. Usardi, R. Bombelli, T. Farkas, and R. Paoletti. 1964. The effect of nicotinic acid on free fatty acid mobilization. Life Sci. 3(3):281-286.

4473. Vetulani, J., and J. Splawinski. 1967. Metabolic activity of some isoxazole and pyrazole derivatives. Diss. Pharm. Pharmacol. 19(2): 131-140.

4474. Via, L. C., and M. Giannini. 1956. Determination of vitamins A, E, B1, B6, niacin, and C in mixtures. Farmaco (Pavia) Ed. Prat. 11:229-234.

4475. Vidal, A. Z. 1945-1946. Photosensitizing and photoprotector substances. II. Trabajos Inst. Nacl. Cienc. Med. (Madrid) 6:465-474.

4476. Vidal, J., and J. J. Guin. 1962a. The pellagroid triad during treatment with 1314 and its treatment with vitamin PP. Poumon Coeur 18:311-319.

4477. Vidal, J., and J. J. Guin. 1962b. The pellagroid triad during treatment with 1314 and its treatment with vitamin PP. Presse Med. 70(18):900.

4478. Vikrot, O., R. Berlin, and C. O. Oldfelt. 1971. Influence of nicotinic acid on individual plasma phospholipids in hypercholesterolemic subjects. Acta Med. Scand. 190(1/2):133-136.

4479. Villa. 1941. Treatment of liver insufficiency with nicotinic acid and nicotinamide. Klin. Wochenschr. 20:1028.

4480. Villa, L., and N. Dioguardi. 1952a. Is the dinucleotide (codehydrase) form of vitamin PP the unique active one? Arch. Studio Fisiopatol. e Clin. Ricambio 16:238-239.

4481. Villa, L., and N. Dioguardi. 1952b. Factors influencing the respiration of the liver in normal and pathological conditions with reference to clinical symptoms. Atti Soc. Lombarda Sci. Med. e Biol. 7:405-408.

4482. Villa, L., and N. Dioguardi. 1953a. Factors influencing the endogenous respiration of liver homogenate; influence of nicotinamide in the oxidation of acetoacetate. Atti Soc. Lombarda Sci. Med. Biol. 8:376-380.

4483. Villa, L., and N. Dioguardi. 1953b. Action of niacinamide on the O2 consumption by homogenates of rat liver. Experientia 9(12):469.

4484. Villa, L., and N. Dioguardi. 1954. Factors influencing the endogenous respiration of liver homogenate: influence of nicotinamide on the oxidation of acetoacetate by liver homogenate. Arch. Sci. Biol. (Italy) 38:449-462.

4485. Villa, L., and N. Dioguardi. 1955. Studies on factors influencing the endogenous respiration of liver homogenates. The action of nicotinamide on a keto-oxidasic activity of rat's liver. Experientia 11:31-33.

4486. Villa, L., N. Dioguardi, L. Contro, and L. Rossi. 1953. An oxidation system of acetoacetate in the liver of the rat. Atti. Soc. Lombarda Sci. Med. Biol. 8:439-442.

4487. Villaret, M., L. Justin-Besancon, and J. M. Inbona. 1940. Clinical forms of nicotinic acid deficiency (not including pellagra). Bull. Mem. Soc. Med. Hop. Paris 56:619-624.

4488. Villeges, M., R. O. Cravioto, G. Massieu, J. Guzman, and M. L. S. Soto. 1956. The effects of cooking on the content of thiamin, riboflavine, and nicotinic acid in some Mexican foods. Ciencia (Mex.) 16:65-75.

4489. Villela, G. G. 1940. The determination of nicotinic acid (vitamin P-P) in blood. Hospital (Rio de Janeiro) 17(3):431-442.

4490. Villela, G. G., and L. T. Queiroga. 1948. Determination of the nicotinic acid in the blood by the "Proteus" test of Lwoff. O. Hospital 479-486.

4491. Villela, G. G., L. A. Abreu, and R. R. Abreu. 1963. Plasma adenosine deaminase in rats with fibrosarcoma. An. Acad. Brasil. Cienc. 35(1):79-81.

4492. Vilter, R. W., S. P. Vilter, and T. D. Spies. 1939a. Determination of the codehydrogenases I and II (cozymase) in the blood of diabetics in severe acidosis. Am. J. Med. Sci. 197(3):322-326.

4493. Vilter, R. W., S. P. Vilter, and T. D. Spies. 1939b. Relationship between nicotinic acid and codehydrogenase (cozymase) in blood of pellagrins and normal persons. J. Am. Med. Assoc. 112:420-422.

4494. Vilter, S. P., T. D. Spies, and A. P. Mathews. 1938a. Absence of nicotinic acid in the urine of pellagrins and a method for its quantitative estimation. J. Am. Chem. Soc. 60:731-732.

4495. Vilter, S. P. 1938b. Determination of nicotinic acid, nicotinamide- and other pyridine-like substances in human urine. J. Biol. Chem. 125:85-98.

4496. Vilter, S. P., R. W. Vilter, and T. D. Spies. 1939. Synthesis of coenzymes I and II. Nature 144:943.

4497. Vitale, J. J., D. M. Hegsted, and H. McGrath, E. Grable, and N. Zamcheck. 1954. The effect of acetate, pyruvate, and glucose on alcohol metabolism. J. Biol. Chem. 210(2):753-759.

4498. Vincke, E. 1963. Systemic absorption of meso-inositol hexanicotinic acid ester. Arzeimittel-Forsch. 13(8):734-735.

4499. Vinuela, M. F. 1969. The use of vitamins in stomatology. An. Espan. Odontoestomatol. 28(6):502-514.

4500. Virasoro, J. E., and R. Monsoliu. 1943. Habitual vomiting and nicotinic acid. Prensa Med. Argentina 30(7/8):292-297.

4501. Visalli, M., A. Dagianti, F. Lloy, and A. Chiavaro. 1962. The hemodynamic effect of sodium nicotinate in 48 chronic bronchopneumopathic subjects with or without arterial O-2 desaturation. Boll. Soc. Ital. Cardiol. 7:76-80.

4502. Visco, S. 1938. Nicotinic acid and pellagra. Quaderni Nutriz. 5: 321-324.

4503. Vitek, V., M. Vojtechovsky, and K. Rysanek. 1965. Analysis of the effect of amino acids on the central action of L-cycloserine with regard to the metabolism of tryptophan. Antibiot., Advan. Res., Prod. Clin. Use, Proc. Congr., Prague 1964 238-243.

4504. Viteri, F. E. 1967. Studies of the mechanism of action of nicotinic acid as a hypocholesterolemic agents. Diss. Absts. (B) 28:1680B-1681B.

4505. Vitkalenko, L. P. 1963. Effect of radiation on the amino acid content of wheat shoots. Fiziol.-Biokhim. Osnovi Pidvishchennya Produktivnosti Rosliu (Kiev) Sb. 358-360.

4506. Vittoria, A., and E. Ascarelli. 1956. Growth of grasses treated with 3-acetylpyridine, an antivitamin to nicotinic acid. Boll. Soc. Ital. Biol. Sper. 32:270-274.

4507. Vivian, V. M., M. M. Chaloupka, and M. S. Reynolds. 1958. Some aspects of tryptophan metabolism in human subjects. I. Nitrogen balances, blood pyridine nucleotides, and urinary excretion of N1-methylnicotinamide and N1-methyl-2-pyridone-5-carboxamide on a low-niacin diet. J. Nutr. 66:587-598.

4508. Vivian, V. M., M. S. Reynolds, and J. M. Price. 1965. Use of ion-exchange resins for the determination of N1-methylnicotinamide in human urine. Anal. Biochem. 10(2):274-281.

4509. Vivian, V. M., R. R. Brown, J. M. Price, and M. S. Reynolds. 1966. Some aspects of tryptophan and niacin metabolism in young women consuming a low tryptophan diet supplemented with niacin. J. Nutr. 88(1):93-99.

4510. Vodova-Capkova, M., and V. Houbova. 1959. Vitamins and mineral substances in cereals. I. Rye. Sbornik Ceskoslov. Akad. Zemedel. Ved. Rostlinnavyroba 5:1571-1582.

4511. Vogel, E. 1947. Chemistry and physiological action of nicotinic acid. Milchwissenschaft 2:128-133.

4512. Vogt, U. 1962. On the conservative therapy of trigeminal neuralgia. Muenchen. Med. Wschr. 104:1565-1566.

4513. Volpe, F. 1942. On the influence of nicotinic acid on intermediary metabolism of carbohydrates in normal and diabetic subjects. Riforma Med. 58:1232-1237.

4514. Von Bruchhausen, F., H. Herken, H. J. Voss, and H. J. Merker. 1967. Effect of triamterene on insulin-stimulated processes in adipose tissue. Naunun-Schmiedebergs Arch. Pharmakol. 256(4):416-429.

4515. Von Euler, H. 1938. Significance of the vitamins in animal feeding. Kgl. Landtbruks-Akad. Handl. Tid. 77:337-356.

4516. Von Euler, H. 1939. Vitamins in animal metabolism. Forschungen u. Fortschr. 15:372-374.

4517. Von Euler, H., and I. Pettersson. 1941. Observations on the blood of rats with implanted Jensen sarcoma. Z. Krebsforsch. 51: 193-198.

4518. Von Euler, H., B. Von Euler, and I. Saeberg. 1942. The vitamin B group. I. Arkiv Kemi, Mineral. Geol., B15(20):5pp.

4519. Von Euler, H., I. Saeberg, and B. Von Euler. 1941. The influence of hormone preparations on the pyruvic acid content of the blood and the tumor production of sarcoma-bearing rats. Hoppe-Seyler's Zeitschr. Physiol. Chem. 270(3/4):125-140.

4520. Von Euler, H., F. Schlenk, H. Heiwinkel, and B. Hoegberg. 1938. Cozymase and nicotinic acid amid content in animal bodies and in yeast. Hoppe-Seyler's Zeitschr. Physiol. Chem. 256(4/6):208-228.

4521. Vorob'ev, S. P. 1962. Some metabolic disturbances and their significance in the treatment of epilepsy. Sb. Tr. Leningr. Nauchn. Obshchestva Nevropatol. i Psikhiatrov (8):162-174.

4522. Wada, E., T. Kisaki, and K. Saito. 1959. Autoxidation of nicotine. Arch. Biochem. Biophys. 79:124-130.

4523. Waddell, W. R., N. Hurley, and R. A. Field. 1962. Treatment of "idiopathic" hyperlipemia. Metabolism 11:290-301.

4524. Wadsworth, G. L., E. Quesnel, E. C. Murphy, M. Gerson, V. Fish, and P. Nozee. 1943. An evaluation of treatment for senile psychosis with vitamin B complex. Am. J. Psychiat. 99:807-812.

4525. Wagner, J. G. 1969. Biopharmaceutics. 14. Disintegration of dosage forms in vitro and in vivo. Part IV. Drug Intelligence Clin. Pharm. Vol. 3:324-330.

4526. Wagner, J. R., F. M. Strong, and C. A. Elvehjem. 1947a. Effect of commercial canning operations on the ascorbic acid, thiamine, riboflavin, and niacin contents of vegetables. Indust. Engineer. Chem. Indust. Ed. 39(8):985-990.

4527. Wagner, J. R., F. M. Strong, and C. A. Elvehjem. 1947b. Effects of blanching on the retention of ascorbic acid, thiamine, and niacin in vegetables. Indust. Engineer. Chem. Indust. Ed. 39(8): 990-993.

4528. Wahl, M. 1962. Nicotinic acid and its associations in the evolutive courses of atherosclerosis. Presse Med. 70(3):122-124.

4529. Wahlqvist, M. L., L. Kaijser, B. W. Lassers, H. Low, and L. A. Carlson. 1972. Glucocorticoid uptake and release by the human heart: Studies at rest, during prolonged exercise, and during nicotinic infusion. Scand. J. Clin. Lab. Invest. 30(3):261-266.

4530. Wahlstrom, R. G. 1954. The effect of penicillin and B vitamins on the growth of pigs fed different levels of protein. Animal Sci. 13:918-926.

4531. Wahlstrom, R. C. 1957. The value of riboflavine, pantothenic acid, and niacin in rations for growing pigs. Proc. S. Dakota Acad. Sci. 35:97-100.

4532. Wainwright, W. W. 1954. Time studies of the penetration of extracted human teeth by radioactive nicotinamide, urea, thiourea, and acetamide. I. Diffuse penetration from the enamel surface. J. Dental Res. 33(6):767-779.

4533. Wainwright, W. W., and H. H. Belgorod. 1955. Time studies of the penetration of extracted human teeth by radioactive nicotinamide, urea, thiourea, and acetamide. II. Penetration of dentin from the pulp chamber. J. Dental Res. 34(1):28-37.

4534. Waisman, H. A., and C. A. Elvehjem. 1941. Chemical estimation of nicotinic acid and vitamin B6. Indust. Eng. Chem. Anal. Ed. 13: 221-225.

4535. Waisman, H. A., O. Mickelsen, J. M. McKibbin, and C. A. Elvehjem. 1940. Nicotinic acid potency of food materials and certain chemical compounds. J. Nutr. 19(5):483-492.

4536. Wakim, K. G., et al. 1961. The influence of heparin, nicotinic acid and ACTH on experimental nephrosis. Fed. Proc. 20(1 Pt. 1): 184.

4537. Wakim, K. G., B. F. McKenzie, W. F. McGuckin, A. L. Brown, Jr., and A. H. Baggenstoss. 1963. The effects of heparin, nicotinic acid, and ACTH (adrenocorticotropin) on experimental nephrosis. Am. J. Med. Sci. 245:259-276.

4538. Waksmundzki, A., and H. Romanowski. 1954. Epichlorohydrin as analytical reagent for nicotinamide. Acta Polon. Pharm. 11:243-248.

4539. Wal, Y. C., S. L. Perti, and P. N. Agarwal. 1971. Use of antimetabolites for protection of woollen textiles against insect attack. Labdev. J. Sci. Technol. Life Sci. 9B(3):212-220.

4540. Walker, N. E. 1968. Use of yolk-chemical mixtures to replace hen egg yolk in toxicity and teratogenicity studies. Toxicol. Appl. Pharmacol. 12(1):94-104.

4541. Walker, N. E. 1971. Effect of malathion and malaoxon on esterases and gross development of the chick embryo. Toxicol. Appl. Pharmacol. 19(4):590-601.

4542. Walsh, M. P. 1965. Separation and estimation of tryptophan-nicotinic acid metabolites in urine by thin-layer chromatography. Clin. Chim. Acta 11(3):263-267.

4543. Walter, P., and R. J. Piquerez. 1971. Effects of nicotinic acid and beta-pyridylcarbinol on the production of glucose and ketone bodies in the isolated perfused rat liver. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 869-877.

4544. Wang, C.-H. 1966. Redox cleavage of S-S bonds by N-benzyl-1,4-dihydronicotinamide. Hua Hsueh (3):A27-A31.

4545. Wang, C-T., and C. Sun. 1965. Studies on liver cancer. II. Metabolic difference of nicotinamide between patients with liver cancer and normal persons-a simple method for the isolation of N-methyl-2-pyridone-5-carboxyamide from urine. Acta Biochim. Biophys. Sinica 5(1):123-124.

4546. Wang, K.-Y., and C. P. Shen. 1966. Increasing the availability of nicotinic acid in maize. Acta Physiol. Sinica 29(1):97-101.

4547. Wang, Y. L., and E. Kodicek. 1943. Vitamin methods. 7. A new modification of the rho-aminoacetophenone method for estimating nicotinic acid in urine. Biochem. J. 37:530-538.

4548. Waravdekar, V. S., V. G. Mangaonkar, and V. R. Khanolkar. 1950. Vitamin B excretion in oral cancer patients. Acta Unio Intern. Contra Cancrum 6:1017-1022.

4549. Warburg, O., and W. Christian. 1936a. Nicotinamide and lumiflavin. Ber. 69B:228.

4550. Warburg, O., and W. Christian. 1936b. Pyridine, the hydrogen transfer due to fermentation. Helvetica Chim. Acta 19:E79-E88.

4551. Warburg, O., S. Lorenz, and A. W. Geissler. 1971. Influence of vitamin B on the tumor formation in chicken embryos. Ger. Offen. 10 pp.

4552. Warembourg, H., G. Biserte, J. Jaillard, G. Sezille, and P. Scherpereel. 1970. Effect of drugs, which stimulate or inhibit lipolysis on modifications of lipid metabolism induced by alcohol. C. R. Soc. Biol. 164(1):132-136.

4553. Warner, R. G., H. F. Travis, C. F. Bassett, B. McCarthy, and R. P. Abernathy. J. Nutr. 95(4):563-568.

4554. Warren, E. W. 1968. Vitamin requirements of the Coccidia of the chicken. Parasitology 58(Pt. 1):137-148.

4555. Washuetti, J. 1971a. Effect of gamma-radiation on the nicotinic acid content in wheat, wheat flour and bread. Ernaehr.-Umsch. 78(3):95-98.

4556. Washuetti, J. 1971b. Effect of gamma-irradiation on aqueous nicotinic acid and nicotinic acid amide solutions with and without the addition of ascorbic acid. Mikrochim. Acta (3):539-546.

4557. Washuetti, J. 1971c. Identification and quantitative determination of a number of radiolysis products of nicotinic acid after gamma-irradiation. Mikrochim. Acta (3):547-553.

4558. Wasilewski, A. 1971. Clinical-pharmacological determination of the activity of acetic acid-(4-(2-dimethylaminoethoxy)-5-isopropyl-2-methyl-phenyl)-ester hydrochloride (moxisylyt). Arzneim.-Forsch. 21(8):1183-1189.

4559. Watanabe, T. 1960. Transductional studies of thiamine and nicotinic acid requiring streptomycin resistant mutants of Salmonella typhimurium. J. Gen. Microbiol. 22:102-112.

4560. Waterman, R., and L. H. Schultz. 1972a. Nicotinic acid treatment of bovine ketosis. II. Effects on long-chain fatty acid compositions of plasma lipid fractions. J. Dairy Sci. 55(10):1454-1460.

4561. Waterman, R., and L. H. Schultz. 1972b. Nicotinic acid loading of normal cows: Effects on blood metabolites and excretory forms. J. Dairy Sci. 55(10):1511-1513.

4562. Waterman, R., J. W. Schwalm, and L. H. Schultz. 1972. Nicotinic acid treatment of bovine ketosis. I. Effects on circulatory metabolites and interrelations. J. Dairy Sci. 55(10):1447-1453.

4563. Watillon, M., et al. 1972. Harmful effects of common drugs on the visual apparatus. Minor analgesics, antipyretics, nonsteroid anti-inflammatory and antirheumatic drugs. Bull. Soc. Belge Ophtalmol. 160:118-169.

4564. Watrous, W. M., D. G. May, and J. M. Fujimoto. 1970. Mechanism of the renal tubular transport of morphine and morphine ethereal sulfate in the chicken. J. Pharmacol. Exp. Ther. 172(2):224-229.

4565. Waugh, W. H., and T. Kubo. 1969. Renal substrates and effect of lipokinetic arylamines on third-factor sodium excretion. Am. J. Physiol. 217(1):267-276.

4566. Waygood, E. R., D. Mishra, and H. R. Godavari. 1968. Responses of nicotinamide nucleotides to kinins in leaves of Elodea and wheat. Biochem. Physiol. Plant Growth Subst., Proc. Int. Conf. Plant Growth Subst., 6th 1967 1495-1514.

4567. Wayne, L. G. 1965. Some statistical approaches to the establishment of subgroups among Runyon's four major groups of unclassified mycobacteria (growth, Tween hydrolysis test, nitrate reduction, urease test, catalase test, aryl sulfatase test, pigment, niacin). Ist. Super. Sanit. Ann. 1(9/10):620-628.

4568. Weidenheimer, J. F., L. Ritter, and G. Sieger. 1958. Tetracycline antibiotics. U.S. Pat. 3,335,055.

4569. Weiner, M. 1963a. The fibrinolytic response to nicotinic acid in abnormal liver states. Am. J. Med. Sci. 246(3):294-300.

4570. Weiner, M. 1963b. Clot lysis in response to nicotinic acid administered to animals (after bile duct ligation). In: 47th Annual meeting of the Federation of American Societies for Experimental Biology, 1963. Fed. Proc. 22(2 Pt. 1):329.

4571. Weiner, M., W. Redisch, and J. M. Steele. 1958. Occurrence of fibrinolytic activity following the administration of nicotinic acid. Proc. Soc. Exptl. Biol. Med. 98(4):755-757.

4572. Weippl, G., S. Sailer, and H. Braunsteiner. 1961. Behavior of serum iron after nicotinic acid injection in patients with disease of the spleen and after splenectomy. Wiener Z. Inn. Med. 42:77-79.

4573. Weiss, W. 1956. The skin response to a nicotinic acid ester: an acute phase reaction. Nicotinic acid blood levels in relation to the skin response to a nicotinic acid ester ointment. Am. J. Med. Sci. 231:13-19, 20-25.

4574. Weits, J., R. Ten Broeke, J. P. Goddijn, N. Gorin, and G. P. Schuetz. 1971. Betaine, nicotinic acid, and free amino acids in regular and adulterated orange juice. Z. Lebensm.-Unters.-Forsch. 145(6):335-338.

4575. Weitzel, G. 1964. The mechanism of cytostatic action of the methylhydrazines. Z. Physiol. Chem. 336(4-6):271-282.

4576. Weitzel, G., F. Schneider, H. Pfeil, and K. Seynsche. 1963. Cytostatic effect of nitrogen-containing organic peroxides. Z. Physiol. Chem. 331:219-238.

4577. Weitzel, G., F. Schneider, A. M. Fretzdorff, K. Seynsche, and H. Finger. 1963. Further tumor inhibiting compounds. I. Cytostatic effects of N- and S-hydroxymethyl compounds. Z. Physiol. Chem. 334:1-25.

4578. Welch, A. D. 1945. Interference with biological processes through the use of analogs of essential metabolites. Physiol. Rev. 25(4):687-715.

4579. Wender, M. 1971. A contribution to the problem of metabolic seizures. Neurol. Neurochir. Pol. 21(6):899-901.

4580. Wendler, N. L., D. Taub, and C. H. Kuo. 1968. Nicotinamide. U.S. Pat. 3,505,342.

4581. Wenner, W. 1949. The reaction of L-ascorbic acid and D-isoascorbic acid with nicotinic acid and its amide. J. Org. Chem. 14(1): 22-26.

4582. Wenusch, A. 1942. Test for nicotinic acid amide in the urine. Oesterr. Chem. Ztg. 45:87-88.

4583. Wenzel, D. G., and R. E. Nichols. 1965. Interactions of positive inotropic agents and metabolites on the rat ventricle strip. Arch. Intern. Pharmacodyn. 156(1):66-77.

4584. Wertheimer, L., W. Redisch, K. Hirschhorn, and J. M. Steele. 1955. Patterns of surface temperature response to various agents. Circulation 11(1):110-114.

4585. Werthessen, N. T. 1958. Chemical agents capable of affecting lipide metabolism in the aorta. Circulation Res. 6:759-764.

4586. Wertman, K., and J. L. Sarandria. 1951. Complement-fixing murine typhus antibodies in vitamin deficiency states. II. Pyridoxine, and nicotinic acid deficiencies. Proc. Soc. Exptl. Biol. Med. 78(1):332-335.

4587. Wertman, K., L. W. Smith, and W. M. O'Leary. 1954. The effects of vitamin deficiencies on some physiological factors of importance in resistance to infection. I. Niacintryptophane deficiency. J. Immunol. 72(3):196-202.

4588. Wertz, A. W., M. E. Lojkin, B. S. Bouchard, and M. B. Derby. 1958. Tryptophan-niacin relation in pregnancy. J. Nutr. 64:339-353.

4589. Wesley-Hadzija, B., and F. Abaffy. 1957. Photometric method for the determination of isonicotinic acid. Acta Pharm. Jugoslav. 7:137-142.

4590. West, R. 1941. Inhibition by sulfapyridine of the curative action of nicotinic acid in dogs. Proc. Soc. Exp. Biol. Med. 46(3):369-371.

4591. Westerman, B. D., H. Dale, and D. L. Mackintosh. 1956. Effect of treatment of animals before slaughter on B vitamins in pork. J. Am. Dietet. Assoc. 32:1175-1178.

4592. Westerman, B. D., B. Oliver, and D. L. Mackintosh. 1955. Influence of chilling rate and frozen storage on B-complex vitamin content of pork. J. Agr. Food Chem. 3:603-605.

4593. Westerman, B. D., G. E. Vail, G. L. Tinklin, and J. Smith. 1949. B-Complex vitamins in meat. II. The influence of different methods of thawing frozen steaks upon their palatability and vitamin content. Food Technol. 3(6):184-187.

4594. Westermann, K., et al. 1969. Tremor and brain acetylcholine content after arecoline in 5- and 30-day-old chickens. Acta Biol. Med. German 22:677-679.

4595. Wetterau, H., and W. Holzschuh. 1963. Degradation of nonprotein nitrogen compounds in the rumen or grazing ruminants. II. In vitro experiments on urease activity of extracted soybean groats. Arch. Tierernaehr. 13:21-35.

4596. Wiederholt, M., K. Hierholzer, G. Senft, and H. Herken. 1968. Localization of natriuretic action of 6-aminonicotinamide in rat kidney. Naunyn Schmiedebergs Arch. Pharmakol. Exp. Pathol. 261(2): 143-151.

4597. Wiegand, C., and W. I. M. Holman. 1948. Synthesis of derivatives of N-methyl-2-pyridone from nicotinic acid and nicotinamide. Nature 162:659-660.

4598. Wiehl, D. G. 1951. Evaluation of diagnostic signs and therapeutic tests for nutritional deficiency states. Amer. J. Publ. Health 41(8):Pt. II 69-74.

4599. Wieland, O., and W. Guder. 1971. Inhibition of gluconeogenesis in kidney by nicotinic acid. Metab. Eff. Nicotinic Acid Its Deriv. Proc. Workshop 1970, pp. 885-894.

4600. Wilkinson, P. B., and A. King. 1944. Amblyopia due to a vitamin deficiency. Lancet I:528-531.

4601. Willheim, R., and F. C. Bocobo. 1941. Effects of high doses of nicotinic acid on human epidermoid carcinoma. Acta Med. Philippina 2(4):445-465.

4602. Wildhert, E. 1965. Significance of the B vitamins in treatment of hepatic diseases, with special reference to the activity of cyanocobalamine. B. Vitamine, Klin. Physiol. Chem. Probl., Symp., Berlin, pp. 231-235.

4603. Williams, H. L., and E. M. Watson. 1947. The effects of various compounds upon the transamination enzyme activity of rat kidney tissue. Rev. Canadienne Biol. 6(1):43-52.

4604. Williams, J. N. Jr., P. Feigelson, S. S. Shahinian, and C. A. Elvehjem. 1951a. Further studies on tryptophan-niacin-pyridine nucleotide relationships. J. Biol. Chem. 189(2):659-663.

4605. Williams, J. N. Jr., P. Feigelson, S. S. Shahinian, and C. A. Elvehjem. 1951b. Interrelationships of vitamin B6, niacin, and tryptophan in pyridine nucleotide formation. Proc. Soc. Exptl. Biol. and Med. 76(3):441-444.

4606. Williams, M. W., C. S. Williams, B. E. Gunning, and J. C. Towne. 1969. Hyperthyroidism, niacin, and isonicotinic acid hydrazide (INAH): effects on sarcoma 180. Oncology 23(4):308-315.

4607. Williams, R. H., S. A. Little, and J. Ensinck. 1969. Adenyl cyclase and phosphodiesterase activities in brain areas of man, monkey, and rat. Amer. J. Med. Sci. 258:190-202.

4608. Williams, R. J. 1942a. The approximate vitamin requirements of human beings. J. Am. Med. Assoc. 119:1-3.

4609. Williams, R. J. 1942b. Microbiological assay methods. Univ. Texas Pub. No. 4237:7-13.

4610. Williams, R. J., F. Schlenk, and M. A. Eppright. 1944. The assay of purified proteins, enzymes, etc., for "B vitamins". J. Amer. Chem. Soc. 66:896-899.

4611. Williams, W. L. 1946. Yeast microbiological method for the determination of nicotinic acid. J. Biol. Chem. 166:397-406.

4612. Williamson, D. H., F. Mayor, D. Veloso, and M. A. Page. 1971. Effects of nicotinic acid and related compounds on ketone body metabolism. Metab. Eff. Nicotinic Acid Its Deriv. Pro. pp. 227-236.

4613. Willis, R. J., and C. C. Kratzing. 1972. Effect of hyperbaric oxygen and norepinephrine on the level of lung ascorbic acid. Am. J. Physiol. 222:1391-1394.

4614. Wilson, P. J. Jr., and J. H. Wells. 1944. 3-Methylpyridine. U.S. Pat. 2,349,896.

4615. Wilson, R. G., and L. M. Henderson. 1960. Niacin biosynthesis in the developing chick embryo. J. Biol.. Chem. 235:2099-2102.

4616. Wilson, W. L., and G. Fostiropoulos. 1959. Observations on the use of nicotinic acid to induce in vivo fibrinolytic activity. Amer. J. Med. Sci. 138(5):591-597.

4617. Winkelmann, R. K. 1966. Nonallergic factors in atopic dermatitis. J. Allergy 37(1):29-37.

4618. Winkelmann, R. K., M. W. Sams Jr., and D. F. Bohr. 1969. Effect of nicotinate ester, acetylcholine, and other vasodilating agents on cutaneous and mesenteric vascular smooth muscle. Cir. Res. 25(6):687-692.

4619. Wintrobe, M. M., H. J. Stein, R. H. Follis Jr., and S. Humphreys. 1945. Nicotinic acid and the level of protein intake in the nutrition of the pig. J. Nutrition 30(6):395-412.

4620. Wintzerith, M., N. Klein, L. Mandel, and P. Mandel. 1961. Comparison of pyridine nucleotides in the liver and in an ascitic hepatoma. Nature 191:467-469.

4621. Winzler, R. J. 1949. Metabolic inhibitors. Ann. Rev. Biochem. 18:535-558.

4622. Wisniewski, K., J. Moniuszko-Jakoniuk, W. Buczko, and J. Braszko. 1972. Role of activation of fibrinolysis and kininogenesis in tissue penetration of some drugs and changes in their potency. Ann. Med. Sect. Pol. Acad. Sci. 17(3-4):303-312.

4623. Wiss, O. 1950. Microbiological determinations of vitamins and amino acids (Suggestions of the Swiss Food Research Commission). Mitt. Lebensm. Hyg. 41:225-258.

4624. Wissow, L. J. 1952. Nicotinamide. U. S. Pat. 2,617,805.

4625. Witiak, D. T., and M. W. Whitehouse. 1969. Species differences in the albumin binding of 2,4,6-trinitrobenzaldehyde, chlorophenoxyacetic acids, 2-(4'-hydroxybenzeneazo) benzoic acid, and some other acidic drugs. Unique behavior of rat plasma albumin. Biochem. Pharmacol. 18(5):971-977.

4626. Witte, S., H. O. Klein, and H. Gerathewohl. 1965. Simultaneous application of anticoagulants and theophylline nicotinate. Med. Klin. 60(26):1046-1049.

* 4627. Wittenborn, J. R., E. S. Weber, and M. Brown. 1973. Niacin in the long-term treatment of schizophrenia. Arch. Gen. Psychiatry 28:308-315.

* 4628. Wittkopp, T. A., and F. S. Abuzzahab. 1972. Nicotinic acid and nicotinamide adenine dinucleotide (NAD) therapy in schizophrenia. Review. Behav. Neuropsychiat. 4(7-8):6-12.

4629. Wittman, W., et al. 1971. The clinical and biochemical effects of riboflavin and nicotinamide supplementation upon Bantu schoolchildren. S. Afr. Med. J. 45:627-630.

4630. Wituszynska, B. 1968. Group B vitamin levels in two varieties of processed fish products. Gdansk. Tow. Nauk., Rozpr. Wydz. 3(5):173-186.

4631. Wituszynska, B., and M. Telegdy-Kovats. 1968. Some B-group vitamins in Polish canned fish products. Z. Lebensm. Unters. Forsch. 135(6):326-327.

4632. Wheatley, V. R., L. T. Hodgins, and W. Coon. 1970. Cutaneous lipogenesis. I. Evaluation of model systems and the utilization of acetate, citrate, and glucose as compared with other tissues. J. Invest. Dermatol. 54(4):288-297.

4633. Wheeler, H. O., B. L. Reid, T. M. Ferguson, and J. R. Couch. 1961. Vitamin-uptake studies on organisms isolated from crop contents of turkeys with pendulous crop. Poultry Sci. 40: 900-904.

4634. White, F. D., and A. Kerr. 1957. The effect of various denaturants on the haemoglobins adult and cord blood. I. Comparative rates of denaturation. Canadian J. Biochem. and Physiol. 35(5):273-279.

4635. White, F. D., G. E. Delory, K. A. Christie, and E. A. Dudley. 1952. Nicotinamide haemochrome as a derivative for the colorimetric determination of the total haem pigments in blood. Canadian J. Med. Sci. 30(2):136-142.

4636. White, H. S., C. Collazos, P. L. White, R. L. Huenemann, R. Benites, A. Castellanos, Y. Bravo, I. Moscoso, and A. Dieseldorff. 1954. Dietary surveys in Peru. 11. Yurimaguas, a jungle town on the Huallaga River. J. Amer. Dietetic Assoc. 30(9):856-864.

4637. White, I. G. 1954. The effect of some seminal constituents and related substances on diluted mammalian spermatozoa. Australian J. Biol. Sci. 7(3):379-390.

4638. White, J., and D. J. Munns. 1953. Quantitative studies on the importance of nutrilites in yeast production. Am. Brewer 86(5): 29-32.

4639. White, J. H., and A. A. Cinotti. 1972. Streptozotocin-produced cataracts in rats. Invest. Ophthalmol. 11:56-57.

4640. Whitfield, J. F., H. Brohee, and T. Youdale. 1964. Prevention of nuclear changes in irradiated rat thyocytes by nicotinamide. Exp. Cell Res. 36(2):335-340.

4641. Whitfield, J. F., H. Brohee, and T. Youdale. 1965a. The effects of x-radiation on lactate metabolism of mammalian cells. Exptl. Cell Res. 37(3):637-649.

4642. Whitfield, J. F., H. Brohee, and T. Youdale. 1965b. Effects of x-radiation and nicotinamide on the respiration of rat thymocytes. Intern J. Radiation Biol. 9(5):421-427.

4643. Whitfield, J. F., T. Youdale, and H. Brohee. 1965. Effect of nicotinamide on x-irradiated suspension cultures of rat bone marrow cells. Sci. Tech. Aerospace Rept. 3(20):3383.

4644. Whitmore, R. A., A. E. Pollard, H. R. Kraybill, and C. A. Elvehjem. 1946. Vitamin content of dehydrated meats. Food Res. 11(5):419-424.

4645. Woessner, J. F. Jr., B. K. Bachhawat, and M. J. Coon. 1958. Enzymic activation of carbon dioxide. II. Role of biotin in the carboxylation of beta-hydroxyisovaleryl coenzyme A. J. Biol. Chem. 233:520-523.

4646. Woesten, B. C. C. 1947. Rapid recovery of a patient with marginal exfoliative glossitis (Moeller type). Nederland. Tijdschr. Geneeskunde 92:111.

4647. Wolf, H., R. R. Brown, J. M. Price, and P. O. Madsen. 1970. Effect of hormones on the biosynthesis of nicotinic acid from tryptophan in man. J. Clin. Endocrinol. Metab. 30(3):380-385.

4648. Wolf, H., J. M. Price, R. R. Brown, and P. O. Madsen. 1970. Tryptophan metabolism in male subjects treated with progestational agents. Scand. J. Clin. Lab. Invest. 25(3):237-249.

4649. Wolff, L. K. 1937. Position of the vitamins in the series of food constituents. Chem. Weekblad 34:314-317.

4650. Wolff, R., J. P. Nicolas, and G. Linden. 1968. Estimation of vitamin B12 in serum by isotope dilution. C. R. Soc. Biol. 162:514-517.

4651. Wolfram, G., and N. Zoellner. 1971. Blood level of cholesterol in humans under the administration of nicotinic acid and derivatives. Metab. Eff. Nicotinic Acid Its Deriv., Proc. pp. 557-561.

4652. Wollenweber, J., B. A. Kottke, and C. A. Owen, Jr. 1966. Effect of nicotinic acid on pool size and turnover of taurocholic acid in normal and hypothyroid dogs. Proc. Soc. Exp. Biol. Med. 122:1070-1075.

4653. Wollenweber, J., B. A. Kottke, and C. A. Owen, Jr. 1967. Pool size and turnover of bile acids in six hypercholesteremic patients with and without administration of nicotinic acid. J. Lab. Clin. Metab. 69(4):584-593.

4654. Wollish, E. G., M. Schmall, and E. G. E. Shafer. 1951. Determination of small quantities of niacin in presence of niacinamide. Analyt. Chem. 23(5):768-771.

4655. Womack, M., and M. W. Marshall. 1955. Starches, sugars, and related factors affecting liver fat and nitrogen balances in adult rats fed low levels of amino acids. J. Nutrition 57(2): 193-202.

4656. Wood, E. E. 1942. Vitamin assay methods. I. Vitamins of the B complex group. Can. Chem. Process Inds. 26:489-492, 494.

4657. Wood, H. N., A. C. Braun, H. Brandes, and H. Kende. 1969. Distribution and properties of a new class of cell division-promoting substances from higher plant species. Proc. Nat. Acad. Sci. U. S. 62(2):349-356.

4658. Wood, W. B., Jr. 1942. Antibacterial action of the sulfonamide drugs. I.The relation of p-aminobenzoic acid to the mechanism of bacteriostasis. J. Exptl. Med. 75:369-81.

4659. Woodard, J. C. 1970. Effects of deficiencies in labile methyl groups on the growth and development of fetal rats. J. Nutr. 100(10):1215-1225.

4660. Wooley, J. G. 1947. Niacin deficiency in rabbits and response to tryptophane and to niacin. Proc. Soc. Exptl. Biol. and Med. 65(2):315-317.

4661. Wooley, J. G., and W. H. Sebrell. 1945. Niacin (nicotinic acid), an essential growth factor for rabbits fed a purified diet. J. Nutrition 29(3):191-199.

4662. Woolley, D. W. 1947. Water-soluble vitamins. Ann. Rev. Biochem. 16:359-386.

* 4663. Woolley, D. W. 1958. Tranquilizing and antiserotonin activity of nicotinamide. Science 128(3334):1277-1278.

4664. Worden, A. N., C. E. Waterhouse, and H. Partington. 1952. Urinary excretion of vitamin B, riboflavine, and nicotinic acid by the dog. Vet. Record 64:836-840.

4665. Worlledge, S. M. 1969. Immune drug-induced haemolytic anemias. Seminars Hemat. 6:181-200.

4666. Wortis, H., and N. Jolliffe. 1941. The present status of vitamins in nervous health and disease. New York State J. Med. 41(14):1461-1468.

4667. Wright, L. D., J. R. McMahan, V. H. Cheldelin, A. Taylor, E. E. Snell, and R. J. Williams. 1941. The "B vitamins" in normal tissues (autolyzates). Univ. Texas Pub. No. 4137:38-60.

4668. Wronska-Nofer, T. 1968. Effect of nicotinic acid on serum lipid levels in rabbits poisoned with carbon disulfide. Med. Pracy 19(5):426-434.

4669. Wronska-Nofer, T. 1972. The influence of low doses of nicotinic acid upon the development of lipid disturbances in rats chronically exposed to carbon disulphide. Int. Arch. Arbeitsmed. 29(4):285-290.

4670. Wronska-Nofer, T., and J. Sokal. 1966. Colorimetric determination of total nicotinic adid in biological material. Chem. Anal. 11(3):573-578.

4671. Wronska-Nofer, T., and J. Sokal. 1967. Determination of nicotinamide in the biological material. Acta Polon. Pharm. 24:89-94.

4672. Wronska-Nofer, T., R. Gorny, and M. Szyc. 1969. Effect of nicotinamide on serum lipid level in rabbits poisoned with carbon disulfide. Med. Pracy 10(6):565-571.

4673. Wronska-Nofer, T., J. Nofer, and J. Sokal. 1963. Excretion of vitamin PP metabolites in men exposed to carbon disulfide. Med. Pracy 14(6):433-437.

4674. Wu Chang, M. L., and B. C. Johnson. 1962. Metabolism of C14-nicotinic acid in pig and sheep. J. Nutrition 76(4):512-514.

4675. Wulff, V. J., H. Quastler, F. G. Sherman, and H. V. Samis Jr. 1965. Effect of specific activity of cytidine-3H on its incorporation into tissues of young and old mice. J. Gerontol. 20(1):34-40.

4676. Wyatt, W. R. 1939. Differentiation of the vitamins of the B complex and their distribution in certain foods. Iowa State Coll. J. Sci. 14:103-104.

4677. Yadava, J. N. S. 1971. Nutritional studies of Escherichia coli strains. Vitamin requirements and their relation to phage susceptibility, auxotrophy and chemotherapy. Indian J. Med. Sci. 25(7):453-459.

4678. Yakovlev, N. N., and O. P. Zhabotinskaya. 1955. Effect of application of a vitamin mixture (vitamins A, B1, B2, C, D, and niacin) on the working ability and carbohydrate metabolism of active muscles. Voprosy Pitaniya 14(3):9-15.

4679. Yakovlev, T. N. 1970. Pathogenesis of vitamin deficiency in patients suffering from chronic gastritis and peptic ulcer. Klin. Med. 48(5):51-54.

4680. Yago, N., S. Omata, S. Kobayashi, and S. Ichii. 1967. Effects of ACTH and whole-body x-irradiation on the concentrations of enzymes, nicotinamide nucleotides, and cytochromes in rat adrenal. J. Biochem. (Tokyo) 62(3):339-344.

4681. Yamada, M. 1969. A microbiological assay method for niacin by cup-plate technique using Lactobacillus arabinosus. Vitamins, Japan. 39:162-167.

4682. Yamada, S., and S. Kimura. 1971. Intrinsic factor and gastric acidity in nicotinic acid deficient rats. Vitamins (Kyoto) 43(1):27-31.

4683. Yamaguchi, K., S. Sakakibara, K. Koga, and I. Ueda. 1971. Induction and activation of cysteine oxidase of rat liver. I. Effects of cysteine, hydrocortisone, and nicotinamide injection on hepatic cysteine oxidase and tyrosine transaminase activities of intact and adrenalectomized rats. Biochim. Biophys. Acta 237(3):502-512.

4684. Yamaguchi, K., M. Shimoyama, and R. K. Gholson. 1967. Measurements of tryptophan pyrrolase in vivo induction and feedback inhibition. Biochim. Biophys. Acta 146(1):102-110.

4685. Yamaguchi, M., B. Robinson, and J. H. MacGillivray. 1952. Some horticultural aspects of the food value of carrots. Proc. Am. Soc. Hort. Sci. 60:351-358.

4686. Yamamoto, I., Y. Kurogochi, T. Kitamura, H. Nishio, and Y. Tamori. 1958. Effects of nornicotine and thiamine on the autonomic ganglion. Nara Igaku Zasshi 9:36-47.

4687. Yamamoto, R., and S. Kawai. 1970. Stabilization of the color of buffered aspirin tablets. Jap. Pat. 70 02,755.

4688. Yamasaki, H., S. Muraoka, M. Sugiyama, and K. Endo. 1961. Mechanism of histamine-release inhibition by nicotinamide in the in vitro antigen-antibody reaction. Japan J. Pharmacol. 11:54-64.

4689. Yamashita, R. 1961. Blue meat of tuna. Reito 36:1018-1019.

4690. Yarosh, S. I., and V. F. Zhalko-Titarenko. 1971. Nicotinamide preparation. U.S.S.R. Pat. 294,622.

4691. Yaryura-Tobias, J. A., and B. Diamond. 1971. Levodopa-nicotinic acid interaction in psychiatric patients. Schizophrenia 3(3-4): 177-180.

4692. Yasui, S., and M. Banno. 1969. Thiazole nicotinates. Brit. Pat. 1,169,660.

4693. Yokoyama, M. 1932. Behavior of the pyridine group in electrochemical oxidation. III. Nicotine. Bull. Chem. Soc. Japan 7: 103-108.

4694. Yokoyama, R., and K. Sawada. 1972. Nicotinic acid from beta-picoline. Jap. Pat. 72 27,515.

4695. Yoshida, A. 1971. Effect of amino acid supplementation to a rice diet on niacin requirement of rats. Agric. Biol. Chem. 35(12):1943-1949.

4696. Yoshida, K., K. Mori, S. Nagano, H. Nakamura, S. Hori, M. Kato, K. Kojima, T. Hasegawa, and T. Aizawa. 1963. Effect of metabolic activators on experimental cerebrovascular disease. Japan Circulation J. 27(11):783-790.

4697. Yoshida, M., et al. 1966. Studies on the vitamin requirements of poultry. 8. Genetic differences in the requirements for niacin and riboflavin of meat-type and egg-type chicks. Poult. Sci. 45:736-744.

4698. Yoshida, M., and H. Morimoto. 1960. Vitamin requirements for poultry. I. Pyridoxine requirement of White Leghorn chicks. Bitamin (Kyoto) 21:324-328.

4699. Yoshida, M., H. Hosi, and H. Morimoto. 1962. Vitamin requirements of poultry. III. Requirements for vitamins A, D, and E of White Leghorn chicks. Bitamin 25(5):384-389.

4700. Yoshida, M., H. Hoshii, and H. Morimoto. 1963. Vitamin requirements for poultry. V. Requirements of B vitamins, especially of nicotinic acid, for White Rock chicks. Bitamin (Kyoto) 28(3): 225-229.

4701. Yoshida, T., T. Tamagawa, and K. Kogure. 1962. Therapy of peripheral facial paralysis. Naika 10:1077-1078.

4702. Yoshimoto, M. 1959. The antagonistic action of niacinamide and its derivatives to 3-acetylpyridine and its derivatives. Bitamin 17(3):480-484.

4703. Yoshiyama, T. 1958a. Nicotinic acid metabolism in the bone marrow. I. Comparative studies on determination of nicotinic acid and total nicotinic acid contents of hematopoietic organs, particularly the bone marrow in normal rabbits. Naika Hokan 5:163-168.

4704. Yoshiyama, T. 1958b. Nicotinic acid metabolism in bone marrow. III. Total nicotinic acid content of the blood and several organs, especially of the bone marrow of rabbits with bone marrow inhibition, and experiments with nicotinic acid enrichment. Naika Hokan 5:717-727.

4705. Young, W. D. Jr., A. Maslansky, M. S. Lefar, and D. P. Kronish. 1970. Development of a paper strip test for detection of niacin produced by mycobacteria. Appl. Microbiol. 20:939-945.

4706. Younger, F. M., and E. H. Harvey. 1945. Stability of added vitamins in beer. Food Res. 10(5):397-400.

4707. Yu, B. S., and Y. Kyogoku. 1970. Association of a reduced riboflavine derivative with purines, pyrimidines, and nicotinamide. Bull. Chem. Soc. Jap. 43(1):239-245.

4708. Yuditskaya, V. I. 1957. Influence of nicotinic acid on blood coagulation of man. Zdravoorkhr. Belorussi. 1957(3):48.

4709. Yuldasheva, L. S., G. I. Samokhvalov, and M. N. Bekhtereva. 1972. Physiologically active compounds produced by the fungus Blakeslea trispora. Mikrobiologiya 41(1):39-43.

4710. Yun, I. G. 1971. The effect of niacin and tryptophan on the chronic toxicity of carbon tetrachloride in rats. J. Cath. Med. Coll. 20:73-88.

4711. Yurchenko, V. I. 1971. Aspects of protein and nicotinic acid metabolism in experimental thermal burns. Med. J. Zambia 5(5):159-165.

4712. Yushina, G. N. 1971. Electrolyte excretory function of the kidneys in subjects with coronary atherosclerosis. Ter. Arkh. 43(11):37-40.

4713. Zaburkin, E. M. 1972. Pyridoxine and nicotinic acid requirements of athletes. Gig. Sanit. 37(4):103-104.

4714. Zaburkin, E. M., and A. A. Minkh. 1972. Changes of some pyridoxine and nicotinic acid metabolic indices under physical loads. Vestn. Akad. Med. Nauk S.S.S.R. 27(1):60-65.

4715. Zaffiri, O. 1969. Action of analeptics on the heart. Circ. Drugs, Proc. Int. Symp. 1967:299-310.

4716. Zaidi, S. H. 1946. Action of nicotinic acid on the heart of Rana tigrina. Indian Med. Gaz. 81:281-282.

4717. Zaidi, S. H. 1947. Some observations regarding the toxicity of thiamin chloride and nicotinic acid. Indian Med. Gaz. 82(4):181-182.

4718. Zaitseva, N. N. 1968. Glycolytic reduction-oxidation connected with phosphorylation in the extracts of muscles of control rabbits and vitamin E-deficient animals. Vop. Med. Khim. 14(1):67-71.

4719. Zakharova, A. V. 1959. The effect of vitamins on carbohydrate metabolism in muscle homogenate. Uchenye Zapiski 1-go Leningrad. Med. Inst. 3:123-129.

4720. Zakrevskaya, L. E. 1969. Physiological-biochemical changes in the germination of corn kernels with varying hereditary bases. Tr. Khar'kov. Sel'skokhoz. Inst. 78:72-76.

4721. Zaky, A., A. T. A. Malek, and M. Salah. 1963. Effect of certain drugs on blood fibrinolytic activity. Alexandria Med. J. 9:1-12.

4722. Zambotti, V., and F. Mancini. 1941. The elimination of nicotinic acid with the feces and urine in pellagrous and in sound individuals. Ricerca Sci. 12:566-570.

4723. Zanetti, M. E., and D. M. Tennent. 1963. Hormonal hypercholesterolemia in the dog: influence of niacin, niacinamide, benzmalecene, and cholestyramine resin. Proc. Soc. Exptl. Biol. Med. 114(4):991-995.

4724. Zangri, G., and A. Lanza. 1946. Cerebrospinal fluid of healthy children after subarachnoid injection of nicotinic acid. Riv. Pediat. Siciliana 1:330-334.

4725. Zapadnyuk, V. 1970. Combining vitamins with other drugs in geriatric practice. Vrach. Delo (4):90-94.

4726. Zatman, L. J. 1952. Spleen DPNase and mechanism of inhibition by nicotinamide. Fed. Proc. 11:215.

4727. Zatman, L. J. 1952. Spleen DPNase and mechanism of inhibition by nicotinamide. Fed. Proc. 11(1):315-316.

4728. Zatman, L. J., N. O. Kaplan, and S. P. Colowick. 1953. Inhibition of spleen diphosphopyridine nucleotidase by nicotinamide, an exchange reaction. J. Biol. Chem. 200:197-212.

4729. Zaverukha, F. M. 1952. Nicotinic acid in glaucoma. 1952. Vestnik Oftalmol. 31(1):31-35.

4730. Zadyb-Guminska, M., and H. Drozdz. 1958. Distribution of B vitamins in the human brain. Acta Biochim. Polon. 5:311-325.

4731. Zelewski, L. 1964. Citrate synthesis in the kidney and liver of rats treated with nicotinamide and estradiol benzoate. Acta Biochim. Polon. 11(1):25-31.

4732. Zelewski, L., Z. Aleksandrowicz, and C. Dziadul. 1962. The influence of oestradiol benzoate and nicotinamide on citrate excretion in female rats. Acta Biochim. Polon. 9(4):351-355.

4733. Zelinskii, V. G. 1966. Nicotinamide methylation in liver-slices of rats irradiated with x-rays. Ukr. Biokhim. Zh. 38(5):539-542.

4734. Zeller, W., H. Schoen, H. Wuest, U. Anders, and H. P. T. Ammon. 1966. Treatment of hyperlipemic atherosclerosis and liver epithelium fatty degeneration with beta-pyridylcarbinol. Klin. Wochschr. 44(17):1022-1028.

4735. Zemlyans'ka, S. T. 1966a. Nicotinic acid metabolism under a corticosteroid load. In: Information on the Fourth Conference of the Young Scientists of Moldavia: Section of Physiology and Medicine. Kishinev 171-173.

4736. Zemlyans'ka, S. T. 1966b. Colorimetric method for quantitative determination of total nicotinic acid in the blood. Ukr. Biokhim. Zh. 38(3):325-327.

4737. Zemlyans'ka, S. T. 1967. Effect of corticosteroids on nicotinic acid metabolism. Ukr. Biokhim. Zh. 39(1):92-95.

4738. Zenker, D. O., and E. P. Fowler. 1963. Medical treatment of sudden deafness, Meniere's disease, and Bell's palsy. New York J. Med. 63:1137-1143.

4739. Zerkowitz, A., G. Hoppe, and G. Bublitz. 1968. Investigation of the activity of vasoactive drugs by measuring xenon-133 muscular clearance. Nucl.-Med., Supp. 1967 (7):195-200.

4740. Zherebtsov, P. I., A. I. Sointsev, and V. I. Georgievskii. 1957. The influence of nicotinic acid on the metabolism of the animal organism. Izvest. Timiryazev. Sel'skokhoz. Akad. (1):140-144.

4741. Zhukova, S. V., and M. A. Krasheninnikova. 1961. Contents of the six B vitamins in the blood of healthy and tubercular subjects. Tr. Inst. Tuberkuleza, Akad. Med. Nauk S.S.S.R. (11):151-154.

4742. Zicha, B., J. Benes, and J. Hrusovsky. 1968. Effect of radiation on the biosynthesis of pyridine nucleotides in liver of rats pretreated with nicotinamide or nicotinic acid. Stud. Biophys. 12:107-112.

4743. Zilber, Y. A., A. K. Belousova, and G. Y. Dubur. 1970. Effect of the nicotinamide analogues of the folic acid cycle-dependent biosynthetic reaction. Biokhimiya 35(5):879-885.

4744. Zimovshchikov, V. I. 1965. Distribution and acetylation of p-aminosalicylic acid during a combined course of treatment with certain B complex vitamins. Tr. Ryazan. Med. Inst. 26:108-112.

4745. Zinnari, A., F. Sorrentino, and A. Musco. 1965. Influence of theophylline-ethylenediamine and nicotinic acid on the cranial rheogram and the longitudinal rheogram of the limbs. Boll. Soc. Med.-Chir. Catania 33:367-375.

4746. Zirm, K. L., and A. Pongratz. 1960. On the knowledge of new amides and esters of nicotinic acid. Part I. Chemistry and pharmacology of 4-nicotinylaminobenzoic acid-(beta-diethylamino)-ethyl ester monohydrochloride. Arzneimittelforsch. 10:412-414.

4747. Zoellner, N. 1971. Effect of nicotinic acid and derivatives on blood levels of triglycerides of man. Metab. Eff. Nicotinic Acid Its Deriv., Pro. 427-430.

4748. Zoellner, N., et al. 1966. Treatment of hypercholesterinemia with beta-pyridylcarbinol. II. Side effects and discussion. Med. Klin. 61:2036-2040.

4749. Zoni, G., E. Lauria, and C. Scandahato. 1969. Separation and assay of vitamins B1, B12, and AMP in pharmaceuticals. Boll. Chim. Farm. 108:390-393.

4750. Zozaya, J., and J. Zuniga. 1945. Determination of nicotinic acid in some Mexican foods by the microbiological method of Snell and Wright. Rev. Inst. Salubridad y Enferm. Trop. 6(2):91-102.

4751. Zubiran, S., F. Gomez-Mont, and J. Laguna. 1955. Endocrine disturbances and their dietetic background in undernourished in Mexico. Ann. Intern. Med. 42(6):1259-1269.

4752. Zubofskaya, A. M., and D. Purev. 1972. Effect of the cordiamine on the oxidative metabolism of mitochondria of the cerebral cortex in rabbits. Byull. Eksp. Biol. Med. 73(3):54-56.

4753. Zuliani, U., L. Cucurachi, P. Cucurachi, A. Borghetti, G. La Greca, and A. Novarini. 1968. Effects of nicotinic acid on the metabolic pattern of obesity. Ateneo Parmense Sez Acta Bio-Med. 39(5):487-496.

4754. Zundel, J. 1966. Nicotinic acid. Fr. Pat. 1,509,120.

4755. Zureck, A. 1969. Comparative investigations on nicotinic acid metabolism in Mycobacterium bovis strain BCG and M. tuberculosis. Zentralbl. Bakteriol., Parasitenk., Infektionskr. Hyg., Abt. 1: Orig. 212(1):125-136.

4756. Zweifler, A. J., and S. W. Hoobler. 1962. Treatment of hypercholesterolemia with aluminum nicotinate. J. Am. Geriat. Soc. 10:893-896.

4757. Zwilling, E. 1949. Reversal of insulin-induced hypoglycemia in chick embryos by nicotinamide and alpha-ketoglutaric acid. Proc. Soc. Exptl. Biol. Med. 71(4):609-612.

4758. Anon. 1943. Effect of methods of cooking on the thiamin and niacin content of pork. Kentucky Agric. Expt. Sta. Ann. Rept. 56:40-41.

4759. Anon. 1944. Effect of methods of cooking fresh and cured pork, and of canning fresh pork, on the thiamin and niacin content. Kentucky Agric. Expt. Sta. Ann. Rept. 57:48-50.

4760. Anon. 1946. National flour (80% extraction) and bread in Britain. Eighth report from the Scientific Adviser's Division, Ministry of Food. Food Manufacture 21(5):213-215.

4761. Anon. 1957. Enriched rice; definition and standard of identity. Fed. Reg. 22:6887-6888.

4762. Anon. 1959. Comparative cholesterol lowering effects of niacin and dietary lipids. Nutr. Rev. 17:291-293.

4763. Anon. 1960. Niacin and sterol metabolism. Nutr. Rev. 18:342-344.

4764. Anon. 1961a. Bound niacin. Nutr. Rev. 19:240-242.

4765. Anon. 1961b. Nicotinic acid and starvation hypercholesteremia. Nutr. Rev. 19:280-281.

4766. Anon. 1961c. Treatment of hypercholesterolemia with nicotinic acid. Nutr. Rev. 19:325-328.

4767. Anon. 1962. In vitro effect of niacin on biosynthesis of cholesterol. Nutr. Rev. 20:23-24.

* 4768. Anon. 1965a. Association of Official Agricultural Chemists. Official Method of Analyses. Washington, D.C. 957pp.

4769. Anon. 1965b. Fetal death from nicotinamide deficiency. Nutr. Rev. 23:58-59.

4770. Anon. 1965c. The quantitative change in the sulfhydryl groups of protein and of low-molecular compounds in different parts of the brain in white rats given vitamin B12 and nicotinic acid in chronic cadmium poisoning. Tr. Ryazan Med. Inst. 26:59-69.

4771. Anon. 1968a. The learning drugs may fight senility. Am. Druggist 157:35-36.

4772. Anon. 1968b. Effect of nicotinic acid on catabolism and synthesis of cholesterol in man. Clin. Chim. Acta 20(1):43-51.

4773. Anon. 1968c. Macaroni products made with nonfat milk and enriched macaroni products made with nonfat milk; definitions and standards of identity. Fed. Reg. 31:5618-5619.

4774. Anon. 1970a. Treatment of Meniere's disease. Brit. Med. J. 1:98.

4775. Anon. 1970b. Macaroni and noodle products. Identity standards for enriched products; listing of inactive dried torula yeast as optional ingredient. Fed. Reg. 35(14):805-806.

4776. Anon. 1971. Clofibrate in ischemic heart disease. Brit. Med. J. 4:765-766.

4777. Anon. 1972. Combination drug containing meclizine and niacin: notice of withdrawal of approval. Fed. Reg. 37:26455-26456.

4778. Anon. 1973. Niacin and myocardial metabolism. Nutr. Rev. 31:80-81.

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Identification of N'-Methyl-4-pyridone-3-carboxamide in Human Plasma*

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After the oral administration of nicotinamide to human subjects, two ultraviolet-absorbing compounds have regularly been detected on chromatograms of plasma extracts. The less polar of these, named Compound Y, has been identified as N'-methyl-2-pyridone-5-carboxamide (1). In the present communication, evidence is presented that the more polar metabolite, Compound X, is N'-methyl-4-pyridone-3-carboxamide.[1]

EXPERIMENTAL PROCEDURE

Six hundred milligrams of nicotinamide were administered orally to a normal, fasting subject. Three hours later, a pint of venous blood was drawn into a heparinized bottle and immediately centrifuged. One-fortieth volume of 1 N NaOH was added to the plasma, which was then extracted four times with 2½ volumes of chloroform. The chloroform extracts were concentrated, and chromatographed in n-butanol-ammonia on washed Whatman No. 1 paper. Two principal ultraviolet-absorbing spots were observed on the chromatograms. The more polar of these, Compound X, was eluted with methanol. The absorption spectrum in ethanol exhibited a maximum at 258 mμ and a shoulder in the neighborhood of 280 to 285 mμ. In 1 N HCl, the 258-mμ maximum showed a hypsochromic shift to 235 mμ, and the 285-mμ shoulder disappeared. These changes are characteristic of authentic N'-methyl-4-pyridone-3-carboxamide (2). R_F values in n-butanol-water (86:14) and n-butanol-ammonia-water (300:4:46) were 0.52 and 0.55, respectively, identical with the values obtained for the authentic compound. The infrared spectrum, shown in Fig. 1, resembled that of the authentic 4-pyridone, allowing for changes attributed to chromatography, in particular, the failure to resolve the peak at 11.75 μ. This peak was, however, resolved in other spectra of the same material. In addition, Compound X was found to possess an unusual degree of sensitivity to ultraviolet light, giving rise to a fluorescent product both on paper and in ethanolic solution. When an authentic sample of the 4-pyridone became available, its behavior after irradiation proved to be identical. This property will be more fully discussed in a separate communication. Neglecting losses in recovery, we have estimated that the concentration of the 4-pyridone in the plasma sample obtained 3 hours after the ingestion of 600 mg of nicotinamide was approximately 54 μg per 100 ml as calculated from ultraviolet absorption measurements.

* This work was aided by United States Public Health Service Grants A-6064 and A-5012.

[1] Also known as N'-methyl-4-pyridone-5-carboxamide.

DISCUSSION

In 1959, Chang and Johnson (2) isolated from rat urine a nicotinic acid metabolite that had previously been reported in the urine of several species as "Band 4" by Leifer et al. (3), and

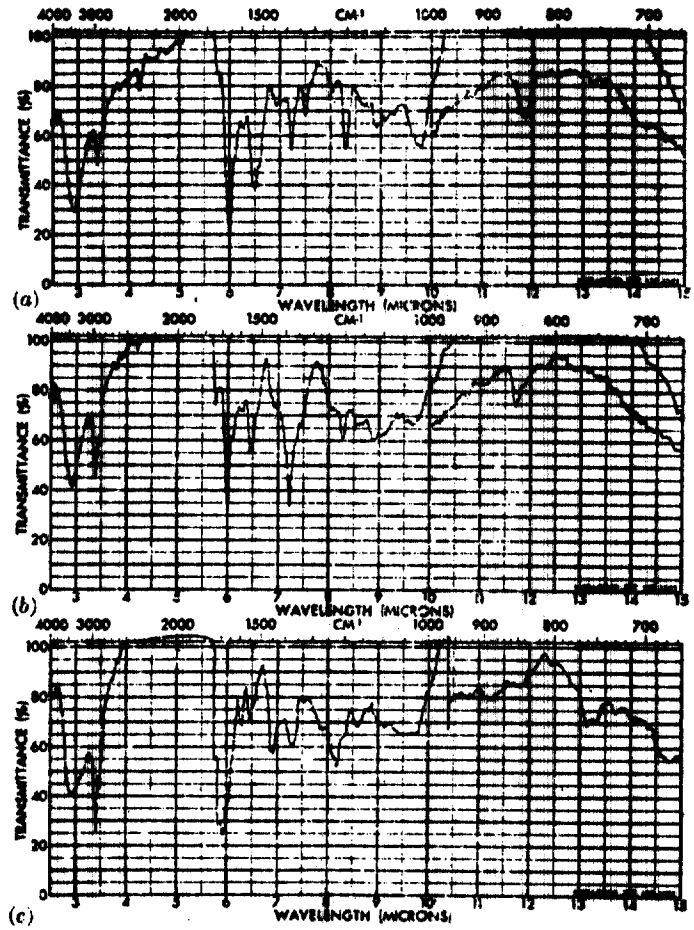

FIG. 1. Infrared spectra in KBr of (a) authentic N'-methyl-4-pyridone-3-carboxamide; (b) N'-methyl-4-pyridone-3-carboxamide after chromatography and elution; (c) Compound X from plasma, after chromatography and elution.

in the urine of rats as "Spot 8" by Lin and Johnson (4). From spectral and other data, Chang and Johnson identified the metabolite tentatively as N'-methyl-4-pyridone 3-carboxamide. Subsequently, they detected the same compound in the urine of man, monkey (5), and pig (6). In 1961, Wieland, Fest, and

Pfleiderer (7) synthesized the 4-pyridone, compared it with the natural product isolated by Chang and Johnson, and found the two to be identical. To our knowledge, this 4-pyridone has not previously been found in the plasma of any species.

Chang and Johnson suggested that in man and the rat, the 4-pyridone arises from the breakdown of pyridine nucleotides and not directly from N'-methylnicotinamide. This conclusion was based on the following evidence.

1. The oral administration of 100 mg of nicotinic acid to human subjects caused only a slight increase in excretion of the 4-pyridone (5).

2. There was no excretion of labeled 4-pyridone after the administration of N'-methylnicotinamide-C^{14} to rats (2).

3. When rats were given nicotinic acid-C^{14}, the excretion of labeled 4-pyridone persisted for several days.

In the monkey, on the other hand, the administration of nicotinic acid-C^{14} leads to prolonged excretion of N'-methyl-2-pyridone-5-carboxamide, which suggests that in this species the latter compound, and not the 4-pyridone, is a product of pyridine nucleotide metabolism.

Recently, nicotinamide N-oxide has been identified in mouse urine (8),[3] and it has been proposed that this substance is also a pyridine nucleotide metabolite. Thus, it appears that the catabolism of pyridine nucleotides may involve oxidation at positions 1, 2, or 4.

[3] Bonavita, Narrod, and Kaplan (8) suggested that "Band 4" of Leifer *et al.* (3) was nicotinamide N-oxide, but inspection of the radioautograms in the latter publication leads us to conclude, in agreement with Chang and Johnson (2), that Band 4 is in fact N'-methyl-4-pyridone-3-carboxamide.

The identification procedures described in the present report were carried out on material isolated from plasma after oral nicotinamide loading. However, traces of ultraviolet-absorbing material are also commonly seen in the same position on chromatograms of plasma extracts from normal subjects not treated with nicotinamide. It is considered that these represent traces of the 4-pyridone, but the amounts are too small to permit positive identification at the present time.

SUMMARY

N'-Methyl-4-pyridone-3-carboxamide has been identified in human plasma after oral administration of nicotinamide.

Acknowledgment—We are grateful for gifts of N'-methyl-4-pyridone-3-carboxamide from Dr. M. L. Wu Chang and Prof. T. Wieland.

REFERENCES

1. Abelson, D., *Federation Proc.*, **21**, 466 (1962).
2. Chang, M. L. W., and Johnson, B. C., *J. Biol. Chem.*, **234**, 1817 (1959).
3. Leifer, E., Roth, L. J., Hogness, D. S., and Corson, M. H., *J. Biol. Chem.*, **190**, 595 (1951).
4. Lin, P. H., and Johnson, B. C., *J. Am. Chem. Soc.*, **75**, 2974 (1953).
5. Chang, M. L. W., and Johnson, B. C., *J. Biol. Chem.*, **236**, 2096 (1961).
6. Chang, M. L. W., and Johnson, B. C., *J. Nutrition*, **76**, 512 (1962).
7. Wieland, T., Fest, C., and Pfleiderer, G., *Liebigs Ann. Chem.*, **642**, 163 (1961).
8. Bonavita, V., Narrod, S. A., and Kaplan, N. O., *J. Biol. Chem.*, **236**, 936 (1961).

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Treatment of Hypercholesterolemia with Nicotinic Acid

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Nicotinic acid was administered orally to 33 patients with hypercholesterolemia in doses varying from 1.5 to 6.0 Gm. per day for periods of 3 months to 1½ years. Significant, sustained, and reproducible decreases in the concentration of cholesterol and total lipids in the plasma and of serum beta-lipoprotein cholesterol were observed in a majority of patients. This form of therapy appears to be effective, practical, and probably free from serious harmful effects.

In 1955 Altschul and co-workers[1] reported a decrease of serum cholesterol in normal and hypercholesterolemic individuals following the ingestion of 1 to 4 Gm. of nicotinic acid over a 24-hour period. Altschul has also described significant decreases of serum cholesterol in hypercholesterolemic rabbits when nicotinic acid was administered for 90 days, and in addition observed that in a majority of animals so treated expected atherosclerotic lesions were either absent or lessened in severity.[2,3]

These interesting observations led us, with Parsons,[4] to investigate the long-term effects of large daily doses of nicotinic acid given orally to persons with hypercholesterolemia. The findings from this preliminary study were sufficiently encouraging to warrant continued investigation employing a greater number of patients over an even longer period. The purpose of this paper is to report our experience to date regarding the use of nicotinic acid as a means of lowering increased concentrations of blood lipids.

Methods

Individuals were selected for this study if their concentration of plasma cholesterol was consistently higher than 250 mg. per 100 ml. before treatment with nicotinic acid.* All those selected were observed as outpatients at the clinic, where they were seen at monthly intervals or more frequently if necessary. At each visit pertinent observations were recorded and necessary examinations made. Upon completing 1 year of treatment, each patient underwent a complete physical and laboratory examination. Each was instructed to continue during the study whichever diet (unrestricted or low in fat) and medications he had employed prior to treatment. Therefore, in each case the only change in management was the addition of nicotinic acid.

Initially, all patients were given 3 Gm. of nicotinic acid daily. This amount was usually taken on the schedule of 2 capsules (1 Gm.)† 3 times daily with meals. Whenever possible, changes in dosage were made only after a study period of at least 3 months in order for the effects of a given dose to become stabilized. After each patient had completed 6 months of treatment, placebo capsules identical in appearance to those containing nicotinic acid were substituted in the same dosage schedule for an additional 3 months. Following this, another 3-month period of nicotinic acid therapy was reinstituted, thus completing a year of study. At this time, a change was made in either the dosage of the drug or the

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*One patient had a pretreatment concentration of plasma cholesterol that averaged 234 mg. per 100 ml.

†The nicotinic acid and placebo preparations were kindly supplied by the Eli Lilly Company, Indianapolis, Ind. Except for the placebo, each capsule contained 0.450 Gm. of nicotinic acid and 0.050 Gm. of lactose. For purposes of calculating total dosage, the approximation of 500 mg. of nicotinic acid per capsule was used.

TABLE 1.—*Decrease in Concentration of Blood Lipids Following Treatment with Nicotinic Acid**

Patients		Study period and change	Plasma cholesterol*	Cholesterol/phospholipid ratio	Total plasma lipids†	Serum beta lipoprotein cholesterol†	Beta/alpha‡ ratio‡
All	With lipoprotein studies						
33	19	Pretreat.	337	1.15	874	238	7.7
		0-3 mo.	282	1.08	729	197	5.1
		% decrease	16	6	17	17	34
21	18	Pretreat.	339	1.09	899	238	7.7
		3-6 mo.	282	1.08	719	203	4.5
		% decrease	17	1	20	15	42
17	16	Pretreat.	322	1.08	809	216	6.5
		6-9mo.(placebo)	322	1.13	824	234	6.0
		% change	0	+4	+2	+8	—8
16	16	Placebo	323	1.15	822	234	6.0
		9-12 mo.	272	1.12	713	182	3.8
		% decrease	16	3	13	22	37

* Values are averages of all determinations on all patients treated for period indicated.
† Concentrations are in milligrams per 100 ml.
‡ Beta-lipoprotein cholesterol/alpha-lipoprotein cholesterol.

content of fat in the diet. The effects of any such change were also observed for 3 months before any additional alteration in management was initiated.

Samples of blood for analysis were obtained at weekly intervals for the first 4 weeks of treatment and every 2 weeks thereafter for the first year. After 1 year, specimens were taken at intervals of 4 weeks. Venipunctures and determination of blood lipids were done in the clinic laboratory as a routine part of the usual work load without special labeling or distinction. This procedure ensured complete separation of clinical management of the patients from determination of the concentration of their blood lipids. Plasma cholesterol was determined by the method of Bloor;[5] plasma phospholipids by the Maclay modification of the Gomori method;[6] and total lipids, by the method of Bloor.[7] Cholesterol in the serum lipoprotein fractions[8] was determined concurrently in 16 patients during the first year of treatment by the procedure previously described.

RESULTS AND COMMENT

At the time of this writing 44 persons have begun the program of study previously outlined. Six individuals have not yet completed 3 months of study. Three additional patients stopped treatment shortly after it was started because of gastrointestinal effects, which will be discussed later. Two other persons moved from the city and subsequently have had infrequent return visits. Data from the remaining 33 patients, who have been observed closely for 3 months or longer, form the basis of this report.*

Effect of Treatment on Concentration of Plasma Lipids. Following the administration of 3 Gm. of nicotinic acid daily for 3 months, the concentration of plasma cholesterol decreased an average of 16 per cent from pretreatment values (table 1). There was also a similar decrease (17 per cent) in the concentration of total plasma lipids, and a lesser decline (6 per cent) in the cholesterol-phospholipid ratio. The various ranges of diminution in concentration of plasma cholesterol are shown in table 2. During the second 3-month period of treatment (3 to 6 months) the decrease in plasma lipids was the same or slightly greater. This improvement may be partly explained by the fact that the average dose of nicotinic acid per person during this second 3-month period was 0.5 Gm. more than the original starting amount. During

*Tabular data on the individual patients are available from the authors to those with special interest in the subject.

the third 3-month period of study (6 to 9 months), when a placebo was administered, concentration of plasma lipids increased so that the average values were remarkably similar to those obtained prior to treatment (table 1). Following the placebo period, treatment with nicotinic acid was reinstituted with the original dose of 3 Gm. per day being used for an additional interval of 3 months, which then completed 1 year of study. The concentration of plasma lipids was again decreased, with the degree of diminution closely approximating that obtained during the initial 3 months of treatment.

Of the 33 patients, 19 had pretreatment concentrations of cholesterol of more than 300 mg. per 100 ml. of plasma. Following treatment for 3 months with nicotinic acid, 13 of these 19 had a decrease in plasma cholesterol of 15 per cent or more, while only 4 of the remaining 14 persons with pretreatment levels of less than 300 mg. had a similar response. This suggests that persons with higher initial concentrations of plasma cholesterol usually obtain a greater response to treatment with nicotinic acid than do those with lower pretreatment levels.

Of the 33 patients treated for at least 3 months, only 1 failed to achieve a decrease in the concentration of plasma lipids; in this instance the levels during treatment were slightly increased from those noted before treatment and during placebo administration. Thus far, 23 patients have maintained concentrations of plasma cholesterol that have averaged less than 260 mg. for at least 1 3-month period of treatment with nicotinic acid.

Effect of Treatment according to Sex, Age, and Diagnosis. An effort was made to determine whether various groups of patients showed significant differences in response to therapy. The women had only slightly higher pretreatment concentrations of plasma cholesterol than did the men, yet their response to treatment was nearly twice as great. Although patients 48 years of age or older had a greater decrease in concentration of plasma cholesterol than did those less than 48, half the older group were women. Hence, the more favorable response to treatment exhibited by the older age group is probably related to the greater proportion of women in this group. The grouping of patients into those with familial hypercholesterolemia, those with disease of the coronary arteries, and those with arterial hypertension did not reveal any significant differences in response to treatment from that obtained by the entire group. As more information was obtained regarding relatives of the patients in this study, more of them could be classed as having familial hypercholesterolemia. It seems likely that if sufficient data were available the hypercholesterolemia of nearly all our patients might be termed "familial," and therefore such distinction serves no useful purpose.

TABLE 2.—*Percentage Decrease in Concentration of Plasma Cholesterol from Placebo or Pretreatment Values Following Therapy with Nicotinic Acid*

Average decrease in plasma cholesterol, %	Patients treated for indicated period with indicated average dose (Gm./day) of nicotinic acid			
	0-3 mo. (3 Gm.)	3-6 mo. (3.5 Gm.)	9-12 mo.* (3 Gm.)	12-15 mo. (5 Gm.)
Increased	1	—	—	—
0–14	16	7	8	2
15–29	13	12	8	5
30–44	3	2	—	4
Total.....	33	21	16	11

* During the third 3-month period (6-9 mo.) a placebo was given.

Effect of Increased Dosage on Concentration of Plasma Lipids. The effects on plasma lipids when the dose of nicotinic acid was increased were studied on 17 occasions, with the results shown in table 3. With the exception of 4 occasions, each increase in the daily amount of nicotinic acid produced a definite further decrease in the average concentration of cholesterol and total lipids in the plasma as compared with values resulting from the lesser dose. Decreases in the cholesterol-phospholipid ratio also occurred, but these were small. As seen in table 2, 48 per cent of all patients treated initially with 3 Gm. of nicotinic acid daily for 3 months obtained

TABLE 3.—*Decrease in Concentration of Plasma Lipids Following Increased Doses of Nicotinic Acid*

Patients	Daily dose of nicotinic acid, Gm.	Plasma cholesterol*		Cholesterol/phospholipids*		Total plasma lipids*	
		Mg./100 ml.	% decrease	Ratio	% decrease	Mg./100 ml.	% decrease
2	0.0	269	—	1.02	—	698	—
	1.5	234	13	0.94	8	612	12
	3.0	217	19	0.92	10	604	13
9	0.0	318	—	1.08	—	807	—
	3.0	282	11	1.08	0	738	9
	4.5	266	16	1.07	1	654	19
6	0.0	378	—	1.20	—	944	—
	3.0	334	12	1.18	2	826	13
	6.0	285	25	1.16	3	670	29

* All values are averages for treatment periods of 3 months.

a lowering of plasma cholesterol by 15 per cent or more. When the average daily dose per person was 3.5 Gm., 67 per cent of the patients achieved a similar decrease in the plasma cholesterol. Following the period of placebo administration, 3 Gm. per day of nicotinic acid was again given for another 3-month period, and again one half of the patients obtained a decrease of 15 or more per cent in the level of plasma cholesterol. Subsequently, an average daily dose of 5 Gm. of nicotinic acid was administered for 3 additional months, which resulted in a reduction in the concentration of plasma cholesterol of 15 or more per cent in 82 per cent of the patients. From these observations it appears that most patients who fail to obtain a satisfactory decrease in cholesterol when treated with nicotinic acid in daily doses of 3 Gm. or less will respond further to increased doses of the drug.

Diet. At the beginning of the study 16 of the 33 patients were eating diets without restriction of fats, 8 avoided "extra fat" in their meals but did not follow any precise diet, 7 were attempting to adhere to diets that contained 40 Gm. or less of fat per day, and 2 were following diets low in calories for reduction of body weight. Although the patients were instructed to continue on these same dietary programs during the study, it became apparent that many did not do so, especially those with diets severely restricted in fat content. Because of these variations in diet and because it was not practical for our patients to eat diets uniform in fat content prepared at a diet kitchen, we could not accurately assess the effect of diet in this study. However, since the pretreatment values for plasma lipids were very similar to those obtained during placebo administration, it is believed that dietary variations did not influence significantly the results obtained. This is supported further by the finding that 16 patients experienced little change in weight during treatment for 1 year, 6 gained a combined total of 37 pounds, 9 lost a combined total of 37 pounds, and 1 had no change.

Effect of Treatment on Concentration of Lipoprotein Cholesterol in Serum. Determinations of lipoprotein cholesterol in the serum were carried out in 19 patients of whom 16 were observed for 1 year (table 1). The percentage decrease of serum beta-lipoprotein cholesterol following treatment with nicotinic acid closely paralleled the percentage decrease of total plasma cholesterol during each period of therapy. Simultaneously, there was a similar percentage increase in the concentration of the serum alpha$_1$-lipoprotein cholesterol. These changes resulted in considerable decrease in the ratio of beta-lipoprotein cholesterol to alpha$_1$-lipoprotein cholesterol, hereinafter referred to as the "beta/alpha$_1$ ratio." Previous data[9] have shown that 95 per cent of normal young women have beta/alpha$_1$ ratios of less than 3.8. This value, or less, was attained during some period of treatment with nicotinic acid in 11 of 18 patients whose ratios were greater than 3.8 before treatment or during placebo administration.

It is clear that further study is needed in order to establish what, if any, practical advantages are to be gained from a knowledge of the serum lipoprotein fractions. Our experience indicates that variations in total plasma cholesterol are nearly always associated with similar changes in the beta-lipoprotein cholesterol, but with the alpha$_1$-lipo-

TABLE 4.—*Symptoms and Signs Occurring with Nicotinic Acid Therapy*

Signs and symptoms		Initial effects, 1–14 days (44 patients)				Late effects (41 patients)	
		Patients	%	Duration, days 1–3	Duration, days 4–14	Patients	%
Cutaneous flushing, burning, and pruritus	Severe	29	66	15	14	1	2
	Moderate	11	25	6	5	5	12
	Mild	4	9	4	0	24	59
	None	0	0	0	0	11	27
Anorexia and nausea		8*	18			3†	7
Increased hair growth (?)		0	0			2	5
Herpes simplex		1	2			1	2
Pityriasis rosea		0	0			2	5
Dry taste in mouth		1	2			1	2

* Three patients stopped study as a result of symptoms.
† One patient had esophagitis which subsided.

protein cholesterol varying in the opposite direction. We believe that an accurate determination of total blood cholesterol is adequate in most instances and offers the most practical method for planning and assessing the results of therapy in patients with hypercholesterolemia.

Symptoms and Signs during Therapy. Symptoms and signs associated with the administration of nicotinic acid are shown in table 4 for all 44 persons who started treatment. The complaints of cutaneous flushing, pruritus, and mild urticaria were noted by all patients at the onset of treatment and were of moderate to marked severity in 91 per cent. An interesting feature of this reaction was the rapid decrease in severity noted by most patients so that after 3 days of treatment only 43 per cent had severe reactions, and after 2 weeks only 14 per cent noted similar effects. Several persons had severe skin flushing and itching with only the first 1 or 2 doses. Of the 30 patients who had persistence of flushing or pruritus after 2 weeks of treatment, 18 experienced this effect only after the first morning dose. Most patients noted that the degree of flushing was lessened considerably by taking the nicotinic acid with meals, and this procedure was usually recommended. Following reinstitution of therapy after administration of the placebo or after lapses in taking the medication, flushing again became prominent and followed the original pattern of reaction. When doses of nicotinic acid were increased there was rarely any increase in flushing, and 6 persons flushed less while taking the increased dose. In no instance was treatment with the drug discontinued because of these cutaneous side-effects.

Anorexia, nausea, and occasionally frequent soft stools were complained of by 18 per cent of the patients during the first 2 weeks of nicotinic acid therapy. Three women felt that these complaints were sufficiently disagreeable to discontinue treatment altogether. After 2 weeks of therapy only 3 additional people (7 per cent) experienced gastrointestinal complaints to any appreciable degree, and therapy was not stop-

ped in these instances. In 1 woman who had a previously known diaphragmatic hernia, esophagitis developed while she was taking 6 Gm. of nicotinic acid daily, but this subsided following appropriate treatment and reduction of the medication to 4.5 Gm. per day.

Herpes simplex, pityriasis rosea, and a questionable increase in growth of facial hair were noted in 2 instances each during the treatment period, but these could not be definitely attributed to therapy with nicotinic acid.

While receiving treatment with nicotinic acid many patients reported subjective improvements in well-being which were not observed during the period of placebo administration, but there did not appear to be any consistent relationship between subjective reactions and objective findings. It is apparent that the taking of a drug with such an obvious effect on the patient (cutaneous flushing and itching) as well as the continued interest shown by sympathetic physicians must exert a considerable psychologic effect. For this reason it is difficult to make any firm conclusions based on subjective evaluation. With this in mind, it can be said that none of the patients with angina pectoris had any increase in their symptoms while being treated with nicotinic acid, and most of them considered that they were improved in this regard. In contrast, it must be pointed out that 1 patient sustained an acute myocardial infarction during treatment. He has continued to take the drug, however, and his recovery has been uneventful. Two additional patients died suddenly and unexpectedly while taking the placebo following 6 months of therapy with nicotinic acid. Necropsy revealed extensive coronary atherosclerosis as the cause of death in both patients. It seems unlikely that treatment with nicotinic acid had any part in the deaths of these patients, but the possibility cannot be entirely excluded.

After 1 year of study all patients underwent a complete physical and laboratory examination including electrocardiograms and tests of hepatic and renal function in a further attempt to evaluate the effects of treatment with nicotinic acid. No untoward results were noted.

Mechanism of Action. The mechanism by which nicotinic acid reduces the concentration of blood lipids is not known. Altschul and co-workers have suggested that intracellular oxidation might be enhanced with a greater formation of oxycholesterols, and that this form may be more readily excreted than cholesterol.

Summary

On the basis of our observations on 33 patients with hypercholesterolemia, it appears conclusively established that in most instances large doses of nicotinic acid administered orally for periods of 3 months to 1½ years significantly decrease the concentration of plasma cholesterol, total lipids, and serum beta-lipoprotein cholesterol. This decrease can be maintained for periods exceeding 1 year, but disappears when treatment is stopped. The degree of response to treatment varies widely but is reasonably reproducible for each individual.

A distinct relationship between dose and effect has been demonstrated for individual patients as well as for the group in which changes in dose were studied. Increasing the daily dose of nicotinic acid resulted in further lowering of concentration of the blood lipids from those values obtained following administration of a lesser dose. This result was reversed when the amount of nicotinic acid was decreased. By using nicotinic acid in amounts of 3 Gm. per day and by increasing this dose as needed, three fourths or more of patients with hypercholesterolemia obtained a satisfactory decrease of their blood lipids. Thus far, 6 Gm. of nicotinic acid daily is the largest amount we have used.

Those persons with higher initial concentrations of cholesterol in the plasma usually obtained a greater response to treatment than did those whose values were lower before treatment. As a group, women had a considerably better result than did men. The

diets of the patients were not changed during the study, and the data suggest that diet remained a rather constant factor which did not appreciably influence the results.

Side reactions to treatment, while frequent, did not create any marked problems of management. Severe cutaneous flushing and pruritus occurred in nearly all patients when treatment with nicotinic acid was started, but this usually subsided rapidly. Many persons experienced mild flushing subsequently, but this did not constitute an appreciable limitation to therapy. Anorexia and nausea occurred much less frequently than did the cutaneous effects, but were sufficiently disagreeable in 3 women to cause them to discontinue treatment permanently. Thorough physical and laboratory examinations revealed no evidence of other untoward effects from treatment.

Nearly all patients experienced subjective improvement in well-being that seemed unrelated to any objective findings. No increase in severity of angina pectoris was noted by patients who had this symptom, and many experienced less angina during treatment. Two patients died suddenly as a result of atherosclerotic heart disease during the period of placebo administration, and another sustained an acute myocardial infarction while on treatment with nicotinic acid. Therefore, while this form of treatment appears safe, further observations will be necessary to verify this impression.

It is not within the scope of this paper to discuss whether or not therapy designed to lower abnormally increased concentrations of blood lipids is an effective form of treatment or prophylaxis for atherosclerosis. However, if such a goal is desired, then large oral doses of nicotinic acid appear to offer yet another means by which blood lipids may be decreased. In our experience this method has been highly effective, very practical to carry out, and is probably quite safe. Further investigation, especially comparative studies with other forms of therapy, is needed before the proper role can be assigned to such use of nicotinic acid.

SUMMARIO IN INTERLINGUA

Super le base de nostre observationes in 33 patientes con hypercholesterolemia, il pare definitivemente establite que in le majoritate del casos grande doses de acido nicotinic administrate oralmente durante periodos de inter 3 menses e 1½ annos effectua reductiones significative in le concentration del cholesterol in le plasma, del lipidos total, e del cholesterol de lipoproteina beta in le sero. Iste reduction pote esser mantenite durante periodos de plus que un anno, sed illo dispare quando le tractamento es interrumpite. Le grado del responsa al tractamento varia grandamente ab un patiente al altere, sed illo es satis reproducibile in un subjecto individual.

Un distincte relation inter le magnitude del dose e su effecto esseva demonstrate in patientes individual e etiam in gruppos in que variationes de dosage esseva studiate. Augmentos del dose diurne de acido nicotinic resultava in reductiones additional del concentration de lipidos del sanguine in comparation con le valores jam obtenite per le administration de doses plus micre. Iste resultato se reverteva quando le quantitate del acido nicotinic administrate esseva reducite. Per le uso de acido nicotinic in doses de 3 g per die, sequite per augmentos de dosage in tanto que indicate, tres quartos o plus del patientes con hypercholesterolemia obteneva reductiones satisfactori del lipidos in lor sanguine. Usque al tempore presente, 6 g de acido nicotinic per die es le maximo unquam usate.

Patientes con plus alte concentrationes initial de cholesterol in lor plasma obteneva usualmente plus pronunciate responsas sub le tractamento, comparate con patientes in qui le valores esseva minus elevate ante le institution del therapia. Considerate como gruppo total, feminas monstrava considerabilemente melior resultatos que homines. Le dieta del patientes non esseva alterate durante le tractamento. Le datos colligite reflecte le facto que le dieta esseva un factor satis constante que non exerceva ulle considerabile influentia super le resultatos.

Le reactiones lateral provocate per le tractamento esseva numerose sed non representava major problemas therapeutic. Sever grados de rubor cutanee con prurito occurreva in quasi omne la patientes quando le tractamento con acido nicotinic esseva initiate, sed in le majoritate del casos iste phenomeno subsideva rapidemente. Minus pronunciate grados de rubor esseva experienciate subsequentemente per multes del patientes, sed isto non constitueva un serie obstaculo al therapia. Anorexia e nausea occurreva multo minus frequentemente que le effectos cutanee, sed illos esseva sufficientemente disagradabile pro inducer le patiente a interrumpér le tractamento permanentemente in non plus que 3 casos. In omne istos il se tractava de feminas. Meticulose examines physic e laboratorial revelava nulle signo de altere effectos adverse de iste forma de tractamento.

Quasi omne le patientes experientiava un melioration subjective de ben-esser que pareva esser sin relation a ulle constatation objective. Nulle augmento del severitate de angina de pectore esseva notate per patientes qui habeva iste symptoma, e multes experientiava minus angina durante le curso therapeutic. Duo patientes moriva subitemente in consequentia de atherosclerotic morbo cardiac durante un periodo de administration de un medicina fictitie. Un altere patiente suffreva un acute infarcimento myocardial durante le curso de acido nicotinic. Per consequente, ben que il pare que iste forma de tractamento es disproviste de risco, observationes additional es requirite pro confirmar iste impression.

Il non es parte del objectivos del presente reporto de discuter si o non un therapia que visa a reducer anormalmente alte concentrationes de lipidos in le sanguine es un efficace forma de therapia o de prophylaxe contra le occurrentia de atherosclerosis. Tamen, si le effectuation de tal reductiones es desirate, grande doses de acido nicotinic representa apparentemente un medio additional pro reducer le nivello del lipidos in le sanguine. In nostre experientia iste methodo ha essite efficacissime, multo practic in su application, e apparentemente satis libere de risco. Investigationes additional, specialmente studios comparative con altere formas de therapia, es requirite ante que le rolo definitive de iste maniera de usar acido nicotinic pote esser determinate.

REFERENCES

1. Altschul, R., Hoffer, A., and Stephen, J. D.: Influence of nicotinic acid on serum cholesterol in man. Arch. Biochem. **54**: 558, 1955.
2. —: Die Beeinflussung des Blutcholesterinspiegels und der experimentellen Atherosklerose durch Nikotinsaure. Ztschr. Kreislaufforsch **45**: 573, 1956.
3. —: Influence of nicotinic acid on cholesterol metabolism. Abstracted, Circulation **14**: 494, 1956.
4. Parsons, W. B. Jr., Achor, R. W. P., Berge, K. G., McKenzie, B. F., and Barker, N. W.: Changes in concentration of blood lipids following prolonged administration of large doses of nicotinic acid to persons with hypercholesterolemia: Preliminary observations. Proc. Staff Meet., Mayo Clin. **31**: 377, 1956.
5. Bligh, W. R.: The determination of cholesterol in blood. J. Biol. Chem. **24**: 227, 1916.
6. Maclay, E.: Two clinical procedures of interest to the medical technologists: With adaptation to the Coleman spectrophotometer. Am. J. M. Tech. **17**: 265, 1951.
7. Bligh, W. R.: The determination of small amounts of lipid in blood plasma. J. Biol. Chem. **77**: 53, 1928.
8. Boyd, G. S.: The estimation of serum lipoproteins: A micromethod based on zone electrophoresis and cholesterol estimations. Biochem. J. **58**: 680, 1954.
9. Barker, N. W., Brandenburg, R. O., and McKenzie, B. F.: Unpublished data.

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The Effect of Nicotinic Acid Upon Serum Cholesterol and Upon Basal Metabolic Rate of Young Normal Adults[1]

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Introduction

In 1955 and 1956, we reported that relatively large doses of nicotinic acid, larger at any rate than given previously for the treatment of pellagra, mental disorder, or peripheral vascular disorder, lowered significantly the serum cholesterol in humans and rabbits (1, 2). Moreover, when given to rabbits over periods of 3 months together with cholesterol, the arteriosclerotic changes which may be expected if no nicotinic acid is given, were absent in nine animals, mitigated in six, and fully developed in two. Later, Parsons, Jr. *et al.* (3) confirmed and elaborated on our findings in humans. They examined also the total lipids and the ratio of β- to α-lipoproteins and found a decrease in a majority of cases. Their patients were treated for periods of 4–12 weeks (and, according to recent personal communications, still longer). In their report, Parsons, Jr. *et al.* stated that these large doses did not cause an increase in pulse rate or blood pressure. In some cases, there were side effects in the form of flushes, urticaria, and nausea, which in almost all cases disappeared without ill effect and only in one case necessitated the discontinuation of the treatment.

This method of decreasing serum cholesterol is of considerable interest in the study of arteriosclerosis and deserves further study. In the present investigation, we studied whether or not large doses of nicotinic acid will influence the basal metabolic rate and whether or not the administration of these quantities over periods longer than 1 day, reported by us i...

[1] This work was supported by grants from the Rockefeller Foundation and from the Teaching and Research Fund, College of Medicine, University of Saskatchewan.

1955, will maintain the cholesterol at the reduced levels. We also examined the relationship of body weight to dosage in order to learn whether in future work the dosage ought to be adjusted according to body weight. Finally, we examined the relationship of cholesterol levels before, during, and after treatment to find out whether or not a hypocholesterolemic effect of nicotinic acid is obtained in cases with low initial serum cholesterol.

Experimental and Results

Twelve students volunteered for this test, two being female and ten male. Their age ranged from 22 to 29 years, the mean age being 24 years. Nicotinic acid at a dose of 3 g./day was given for 14 days. Before, during and after this treatment, fasting serum cholesterol was determined in duplicate by the Schoenheimer-Sperry method modified by McArthur, and the basal metabolic rate was determined.

Each volunteer received the following schedule of testing and treatment:

Day 1, basal metabolic rate (BMR).

Day 7, BMR.

Day 8, BMR, blood sample for cholesterol determination. Treatment started.

Day 12, blood sample for cholesterol determination.

Day 16, BMR, blood sample for cholesterol determination.

Day 19, blood sample for cholesterol determination.

Day 22, BMR.

Day 23, BMR, blood sample for cholesterol determination. Treatment discontinued.

Day 27, blood sample for cholesterol determination.

Day 30, BMR, blood sample for cholesterol determination.

The initial basal metabolic rate (BMR) was not included in the calculations. It was given in order to accustom the volunteer to the BMR procedure. When a blood sample was drawn on the same day as the BMR, it was done within 5–10 min. after completion of the BMR. The results are shown in Tables I, II and III.

There was a marked and significant decrease in cholesterol level by the eighth day after starting the treatment. At the end of this period, the BMR was elevated significantly but moderately (for increase in BMR: $t = 2.44$, $P = 0.03$). The increase, however, is not sufficiently great to postulate a thyroidlike effect of nicotinic acid. The decrease in cholesterol was correlated positively with the initial level. The partial correlation of decrease in level of serum cholesterol against initial level of serum cholesterol was 0.60 ($t = 2.4$).

The decrease in cholesterol is positively correlated with initial cholesterol level and negatively correlated with body weight when the

TABLE I

The Effect of Nicotinic Acid upon Serum Cholesterol

Subject	Body weight	Cholesterol level, mg./100 ml.						
		Before treatment	After treatment				After discontinuing treatment	
			4th day	8th day	11th day	15th day	4th day	7th day
	lb.							
1	72	297	312	225	270	179	243	273
2	127	206	180	155	174	148	191	217
3	148	203	205	179	194	169	210	204
4	150	174	160	144	150	129	173	166
5	152	200	200	160	168	146	191	174
6	156	170	178	152	180	170	184	160
7	158	200	213	182	191	161	204	190
8	166	235	255	207	234	200	254	228
9	167	200	182	165	173	151	177	169
10	170	177	185	157	169	155	195	187
11	171	202	228	179	158	148	202	173
12	197	197	188	157	172	173	194	207
Mean		205	207	172	186	161	202	198

TABLE II

The Effect of Nicotinic Acid upon BMR

Subject	Basal metabolic rate					
	Before treatment		During treatment			After discontinuing treatment
	1st day	2nd day	8th day	14th day	15th day	7th day
1	−12	0	12	7	−6	+5
2	−24	−20	−8	−12	−9	−9
3	−13	−6	+1	−4	−2	−5
4	−14	−10	+2	+6	−5	−3
5	+1	−1	−1	−14	−1	−9
6	−1	−5	0	+5	+4	−2
7	−18	−11	6	+3	+3	+4
8	−15	−15	−2	+3	+3	−7
9	−12	−12	−12	−13	−1	−5
10	+1	−9	−6	−10	−13	+6
11	0	−11	−13	−5	+1	−7
12	−23	−14	−12	−3	−16	−9
Mean	−10.0	−9.5	−3.75	−3.1	−3.5	−3.4

TABLE III

The Relationship between Body Weight and Cholesterol Response

Weight range	Number	Mean weight	Mean initial cholesterol level	Change	
				Found	Expected from initial cholesterol level[a]
lb.		*lb.*	*mg./100 ml.*	%	%
72	1	72	207	−40	−28
127–150	3	142	194	−23	−15
152–166	4	158	201	−16	−17
167–197	4	176	194	−19	−15

[a] Hoffer and Callbeck.[3]

Equation: expected decrease = 0.52 × initial value (mg.) − 71.

dosage of nicotinic acid is 3 g./day for a group of younger schizophrenic patients[2] and for a group of older schizophrenics and arteriosclerotic patients.[3] In both of these studies[2, 3] the actual decrease in cholesterol for body weights below 150 lb. was greater than would be expected on the basis of the regression equation relating decrease in cholesterol to initial cholesterol level. Apparently this also held for this small series of normals where again, when the body weight was below 150 lb., the actual decrease was greater than would be expected. The following equation relates decrease in cholesterol level, initial level and body weight.

$$\text{Decrease} = (0.95 \times \text{initial level}) - (0.39 \times \text{body weight}) - 90$$

In Table III, we have set aside one female volunteer with a very low body weight and a very high initial cholesterol level. When this is done, there is no apparent relationship of body weight to initial cholesterol levels.

There is thus a closer relationship between dosage in relation to body weight and cholesterol reduction than foreseen. In other words, doses of 3 g./day are apparently more effective in persons of lower body weight. The change in BMR for any individual was not related to the variations in cholesterol levels.

A few days after termination of treatment, the cholesterol levels returned to pretreatment levels. The BMR at the same period was still

[3] Hoffer, A., and Callbeck, M. J., personal communication, 1957.

[3] O'Reilly, O., Demay, M., and Kotlowski, K., personal communication, 1957.

slightly increased over initial values. Because of the relationship between body weights and response, it might be desirable in the future to pay attention to the relation between dosage and body weight.

Acknowledgments

Merck & Co. provided the nicotinic acid. The basal metabolic rates were determined in the Pathological Laboratory, University Hospital, Saskatoon; Director, Dr. D. F. Moore.

Summary

Nicotinic acid in relatively large doses (3 × 1 g. daily) lowered the serum cholesterol in eleven out of twelve healthy medical students. The basal metabolic rates increased slightly but significantly. It seems that the relative response of cholesterol levels to nicotinic acid is related to the dosage in terms of body weight as well as to the initial cholesterol level. With dosage constant in terms of weight, the response may depend upon the initial cholesterol levels.

References

1. Altschul, R., *Z. Kreislaufforsch.* **45**, 573–6 (1956).
2. Altschul, R., Hoffer, A., and Stephen, J. D., *Arch. Biochem. Biophys.* **54**, 558–9 (1955).
3. Parsons, W. B., Jr., Achor, R. W. P., Berge, K. G., McKenzie, B. F., and Barker, N. W., *Proc. Staff Meetings Mayo Clinic* **31**, 377–90 (1956).

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Use of Nicotinic Acid in Hypercholesteremia

The Council was requested to evaluate the usefulness and safety of large oral doses of the vitamin, nicotinic acid (Niacin), for the treatment of hypercholesteremia. The rationale for such use of the drug stems from the statistical relationship which is commonly accepted to exist between elevated serum cholesterol levels and the clinical manifestations of atherosclerosis. There seems to be little doubt that nicotinic acid, when given in large doses to hypercholesteremic subjects, will frequently bring about a marked reduction in cholesterol levels; the lowering of cholesterol is less impressive in subjects with normal or near normal levels. Theoretically, sustained reduction of circulating cholesterol levels appears to be desirable. However, to date, there is no valid evidence that lowered blood cholesterol levels cause clinical improvement of the patient. Although the large doses of nicotinic acid (3 to 6 Gm. per day) employed for the treatment of hypercholesteremia have not been associated with serious toxic effects, the possibility of adverse reactions should be kept in mind. Pending the accumulation of evidence to show a bona fide beneficial effect in patients, either from the viewpoint of prophylaxis or therapy of atherosclerotic cardiovascular disease, the use of nicotinic acid for purposes other than the prevention or treatment of pellagra must be considered experimental.

The Council voted to expand New and Nonofficial Drugs to describe the use of nicotinic acid in hypercholesteremia.

Eli Lilly & Company cooperated by furnishing scientific data to aid in the evaluation of this additional use of nicotinic acid.

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THE EFFECT OF NICOTINIC ACID ON GLYCOLYTIC CARBOHYDRATE BREAKDOWN IN THE LIVER

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Nicotinic acid is one of the drugs which by diminishing the mobilisation of depot fat decrease the levels of free fatty acids (FFA) in the plasma (1).As the FFA are source of energy in various organs,especially the skelettal muscle and the liver, carbohydrates were supposed to be metabolized to a greater extent after the administration of nicotinic acid because of the reduced availability of FFA (2).

Therefore we investgated the influence of 2oo mg/kg nicotinic acid on the glycolytic carbohydrate breakdown in the liver of white mice by determining the contents of : glycogen,glucose-6-P, fructose-1,6-P_2,dihydroxyacetone-P,1-glycerol-P,pyruvate,lactate and glucose in the liver,because the stationary contents of these metabolites may indicate an accelerated respectively diminished carbohydrate breakdown.

Besides we investigated the glycogen content of the brain,the skelettal muscle and the adipose tissue.

Materials and Methods

All experiments were performed on male NMRI-mice which had free access to standard diet Altromin (Altromin GmbH Lage/Lippe) and tap-water before and during the experiments and which were

caged at 25°C environmental temperature. The animals were killed 1,2 or 4 hours after i.p. administration of 2oo mg/kg nicotinic acid (Na-salt) by freezing in liquid air. Animals that had not been treated were used as a control.

The brain, the liver and the muscular tissue from the hind legs were prepared while still being frozen. The adipose tissue was prepared within 15 sec after the breaking of the neck and put into liquid air. Blood samples were taken from the tail before the sacrificing of the animals.

Analyses were made in accordance with the following methods: Glycogen according to Kemp and Kits van Heijningen (3), pyruvate according to Bücher (4), lactate according to Scholz et al., fructose-1,6-P_2 and dihydroxyacetone-P according to Bücher and Hohorst (6), 1-glycerol-P according to Hohorst (7), glucose-6-P according to Hohorst (8) and glucose according to Huggett and Nixon (9).

The values presented in the figures are means and their standard errors calculated from 1o-15 single determinations. The results were checked by means of the Student's t-test and differences between treated and not treated animals were regarded as significant, if $P \leq o,o5$.

Results and Discussion

1,2 and 4 hours after the administration of nicotinic acid, the glycogen content of the liver is diminished, while the glucose-6-P content did not change. The fructose-1,6-P_2 content of the liver is raised significantly after 2 hours as well as the content of dihydroxyacetone-P after 2 and 4 hours and the content of pyruvate after 1 and 2 hours. The content of 1-glycerol-P in

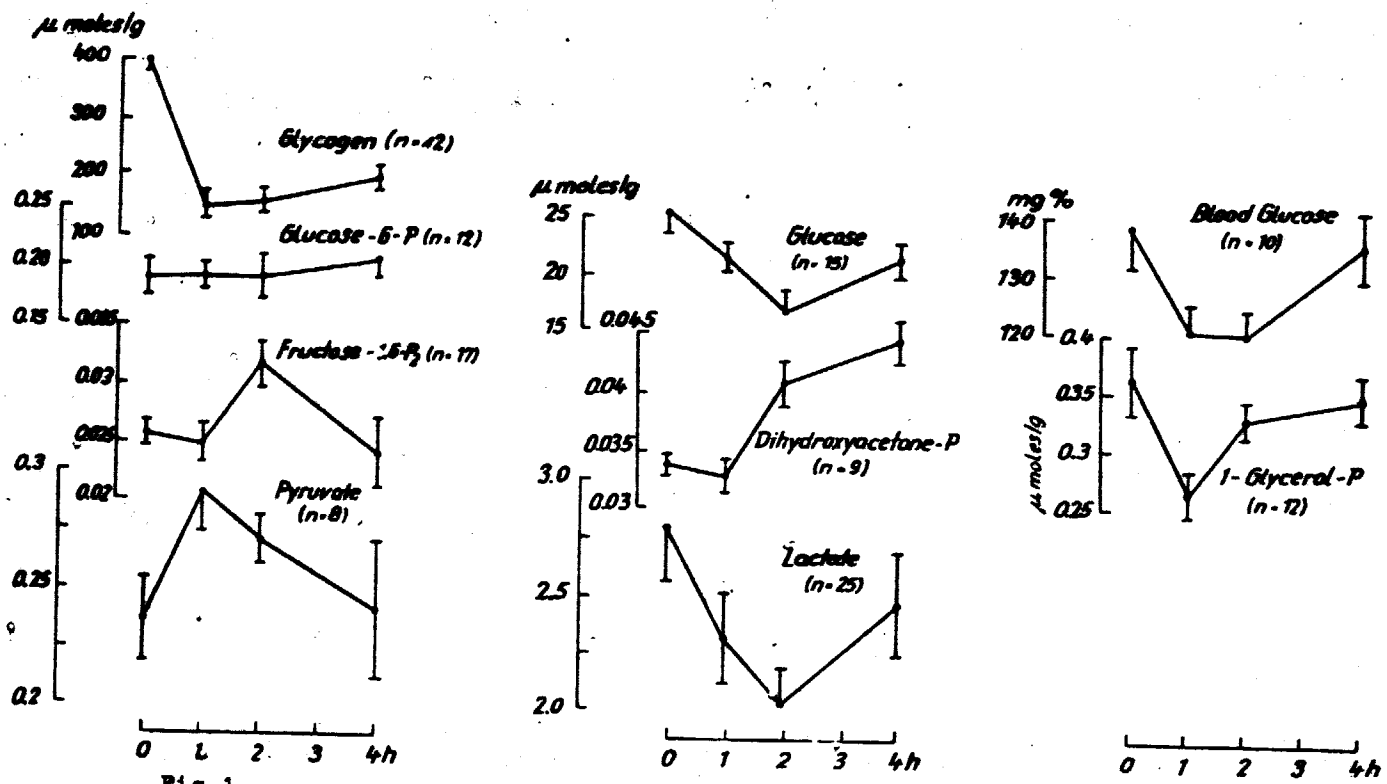

Fig.1

Contents of glycogen, glucose-6-P, glucose, fructose-1,6-P_2, dihydroxyacetone-P, 1-glycerol-P, pyruvate and lactate in the liver and blood glucose of white mice after i.p.administration of 2oo mg/kg nicotinic acid.

the liver decreased after 1 hour, the content of lactate after 2 hours.

The reduction of the glycogen content in the liver by about 63%, the increasing amounts of the intermediates of the glycolysis, namely fructose-1,6-P_2 and dihydroxyacetone-P together with the increased pyruvate content show an elevated carbohydrate breakdown in the Emden Meyerhof pathway. The elevation of dihydroxyacetone-P and pyruvate contents on the one hand and the decrease of 1-glycerol-P and lactate contents on the other cause a reduction of the 1-glycerol-P/dihydroxyacetone-P ratio and of the lactate/pyruvate ratio, which are supposed to be a parameter of the NADH / NAD ratio in the cytoplasma (1o,11). The reduction of the NADH / NAD ratio shows that the increased glycolysis is not likely to be the consequence of a deficiency of oxygen. Thus the increased glycolysis confirms the view that the carbohydrate breakdown is increased after an administration of nicotinic acid probably because of the reduced availability of FFA.

The reduction of the blood glucose, which is in equilibrium with the glucose content of the liver, may reasonably be explained by an increased removal of glucose from the blood by these organs, which derive their energy partly from the breakdown of FFA.

As nicotinic acid directly inhibits the lipolysis of the adipose tissue we investigated wether an encreased glycogenolysis is the direct or indirect result of the administration of nicotinic acid. Therefore we investigated the influence of nicotinic acid on the glycogen content of the liver, the muscular tissue, the brain and the adipose tissue. Autoradiographic investigations show that nicotinic acid accumulates primarily in the adipose tissue and in the liver, whereas it cannot be shown

in the brain and in the muscular tissue by this method (12).

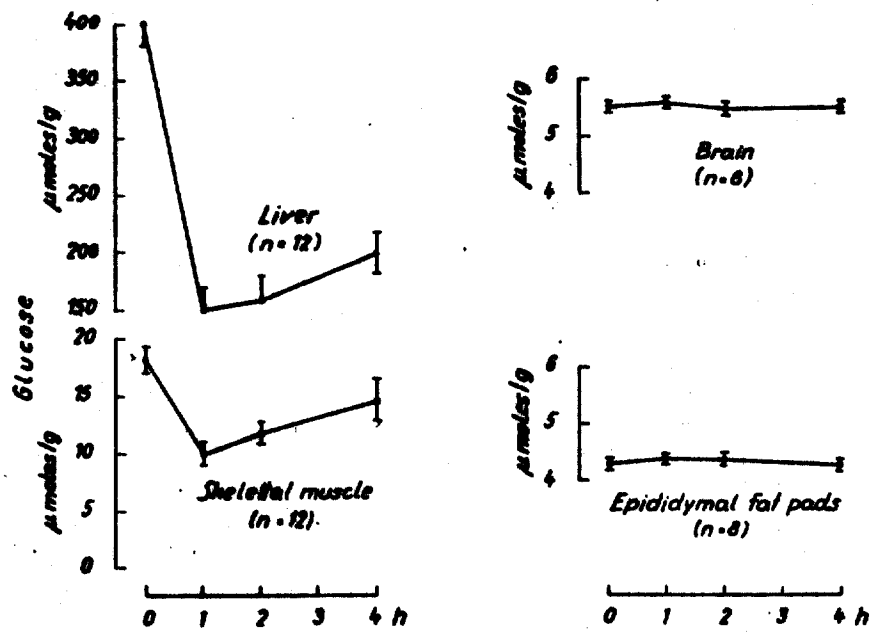

Fig.2

Glycogen contents in liver,brain,muscular tissue and epididymal fat pads after i.p. administration of 2oo mg/kg nicotinic acid.

1,2 and 4 hours after the administration of nicotinic acid the glycogen content of the liver is decreased as well as that of the muscular tissue after 1 and 2 hours.The glycogen content of the brain and of the adipose tissue is not altered (Fig.2).

These results show that after the application of nicotinic acid the muscular tissue mobilises glycogen on its own although nicotinic acid is not detectable in this tissue.In the adipose tissue however the glycogen content remains unchanged although

nicotinic acid accumulates in this organ.The glycogen content of the brain remains unaffected as well.This result may have two reasons: 1.Nicotinic acid is not found in the brain by the autoradiographic method. 2.The brain tissue does not metabolize FFA to obtain energy.Considerating these results one may conclude that the mobilisation of glycogen in the liver and in the muscular tissue is not caused by nicotinic acid itself but by another indirect effect probably in consequence of the reduced availability of FFA.

Summary

Under the influence of such amounts of nicotinic acid,as are able to lower the concentration of FFA in the blood,there is a reduction of the glycogen content and an elevation of the contents of fructose-1,6-P_2,dihydroxyacetone-P and pyruvate in the liver.The 1-glycerol-P/dihydroxyacetone-P ratio and the lactate /pyruvate ratio are diminished.These results show an accelerated carbohydrate breakdown which is probably due to a reduced supply of FFA,because FFA contribute to the winning of energy in this organ.The unchanged glycogen content in the adipose tissue,an organ in which nicotinic acid accumulates,and the reduction of the glycogen content in the muscular tissue,an organ where nicotinic acid is not detectable,but which is able to oxidize FFA,show that the increased glycogenolysis in the liver and in the muscular tissue is not due to nicotinic acid itself but to an indirect effect of nicotinic acid.

References

1. L.A.CARLSON and L.ORÖ,Acta med.scand. 172,641 (1962).
2. L.A.CARLSON and E.R.NYE,Acta med.scand. 179,453 (1966).

3. A.KEMP and A.J.M.KITS VAN HEIJNINGEN, Biochem.J. 56, 646 (1954)
4. Th.BÜCHER unpublished data.
5. R.SCHOLZ, H.SCHMITZ, Th.BÜCHER and J.O.LAMPEN, Biochem.Z. 331, 71 (1959)
6. Th.BÜCHER und H.J.HOHORST in: Methoden der enzymatischen Analyse, by H.U.BERGMEYER, Verlag Chemie, Weinheim/Bergstrasse, p.246 (1962).
7. H.J.HOHORST in: Methoden der enzymatischen Analyse, by H.U.BERGMEYER, Verlag Chemie, Weinheim/Bergstrasse, p.134 (1962)
8. H.J.HOHORST in: Methoden der enzymatischen Analyse, by H.U.BERGMEYER, Verlag Chemie, Weinheim/Bergstrasse, p.215 (1962)
9. A.S.G.HUGGETT and D.A.NIXON, Lancet 273 II, 368 (1957).
10. H.J.HOHORST, F.H.KREUTZ and Th.BÜCHER, Biochem.Z. 332, 18 (1959).
11. M.KLINGENBERG in: Zur Bedeutung der freien Nucleotide. 11. Colloquium d.Gesellschaft f.Physiol.Chemie in Mosbach/Baden, 1961, p.82, Springer Verlag, Berlin, Göttingen, Heidelberg.
12. L.A.CARLSON and A.HANNGREN, Life Sci. 3, 867 (1964).

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THE EFFECTS OF NICOTINIC ACID, NICOTINAMIDE, AND PLACEBO ON THE CHRONIC SCHIZOPHRENIC

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For various reasons we became interested in the possibility that nicotinic acid or nicotinamide might be of some benefit to the chronic schizophrenic. Many workers have noticed clinical similarities between the acute schizophrenias and the encephalopathies of nicotinic acid deficiency (4). Nicotinic acid is known to be of value in pellagra (2) and in the treatment of delirium tremens and allied states (1), and Osmond and Hoffer have had promising results with these substances in the treatment of schizophrenia in its acute phase (3). There seemed therefore to be sufficient reason for an investigation of their effects in the schizophrenic in the chronic phase, for, as far as we are aware, the therapeutic possibilities have not been explored. Since patients often respond strikingly to the giving of any tablet, regardless of its contents, we also gave similar tablets of an innocuous substance, here referred to as Placebo. For convenience the three preparations employed will be referred to in future as *A* (Nicotinic Acid), *M* (Nicotinamide) or *P* (Placebo).

The Test

The group tested consisted of chronic schizophrenics, of ages from forty to seventy.

The design of the test was arranged so that certain errors were avoided. One of these was that different patients would tend to be at different clinical levels throughout the test. This fact can be allowed for by giving all three treatments to each patient, and then making comparisons only between results from the same patient, by taking differences say, so that each patient acts as his own control.

Another error is introduced by secular changes, whether by the patient being at first stimulated by the mere fact of being given something, or by the clinician's standard of what is "good" changing slowly throughout the test. These errors were avoided by testing the patients in triples, in which one patient

received the drugs in the order *A*, *M*, *P*, while the other two received them in the orders *M*, *P*, *A*, and *P*, *A*, *M*. Thus each substance occurred once in the first place, once in the second, and once in the third. The *sums* over such a triple have the errors balanced out.

Such a set of three patients, chosen to be as alike as possible in age, clinical condition, sex, past history, etc., formed the primary block for the test. From this block the basic information that we require is obtainable. Random sampling was then reduced as far as was possible by the provision of further blocks, each as homogeneous as possible internally. Thirteen such blocks went through the test to completion, involving thirty-nine patients. Thirty patients (ten blocks) were of women, nine (three blocks) of men.

Some time might be necessary for the treatment to show its effect, but we considered that eight weeks on each substance might well be sufficient for any action to declare itself. Accordingly each substance was given for eight weeks continuously. One week without treatment was allowed between each eight week period; so the patient was under observation over twenty-six weeks in all.

In each eight-week period on one substance, the first week was used to raise the dosage to its maximal level. Three hundred mg. t.d.s. was given on the first day and each day the dosage was increased by this amount so that on the seventh day the dosage was 2·1 grams t.d.s. (i.e. 6·3 grams per day). This last level was then sustained for seven weeks.

Assessment

We were interested chiefly in the patients' *general clinical condition*, rather than in their response to specialized psychological tests (and in any case the chronic schizophrenic would often be quite unco-operative in the employment of any special tests). So we assessed the patients' clinical state by the following twenty-three criteria:

1. Does he have to be fed?
2. Has he been mute?
3. Has he talked to himself?
4. Does he sleep badly?
5. Does he daydream?
6. Does he keep to himself?
7. Does he laugh without cause?
8. Is he apathetic?
9. Is his behaviour childish?
10. Is he upset easily?
11. Is he untidy in his dress?
12. Does he hoard rubbish?
13. Has he been dirty in his habits?
14. Is he deluded?
15. Has he masturbated?
16. Is he destructive?
17. Is he suspicious?
18. Is he hallucinated?
19. Is he homicidal?
20. Is he suicidal?
21. Has he been impulsive?
22. Does he employ himself in any way?
23. Has he any interests?

Each question was answered by "Yes", "No" or "Variable". At the end of each fortnight the patient was assessed by the twenty-three questions, and a score derived. One point was given for each "Variable", two points for each "No" occurring in the first twenty-one questions and two points for each "Yes" occurring in the last two questions. Thus the maximal score at one assessment was 46; a high score corresponded to a good clinical condition.

The questionnaire was filled in by the Ward Sister who had had the patient under observation during the previous fortnight, in consultation with the psychiatrist. Each patient, over the twenty-six weeks, was thus given twelve assessments of his condition.

To ensure that the person filling in the questionnaire was unbiased, the three drugs were given in an order known only to the dispenser, who allotted one of the three orders mentioned above to each of the three patients. Thus

the person marking the questionnaire would know, on a particular week, that one of the patients was on nicotinic acid, one on nicotinamide, and one on placebo, but she would have no way of telling which was which other than by whatever was clinically observable.

In all, thirty-nine patients contributed to the test by completing the course. Although the whole group was, naturally, somewhat heterogeneous, the blocks of three were so arranged that each block was fairly homogeneous internally. As will be shown below, all the comparisons were made primarily within the blocks; thus the comparisons are based on material much more homogeneous than the total range of patients in the group.

Results

It is convenient first to dispose of some minor matters. The thirty-nine patients mentioned above were those remaining after nine patients had refused to continue the treatment. One patient refused while receiving the acid, six during the amide, and two during the placebo. Although the refusals were mostly against the amide, the multinomial distribution shows that, as the probability of exactly one, two, and six is 56/729, i.e. about 1/13, the difference can hardly count as significant.

Nicotinic acid is, of course, well known to cause vaso-dilation. Each form recorded whether flushing had occurred, and the occurrences were divided into "slight" and "marked". The three substances gave flushings as shown in Table I

Table I

	Degree of Flushing			
	0	Slight	Marked	Total
Acid	106	42	12	160
Amide	146	13	1	160
Placebo	137	18	5	160
Total	389	73	18	480

Table I includes the results for one patient who completed the course but whose Block was not completed.

χ^2 is 36·7: n=4: p is less than 0·001.

It is clear that the nicotinic acid produced flushing much more than the others. One cannot help noticing, however, that the nursing staff, otherwise highly trustworthy, have recorded flushing in no less than twenty-three occasions when the patient in fact was on placebo. We do not regard this as a suggestion that the staff was unduly careless; we regard it rather as showing how essential it is that any question involving some degree of judgment should be made in ignorance of the factor at work.

We can now turn to the main matter of interest: whether, if the drug acts quickly, the general level of clinical condition tends to be better on either of the two drugs than on the placebo.

For this purpose the four scores (over the 8 weeks under each drug) were added together. Thus, each patient now gave three totals, one for acid, one for amide and one for placebo occurring in some order. The three patients in a block each gave three results, forming a Latin square. Thus, patients Nos. 13, 14 and 15 gave the scores shown in Table II, where the columns show the three periods, and the letter after each entry shows the drug given.

TABLE II

Patient No.	Period 1	Period 2	Period 3
13	127 (*A*)	121 (*M*)	118 (*P*)
14	95 (*M*)	108 (*P*)	109 (*A*)
15	134 (*P*)	176 (*A*)	174 (*M*)

The difference between rows represents the fact that, e.g., patient 15 was consistently in a better clinical condition than patient 14. The difference between columns reflects the fact that secular changes (such as a drift in the markers' standards) might be occurring. The other differences show the usual effects of treatment or of interaction. Thirteen blocks provide the necessary replication.

The analysis of variance of the 117 observations need not be given in detail. The essential part occurs in Table III, which gives the totals for the treatments.

TABLE III

Period 1	Period 2	Period 3
1,504 (*A*)	1,641 (*M*)	1,590 (*P*)
1,525 (*M*)	1,687 (*P*)	1,654 (*A*)
1,610 (*P*)	1,705 (*A*)	1,736 (*M*)

A 4,863 *M* =4,902 *P* =4,887 F_1=4,927 F_2=4,005 F_3=4,820

It also gives (as *F*'s) the three diagonal totals whose differences represent high-order interactions. What interests us especially are the differences between the totals for *A*, *M*, and *P*.

The eight degrees of freedom in Table III can be divided into the following:

1. Two degrees of freedom between columns; these are of no interest since they represent secular changes in the experiment, and are required only for elimination.

2. Two degrees of freedom between rows; these represent differences between three sets of 13 patients, and are required only for elimination.

3. Two degrees of freedom between the treatments *A*, *M*, and *P*. These may meaningfully be divided into one degree of freedom which compares the condition under placebo with the average condition under acid and amide, and one degree of freedom which compares the acid and the amide.

4. Two degrees of freedom due to high-order interaction; they are represented by the variance between the three totals *F*, and provide the appropriate estimate of error.

The analysis is shown in Table IV

TABLE IV

Variance	D.F.	Sum of Square	Mean Square
Acid v. Amide	1	19·5	19·5
Placebo v. Drug	1	0·3	0·3
Rows	2	1292·7	—
Columns	2	2344·7	—
Interaction	2	163·8	81·9
Total	8	3820·9	—

In the Table the divisors used in forming the sums of squares have been those appropriate to the full analysis of 116 degrees of freedom.

The results in the right-hand column show unequivocally that there is no evidence for any change in the clinical condition so far as a general change in the level is concerned. "Drug" is not significantly better than placebo, and the two forms of the drug show no significant difference.

There remains the possibility that the drugs may have had a cumulative effect, so that the clinical condition at the end of the eight weeks' treatment was significantly different from that at the beginning. This question can be examined simply by using, as the estimator over the eight weeks, not the sum of the four scores but the difference between the last and the first. The difference under nicotinic acid can then be compared with that under the amide, and so on. The null hypothesis is then that these quantities are normally distributed about zero, so *t*-tests are appropriate. Again the two main matters of interest were:

1. Whether the change under placebo differed significantly from the average change under the drugs (within each triple);

2. Whether the acid and the amide differed in the amounts of change they produced.

T-tests showed, in fact, that both the changes were insignificant.

Summary

The effects of massive doses of nicotinic acid and of nicotinamide were tested on the chronic schizophrenic, together with an inert placebo. Thirty-nine patients were tested, each over 24 weeks. The results were assessed on a prepared scale.

Analysis of the results failed to show any evidence that the treatments were influencing the patients.

Acknowledgments

Our thanks are due to British Drug Houses Ltd., who willingly provided supplies of Nicotinic Acid, Nicotinamide and Placebo for the clinical trial, and to the Ward Sisters and Nursing Staff, without whose co-operation the trial could never have been completed.

References

1. Armstrong, R. W., and Gould, J., *J. Ment. Sci.*, 1955, **101**, 422.
2. Gregory, I., *ibid.*, 1955, **101**, 422.
3. Osmond, H., and Hoffer, A., Personal communication.
4. Spillane, J. D., *Proc. Roy. Soc. Med.*, 1946, **39**, 357.

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FINE STRUCTURAL CHANGES IN THE LIVER IN HYPERCHOLESTEREMIC PATIENTS RECEIVING LONG-TERM NICOTINIC ACID THERAPY*

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The experimental, epidemiologic, and clinical evidence indicating a relationship between hypercholesteremia and atherosclerosis has led to a search for a safe, effective, and practical long-term therapeutic approach to the clinical treatment of hypercholesteremia. For patients whose hyperlipidemia is unresponsive to an acceptable dietary regimen, nicotinic acid in large doses has proved to be one of the most effective agents for which long-term data are available. The side effects encountered with nicotinic acid have included cutaneous flushing, pruritus, ichthyosis, and hyperpigmentation; gastrointestinal irritation and ulceration; asymptomatic hyperuricemia and hyperglycemia; and clinical and laboratory evidence of hepatic dysfunction including rare instances of jaundice.[1-]

The recent occurrence of jaundice in a patient receiving long-term treatment with large doses of plain, powdered nicotinic acid led us to reassess hepatic effects of this treatment by studies including electron microscopic examination of hepatic tissue obtained by needle biopsy from patients without signs or symptoms of hepatic disease. To our knowledge, this is the initial study of its kind; for this reason, a some

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what detailed review and analysis of the literature will be included with the report of the study.

MATERIAL AND METHODS

Eight patients, four males and four females aged 32 to 71 years who had hypercholesteremia and were receiving plain nicotinic acid in oral doses of 1.5 to 6 gm daily, constitute the series studied. The period of continuous treatment with nicotinic acid ranged from 1 5/6 to 9 years. None had diabetes, nephrosis, myxedema, or other known causes of secondary hypercholesteremia.

Three other patients, all males aged 14 to 37 years who had hypercholesteremia but were not being treated with nicotinic acid, served as controls. One of the three had diabetes mellitus, recently discovered and controlled without insulin. They presented no evidence of other known causes of secondary hypercholesteremia.

In all 11 patients, blood was drawn in the fasting state for the determination of serum glutamic-oxalacetic transaminase (SGOT), serum bilirubin, sulfobromophthalein retention 1 hour after injection, serum proteins by electrophoresis, alkaline phosphatase, prothrombin time, and plasma lipids including cholesterol, cholesterol esters, fatty acids, and total lipids by standard laboratory methods.

After hypodermic administration of 50 mg of meperidine (Demerol), percutaneous needle biopsy of the liver was performed and the specimen divided into three portions. One portion was fixed in formalin, embedded in paraffin, cut in sections 8μ thick, and stained with hematoxylin and eosin, periodic acid-Schiff stain with and without diastase, and azure eosin at pH 4 and pH 6. The second portion after fixation in formalin was utilized for frozen sections stained with Sudan IV. The small, third portion was fixed in ice-cold, buffered, 1% solution of osmium tetroxide, embedded in Epon, and sectioned at 600 angstroms (A) with the Porter-Blum microtome. These sections were mounted on a copper grid and were studied and photographed at 50 kv in an RCA model EMU-3E electron microscope. Additional sections were cut 1μ thick, stained with azure methylene blue, and examined with the light microscope for orientation.

RESULTS

Lipids.—Concentrations of blood lipids at the time of study and other data characterizing the study and control groups are listed in Table 1. Three of the eight patients on treatment

Table 1
Data Characterizing Untreated and Treated (Nicotinic Acid) Patients With Hypercholesteremia

Case	Sex, age	Known familial hyperlipidemia	Xanthoma (tuberous or tendinous)	Type of clinical atherosclerosis*	Treatment at time of biopsy: Nicotinic acid: Duration, years	Nicotinic acid: Dose, gm/day	Other	Plasma lipids, mg/100 ml: Cholesterol (150-250): Before therapy	Cholesterol: At biopsy	Cholesterol esters (100-175)† at biopsy	Fatty acids (250-400)†: Before therapy	Fatty acids: At biopsy
Treated with nicotinic acid												
1	F 50	No	No	Aorta	3 7/12	4.5	None	402	290	181	463	370
2	M 65	No	No	CHD	8 1/2	3	None	365	275	267	658	696
3	F 32	Yes	No	CHD	1 5/6	6	Glyceryl trinitrate, sodium warfarin, digoxin, pentaerythritol tetranitrate, medroxyprogesterone acetate, ethinyl estradiol, diazepam	367	236	170	670	420
4	F 71	No	Yes	CHD, CNS, ASO	7 3/4	4.5	Glyceryl trinitrate, sodium warfarin, pentaerythritol tetranitrate	294	232	182	515	407
5	M 60	No	Yes	CHD, ASO	3 1/2	6	Glyceryl trinitrate	420	300	203	623	455
6	M 66	No	No	CHD, ASO	6 1/4	3	Glyceryl trinitrate, bishydroxycoumarin, pentaerythritol tetranitrate	322	210	156	507	311
7	F 76	No	No	CHD, CNS, ASO	8 5/6	3	Glyceryl trinitrate, sodium warfarin, propoxyphene HCl, acetylsalicylic acid	293	178	124	606	297
8	M 62	Yes	Yes	CHD	9	3	Glyceryl trinitrate	360	282	207	459	470
Untreated (controls)												
[illegible]	[illegible]	Yes	No	CHD	0	0	Glyceryl trinitrate	353	356	267	396	451
[illegible]	M [illegible]	Yes	Yes	None	0	0	Acetylsalicylic acid	322	380	238	447	488
[illegible]	[illegible]	No	No	None	0	0	None	343	242	167	1,761	731

*Abbreviations: CHD = coronary heart disease; ASO = arteriosclerosis obliterans; CNS = cerebrovascular disease; aorta = calcification of aorta.
†Normal ranges given in parentheses.

Table 2
Tests of Hepatic Function During Treatment With Nicotinic Acid

Case	Years of therapy	BSP*	SGOT*	Alk. phos.*	Ceph. chol.*	Serum protein alb./glob.*
1	3 7/12	Normal (5)†	Normal (4); 1.9 (1)	Normal (5)†	Normal (4)†	2.87/2.48 (1)
2	8 1/2	Normal (12)	Normal (7)	Normal (7)	Normal (6)	Normal (1)
3	4 5/6	Normal (10); 6% (1)	Normal (8)	Normal (6); 14.4 (1)	Normal (8); 3+ to 4+ (2)	Normal (1)
4	7 3/4	Normal (10)	Normal (11); 2.13 (1)	Normal (9)	Normal (8); 4+ to 4+ (3)	Normal (2)
5	3 1/2	Normal (9)	Normal (9)	Normal (9)	Normal (9)	Normal (1)
6	6 1/4	Normal (6); 8% (1)	Normal (6)	Normal (6)	Normal (5)	Normal (1)
7	8 5/6	Normal (9); 6 to 14% (3)	Normal (7)	Normal (7); 14.8 to 17.6 (2)	Normal (8); 4+ to 4+ (2)	Normal (3); 2.13/3.7 (1); 2.61/2.93 (1)
8	5	Normal (12)	Normal (7); 1.71/2.44 (3)	Normal (10)	Normal (7); 4+ to 4+ (2)	Normal (2)

*Abbreviations: BSP = sulfobromophthalein retention (normal <5%, in 1 hr); SGOT = serum glutamic-oxalacetic transaminase (normal upper limit: 1.43 μmoles/hr/ml); Alk. phos. = alkaline phosphatase (normal: 5-14 K-A units); Ceph. chol. = cephalin-cholesterol flocculation (normal: 0 to 2+); Alb./glob. = albumin/globulin (normal: 3.4-4.3/2.2-3.9 gm/100 ml).
†Numbers in parentheses = number of determinations

with nicotinic acid exhibited mild hypercholesteremia at the time of biopsy, despite nicotinic acid therapy.

Tests of Hepatic Function.—Data obtained at periodic examinations during long-term treatment with nicotinic acid are given in Table 2. Though occasionally various tests of hepatic function were abnormal during treatment, at the time of liver biopsy the values for SGOT, serum bilirubin, and alkaline phosphatase were normal in all patients. Serum albumin concentration exceeded 3.3 gm/100 ml in all but cases 1 and 7 (2.87 and 2.61 gm/100 ml respectively) at the time of biopsy. The total globulin fraction and gamma globulin levels were normal in all cases. Only one patient (case 7) exhibited abnormal cephalin flocculation (grade 3) and sulfobromophthalein retention (6%). The results of these tests of hepatic function at the time of biopsy were normal in all three untreated patients (controls) except for a slight increase in SGOT (2.88 μmoles/hr/ml) in one.

Hepatic Biopsy.—Light microscopic findings were essentially normal in all eight patients treated with nicotinic acid. Fatty change was mild in five cases and moderate in three. Lipofuscin deposition in the central cells of the lobule was mild in seven and moderate in one. The glycogen content of the liver cells appeared to be normal. Vacuolization of the hepatic cell nuclei was mild in three cases and moderate in one. Hyperchromatic and hypertrophied nuclei were observed in three cases. Occasional lytic or acidophilic necrosis of individual cells was observed in two cases, and focal necrosis

Fig. 1 (case 1). Replacement of rough endoplasmic reticulum by vesicles with loss of ribosomal granules. (Uranyl acetate; x16,000.)

with a lymphocytic reaction in only one. Mild focal proliferation of Kupffer cells was observed in one case. Slight broadening of the portal tracts was noted in two cases, and focal fibrous scars outside the portal tract in only one.

Light microscopic findings also were essentially normal in all three untreated patients who had hypercholesteremia. In one case fatty change was mild and in two cases it was moderate. A small focus of necrosis with a lymphocytic reaction was noted in one case and a small focus of proliferating Kupffer cells in another. There was a slight increase in fibroblasts in the portal tracts in one case.

Electron Microscopic Features.—The electron microscopic appearance in the three untreated patients who had hypercholesteremia was normal in all respects. In those treated with nicotinic acid, the most pronounced alteration observed was dilatation of the endoplasmic reticulum with the formation of vesicles and sacs of various sizes and shapes (Fig. 1). This was accompanied by a diminution of parallel arrays of rough endoplasmic reticulum. The vesicles were generally small, but occasionally large. They usually presented a smooth, thin-

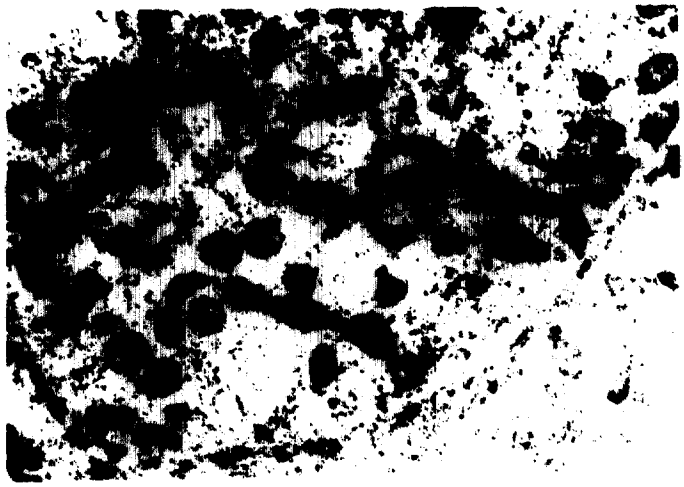

Fig. 2 (case 5). Elongation of mitochondria. Increase of smooth endoplasmic reticulum. (Uranyl acetate; x7,700.)

face, but sometimes a few ribosomes could still be detected on the outer surface. This yielded a configuration similar to that assumed by the smooth endoplasmic reticulum except that many vesicles still contained a few ribosomal particles. Within some of the vesicles clusters of ribosome-like particles could be observed, and in some instances papillary projections were lined by particles extending into the vesicular space (Fig. 1). Replacement of the rough endoplasmic reticulum by vesicles with loss of ribosomal granules was observed in all biopsy specimens and was mild in one, moderate in three, and severe in four cases. Numerous ribosomes were observed in the intervesicular spaces of the cytoplasm.

The mitochondria varied greatly in size and shape but seemed to be present in normal numbers. Some were markedly enlarged and others appeared in unusual forms (Fig. 2 and 3). Enlargement by elongation appeared more frequently than increase in diameter. Some appeared to have elongated by fusion, and in a few cases one could see attenuated bridges between them. Others had bud-like projections, and some of the giant forms appeared to have an irregular outer surface. Cristae were often absent or reduced in number, and there appeared to be a diffuse increase in matrix density. Dense bodies and focal increase in density of irregular forms were often observed. In three cases, both the enlarged and the normal-sized mitochondria contained so-called crystalloid bodies (Fig. 4). The crystalloid inclusions were roughly square or

Fig. 5 (case 7). Giant mitochondrion with focal increase in density of matrix and irregular external membrane. (Uranyl acetate; x16,000.)

rectangular in profile and commonly of the order of 200 to 350 mμ. They always occurred in the matrix and were usually close to the internal limiting membrane. In some cases they could be observed in close relationship to a perpendicular row of tubular cristae. They had the appearance of groups of straight, parallel, electron-dense lines regularly spaced. Both the thickness of the dense lines and the distance between them measured about 75 A.

The Golgi apparatus in the five cases in which it was identified did not appear abnormal in size or configuration. Lysosomes, lipoid vacuoles, and glycogen did not appear to be quantitatively or qualitatively abnormal.

COMMENT

Engelberg[6] found tests of hepatic function to be normal in untreated hypercholesteremia except for slightly abnormal retention of sulfobromophthalein in 10 to 15% of patients. Although hepatic function is occasionally disturbed by atherosclerotic

[illegible] crystalloid formations; loss of [illegible] and vesicle formation. (Uranyl acetate; [illegible])

acid administration,[1-4] histologic findings on biopsy of the liver are usually normal.[6] Parsons[7] has described histologic alterations in four patients who were on long-term nicotinic acid

therapy, but the interpretation of these changes is difficult because of possible complicating factors in three of the cases (exposure to carbon tetrachloride, uncontrolled diabetes, and prochlorperazine therapy respectively). In the single uncomplicated case, only cloudy swelling was described and electron microscopic studies were not made. Because histologic alterations are rare in the liver of patients treated with nicotinic acid, Parsons[8] has suggested that alterations in certain enzymatic function of hepatic cells may occur without histologic damage.

Fine structural alterations in the endoplasmic reticulum of hepatic cells in man, similar to those observed in our patients, have been described in kwashiorkor,[9] in chronic hepatitis and cirrhosis,[10] in prolonged extrahepatic cholestasis,[11] and in severe alcoholism.[12-15]

The vulnerability of the rough endoplasmic reticulum to injuries of various types has been demonstrated repeatedly in experimental animals, and the literature has been well-reviewed by Rouiller and Jézéquel[16] and by David.[17] As Rouiller and Jézéquel[16] point out, the vesicles or vacuoles observed do not all come from an alteration of the rough endoplasmic reticulum but can have other origins such as artifacts of preparation, smooth membranes, Golgi apparatus, degenerated mitochondria, and pinocytotic vesicles. It has also been observed experimentally that the same factors (for example, carcinogenic agents,[18] hepatotoxins,[19] and phenobarbital[20-22]) that alter the rough endoplasmic reticulum also lead to hypertrophy of the smooth endoplasmic reticulum. This latter alteration in the sense of dense, closely packed agglomerations of smooth tubular elements was not a frequent feature of our cases, however. It appeared that the rough endoplasmic reticulum was replaced by dilated sacs and vesicles, many of which still contained a few ribosomal particles, and for this reason we hesitate to suggest a hypertrophy or an increase of the smooth endoplasmic reticulum.

Administration of many of the hepatotoxins, such as carbon tetrachloride,[23] diethylnitrosamine,[24] yellow phosphorus, thioacetamide,[19] ethionine, and orotic acid,[25] is also associated with depression of protein synthesis or fatty change or both. Barker and colleagues[19] have suggested that dislocation of the ribosomes from the rough endoplasmic reticulum is an effect common to hepatotoxins which inhibit protein synthesis, and that deficient protein formation may be responsible for the fatty change. In our cases, however, fatty change was usually

mild, never severe, and serum albumin values at the time of biopsy were less than 3 gm/100 ml in only two cases.

Abnormal mitochondria such as the greatly elongated or giant forms and those containing crystalloid structures observed in our cases have been described in various hepatic conditions. Rouiller and Jézéquel[11] and David[12] give a thorough and excellent review of the literature up to 1963. The alterations have been observed in steatosis, in various hepatic infections, in both extrahepatic and intrahepatic cholestasis, in methandrostenolone administration, in Waldenström's macroglobulinemia, and in a case of unexplained hepatosplenomegaly. They have also been observed in chlorpropamide therapy,[26] in chronic familial nonhemolytic acholuric jaundice,[27] in amyloidosis,[28] in chronic hepatitis and cirrhosis,[10] and in diabetes mellitus.[13,29] More recently, they have been described by numerous observers in alcoholic hepatitis and cirrhosis.[12,13,15,30-32]

Neither the nature nor the origin of the mitochondrial alterations is well understood. That the enlargement is not simply swelling is indicated by the absence of a decrease in density of the matrix such as occurs in osmotic disturbances. In our cases the electron density was either normal or focally increased. Lehninger[33] has noted that mitochondria have a surprisingly constant thickness but considerable variation in length, an observation that suggests that they add or lose substance at their extremities. End-to-end fusion, as contrasted with side-to-side fusion, is very common in different cell types. He also noted that arrangement of cristae often undergoes pronounced alteration as a function of developmental change, nutritional state, and endocrine manipulation.

The nature and origin of the crystalline structures observed are also not well understood. It is usually stated that they are identical with myelin figures.[15,16] Jézéquel[34] demonstrated a close relationship and in some instances a continuity between the inclusions and the cristae. Svoboda and Manning[15] also noted this, and derived the crystalline structures from the membranes of the cristae and observed that mitochondria with inclusions frequently showed diminution of the number of cristae. This was also true of the mitochondria with crystalloids in our cases. Daems and Van Rijssel[35] have described crystalloids in peribiliary dense bodies and interpreted them as degenerating mitochondria within lysosomes.

It is noteworthy that mitochondrial crystalloids have been reported in a clinically and histologically normal liver by David,[17] Mugnaini,[36] and Wills.[37] The latter two authors assert

that a distinction should be made between myelin figures (myelin degeneration), which consist of parallel rows of altered membranes, and "crystals" or "paracrystals," which they interpret as regularly disposed filaments. The filamentous nature is apparent when the structures are observed in cross section. The cross-sectional view was not observed in our cases, but was described by Mugnaini,[36] Svoboda and Manning,[15] and Wills.[37] Mugnaini[36] and Wills[37] also assert that inclusions in hepatic mitochondria have not been reported in laboratory animals. Recently, however, Watrach[38] has observed them in lead poisoning of swine.

The crystalloids have been considered to be composed of phospholipids. Mugnaini[36] raises the question of a possible relationship between the crystalline inclusions and the elementary particles attached to mitochondrial membranes described by Fernández-Morán.[39] In view of the arrangement of elementary particles in the mitochondrial inner membrane and cristae, it is difficult to imagine that the electron microscopic image of crystalloids is derived from them. It appears more likely that the crystalloids are related to the mitochondrial membrane. Myelin figures have been produced in vitro by hydrating phospholipids[40] and various extracts of nerve,[41] egg yolk,[42] and brain.[43] The structures produced have been interpreted as consisting of a single bimolecular leaflet of lipid with electron-opaque outer layers representing the aligned polar ends of the lipid molecules. Stoeckenius[43] has pointed out that when such a figure consists of only two bimolecular leaflets of lipid covered with globulin, it shows a striking similarity to the image of cell membranes in fixed tissue sections. Since mitochondrial membranes are composed of 35 to 40% lipids and since 90% of the mitochondrial lipid is phospholipid,[33] it appears plausible that changes in the state of hydration or other modification of the mitochondria could result in condensation and crystallization of mitochondrial phospholipids.

It has already been noted that various hepatic lesions are associated with these mitochondrial changes. Rouiller and Jézéquel[16] considered a disturbance of lipid metabolism as a possible cause of the mitochondrial abnormalities. Since the changes have been observed in various conditions in which fat metabolism is disturbed, such as cholestasis, diabetes mellitus, chronic alcoholism, and treated hypercholesteremia (in our own cases), the concept does have some support. Fatty acids have been shown to affect mitochondrial processes and to induce the swelling of mitochondria.[44-47] Unfortunately, the

influence of nicotinic acid on the composition and concentration of lipids in mitochondria remains unknown.

The fact that the mitochondrial changes are also observed in various conditions unrelated to disturbances of fat metabolism, however, suggests that they are a nonspecific reaction to cellular injury of many different types.

It is difficult at present to rationalize the alterations observed in the endoplasmic reticulum and mitochondria in terms of a biochemical effect of the drug. Of the known biochemical effects of nicotinic acid, one especially might exert a strong, broad influence on the mitochondrial processes. This effect is an increase of the availability of pyridine nucleotides.[48] Specifically in the case of rat liver, the increase of pyridine nucleotides has been accompanied by an increase of the oxidative capacity of the tissue, as measured in vitro.[49] An effect of nicotinic acid on the concentrations of nicotinamide adenine dinucleotide (NAD) and NAD-phosphate in liver might influence many processes, which would include glycolysis, pyruvate and pentose metabolism, lipid synthesis and metabolism, and the production of high-energy phosphate bonds. However, any relationship between the biochemical effects of nicotinic acid and the morphologic alterations in the endoplasmic reticulum and mitochondria is completely obscure.

Our own observations support the statements of David,[17] Svoboda and Manning,[15] and Wills[37] that the presence of inclusions in the mitochondria does not necessarily indicate preceding or impending cell death, since they were frequently found in cells that showed no obvious retrogressive changes in the remaining mitochondria or other organelles. In two cases of alcoholism reported by Svoboda and Manning,[15] rebiopsy after 3 months of an adequate diet with elimination of alcohol intake showed that fatty change was no longer apparent and crystalline inclusions could not be detected by electron microscopy. Because of these facts, the inclusions can perhaps best be interpreted as evidences of focal cystoplasmic degradation.[50] Their presence in clinically and histologically normal livers would indicate that they at times may represent a physiologic process of intracellular breakdown and repair and do not contraindicate the use of nicotinic acid in the treatment of hypercholesteremia in carefully supervised patients.

We believe, however, that the occurrence of jaundice in a patient receiving large doses of nicotinic acid constitutes a contraindication to continued use of the drug. Fortunately, this complication is rare, and when it does occur the jaundice

disappears rather promptly (within 1 or 2 weeks) and hepatic function usually returns to normal within 6 to 8 weeks after use of the drug is discontinued.

SUMMARY AND CONCLUSIONS

Needle biopsy specimens of the liver were studied in eight patients with hypercholesteremia who had received continuous treatment with nicotinic acid for periods of 1 5/6 to 9 years and in three patients with hypercholesteremia who were not treated. At the time of biopsy of the treated patients, plasma cholesterol values ranged from 178 to 300 mg/100 ml. The values for serum glutamic-oxalacetic transaminase (SGOT), alkaline phosphatase, and serum bilirubin, though occasionally abnormal during treatment, were normal at the time of biopsy in all eight patients. One patient had sulfobromophthalein retention of 6% and grade 3 cephalin flocculation. The concentration of serum albumin was less than 3 gm/100 ml in only two patients. In the untreated patients the plasma cholesterol values ranged from 242 to 356 mg/100 ml. Only one untreated patient had an abnormal SGOT value (2.88 μmoles/hr/ml).

Histologic examination revealed normal liver or only minor histologic alterations in both treated and untreated patients. In treated patients, electron microscopic studies disclosed dilatation of the endoplasmic reticulum with formation of numerous vesicles and sacs of various sizes and shapes. These were largely smooth-surfaced, but many still had a few particles attached. Numerous ribosomes were observed in the ground substance. The mitochondria revealed unusual shapes and markedly elongated and giant forms. In three patients, crystalloids were observed in the mitochondrial matrix. Other organelles, glycogen, and lipid appeared to be normal. The alterations are interpreted as evidence of focal cytoplasmic degradation of endoplasmic reticulum and mitochondria, which, in most instances, has not become severe enough to interfere seriously with cell function or produce clinical or laboratory evidence of hepatic dysfunction. The fact that changes in the endoplasmic reticulum and the mitochondria may at times occur in clinically and histologically normal livers would suggest that their presence does not contraindicate the use of nicotinic acid in the treatment of carefully supervised patients with hypercholesteremia.

REFERENCES

1. Rivin, A. U.: Jaundice Occurring During Nicotinic Acid Therapy for [illegible] JAMA 170:2068-2069 (Aug. 22) 19[illegible]

2. Pardue, W. O.: Severe Liver Dysfunction During Nicotinic Acid Therapy. JAMA *177*:137-138 (Jan. 14) 1961.

3. Berge, K. G., Achor, R. W. P., Christensen, N. A., Mason, H. L., and Barker, N. W.: Hypercholesteremia and Nicotinic Acid: A Long-Term Study. Amer J Med *31*:24-36 (July) 1961.

4. Christensen, N. A., Achor, R. W. P., Berge, K. G., and Mason, H. L.: Nicotinic Acid Treatment of Hypercholesteremia: Comparison of Plain and Sustained-Action Preparations and Report of Two Cases of Jaundice. JAMA *177*:546-550 (Aug. 26) 1961.

5. Engelberg, J.: Liver Function Studies in Humans With Elevated Levels of Serum Cholesterol and/or Low Density Lipoproteins. (Abstr.) Circulation *20*:983-984 (Nov.) 1959.

6. Parsons, W. B., Jr., and Flinn, J. H.: Reduction of Serum Cholesterol Levels and Beta-Lipoprotein Cholesterol Levels by Nicotinic Acid. Arch Intern Med (Chicago) *103*:783-790 (May) 1959.

7. Parsons, W. B., Jr.: Studies of Nicotinic Acid Use in Hypercholesteremia: Changes in Hepatic Function, Carbohydrate Tolerance, and Uric Acid Metabolism. Arch Intern Med (Chicago) *107*:553-567 (May) 1961.

8. Parsons, W. B., Jr.: The Effect of Nicotinic Acid on the Liver: Evidence Favoring Functional Alteration of Enzymatic Reactions Without Hepatocellular Damage. In Altschul, R. (ed.): Niacin in Vascular Disorders and Hyperlipemia. Springfield, Illinois, Charles C. Thomas, Publisher, 1964, pp. 263-286.

9. Camain, R., Rouiller, C., and Dupin, H.: Evolution de la steatose hépatique dans le Kwashiorkor sous l'influence du regime hyperprotidique. Etude en microscopie normale et électronique. Ann Anat Path (Paris) *4*:220-241, 1959.

10. Hübner, G.: Electronmikroskopische Untersuchungen bei chronischen Lebererkrankungen des Menschen. Ver Deutsch Ges Path *46*:224-229, 1962.

11. Steiner, J. W., Jézéquel, Anne Marie M., Philips, M. J., Miyai, K., and Arakawa, K.: Some Aspects of the Ultrastructural Pathology of the Liver. In Popper, H., and Schaffner, F. (eds.): Progress in Liver Disease. New York, Grune & Stratton, Inc., vol. 2, 1965, pp. 203-372.

12. Schaffner, F., Loebel, A., Weiner, H. A., and Barka, T.: Hepatocellular Cytoplasmic Changes in Acute Alcoholic Hepatitis. JAMA *183*:433-436 (Feb. 2) 1963.

13. Reppart, J. T., Peters, R. L., Edmondson, H. A., and Baker, R. F.: Electron and Light Microscopy of Sclerosing Hyaline Necrosis of the Liver: The Development of Alcoholic Hyaline Bodies. Lab Invest *12*:1138-1153 (Dec.) 1963.

14. Biava, C.: Mallory Alcoholic Hyalin: A Heretofore Unique Lesion of Hepatocellular Ergastoplasm. Lab Invest *13*:401-420 (Apr.) 1964.

15. Svoboda, D. J., and Manning, R. T.: Chronic Alcoholism With Fatty Metamorphosis of the Liver. Amer J Path *44*:045-054 (Apr.) 1964.

16. Rouiller, C., and Jézéquel, A. M.: Electron Microscopy of the Liver. In: The Liver: Morphology, Biochemistry, Physiology. New York, Academic Press, Inc., vol. 1, 1963, pp. 195-364.

17. David, H.: Submicroscopic Ortho- and Pathomorphology of the Liver. [Translated by H. G. Epstein.] New York, The Macmillan Company, 1964, 412 pp.

18. Porter, K. R., and Bruni, C.: An Electron Microscope Study of the Early Effects of 3'-Me-DAB on Rat Liver Cells. Cancer Res *19*:997-1009 (Nov.) 1959.

19. Barker, E. A., Smuckler, D. A., and Benditt, E. P.: Effects of Thioacetamide and Yellow Phosphorus Poisoning on Protein Synthesis *In Vivo*. Lab Invest *12*:955-960, 1963.

20. Remmer, H., and Merker, H. J.: Enzyminduktion und Vermehrung von endoplasmatischem Reticulum in der Leberzelle während der Behandlung mit Phenobarbital (Luminal). Klin Wschr *41*:276-283 (Mar. 15) 1963.

21. Herdson, P. B., Gervin, P. J., and Jennings, R. B.: Fine Structural Changes in Rat Liver Induced by Phenobarbital. Lab Invest *13*:1032-1037, 1964.

22. Orrenius, S., Ericsson, J. L. E., and Ernster, L.: Phenobarbital-Induced Synthesis of the Microsomal Drug-Metabolizing Enzyme System and Its Relationship to the Proliferation of Endoplasmic Membranes. A Morphologic and Biochemical Study. J Cell Biol *25*:627-639 (June) 1965.

23. Oberling, C., and Rouiller, C.: Les effets de l'intoxication aiguë au tétrachlorure de carbone sur le foie du rat: Etude au microscope électronique. Ann Anat Path (Paris) *1*:401-427, 1956.

24. Mölbert, E., Hill, K., and Büchner, F.: Die Kanserisierung der Leberparenchymzelle durch Diäthylnitrosamin im elektronenmikroskopischen Bild. Beitr Path Anat *126*:218-240 (June) 1962.

25. Jatlow, P., Adams, W. R., and Handschumacher, R. E.: Pathogenesis of Orotic Acid-Induced Fatty Change in the Rat Liver. Amer J Path *47*:125-136 (July) 1965.

26. Reichel, J., Goldberg, S. B., Ellenberg, M., and Schaffner, F.: Intrahepatic Cholestasis Following Administration of Chlorpropamide: Report of a Case With Electron Microscopic Observations. Amer J Med *28*:654-660 (Apr.) 1960.

27. Novikoff, A. B.: Mitochondria (Chondriosomes). In Brachet, Jean, and Mirsky, A. E. (eds.): The Cell: Biochemistry, Physiology, Morphology; Cells and Their Component Parts. New York, Academic Press, Inc., vol. 2, 1961, pp. 299-421.

28. Thiéry, J. P., and Caroli, J.: Étude au microscope électronique de l'amylose hépatique primaire de l'homme. Sem Hop Paris 37:29-40 (Jan. 2) 1961

29. Lagunes, R., and Bianchi, N.: Fine Structure of the Liver in Human Idiopathic Diabetes Mellitus. I. Parenchymal Cell Mitochondria. Exp Molec Path 2:203-214 (June) 1963

30. Kiessling, K. H., Lindgren, L., Strandberg, B., and Tobe, U.: Electron Microscopic Study of Liver Mitochondria From Human Alcoholics. Acta Med Scand 176:595-598, 1964.

31. Hudek, R., Szanto, P. B., and Steigmann, F.: Mitochondrial Crystalloids in Human "Alcoholic" Hepatitis. (Abstr.) Amer J Path 44:26a (Apr.-June) 1964.

32. Porta, E. A., Bergman, B. J., and Stein, A. A.: Acute Alcoholic Hepatitis. Amer J Path 46:657-676 (Apr.) 1965.

33. Lehninger, A. L.: The Mitochondrion: Molecular Basis of Structure and Function. New York, W. A. Benjamin, Inc., 1964, 263 pp.

34. Jézequel, A. M.: Myelin Degeneration of the Mitochondria of the Human Liver in Epithelioma of the Choledochus and in Viral Jaundice: Study With the Electron Microscope. J Ultrastruct Res 3:210-215 (Dec.) 1959.

35. Daems, W. T., and Van Rijssel, T. G.: The Fine Structure of the Peribiliary Dense Bodies in Mouse Liver Tissue. J Ultrastruct Res 5:263-290 (June) 1961.

36. Magnaini, E.: Filamentous Inclusions in the Matrix of Mitochondria From Human Livers. J Ultrastruct Res 11:525-544 (Dec.) 1964.

37. Wills, E. J.: Crystalline Structures in the Mitochondria of Normal Human Liver Parenchymal Cells. J Cell Biol 21:511-514 (Mar.) 1965.

38. Watrach, A. M.: Degeneration of Mitochondria in Lead Poisoning. J Ultrastruct Res 10:177-181 (Apr.) 1964.

39. Fernández-Morán, H.: Cell-Membrane Ultrastructure: Low Temperature Electron Microscopy and X-ray Diffraction Studies of Lipoprotein Components in Lamellar Systems. Circulation 26:1039-1065 (Nov.) 1962.

40. Dervichian, D. G.: Swelling and Molecular Organisation in Colloidal Electrolytes. Trans Faraday Soc 42B:180-187, 1946.

41. Robertson, J. D.: Structural Alterations in Nerve Fibers Produced by Hypotonic and Hypertonic Solutions. J Biophys Biochem Cytol 4:349-364, 1958.

42. Revel, Jean P., Ito, S., and Fawcett, D. W.: Electron Micrographs of Myelin Figures of Phospholipids Simulating Intracellular Membranes. J Biophys Biochem Cytol 4:495-496, 1958.

43. Stoeckenius, W.: An Electron Microscope Study of Myelin Figures. J Biophys Biochem Cytol 5:491-500 (May 25) 1959.

44. Avi-Dor, Y.: A Spectrophotometric Study of the Spontaneous and Microsome-Induced Swelling of Rat-Liver Mitochondria. Biochem Biophys Acta 39:53-61, 1960.

45. Pressman, B. C., and Lardy, H. A.: Effect of Surface Active Agents on the Latent ATPase of Mitochondria. Biochem Biophys Acta 21:458-466, 1956.

46. Lehninger, A. L.: The Relationship of the Adenosine Polyphosphates to Fatty Acid Oxidation in Homogenized Liver Preparations. J Biol Chem 157:363-381 (Jan.) 1945.

47. Björntorp, P., Ells, H. A., and Bradford, R. H.: Albumin Antagonism of Fatty Acid Effects on Oxidation and Phosphorylation Reactions in Rat Liver Mitochondria. J Biol Chem 239:339-344 (Jan.) 1964.

48. Gaylor, J. L., Hardy, R. W., and Baumann, C. A.: Effects of Nicotinic Acid and Related Compounds on Sterol Metabolism in the Chick and Rat. Nutrition 70:293-301 (Mar.) 1960.

49. Perry, W. P.: Effect of Nicotinic Acid and Nicotinamide on Incorporation of Acetate Into Cholesterol, Fatty Acids and CO_2 by Rat Liver Slices. Metabolism 9:686-689 (July) 1960.

50. Hruban, Z., Spargo, B., Swith, H., Wissler, R. W., and Kleinfeld, R. G.: Focal Cytoplasmic Degradation. Amer J Path 43:657-664 (June) 1963.

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NICOTINIC ACID AND ALCOHOL-INDUCED LIPEMIA

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SUMMARY

Nicotinic acid, administered orally in six 100 mg doses spaced one hour apart, markedly reduced the usual alcohol-induced enhancement of alimentary lipemia in man. In rats, 200 mg of nicotinic acid/kg body weight inhibited the increase in postprandial plasma and liver triglycerides associated with ingestion of a corn oil–alcohol mixture, and reduced incorporation of the ^{14}C-labeled dietary fat into plasma triglycerides.

Key words: *Beta-adrenergic blockers – High fat diet – Hyperlipemia – Nicotinic acid*

A number of studies have shown that ingestion of alcoholic drinks before a meal enhances the postprandial rise of plasma triglycerides in man[1–6]. A similar enhancement of lipemia has been seen in rats receiving ethanol and corn oil[7,8]. Comparison of the ^{14}C content, or fatty acid distribution of postprandial plasma triglycerides with that of the administered dietary fat suggests that the plasma triglycerides were mainly derived from the diet[4,6]. Little definite information is available about the metabolic processes involved in the alcohol-induced lipemic effects or about the modification of these effects by various hypolipemic agents. It was decided, therefore, to investigate whether nicotinic acid, a compound blocking the release of free fatty acids from the adipose tissue[9,10] inhibits the lipemia-enhancing effects of preprandial alcohol in man and animals.

METHODS

Human studies

Seven 24 to 25-year-old subjects volunteered for the study. After an overnight fast they received 120 ml (4 oz) of bourbon whiskey (100 proof, 50% ethanol)

diluted with water to about 200 ml. The drink was consumed over a 15-minute period. The subjects then ate a standardized mixed meal consisting of two eggs, toast and butter, milk and coffee[4]. The test was repeated within one week. Nicotinic acid, in a total amount of 600 mg divided into six 100 mg doses, was taken with one of the meals. The first dose was given just prior to the ingestion of the alcohol, the other 5 doses were administered at hourly intervals after completion of the meal. To eliminate the possibility of a sequence bias, 3 subjects received the drug with their first meal and the remaining 4 with the second meal. Venous blood samples were taken before ingestion of whiskey and 3 and 6 hours after completion of the meal. Plasma was separated in a refrigerated centrifuge and the triglyceride and alcohol levels were measured[11,12].

Animal studies

Two different series of experiments were carried out. Female Sprague-Dawley rats weighing about 250 g each were used in the first series. After an overnight fast, 18 of the animals received, by stomach tube, 5 g ethanol and 5 g of corn oil/kg of body weight. Nine of the rats were pretreated with 200 mg nicotinic acid/kg body given intraperitoneally; one-half of the dose was administered 60 min and the other 10 min before the administration of the alcohol corn oil mixture. An additional 7 rats received 5 g of corn oil/kg body weight and glucose in amounts isocaloric with ethanol, and served as the controls. Sixteen hours after the meal the animals were bled by heart puncture and their livers were removed. Blood samples were processed in a refrigerated centrifuge and plasma and liver triglycerides measured[11,13]. A similar experimental arrangement was used in the second series, except that 15 animals were used, and the oil contained trace amounts of [1-^{14}C]triolein. On thin-layer chromatography[14], more than 95% of the radioactivity was associated with the triolein moiety of the labeled preparation. Aliquots of the lipid extracts prepared for triglyceride determination in plasma and liver were evaporated, redissolved in a toluene–triton–scintillation fluid and counted in a liquid scintillation spectrometer (Packard Instrument, LaGrange, Ill.).

RESULTS

Human studies

Administration of nicotinic acid markedly reduced the postprandial lipemic response (Fig. 1). Three hours after the meal, the plasma triglyceride levels in the series without nicotinic acid increased 81 mg/100 ml over the initial value of 67 mg/100 ml; the corresponding 3 hour rise in the series with nicotinic acid amounted to 41 mg/100 ml over the initial value of 66 mg/100 ml ($P < 0.05$, paired comparison). A similar difference was observed 6 hours after the meal. An even more pronounced nicotinic acid effect was observed in an additional volunteer who demonstrated an unexpected high fasting triglyceride level. Without nicotinic acid, his plasma triglyceride levels increased from the initial value of 338 mg/100 ml to 840 mg/100 ml,

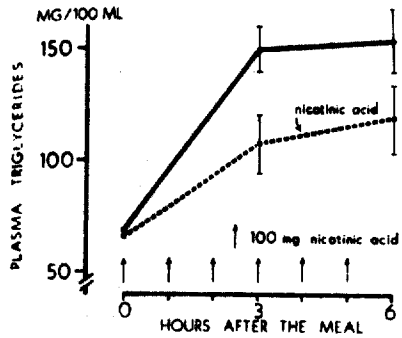

Fig. 1. Effect of nicotinic acid on alcohol-induced postprandial lipemia in man. The arrows indicate the time of nicotinic acid administration; the vertical lines represent the standard error of the mean.

6 hours after the meal plus alcohol. With nicotinic acid, his 6-hour plasma triglyceride decreased 42 ml below the initial levels of 494 mg/100 ml.

The average plasma alcohol levels measured 3 and 6 hours after the meal were 35 and 11 mg/100 ml, respectively, for the series without nicotinic acid and 30.3 and 9.0 mg /100 ml for the series with nicotinic acid. No definite correlation seemed to exist between the individual plasma alcohol levels and the changes in plasma triglycerides.

Animal studies

The results of the first series are shown in Fig. 2. Sixteen hours after administration of the corn oil-ethanol mixture the average plasma triglyceride level amounted to 254 ± 69 mg/100 ml (mean ± standard error), while the corresponding average level of the control animals was 41 ± 4 mg/100 ml only. Pretreatment with nicotinic

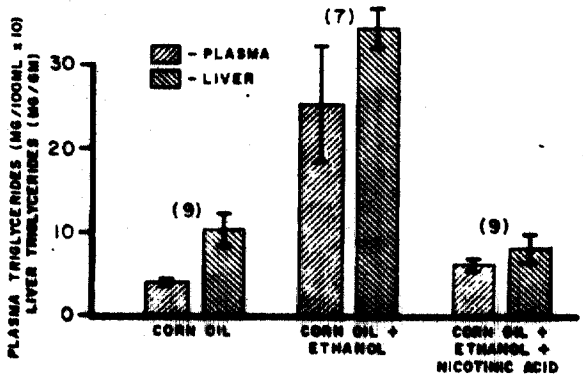

Fig. 2. Effect of nicotinic acid on postalcoholic plasma and liver triglycerides in the rats. The vertical lines represent the standard error of the mean; the number of animals is shown in parenthesis.

TABLE 1

EFFECT OF NICOTINIC ACID ON POST-ETHANOLIC LIPEMIA IN THE RAT[a]

	Corn oil	*Corn oil and ethanol*	*Corn oil and ethanol and nicotinic acid*
Plasma triglycerides, mg/100 ml	20.4 ± 2.6	134.6 ± 33.7[b]	52.8 ± 4.6[b]
Plasma ^{14}C-activity, counts/min/ml	53 ± 7	622 ± 151[b]	75 ± 13[b]
Liver triglycerides, mg/g	17.5 ± 1.4	33.0 ± 5.3[b]	11.9 ± 3.5
Liver ^{14}C-activity, counts/min/g	3544 ± 901	3840 ± 1063	2347 ± 1367

[a] Each group consisted of 5 animals. Corn oil (5 g/kg body weight) and ethanol (5 g/kg body weight) were administered by stomach tube, nicotinic acid (2 doses of 100 mg/kg body weight) was injected intraperitoneally 60 and 10 min before the oil. The animals were sacrificed 16 h after the meal.

[b] $P < 0.05$ against the corn oil group.

acid significantly reduced the ethanol-induced enhancement of lipemia ($P < 0.01$). The protective effect of nicotinic acid was even more pronounced in the values for liver triglycerides in the group receiving corn oil and ethanol. Nicotinic acid reduced the hepatic triglyceride level below that of the control animals. Similar effects of nicotinic acid were also observed in the second series (Table 1). The rise in plasma triglyceride seen after administration of the alcohol-corn oil mixture was associated with a rise in plasma ^{14}C counts; the increase in liver triglycerides was, however, not reflected in corresponding changes in ^{14}C activity. The lower plasma triglyceride levels seen after pretreatment with nicotinic acid were paralleled by lower plasma ^{14}C counts.

DISCUSSION

The results obtained in the present study suggest that nicotinic acid can effectively counteract the enhanced lipemic response to an alcohol–dietary fat combination in both man and rats. In man, this response was observed with a relatively low dose of 600 mg. Daily doses of up to 6 g of nicotinic acid are being used in the treatment of hypercholesteremia[15]. In the rat, pretreatment with a dose of 200 mg/kg body weight offered almost total protection against the lipemic effects of alcohol.

The metabolic processes involved in the observed modification of the alcohol-induced enhancement of alimentary lipemia by nicotinic acid have not been definitely clarified. The low ^{14}C counts in the plasma lipids of rats suggest a decreased incorporation of the dietary fat into circulating triglycerides. Furthermore, nicotinic acid prevented the alcohol-induced rise of hepatic triglycerides. Since the rise of hepatic lipids in animals receiving corn oil and alcohol was not associated with a corresponding elevation of ^{14}C activity, one can assume that these triglycerides represent the re-esterified endogenous fatty acids mobilized by a large dose of ethanol[16,17]. Nicotinic acid probably inhibited such mobilization of FFA from the endogenous lipid stores. A similar reduction of hepatic triglycerides by nicotinic acid has been observed in

animals receiving a large dose of ethanol without dietary fat[18]. Additional properties of nicotinic acid, which have been previously reported and which might have contributed to the results found in our animal study, include reduction of fasting and postprandial plasma triglycerides[19,20] and retention of dietary fat in the gastrointestinal tract[21].

ACKNOWLEDGEMENT

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REFERENCES

1 TALBOTT, G. D. AND B. M. KEATING, Effect of preprandial whiskey on postalimentary lipemia, *Geriatrics*, 1962, 17: 802.
2 BREWSTER, A. C., H. G. LANKFORD, M. G. SCHWARTZ AND J. F. SULLIVAN, Ethanol and alimentary lipemia, *Am. J. Clin. Nutrition*, 1966, 19: 255.
3 VERDY, M. AND A. GATTEREAU, Ethanol, lipase activity and serum lipid level, *Am. J. Clin. Nutrition*, 1967, 20: 997.
4 BARBORIAK, J. J. AND R. C. MEADE, Enhancement of alimentary lipemia by preprandial alcohol, *Am. J. Med. Sci.*, 1968, 255: 245.
5 MCMAHON F. G. AND J. R. RYAN, Alcohol-exaggerated postprandial lipemia, *J. Louisiana State Med. Soc.*, 1969, 121: 181.
6 WILSON, E. D., P. H. SCHREIBMAN, A. C. BREWSTER AND R. A. ARKY, The enhancement of alimentary lipemia by ethanol in man, *J. Lab. Clin. Med.*, 1970, 75: 264.
7 DILUZIO, N. R. AND M. POGGI, Abnormal lipid tolerance and hyperlipemia in acute ethanol-treated rats, *Life Sci.*, 1963, 2: 751.
8 BARBORIAK, J. J. AND R. C. MEADE, Postalcoholic lipemia in the rat, *Quart. J. Studies Alc.*, 1968, 29: 283.
9 CARLSON, L. A. AND L. ORO, The effect of nicotinic acid on the plasma free fatty acids: Demonstration of a metabolic type of sympathicolysis, *Acta Med. Scand.*, 1962, 172: 641.
10 CARLSON, L. A., Inhibition of the mobilization of free fatty acids from adipose tissue, *Ann. N.Y. Acad. Sci.*, 1965, 131: 119.
11 VANHANDEL, E., AND D. B. ZILVERSMIT, Micromethod for the direct determination of serum triglycerides, *J. Lab. Clin. Med.*, 1957, 50: 152.
12 AULL, J. C. AND W. M. MCCORD, A simple apparatus and procedure for the determination of blood alcohol, *Tech. Bull. Registry Med. Technologists*, 1964, 34: 125.
13 BUTLER, JR., W. M., H. M. MALING, M. G. HORNING AND B. B. BRODIE, The direct determination of liver triglycerides *J. Lipid Res.*, 1961, 2: 95.
14 TUNA, N., H. K. MANGOLD AND D. G. MOSSER, Re-evaluation of the ^{131}I-triolein absorption test. Analysis and purification of commercial radioiodinated triolein and clinical studies with pure preparations, *J. Lab. Clin. Med.*, 1968, 61: 620.
15 PARSONS, JR., W. B. AND J. H. FLINN, Reduction in elevated blood cholesterol levels by large doses of nicotinic acid, *J. Am. Med. Assoc.*, 1957, 165: 234.
16 MALLOV, S., Effect of ethanol intoxication on plasma-free fatty acids in the rat, *Quart. J. Studies Alc.*, 1961, 22: 250.
17 BRODIE, B. B., W. M. BUTLER, JR., M. G. HORNING, R. P. MAICKEL AND J. M. MALING, Alcohol-induced triglyceride deposition in liver through derangement of fat fransport, *Am. J. Clin. Nutrition*, 1961, 9: 432.
18 FEX, G. AND T. OLIVECRONA, Role of uptake and oxidation of plasma-free fatty acids by the liver in the development of ethanol-induced fatty liver, *Acta Physiol. Scand.*, 1969, 75: 78.
19 CARLSON, L. A. AND E. R. NYE, Acute effects of nicotinic acid in the rat, Part I (Plasma and liver lipids and blood glucose), *Acta Med. Scand.*, 1966, 179: 453.
20 JACOBS, R. S., M. S. GREBNER AND D. C. COOK, Effect of nicotinic acid on serum triglyceride, cholesterol and chylomicrons in rat, *Proc. Soc. Exptl. Biol. Med.*, 1965, 119: 1117.
21 BARBORIAK, J. J., R. C. MEADE, J. OWENBY AND R. A. STIGLITZ, Blockers of free fatty acid release and postprandial lipemia, *Arch. intern. pharmacodynamie*, 1968, 176: 249.

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15356

Toxicity of Nicotinic Acid and Some of Its Derivatives.

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Handler and Dann[1] observed that the incorporation of large amounts of nicotinamide into the diet caused a decreased growth rate in young rats whereas nicotinic acid and trigonelline had little effect. It was concluded that the decreased growth rate was due to the depletion of the stores of methionine (which was deemed essential for the methylation of nicotinamide) since in the process of detoxication nicotinamide was methylated and excreted as what appeared to be trigonelline. Later investigations[2] indicate that the principal detoxication product is more probably nicotinamide methochloride (N^1-methylnicotinamide).

The marked toxicity of nicotinamide when administered subcutaneously leads one to suspect that the molecule itself exerts a toxic action which is independent of the effect of the compound on the depletion of the stores of "methyl donors." To determine the influence of molecular configuration on toxicity highly purified preparations of pyridine, nicotinic acid (as the sodium salt), nicotinamide, coramine (N,N-diethylnicotinamide), and the respective methyl derivatives of these compounds were administered subcutaneously to young rats of both sexes weighing between 50 and 100 g. The dose needed to kill one-half of the animals in each group was determined. The results appear in Table I.

TABLE I.
Relative Toxicity of Some Derivatives of Pyridine (Subcutaneous Injection).

	LD_{50}* g/kilo	Relative-order of toxicity
Pyridine	1.00	5.00
Pyridine methochloride	0.28	17.9
Nicotinic acid	5.0	1.0
Trigonelline	5.0	1.0
Nicotinamide	1.68	3.0
Nicotinamide methochloride	2.40	2.08
Coramine	0.24	20.8
Coramine methochloride	1.90	2.63

* LD_{50} = dose needed to kill one-half of the animals.

Methylation decreases the toxicity of coramine and nicotinamide, increases the toxicity of pyridine and has little or no apparent influence on the toxicity of nicotinic acid. It is certain that methylation is not the only factor concerned in the toxicity of these compounds since nicotinamide methochloride is more toxic than nicotinic acid. If pyridine is methylated in the rat as it is in the dog[3] this is an example of the conversion of a toxic compound into one which is even more toxic in the process of "detoxication."

Nicotinamide, coramine and the methyl derivatives of these compounds cause paralysis of the respiratory center when administered in large doses. The injection of pyridine and pyridine methochloride in amounts slightly below the lethal dose produced a deep anesthesia of about 2 hours' duration. These compounds had no apparent effect on respiration. Trigonelline and nicotinic acid have such a low order of toxicity that an accurate estimation is impossible since in the massive doses employed the principal effect may be due to the administration of large amounts of hypertonic solutions.

With regard to the effect of the configura-

[1] Handler, P., and Dann, W. J., *J. Biol. Chem.*, 1942, **146**, 357.

[2] Huff, J. W., and Perlzweig, W. A., *Science*, 1943, **97**, 538; Ellinger, P., and Coulson, R. A., *Nature*, London, 1943, **152**, 383.

[3] His, W., *Arch. exp. Path. u. Pharm.*, 1887, **22**, 253.

tion on the β position of pyridine it is evident that the presence of the carboxyl group decreases the toxicity of the molecule. Conversion of this group to the simple amide markedly increases toxicity; the presence of a substituted amide on this position increases the toxicity so that it exceeds that of the unsubstituted pyridine. The high toxicity of coramine suggests the necessity for caution in its administration.

Summary. The relative toxicity of subcutaneous injections of nicotinic acid, nicotinamide, coramine, pyridine and their respective methyl derivatives has been determined. Methylation decreases the toxicity of coramine and nicotinamide, increases the toxicity of pyridine and has little or no apparent influence on the toxicity of nicotinic acid. The toxicity of the non-methylated compounds appears to be due directly to the structure of the compounds rather than to the depletion of the body stores of methyl donors in the process of detoxication.

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The Determination of Nicotinic Acid by Fluorimetric Densitometry

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A method is reported for the rapid determination of added nicotinic acid in meat. Nicotinic acid is converted on silica plates into a fluorescent compound by ultraviolet irradiation. After chromatographic separation from nicotinamide, the concentration is measured by means of a densitometer.

The use of nicotinic acid for the preservation of the red colour of raw minced meat is allowed in The Netherlands up to a concentration of 0·015 per cent. In order to determine this concentration we have used thin-layer chromatography on silica mixed with a fluorescence indicator that makes the spots visible by fluorescence quenching under ultraviolet light at a wavelength of 254 nm. The determination was carried out spectrophotometrically at 263 nm after extraction of the spots with ethanol (laboratory method of Keuringsdienst van Waren, unpublished).

By use of this method it was found that, after ultraviolet irradiation at a wavelength of 254 nm, fluorescence at 365 nm was induced. With a Vitatron densitometer - fluorimeter it is easy to detect and determine small amounts of the additive so that the time-consuming and unreliable extraction procedure can be omitted.

Experimental

Apparatus and materials—

Vitatron flying-spot densitometer, TLD 100.

Filters—A filter that operated at a wavelength of 365 nm was used as the primary filter and we selected one that operated at 435 nm as the secondary filter. The light source was a mercury lamp and the recorder was a Vitatron UR402.

Philips Blacklight lamp HPW, 125 *W*—The maximum emission of this lamp occurred at a wavelength of 365·5 nm.

Pleuger Chromatolux 44 *U* 100 *lamp*—The maximum emission of this lamp occurred at a wavelength of 253·7 nm.

Merck DC ready-made Kieselgel plates (*without fluorescence indicator*)—These were 20 × 20-cm plates with a layer thickness of 0·25 mm.

Standard nicotinic acid solution—This solution consisted of 20·0 mg of nicotinic acid in 1 litre of 96 per cent. ethanol.

Chromatographic solvent mixture—The solvent mixture used was benzene - acetone - methanol - acetic acid (56 + 44 + 16 + 4).

Determination of the irradiation time—

Amounts of 100 to 2000 ng of nicotinic acid (*i.e.*, 5 to 100 μl of standard nicotinic acid solution) were applied to the plates. The plates were developed for half an hour in an equilibrated tank, dried for half an hour at 105 °C and irradiated with the Chromatolux lamp at a distance of 6 cm for different lengths of time. Measurements of the fluorescence were made with the densitometer. The results of these measurements are given in Tables I and II.

From the tables it is clear that a reaction takes place which is almost completed in 25 minutes, so that half an hour must be sufficient for maximum fluorescence to occur. The meter readings show good proportionality with the amounts used.

Procedure—

A 15-g sample of minced meat is weighed into a 150-ml beaker and 50 ml of 96 per cent. ethanol are added. The beaker, covered with a watch-glass, is heated for half an hour on a boiling water bath. The ethanolic extract is then filtered through cotton-wool into a 100-ml calibrated flask. The residue is washed three times with 20, 20 and 15 ml of ethanol. After dilution to the calibration mark, 20 μl of the solution are spotted on to a thin-layer plate.

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TABLE I

MEASUREMENT OF FLUORESCENCE IN COUNTS

[illegible]15 counts = 1 cm² of peak area

Time of irradiation/minutes ..	2	5	10	15	20	25	30	60
Amount of nicotinic acid added/ng—								
100	2	5	6	8	9	10	10	9
200	8	12	13	17	19	20	19	18
400	7	15	27	33	36	39	38	37
600	9	18	36	46	48	57	58	54
800	13	29	48	63	65	76	77	71
1000	22	41	64	80	85	86	96	90
1500	31	60	95	117	128	138	141	133
2000	43	81	124	156	160	166	166	158

Instrument settings: level, F; zero, 7; damping, 2; diaphragm, 0·25 mm; mode, linear II [illegible], primary filter, [illegible] nm; secondary filter, 435 nm; amplitude, 14 (7 mm); paper velocity, 6 (4 cm min⁻¹); integrator, 7 ([illegible] counts min⁻¹ cm⁻¹); span, 8; and scanning speed, 3 cm min⁻¹.

On the same plate amounts of standard solution equivalent to 400 and 600 ng of nicotinic acid are also applied. The plate is developed for half an hour and dried for another half hour at 105 °C. It is next irradiated for half an hour with the Chromatolux lamp at a distance of 6 cm. The spots are then made visible under the Blacklight lamp and the plate is marked so that the measurements with the densitometer can be made in one run. The result is obtained by comparing the fluorescence of the sample with those of the standards.

Under the conditions described the R_F value of nicotinic acid is 0·35, while that of nicotinamide is 0·45. The amplitude of the flying spot of the densitometer should be adjusted so that only nicotinic acid is measured.

TABLE II

MEASUREMENT OF FLUORESCENCE IN COUNTS

Conditions as in Table I, but with span equal to 10

Time of irradiation/minutes ..	2	5	10	15	20	25	30	60
Amount of nicotinic acid added/ng—								
100	6	9	16	21	22	22	22	20
200	18	26	41	40	43	42	43	40
400	18	39	60	76	87	84	83	79
600	19	47	72	108	113	126	126	120
800	26	67	110	144	154	168	164	158
1000	51	90	142	180	190	212	210	201
1500	64	139	215	—	—	—	—	—
2000	92	172	—	—	—	—	—	—

RESULTS AND DISCUSSION

To 15-g samples of minced meat were added 750, 1500, 2250, 3000 and 3750 μg of nicotinic acid. The recoveries were 98·0, 99·3, 97·8, 101·8 and 96·3 per cent., respectively. No nicotinic acid was found in a blank sample of the meat. The sensitivity of the method for nicotinamide is about 1½ times as great as that for nicotinic acid. Among chemically similar compounds, benzoic acid does not show the induced fluorescence, but the herbicides paraquat and diquat do, with a higher sensitivity than that for nicotinic acid (two and five times greater, respectively). Ascorbic acid shows some fluorescence before irradiation, but in the concentration used in practice the ultraviolet light destroys this compound.

Better separation from nicotinamide is achieved by use of a solvent mixture of propanol - 10 per cent. ammonia solution (95 + 5), but the time required (3 hours) is much longer.[1]

REFERENCE

1. Randerath, K., "Dünnschicht Chromatographie," Verlag Chemie GmbH, Weinheim, 1962, p. 156.

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INTERACTION OF NICOTINAMIDE WITH RESERPINE AND CHLORPROMAZINE

II. Some effects on the central nervous system of the mouse (1), (2)

BY

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(Received for publication 14-3-1960).

During the course of investigating the biochemical interaction of nicotinamide and tranquillizing drugs on diphosphopyridine nucleotide (DPN) synthesis in liver, it was observed that nicotinamide in conjunction with reserpine or chlorpromazine produced a greater degree of sedation than would have been expected from either drug alone. KORNETSKY has obtained preliminary evidence in man which is consistent with this observation (2). Coupled with the observations of HOFER and his co-workers (5) that nicotinamide and nicotinic acid are useful in the treatment of early schizophrenia and the report by WOOLLEY (8) that nicotinamide has a tranquillizing action in mice, our experiments indicate a central nervous system action for nicotinamide. This report presents the results of studies of the effect of nicotinamide and the tranquillizing drugs on the spontaneous activity of mice and upon the ability of nicotinamide in combination with reserpine and chlorpromazine to potentiate anesthesia induced by pentobarbital in mice.

(1) A preliminary report of this work was presented at the American Chemical Society, 135th National Meeting, Boston, April 1959.

(2) This investigation was supported by a grant [M 2438 (C)] from the National Institute of Mental Health, National Institutes of Health, United States Public Health Service.

METHODS

Hybrid male mice [(BALB/c An ♂ DBA/2J)F_1, 8 to 10 weeks old, of 20 to 25 grams body weight] were used in all experiments reported. A small light weight cage suspended on a spring and attached to a ink writer lever and a kymograph was used for the "jiggle" cage experiment (7). Each mouse was placed in the jiggle cage and allowed to accustom himself to the cage. The mouse was then removed and injected with the appropriate drug or placebo and replaced in the cage. Continuous recordings were made during the time the mouse was in the jiggle cage. The jiggle cage apparatus allowed a simple measure of the spontaneous activity of the mouse. The experiments reported are representative of at least 10 animals.

The duration of anesthesia is defined as the time interval from the loss of the righting reflex of mice until the reflex is regained.

RESULTS

The effect of nicotinamide on spontaneous activity of mice. The tracings presented in Figure 1 show the results of an experiment which studied the effect on spontaneous activity of treating mice with both reserpine and nicotinamide. The upper tracing presents first a control interval followed by the injection of reserpine (1 mg/kg). At this level reserpine apparently exerted no detectable effect on the reduction of spontaneous activity of the mouse. However, 55 minutes following the reserpine treatment nicotinamide was injected into the mouse and within 2 or 3 minutes spontaneous activity of the mouse had almost entirely disappeared. Visual observation of these animals showed them to be very lethargic, moving only when prodded. The lower tracing presented in Figure 1 shows the results of injecting reserpine, following a control interval, into the mouse. This time there appeared to be a slight reduction in spontaneous activity observable in the 50 to 55 minute interval. Following placebo (1) treatment of the animal in place of nicotinamide, no further reduction in spontaneous activity was observed. Thus, nicotinamide and reserpine appear to interact in such a manner that the spontaneous activity of the mouse is greatly reduced. A similar experiment showing the interaction of chlorpromazine and nicotinamide

(1) The placebo treatment consisted of the injection of water using the same volume replaced for the injection of the nicotinamide solution.

on spontaneous activity is presented by means of tracings in Figure 2. The upper line presents a short control interval followed by the injection of chlorpromazine (10 mg/kg). The chlorpromazine may be observed to have somewhat reduced spontaneous activity of the mouse. This reduction was still observed after 50 minutes. The injection of nicotinamide produced the complete cessation of spontaneous activity after

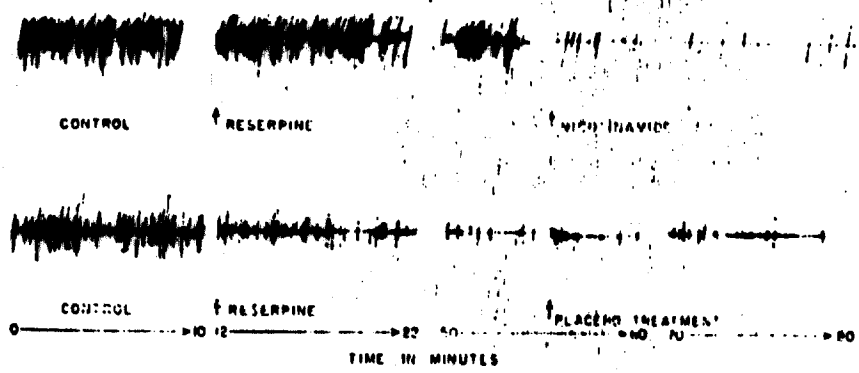

FIG. 1

The Interaction of Nicotinamide and Reserpine on Spontaneous Activity of the Mouse. The experimental details are described in the methods section. The upper tracing is for one mouse, the lower tracing for another mouse. The arrows indicate the time of injection.

5 minutes. The placebo control is presented in the lower line of Figure 2. The control interval records the spontaneous activity of the mouse followed by the injection of chlorpromazine which shows a reduction of spontaneous activity. This activity is reduced even after 50 minutes and occurs in bursts. The placebo treatment showed little or no effect

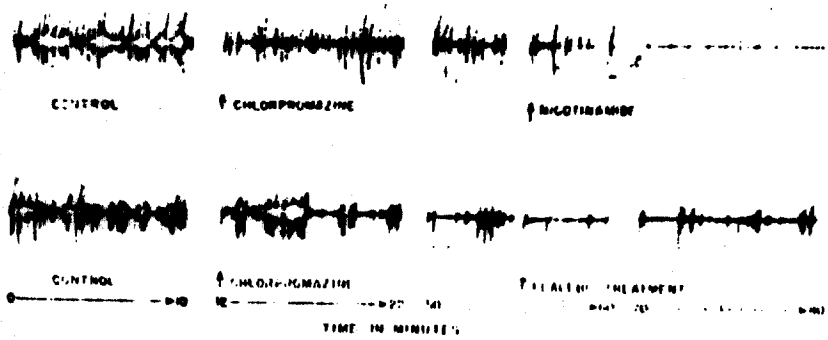

FIG. 2

The Interaction of Nicotinamide and Chlorpromazine on Spontaneous Activity of the Mouse. The details are described in Figure 1 and in the methods section.

on the reduction of spontaneous activity. In particular, the 70 to 80 minute interval which is presented should be compared to the corresponding chlorpromazine-nicotinamide tracing where activity has been completely suppressed. Of considerable interest is the data presented in Figure 3 which shows that nicotinamide alone was able to reduce spontaneous activity of the mouse. This indicates that nicotinamide itself can affect the central nervous system. The first part of the tracing presents a control interval. It may be seen that within 3 or 4 minutes following the injection of nicotinamide the spontaneous activity of th

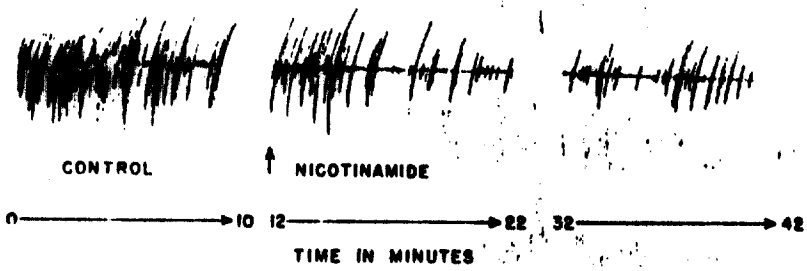

FIG. 3

Effect of Nicotinamide on Spontaneous Activity. The details are described in Figure 1 and in the methods section.

TABLE I

Effect of Nicotinamide and Chlorpromazine on Pentobarbital Anesthesia

Chlorpromazine (10 mg/kg body weight) was administered subcutaneously to mice 4 hours prior to the intraperitoneal injection of pentobarbital (70 mg/kg). When given, nicotinamide was injected intraperitoneally 30 minutes prior to the pentobarbital. The duration of anesthesia was measured by continuous observation of the animals. The value reported represents the average duration of anesthesia for each group of 10 mice

Nicotinamide	Average Duration of Anesthesia (1)					
	Without Chlorpromazine			With Chlorpromazine		
mg per kg	Minutes	± S.E.		Minutes	± S.E.	
0	30	1	—	142	± 21	—
125	29	1	−1 (2)	165	± 7	23 (2)
250	42	3	12 (2)	264	± 13	122
500	45	6	15 (2)	216	± 11	74

(1) Time interval from the loss of the righting reflex until it is regained.
(2) Not significant at the 5 % level.

mouse had been considerably reduced; even after 30 minutes a considerable reduction in the spontaneous activity was noted.

Interaction of nicotinamide with reserpine and chlorpromazine to increase pentobarbital anesthesia of mice. The data presented in Tables I and II shows that pentobarbital anesthesia is probably not significantly affected

TABLE II

Interaction of Nicotinamide and Reserpine on Pentobarbital Anesthesia

Reserpine (5 mg/kg body weight) was administered subcutaneously to the mice 4 hours prior to the intraperitoneal injection of pentobarbital (70 mg/kg). Nicotinamide (500 mg/kg) was injected 30 minutes before the pentobarbital. Other details are as described in the legend to table I

	Average Duration of Anesthesia (1)		Increase Due To Nicotinamide	
	Expt. 1	Expt. 2	Expt. 1	Expt. 2
	Minutes	Minutes	Minutes	Minutes
1. Pentobarbital	34	30	—	—
2. Reserpine	0	0		
3. Nicotinamide	0	0		
4. Pentobarbital plus Nicotinamide	25	41	—9 (2)	11 (2)
5. Pentobarbital plus Reserpine	101	111	—	—
6. Pentobarbital plus Reserpine plus Nicotinamide	175	157	74	46

(1) Time interval from the loss of the righting reflex until it is regained.
(2) Not significant at the 5 % level (Expt. 1, $t = 2.05$; Expt. 2, $t = 2.00$).

by nicotinamide. Chlorpromazine increased the duration of pentobarbital anesthesia from 30 minutes to 142 minutes (TABLE I). The addition of 125 mg/kg of nicotinamide produces an additional 23 minutes of anesthesia, doubling the dose of nicotinamide increased the average duration of anesthesia 122 minutes while at 500 mg/kg of nicotinamide, an increase of 74 minutes was noted. A similar pharmacological interaction between nicotinamide and reserpine may be seen from the data presented in Table II. The average duration of pentobarbital anesthesia was increased 3 to 4 fold following the administration of reserpine; when nicotinamide was given in addition to reserpine and pentobarbital, the

increase was 5 to 6 fold. The data presented indicates that nicotinamide does act in combination with chlorpromazine and reserpine to extend further the duration of pentobarbital anesthesia in the mouse.

Discussion

The results reported in this paper suggest that there is potentiation by nicotinamide of certain actions of the two tranquillizing drugs, reserpine and chlorpromazine. Both chlorpromazine and reserpine have been shown to extend the duration of anesthesia produced by pentobarbital (1). The administration of nicotinamide in addition to chlorpromazine and reserpine prolongs the anesthesia to a much greater extend than either tranquillizing drug alone. Nicotinamide alone shows no ability to prolong pentobarbital anesthesia. It is worthy of note that Hoffer and his collaborators have observed a potentiation of the action of barbiturates by nicotinamide or nicotinic acid in patients (5). A pharmacological interaction between nicotinamide and chlorpromazine and reserpine was observed when measurements were made of the spontaneous activity of the mice before and after drug treatment. It was found that the combination of nicotinamide with the tranquillizing drugs almost totally suppressed spontaneous activity of mice, but more important, it was observed that nicotinamide alone would considerably reduce spontaneous activity as measured by the simple jiggle cage apparatus.

Two independent test systems have been used to show that nicotinamide does act on the central nervous system. The chemical basis of this action is not known. Wooley has shown that nicotinamide is an antagonist of serotonin and has related the tranquillizing action of nicotinamide to its antiserotonin activity (8). It is possible, however, that the central nervous system effects of nicotinamide may be related to changes in the concentration of its coenzyme form, DPN. It has recently been shown that nicotinamide will produce an increase in DPN levels in animal tissues (6). It has further been found that reserpine and chlorpromazine will act in conjunction with nicotinamide to maintain high levels of DPN in liver tissue (2, 3, 4). Further studies should reveal whether or not a relationship does exist between the central nervous system effect of nicotinamide and DPN levels.

Summary

It has been shown that nicotinamide will act in conjunction with reserpine and chlorpromazine to reduce the spontaneous activity of mice and to increase the duration of anesthesia in mice.

Acknowledgement

The reserpine [Serpasil (R)] used in these experiments was a gift from the Ciba Pharmaceutical Company; The chlorpromazine [Thorazine (R)] was given by Smith, Kline and French, Inc.; and the nicotinamide was a gift of Hoffman-La Roche, Inc.

References

1. — Brodie, B. B., Shore, P. A. and Silver, S. L. *Nature*, 1955, *175*, 1133.
2. — Burton, R. M., Kaplan, N. O., Goldin, A., Leitenberg, M., Humphreys, S. R. and Sodd, M. A. *Science*, 1958, *127*, 30.
3. — Burton, R. M., Kaplan, N. O., Goldin, A., Salvador, R., Leitenberg, M. and Humphreys, S. R. *Collegium Int. Neuro-psycho-pharmacologium*, 1958, p. 15.
4. — Burton, R. M., Kaplan, N. O., Goldin, A., Leitenberg, M. and Humphreys, S. R. *Arch. int. Pharmacodyn.* submitted (1960).
5. — Hoffer, A., Osmond, H., Callbeck, M. J. and Kahan, I. *J. Clin. Exptl. Psychopath.*, 1957, *38*, 131.
6. — Kaplan, N. O., Goldin, A., Humphreys, S. R., Ciotti, M. M. and Stolzenbach, F. E. *J. Biol. Chem.*, 1956, *219*, 287.
7. — Shirley, M. *Psychol. Bull.*, 1929, *26*, 341.
8. — Woolley, D. W. *Science*, 1958, *128*, 1277.

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THE EFFECT OF NICOTINIC ACID ON SERUM LIPIDS IN NORMAL SUBJECTS

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SUMMARY

Investigations were carried out to study in man the effect of single intravenous administrations of nicotinic acid and of a prolonged treatment for 35 days.

To this end, total lipemia and various lipid fractions were checked in 15 subjects after the administration of 100 mg, 500 mg and 1 g of nicotinic acid, respectively. The subjects were examined hourly for 8 consecutive hours and again 24 hours after the injection. Also, the behaviour of the various serum lipid fractions was checked every week during treatment with nicotinic acid in 9 subjects. It was found that neither single administrations, even of large doses, nor prolonged intravenous treatment with nicotinic acid induce significant variations in the lipid levels and composition.

After the communication of Altschul and coll.[1], who reported that the administration of nicotinic acid induces a reduction of the serum cholesterol level in man, several authors have studied the influence of the drug both on the cholesterol and on other lipid fractions of serum. The results of many investigations confirmed the observation of Altschul and showed a reduction also of the free fatty acids, the triglycerides and the phospholipids of blood serum under the influence of nicotinic acid. However, several investigations carried out in man have resulted in differing conclusions. Biava[2], who was the first to study, 1939, the effect of nicotinic acid on cholesterolemia in man, showed a certain hypercholesterolemic action produced by doses of 100 mg per day. O'Reilly[3] found a reduction in the serum cholesterol level in hypercholesterolemic subjects, but observed an increase in normal subjects, especially in those with low serum cholesterol levels. Antonini and coll.[4], using doses varying from 150 mg to 3 g per day of nicotinic acid for periods of 1–4 months, in normal subjects and in atherosclerotic patients, found no significant variations of the total and esterified cholesterol values, of the phospholipids and of the total serum lipids, and showed only a constant diminution in the β/α lipoprotein quotient.

Investigations carried out on experimental animals have produced rather discordant results. Whereas Comesana *et al.*[5] observed a hypocholesterolemic effect of

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nicotinic acid in dogs and Bruce and coll.[6], observed an analogous effect in dogs with hypercholesterolemia caused by hypothyroidism, Norcia *et al.*[7] and Grande and Amatuzio[8] found no variations in the serum cholesterol levels in the same animal after the administration of nicotinic acid.

Merrill and Lemley-Stone[9] and Cava and coll.[10] demonstrated a definite protective action produced by nicotinic acid in rabbits against hypercholesterolemia and vascular lesions caused by hyperlipidic diet, an action which was not shown by Nath and coll.[11]. Friedmann *et al.*[12] stated that in rabbits and rats kept on a cholesterol-rich diet, the protective effect of nicotinic acid against dietary hypercholesterolemia is only apparent: the animals, rendered anorexic by the drug, consume a smaller quantity of food; when the animals used for control consume the same amount of food as the nicotinic acid-treated ones, the difference between the serum cholesterol levels of the two groups is not appreciable. Also Duncan and Best[13] obtained completely negative results in rats. Gaylor and coll.[14] found an increase in the blood cholesterol level induced by nicotinic acid in these animals.

From this brief review, it is clear that the action of nicotinic acid on the various lipid fractions and on cholesterol in particular has not yet been ascertained. We therefore considered it useful to carry out the investigations described in this paper, that is, to study in man the behaviour of the various serum lipid fractions after single administrations of nicotinic acid, and in the course of prolonged treatment for longer than one month. Besides, we wanted to contribute to the knowledge of the side-effects of a therapy used in several diseases of the cardiovascular system.

MATERIALS AND METHOD

In 15 normal subjects, whose ages varied from 28 to 74 years, a single intravenous dose of nicotinic acid was given. In 5 subjects fasted for 12 h, the dose was 100 mg, in further 5 subjects 500 mg, and in the remaining 5 1 g each. In each case a blood sample was taken before the injection and thereafter every 60 min for 8 h, a last sample being taken the following morning, 24 h after the injection.

In another 9 subjects 1 g of i.v. sodium nicotinate was injected every 6 h (4 g/day) for 5 consecutive weeks, and a venous blood sample was taken before the beginning of treatment and thereafter every 7 days up to the fifth week.

The various lipid fraction of each blood sample were determined by the Bang-Condorelli method[15], which gives a sufficiently accurate estimation of the total lipemia and of the various serum lipid fractions.

RESULTS AND DISCUSSION

The results obtained after the single administration of nicotinic acid in the various cases show very slight variations in the order of spontaneous oscillations or limits of error, compared to the initial values. This was found both after the administration of 100 mg, 500 mg and 1 g of nicotinic acid. In all cases, the characteristic vasomotor reaction of the drug was noted.

The consistency of the results in the various cases studied enables us to show, for brevity, the mean values of the determinations in the 15 subjects examined (Table I).

TABLE I

TOTAL LIPIDS AND LIPID FRACTIONS OF SERUM AFTER SINGLE I.V. ADMINISTRATION OF SODIUM NICOTINATE

Mean values (g‰) of determinations in 15 subjects.

	Before injection	*After i.v. sodium nicotinate*								
		1 h	*2 h*	*3 h*	*4 h*	*5 h*	*6 h*	*7 h*	*8 h*	*24 h*
Total lipids	8.26	8.26	8.29	8.27	8.22	8.26	8.20	8.40	8.50	8.32
Triglycerides	1.37	1.34	1.36	1.34	1.35	1.36	1.33	1.38	1.47	1.39
Phospholipids	2.77	2.75	2.79	2.80	2.77	2.80	2.78	2.82	2.90	2.74
Free fatty acids	0.48	0.52	0.51	0.50	0.47	0.50	0.50	0.48	0.49	0.51
Free cholesterol	0.93	0.92	0.92	0.92	0.90	0.90	0.89	0.90	0.96	1.00
Cholesterol esters	2.71	2.73	2.71	2.71	2.73	2.70	2.70	2.82	2.77	2.68
Esterified cholesterol	1.47	1.40	1.51	1.46	1.48	1.46	1.46	1.56	1.46	1.32
Total cholesterol	2.40	2.32	2.43	2.38	2.38	2.36	2.35	2.46	2.42	2.32

The results obtained before and after prolonged treatment with nicotinic acid are given in Table II, as values of the mean. As can be seen from the table, no significant variations were found either in the lipid content of serum or in its composition.

In conclusion, our investigation points to the absence of any significant influence, both of a single dose of nicotinic acid and of repeated administrations of fairly large doses on the lipid fractions of blood serum.

This observation, in addition to the others quoted above, leads us to doubt the existence of the hypocholesterolemic effect of nicotinic acid in man, and shows the need for further research to investigate this controversial problem more closely.

TABLE II

TOTAL LIPIDS AND LIPID FRACTIONS OF SERUM BEFORE AND DURING TREATMENT WITH SODIUM NICOTINATE

1 g every 6 h for 5 weeks i.v. Mean values (g‰) of determinations in 9 subjects.

	Before treatment	*During treatment*				
		7th day	*14th day*	*21st day*	*28th day*	*35th day*
Total lipids	7.74	7.58	7.60	7.98	7.62	7.67
Triglycerides	1.10	1.06	1.08	1.14	1.14	1.05
Phospholipids	2.72	2.65	2.78	2.71	2.65	2.81
Free fatty acids	0.53	0.47	0.49	0.55	0.52	0.50
Free cholesterol	0.90	0.98	0.98	0.94	0.89	0.96
Cholesterol esters	2.49	2.42	2.27	2.64	2.42	2.35
Esterified cholesterol	1.35	1.32	1.24	1.41	1.32	1.27
Total cholesterol	2.25	2.30	2.22	2.35	2.21	2.23

REFERENCES

1 R. Altschul, A. Hoffer and J. D. Stephen, *Arch. Biochem. Biophys.*, 54 (1955) 558.
2 L. Biava, *Riforma Med.*, 55 (1939) 1635.
3 P. O. O'Reilly, *Can. Med. Assoc. J.*, 78 (1958) 402.
4 F. M. Antonini, R. Masi and G. Verdi, *Giorn. Gerontol.*, 7 (1959) 783.
5 F. Comessana, A. Nava, B. L. Fishleder and D. Sodi-Pallares, *Am. Heart J.*, 55 (1958) 476.
6 A. Bruce, M. D. Kottke, L. Jesse, M. D. Bolluran and J. L. Juergens, *Circulation Res.*, 11 (1962) 108.

7 L. N. NORCIA, H. J. BROWN AND R. H. FURMAN, *Lancet*, i (1959) 1255.
8 F. GRANDE AND D. S. AMATUZIO, *Federation Proc.*, 19 (1960) 237.
9 J. M. MERRILL AND J. LEMLEY-STONE, *Circulation Res.*, 5 (1957) 617.
10 E. E. CAVA, R. W. ACHOR, K. G. BERGE, K. G. WAKIM, J. E. EDWARDS, B. F. MCKENZIE AND N. W. BARKER, *Proc. Mayo Clin.*, 34 (1959) 502.
11 N. NATH, A. E. HARPER AND C. A. ELVEHJEM, *Proc. Soc. Exptl. Biol. Med.*, 102 (1959) 471.
12 M. FRIEDMANN AND S. O. BYERS, *J. Clin. Invest.*, 38 (1959) 1328.
13 C. H. DUNCAN AND M. M. BEST, *J. Lipid Res.*, 1 (1960) 159.
14 J. L. GAYLOR, R. W. F. HARDY AND C. A. BAUMANN, *J. Nutr.*, 70 (1960) 293.
15 L. CONDORELLI, *Tecnica Microchimica*, Ed. Idelson, Napoli, 1926.

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Acute Effects of Nicotinic Acid in the Rat

I. Plasma and Liver Lipids and Blood Glucose

By

LARS A. CARLSON and EDWIN R. NYE[1]

Nicotinic acid was shown by Altschul in 1955 to lower the level of plasma cholesterol (2). Later work has confirmed this observation and also demonstrated that the plasma triglycerides are depressed (cf. 1). Carlson and Orö reported in 1962 that nicotinic acid rapidly lowers the level of free fatty acids (FFA) in plasma and also effectively inhibits the stimulation of mobilization of FFA from adipose tissue by noradrenaline (10). The inhibition of the mobilization of FFA by nicotinic acid has been extensively confirmed (cf. 7).

It has been suggested that the effect of nicotinic acid on plasma cholesterol and triglycerides is at least partly due to its inhibition of FFA mobilization (10, 5, 7). Through inhibition of this mobilization less FFA would be available to the liver for the formation of hepatic and subsequently plasma triglycerides. There is, however, insufficient information on the time relationship between the effects of inhibition of FFA release by nicotinic acid and the effect on plasma and liver triglycerides.

The present study attempts therefore to define the metabolic consequences of NA administration in rats, in the first few hours after administration, with attention to the major effects of the substance, namely on plasma FFA, triglycerides and cholesterol, on blood glucose and on liver triglycerides and cholesterol.

Material and methods

Male Sprague-Dawley strain rats (A.B. Anticimex, Stockholm) weighing 180–200 g were used. The animals were accustomed to the laboratory surroundings for 24 hours before use. The nicotinic acid solution used consisted of a 5 % solution of the sodium salt and was injected subcutaneously. Control animals were injected with an equivalent volume of a sterile physiological saline solu-

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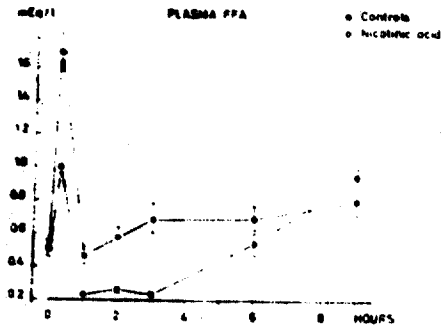

Fig. 1. The concentration of free fatty acids (FFA) in plasma of control and nicotinic acid-injected fasted rats. The bars indicate the standard error of the mean.

tion. The dose was 50 mg of nicotinic acid per rat, equivalent to 250 mg/kg. All rats were fasted for 18 to 20 hours before injection but drinking water was provided. The experiments started at about 9 a.m.

Control and test animals were sampled alternately and were bled by heart puncture after stunning by a blow on the head. Livers and epididymal fat pads were immediately removed after bleeding, and were frozen in liquid nitrogen. The data for the various time periods after injection were drawn from experiments carried out on different days, and as a precaution it was ensured that any given sampling time was represented in several experiments.

TABLE I. Values for plasma FFA, blood glucose, plasma triglycerides, plasma cholesterol, liver tri-

Time after injection (hrs)		Plasma FFA (meq/l)			Blood glucose (mg/100 ml)			Plasma triglycerides (mmoles/l)		
		C	NA	P	C	NA	P	C	NA	P
0	M	0.50	—	—	70.9			0.30		
	SEM	0.05	—		3.3	—		0.028		
	n	9	—		9	—		10	—	
0.25	M	1.68	1.08	<0.001	55.7	56.6	>0.05	0.24	0.25	>0.05
	SEM	0.12	0.02		2.0	2.3		0.028	0.011	
	n	10	10		10	10		10	10	
1	M	0.46	0.22	<0.001	64.6	47.6	<0.001	0.24	0.18	<0.01
	SEM	0.07	0.02		3.7	1.9		0.022	0.014	
	n	9	14		9	14		10	14	
2	M	0.58	0.26	<0.01	54.2	45.6	<0.01	0.24	0.11	<0.001
	SEM	0.06	0.02		3.1	1.8		0.016	0.007	
	n	15	21		11	16		21	23	
3	M	0.58	0.23	<0.001	60.3	44.1	<0.001	0.22	0.09	<0.001
	SEM	0.05	0.01		3.6	1.6		0.031	0.009	
	n	10	13		10	11		9	12	
6	M	0.70	0.54	>0.05	55.7	51.2	>0.05	0.25	0.08	<0.001
	SEM	0.07	0.07		3.1	4.0		0.021	0.001	
	n	6	9		6	9		6	9	
9	M	0.80	0.95	>0.05	54.4	48.8	>0.05	0.20	0.17	>0.05
	SEM	0.08	0.05		2.5	2.3		0.001	0.016	
	n	5	6		5	6		5	6	

C = control rats. NA = nicotinic acid-injected rats. P indicates the statistical significance for the n = number.

Biochemical determinations

Blood glucose was determined by the method of Marks (21), FFA by the Trout (25) modification of the Dole (13) method. Plasma and liver lipids were extracted with chloroform-methanol (4). Triglycerides were measured by the method of Carlson (4) and cholesterol by the Tschugaeff color reaction as described by Hanel and Dam (14). Nicotinic acid in plasma was determined by the method of Carlson which measures free acid (6). In this method nicotinamide gives only 10–15 per cent of the optical density of equimolar amounts of nicotinic acid. The nicotinic acid content of liver and adipose tissue was determined by homogenisation of the tissues in distilled water and subsequent [illegible] homogenates as described for plasma. In some instances the amount of [illegible] acid in the tissues was determined as follows. An aliquot of the tissue [illegible] was hydrolysed with strong KOH [illegible] in a boiling water bath, neutralized [illegible] and made up to [illegible] taken for analysis of [illegible] as described above.

Results

Plasma free fatty acids

Both the control and nicotinic acid-injected animals showed within fifteen

glycerides and liver cholesterol in control and nicotinic acid-injected rats

Plasma cholesterol (mg/100 ml)			Liver triglycerides (μmoles/g)			Liver cholesterol (mg/g)		
C	NA	P	C	NA	P	C	NA	P
75.7	—	—	5.01	—		4.1	—	
3.5	—		0.51	—		0.1		
10	—		8	—		10		
—	—	—	—	—	—	—	—	
—	—		—	—		—		
—	—		—	—		—		
81.7	85.4	—	6.05	5.92	>0.05	4.4	4.2	>0.05
3.5	2.93		0.97	0.80		0.2	0.2	
10	14		10	14		10	13	
80.6	72.6	<0.01	4.58	3.41	<0.01	4.0	4.0	>0.05
3.0	2.3		0.35	0.39		0.2	0.1	
21	23		21	23		21	22	
82.4	73.9	>0.05	6.58	2.13	<0.001	4.3	4.4	>0.05
5.0	3.4		0.67	0.35		0.2	0.2	
10	13		10	14		9	14	
87.8	74.4	<0.01	4.35	1.90	<0.01	3.9	4.1	>0.05
2.7	3.9		0.47	0.10		0.1	0.1	
6	9		6	9		6	9	
84.6	79.0	>0.05	3.82	8.20	<0.05	3.3	3.7	>0.05
4.0	2.8		0.73	1.78		0.2	0.2	
5	6		5	6		5	6	

[illegible]ifference between C and NA (t-test). M = mean value. SEM standard error of the mean.

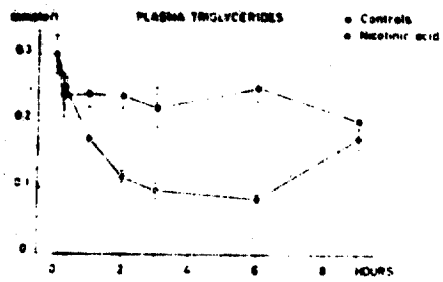

Fig. 2. The concentration of triglycerides in plasma of control and nicotinic acid-injected fasted rats. The bars indicate the standard error of the mean.

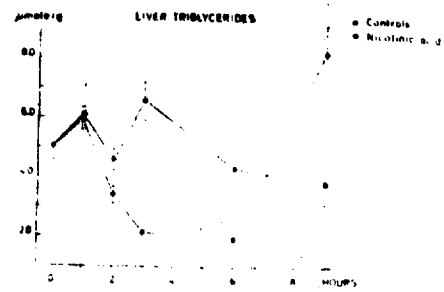

Fig. 3. The concentration of triglycerides in the livers of control and nicotinic acid-injected fasted rats. The bars indicate the standard error of the mean.

minutes of injection an elevation of FFA levels compared with the '0' time value; but the level in the nicotinic acid-injected group was significantly lower than in the controls (fig. 1, table I). Significant depression of FFA levels in the nicotinic acid-injected group, compared with the controls, continued at one, two and three hours, but although the former still had a lower value at six hours the difference was no longer statistically significant. Nor was any significant difference present at nine hours after injection, although the nicotinic acid group had higher values.

Plasma triglycerides

Fig. 2 and table I show that as early as one hour after injection the nicotinic acid-injected animals had a significant depression of their plasma triglycerides, which became more pronounced and persisted until the sixth hour. At nine hours there was no longer any difference between the groups.

Liver triglycerides

A significant depression of liver triglycerides in the nicotinic acid group was recorded at two, three and six hours after injection (fig. 3, table I). At nine hours after injection the nicotinic acid-treated animals had appreciably higher triglycerides than the controls, the mean value exceeding that of the controls by 4.3 μ moles/g, a difference significant at the 5 % level although the number of animals was small in both groups. There was also at this time an appreciable variation in the content of triglycerides in the livers of the nicotinic acid-treated rats.

Plasma cholesterol

A slight depression of cholesterol was seen in the nicotinic acid-treated animals from two to nine hours after injection (fig. 4, table I). The depression was only significant, however, at two and six hours.

Liver cholesterol

No significant change was seen at any time after injection in liver cholesterol values (table I).

Blood glucose

No alteration in blood glucose was produced within 15 minutes of injection,

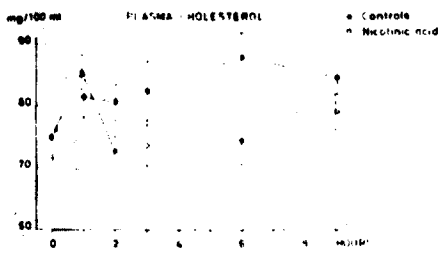

Fig. 4. The concentration of cholesterol in plasma of control and nicotinic acid-injected fasted rats. The bars indicate the standard error of the mean.

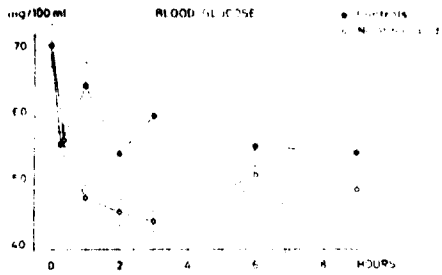

Fig. 5. The concentration of blood glucose in control and nicotinic acid-injected fasted rats. The bars indicate the standard error of the mean.

but a significant depression was seen in the nicotinic acid-treated group at one, two and three hours (fig. 5, table I). The effect has disappeared at six hours.

Nicotinic acid levels

The level of free nicotinic acid in plasma was highest 15 minutes after the injection (table II) and then declined. Six hours after the injection there was no difference between the plasma levels in control and nicotinic acid-treated rats. The same pattern was seen for free nicotinic acid in the liver, although there was a slightly higher level of nicotinic acid present in the livers of treated rats at 6 hours. This level, however, was not statistically different from that found in untreated rats at 0 hours. Table II shows that the course of events was slightly different in adipose tissue, where the amount of free nicotinic acid tended to be higher at 1 hour than at 15

TABLE II. Levels of free nicotinic acid in control and nicotinic acid-injected rats. Mean value ± standard error of mean and numbers of rats are given

Time after injection (hrs)		0	0.25	1	2	3	6
Plasma	C	0.1±0.1	4.8±2.6	—	3.0±1.3	0.5±0.3	0±0
μg/ml		7	8		10	4	4
	NA	—	488±18	248±7	219±9	102±33	0.8±0.5
			7	4	10	4	5
Liver	C	23±2	27±1	15±4	27±2	16±3	11±2
μg/g		8	10	4	15	4	4
	NA	—	210±17	140±17	133±7	59±15	20±2
			10	6	15	6	6
Adipose	C	1.0±0.4	0.3±0.4	−0.1±0.6	2.9±1.3	0.6±0.8	0.8±0.7
tissue		8	10	4	15	4	4
μg/g	NA	—	39±5	52±12	33±3	11±3	0.6±0.4
			10	6	14	6	6

C = control rats. NA = nicotinic acid-injected rats.

minutes. At 3 hours free nicotinic acid was still present in adipose tissue but not at 6 hours. It should be stressed that the levels found in this tissue and also in plasma at 0 and 6 hours are at the lower limit of the method.

The total content of nicotinic acid — this including free and bound acid — was determined in liver and adipose tissue at 2 hours. For control and nicotinic acid rats the values, in μg/g wet tissue, were in the liver 193 ± 14 and 208 ± 14 and in adipose tissue 9 ± 1 and 13 ± 1, the differences between controls and treated being of doubtful significance. Nor was there any significant difference in this regard between the two groups at 15 minutes.

Discussion

The results of the present study confirm the effect of NA in reducing plasma FFA. The effect is seen within fifteen minutes of injection since, although both NA-treated and control animals show a rise of FFA at the fifteen-minute sampling time compared with the '0' time value, the NA group have significantly lower FFA levels than the controls. It is likely that the early rise seen in both groups was due to catecholamine-stimulated release of FFA resulting from the injection procedure, this release having been partially suppressed by the NA. After 15 minutes the control animals reverted to a steady level of plasma FFA with some indication of a rise six hours after injection. A significant depression of plasma FFA in the NA-treated group was seen at 15 minutes, one, two and three hours after injection but not at six hours.

The induced fall in plasma FFA confirms the work of Carlson and Oro and of Carlson, who considered that the effect is due to inhibition of lipolysis in adipose tissue by NA (10, 5).

The present study shows also the temporal relationship between NA concentration in blood, liver and adipose tissue and the lipid levels in these regions. The amount of plasma present in liver and adipose tissue was estimated by injecting I^{125}-labelled albumin intravenously and analysing the content of label present in plasma and tissues 10 minutes after injection. In the liver, plasma constituted approximatively 10 per cent and in adipose tissue 1 per cent of the wet weight at 15 as well as 60 minutes after nicotinic acid was given. Thus the plasma content of these two organs did not contribute more than 10 - 20 per cent of the values obtained for the nicotinic acid concentration of the organs, as can be seen from table II. The rapidity of action of NA in depressing plasma FFA, through its action on adipose tissue, is consistent with the finding of increased adipose tissue NA levels at 15 minutes, and is in keeping with the observation of Carlson and Hanngren that intravenously administered tritium labelled NA is found in adipose tissue of mice within five minutes of injection (8).

The low levels of FFA at one, two and three hours and the normal level at six hours also correlate well with the presence of elevated concentrations of free nicotinic acid in adipose tissue at one, two and three hours but of a normal content at six hours.

Of particular interest in the present work is the observation that a significant

reduction of plasma triglycerides was seen already at one hour after NA injection, this reduction anticipating the fall in liver triglycerides one hour later. Similar results have been obtained in alloxan-diabetic rats treated with nicotinic acid, which two hours after the injection had significantly lowered plasma levels of FFA and triglycerides unaccompanied by any depression of liver triglycerides (11). If the liver is the main source of plasma triglycerides (15, 3, 18), then on general grounds it would seem that a reduction in plasma triglycerides should follow, not precede, a reduction in liver triglycerides. Among possible explanations for the present finding are:

1. Another source of plasma triglycerides, such as the gastro-intestinal tract, may be affected more rapidly than the liver.

2. Increased removal of plasma triglycerides, linked for example with perfusion of an enlarged vascular bed in tissues extracting triglycerides as the result of the vasodilatation effect of NA, or with an increased lipoprotein lipase content of such tissues.

3. Decreased hepatic production of plasma triglycerides due to decreased splanchnic blood flow.

4. That reduction of liver triglycerides does in fact occur but rather in the early stages of FFA depletion, chiefly in a small liver triglyceride pool which is a source of plasma triglycerides more readily available to plasma than the larger, and perhaps less easily mobilized, fat stores. In keeping with this, Havel et al. have presented data and discussed the possibility that the "floating fat" in the liver serves as a storage reservoir for [illegible] patic triglyceride fatty acids whereas the plasma triglycerides are the immediate precursors probably those contained in cell particulates or the cell sap (17). It should be noted that a small reduction in liver triglycerides could occur but remain undetected because of the variability in liver triglyceride level.

In any event the time course for the levels of FFA and plasma triglycerides clearly shows that the early fall as well as the later rise in FFA precedes the fall and later rise of the triglycerides. This strongly supports the earlier proposed concept that the effect of nicotinic acid on the plasma triglyceride level is at least partly ascribable to the inhibition of FFA mobilization induced by nicotinic acid (10, 5, 7).

The present data offer no explanation for the finding that the hepatic triglycerides tended to increase at 9 hours in the nicotinic acid-treated group. There may, however, have been a marked rise in the FFA levels between 6 and 9 hours, by analogy with the overshoot in FFA levels seen earlier when the effect of nicotinic acid vanishes (10). If so, this might have led to a marked uptake of FFA in the liver with concomitant increased formation of hepatic triglycerides.

At least three effects of NA may, separately or combined, play a part in the reduction of plasma cholesterol seen from two to six hours after injection: 1. decreased availability of acetate for cholesterol synthesis resulting from reduced FFA concentration in the liver; 2. reduction of plasma very low density lipoproteins associated with the induced fall [illegible] acting by

reason of the cholesterol content of the very low density lipoproteins (density < 1.006); 3. increased oxidation of cholesterol via increased pyridine nucleotide synthesis (19, 20). Without knowledge of the dynamics of cholesterol metabolism it is not possible from the present study to prefer any of the above modes of action of NA, but possibly a slight weighting in favour of the second hypothesis exists by virtue of the failure to detect any change in liver cholesterol.

The effect of NA in reducing blood glucose confirms the findings of Cherkes and Rozenfeld and of Mirsky et al. who investigated normal and alloxan-diabetic rats, the latter concluding, as did Carlson and Östman that NA has no major effect on the blood glucose of diabetic rats (12, 22, 11). Root and Ashmore have shown, however, that NA in the same dosage as used by us does significantly reduce the blood sugar in diabetic, as well as normal rats, and that the reduction is associated with increased utilization of glucose as a respiratory substrate and with a fall in liver and heart glycogen (24).

The finding of reduction of blood glucose under the influence of NA, is compatible with the hypothesis of Randle et al. that the concentration of FFA in plasma has a regulatory effect on the uptake of glucose by muscle, even if only through the preferential use of glucose as a respiratory substrate when the concentration of FFA is low (23). It is also understandable that in the acute situation of inhibited mobilization of FFA from adipose tissue combined with no access to food, glycogen and lipid stores other than those of adipose tissue have to be oxidized for energy purposes. This is supported by the finding that in the resting state and during exercise the RQ increases acutely in man after nicotinic acid administration (16, 9).

Summary

Fasted rats were given saline or nicotinic acid (250 mg/kg) subcutaneously and followed for up to nine hours. Plasma levels of FFA were significantly reduced from 15 minutes up to three hours, triglycerides were significantly reduced from one to six hours, cholesterol was significantly reduced at two and six hours. Liver triglycerides were significantly reduced from two to six hours and elevated at nine hours while liver cholesterol was unaffected. Blood glucose was significantly reduced from one to three hours.

Nicotinic acid levels in plasma, epididymal fat pads and liver were also followed during the study. Free nicotinic acid rapidly appeared in adipose tissue, but after 3 hours was not demonstrably higher than in the control rats. The presence of increased levels of free nicotinic acid in adipose tissue correlated well with the presence of reduced FFA levels in plasma.

The time sequence of events supports the hypothesis that the inhibition of FFA mobilization caused by nicotinic acid is at least partly the cause of the depression of plasma triglyceride and cholesterol levels.

Acknowledgement

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References

1. ALTSCHUL, R.: Niacin in vascular disorders and hyperlipemia, pp. 3–135. Charles C. Thomas, Springfield, Ill. USA. 1964.
2. ALTSCHUL, R., HOFFER, A. & STEPHEN, J. D.: Influence of nicotinic acid on serum cholesterol in man. Arch. Biochem. *54:* 558, 1955.
3. BORGSTROM, B. & OLIVECRONA, T.: The metabolism of palmitic acid-1-C^{14} in functionally hepatectomized rats. J. Lipid Res. *2:* 263, 1961.
4. CARLSON, L. A.: Determination of serum triglycerides. J. Atheroscler. Res. *3:* 334, 1963.
5. CARLSON, L. A.: Studies on the effect of nicotinic acid on catecholamine stimulated lipolysis in adipose tissue in vitro. Acta med. scand. *173:* 719, 1963.
6. CARLSON, L. A.: Determination of free nicotinic acid in blood plasma. Clin. chim. Acta. In print.
7. CARLSON, L. A.: Inhibition of the mobilization of free fatty acids from adipose tissue. Ann. N.Y. Acad. Sci. *131:* 119, 1965.
8. CARLSON, L. A. & HANNGREN, Å.: Initial distribution in mice of ^{3}H-labeled nicotinic acid studied with autoradiography. Life Sciences *3:* 867, 1964.
9. CARLSON, L. A., HAVEL, R. J., EKELUND, L.-G. & HOLMGREN, A.: Effect of nicotinic acid on the turnover rate and oxidation of free fatty acids of plasma in man during exercise. Metabolism *12:* 837, 1963.
10. CARLSON, L. A. & ORÖ, L.: The effect of nicotinic acid on the plasma free fatty acids. Demonstration of a metabolic type of sympathicolysis. Acta med. scand. *172:* 641, 1962.
11. CARLSON, L. A. & ÖSTMAN, J.: Inhibition of the mobilization of free fatty acids from adipose tissue in diabetes. I. Effect of nicotinic acid on the alloxan-diabetic state in rats. Acta med. scand. *177:* 631, 1965.
12. CHERKES, L. A. & ROZENFELD, E. L.: Effect of nicotinic acid on the blood sugar level and its relationship to adrenaline hyperglycemia. Biokhimiya *6:* 58; *35:* 6321, 1941.
13. DOLE, V. P.: A relation between nonesterified fatty acids in plasma and the metabolism of glucose. J. clin. Invest. *35:* 150, 1956.
14. HANEL, H. K. & DAM, H.: Determination of small amounts of [illegible] cholesterol [illegible] Tschogaell [illegible] determination [illegible] scand. *9:* 677, [illegible]
15. HARPER, P. V., [illegible] CEK, G. R.: Lipid [illegible] the dog. Metabolism [illegible]
16. HAVEL, R. J., [illegible] L.-G. & HOLMGREN, A.: [illegible] tion between mobilization [illegible] and energy metabolism [illegible] norepinephrine and nicotinic acid. Metabolism *13:* 1102, 1964.
17. HAVEL, R. J., ELLIS, J. M., [illegible] C. M.: Formation and fate of [illegible] triglycerides in blood plasma [illegible] J. Lipid Res. *3:* 297, 1962.
18. HAVEL, R. J. & GOLDFIEN, A.: [illegible] the liver and of extrahepatic tissues in the transport and metabolism of fatty acids and triglycerides in the dog. J. Lipid Res. *2:* [illegible] 1961.
19. KRITCHEVSKY, D. & TEPPER, S. A.: Influence of nicotinic acid homologs on oxidation of cholesterol-26-C^{14} by rat liver mitochondria. Arch. int. Pharmacodyn. *138:* 319, 1962.
20. KRITCHEVSKY, D., WHITEHOUSE, M. W. & STAPLE, E.: Oxidation of cholesterol-26-C^{14} by rat liver mitochondria. Effect of nicotinic acid. J. Lipid Res. *1:* 154, 1960.
21. MARKS, V.: An improved glucose-oxidase method for determining blood, C.S.F. and urine glucose levels. Clin. chim. Acta *4:* 395, 1959.
22. MIRSKY, A., PERISUTTI, G. & JINKS, R.: The hypoglycemic action of metabolite derivates of L-tryptophan. Endocrinology *60:* 318, 1957.
23. RANDLE, P. J., GARLAND, P. B., NEWSHOLME, E. A. & HALES, C. N.: The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet *1:* 785, 1963.
24. ROOT, M. A. & ASHMORE, J.: The hypoglycemic activity of nicotinic acid in rats. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. *248:* 117, 1964.
25. TROUT, D. L., ESTES, E. H. & FRIEDBERG, S. J.: Titration of free fatty acids of plasma: a study of current methods and a new modification. J. Lipid Res. *1:* 199, 1960.

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EFFECT OF A SINGLE DOSE OF NICOTINIC ACID ON PLASMA LIPIDS IN PATIENTS WITH HYPERLIPOPROTEINEMIA

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Abstract. Eleven patients with uncomplicated ischemic cardiovascular diseases and moderate hyperlipoproteinemia were studied for 6 hours after the administration of one gram of placebo and two days later one gram of nicotinic acid.

Plasma levels of free fatty acids were significantly depressed by nicotinic acid as compared to the control study during the first three hours after administration. Then, however, there was a pronounced rebound of FFA. The concentration of glycerol in plasma followed the same pattern as the free fatty acids.

The values for cholesterol in plasma remained unchanged during the six-hour period in both the placebo and the nicotinic acid study. While the level of triglycerides as well was unchanged in the placebo study, the concentration of triglycerides decreased significantly 4 and 6 hours after the administration of nicotinic acid.

The concentration of blood glucose was not significantly different in the two groups during the study.

The concentration of free nicotinic acid in plasma reached a peak value 30 to 60 minutes after nicotinic acid was taken by mouth. At 5–6 hours the level had returned to pretreatment values. The values for the plasma levels of free nicotinic acid and free fatty acids indicated that a concentration of nicotinic acid above 1 μg ml plasma is needed to maintain low free fatty acid levels.

The interrelation between free fatty acids, triglycerides and cholesterol in plasma is discussed. The results from these studies are compatible with the hypothesis that acute inhibition of FFA mobilization reduces the concentration of plasma triglycerides but not plasma cholesterol. They do not explain the mechanism behind the cholesterol-lowering effect of nicotinic acid seen after chronic administration.

There is a strong association between high levels of lipids in plasma and ischemic cardiovascular diseases based on atherosclerosis such as myocardial infarction, angina pectoris and intermittent claudication. Retrospective studies have shown that groups of patients who have recovered from a myocardial infarction or who suffer from angina pectoris or intermittent claudication when compared to clinically healthy control subjects have hyperlipoproteinemia, expressed as elevated levels of cholesterol and/or triglycerides in plasma (1, 4, 7). In Stockholm about 50% of male patients with ischemic cardiovascular disease have an elevation of the concentration of either cholesterol or triglycerides in plasma above the upper "normal limit" (7, 21) defined as the mean value +2 times the standard deviation for values obtained from clinically healthy men of comparable age (6). Prospective studies, so far limited to plasma cholesterol, have also indicated that the future incidence of cardiovascular ischemic disease is directly correlated to the concentration of cholesterol in plasma (23, 25, 26, 28, 29, 30, 33, 36).

Treatment of the various kinds of hyperlipoproteinemia, with the ultimate goal of reducing the incidence and clinical manifestations of atherosclerosis, is gaining increasing interest. There is no doubt that changes in our environmental conditions may have important effects on plasma lipid levels. For instance the cholesterol level can be reduced by rather simple dietary means. Such treatment has been reported to reduce the occurrence of coronary heart disease in healthy men (22). Treatment of survivors from myocardial infarction with a diet lowering plasma cholesterol levels has been shown to reduce the recurrence of new infarcts by about 50% when the cholesterol level on the average was decreased by about 15% (31). However, the more pronounced forms of hyperlipoproteinemia cannot be

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Table I. *Age, sex, height, weight, plasma lipids, blood sugar, intravenous glucose tolerance (k-value) and plasma FFA*

Case	Sex	Age (y.)	Height (cm)	Weight (kg)	Cholesterol (mg/100 ml)	Phospholipids (mg/100 ml)	Triglycerides (mmol/l)	Fasting blood sugar (mg/100 ml)	k-value[a] (%/min)	FFA[b] (mEq/l)	
										Placebo	Nic. ac.
E. A.	♀	58	171	70.2	428	431	3.27	61	1.35	0.40	0.65
K. L.	♂	55	170	74.2	369	378	2.87	95	1.33	0.51	0.57
N. O. a	♂	72	170	63.2	591	454	2.37	100	1.33	0.37	0.40
S. S.	♂	45	172	67.1	286	338	2.73	—	1.12	0.51	0.52
V. C.	♂	57	177	68.3	226	261	2.28	106	1.73	0.45	1.12
K. S.	♂	68	169	57.5	249	304	3.26	87	0.72	0.53	0.60
K. H.	♂	50	182	84	294	306	2.61	86	0.48	0.52	0.49
K. B.	♀	47	162	59	271	300	1.85	95	0.47	0.98	0.47
S. J.	♂	44	161	61.8	343	314	4.14	99	0.65	0.49	0.31
K.-A. S.	♂	54	171	84.2	451	496	9.97	105	1.08	0.66	0.57
N. O. b	♂	57	—	86.0	191	235	1.59	82	1.01	0.83	0.63

[a] The *k*-value was calculated from the apparent straight line in the semilogarithmic plot of blood glucose concentration against time after the intravenous injection of 50 g glucose. Values above 1.10 normal and below 0.90 definitely pathological.
[b] The first value for FFA obtained in the placebo and in the nicotinic acid study is given.

normalised by diet, they need other treatment such as chemotherapy against their metabolic derangement. Furthermore it has been argued that it is often difficult to change a patient's habits with regard to factors influencing plasma lipid levels such as diet, exercise, smoking and emotional stress, even if the patient may be well motivated due to his disease (38). A chemotherapeutic compound acting without detriment to health and having a well established and sound mode of action would be a useful therapeutic agent in a study of the effect of a plasma lipid lowering program on mortality and morbidity of ischemic cardiovascular diseases.

Nicotinic acid was shown in 1955 to lower plasma cholesterol levels by Altschul and coworkers (3) and has since been used with increasing frequency in the treatment of hyperlipoproteinemia (2). We demonstrated in 1962 that nicotinic acid inhibits the mobilization of free fatty acids (FFA) from adipose tissue and postulated that this was a possible mechanism by which it reduced lipoprotein levels in plasma (9, 19). An excessive rate of mobilization of FFA may be related to vascular disease in several ways, e.g. by increasing the hepatic formation of triglyceride-rich plasma lipoproteins, by causing an increased uptake of fatty acids into the arterial wall and by possible influences on the process of thrombosis (13). We have demonstrated that acute exposure of men to emotional stress rapidly raises plasma FFA levels and within a few hours causes an increase in the content of triglycerides in plasma and that these reactions were inhibited by nicotinic acid (15). In addition to reduction of cholesterol concentration it is evident that nicotinic acid possesses the new pharmacologic principle for inhibition of FFA mobilization. This effect is now well established (10, 12) and might be of value in the treatment of hyperlipoproteinemia. We decided to explore in detail different metabolic and clinical effects of nicotinic acid on patients with ischemic cardiovascular disease and with various types of hyperlipoproteinemia from the acute effect of a single dose to the effects of prolonged treatment.

In this first communication patients have been observed for 6 hours after administration of a single dose of one gram of nicotinic acid or placebo.

METHODS

All studies were done on hospitalized patients. They all had ischemic cardiovascular disease, either as a definite myocardial infarction (characteristic ECG and transaminase changes) at least 6 months before the study or as typical angina pectoris, with ECG changes during exercise suggesting myocardial ischemia, or intermittent claudication, with oscillometric recordings typical of obliterating arterial disease. None had any complicating disease, all were in good nutritional condition and the

Table II. *Plasma levels of FFA (mEq/l) in the placebo and the nicotinic acid study*

Mean value ± standard error of the mean and range are given

Time, h	0	½	1	1½	2	3	4	5	6
Placebo (n = 11)									
M ± S.E.M.	.59 ± .05	.44 ± .03	.42 ± .05	.49 ± .06	.60 ± .07	.71 ± .06	.76 ± .05	.78 ± .05	.78 ± .06
Range	.40 – .98	.24 – .60	.24 – .80	.20 – .81	.17 – .97	.27 – 1.06	.53 – 1.01	.54 – 1.09	.47 – 1.11
Nicotinic acid (n = 11)									
M ± S.E.M.	.53 ± .03	.30 ± .02	.22 ± .02	.20 ± .02	.22 ± .02	.31 ± .04	1.29 ± .16	1.71 ± .15	1.53 ± .17
Range	.31 – 1.12	.18 – .41	.14 – .31	.15 – .32	.12 – .37	.10 – .55	.52 – 2.08	1.04 – 2.87	.91 – 2.78

only symptoms present in some were ischemic pains on effort. No clinical diabetes with glucosuria and ketonuria was present although some patients had slightly elevated fasting blood glucose values and some had a lowered intravenous glucose tolerance in response to an intravenous glucose load (Table I). The patients had moderate hyperlipoproteinemia (hypercholesterolemia and/or hypertriglyceridemia) as set forth in Table I. All patients had been followed by us at the outpatient department for at least several months, many for years. During this time they had had repeated blood samples withdrawn for lipid analysis, which showed that the lipid levels were fairly stable. In no case did the lipid values at the time of the study show any deviation from the individual's usual level. No patient was on any special diet at the time of the study and in the hospital they had the ordinary hospital diet. Nor was any patient on drugs known to affect lipid metabolism or on antihypertensive drugs. They had not taken nicotinic acid earlier.

The patients were carefully instructed about the purpose, nature and possible side-effects of the study. In the morning after fasting over night a teflon catheter was inserted into an antecubital vein. A slow infusion of 0.9% saline kept the catheter patent and no heparin was used. The patients, who stayed in bed throughout the study, were then given a light breakfast, consisting of one cup of tea and two slices of bread without butter. The main purpose of the light breakfast was to reduce possible gastro-intestinal discomfort caused by nicotinic acid. They were then allowed only water to drink. About 45–60 min after the breakfast the first blood sample was withdrawn and a one gram tablet given by mouth, at the first study a placebo and at the second, performed two days after the first, nicotinic acid as Nicangin® (Draco, Lund, Sweden). Blood samples, about 10 ml each time, were then drawn into heparinized syringes and in most instances without stasis. Blood was immediately precipitated for glucose determination and the rest stored in ice water, brought to the laboratory and processed within a few hours.

Plasma FFA was determined according to Dole (24) as modified by Trout et al. (37), cholesterol according to Sperry Webb (35) and triglycerides by the method of Carlson and Wadström (20) as modified by Carlson (8). Blood glucose (32) and plasma glycerol (39) were determined enzymatically. Plasma proteins were estimated in triplicate by the biuret method. All lipid values in plasma were corrected for the minor changes in protein concentration that occurred. The concentration of *free* nicotinic acid in plasma was also determined in some studies (11). Statistical calculations were made as recommended by Snedecor (34).

RESULTS

Plasma FFA

The mean values are given in Table II and shown in Fig. 1. When placebo was given the concentration of FFA fell at 30 and 60 min, presumably as a result of the light breakfast. From one hour onwards the FFA level rose slowly and remained fairly constant during the last two hours. In the nicotinic acid study the initial values were not

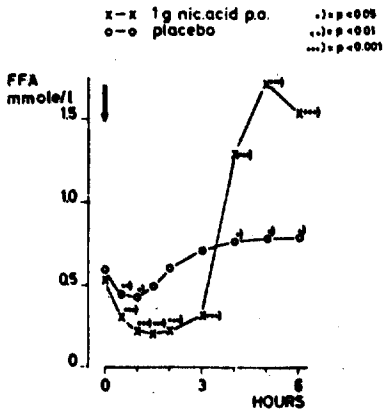

Fig. 1. Effect of nicotinic acid on free fatty acids (FFA) of blood plasma in 11 patients with ischemic-cardiovascular disease. The subjects were first given placebo (O — O) and two days later 1 g of nicotinic acid (× — ×) by mouth as indicated in the figure. The statistical calculations were made on the individual changes from the FFA concentration at zero time. The P-values indicate the statistical significance for the changes from zero time.

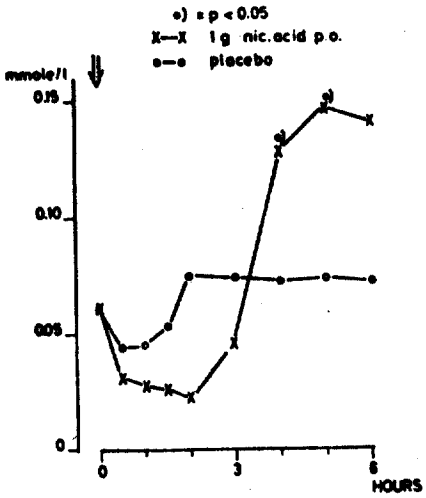

Fig. 2. Effect of nicotinic acid on plasma glycerol in 8 patients. For details see text to Fig. 1.

significantly different from those in the placebo study. Nicotinic acid rapidly depressed the FFA level and, already after 30 min, the level was significantly below the placebo value. The FFA level remained significantly depressed for 3 hours and then increased rapidly into an "overshoot" and was significantly elevated above the initial value and also above those for the controls.

Plasma glycerol

The concentration of glycerol is shown in Fig. 2. Glycerol followed the same pattern as FFA after both placebo and nicotinic acid but showed greater variability and was studied in fewer cases. The changes in glycerol levels from the initial values were only statistically significant during the "overshoot" period at 4 and 5 hours. However, when comparing the individual glycerol

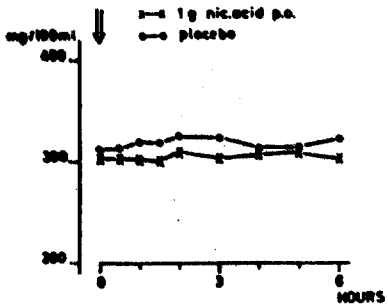

Fig. 3. Effect of nicotinic acid on plasma cholesterol in 11 patients. For details see text to Fig. 1.

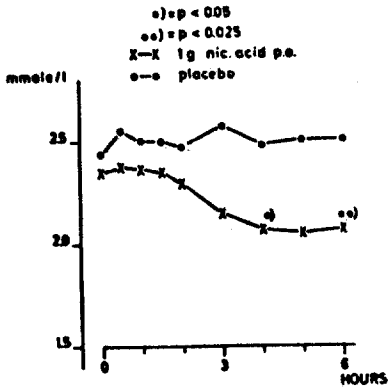

Fig. 4. Effect of nicotinic acid on plasma triglycerides in 11 patients. For details see text to Fig. 1.

levels after nicotinic acid and after placebo it was found that nicotinic acid caused a significant decrease in glycerol. The mean individual differences between the two studies were after 1 h, 2 and 3 hours 0.026 ± 0.010 ($P < 0.05$), 0.054 ± 0.012 ($P < 0.01$) and 0.025 ± 0.010 ($P < 0.05$) mmol/l respectively.

Plasma cholesterol

The mean initial concentration of cholesterol was 313 ± 24 mg/100 ml in the placebo study and 302 ± 25 mg/100 ml in the nicotinic acid study. During both studies the cholesterol level remained unchanged during the 6-hour period as indicated in Fig. 3. The average change from 0 to 6 hours in concentration of cholesterol and its standard error of mean was 9 ± 7 mg/100 ml after placebo and 0 ± 6 mg/100 ml after nicotinic acid.

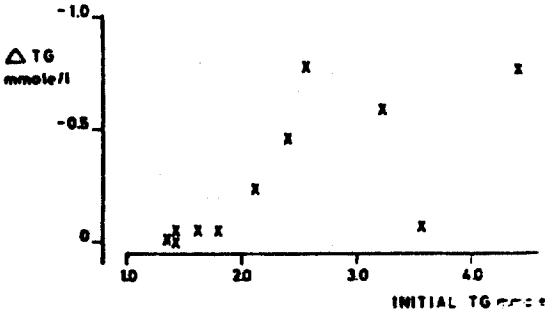

Fig. 5. Effect of nicotinic acid on plasma triglycerides in 11 patients. The figure shows the relation between the changes in plasma triglyceride concentration 6 hours after 1 g of nicotinic acid by mouth and the triglyceride concentration at zero time.

Table III. *Plasma levels of FFA (mEq/l) and nicotinic acid (μg/ml) after 1 g Nicangin® by mouth at 0 hours*

Case	Time, h	0	½	1	1½	2	3	4	5	6
E. A.	FFA	0.65	0.34	0.27	0.23	0.37	0.54	1.82	1.80	1.49
	Nic.	0.3	15.9	28.7	26.0	13.0	1.9	0.2	0	0
K. L.	FFA	0.57	0.28	0.20	0.22	0.25	0.26	1.93	2.87	2.78
	Nic.	0.1	17.5	29.3	26.0	18.4	4.1	1.0	0.5	0.3
N. O. b	FFA	0.63	0.38	0.23	0.17	0.15	0.10	1.11	1.47	1.31
	Nic.	0	30.8	34.0	23.0	15.7	3.2	0.9	0.5	0.2
S. S.	FFA	0.52	0.27	0.21	0.17	0.15	0.55	2.08	2.03	1.20
	Nic.	0	38.5	26.7	16.3	10.0	1.4	0.6	0.2	0.2
K. S.	FFA	0.60	0.39	0.31	0.32	0.34	0.32	0.66	2.06	2.14
	Nic.	0.4	34.0	28.4	32.1	22.6	9.7	2.6	0.9	0.3
K. H.	FFA	0.49	0.30	0.18	0.19	0.18	0.23	1.07	1.04	0.91
	Nic.	0.4	9.4	20.9	19.5	12.9	4.9	1.2	0.7	0.4
K. B.	FFA	0.47	0.27	0.21	0.15	0.18	0.27	1.44	1.47	1.37
	Nic.	0	32.2	24.1	19.0	11.2	1.4	0.1	0.2	0.1
S. J.	FFA	0.31	0.20	0.14	0.15	0.21	0.20	0.96	1.13	1.05
	Nic.	0.2	32.9	33.0	31.7	15.4	3.3	1.0	0.3	0
K.-A. S.	FFA	0.57	0.25	0.21	0.18	0.19	0.28	0.52	1.71	1.99
	Nic.	0	23.6	23.0	20.0	14.0	4.3	1.2	0.1	0
Mean	FFA	0.53	0.28	0.22	0.20	0.22	0.31	1.29	1.73	1.58
	Nic.	0.1	26.1	27.6	23.7	14.8	3.8	1.0	0.4	0.2

Plasma triglycerides

The triglyceride level was 2.44 ± 0.30 and 2.36 ± 0.30 mmol/l at the beginning of the placebo and the nicotinic acid study respectively. After administration of placebo the concentration of triglycerides did not change, as shown in Fig. 4. After nicotinic acid, however, there was a fall beginning after 2 hours from around 2.4 to 2.1 mmol/l which was significant at 4 and 6 hours. The average change in the concentration of triglycerides and its standard error of mean after 6 hours was + 0.06 ± 0.06 mmol/l ($P > 0.05$) and − 0.28 ± 0.09 mmol/l ($P < 0.025$) in the placebo and the nicotinic acid group respectively. The same statistical significance was obtained when the calculations were performed on logarithmic values (6).

The effect on the plasma triglycerides was generally related to the triglyceride concentration. Fig. 5 shows that the patients with triglyceride levels below 2 mmol/l had fairly small decreases 6 hours after administration of nicotinic acid. Patients with higher triglyceride concentration generally exhibited more pronounced effects.

Blood glucose

The behaviour of blood glucose was identical in the two groups. The initial values were 99 ± 5 and 96 ± 4 mg/100 ml (mean ± S.E.M.) in the placebo and the nicotinic acid study. At 2, 4 and 6 hours the corresponding mean values in these two studies were: 90 and 86, 78 and 80, 73 and 75.

Free nicotinic acid in plasma

In nine patients the concentration of free nicotinic acid was determined in plasma. These values and the corresponding FFA values are listed in Table III. Free nicotinic acid reached a peak value of around 30 μg/ml already after 30 min in four of the patients, and at one hour in the rest. After one hour the concentration started to fall, first slowly and then more rapidly. At three and four hours the plasma level of nicotinic acid had fallen to around 4 and 1 μg/ml respectively. Inspection of Table III gives some information about the relationship between plasma levels of free nicotinic acid and the effect on FFA mobilization. Thirty min after nicotinic acid had been taken the FFA level had decreased in all cases and at that time the lowest concentration of free nicotinic acid was 9.4 μg/ml. If we consider an increase in FFA concentration of 0.10 mEq/l significant, we may say that the FFA level was still depressed at an average nicotinic acid concentration of 8.8 μg/ml (range 1.4–26.0) but had started to rise on the average at a nicotinic acid concentration of 2.7 μg/ml (0.1–13.0).

Table IV. *Symptoms after administration of 1 g nicotinic acid by mouth at 0 hours*

Case	Time, h	½	1	1½	2	3	4	5	6
E. A.	Flush	++	+++	++	+	–	–	–	–
	Other					C			
K. L.	Flush	+++	+++	++	–	–	–	–	–
	Other					C			
N. O. a	Flush	+++	+++	++	+	–	–	–	–
	Other	T	T	T	T	T, C	T	T	
S. S.	Flush	+++	++	+	–	–	–	–	–
	Other					C			
V. C.	Flush	+++	++	–	–	–	–	–	–
	Other				C				
K. S.	Flush	++	+	–	–	–	–	–	–
	Other				C				
K. H.	Flush	+++	+++	++	+	–	–	–	–
	Other						C		
K. B.	Flush	+++	++	–	–	–	–	–	–
	Other				C				
S. J.	Flush	+	–	–	–	–	–	–	–
	Other								
K.-A. S.	Flush	+++	+++	++	–	–	–	–	–
	Other				C	V			
N. O. b	Flush	+++	+	+	–	–	–	–	–
	Other					C			

C = Chilly. T = Tinnitus. V = Vomiting. – = No visible flush. + = Slight flush in the face. ++ = Marked flush in the face, neck and upper part of the body. +++ = Marked flush in the face and the whole body.

Symptoms

Nicotinic acid causes a pronounced flush when given for the first time to a human being. This effect is significantly reduced or even disappears during long-term treatment. One gram of nicotinic acid as a single dose is usually the minimal dosage used during treatment of hyperlipoproteinemia. However, as a first dose one gram is an unusually high dose. The symptoms produced by this high dose are therefore of clinical interest and are recorded in Table IV. All patients flushed. One had flush only in the face, all the others over the entire body. The maximal flush appeared already after 30 min in all but one of the patients. The flush had disappeared completely within 3 hours. With the exception of the patient having flush only in the face all cases felt cold when the flush had disappeared.

DISCUSSION

Our main interest in this study concerns the relationship between the levels of plasma FFA and the concentration of cholesterol and triglycerides in plasma. One gram of nicotinic acid in comparison to administration of placebo lowered the FFA level significantly for three hours and reduced the concentration of triglycerides at 4 and 6 hours. The cholesterol level, however, remained unchanged during the entire study in both groups. This suggests that only one of the three main plasma lipoprotein classes had been affected by nicotinic acid, namely the very low density class. The very low density lipoproteins have triglycerides as their main constituent and these lipoproteins are believed to transport fatty acids, as triglyceride fatty acids, from the liver to peripheral tissues. In the fasting state FFA

from adipose tissue are the main precursor to the fatty acids of the very low density lipoprotein triglycerides. It is thus conceivable that, at least in the fasting state, lowering of FFA mobilization from adipose tissue should decrease the liver uptake of FFA and consequently the hepatic formation of the triglyceride-rich very low density lipoproteins. Our results strongly support this hypothesis. In the fasting rat we have previously demonstrated similar effects. Subcutaneous administration of nicotinic acid to rats lowered FFA levels for about four hours and decreased the plasma triglyceride concentration within 2 hours by more than 50 per cent (14, 18). In these studies analysis of liver lipids revealed that also the hepatic triglyceride content had been reduced by more than 50% in analogy with the hypothesis set forth above. Experiments with stimulation of FFA mobilization also strongly support the hypothesis relating the rate of mobilization of FFA to plasma triglyceride metabolism. Increasing FFA mobilization by noradrenaline rapidly increases the amount of triglycerides in the liver (16, 17, 27) and raises their concentration in plasma (17). This increase in plasma triglyceride concentration was demonstrated to be due to an increase in the content of very low density lipoproteins (17).

That the relationship between FFA mobilization and plasma lipoprotein levels has a not only academic interest but may be related to every day situations was borne out by our studies with a standardized emotional stress procedure which may well correspond to situations in everyday life. It was found that exposure of men for two hours to such a procedure rapidly increased FFA levels and raised triglyceride but not cholesterol concentration in plasma (15). In conformity with this study administration of nicotinic acid largely prevented the stress-induced FFA increase and lowered plasma triglycerides but not cholesterol (15).

This study does not answer the question how chronic treatment with nicotinic acid lowers the concentration of cholesterol in plasma, which was the effect first found with nicotinic acid on plasma lipids 12 years ago (3). Our data demonstrate that nicotinic acid first lowers FFA levels in plasma and then triglycerides. The effect on plasma cholesterol must be a later event. Whether or not the effect on cholesterol may be related to the inhibition of FFA mobilization will be studied later on.

When the concentration of nicotinic acid in plasma had fallen to around 3 μg/ml the FFA levels started to rise. This may appear somewhat surprising compared to studies with adipose tissue incubated in vitro. In studies with rat (5, 9) and human (10, 12) adipose tissue, nicotinic acid had a maximal inhibitory action on FFA mobilization at a concentration of around 0.1 μg/ml. This concentration is apparently about 10 times less than the plasma concentration needed in vivo to obtain maximal suppression of FFA mobilization. However further in vitro studies, in which whole serum was used as incubation medium instead of the usual albumin-Krebs-Ringer buffer solution, showed that, in the medium with serum, in fact much higher concentrations of nicotinic acid were needed than in albumin media to inhibit lipolysis (12). We have no explanation of the discrepancy between these two media, but it was shown that binding of nicotinic acid to serum proteins could not be a factor of importance in this connection (12).

The rather pronounced FFA rebound occurring at 4 to 6 hours after 1 gram of nicotinic acid had been given by mouth deserves attention and clinical consideration. An overshoot in the FFA levels after nicotinic acid was evident in the first three published cases in which smaller doses had been given (19). The cause of this rebound is not known. It may be elicited locally in adipose tissue by operation of local feedback mechanisms or may be due to some systemic reaction to nicotinic acid. The overshoot may partly explain why some patients need so large and frequent doses of nicotinic acid in order to keep lipoprotein levels low. The overshoot is very likely not a desirable therapeutic effect and will be studied in more detail.

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REFERENCES

1. Albrink, M. J. & Man, E. B.: Serum triglycerides in coronary artery disease. Arch. intern. Med. 103: 4, 1959.

2. Altschul, R.: Niacin in vascular disorders and hyperlipemia. Thomas, Springfield, Ill., 1964.
3. Altschul, R., Hoffer, A. & Stephen, J. D.: Influence of nicotinic acid on serum cholesterol in man. Arch. Biochem. 54: 558, 1955.
4. Antonis, A. & Bersohn, I.: Serum-triglyceride levels in South African Europeans and Bantu and in ischaemic heart disease. Lancet 1: 998, 1960.
5. Bergström, S. & Carlson, L. A.: Influence of the nutritional state on the inhibition of lipolysis in adipose tissue by prostaglandin E_1 and nicotinic acid. Prostaglandin and related factors 46. Acta physiol. scand. 65: 383, 1965.
6. Carlson, L. A.: Serum lipids in normal men. Acta med. scand. 167: 377, 1960.
7. — Serum lipids in men with myocardial infarction. Acta med. scand. 167: 399, 1960.
8. — Determination of serum triglycerides. J. Atheroscler. Res. 3: 334, 1963.
9. — Studies on the effect of nicotinic acid on catecholamine stimulated lipolysis in adipose tissue in vitro. Acta med. scand. 173: 719, 1963.
10. — Inhibition of the mobilization of free fatty acids from adipose tissue. Ann. N.Y. Acad. Sci. 131: 119, 1965.
11. — Determination of free nicotinic acid in blood plasma. Clin. chim. Acta 13: 349, 1966.
12. — Consequences of inhibition of normal and excessive lipid mobilization. Studies with nicotinic acid. In: Progr. biochem. Pharmacol. 3: 151, 1967. Karger, Basel and New York.
13. Carlson, L. A., Boberg, J. & Högstedt, B.: Some physiological and clinical implications of lipid mobilization from adipose tissue. In: Handbook of Physiology, vol. V. Adipose tissue, p. 625. American Physiological Society, Washington 1965.
14. Carlson, L. A., Fröberg, S. O. & Nye, E. R.: Acute effects of nicotinic acid on plasma, liver, heart and muscle lipids. Nicotinic acid in the rat. II. Acta med. scand. 180: 571, 1966.
15. Carlson, L. A., Levi, L. & Orö, L.: Plasma lipids and urinary excretion of catecholamines in man during experimentally induced emotional stress, and their modification by nicotinic acid. J. clin. Invest. 1968. In print.
16. Carlson, L. A. & Liljedahl, S.-O.: Lipid metabolism and trauma. II. Studies on the effect of nicotinic acid on norepinephrine induced fatty liver. Acta med. scand. 173: 787, 1963.
17. Carlson, L. A., Liljedahl, S.-O. & Wirsén, C.: Blood and tissue changes in the dog during and after excessive free fatty acid mobilization. A biochemical and morphological study. Acta med. scand. 178: 81, 1965.
18. Carlson, L. A. & Nye, E. R.: Acute effects of nicotinic acid in the rat. I. Plasma and liver lipids and blood glucose. Acta med. scand. 179: 453, 1966.
19. Carlson, L. A. & Orö, L.: The effect of nicotinic acid on the plasma free fatty acids. Demonstration of a metabolic type of sympathicolysis. Acta med. scand. 172: 641, 1962.
20. Carlson, L. A. & Wadström, L. B.: Determination of glycerides in blood serum. Clin. chim. Acta 4: 197, 1959.
21. Carlson, L. A. & Wahlberg, F.: Serum lipids, intravenous glucose tolerance and their interrelation studied in ischaemic cardiovascular disease. Acta med. scand. 180: 307, 1966.
22. Christakis, G., Rinzler, S. H., Archer, M., Winslow, G., Jampel, S., Stephenson, J., Friedman, G., Fein, H., Kraus, A. & James, G.: The anticoronary club. A dietary approach to the prevention of coronary heart disease—a seven-year report. Amer. J. publ. Hlth. 56: 299, 1966.
23. Dawber, T. R., Kannel, W. B., Revotskie, N., Stokes, J., Kagan, A. & Gordon, T.: Some factors associated with the development of coronary heart disease. Six years follow-up experience in the Framingham Study. Amer. J. publ. Hlth. 49: 1349, 1959.
24. Dole, V. P.: A relation between nonesterified fatty acids in plasma and the metabolism of glucose. J. clin. Invest. 35: 150, 1956.
25. Doyle, J. T., Heslin, A. S., Hilleboe, H. E. & Formel, P. F.: Early diagnosis of ischemic heart disease. New Engl. J. Med. 261: 1096, 1959.
26. Doyle, J. T., Heslin, A. S., Hilleboe, H. E., Formel, P. F. & Korns, R. F.: A prospective study of degenerative cardiovascular disease in Albany. Amer. J. publ. Hlth. 47: 25, 1957.
27. Feigelson, E. B., Pfaff, W. W., Karmen, A. & Steinberg, D.: The role of plasma free fatty acids in development of fatty liver. J. clin. Invest. 40: 2171, 1961.
28. Kannel, W. B., Dawber, T. R., Friedmann, G. D., Glennon, W. E. & McNamara, P. M.: Risk factors in coronary heart disease. An evaluation of several serum lipids as predictors of coronary heart disease. The Framingham Study. Ann. intern. Med. 61: 888, 1964.
29. Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N. & Stokes, J.: Factors of risk in the development of coronary heart disease. Six-year follow-up experience. The Framingham study. Ann. intern. Med. 55: 33, 1961.
30. Keys, A., Taylor, H. L., Blackburn, H., Brozek, J., Anderson, J. T. & Simonson, E.: Coronary heart disease among Minnesota business and professional men followed 15 years. Circulation 28: 381, 1963.
31. Leren, P.: The effect of plasma cholesterol lowering diet in male survivors of myocardial infarction. Acta med. scand. Suppl. 466, 1966.
32. Marks, V.: An improved glucose-oxidase method for determining blood, C.S.F. and urine glucose levels. Clin. chim. Acta 4: 395, 1959.
33. Oglesby, P. et al.: A longitudinal study of coronary heart disease. Circulation 28: 20, 1963.
34. Snedecor, G. W.: Statistical methods. The Iowa State University Press. Ames, Iowa 1961.
35. Sperry, W. M. & Webb, M.: A revision of the Schoenheimer-Sperry method for cholesterol determination. J. biol. Chem. 187: 97, 1950.

36. Stamler, J., Berkson, D. M., Lindberg, H. A., Hall, Y., Miller, W., Mojonnier, L., Levinson, M., Cohen, D. B. & Young, Q. D.: Coronary risk factors. Their impact, and their therapy in the prevention of coronary heart disease. Med. Clin. N. Amer. 50: 229, 1966.
37. Trout, D. L., Estes, E. H. & Friedberg, S. J.: Titration of free fatty acids of plasma: a study of current methods and a new modification. J. Lipid Res. 1: 199, 1960.
38. Walker, A. R. P.: The prevention of coronary heart disease. Amer. Heart J. 72: 721, 1966.
39. Wieland, O.: Eine enzymatische Methode zur Bestimmung von Glycerin. Biochem. Z. 329: 313, 1957.

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NICOTINIC ACID IN THE TREATMENT OF HYPERCHOLESTEROLEMIA

A Long Term Study

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AND CHARLOTTE BRAEULER

Evidence implicating hyperlipidemia in the pathogenesis of atherosclerosis continues to accumulate. As a result, methods for reducing lipid levels in man, both dietary and pharmacological, become increasingly important. Any practical lipid control program must be economical and must not produce undesirable side effects.

Altschul et al. first reported a decrease in plasma cholesterol following large oral doses of nicotinic acid.[1] Many subsequent studies have confirmed these results.[2, 3] Large scale prospective clinical trials are underway at present. Studies published to date, however, contain few references to experiences totaling more than five years of continuous nicotinic acid therapy and evidence of the safety of long term use is still lacking. Nicotinic acid has been used as a treatment for hypercholesterolemia in this institution since 1957. We have reviewed our clinical experience with this drug in terms of its efficacy in lowering plasma cholesterol and its toxicity and practicality as a longterm agent. This report concerns 160 patients, some of whom have been followed for more than a decade. Our experience includes 868 patient years of treatment.

MATERIALS AND METHODS

Patients entered the study from 1957 through 1968.

Patients were seen initially in the Vascular Clinic for evaluation of various clinical manifestations of atherosclerosis. Patients whose plasma cholesterol was greater than 260 mgs. per cent were instructed in a diet containing less than 300 mgs. of cholesterol daily and a polyunsaturated to saturated fat ratio of approximately 1.5 to 1. The caloric level was adjusted to bring each patient toward ideal body weight. Patients whose blood cholesterol remained above 260 mgs.% after 8 weeks of diet therapy were selected for treatment. There were four patients in this series whose initial cholesterol was less than 260 mgs.% in whom treatment was started because of clinical evidence of extensive symptomatic atherosclerosis.

All patients were screened for secondary causes for hypercholesterolemia such as hypothyroidism, uncontrolled diabetes mellitus, nephrotic syndrome or obstructive biliary tract disease. Unless intercurrent illness demanded hospitalization, all followup examinations were carried out in the outpatient department.

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A complete history and physical examination, including oscillometry complete blood count, urinalysis and electrocardiogram, were obtained initially and at appropriate intervals. Blood glucose levels, liver function tests and uric acid determinations were performed when clinically indicated. Cholesterol determinations with the method of Carr and Drekter[4] were performed on venous blood drawn in the fasting state. Samples were obtained prior to initiation of treatment at intervals of 3–6 weeks initially in the first six months of therapy and at 6–18 month intervals thereafter.

Nicotinic acid therapy was begun at a level of 100 mgs. given immediately after each meal. This dose was increased gradually over 11 days to a level of 1 gram after each meal, a total of 3 gms. per day. Side effects were discussed thoroughly with each patient before treatment was begun, and, more recently, a mimeographed sheet of instructions and list of side effects have also been presented to him for home reference.

RESULTS

By 1969, a total of 160 patients had been taking nicotinic acid. The principal diagnoses are listed in Table 1. The mean age of the patients was 53. The male to female ratio was approximately 4 to 1, representing the approximate sex ratio of patients seeking medical help for symptomatic atherosclerosis. 106 patients completed at least one year of treatment. The mean followup was 6.6 years and the maximum followup was 12 years. Reasons for discontinuation of therapy are presented later in this report.

Plasma cholesterol

Changes in plasma cholesterol in patients followed for at least one year are shown in Table 2. Maximum cholesterol reduction occurred within six weeks of initiation of full dosage of nicotinic acid. The baseline average prior to treatment was 340 mgs.%; the mean decrease noted at one year was 26%. The effectiveness of drug was not influenced by age but a better response did occur in women, a fact noted by others. The initial response to nicotinic acid was

TABLE 1

Presenting diagnosis at initiation of drug therapy

	No.	Per Cent
Atherosclerosis obliterans	51	32
Cerebrovascular atherosclerosis	30	18
Coronary atherosclerosis	50	31
Hypercholesterolemia only	13	9
Combined vascular disease	16	10
Total	160	100

TABLE 2

Mean plasma cholesterol response after 1 year

	No.	Mean Cholesterol Pretreatment	Mean Cholesterol after One Year of Treatment	Percentage Decrease
Total	106	340 mg.%	251 mgs.%	-26
Age <50	46	350 mg.%	248 mgs.%	-26
Age >50	60	329 mg.%	242 mgs.%	-26
Males	81	321 mg.%	242 mgs.%	-24
Females	25	360 mg.%	254 mgs.%	-28

TABLE 3

Duration of nicotinic acid therapy and reasons for discontinuation

Duration of Therapy and Followup	1 yr.	1-3 yrs.	3-5 yrs.	6-10 yrs.	10 yrs	Total
Lost to followup	13	3	1	2	0	19
Deaths	6	2	3	3	0	14
Side effects	27	9	2	0	0	38
Miscellaneous	8	5	1	1	1	16
Still taking N.A.	0	16	10	32	15	73
Total	54	35	17	38	16	160

maintained as long as the drug was continued. Fifty-one patients have been followed for more than five years, 16 patients for more than 10 years.

Discontinuation of therapy and side effects

The reasons for discontinuation of therapy are summarized in Table 3. Eighty-four per cent of those patients who discontinued therapy did so within the first two years and 91% of such patients did so within the first three years. Side effects were the principal reason for stopping treatment. Relative importance of various side effects in causing drug discontinuation is illustrated in Table 4.

Although all patients experienced some degree of skin flushing and pruritus, only ten patients were bothered sufficiently to discontinue therapy. It is of interest that this reaction often decreased or disappeared within a few weeks. Tolerance was shown by the fact that the breakfast dose caused the most flushing and flushing was always worse after inadvertently skipping medication for several days. Dry skin, although noted in 82% of patients, seemed to cause little problem. A subtle change resembling acanthosis nigricans was noted in 24% of patients. This change appeared to be related to the duration of drug therapy and has been unassociated with malignancy in our experience.

Some 28% of patients experienced dyspepsia or nausea and vomiting and of this group 45% discontinued nicotinic acid altogether. Lowering the total dos-

TABLE 4

Side effects of nicotinic acid in 160 patients

	No.	Per Cent	No. Discontinued
Flushing or pruritus	160	100	10
Dry skin	121	82	0
Nausea and vomiting	42	26	[illegible]
Peptic ulcer	9	5.6	8
Acanthosis nigricans	41	24	1
Carbohydrate intolerance	4	2.5	[illegible]
Hepatic	3	1.8	[illegible]
Gout	3	1.8	[illegible]
Skin rash	3	1.8	3

age of drug often relieved the symptoms. In such patients significant cholesterol reduction often continued in spite of lowered dosage, suggesting a relationship between gastrointestinal toxicity and cholesterol lowering efficacy in a given patient. In nine patients clinical evidence of active peptic ulcer disease developed. Eight of these ulcers were documented by radiographic studies. Three of these patients had previously known duodenal ulcer disease; all showed improvement when nicotinic acid was discontinued. One patient continued the drug during intensive medical therapy for an ulcer. She is presently asymptomatic and still taking nicotinic acid.

In three patients evidence of liver disease developed with hepatomegaly, jaundice, elevation of SGOT and alkaline phosphatase and in one case ascites. Liver biopsy was performed in two patients. One showed patchy fibrosis with mononuclear inflammation and some areas of necrosis. The other showed intrahepatic cholestasis with periportal hepatitis. All liver function tests returned to normal following discontinuation of nicotinic acid. Each of these patients remained well after several years of followup.

Eight patients had diabetes mellitus when drug therapy was initiated, but only two were insulin dependent. A moderate increase in glycosuria was noted in three patients. A small increased insulin requirement was noted in one case. Only one patient without previously recognized diabetes mellitus manifested hyperglycemia on nicotinic acid therapy. No patients discontinued therapy because of carbohydrate intolerance.

Three patients had known gout prior to treatment, but only one had an acute attack after therapy was begun. Discontinuation of nicotinic acid was not required and recurrent attacks of gout have not been a problem.

In three patients a skin rash developed during therapy and was aggravated by each periodic flush. The rash disappeared in each patient when the nicotinic acid therapy was discontinued.

Fourteen patients died, three with complications of progressive peripheral atherosclerosis, and two in congestive heart failure, one having an acute my-

ocardial infarction. Sudden death occurred in three patients outside the hospital, presumably due to arteriosclerotic heart disease. Two patients died of documented malignancies.

DISCUSSION

There is little doubt that oral administration of nicotinic acid in the range of 3 gms. per day will produce a significant depression of plasma cholesterol and that this will be sustained as long as the drug is continued, even for periods of time up to 12 years. Side effects remain a major deterrent to continued use of the drug, however, with nausea and vomiting being the major cause of drug discontinuation. Buffered nicotinic acid preparations have not been very helpful in our hands, but routinely taking each dose during or immediately following a meal seemed to help considerably. Careful preparation of patients for possible side effects, including a printed sheet of instruction, reassured many of them sufficiently to carry on through the first several weeks of dyspepsia. After this time, many patients develop tolerance to these side effects. The occurrence of active peptic ulcer disease in nine patients was of interest and concern. This finding has been reported by Parsons, but not by Berge.[5, 6] Since the pH of a saturated solution of nicotinic acid is approximately 2.2, it is reasonable to assume that its acidity is a causative factor in ulcer development. However, we know of no studies which confirm or deny this. Although discontinuation of drug improved ulcer symptoms, we have come to regard previously documented peptic ulcer disease as a relative contraindication to initiation of nicotinic acid therapy.

Flushing of the skin and pruritus were common problems, but again, careful preparation of the patient by preparatory discussion reduced the dropout rate considerably. The frequency of acanthosis nigricans is higher than previously reported, but this may be related to the length of treatment as well as to our increased awareness of minimal skin changes.[7] Several patients followed for more than ten years have shown no evidence of malignancy. There is no evidence that this condition when appearing during nicotinic acid therapy is related to the treatment.

Although liver disease appeared in three of our patients, the actual frequency of liver dysfunction in our series is not known, for routine liver function tests were not performed. Two of these patients presented with jaundice initially, one being in a distant hospital where an exploratory laparotomy was performed. The relative safety of this drug is manifested by the complete recovery of these three patients when the medication was discontinued. Our experience has also been noted by others.[8, 9]

Since none of our patients developed marked changes in carbohydrate tolerance, we do not consider insulin-dependent diabetes an obligatory contraindication to nicotinic acid.

Three of our patients had clinical gout by history. Their failure to show exacerbation with nicotinic acid suggests that this condition, too, is not a

contraindication to nicotinic acid, although as with diabetes, reasonable caution is necessary.

Despite extensive investigation, the mechanisms of action of cholesterol lowering by nicotinic acid is unknown. A variety of possibilities have been considered. These have included inducement of relative lack of coenzyme A, direct inhibition of cholesterol synthesis, and depression of plasma cholesterol related to the lowering of free fatty acids.[10, 11, 12] All of these hypotheses need further investigation and confirmation.

The past five years have produced a new classification of the hyperlipoproteinemias which offer a more rational guide to dietary and drug therapy. With reference to the Frederickson classification, nicotinic acid has proven to be an effective mode of therapy in three of the five types (Type II, Type IV, and Type V) of the familial hyperlipoproteinemias.[13, 14]

Because ours is a retrospective study with no control population, we have purposely avoided comment on the question of progression of atherosclerosis in these patients. Obviously prospective studies are needed to evaluate this point. Such a study is now underway with regard to coronary artery disease.[15]

Our experience shows, as have others, that side effects are a definite deterrent to some users of nicotinic acid. However, in 106 patients followed on the drug for more than one year, including 55 patients followed for more than five years, not a single episode of irreversible side effects has occurred. We, therefore, consider this drug to be of major importance in the pharmacological approach to hypercholesterolemia.

SUMMARY

One hundred and sixty patients were treated with nicotinic acid for hypercholesterolemia and followed for periods up to twelve years. The mean percentage decrease of serum cholesterol was 26%. The majority of dropouts occurred during the early phases of treatment. The major side effects demonstrated were gastrointestinal symptoms including a 5.6% incidence of peptic ulcer. No evidence of serious irreversible side effects was demonstrated in a total 868 patient-years of treatment. Although side effects are a definite deterrent to some users of nicotinic acid, the drug is still of major importance in the therapy of hypercholesterolemia.

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REFERENCES

1. Altschul, R., Hoffer, A., Stephen, J.: Influence of Nicotinic Acid on Serum Cholesterol. Arch. Biochem., 54: [illegible], [illegible].
2. Parsons, W. B., Jr., Flinn, J. H.: Reduction Serum Cholesterol Levels and Beta Lipoprotein Cholesterol Levels by Nicotinic Acid. Arch. Int. Med., [illegible]: 788, [illegible].
3. Mahl, M., Lange, K.: A Long Term Study of the Effect of Nicotinic Acid Medication on Hyp[illegible]. Am. J. Med. Sc., [illegible]: [illegible], [illegible].
4. Carr, J., [illegible], I.: [illegible] for the Extraction and Determination of [illegible]. Clin. Chem., [illegible]: [illegible], [illegible].

5. Parsons, W. B., Jr.: Activation of Peptic Ulcer by Nicotinic Acid. JAMA., [illegible] 1960.
6. Berge, K. G., Achor, R. W. P., Christensen, N. A., Mason, H. L.: Hypercholesterolemia and Nicotinic Acid Am. J. Med., *31:* 24. 1961.
7. Ruiter, M., Meyler, C.: Skin Changes after Therapeutic Administration of Nicotinic Acid in Large Doses. Dermatologica. *120:* 139. 1960.
8. Purdue, W. O.: Severe Liver dysfunction during Nicotinic Acid. JAMA., *175:* 137. 1961.
9. Rivin, A. U.: Jaundice Occurring During N. A. Therapy for Hypercholesterolemia JAMA., *170:* 2068. 1959.
10. Schade, H., Saitman, P.: Influence of Nicotinic Acid on Hepatic Cholesterol Synthesis in Rabbits. Proc. Soc. Exper. Biol. Med., *102:* 265. 1959.
11. Parsons, W. B., Jr.: Reduction in Hepatic Synthesis of Cholesterol from C^{14}-Acetate in Hypercholesterolemic Patients by Nicotinic Acid. Circulation. *24:* 1099. 1961.
12. Carlson, L. A., Oro, L. J.: Persistence of the Inhibitory Effect of Nicotinic Acid on Catecholamine. Stimulated Lipid Mobilation during prolonged treatment with Nicotinic Acid. J. Atherscler Res., *5:* 436. 1965.
13. Carlson, L. A.: The Effect of Nicotinic Acid treatment on the Chemical Composition of Plasma Lipoprotein Classes in Man. in Proceedings of the Third International Symposium on Drugs Effecting Lipid Metabolism. Plenum Press, New York, 1969 pp 327.
14. Levy, R. I., Glueck, C. J.: Hypertriglyeridemia, Diabetes and Coronary Vessel Disease. Arch. Int. Med., *123:* 220. 1969.
15. Parsons, W. B., Jr.: Coronary Drug Project Deserves Support of Nation's Physicians Card. Dig., 13. 1967.

5. Parsons, W. B., Jr.: Activation of Peptic Ulcer by Nicotinic Acid. JAMA., *1[illegible]:* [illegible] 1960.
6. Berge, K. G., Achor, R. W. P., Christensen, N. A., Mason, H. L.: Hypercholesterolemia and Nicotinic Acid Am. J. Med., *31:* 24, 1961.
7. Ruiter, M., Meyler, C.: Skin Changes after Therapeutic Administration of Nicotinic Acid in Large Doses. Dermatologica, *120:* 139, 1960.
8. Pardue, W. O.: Severe Liver dysfunction during Nicotinic Acid. JAMA., *175:* 137, 1961.
9. Rivin, A. U.: Jaundice Occurring During N. A. Therapy for Hypercholesterolemia JAMA., *170:* 2088, 1959.
10. Schade, H., Saitman, P.: Influence of Nicotinic Acid on Hepatic Cholesterol Synthesis in Rabbits. Proc. Soc. Exper. Biol. Med., *102:* 265, 1959.
11. Parsons, W. B., Jr.: Reduction in Hepatic Synthesis of Cholesterol from C^{14}-Acetate in Hypercholesterolemic Patients by Nicotinic Acid. Circulation, *24:* 1099, 1961.
12. Carlson, L. A., Oro, L. J.: Persistence of the Inhibitory Effect of Nicotinic Acid on Catecholamine. Stimulated Lipid Mobilation during prolonged treatment with Nicotinic Acid. J. Atherscler Res., *5:* 436, 1965.
13. Carlson, L. A.: The Effect of Nicotinic Acid treatment on the Chemical Composition of Plasma Lipoprotein Classes in Man, in Proceedings of the Third International Symposium on Drugs Effecting Lipid Metabolism. Plenum Press, New York, 1969 pp 327.
14. Levy, R. I., Glueck, C. J.: Hypertriglyeridemia, Diabetes and Coronary Vessel Disease. Arch. Int. Med., *123:* 220, 1969.
15. Parsons, W. B., Jr.: Coronary Drug Project Deserves Support of Nation's Physicians Card. Dig., 13, 1967.

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Effect of nicotinic acid on blood cholesterol

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Nicotinic acid in dosages of 3 gm. daily lowers the level of blood cholesterol. This effect is greater when the initial cholesterol level is higher. No serious toxic effects were observed. The side reactions are discussed. If development of arteriosclerosis depends on the level of blood cholesterol, this may be an effective means of reducing the hypercholesteremia.

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Hypercholesteremia and its relationship to arteriosclerosis has been the subject of many investigations in recent years. Although there is a general consensus of opinion that pathogenesis of arteriosclerosis is accompanied by a disturbance of lipid metabolism,[1] cholesterol and lipoproteins have been the two outstanding fractions which have been most frequently implicated.[2] It is generally agreed that there is a relationship between the concentration of cholesterol in the blood and the development of arteriosclerosis. The importance of this relationship led to different attempts to lower the blood level of cholesterol by means of diet, hormones, and various drugs. Since Altschul and associates[3] showed in 1955 that large doses of nicotinic acid result in lowering the blood serum cholesterol, several other investigators have confirmed this finding.[4,5] In view of the great prevalence of arteriosclerosis in our domiciliary population, nicotinic acid was administered to 20 patients whose blood cholesterol was 250 mg. or higher.

TABLE **Complete Laboratory Data on 20 Patients with Cholesterol Levels Prior to Study and at 4, 8, and 12 Weeks of Nicotinic Acid Treatment**

Patient	Age	Cholesterol (mg. %)				Esters (%)		BUN (mg.)		Alkaline phosphatase (units)		Thymol turbidity		Hemoglobin (gm.)	
		Prior	4 wks.	8 wks.	12 wks.	Prior	12 wks.	Prior	12 wks.	Prior	12 wks.	Prior	12 wks.	Prior	12 wks.
1. W.K.	70	360	225	242	236	78	77	25	26	-	-	1.5	1.5	13.2	[illegible]
2. E.A.	63	315	301	199	200	62	77	19	21	-	-	3.0	3.1	14.6	[illegible]
3. A.L.	80	313	199	187+	-	80	75	24	25	-	-	3.9	3.9	15.2	[illegible]
4. S.W.	61	313	336	199†	-	80	64	14	24	-	-	3.9	3.9	14.6	[illegible]
5. C.W.	61	300	318	229	236	78	65	24	24	-	-	2.9	1.8	13.8	[illegible]
6. H.V.	59	284	187	199	187	65	77	19	18	7.5	-	-	1.1	12.8	[illegible]
7. R.C.	61	278	241	199	186	75	74	19	23	2.8	3.4	-	-	13.6	[illegible]
8. L.D.	64	276	235	236	236	73	74	23	23	2.5	2.5	-	-	16.0	[illegible]
9. C.G.	60	278	229	236	210	73	68	26	25	3.3	3.4	-	-	14.6	[illegible]
10. C.F.	73	270	172	210	140	69	67	25	25	-	4.8	1.7	-	13.2	[illegible]
11. T.G.	58	270	187	181	185	71	70	26	15	2.7	2.9	1.5	3.7	13.6	[illegible]
12. C.M.	54	269	236	256	210	69	71	18	21	-	-	1.5	1.5	12.7	[illegible]
13. A.W.	64	263	327	229	140*	75	72	23	24	-	-	2.9	2.9	13.6	[illegible]
14. R.R.	33	256	228	181	199	75	72	19	13	-	-	1.5	1.5	14.8	[illegible]
15. D.I.	63	256	222	256	210	75	73	15	-	2.5	2.5	-	-	14.2	[illegible]
16. E.E.	67	255	224	192	181	76	68	19	26	-	-	2.3	2.3	12.8	[illegible]
17. M.E.	51	238‡	210	199	184	77	69	24	19	3.6	2.9	-	-	12.8	[illegible]
18. J.S.	56	199	199	223	155	71	60	21	13	4.1	3.8	-	-	14.2	[illegible]
19. T.C.	56	181	150	131	149	79	69	17	22	8.8	6.4	2.0	-	14.0	[illegible]
20. R.F.	52	150	140	140	154	60	54	18	16	3.2	3.6	0.8	1.5	12.6	[illegible]

* Nicotinic acid stopped at 10 weeks because proptosis and edema of right eye developed, which cleared under treatment.
† Began to drink, diarrhea developed; blamed diarrhea on nicotinic acid, which was discontinued at end of 10 weeks.

WC (cells)	Neutrophils (%)		Urine				Blood glucose		Major diagnosis	Decrease in cholesterol level—12 wks	
			Prior		12 wks.						
12 wks.	Prior	12 wks.	alb.	sug.	alb.	sug.	Prior	12 wks		(mg. %)	(%)
6.6	53	62	0	0	0	0	—	—	Chronic arthritis; obesity	124	33
6.5	64	64	+	0	24	0	150	200	Central nervous system lues, with hemiplegia; diabetes mellitus; ASHD	115	37
5.6	71	70	0	0	0	0	—	—	Pulmonary emphysema	126	40
6.5	64	64	0	0	0	0	—	—	Hypertrophic heart disease, old cerebrovascular accident	114	36
6.0	71	57	0	0	0	0	—	—	Pulmonary emphysema, deafness	64	20
7.7	64	69	0	0	0	0	—	—	Vascular hypertensive disease; postoperative abscess of brain	97	34
8.0	61	60	0	0	1+	0	195	200	Diabetes mellitus; diabetic neuropathy	102	36
8.2	59	59	0	0	0	0	—	—	Late latent syphilis; arteriosclerosis obliterans	42	15
8.2	60	62	0	0	0	0	—	—	Post-traumatic arthritis	68	24
10.0	50	52	1+	0	0	0	169	173	Diabetes mellitus; ASHD	130	48
6.5	75	75	1+	0	0	0	127	188	Diabetes mellitus; ASHD	85	31
12.8	62	63	0	0	0	0	—	—	Schizophrenia	59	22
6.7	60	60	0	0	0	0	—	—	Chronic arthritis; amputation of both lower legs	123	48
6.0	72	61	0	0	0	0	165	107	Diabetes mellitus; anxiety reaction	57	22
10.7	53	54	0	0	0	0	—	—	Osteoarthritis	46	18
9.6	51	66	0	0	0	0	—	—	ASHD; pulmonary emphysema	76	30
5.2	60	66	0	0	0	0	—	—	Hypertensive cardiovascular disease	54	22
5.3	50	52	0	0	0	0	—	—	Stricture of urethra; pulmonary emphysema	34	17
6.7	57	74	0	0	0	0	—	—	Pulmonary emphysema; chronic bronchitis	32	17
6.8	72	60	0	0	0	0	119	—	Asthma; central nervous system lues	44	42

+ Left AWOL, has been drinking, study discontinued after 10 weeks.
‡ Initial cholesterol level was 283; second determination prior to study was [illegible] of the two determinations was 238 mg. %, but he was included in the study.

for a period of three months, each new admission had his blood cholesterol determined. All those with cholesterol levels above 250 mg. were included in the study. All the patients were told that it would take ninety days, and most of them volunteered for that period. The patients agreed to continue longer. Two determinations were done, and the average of the two was taken as the initial value. Every patient had a complete physical examination, chest film, blood serology, electrocardiogram, and the following laboratory examinations done prior to the study: total cholesterol and cholesterol esters, blood urea nitrogen, alkaline phosphatase or thymol turbidity, complete blood count, and urinalysis. The laboratory examinations were repeated every month.

Every patient included in the study was started on 250 mg. of nicotinic acid three times a day. Two weeks later the dosage was doubled, and in another two weeks it was doubled again—that is, 1 gm. was given three times a day. No patient received more than 3 gm. of nicotinic acid daily. Every dose was given by a nurse, and the drug was taken by the patient in her presence. Fifteen patients received the drug for three months, 1 patient took it for four months, and it was given to 4 patients for five months.

Two patients were hospitalized early in the study for nonrelated conditions, and 1 patient was discharged. Since no patients were available with hypercholesteremia, these 3 men were replaced by 3 others whose initial cholesterol levels were 199, 181, and 150 mgs., respectively (table 1).

the lowest dose of nicotinic acid and fell still more when this dose was increased. Two patients did not show any effect until the end of the second month of administration of nicotinic acid. If only patients with cholesterol levels above 250 mg. are included, the average fall for the 15 patients with hypercholesteremia who had been on nicotinic acid for three months was 29.5 mg. per cent (figure 1). In 1 case, cholesterol fell almost 50 per cent, from 263 mg. per cent to 140 mg. per cent. Although the cholesterol level fell in every case, there were individual variations. If table 1 is analyzed more closely, these variations will be noted. Three patients had practically identical cholesterol levels initially: 255, 256, and 256 mg. per cent. At the end of three months, these values were

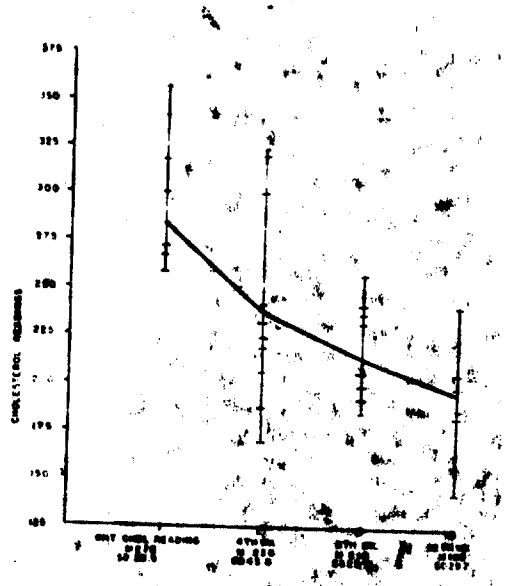

FIG. 1. *Mean cholesterol levels of 15 patients with hypercholesteremia. Range distribution indicated at each stage of study.*

reduced by 30 per cent, 18 per cent, and 22 per cent. Two patients with cholesterol levels of 270 mg. initially had this figure decreased by 48 per cent and 31 per cent at the end of three months. Does this variation mean that some other factor besides the nicotinic acid effect is involved or is it simply individual response to this drug?

Figure II gives a representative case of marked hypercholesteremia with pronounced fall in cholesterol level—33 per cent—while figure III is a typical case of mild hypercholesteremia with moderate fall in cholesterol level—22 per cent.

Patients with normal cholesterol values also had these levels reduced from 199 mg. per cent to 165 mg. per cent—17 per cent.

The laboratory examinations at the end of the study were essentially at the same levels as they were at the beginning except for the cholesterol level. The liver function tests especially were watched carefully in view of the recent report of jaundice occurring during the administration of nicotinic acid in a patient who had been taking the drug for seventy-two weeks.[16]

All of the patients remained on their previous diet except those with diabetes who were on special diets. Several patients gained 7 to 8 lb. One overweight patient lost 8 lb. during the first month. In others, the weight remained stable. Three of the 4 diabetic patients were receiving insulin and 1, Orinase.

Side Reactions

All of the patients complained of hot flushes at one time or another. However, in no case were they severe or annoying enough to necessitate stopping the drug. They eventually diminished in intensity despite the continuation of the drug. Pruritus was the complaint in 5 cases.

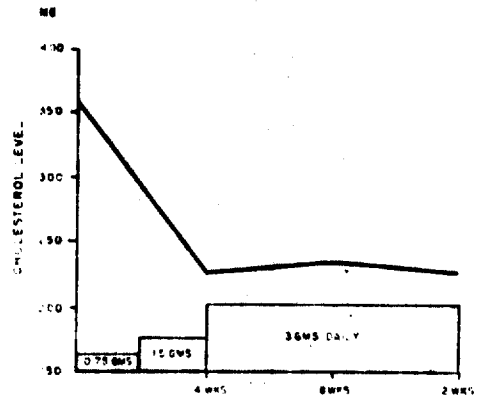

FIG. II. *Case of marked hypercholesteremia and its response to nicotinic acid*

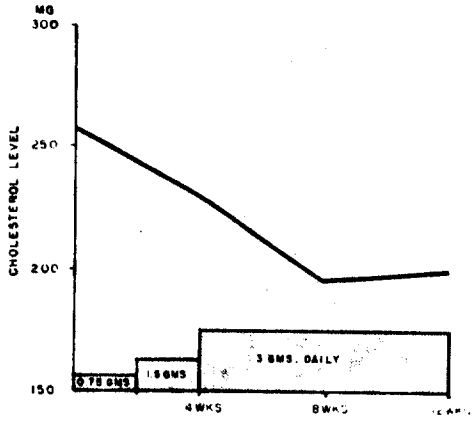

FIG. III. *Case of mild hypercholesteremia and its response to nicotinic acid*

One patient complained of diarrhea, which was treated and cleared while the drug was continued. Several patients stated that the cramps in their legs, which they experienced prior to the study, disappeared after taking nicotinic acid for two months.

Discussion

The results of this study are in agreement with previous observations[3,4,9,11] that large doses of nicotinic acid lower the level of blood serum cholesterol. The higher the initial level of serum

cholesterol, the greater the lowering effect of the drug.[4,8] Cholesterol values within normal range—199 and 181 mg. per cent—were reduced by 17 per cent, while a cholesterol level of 313 mg. per cent initially decreased 40 per cent. The average fall in cholesterol level was 29.5 mg. per cent at the end of three months. Other investigators[4,8] noted that when a placebo was substituted for nicotinic acid, the cholesterol level returned to the original figure. When the drug was stopped, the blood cholesterol also returned to the previous level.

No serious toxic effects were observed in this study. Side reactions consisted primarily of hot flushes and, in some cases, of pruritus. Transient diarrhea developed in 1 patient, but the drug was continued. Half of the patients experienced a subjective feeling of well-being. There was no evidence of liver damage or toxic effects on the hematopoietic, cardiovascular, or renal systems.

The mechanism of action of nicotinic acid is unknown at present and is now under investigation. In their original work on this subject, Altschul and associates[3] stated that the chief effect may be through the formation of oxycholesterols, which are more readily excreted than pure cholesterol or less readily reabsorbed from the intestines. Other investigators believe that nicotinic acid affects the biosynthesis of cholesterol. Merrill concluded from his experiments on rats that nicotinic acid has a definite effect on cholesterol metabolism.[17]

It may be assumed that nicotinic acid as such, as well as some of its metabolic derivatives, especially nicotinuric acid, plays a role in the metabolism of cholesterol, the nature of which still has to be studied.[12]

Summary

Nicotinic acid in daily dosages of 3 gm. lowers the level of blood cholesterol. When the initial cholesterol level is higher, the effect is greater. The mechanism by which this effect is achieved is unknown and requires further investigations. There are individual variations in response to the drug in patients with identical cholesterol values.

No serious toxic effects were observed in the present study. The side reactions are discussed.

If one accepts the view that there is a definite relationship between the cholesterol level of the blood and arteriosclerosis, large doses of nicotinic acid are an effective means of reducing the blood cholesterol.

All the patients were told that the study would take ninety days, and most of them volunteered for that period. Five patients agreed to continue longer.

The drug for this study was supplied through the courtesy of Merck & Co., Inc., Rahway, New Jersey.

I wish to extend my appreciation to Miss Ethel Kufahl, Mrs. Grace Roeder, and Mrs. Ethel Smith for their assistance in this study and to J. J. Moylan, Ph.D., for his assistance in preparing the graph in figure 1.

REFERENCES

1. BARR, D. P.: Some chemical factors in pathogenesis of atherosclerosis. Circulation 8: 641, 1953.
2. GOFMAN, J. W., and others: Blood lipids and human atherosclerosis. Circulation 2: 161, 1950.
3. ALTSCHUL, R., A. HOFFER, and J. D. STEPHEN: Influence of nicotinic acid on serum cholesterol in man. Arch. Biochem. 54: 558, 1955.
4. PARSONS, W. B., JR., and others: Changes in concentration of blood lipids following prolonged administration of large doses of nicotinic acid to persons with hypercholesterolemia: preliminary observations. Proc. Staff Meet. Mayo Clin. 31: [illegible], 1956.
5. PARSONS, W. B., JR., and others: Effect of large doses of nicotinic acid on the plasma and serum lipids in human beings with hypercholesterolemia. Circulation 14: 495, 1956.
6. PARSONS, W. B., JR., and J. M. FLINT: Reduction in elevated blood cholesterol levels by large doses of nicotinic acid: preliminary report. J.A.M.A. 165: 234, 1957.
7. ALTSCHUL, R., and [illegible]: Effect of large doses of

Chen-'38
Bib No. 808

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Toxicity of Nicotinic Acid.

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Nicotinic acid (I), chemically pyridine-β-carboxylic acid, was prepared as early as 1867 by Huber[1] from the oxidation of nicotine (II). During the early investigation of vitamin B, nicotinic acid was isolated from rice polishings,[2, 3, 4] and suspected to have an antineuritic action in pigeons, although subsequent tests definitely excluded this possibility.[5] A renewal of interest was aroused by the publication of Elvehjem, Madden, Strong, and Woolley,[6] who showed that nicotinic acid or its amide isolated from the liver extract cures canine blacktongue of the Goldberger type.[7] Their

[1] Huber, C., *Liebigs Ann. Chem.*, 1867, **141**, 271; *Ber. deut. chem. Gesellsch.*, 1870, **3**, 849.

[2] Funk, C., *J. Physiol.*, 1911-12, **43**, 395; 1912-13, **45**, 489; 1913, **46**, 173.

[3] Suzuki, U., Shimamura, T., and Odake, S., *Biochem. Z.*, 1912, **43**, 89.

[4] Drummond, J. C., and Funk, C., *Biochem. J.*, 1914, **8**, 598.

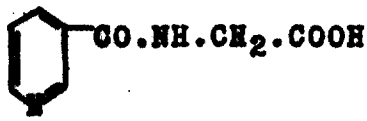
[5] Funk, C., *J. A. M. A.*, 1937, **109**, 2086.

[6] Elvehjem, C. A., Madden, R. J., Strong, F. M., and Woolley, D. W., *J. Am. Chem. Soc.*, 1937, **59**, 1767; *J. B. C.*, 1938, **123**, 137.

[7] Smith, D. T., *J. A. M. A.*, 1937, **109**, 2086.

(I)

(II)



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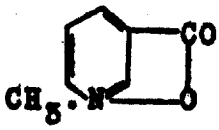

(IV)

work has been confirmed by Street and Cowgill.[8] Favorable clinical results in the treatment of human pellagra with nicotinic acid have already been obtained by Spies, Cooper, and Blankenhorn,[9] Fouts, Helmer, Lepkovsky, and Jukes,[10] Smith, Ruffin, and Smith,[11] and Margolis, Margolis, and Smith.[12]

Pharmacologically, Hunt and Renshaw[13] failed to observe any effect upon the autonomic nervous system with nicotinic acid and its derivatives. In dogs Ackermann[14] and Komori and Sendju[15] reported that nicotinic acid is excreted in urine partly as nicotinyl glycine (III) and trigonelline (IV), and partly unchanged. It is also apparent from these publications that nicotinic acid has a relatively low toxicity.

In view of the present interest in nicotinic acid (I) for the management of pellagra, and its suggestive relationship, although chemically remote, to nicotine (II), it appears desirable to have some precise information concerning its toxicity in animals. The sample of nicotinic acid we investigated was entirely colorless and melted at 236-237°C. (corrected). The solutions employed for injection were neutralized with adequate amounts of sodium carbonate—a

[8] Street, H. R., and Cowgill, G. R., PROC. SOC. EXP. BIOL. AND MED., 1937, 37, 547.

[9] Spies, T. D., Cooper, C., and Blankenhorn, M. A., *J. Am. Med. Assn.*, 1938, 110, 622 and 706.

[10] Fouts, P. J., Helmer, O. M., Lepkovsky, S., and Jukes, T. H., PROC. SOC. EXP. BIOL. AND MED., 1937, 37, 405.

[11] Smith, D. T., Ruffin, J. M., and Smith, S. G., *J. A. M. A.*, 1937, 109, 2054.

[12] Margolis, L. H., Margolis, G., and Smith, S. G., cited by Smith *et al.*

[13] Hunt, R., and Renshaw, R. R., *J. Pharmacol. and Exp. Therap.*, 1929, 35, 75; 1929, 37, 177.

[14] Ackermann, D., *Z. f. Biol.*, 1912, 59, 17.

[15] Komori, Y., and Sendju, Y., *J. Biochem.* (Japan), 1926, 6, 163.

1% solution having a pH of 7.4, one of 10% that of 7.8, and one of 20% that of 8.1. Minimal lethal doses were determined in white mice, white rats, and guinea pigs by intravenous injection with nicotine and nicotinic acid, respectively. The body weight of mice varied from 15 to 20 gm., that of rats 80 to 110 gm., and that of guinea pigs from 250 to 280 gm. As shown in Table I, nicotine is approximately 5625 times as toxic as nicotinic acid in mice, 3500 times as toxic in rats, and 778 times as toxic in guinea pigs. With lethal or near-lethal doses of both nicotine and nicotinic acid, all animals developed clonic convulsions, and either died promptly or recovered without apparent after effects.

TABLE I.
Acute Toxicity of Nicotine and Nicotinic Acid.

Compound	Species	Dose, mg. per kg.	No. of Animals used	No. died	Minimal lethal dose, mg. per kg.
Nicotine	Mice	0.4	1	0	0.8
		0.5	1	0	
		0.6	6	0	
		0.7	7	0	
		0.8	10	7	
		0.9	5	5	
	Rats	0.5	1	0	1.0
		0.7	5	0	
		0.8	5	2	
		0.9	5	2	
		1.0	5	3	
		1.1	5	5	
		1.2	3	3	
	Guinea Pigs	3.0	4	1	4.5
		4.0	3	0	
		4.5	4	3	
		5.0	3	3	
Nicotinic Acid	Mice	2500.0	3	0	4500.0
		3000.0	3	0	
		4000.0	3	0	
		4500.0	3	3	
	Rats	3000.0	5	2	3500.0
		3500.0	5	3	
	Guinea Pigs	3000.0	3	0	3500.0
		3500.0	5	3	

A group of 5 mice, injected daily by the tail vein, each with 500 mg. of nicotinic acid per kg. of body weight for 4 weeks except Saturdays and Sundays, survived with an increase in body weight.

Two adult dogs, weighing 13.8 and 15 kg., respectively, each received daily *per os* 2 gm. of nicotinic acid dispensed in capsules. The smaller animal began to excrete bloody feces on the 11th day, de-

veloped a series of convulsions on the 12th day, became increasingly irritable and bit the attendants. Since it was suspected of having rabies, medication was stopped on the 13th day. The dog was found dead on the 19th day, with a total loss of 4.2 kg. of body weight, not from rabies but apparently from poisoning due to nicotinic acid. The larger dog received a total amount of 40 gm. of nicotinic acid in the course of 20 days, gradually lost appetite until it refused to eat, and began to have occasional convulsions after the second week of experimentation. On the 20th day, the convulsions, tonic in character, became increasingly frequent, each series lasting from 1 to 4 minutes. The animal was unable to stand up during interconvulsive periods. Bloody feces were expelled. The condition was so critical that it was considered advisable to sacrifice the animal in order to avoid postmortem changes. The total loss of body weight in this animal was 3.6 kg. Autopsies were performed by Dr. Paul N. Harris. In the smaller dog, there were fatty metamorphosis of the liver and intussuception of small intestines which apparently existed for some time but was not sufficient to account for the death. In the larger dog, there were 6 erosions, 2 to 5 mm. in diameter, in the lesser curvature of the stomach which was filled with some bloody fluid; slight hyperemia of both small intestines and colon; petechiæ in the mucosa of the colon; a small amount of blood in colon contents; and fatty metamorphosis of the liver. Perhaps a more significant finding was the fact that in both dogs a few ganglion cells of the cortex, hippocampus and basal ganglia were shrunk and deeply stained. If this indicated an injury caused by excessive doses of nicotinic acid, it might be then that the convulsions observed before death were merely its manifestations. Further investigation will be necessary before this point can be settled.

Four additional dogs were given daily for a period of 8 weeks, except Saturdays and Sundays, smaller doses by mouth. They were 1, 0.5, 0.2, and 0.06 gm., respectively. At the end of the 8th week, all 4 animals appeared in good health and had gained in weight. A trace of albumin was found twice in the urine of the dog on the 1 gm. dose and in that of the dog on the 0.5 gm. dose. A trace of sugar was also detected once in the urine of both animals.

Unlike nicotine, nicotinic acid has no action upon the autonomic ganglia as already proved by Hunt and Renshaw.[18] A concentration of 1:5,000 of the acid did not elicit any response from the isolated rabbit's intestine. Similarly, a solution of 1:2,000 was inert to the isolated guinea pig's uterus. An intracutaneous injection of 0.1 cc.

of a 1% solution of nicotinic acid was followed by no hyperemia or ulceration. The substance has therefore little irritating action. Since nicotinic acid is often prepared from nicotine,[16] caution should certainly be exercised to eliminate any possibility of contamination by the alkaloid. Simple animal tests will detect such an impurity.

Summary. Nicotinic acid is at least several hundred times less toxic in mice, rats, and guinea pigs than nicotine. Nicotinic acid is devoid of action upon the autonomic ganglia. Nevertheless, repeated administration of large doses, 2 gm. daily, in dogs has resulted in poisoning and deaths.

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Biochem. J. 125(4):117. 1971.

Comparative Metabolism of Nicotinamide and Nicotinic Acid in Mice

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It is suggested that, in the mouse, metabolism is designed for the utilization of nicotinamide as a precursor of NAD and that the Preiss–Handler pathway (Preiss & Handler, 1958) functions primarily for the purpose of converting nicotinic acid into nicotinamide. It also appears that deamidation of nicotinamide to nicotinic acid is not a prerequisite to either its absorption from the gut or to its utilization as a precursor of NAD.

Adult female C3HeB/FeJ mice were injected intraperitoneally with [7-^{14}C]nicotinamide or [7-^{14}C]nicotinic acid at a dose of 0.9μmol/animal. Mice fed on Purina chow *ad libitum* ingest approximately this same quantity of the vitamin per day. At intervals from 5 to 90min after injection animals were killed and tissues were analysed for labelled nicotinamide coenzymes and precursors by paper chromatography.

In all the tissues examined more label was found in NAD after [7-^{14}C]nicotinamide injection than after [7-^{14}C]nicotinic injection. Nicotinic acid was rapidly cleared from all tissues, whereas nicotinamide persisted for 90min. This finding agrees with observations by Chaykin, Dagani, Johnson & Samli (1965) and Chaykin, Dagani, Johnson, Samli & Battaile (1965). These authors found that nicotinamide is ordinarily the only form of the vitamin found in mice. In liver, after [7-^{14}C]-nicotinic acid injection, label in nicotinic acid rapidly disappeared. At 5min label appeared primarily in desamido-NAD and NAD. By 10min the concentrations of these compounds had fallen with a concomitant increase in labelled nicotinamide. By 20min 90% of the total liver radioactivity was in the form of nicotinamide.

With regard to the metabolism of the vitamin in mice, a further question remained: namely, in what form does the vitamin pass the gut? When nicotinamide was administered, either by stomach tube or by direct injection into the intestine, the only form of the vitamin detectable in blood was nicotinamide. By contrast, 5min after [7-^{14}C]nicotinic acid administration by the same routes, 30% of the radioactivity added to the blood during passage through the intestine was in the form of nicotinamide. Subsequent passage through the liver resulted in the removal of nicotinic acid from the blood and its replacement by nicotinamide.

These findings suggest that metabolism in mice is adapted to the utilization of nicotinamide and that nicotinic acid is converted into nicotinamide for this purpose.

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Chaykin, S., Dagani, M., Johnson, L. & Samli, M. (1965). *J. biol. Chem.* **240**, 932.

Chaykin, S., Dagani, M., Johnson, L., Samli, M. & Battaile, J. (1965). *Biochim. biophys. Acta*, **100**, 351.

Preiss, J. & Handler, P. (1958). *J. biol. Chem.* **233**, 488.

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The Management of Nicotinamide and Nicotinic Acid in the Mouse*

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SUMMARY

The metabolism of nicotinic acid and nicotinamide has been examined in a number of mouse tissues following intraperitoneal injection of 0.9 μmole of ^{14}C-labeled nicotinic acid and nicotinamide. In all the tissues except liver, and to some extent intestine, nicotinamide was clearly a better precursor of DPN than was nicotinic acid. In the case of liver and intestine [^{14}C]nicotinic acid produced a transient and considerable labeling of DPN. By 30 min after injection of nicotinic acid, label in the DPN pools of these two tissues had fallen to levels below that found after the administration of [^{14}C]nicotinamide. The amounts of [^{14}C]nicotinamide in the liver following [^{14}C]nicotinic acid injection were far higher than the amounts found after injection of [^{14}C] nicotinamide. Following the oral administration of nicotinic acid to mice, levels of nicotinic acid and nicotinamide in the blood changed in a fashion compatible with the liver and intestine serving as centers for the conversion of nicotinic acid to nicotinamide. Furthermore, it was shown that deamidation of nicotinamide to nicotinic acid was not a prerequisite for absorption of nicotinamide from the digestive tract. These observations are compatible with the hypothesis that metabolism in the mouse is designed for the utilization of nicotinamide as a precursor of DPN and that nicotinic acid is converted to nicotinamide for that purpose.

Two pathways for the biosynthesis of the pyridine coenzymes are currently believed to be predominant in mammals. Preiss and Handler (1) have described a pathway by which nicotinic acid is converted to DPN via desNMN[1] and desDPN. More recently, Dietrich *et. al* (2) have shown that mammalian tissues can convert convert nicotinamide to DPN via NMN. At the present time the physiological roles of these two pathways relative to DPN synthesis are uncertain. The fact that the amide appears to be both the primary dietary form and the primary circulating form of the vitamin in animals (3, 4) lends support to the idea that the Dietrich pathway operates *in vivo*. However recent studies (5, 6) have suggested that nicotinic acid is a better precursor of DPN in animals than is nicotinamide. Some reports have also suggested that in mice (5) and in rats (7) nicotinamide is deamidated to nicotinic acid, by microorganisms present in the digestive tract, prior to its utilization as a precursor of DPN.

In view of the fact that current knowledge of nicotinic acid and nicotinamide metabolism has been derived from studies which dealt with very few organs or utilized hyperphysiologic levels of the vitamin, it seemed worthwhile to undertake a study of the total management of nicotinamide and nicotinic acid by intact mice. This is a report of such an investigation. It focuses on questions of storage, excretion, the interconversion between forms of the vitamin, and the relative efficiency of both forms of the vitamin as precursors of DPN in a large number of mouse tissues.

EXPERIMENTAL PROCEDURE

The animals used throughout this work were female C3HeB/FeJ mice, 13 to 16 weeks old, purchased from the Jackson Laboratories, Bar Harbor, Me. The animals were maintained in our animal quarters 8 to 12 weeks before use. The principles of laboratory animal care as promulgated by the National Society for Medical Research were observed. [7-^{14}C]Nicotinamide (48 mCi per mmole) and [7-^{14}C]nicotinic acid (7.82 mCi per mmole) were purchased from New England Nuclear Corp. Crystalline rabbit muscle glyceraldehyde 3-phosphate dehydrogenase was obtained from Sigma Chemical Co. Prior to administration, the specific activity of the [7-^{14}C]nicotinamide was adjusted to approximately that of [7-^{14}C]nicotinic acid by addition of unlabeled nicotinamide. The radioactive compounds were, for the most part, administered by intraperitoneal injection. In some experiments, however, adminstration was via stomach tube or by direct injection into the stomach or intestine with the pyloris tied. In these experiments animals were anesthetized by injection of Avertin (Winthrop Laboratories, New York) in order to facilitate blood sampling. Unless otherwise indicated, the vitamin was administered at a level of 0.9 μmole per animal. Mice fed Purina chow *ad libitum* ingest approximately this same quantity of the vitamin per day. Urine samples were collected prior to killing. Animals were killed by decapitation at intervals from 5 to 90 min after administration of the vitamin. Tissues were rapidly removed, immediately frozen by immersion in liquid nitrogen, and

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[1] The abbreviations used are: desNMN, nicotinic acid mononucleotide; desDPN, nicotinic acid adenine dinucleotide; NA, nicotinic acid; NAm, nicotinamide.

lyophilized. The tissues were then ground to a powder, suspended in ethanol, and heated at 60–70° for 5 min to destroy enzyme activity. Ethanol was removed under a stream of dry nitrogen. The last traces of ethanol were removed under vacuum. Each tissue was then extracted with a small volume (0.5 to 2.0 ml) of water.

Chromatographic analyses of the tissue extracts and urine were carried out as follows. Strips of Whatman No. 1 filter paper, 1½ inches wide, were cut into 45-inch lengths. The tissue extract was applied to the middle of the strip and the strips were developed in 1-butanol saturated with water (8) in such a manner as to cause migration of the sample toward one end of the strip. This procedure brought about separation of most of the excretory forms of the vitamin (3). The nucleotides remained at the origin. Nicotinic acid and N^1-methylnicotinamide have identical R_F values in this solvent system. Their separation was effected, after elution, by rechromatography in a solvent prepared by adding 1 ml of glacial acetic acid to 60 ml of 1-butanol saturated with water (3). The separation of the pyridine nucleotides was accomplished by cutting the strips just past the origin on the side in which the first chromatography was carried out. A 2-inch length of chromatography paper was sewed to the portion of the strip containing the origin (to serve as a wick) and the strips were developed in ethanol-pH 5.0 ammonium acetate (1 M) (7:3) for 60 to 65 hours.

Radioactive materials were located with the Nuclear Chicago Actigraph II paper strip counter. Ultraviolet absorbing chromatographic standards were detected by means of an ultraviolet lamp. Portions of the strip containing radioactive substances were cut out and counted in a Packard Tri-Carb liquid scintillation spectrophotometer with toluene-BBOT (2,5-bis-[2-(5-*tert*-butylbenzoxazolyl)]-thiophene) as scintillation fluid. Metabolites were identified by comparison of their rates of migration with cochromatographed standards. DPN, TPN, and NMN were purchased from Sigma Chemical Co. desDPN was prepared according to the method of Hondo *et al.* (9) and desNMN by hydrolysis of desDPN was snake venom phosphodiesterase (Worthington). Nicotinamide was assayed by the cyanogen bromide method of Mueller and Fox (10).

RESULTS AND DISCUSSION

The pattern of labeled metabolites found in mouse liver following intraperitoneal injection of nicotinamide and nicotinic acid is shown in Fig. 1. A relatively simple situation was found following injection of [7-^{14}C]nicotinamide, namely, 90% or more of the label was found in just two compounds, nicotinamide and DPN. Radioactive nicotinamide increased rapidly and essentially levelled off at 10 min. DPN synthesis continued for 90 min. It would appear that this was indeed synthesis, rather than exchange, since trace amounts of NMN were detected. The appearance of NMN is indicative of the synthesis of DPN via the Dietrich pathway. The situation in liver following nicotinic acid injection was much more complex. Label appeared rapidly in desDPN and DPN, reached a maximun in both at 5 min, and then fell off rapidly. Nicotinic acid had only a transient existence and was gone at 10 to 15 min. The most dramatic aspect of these experiments was the rapid increase in nicotinamide and the extent to which it accumulated in liver following nicotinic acid injection. At 20 min the bulk of the radioactivity in liver was in the form of nicotinamide. Furthermore, this constituted 25% of the injected dose of nicotinic acid. The striking nature of this

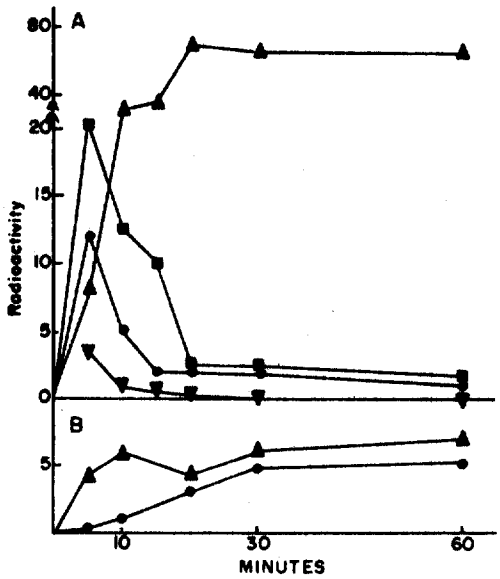

FIG. 1. Radioactive metabolites in mouse liver following the injection of 0.9 μmole of [7-^{14}C]nicotinic acid or [7-^{14}C]nicotinamide. *A*, [^{14}C]nicotinic acid injected; *B*, [^{14}C]nicotinamide injected. ▼——▼, nicotinic acid; ●——●, DPN; ■——■, desDPN; ▲——▲, nicotinamide. Each *point* represents the mean of data from two animals. Experimental procedures are described in the text. Radioactivity is expressed as (counts per min per 50 mg dry weight of tissue) × 10^{-4}.

observation is further emphasized by the fact that the levels of radioactivity in nicotinamide, following nicotinic acid injection, were only one-eighth as high. The nature and early course of the appearance of label in the liver metabolites is most compatible with either the operation of the Preiss-Handler pathway or a direct exchange between [^{14}C]nicotinic acid and DPN resulting in the formation of [^{14}C]desDPN. This is to be contrasted with the apparent utilization of the Dietrich pathway for the metabolism of injected nicotinamide. The time course of appearance of label in the metabolites which appeared after nicotinic acid injection is also in accord with the idea that, in the liver, the origins of nicotinamide lie in the conversion of nicotinic acid to DPN via desDPN followed by release of nicotinamide by DPN glycohydrolase. Although confounded by unanswered questions regarding compartmentalization and the relative specific activities of different pools, these data are suggestive of a special role of the liver in the metabolism of nicotinic acid, namely, the rapid conversion of nicotinic acid to nicotinamide. The intestine had some characteristics in common with the liver, namely, early appearance of DPN and nicotinamide after nicotinic acid injection (Fig. 2). There was, however, no accumulation of radioactivity in desDPN. Although, no specific data are available on the question of the differences in these patterns, they might be due to differing levels of the enzymes responsible for the metabolism of nicotinic acid in the two tissues.

The patterns of metabolites found in liver and the intestine were unique. This can be seen from a consideration of a pattern typical of the other tissues which were examined, such as that of the spleen (Fig. 3). The metabolites found in the spleen after nicotinamide and nicotinic acid injection were the same as those found in the liver, namely the amide, desDPN, and DPN, following nicotinic acid injection, and only the amide and DPN after the injection of nicotinamide. There were, however, some very

interesting quantitative differences. First, with respect to nicotinamide levels following injection of the acid and the amide, a reversal of the liver situation was found. Far more label was found in nicotinamide after injection of the amide than after injection of the acid. Second, following injection of nicotinic acid, high levels of desDPN persisted for 15 min longer in the spleen than in the liver. Third, the synthesis of DPN following nicotinic acid injection did not correlate well with the time course of desDPN synthesis as it did in liver. Unlike the liver situation in the spleen DPN synthesis seemed to correlate with nicotinamide availability. Thus, in the spleen, DPN does not appear to be the source of nicotinamide as it was in the liver. The reverse situation appears to obtain, DPN originated from nicotinamide. Thus, the Dietrich pathway may be the only functional route to DPN synthesis in the spleen. This line of reasoning leads to two questions: first, what is the significance of the appearance of desDPN, a characteristic intermediate of the Preiss-Handler pathway and, second, why does it have such a long lifetime. The results obtained from skeletal muscle (Fig. 4) hold a possible answer to both these questions. In general, the pattern of metabolites found in muscle was similar to that found in spleen but several features were exaggerated. For example, desDPN levels remained high for 60 min following nicotinic acid injection. Essentially no DPN was synthesized in the presence of these high levels of desDPN. It would seem, therefore, that no mechanism exists for converting desDPN to DPN in muscle. This might be an indication of the absence of DNP synthetase or a physical separation of this enzyme from its substrates. On the other hand, DPN synthesis from nicotinamide does seem possible in muscle, since after nicotinamide injection DPN was formed (Fig. 4*B*). Another interesting aspect of the data presented in Fig. 4*A* is the relatively large decrease in the level of desDPN which occurred during the period from 30 to 60 min and the absence of an increase in the other muscle metabolites. The total increase in label in nicotinamide and DPN was only 25% of the decrease in label in desDPN. Clearly, radioactivity left the muscle during the 30- to 60-min time period. The form in which it exited is not clear, but in view of the apparent lack of conversion of desDPN it seems reasonable to assume that it left as nicotinic acid, after cleavage from desDPN. This assumption could provide an explanation for the maintenance of high levels of nico-

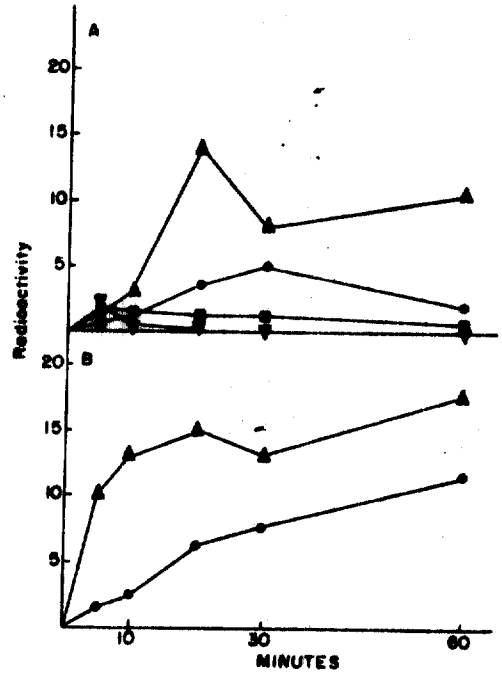

FIG. 2. Radioactive metabolites in mouse intestine following the injection of 0.9 μmole of [7-^{14}C]nicotinic acid or [7-^{14}C]nicotinamide. *A*, [^{14}C]nicotinic acid injected; *B*, [^{14}C]nicotinamide injected. ▼——▼, nicotinic acid; ●——●, DPN; ■——■, desDPN; ▲---▲, nicotinamide. Each *point* represents the mean of data from two animals. Experimental procedures are described in the text. Radioactivity is expressed as (counts per min per 50 mg dry weight of tissue) × 10^{-4}.

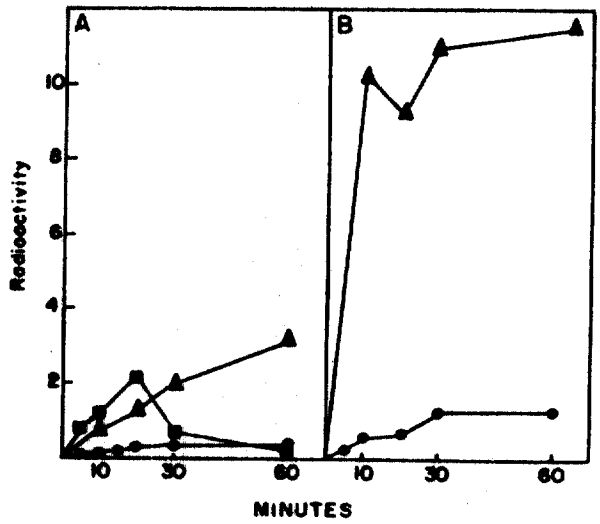

FIG. 3. Radioactive metabolites in mouse spleen following intraperitoneal injection of 0.9 μmole of [7-^{14}C]nicotinic acid or [7-^{14}C]nicotinamide. *A*, [^{14}C]nicotinic acid injected; *B*, [^{14}C]-nicotinamide injected. ●——●, DPN; ■——■, desDPN; ▲——▲, nicotinamide. Each *point* represents the mean of data from two animals. Experimental procedures are described in the text. Radioactivity is expressed as (counts per min per 50 mg dry weight of tissue) × 10^{-4}.

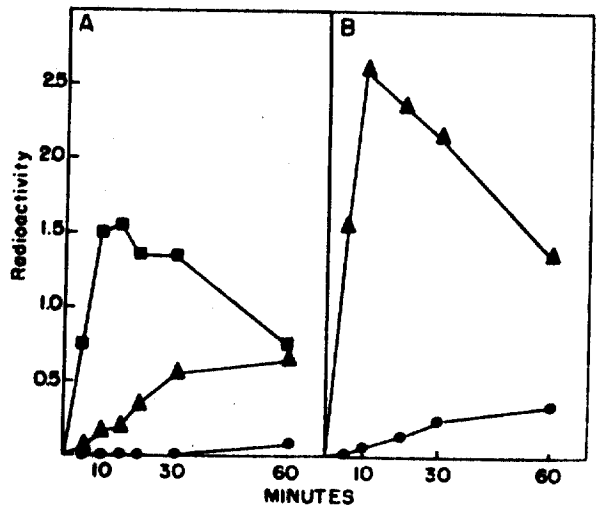

FIG. 4. Radioactive metabolites in mouse skeletal muscle following intraperitoneal injection of 0.9 μmole of [7-^{14}C]nicotinamide and [7-^{14}C]nicotinic acid. *A*, [^{14}C]nicotinic acid injected. *B*, [^{14}C]nicotinamide injected. ●——●, DPN; ■——■, desDPN; ▲---▲, nicotinamide. Each *point* represents the mean of data from two animals. Experimental procedures are described in the text. Radioactivity is expressed as (counts per min per 50 mg dry weight of tissue) × 10^{-4}.

namide in the liver for 60 min after the injection of nicotinic acid. Thus, it might be the continued infusion of nicotinic acid from the peripheral tissues which was responsible. The hypothesis that desDPN might be cleaved in the peripheral tissues is without precedent in the literature and is currently being tested in this laboratory.

The extent and time course of the labeling of metabolites in the other tissues examined are presented in Table I. In these tissues, at 1 hour, considerably more label was found in DPN after nicotinamide injection than after nicotinic acid injection. This might be interpreted as an indication that nicotinamide is a better precursor of DPN than is nicotinic acid. Since the question of multiple pools has not been resolved, a final conclusion on this matter will have to be reserved until a later time. Another interesting feature of the data in Table I is the apparent lag in the appearance of label in DPN following nicotinic acid injection. The appearance of label in DPN in these tissues was slow up to 10 min and then increased more rapidly. By contrast, when nicotinamide was injected, label appeared rapidly in DPN, and no lag was apparent. A lag in the appearance of label in DPN in these tissues, following nicotinic acid injection, but not after nicotinamide injection, might be indicative of the need for the conversion of nicotinic acid to nicotinamide by the liver before synthesis can occur. The duration of the lag and the rate of appearance of labeled nicotinamide in liver are such as to suggest that the two phenomena might be interrelated. No label was detected in nicotinic acid in any tissue 1 hour after administration of either form of the vitamin. This finding suggests that nicotinic acid is rapidly cleared in the mouse. The only tissue where the total radioactivity following nicotinic acid injection exceeded that following nicotinamide injection was the liver. This finding is compatible with the idea that the liver is the major site of nicotinic acid metabolism.

The pattern of metabolites which was found to exist in blood was unlike those of the other tissues. No label was detected in DPN in this tissue irrespective of the form of the vitamin which was administered. The only labeled nucleotides found were desNMN, after nicotinic acid injection, and NMN, after injection of nicotinamide.

Lest the reader assume the results of the above studies are unique to the females of the C3HeB/FeJ strain, it should be pointed out that in a comparable series of experiments [7-^{14}C]-nicotinic acid was administered to male mice of the DBA/2J strain with results essentially identical with those obtained with the C3HeB/FeJ strain.

The picture which seemed to be developing then was that, in the mouse at least, the total animal is geared to work with nicotinamide as the starting material for DPN synthesis and that the Preiss-Handler pathway functions primarily in the liver and then for the purpose of converting nicotinic acid to nicotinamide. No evidence was obtained in any of the foregoing experiments which was compatible with deamidation of nicotinamide to nicotinic acid. In view of the low levels of nicotinamide employed in this study and the high K_m value (4×10^{-2} to 2.5×10^{-1} M) of mammalian nicotinamide deamidase for nicotinamide (11, 12), such a finding was not unexpected. Since a previous report (5) of data indicative of nicotinamide deamidation *in vivo* was based on experiments in which high levels of nicotinamide were administered, a restudy was initiated. This was necessay in order to obtain data which could be directly compared with the data presented above. Administration of large doses of nicotinamide could provide evidence of the *in vivo* functioning of nicotinamide deamidase. Also, the suggested role (5, 7) of gastrointestinal microorganisms in nicotinamide deamidation, a role not evident when low levels of nicotinamide were employed, could perhaps become manifest on administration of larger doses of nicotinamide. Therefore, in order to test these possibilities, mice were injected intraperitoneally with 90 μmoles of [7-^{14}C]nicotinamide (0.078 mCi per mmole). The data derived from these experiments are presented in Table II. The total amount of radioactivity in the urine represented 1.5 and 3.9% of the injected dose at 30 and 90 min, respectively. At both these times label was found primarily in the form of unchanged nicotinamide (70%) with the remainder (30%) in the various excretory metabolites of nicotinamide. No label was found in nicotinic acid or nicotinuric acid. On the basis of the observations of Chaykin *et al.* (3), it was to be expected that had nicotinic acid arisen from nicotinamide and entered the bloodstream nicotinuric acid would have appeared in the urine. Over 80% of the label found in the intestinal contents at 90 min was nicotinamide. As in urine, considerable label

TABLE I

Major radioactive metabolites in variety of mouse tissues following intraperitoneal injection of [7-^{14}C]nicotinic acid and [7-^{14}C]-nicotinamide

Experimental procedures are described in the text.

Tissue	Time after injection	Radioactivity[a]							
		[^{14}C]Nicotinic acid injected					[^{14}C]Nicotinamide injected		
		Total[b]	DPN	desDPN	NA	NAm	Total	DPN	NAm
	min								
Kidney	5	205	5	26	86	15	75	8	60
	10	172	8	33	49	40	91	20	62
	30	150	25	13	2	90	128	65	46
	60	140	27	3		98	158	94	43
Ovaries	5	77		2	65	5	88	11	71
	10	51		5	30	6	96	13	68
	30	41	5	6	4	20	112	20	82
	60	36	5	5	1	20	74	20	45
Lung	5	39	1	7	24	1	60	5	46
	10	36	1	13	16	5	85	9	65
	30	33	3	10	2	18	84	20	52
	60	28	8	4		12	73	30	36
Heart	5	66		16	35	2	54	6	46
	10	71	1	30	23	9	93	12	67
	30	55	13	31		8	77	23	45
	60	47	22	20		12	96	42	38
Brain	5	5		1	2		23	2	16
	10	9	1	3	1	2	53	6	41
	30	18	3	2		8	61	15	39
	60	16	3	2		7	50	18	24

[a] (Counts per min per 50 mg of tissue, dry weight) $\times 10^{-2}$.

[b] Discrepancies between this value and the sum of the metabolites listed can be attributed to small amounts of label in other metabolites. An exception, however, was kidney where considerable amounts of label in nicotinuric acid were detected at 5 and 10 min after injection of nicotinic acid (6.3×10^4 and 2.3×10^4 cpm, respectively).

TABLE II

Radioactive metabolites present in mouse following intraperitoneal injection of large dose of nicotinamide

Animals were injected with 90 μmoles of [7-^{14}C]nicotinamide (0.078 mCi per mmole). Each value represents the mean of data derived from two animals. Experimental details are described in the text.

Tissue	Time after injection	Administered radioactivity	Total radioactivity in tissue in each component					
			Nicotinamide	Excretory products of nicotinamide[a]	Nicotinic acid	Nicotinuric acid	DPN	desDPN
	min	%	%	%	%	%	%	%
Liver	30	2.7	82.0	4.0	0	0	9.6	4.5
	90	2.8	60.0	2.8	0	0	22.5	12.3
Intestine	30	2.1	92.0	4.0	0.6	0	3.3	0
	90	1.5	88.0	5.1	0.8	0	6.1	0
Intestinal contents	30	1.1	88.0	6.9	2.6	0.3	1.6	0
	90	0.6	81.0	13.2	3.0	0.5	2.1	0
Urine	30	1.5	71.9	28.1	0	0	0	0
	90	3.9	69.4	30.6	0	0	0	0

[a] The excretory products of nicotinamide found were nicotinamide *N*-oxide, N^1-methylnicotinamide, and the 2- and 4-pyridone derivatives of N^1-methylnicotinamide.

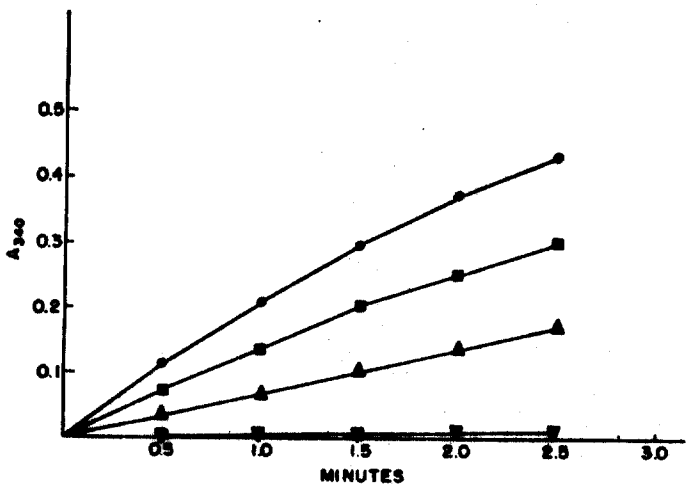

FIG. 5. Effect of desDPN on glyceraldehyde 3-phosphate dehydrogenase *in vitro*. Reaction mixtures constituents were at the following final concentrations: pyrophosphate buffer, 0.1 M, pH 8.5; sodium arsenate, 0.17%; glyceraldehyde 3-phosphate, 4.2×10^{-4} M; DPN, 2.5×10^{-4} M; and 100 μg of rabbit muscle glyceraldehyde 3-phosphate dehydrogenase; all in a final volume of 3 ml. Activity was measured spectrophotometrically at 340 nm (13). The effects of desDPN on enzyme activity were determined after prior incubation of the enzyme with desDPN for 5 min prior to assay at the same concentration of desDPN as that used in the preliminary incubation procedure. ●——●, 2.5×10^{-4} M DPN; ■——■, 2.5×10^{-4} M DPN + 2.28×10^{-4} M desDPN; ▲——▲, 2.5×10^{-4} M DPN + 4.56×10^{-4} M desDPN; ▼——▼, 4.56×10^{-4} M desDPN.

TABLE III

Changes in pattern of metabolites in blood as it crosses intestine and liver

Experimental procedures are described in the text.

Tissue	Radioactivity			
	Total	Nicotinic acid	Nicotinamide	Other
	(cpm/ml of blood) × 10^{-4}			
Arterial blood (reference)	151	125	6	20
Change across the intestine	+87	+57	+25	+5
Change across the liver	−70	−72	+12	−10

(13.2%) was found in the excretory metabolites of nicotinamide. Of particular note is the finding that label appeared in nicotinic acid (2.1%) and in nicotinuric acid (0.5%). A trace amount of label (0.8%), in the form of nicotinic acid, was also detected in the intestinal wall. It appears, therefore, that very small amounts of label do appear in nicotinic acid following administration of large doses of [7-^{14}C]nicotinamide, due possibly to the action of an intestinal or bacterial deamidase. The striking aspect of this experiment is the gradual, but extensive, appearance of label in desDPN in liver. No label was detected in nicotinic acid in this organ. The gradual appearance of label in desDPN in liver is to be contrasted with the rapid appearance and disappearance of label in desDPN in liver following injection of a small dose of nicotinic acid (Fig. 1A). Since the most obvious source of the label is desDPN was labeled nicotinic acid, the origins of that nicotinic acid came into question. Two possibilities exist: slow absorption from the gut, where low levels of labeled nicotinic acid were detected or deamidation of nicotinamide in the liver by the liver nicotinamide deamidase. The experimental data favor the latter alternative for two reasons. First, as has already been mentioned, no nicotinuric acid was found in the urine. This finding suggests that the nicotinic acid found in the intestinal contents did not enter the bloodstream to any appreciable extent. Second, following administration of a large dose of nicotinamide, the nicotinamide concentration in liver was determined to be of the order of 3×10^{-3} to 5×10^{-3} M, a value approaching the K_m value of the liver deamidase for nicotinamide. Therefore, it is possible that the labeled nicotinic acid arose within the liver through the action of this enzyme on nicotinamide. Thus, it appears that, in mice, deamidation of nicotinamide occurs only after administration of a large dose of nicotinamide, and even then, only to a limited extent.

The pattern of metabolites found in the urine is also compatible with the conclusion that nicotinamide is the form of the vitamin physiologically most important in the mouse. When nicotinamide (0.9 μmole per animal) was injected intraperitoneally into mice, less than 3% of the dose was excreted in the urine in 1 hour. Under the same conditions, 36% of an injected dose of nicotinic acid was excreted, entirely as nicotinuric acid. This rapid excretion of nicotinic acid may be a physiological response to the pharmacological potency of this compound and hence its undesirability as a vitamin form. In this connection, the most notable observation following injection of nicotinic acid was the accumulation and persistence of desDPN in most tissues, and particularly muscle (Fig. 4A). It is possible that the different pharmacological potentials of nicotinamide and nicotinic acid

may well reside in the ability of the latter compound to give rise to desDPN. This compound, being an analogue of DPN, could compete with DPN in DPN-dependent dehydrogenase systems. In order to test this possibility, the effect of desDPN on rabbit muscle glyceraldehyde 3-phosphate dehydrogenase *in vitro* was determined. The results of such determinations are presented in Fig. 5. It can be seen that desDPN at a concentration of 4.56×10^{-4} M did not function as a coenzyme with glyceraldehyde 3-phosphate dehydrogenase. Following preincubation with desDPN, at a concentration of 2.28×10^{-4} M, the ability of the enzyme to reduce exogenous DPN (2.5×10^{-4} M) in the presence of substrate was only 70% of the control value. On preliminary incubation with 4.56×10^{-4} M desDPN, the enzyme was only 40% as active as the control. Thus, it appears that, *in vitro* at least, desDPN is not only ineffective as a coenzyme for glyceraldehyde 3-phosphate dehydrogenase, but it also competes with the normal functioning of DPN in this dehydrogenase system. It was also determined that the inhibition of DPN reduction by desDPN was reversible on dilution. Since nicotinic acid has reversible pharmacological effects, this finding is a prerequisite of desDPN being the pharmacologically active form of nicotinic acid. Whether desDPN has similar effects on glyceraldehyde 3-phosphate dehydrogenase and other DPN-dependent dehydrogenases *in vivo* has yet to be determined.

From the point of view of the total physiological management of the vitamin a final question remained; namely, what is the form in which the vitamin passes the gut? Following administration of nicotinamide, either by stomach tube or by direct injection into the intestine, the only form of the vitamin detectable in portal blood was nicotinamide. Thus, it appears that nicotinamide enters the bloodstream from the gastrointestinal tract solely as nicotinamide. Administration of nicotinic acid by the same routes produced an entirely different picture. The data presented in Table III were obtained by simultaneous collection of blood from the portal vein, the inferior vena cava, and the heart following the administration of [^{14}C]nicotinic acid by stomach tube. Similar results (not shown) were obtained when the radioactivity was injected directly into the intestine with the pyloris tied. In Line 1, the prevailing levels of radioactivity in circulating blood are presented as a point of reference. From the data in Line 2, it is evident that both nicotinic acid and nicotinamide were added to the blood as it crossed the intestine, approximately 66% being in the form of acid and 33% the amide. Then on passage through the liver a considerable portion of nicotinic acid was removed and additional nicotinamide put back in its place. Presumably the lack of balance between counts taken up and put back out is due to the fact that pools in the liver were still building (Fig. 1*A*). In any event the trend is clear, namely that both the liver and the intestine engaged in the removal of nicotinic acid from possible circulation to the peripheral tissues by converting it to nicotinamide. These data are, therefore, in agreement with those obtained following administration of nicotinic acid by intraperitoneal injection.

It appears, therefore, that metabolism in the mouse is designed for the utilisation of nicotinamide as a precursor of DPN and when nicotinic acid is provided it is rapidly cleared by conversion to nicotinamide and excretion as nicotinuric acid.

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REFERENCES

1. Preiss, J., and Handler, P. (1958) *J. Biol. Chem.*, **233**, 488.
2. Dietrich, L. S., Fuller, L., Yero, I. L., and Martinez, L. (1966) *J. Biol. Chem.*, **241**, 188.
3. Chaykin, S., Dagani, M., Johnson, L., and Samli, M. (1965) *J. Biol. Chem.*, **240**, 932.
4. Chaykin, S., Dagani, M., Johnson, L., Samli, M., and Battaile, J. (1965) *Biochim. Biophys. Acta*, **100**, 351.
5. Ijichi, H., Ichiyama, A., and Hayaishi, O. (1966) *J. Biol. Chem.*, **241**, 3701.
6. Hagino, Y., Lan, S. J., Ng, C. Y., and Henderson, L. M. (1968) *J. Biol. Chem.*, **243**, 4980.
7. Tanigawa, Y., Shimoyama, M., Murashima, R., Ito, T., Yamaguchi, K., and Ueda, I. (1970) *Biochim. Biophys. Acta*, **201**, 394.
8. Bonavida, V., Narrod, S. A., and Kaplan, N. O. (1961) *J. Biol. Chem.*, **236**, 936.
9. Hondo, T., Ikeda, M., Andreoli, A., Nishizuka, Y., and Hayaishi, O. (1964) *Biochim. Biophys. Acta*, **89**, 549.
10. Mueller, A., and Fox, S. H. (1951) *J. Amer. Pharm. Ass.*, **40**, 513.
11. Kirchner, J., Watson, J. G., and Chaykin, S. (1966) *J. Biol. Chem.*, **241**, 953.
12. Petrack, B., Greengard, P., Cratson, A., and Kalinsky, H. J. (1963) *Biochem. Biophys. Res. Commun.*, **13**, 478.
13. Kaplan, N. O., Ciotti, M. M., and Stotzenbach, F. E. (1956) *J. Biol. Chem.*, **221**, 833.

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Nicotinamide in the Treatment of Schizophrenia

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Introduction

The use of nicotinic acid and nicotinamide in the treatment of schizophrenia has been recommended by Hoffer and coworkers[1] on the basis of a review of the literature and their own favorable results in a large number of cases. At present, the field of somatic therapy is dominated by the phenothiazine derivatives, and the possible applications of Hoffer's work remain largely unexplored.

During the course of his clinical duties in a mental hospital, the writer treated a small number of schizophrenic patients with nicotinic acid in the recommended dosage of one gram three times a day. Because the results were equivocal he decided to seek objective evidence of the action, or lack of action, which this vitamin might have in schizophrenia.

A blind trial of nicotinic acid is difficult or impossible, since even small doses produce a characteristic cutaneous vasodilatation, with pruritus and headache in some cases. For this reason, nicotinamide, which is free from immediate sensible effects, was chosen for the experiment.

Method

Schizophrenics selected from those entering the hospital were allocated in alternation to an experimental group and a control group.[2] All the patients received standard treatment prescribed by the admitting physicians according to individual needs. In addition, members of the experimental group took nicotinamide for five weeks shortly after entering the hospital, and the controls took placebo during the corresponding period. Duration of stay in hospital, which provided a ready, objective standard, was the criterion for comparison of therapeutic effects.

Selection of Patients

The subjects of this trial were male schizophrenics entering the Saskatchewan Hospital, North Battleford as new admissions or readmissions. A few of them were certified patients returning from trial leave. Because of the relative certainty of the diagnosis in more severe cases of schizophrenic illness, only those patients who required electroconvulsive therapy were chosen. Voluntary and committed patients were included in the cohort, but cases complicated by mental defect, alcoholism, personality disorder, physical illness, or special legal considerations were rejected. By selecting our patients in this manner we hoped to eliminate borderline cases and to reduce the number of patients in our sample whose stay in the hospital might be determined by factors other than the response to treatment.

Selection of patients continued for one year, and 41 cases were chosen for the study. Five of these patients were removed from the cohort before they had completed the course of therapy with nicotinamide or placebo; two of them had refused treatment, and in the other three cases the diagnosis of schizophrenia was not confirmed in conference. The remaining 36 patients (17 patients in Group A and 19 patients in Group B) completed the course and form the material of this study. They represent approximately one third of the total number of male schizophrenic patients who entered the hospital during the period of selection.

Drugs and Therapy

Two lots of large white tablets, identical in appearance and flavor, were sup-

From MacNeill Clinic, Saskatoon, Sask., and Department of Psychiatry, University Hospital, Saskatoon, Sask.

plied from the pharmacy of the University Hospital, Saskatoon, under the ciphers HA 05 and HB 70. It was understood that one lot of tablets would consist of nicotinamide (U.S.P.) in the half gram size, and that the other substance would be a placebo; the identities of the tablets remained unknown to all the patients and staff of the mental hospital during the entire period of the trial.

Electroconvulsive therapy began within two weeks of admission, and administration of the tablets was started at approximately the same time. Group A received HA 05 and Group B, HB 70. Both groups took three tablets twice a day, for a period of five weeks. Any patient who left the hospital before the completion of this period was given an appropriate quantity of tablets to take at home. Each member of the cohort received one course of medication with one type of tablet, plus the therapy prescribed by his physician. On all subsequent admissions, only standard treatment was administered.

No side effects which could be attributed to these tablets alone, or to their combination with other forms of treatment, were observed, and there was no means of determining which patients had received the active substance. The admitting physicians were asked to ignore the trial, as far as possible, and to apply accepted techniques of therapy in accordance with the symptoms of the individual case. Most of the patients received ataractic drugs before, during, and after the five week period, and in neither group was any modification of dosage necessary.

No attempt was made to observe or measure possible differences in behavior between the two groups, and all assessments of performance were made from the dates of entry and separation in the hospital files.

A preliminary assessment twelve months after the beginning of the trial did not show any significant difference in the performances of the two groups. A second assessment, carried out some eight months later, indicated that Group A had done markedly better than Group B. At this juncture, the writer, who had left the staff of the institution some six months previously, learned from the pharmacy that HA 05 was indeed nicotinamide. This information was not given to members of the hospital staff until after the completion of the project, which started May 1959 and terminated April 1961.

Results

The principal characteristics of the patients in the sample are shown in Table I. Subdivisions of schizophrenia correspond to the categorical definitions of the Dominion Bureau of Statistics.[1] By inspection, the two groups are seen to be homogeneous for all the items listed.

With reference to the race of the patients, each group contains one North American Indian, and one member of Group A is a half-breed of Scottish-Indian extraction. The remaining 33 patients are of European origin, with a predominance of English, Scottish, Irish, Ukrainian and German strains.

The treatment received by each patient during the first few weeks of his stay in the hospital has been symbolized in Table II. The daily doses of ataractic drugs are representative estimates based upon the figures in the clinical records, but not precisely calculated. Benztropine methanesulfonate and procyclidine were administered in order to suppress the neuromuscular side effects of trifluoperazine. Again the two groups display only minor differences for all the variables which have been tabulated.

Table III shows for each patient whether or not he was in hospital at the end of each of the 52 weeks following admission to the institution. The columns of figures to the right of the tables give the exact number of days which the patients spent in the hospital during the 364 day period. In computing these tables recreation leaves, which are granted for not more than 30 days, were ignored; but

TABLE I—GROUP A

Characteristics of Patients

Pt	Age	Admission Type	Admission No.	Subdivision of Schizophrenia	ECT's	Chemotherapy* Drug	Chemotherapy* Mg.	Other Treatment	
A 1	39	C	3	Paranoid	9	Chlor	300	GP	OT
A 2	28	C	2	Unspecified	10	Per	36	GP	
A 3	30	V	2	Simple	9	Tri	15	GP	
A 4	37	C	1	Paranoid	11	Per	24		
A 5	26	R	2	Unspecified	12	Chlor	150		
A 6	30	V	2	Acute	6	Chlor	200	GP	
A 7	40	C	3	Unspecified	16	Per	16		
A 8	21	R	1	Hebephrenic	14	Prom	150	GP	
A 9	31	R	1	Unspecified	10	Tri	30	GP	OT
A10	37	C	1	Unspecified	12	Chlor	150	GP	
A11	29	V	1	Paranoid	5	Tri	20	GP	W
A12	30	V	1	Hebephrenic	5	Tri	20	GP	
						Meth	4		
A13	44	V	1	Acute	3	Tri	20	GP	
A14	39	C	1	Paranoid	5	Chlor	300	GP	
A15	33	C	1	Catatonic	5	Tri	15		
A16	37	C	C	Paranoid	6	Tri	40	—	W
						Meth	2		
A17	45	V	2	Schizo-Affective	4	Tri	15	—	
						Imip	75		

Mean Age—34.3 years. Mean Number of ECT—8.35.

C–Certified; V–Voluntary; R–Returning from trial leave. (These certified patients are given the number of the previous admission.)

All patients in this group received three grams of nicotinamide daily for five weeks in addition to the treatment shown in the table.

*Show principal drugs used and representative daily doses in milligrams.

Chlor – Chlorpromazine; Imip – Imipramine; Meth – Benztropine Methanesulfonate; Per – Perphenazine; Procyc – Procyclidine; Prom – Promazine; Thio – Thioridazine; Tri – Trifluoperazine. GP – Group Psychotherapy; OT – Occupational Therapy; W – Industrial Therapy.

patients in the community on trial leave were considered to be out of hospital.

For group A (17 patients), a total of 1810 days were spent in the hospital during this period, giving an arithmetical mean of 106.4 days per patient. For Group B (19 patients), the corresponding figures are 3373 days and 177.5 days per patient. The difference between the two means is 71.1 days, or just over ten weeks per patient.

Expressing these results in round figures, we can say that the patient who received a placebo spent, on the average, 25 weeks in the hospital during the year following entry; whereas the patient who took nicotinamide stayed only 15 weeks.

Statistical Significance of Results

The comparison of lengths of stay in hospital within a limited period of time precludes a normal distribution of the variate, so that the Standard Error Test cannot be used. A suitable non-parametric test of significance[2] is Van der Waerden's X-test, the use of which permits us to decide whether the durations of stay for Group B are really longer than those for Group A. Calculation of Van der Waerden's X for the figures in Table III gives a value of 5.67. The confidence limits for X with thirty-six degrees of freedom are 5.41 and 6.39 at the 5% and 1% levels, respectively.[3] Thus for our results $0.05 > p > 0.01$.

Another approach to the problem of significance is to consider the numbers of patients in and out of the hospital at various points along the time ordinate. Because schizophrenia is usually a chronic disease whose duration is measured in years, and our therapy with nicotinamide was applied for only five weeks, we might expect that the difference in performance between the two groups would reach a maximum and then diminish. This is in

fact what seems to happen, and the maximum difference is found during the eighth and ninth weeks of the second quarter, where we have:

	In Hospital	Out of Hospital	Total
Group A	1	16	17
Group B	8	11	19
Totals	9	27	36

With Yates' correction for continuity this gives a value of Chi-square equal to 4.51. The confidence limits for Chi-square at the 5% and 1% levels, with one degree of freedom, are 3.84 and 6.63 respectively, so that again we have for our results $0.05 > p > 0.01$.

Discussion

The use of duration of stay in mental hospital as a criterion for the comparison of therapeutic effects would seem to offer an easy approach to the objective assessment of treatment methods; but the way is beset with pitfalls, which must be foreseen to be avoided successfully.

The inclusion in the sample of patients whose stay is influenced by factors other than the illness under study is likely to vitiate the results, especially when the numbers are small. On the other hand, if we permit ourselves to remove patients from the cohort we introduce an undesirable subjectivity which may produce even greater fallacies. The position is most difficult when the factors in question arise late in the course of the experiment and no decision has been taken as to the appropriate means of allowing for their effects. We have in mind such developments as a serious physical illness, the death of a patient, or his unauthorized departure from the institution.

TABLE II—GROUP B
Characteristics of Patients

Pt.	Age	Admission Type	Admission No.	Subdivision of Schizophrenia	ECT's	Chemotherapy* Drug	Chemotherapy* Mg.	Other Treatment	
B 1	35	C	3	Unspecified	12	—		—	—
B 2	28	V	1	Acute	7	Prom	300	GP	—
B 3	35	C	4	Unspecified	12	—		—	W
B 4	52	C	1	Hebephrenic	8	Tri	15	G	—
B 5	38	V	1	Paranoid	6	Per	16	GP	OT
B 6	17	C	1	Acute	9	Prom	300	—	—
B 7	25	C	1	Hebephrenic	8	Tri	45	GP	
						Procyc	5		
B 8	23	C	1	Catatonic	12	—		—	—
B 9	23	C	1	Unspecified	12	Tri	30	GP	—
						Procyc	5		
B10	26	C	5	Catatonic	6	Thio	450	—	—
B11	24	C	3	Catatonic	12	Tri	15	GP	—
B12	41	C	3	Unspecified	3	Chlor	300	—	—
B13	41	C	5	Catatonic	8	Tri	20	—	—
						Procyc	10		
B14	18	C	1	Simple	5	Tri	50	GP	W
						Meth	4		
B15	17	C	1	Paranoid	12	Tri	30	—	—
B16	27	C	1	Simple	5	Tri	40	GP	W
B17	21	C	2	Unspecified	8	Tri	20	—	OT
B18	23	R	3	Unspecified	6	Chlor	450	—	—
B19	28	V	2	Unspecified	4	Tri	30	—	OT

Mean Age 30.2 years.

Mean number of ECT—8.15.

C—Certified; V—Voluntary; R—Returning from trial leave. (These certified patients are given the number of the previous admission.)

*Shows principal drugs used and representative daily doses in milligrams.

Chlor—Chlorpromazine; Imip—Imipramine; Meth—Benztropine Methanesulfonate; Per—Perphenazine; Procyc—Procyclidine; Prom—Promazine; Thio—Thioridazine; Tri—Trifluoperazine; GP—Group Psychotherapy; OT—Occupational Therapy; W—Industrial Therapy.

TABLE III

Duration of Stay in Hospital During First Year Following Entry

GROUP A PATIENTS

Pat.	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total Days
A 1	**13**	1—**12**	**13**	**13**	100
A 2	**13**	4—**9**	**13**	**13**	120
A 3	4—**1—8**	4—**9**	**13**	4—**9**	172
A 4	6—**7**	**13**	4—**9**	**13**	190
A 5	10—**3**	**13**	**13**	**13**	75
A 6	4—**9**	**13**	**13**	**13**	30
A 7	**13**	5—**8**	**13**	**13**	130
A 8	**13**	7—**6**	**13**	**13**	140
A 9	9—**4**	**13**	**13**	**13**	66
A 10	8—**5**	**13**	**13**	**13**	56
A 11	7—**6**	**13**	**13**	2—**11**	149
A 12	5—**8**	2—**11**	7—**6**	**13**	164
A 13	3—**10**	**13**	**13**	**13**	27
A 14	6—**7**	**13**	**13**	**13**	48
A 15	**13**	5—**8**	**13**	**13**	131
A 16	3—**10**	12—**1**	**13**	1—**12**	129
A 17	4—**3—6**	2—**11**	**13**	**13**	83
				Grand Total (Days)	1810

GROUP B PATIENTS

B 1	7—**6**	**13**	**13**	8—**5**	178
B 2	5—**8**	**13**	**13**	**13**	38
B 4	8—**5**	**13**	**13**	**13**	62
B 5	6—**7**	2—**11**	**13**	2—**3—8**	280
B 6	8—**5**	**13**	**13**	10—**3**	77
B 7	**13**	**13**	4—**9**	**13**	210
B 8	7—**6**	**13**	**13**	**13**	52
B 9	**13**	2—**11**	**13**	**13**	106
B 10	**13**	**13**	3—**9—1**	**13**	297
B 11	**13**	**13**	6—**7**	**13**	224
B 12	**13**	**13**	8—**5**	**13**	240
B 13	**13**	9—**4**	**13**	**13**	157
B 14	**13**	**13**	**13**	**13**	364
B 15	**13**	**13**	**13**	**13**	364
B 16	**13**	5—**8**	2—**11**	4—**9**	237
B 17	6—**7**	12—**1**	**13**	6—**7**	185
B 18	2—**11**	**13**	5—**8**	1-**5-5 7**	118
B 19	2—**11**	**13**	**13**	**13**	16
				Grand Total (Days)	3373

There are 13 weeks in each quarter.

Light face numerals show number of weeks in quarter patient was in hospital.

Bold face numerals show number of weeks in quarter patient was out of hospital.

In the experiment which has been described we did not remove a patient from the cohort if he had completed the course of therapy with nicotinamide or placebo, and in two cases the duration of hospitalization was influenced by chance events which are reflected in our results.

Patient A 4, whose mental illness responded promptly to treatment, returned to the hospital in the third quarter with a broken leg. He had suffered a severe relapse and had been injured in a car accident while wandering around the province in search of employment. A plaster cast was applied to the lower limb, but the fractured tibia failed to unite, and after some months of unsuccessful conservative treatment an orthopedic operation was performed to promote healing. A large proportion of the time which this patient spent in hospital during the third and fourth quarters of the year can be attributed to his surgical condition and not to his schizophrenic illness. Nevertheless, this time has been included in the figure of 190 days, his total stay in hospital.

Patient A 16 made an unauthorized departure from the institution during the third quarter, and with the assistance of his family he began to establish himself in the community. Fifty-nine days later, he was discharged by the superintendent, without having returned to the hospital. Our figure of 129 days for the duration of his stay takes into account only the time he spent in hospital, and does not include the 59 day period between his departure and his discharge. Any unauthorized separation which is successful implies some ability to live in the community and intimates that a therapeutic goal has been reached.

Because the separation of a patient from a mental hospital depends upon social circumstances, one can argue that duration of stay in hospital is a poor criterion for the comparison of therapeutic effects. We must remember in this connection that all the patients in our sample had just entered the hospital, and a further factor of homogeneity in the cohort is the existence throughout of a social environment which had permitted each patient to remain in the community up to the date of entry, i.e. the start of the experiment. Any important changes which modified the potential environments of individual patients while they were in the

institution are likely to have affected both groups at random.

A final criticism is the possibility that some of the patients who left the hospital entered other mental institutions, and did not remain in the community. Three members of Group A are in the hospital at the time of this writing and their records show that they have not taken treatment elsewhere. Questionnaires have been sent to the other fourteen members of the group, and ten patients have replied directly, stating that they have not received any other psychiatric care during the past two years. In three other cases, the same information has been obtained from relatives. In only one case have we found that a member of this group has taken other psychiatric treatment. Patient A 14 spent the entire fourth quarter of the year, 91 days, in the psychiatric wing of a general hospital. This period might be equated to a similar period spent in a mental institution, and our results could be recalculated on that basis. The total duration of this patient's stay in hospital would become 139 days, instead of 48 days, and the new value of Van der Waerden's X would be 5 25. This figure is close to the 5% confidence limit of 5.41.

Conclusions

The results of this experiment suggest that nicotinamide therapy can shorten the length of stay in hospital for schizophrenic patients, and support the hypothesis that nicotinamide is of value in the treatment of schizophrenia.

Summary

1. A blind study of the effect of nicotinamide on the duration of stay in a mental hospital is described.

2. Schizophrenic patients who received nicotinamide spent an average of ten weeks less in hospital during the year following entry, than did the control group.

3. These results are significant at the 5% level of probability.

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REFERENCES

1. Dominion Bureau of Statistics, Health and Welfare Division. "Mental Statistics Handbook." Ottawa, 1954.
2. Herdan, G.: *Personal Communication*, 1961.
3. Herdan, G.: "Statistics of Therapeutic Trials." *Elsevier Publishing Co.*, 1955.
4. Hoffer, A., Osmond, H., Callbeck, M. J., and Kahan, I.: *J. Clin. Exptl. Psychopath.*, 18, 131, 1957.
5. Van der Waerden, B. L., and Nievergelt, E.: "Tafeln zum Vergleich zweier Stichproben mittels X-Test und Zeichentest." *Springer-Verlag*, 1956.

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Regulation of nicotinamide metabolism[1]

L. S. Dietrich, Ph.D.

It has been many years since Warburg and co-workers (1, 2) and von Euler et al. (3) demonstrated that nicotinamide is a component of certain hydrogen transporting coenzymes. Since then an abundance of work has appeared regarding the fate of nicotinamide in the living cell, the complex organisms, and at all levels of evolutionary development. In the last few years, several reviews on pyridine nucleotide metabolism have appeared (4–8).

Nicotinamide is the end product of the catabolism of nicotinamide adenine dinucleotide (NAD). It can be converted into nicotinic acid, resynthesized directly to NAD, methylated to N^1-methylnicotinamide or excreted as free nicotinamide. The fate of nicotinamide in the different cell types and organisms varies markedly. However, they all appear to have one thing in common, namely, the regulation of the cellular levels of pyridine dinucleotide coenzymes. An abbreviated scheme of NAD synthesis and nicotinamide metabolism is presented in Fig. 1. The de novo synthesis of NAD proceeds through the key intermediate quinolinic acid. As can be seen in Fig. 1, quinolinic acid is formed from tryptophan (9) or synthesized de novo (10, 11) from amino acid and carbohydrate intermediates. The synthesis of quinolinate from compounds other than tryptophan (reaction 9) is apparently restricted to microorganisms and plants. The synthesis of quinolinic acid from tryptophan is of particular importance to higher animals and man. The enzyme quinolinate phosphoribosyltransferase (reaction 8) converts quinolinate into nicotinic acid mononucleotide (12, 13), which is also an intermediate in the synthesis of NAD from nicotinate (14, 15). This particular enzyme does not appear to be under regulatory control, in contrast to the nicotinamide mononucleotide phosphoribosyltransferase (reaction 1) and nicotinic acid mononucleotide phosphoribosyltransferase (reaction 2). Control of NAD metabolism from tryptophan appears to be asserted at an earlier step in tryptophan metabolism, probably at the tryptophan oxygenase step. Indeed, there is evidence that reduced and oxidized pyridine nucleotides do definitely affect the activity of tryptophan oxygenase (16, 17).

Formation of NAD from nicotinamide or nicotinate is via scavenger pathways, i.e., the reutilization of pyridine bases that had at one time been part of the NAD structure. In microorganisms, the nicotinic acid pathway (reactions 2 to 4) is predominant. The only exception to this pathway in microorganisms is found among certain of the lactobacilli. *Lactobacillus fructosus*, for example, cannot utilize nicotinic acid and has a very active nicotinamide mononucleotide phosphoribosyltransferase (18). The nicotinamide obtained as a result of the NAD glycohydrolase reaction (reaction 6) (19) is converted by microorganisms into nicotinic acid via nicotinamide deamidase (reaction 11) (20). In higher organisms, reaction 1, which permits the direct utilization of nicotinamide to NAD via nicotinamide mononucleotide (NMN) (21, 22), is also present along with reaction 2 in most cell types studied to date. Human tissues are an exception in that they contain a nicotinamide mononucleotide phosphoribosyltransferase, which is inactive at physiological levels of nicotinamide (23). The phenomena of recycling nicotinamide and nicotinate have been named by Gholson as the pyridine nucleotide cycle (24). Recently, evidence that this is a cycle of significance in both microorganisms (25) and higher organisms (26) has been forthcoming.

Nicotinamide deamidase activity observed in mammals is restricted to the liver. The kinetic parameters of this enzyme are such that unless this enzyme is under some sort of regulatory control one would predict that it would

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have little activity at physiological levels of nicotinamide. To date, attempts to find modifiers for nicotinamide deamidase and attempts to remove hypothetical inhibitors from the enzyme have failed (27, 28). Furthermore, all studies that have been done indicating that nicotinamide is converted into nicotinate in vivo have been carried out under test loads of nicotinamide (500 mg/kg by intraperitoneal injection) (29). Under these conditions, intermediate nicotinamide reaches a level that permits hepatic nicotinamide deamidase to function operative. When studies are carried out employing either whole animals (30) or liver perfusion techniques (31), and the administered nicotinamide is kept at a physiological level, the evidence indicates that NAD is formed directly from nicotinamide via nicotinamide mononucleotide. However, when higher levels of nicotinamide are given, one can demonstrate that nicotinamide deamidase is functioning and that NAD is synthesized via nicotinic acid. Thus, it would appear that the nicotinate available to the animal under normal conditions is either of dietary origin or represents nicotinamide that has been excreted into the gastrointestinal tract, deamidated by intestinal flora, and then reabsorbed into the general circulation, i.e., little or no conversion of nicotinamide into nicotinate occurs intracellularly.

Both nicotinamide mononucleotide phosphoribosyltransferase and nicotinate mononucleotide phosphoribosyltransferase are under regulatory control. Adenosine triphosphate (ATP) serves as a positive modifier in the case of the nicotinamide mononucleotide phosphoribosyltransferase (32). It is also essential for activity of some, but not all, nicotinate mononucleotide phosphoribosyltransferases (14, 33–37). Evidence has been presented that in the case of this enzyme, ATP is consumed in a stoichiometric manner (37–39). The pyridine nucleotides inhibit these reactions in a specific manner, e.g., NAD inhibits nicotinamide mononucleotide phosphoribosyltransferase (21), and nicotinic acid adenine dinucleotide inhibits nicotinate mononucleotide phosphoribosyltransferase (32). Specificity for these reactions is very striking. Nicotinic acid adenine dinucleotide has no effect on the formation of nicotinamide mononucleotide from nicotinamide (reaction 1) (Table 1) and, in contrast, NAD has no effect on the conversion of nicotinate into nicotinate mononucleotide (reaction 2) (Table 2). Substrate specificity for these two enzymes is extremely striking in spite of the similarity in structure of the substrates involved. Nicotinamide mononucleotide phosphoribosyltransferase appears to be under hormonal control (40). No such indication was obtained for nicotinate mononucleotide phosphoribosyltransferase or quinolinate phosphoribosyltransferase (40). Liver tissue also methylates nicotinamide, forming N^1-methylnicotinamide (41). Recent evidence by Gholson indicates that this enzyme may be important in regulating the systemic levels of nicotinamide (unpublished data). Recently, it has become apparent that NAD plays a

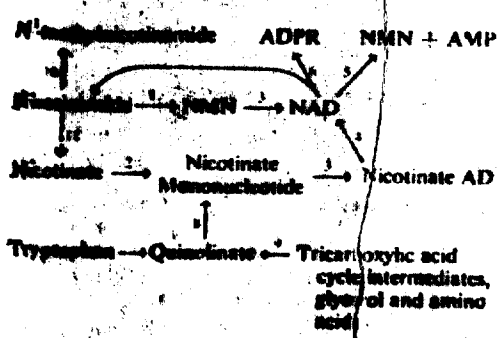

FIG. 1. Pathways of NAD metabolism. AMP = adenosine monophosphate.

TABLE 1

Effect of various pyridine nucleotides on the activity of nicotinamide mononucleotide phosphoribosyltransferase

Nicotinamide concentration	Addition	Enzymatic activity, cpm/0.1 ml reaction mixture/30 min
1×10^{-4} M	None	11,500
	NMN	5,200
	NAD	5,150
	Nicotinate AD	11,600
1×10^{-5} M	None	9,900
	NMN	1,300
	NAD	1,250
	Nicotinate AD	9,750

All pyridine nucleotides added to a final concentration of 5×10^{-4} M. Ammonium sulfate fraction of rat liver served as the enzyme source.

role in addition to that of oxidation-reduction in cells. Nicotinamide adenine dinucleotide has been shown to be a substrate for the polynucleotide ligase of *Escherichia coli* and *Bacillus subtilis* (42, 43). It is therefore required for DNA synthesis, repair, et cetera. A required cofactor for the toxic action of diphtheria toxin in mammalian cells (44–46), NAD is polymerized by an enzyme that has an as yet unknown function and is found only in the nuclei of certain cells (47–49). In all of these reactions NAD is consumed, yielding nicotinamide plus adenosine diphosphoribose (ADPR) or a polymer consisting of ADPR units. Thus, one could envision a rather high turnover of NAD in various cells and this emphasizes the importance of reutilizing nicotinamide in an efficient manner. Higher organisms have accomplished this by superimposing a systemic pyridine nucleotide cycle (50) on the cellular pyridine nucleotide cycle (24). The schematic outline of the systemic pyridine nucleotide cycle is shown in Fig. 2. Dietary proteins containing tryptophan and pyridine nucleotide derivatives are digested in the gastrointestinal tract, yielding free tryptophan and nicotinic acid. Both of these compounds are then absorbed into the general circulation and via portal circulation reach the liver. Tryptophan and nicotinate are then converted into NAD, which is then catabolized via the reactions mentioned above, releasing nicotinamide that is then excreted back into the general circulation. Nicotinamide synthesized in the liver, as well as nicotinate that had escaped hepatic metabolism, can then be transported to all the various cell types in the body via the general circulation and be utilized by them to carry out the synthesis of their intracellular pyridine nucleotides. Nicotinamide, on the other hand, might also be excreted back into the gastrointestinal tract, be converted there into nicotinate by the intestinal flora of the tract, and then be reassimilated into the general circulation. On the other hand, in the liver, nicotinamide is converted into N^1-methylnicotinamide, which is readily excreted. Thus, one sees a series of checks and balances at the cellular and the systemic levels, all combined to control the level of nicotinamide, and thus guarantee adequate concentrations of pyridine compounds for NAD synthesis for the cells of the organism.

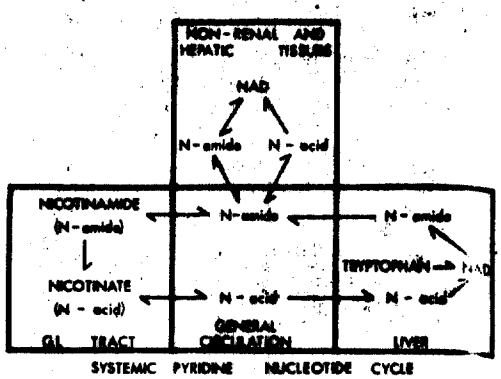

FIG. 2. Systemic pyridine nucleotide cycle.

TABLE 2

Effect of various pyridine nucleotides on nicotinate mononucleotide phosphoribosyltransferase

Nicotinate concentration	Addition	Enzymatic activity, cpm/0.1 ml reaction mixture/hr
1×10^{-4} M	None	17,590
	NMN	17,206
	NAD	18,855
	Nicotinate AD	8,200
1×10^{-5} M	None	15,613
	NMN	17,482
	NAD	17,492
	Nicotinate AD	2,153

All pyridine nucleotides added to a final concentration of 5×10^{-4} M. Ammonium sulfate fraction of rat liver served as the enzyme source.

References

1. WARBURG, O., AND W. CHRISTIAN. Co-Ferment-problem. *Biochem. Z.* 275: 464, 1935.
2. WARBURG, O., W. CHRISTIAN AND A. GRIESE. Die Wirkungsgruppe des Co-Ferments aus roten Blutzellen. *Biochem. Z.* 279: 143, 1935.
3. VON EULER, H. V., H. ALBERS AND F. SCHLENK. Highly purified cozymase. *Z. Physiol. Chem.* 234: 1, 1935.
4. MAHLER, H. R. Biological oxidations. *Ann. Rev. Biochem.* 26: 17, 1957.
5. KAPLAN, N. O. *The Pyridine Coenzymes.* New York: Academic, 1960, vol. 3, p. 105.
6. SUND, H., H. DIEKMANN AND K. WALLENFELS. *Die Wasserstoffübertragung mit Pyridinnucleotiden.* New York: Interscience, 1964, vol. 26, p. 115.
7. COLOWICK, S. P., J. VAN EYS AND J. H. PARE.

Dehydrogenation. Amsterdam: Elsevier, 1966, vol. 14, p. 1.

8. SUND, H. *The Pyridine Nucleotide Coenzymes*. New York: Interscience, 1968, p. 603.
9. HENDERSON, L. M., AND H. M. HIRSCH. Quinolinic acid metabolism. I. Urinary excretion by the rat following tryptophan and 3-hydroxyanthranilic acid administration. *J. Biol. Chem.* 181: 667, 1949.
10. ORTEGA, M. V., AND G. M. BROWN. Precursors of nicotinic acid in *Escherichia coli*. *J. Biol. Chem.* 235: 2939, 1960.
11. LEETE, E. Biosynthesis of alkaloids. *Science* 147: 1000, 1965.
12. NISHIZUKA, Y., AND O. HAYAISHI. Studies on the biosynthesis of nicotinamide adenine dinucleotide. I. Enzymic synthesis of niacin ribonucleotides from 3-hydroxyanthranilic acid in mammalian tissues. *J. Biol. Chem.* 238: 3369, 1963.
13. GHOLSON, R. K., I. UEDA, N. OGASAWARA AND L. M. HENDERSON. The enzymatic conversion of quinolinate to nicotinic acid mononucleotide in mammalian liver. *J. Biol. Chem.* 239: 1208, 1964.
14. PREISS, J., AND P. HANDLER. Biosynthesis of diphosphopyridine nucleotide. I. Identification of intermediates. *J. Biol. Chem.* 233: 488, 1958.
15. PREISS, J., AND P. HANDLER. Biosynthesis of diphosphopyridine nucleotide. II. Enzymatic aspects. *J. Biol. Chem.* 233: 493, 1958.
16. WAGNER, C. Regulation of the tryptophan–nicotinic acid–DPN pathway in the rat. *Biochem. Biophys. Res. Commun.* 17: 668, 1964.
17. CHO-CHUNG, Y. S., AND H. C. PITOT. Feedback control of rat liver tryptophan pyrrolase. I. End product inhibition of tryptophan pyrrolase activity. *J. Biol. Chem.* 242: 1192, 1967.
18. OHTSU, E., A. ICHIYAMA, Y. NISHIZUKA AND O. HAYAISHI. Pathways of nicotinamide adenine dinucleotide biosynthesis in nicotinic acid or nicotinamide requiring microorganisms. *Biochem. Biophys. Res. Commun.* 29: 635, 1967.
19. HANDLER, P., AND J. R. KLEIN. The inactivation of pyridine nucleotides by animal tissues *in vitro*. *J. Biol. Chem.* 143: 49, 1942.
20. HUGHES, D. E., AND D. H. WILLIAMSON. The deamidation of nicotinamide by bacteria. *Biochem. J.* 55: 851, 1953.
21. DIETRICH, L. S., L. FULLER, I. L. YERO AND L. MARTINEZ. Nicotinamide mononucleotide pyrophosphorylase activity in animal tissue. *J. Biol. Chem.* 241: 188, 1966.
22. DIETRICH, L. S., O. MUNIZ AND M. POWANDA. NAD synthesis in animal tissues. *J. Vitaminol. (Kyoto)* 14 (Suppl): 123, 1968.
23. DIETRICH, L. S., AND O. MUNIZ. Aberrant form of NMN pyrophosphorylase in human tissues. *Federation Proc.* 29: 344, 1970 (abstr.).
24. GHOLSON, R. K. The pyridine nucleotide cycle. *Nature* 212: 933, 1966.
25. GHOLSON, R. K., G. R. WALLER, J. SUIT, T. GROVER AND A. J. ANDREOLI. The pyridine nucleotide cycle in *E. coli* and its possible role in DNA synthesis. *Federation Proc.* 29: 881, 1970 (abstr.).
26. DIETRICH, L. S., L. FRANKLIN AND B. FARINAS. Effect of hyperphysiological levels of hexestrol on the hepatic metabolism of nicotinate in the mouse. *Proc. Soc. Exptl. Biol. Med.* 133: 160, 1970.
27. PETRACK, B., P. GRILLINGARD, A. CRASTON AND F. SHIPPEY. Nicotinamide deamidase from mammalian liver. *J. Biol. Chem.* 240: 1725, 1965.
28. SU, S., L. ALBIZATI AND S. CHAYKIN. Nicotinamide deamidase from rabbit liver. II. Purification and properties. *J. Biol. Chem.* 244: 2956, 1969.
29. NARROD, S. A., V. BONAVITA, E. R. EHRENFELD AND N. O. KAPLAN. Effect of azaserine on the biosynthesis of diphosphopyridine nucleotide in mouse. *J. Biol. Chem.* 236: 931, 1961.
30. IJICHI, H., A. ICHIYAMA AND O. HAYAISHI. Studies on the biosynthesis of nicotinamide adenine dinucleotide. III. Comparative *in vivo* studies on nicotinic acid, nicotinamide, and quinolinic acid as precursors of nicotinamide adenine dinucleotide. *J. Biol. Chem.* 241: 3701, 1966.
31. HAGINO, Y., S. J. LAN, C. Y. NG AND L. M. HENDERSON. Metabolism of pyridinium precursors of pyridine nucleotides in perfused rat liver. *J. Biol. Chem.* 243: 4980, 1968.
32. POWANDA, M. C., O MUNIZ AND L. S. DIETRICH. Studies on the mechanism of rat liver nicotinamide mononucleotide pyrophosphorylase. *Biochemistry* 8: 1869, 1969.
33. IMSANDE, J., AND P. HANDLER. Biosynthesis of diphosphopyridine nucleotide. III. Nicotinic acid mononucleotide pyrophosphorylase. *J. Biol. Chem.* 236: 525, 1961.
34. IMSANDE, J. Pathway of diphosphopyridine nucleotide biosynthesis in *Escherichia coli*. *J. Biol. Chem.* 236: 1494, 1961.
35. IMSANDE, J. A cross-linked control system. I. Properties of a triphosphate-dependent nicotinic acid mononucleotide pyrophosphorylase from *Bacillus subtilis*. *Biochim. Biophys. Acta* 85: 255, 1964.
36. KAHN, V., AND J. J. BLUM. ATP-independent nicotinic acid mononucleotide pyrophosphorylase of *Astasia longa*. *Biochim. Biophys. Acta* 146: 305, 1967.
37. SMITH, L. D., AND R. K. GHOLSON. Allosteric properties of bovine liver nicotinate phosphoribosyltransferase. *J. Biol. Chem.* 244: 68, 1969.
38. MUGHARBIL, U., AND C. WAGNER. Nicotinic acid phosphoribosyltransferase from *Xanthomonas pruni*. *Federation Proc.* 29: 909, 1970 (abstr.).
39. SPIVEY, H. O., A. KOSAKA AND R. K. GHOLSON. Reaction mechanism of yeast nicotinate phosphoribosyl transferase. *Federation Proc.* 29: 932, 1970 (abstr.).
40. DIETRICH, L. S., L. MARTINEZ, O. MUNIZ AND B. FARINAS. Effect of hypophysectomy and adrenalectomy on enzymes concerned with nicotinamide adenine dinucleotide synthesis. *Endocrinology* 81: 779, 1967.

41. CANTONI, G. L. Methylation of nicotinamide with a soluble enzyme system from rat liver. *J. Biol. Chem.* 189: 203, 1951.
42. OLIVERA, B. M., AND I. R. LEHMAN. Diphosphopyridine nucleotide: a cofactor for the polynucleotide-joining enzyme from *Escherichia coli*. *Proc. Natl. Acad. Sci.* 57: 1700, 1967.
43. OLIVERA, B. M., Z. W. HALL AND I. R. LEHMAN. Enzymatic joining of polynucleotides. V. A DNA-adenylate intermediate in the polynucleotide-joining reaction. *Proc. Natl. Acad. Sci.* 61: 237, 1968.
44. COLLIER, R. J. Effect of diphtheria toxin on protein synthesis: inactivation of one of the transfer factors. *J. Mol. Biol.* 25: 83, 1967.
45. JOHNSON, W., R. KUCHLER AND M. SOLOTOROVSKY. Site in cell-free protein synthesis sensitive to diphtheria toxin. *J. Bacteriol.* 96: 1089, 1968.
46. HONJO, T., Y. NISHIZUKA AND O. HAYAISHI. Diphtheria toxin-dependent adenosine diphosphate ribosylation of aminoacyl transferase II and inhibition of protein synthesis. *J. Biol. Chem.* 243: 3553, 1968.
47. CHAMBON, P., J. D. WEILL, J. DOLY, M. T. STROSSER AND P. MANDEL. On the formation of a novel adenylic compound by enzymatic ex tracts of liver nuclei. *Biochem. Biophys. Res Commun.* 25: 638, 1966.
48. FUJIMURA, S., S. HASEGAWA, Y. SHIMIZU AND T. SUGIMURA. Polymerization of the adenosine 5'-diphosphate-ribose moiety of nicotinamide adenine dinucleotide by nuclear enzyme. I. Enzymatic reactions. *Biochim. Biophys. Acta* 14 247, 1967.
49. HASEGAWA, S., S. FUJIMURA, Y. SHIMIZU AND T. SUGIMURA. The polymerization of adenosine 5' diphosphate-ribose moiety of NAD by nuclear enzyme. II. Properties of the reaction produc *Biochim. Biophys. Acta* 149: 369, 1967.
50. DIETRICH, L. S., L. MARTINEZ AND L. FRANKLIN. Role of the liver in systemic pyridine nucleotide metabolism. *Naturwissenschaften* 55: 231, 1968.

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The nicotinic acid content of saliva and dental caries activity*

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Clinical and laboratory studies reported from the Nutrition Clinic of the Hillman Hospital, Birmingham, Alabama, have shown that persons with chronic endemic pellagra have a low incidence of dental decay and little or no dental caries activity in their saliva (1, 2, 3). Similar clinical findings have been reported from other parts of the world in which pellagra is endemic (1.

* This study was supported by grants from the Clayton Foundation for Research.

5, 6). The discovery of the specificity of nicotinic acid for pellagra has reduced the prevalence of this disease in Alabama to the point where there has not been a single case seen at the Nutrition Clinic in the past three years (7). In contrast, the extremely great prevalence of dental caries has made this disease one of the major public health problems in the United States today.

That a relationship may exist between a low incidence of dental caries and a deficiency of nicotinic acid is suggested by the clinical observations referred to above, by the animal studies of Orland, Hemmens and Harrison (8), who found that the ommission of nicotinic acid from an otherwise adequate diet reduced the incidence of dental caries in Syrian hamsters by approximately fifty per cent, and by the metabolic functions of nicotinic acid. Nicotinic acid is a constituent of coenzymes I and II and an essential growth factor for many of the lactic acid producing oral bacteria. As such, it may play an important role in the degradation of carbohydrates by acidogenic bacteria (9, 10, 11). The breakdown of fermentable carbohydrates by oral bacteria to acids capable of dissolving tooth structure is the basis of the most widely accepted present day theory of the etiology of dental caries (12). Since nicotinic acid, or a substance which acts similarly, has been shown recently to be a normal constituent of human whole saliva (13), it was decided to test the hypothesis that the nicotinic acid content of human whole saliva may, at times, be a limiting factor in the fermentation of carbohydrates by oral acidogenic bacteria.

Materials and Methods: Ninety samples, each containing at least 40 cm^3 of paraffin stimulated whole saliva, were obtained from 43 subjects and analyzed for their nicotinic acid content and dental caries activity. The samples were collected in sterile flasks between 8:00 and 10:00 A. M. The nicotinic acid content of each sample was determined by the collaborative A. O. A. C.-U. S. P. bioassay method, a modification of the Snell and Wright method (14), in which the Lactobacillus arabinosus 17-5 (ATCC ***8014) serves as the test organism. The composition of the test medium is shown in Table I. Dental caries activity was determined by the method of Fosdick, Hansen and Epple (15). Seventeen cm^3 of saliva were used in the analysis for nicotinic acid and 20 cm^3 in the test for dental caries activity.

Observations: In Table II, the 90 samples of saliva have been grouped according to the Fosdick, Hansen and Epple (15) classification of dental caries activity. Twenty of the samples were classified as negative, 3 as one plus, 12 as two plus, 18 as

TABLE I

Composition of Test Medium*

Constituent	Amount per 100 cm³ of double strength Medium
Acid hydrolyzed casein	1.0 Gm.
Glucose	4.0 Gm.
Sodium acetate	2.0 Gm.
L-Cystine	0.04 Gm.
L-Tryptophane	0.01 Gm.
Adenine	2.0 mg
Guanine	2.0 mg
Uracil	2.0 mg
Riboflavin	40.0 μg
Thiamine	20.0 μg
Calcium pantothenate	20.0 μg
Pyridoxine	20.0 μg
Para-aminobenzoic acid	20.0 μg
Biotin	0.08 μg
Inorganic salts:	
Solution A**	1 cc
Solution B***	1 cc

* Collaborative A. O. A. C.-U. S. P. modification of Snell and Wright Medium.

** Salt Solution A:	Amount per cm³
K_2HPO_4	100 mg
KH_2PO_4	100 mg

*** Salt Solution B:	Amount per cm³
$MgSO_4 \cdot 7H_2O$	40 mg
NaCl	2 mg
$FeSO_4 \cdot 7H_2O$	2 mg
$MnSO_4 \cdot 4H_2O$	2 mg

three plus, and 37 as four plus. The mean nicotinic acid content of the samples with no demonstrable caries activity was 0.053 micrograms per cm³ of whole saliva. The mean nicotinic acid level of the samples with very slight caries activity (one plus), moderate caries activity (two plus), high caries activity (three plus), and pronounced caries activity (four plus) were 0.051, 0.082, 0.126 and 0.158 micrograms per cm³ of whole saliva respectively.

The nicotinic acid values of the 90 samples ranged from 0.0234 to 0.4090 micrograms per cm³ of saliva. The range for each group is shown in Table II. They extend from 0.0234 to 0.1011 micrograms per cm³ of saliva for the negative samples to 0.0478 to 0.4090 micrograms per cm³ of saliva for the samples with four plus activity. With the exception of the upper value in the range for the samples with one plus caries activity, the upper and lower limits of the ranges of the groups with positive caries activity greatly exceeded those of the group with no dental caries activity.

TABLE II

The relationship between the Nicotinic Acid Content of whole Saliva and Dental Caries Activity

Dental Caries Activity*	Number of samples	Range Nicotinic Acid Content $\mu g/cm^3$	Mean Nicotinic Acid Content $\mu g/cm^3$
—	20	0.0234—0.1011	0.052875
+	3	0.0470—0.0596	0.05436
+ +	12	0.0306—0.1530	0.032408
+ + +	18	0.0521—0.2880	0.12565
+ + + +	37	0.0478—0.4090	0.158037

* Fosdick, Hansen and Epple Classification.

The distribution of the nicotinic acid values of the component samples in each group is shown in Figure I. The nicotinic acid content of 65 per cent of the negative samples was below the mean for this group. A similar finding was observed for 33 per cent of the one plus samples, 58 per cent of the two plus samples, 56 per cent of the three plus samples, and 48 per cent of

THE DISTRIBUTION OF DENTAL CARIES ACTIVITY
AND NICOTINIC ACID CONTENT
OF NINETY SAMPLES OF HUMAN WHOLE SALIVA

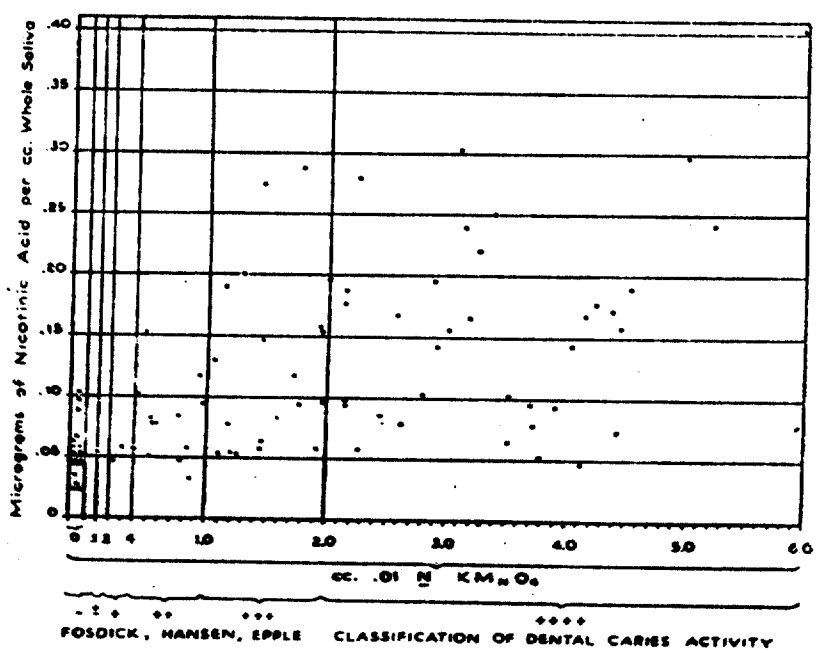

Figure 1

the four plus samples. The extreme deviates in the series of 90 samples consisted of three (15 per cent) of the 20 samples devoid of caries activity in which the nicotinic acid levels exceded the mean value for the group by more than 25 per cent and seven (10 per cent) of the 70 samples with demonstrable caries activity in which the nicotinic acid levels fell below the mean value of the group with no caries activity.

Discussion: The findings indicate that the nicotinic acid content of saliva may be a determining factor in dental caries activity. A close relationship between the nicotinic acid content and the dental caries activity has been demonstrated in 80 (89 per cent) of the series of 90 samples of saliva analyzed in this study. The 10 exceptions to the general trend may be explained on the basis of a number of factors contained in saliva which are capable of affecting this relationship adversely. Included among this group are either a high or low buffer capacity, the presence or absence of enzyme activators or inhibitors, the presence or absence of growth factors other than nicotinic acid, the presence or absence of acidogenic microorganisms which can either synthesize or which do not require nicotinic acid as a growth factor, and the presence or absence of specific immunologic principles.

Summary and Conclusions

As seen in Figure I, eighty-nine per cent of a series of ninety samples of saliva showed a close relationship between their nicotinic acid content and dental caries activity. These laboratory findings are of aid in interpreting the clinical observations that endemic pellagrins have a low incidence of dental caries.

ZUSAMMENFASSUNG

Der Nikotinsäuregehalt des Speichels und Zahnkaries. Von S. Dreizen. A. I. Reed und Tom D. Spies.

In 89% von 90 Speichelproben wurde eine Beziehung zwischen dem Nikotinsäuregehalt des Speichels und der Zahnkaries festgestellt. Diese Laboratoriumsversuche bestätigen die klinischen Beobachtungen, wonach bei der endemischen Pellagra ein geringeres Auftreten von Zahnkaries beobachtet wird.

CONCLUSION

Le taux de l'acide nicotinique dans la salive et la carie dentaire. Par S. Dreizen, A. I. Reed et Tom D. Spies.

Dans 89% de 90 salives on a pu démontrer une correlation entre le taux de l'acide nicotinique et la carie dentaire. Ces essais expliquent le fait que les pellagreux ont rarement une carie dentaire.

BIBLIOGRAPHY

1. *Kniesner A. H., Mann A. W. and Spies T. D.*, The relationship of Dental Caries to Deficiencies of the Vitamin B Group, J. D. Res. 1942, *21*, 259.

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Nicotinamide Metabolism in Mammals

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A number of compounds have been described as metabolites of nicotinic acid or nicotinamide in mammals. These are nicotinic acid (Komori & Sendju, 1920), nicotinamide, nicotinuric acid (Ackermann, 1913), trigonelline (Ackermann, 1913), nicotinamide methochloride (Najjar & Wood, 1940; Huff & Perlzweig, 1943*a*; Ellinger & Coulson, 1943; Coulson & Ellinger, 1943) and, recently, 1-methyl-6-pyridone-3-carbonamide (Knox & Grossmann, 1946, 1947). Dinicotinyl ornithine is a metabolite in the chick (Dann & Huff, 1947) and nicotinamide methochloride is formed by insects and bacteria (Ellinger, Fraenkel & Abdel Kader, 1947). In the earlier papers the metabolites were isolated from urine and identified by chemical analysis. When the physiological importance of nicotinamide was established, large series of analyses were carried out by methods allowing routine assay. Most of them were based on the König (1904) principle. The majority of the investigators were satisfied to estimate 'total nicotinic acid' which generally includes nicotinic acid, nicotinamide, nicotinuric acid and trigonelline. When nicotinamide methochloride was found to be a metabolite, this substance was assayed by special methods (Huff & Perlzweig, 1943*b*; Coulson, Ellinger & Holden, 1944; Najjar, 1944). It soon became evident that most of the metabolite previously described as trigonelline was in fact nicotinamide methochloride (Sarett, 1943; Huff & Perlzweig, 1943*a*). Although single observations have been carried out on man, dog, ferret, rat, mouse, calf, horse, rabbit and guinea pig, apart from the investigations of Johnson, Hamilton & Mitchell (1945) on man, and of Johnson, Wiese, Mitchell & Nevens (1947) on the calf, no distinction was made between

* Some of the results presented in this paper were communicated to the Biochemical Society on 24 January 1948 (Ellinger & Abdel Kader, 1948).

urinary nicotinamide and nicotinic acid. In this paper the elimination of all possible nicotinamide metabolites, with the exception of 1-methyl-6-pyridone-3-carbonamide, was determined under normal conditions, and after the ingestion of nicotinamide, nicotinic acid, nicotindiethylamide (nikethamide) and a few other compounds in man, dog, cat, rat, rabbit and guinea pig.

EXPERIMENTAL

Plan of experiments

Man. From a normal healthy male (subject no. 1, Table 2*a*) 24 hr. samples of urine were tested for nicotinic acid, nicotinamide, nicotinuric acid, trigonelline and nicotinamide methochloride. After a preliminary period of 3 weeks, single doses of nicotinamide, nicotinic acid or nikethamide were given orally or subcutaneously at intervals of 3–4 days. In addition 24 hr.-urine samples were collected from seven other healthy persons, and 1 diabetic balanced by insulin and diet; there was no extradietary ingestion of nicotinamide derivatives in the latter experiments.

Animals. These were kept in metabolism cages in which 24 hr.-urine samples were collected separately from the faeces. Particulars of the weights of the animals, their diets and particularly their intake of nicotinic acid and nicotinamide are given in Table 1. Since all metabolites were found to be stable in urine at low temperature, no preservative was added and the samples were kept at 5°. Two rats of the same strain were kept in the same cage on account of their small urine volume. All extradietary administrations were given intraperitoneally. The animals were given single test doses of nicotinamide, nicotinic acid, nikethamide or occasionally nicotinuric acid or nicotinamide methochloride at intervals of 3–4 days. Rats were on some occasions given methionine with the nicotinamide derivatives. In addition the dogs were given 9 g. of nicotinic acid, dissolved as sodium salt in the milk; 1 g. was given on the first and 2 g. on each of the 4 following days. The urine was collected during these 5 and the following 2 days and examined for metabolites.

Estimation of metabolites

In view of the large number of quantitative estimations of the various metabolites to be performed, routine methods had to be found and their specificity examined. The designation of the metabolites should correctly be given as 'compound reacting like nicotinic acid' rather than as 'nicotinic acid', etc. As techniques based on the König (1904) principle have been criticized by various authors, the methods of Bandier & Hald (1939), Bandier (1939), Melnick, Robinson & Field (1940), Perlzweig, Levy & Sarett (1940), Sarett, Huff & Perlzweig (1942), Sarett (1942), Huff & Perlzweig (1942), Wang & Kodicek (1943) and Carter & O'Brien (1945) were tested. The various methods used for removing interfering pigments were also studied, the colour developed with various aromatic amines was tested for stability and intensity, and the effect of the different types of hydrolysis and the colour intensities obtained with the different metabolites before and after hydrolysis were examined. As the result of our findings the following procedure was adopted.

Without extradietary administrations of nicotinamide derivatives the urine contained the various metabolites in low concentration; a portion of the 24 hr. urine was, therefore, concentrated *in vacuo* at 80° to 50–60% of its volume. The concentrate was saturated with NaCl and acetone (9 vol.) was added. The precipitated pigments were removed by centrifugation and acetone by evaporation *in vacuo* at 40°. The aqueous solution was made up with water to a definite volume and portions of it were used for the

Table 1. *Weights and diets of the animals used*

Species	No. of animals	Weight (kg.)	Diet (food given/day)	Dietary intake of: Nicotinic acid (mg./day)	Dietary intake of: Nicotinamide (mg./day)
Dog	2	1·8–3·5	Meat, bread and vegetables, 300 g.; milk, fresh, 200 ml.	6·1	10·0
Cat	3	0·76–0·88	Powdered milk, 15 g.; fish, 70 g.; bread, 30 g.	4·5	1·3
Rat (adult):					
Albino (stock of P.E.)	21	0·20–0·26	Grain mixture, 4·0 g.; extracted liver residue 3·5 g.; wheat germ, 1·0 g.; dried yeast 0·3 g.; salt mixture (McCallum 185), 0·5 g.; maize oil, 0·6 g.; cod-liver oil, 0·1 g.; national bread, 13·0 g.; milk powder, 1·5 g.	0·37	0·21
Hooded (Lister stock)	21	0·20–0·34			
Rat (young):					
Albino	5	Average 0·069			
Hooded	5	Average 0·039			
Rabbit	8	2·90–3·00	Either (*a*) cabbage, 200 g.; swedes, 100 g.; or (*b*) oats, 100 g.	1·60 0·34	1·60 0·21
Guinea pig	6	0·40–0·47	Pellets (containing grass meal 30%, bran 15%, ground-nut cake 15%, linseed cake 10%, barley meal 20%, meat and bone meal 8%, $CaCO_3$ 1%, NaCl 1%), 50 g.; cabbage, 50 g.	0·32	0·88

All animals obtained water *ad lib.*

different estimations, without hydrolysis and after hydrolysis with N-HCl, N-NaOH and 10N-NaOH with addition of urea.

To develop the colour in each solution the pH was adjusted to 5·5 with KH_2PO_4 and NaOH using bromocresol purple as external indicator: 4 and 8 ml., respectively, of these solutions were used, the former being made up to 8 ml. with water; the solutions were heated to 75–80° and 0·8 ml. of freshly prepared CNBr was then added in a test tube graduated at 10 ml.; the solution was heated to 75–80° for another 5 min. After cooling to room temperature the volume was made up to 10 ml. with water and 0·4 g. *p*-methylaminophenol sulphate (metol) was added and allowed to dissolve completely. Blanks were developed simultaneously by adding to similar volumes of urine 0·15 ml. N-H_2SO_4 instead of the metol. Standards were made from solutions containing 2 and 4 μg./ml., respectively of nicotinic acid. After 1 hr. in the dark the concentration was measured by comparing the extinction with that of the standard in a Bausch and Lomb 'Colorimeter' used as a photometer with a Wratten filter no. 39.

On an equimolecular basis, nicotinamide (*Nam*) gave 50% of the extinction given by nicotinic acid (*Nac*) before and 100% after hydrolysis with N-HCl or N-NaOH. Nicotinuric acid (*Nur*) gave values of 30% before hydrolysis and no increase after hydrolysis with N-HCl, but 100% after hydrolysis with N-NaOH. Trigonelline (*Trig*) and nicotinamide methochloride (*NM*) gave no coloured compounds before or after hydrolysis with N-acid, N-NaOH or 10N-NaOH. After hydrolysis with 10N-NaOH, in the presence of urea, a colour equivalent to 63% of that of nicotinic acid was obtained.

Calculation of the concentrations of the different metabolites was carried out as follows: If the value obtained before hydrolysis is called *A*, that after hydrolysis with acid *B*, that after hydrolysis with N-NaOH *C*, and that after hydrolysis with 10N-NaOH in the presence of urea *D*, then these equations follow from the figures given above:

$$A = 1\ Nac + 0{\cdot}5\ Nam + 0{\cdot}3\ Nur,$$

$$B = 1\ Nac + 1\ Nam + 0{\cdot}3\ Nur,$$

$$C = 1\ Nac + 1\ Nam + 1\ Nur,$$

$$D = 1\ Nac + 1\ Nam + 1\ Nur + 0{\cdot}63\ (Trig + NM),$$

$$Nam = 2\ (B - A),$$

$$Nur = \frac{C - B}{0{\cdot}7},$$

$$Nac = C - 2\ (B - A) - \frac{C - B}{0{\cdot}7},$$

$$Trig + NM = \frac{D - C}{0{\cdot}63},$$

NM is estimated separately by a method described later, and

$$Trig = \frac{D - C}{0{\cdot}63} - NM \text{ (in terms of } Nac)$$

Since all values are obtained in terms of nicotinic acid, the values have to be multiplied by the mol.wt. of the metabolite and divided by that of nicotinic acid. The values obtained in that way in terms of μg./ml. are multiplied by the urine volume to obtain the value of the 24-hr. elimination. The maximum error of the method, as estimated from recovery tests of each of the metabolites added to urine, is in the region of ±10%, when all metabolites are present; when only nicotinic acid and nicotinamide have to be estimated, the maximum error found was less than ±5%. The smallest concentration which can be estimated by this method is 0·8 μg./ml.

Nicotinamide methochloride was estimated by a modification of the acetone method of Huff & Perlzweig (1947), since non-fluorescent KCl was unobtainable and the method of Coulson *et al.* (1944) could thus not be used. The procedure differed from that described by Huff & Perlzweig in one respect: the fluorescence was compared visually with that of standards prepared from synthetic nicotinamide methochloride in a similar manner. Recoveries of 95–105% were obtained with added nicotinamide methochloride. Filter paper was chosen which neither adsorbed nicotinamide methochloride nor released fluorescent pigments, the charcoal used adsorbed interfering pigments; but not nicotinamide methochloride. Acetone was freed from fluorescent pigments by distillation over $KMnO_4$. The maximum error was about ±5%. The range of the method was found to be 0·01–1·0 μg./ml. Urines containing higher concentrations were diluted before the estimation. All analyses were carried out in duplicate. Negative or dubious results obtained with the König reaction were checked microbiologically with the method of Barton-Wright (1944) using *Lactobacillus arabinosus*. The presence of the coenzymes which give a positive reaction with the acetone method was checked microbiologically by the method of Pittman & Fraser (1940) using *Haemophilus parainfluenzae* (National Collection of Type Cultures, no. 4101).

RESULTS

Man. In man (Table 2*a*) nicotinamide methochloride is the main end product of nicotinamide metabolism forming on the average 71·2%, whilst nicotinamide represents 24·2% and nicotinic acid 4·6% of the output. These values may be compared with those of Johnson *et al.* (1945), who found, however, absolute values for nicotinamide methochloride (average 18·7 mg.) far higher than either those found in the present work or any values published by previous investigators (Ellinger & Coulson, 1944; Ellinger, Benesch & Hardwick, 1945; Hochberg, Melnick & Oser, 1945; Ellinger & Hardwick, 1947). Ingested nicotinic acid (Table 2*b*) is amidated and nikethamide is de-ethylated. In all cases nicotinamide methochloride forms the main metabolite. After subcutaneous administration the elimination is greater than after oral administration, in agreement with the findings of Ellinger & Hardwick (1947). The total recovery of the ingested compounds is much lower than in any other mammal examined. This might be due to the fact that part of the methylated compound is immediately oxidized to the corresponding pyridone (Rosen, Perlzweig & Handler, 1948) and not determined by the methods of assay used. It might also be due to a relatively low saturation state of the subject examined, indicated by the considerable rise in output of the three metabolites in the course of administration of nicotinamide derivatives. Similar observations have

Table 2a. *Daily elimination of nicotinamide derivatives by man*

Subject				Metabolites eliminated (mg./24 hr.)			
No.	Sex	Age (yr.)	Wt. (kg.)	Nicotinamide	Nicotinic acid	Nicotinamide methochloride*	Remarks
1†	♂	27	80	2·000	0·810	8·030	No smoking, no coffee
R1‡	♂	27	80	1·342	0·360	6·681	
R1§	♂	27	80	3·622	1·233	11·420	
2	♀	61	50	3·320	0·680	6·160	No smoking, coffee
3	♀	19	70	1·400	0·480	9·360	No smoking, no coffee
4	♀	19	65	2·180	0·370	9·440	
5	♂	47	67	1·980	0·215	12·040	
6	♂	22	70	1·590	0·264	12·480	
7	♀	25	58	1·175	0·100	10·840	
8	♂	53	64	2·540	0·145	6·050	
9	♂	60	68	3·000	0·440	5·040	Balanced diabetic; no smoking, no coffee
Average				2·132	0·399	8·894	

Neither trigonelline nor nicotinuric acid were eliminated.
* Absolute, not in terms of nicotinic acid.
† Average of daily output estimated on 22 control days spread over the whole period.
‡ Average of 3 days before the first injection.
§ Average of 3 days, 14 days after last injection.

Table 2b. *Response to extradictary nicotinamide derivatives by man (subject no. 1)*

Compound administered	Dose (mg.)	Route	Metabolites eliminated (% of ingested)*			
			Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Total
Nicotinamide	100	Oral	0	0	18·9 [3]	18·9
		Subcutaneous	1·8	0	24·9 [3]	26·7
Nicotinic acid	100	Oral	2·3	0·8	16·5 [2]	19·6
		Subcutaneous	2·1	0·9	21·1 [2]	24·1
Nicotindiethylamide	100	Oral	6·2	0	5·8 [2]	12·0
		Subcutaneous	6·3	0	15·5 [2]	21·8

[ ] indicates time in days over which elimination occurred.
* *Note.* Dose of administered compound is in terms of nicotinic acid. The response (percentage of ingested), also in terms of nicotinic acid, is calculated as

$$\frac{\text{(output until predosing level is reached)} - \text{(average predosing output} \times \text{days of increased output)}}{\text{dose administered}} \times 100.$$

Neither trigonelline nor nicotinuric acid was eliminated.

been made by Ellinger & Hardwick (1947). The smaller elimination of metabolites after oral than after parenteral administration indicates destruction by the intestinal flora which has been observed by Koser & Baird (1944), Benesch (1945), Ellinger & Emmanuelowa (1946), Ellinger (1947) and Ellinger, Abdel Kader & Emmanuelowa (1947).

Dog. In this species (Table 3) nicotinamide and nicotinamide methochloride are the only urinary metabolites; the relative proportion of the two compounds eliminated differed considerably in the two animals examined, but was fairly constant from day to day in the same animal. The total elimination was high compared with that of other species. After administration of nicotinamide and nikethamide (Table 4), the only metabolites found were nicotinamide and nicotinamide methochloride, while after nicotinic acid injection some unchanged nicotinic acid appeared in the urine. This, and particularly the absence of nicotinuric acid, contradicts the findings of Ackermann (1913), Komori & Sendju (1926) and Sarett (1942). The last-named found a recovery of 75 % in the form of 'trigonelline' and 25 % in that of nicotinuric acid. When Ackermann's (1913) experiment was repeated, neither dog eliminated either trigonelline or nicotinuric acid. Dogs gave a much higher response to injected compounds than man. The relatively greater elimination of the methylated product with smaller than with larger doses suggests that the methylating mechanism is the limiting factor. The relative proportion of the methylated to the unmethylated metabolites is considerably greater after administration of nicotinamide and nikethamide than after that of nicotinic acid. The relative total response is greater after small than after big doses.

Table 3. *Average daily urinary elimination of nicotinamide derivatives by various mammalian species*

Species	Metabolites eliminated (Averages, limiting values in parentheses) (mg./day)		
	Nicotinamide	Nicotinic acid	Nicotinamide methochloride
Dog	4·590 (3·480–5·720)	0	5·370 (1·000–10·250)
Cat	0	0	0·290 (0·070–0·400)
Rat (albino):			
Adult	0·080 (0·054–0·130)	0	0·100 (0·030–0·260)
Young	0·035	0	0·292
Rat (hooded):			
Adult	0·140 (0·100–0·170)	0	0·060 (0·450–1·700)
Young	0·0214	0	0·150
Rabbit	0	0·880 (0·500–1·350)	0*
(On cabbage)			
(On oats)	0	1·190 (1·010–1·540)	0*
Guinea pig	0	0	0*

Neither trigonelline nor nicotinuric acid were eliminated.
* Indicates a small positive reaction with the acetone, but none with the König (1904) method.

Table 4. *Average response to extradietary nicotinamide derivatives by dogs*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*			
		Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Total
Nicotinamide	200	31·7 [2]	0	50·1 [2]	81·8
	500	43·0 [2]	0	31·6 [3]	74·6
Nicotinic acid	200	48·8	13·1	31·6 [2]	93·5
	500	49·0 [2]	16·7	21·5 [2]	87·2
	9000†	10·0	49·4	5·6	65·0
Nicotindiethylamide	100	43·5	0	52·1 [2]	95·5
Nicotinuric acid	67·7	31·4	41·8	18·1 [2]	91·2

[ ] indicates time in days over which elimination occurred, if more than one.
Neither trigonelline nor nicotinuric acid were eliminated.
* See note to Table 2*b*.
† Orally within 5 days.

Table 5. *Average response to extradietary nicotinamide derivatives by cats*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*			
		Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Total
Nicotinamide	40	34·5	0	28·3 [3]	63·3
	80	37·6 [2]	0	20·4 [2]	58·0
	200	47·0 [2]	0	34·1 [4]	81·1
Nicotinic acid	40	12·8	10·5	24·1 [2]	47·4
	100	24·1 [2]	29·0	18·7 [3]	71·8
Nicotindiethylamide	40	19·0	0	16·1 [2]	35·0

[ ] indicates time in days over which elimination occurred, if more than one.
Neither trigonelline nor nicotinuric acid were eliminated.
* See note to Table 2*b*.

Cats normally eliminate small amounts of nicotinamide methochloride only (Table 3). Nicotinamide and nicotinamide methochloride were eliminated after administration of nicotinamide and nikethamide and in addition some nicotinic acid when this compound was given (Table 5). As in dogs, the relative proportion of methylated to unmethylated metabolites decreases with rising doses. The total response was lower than in dogs.

similar to those observed by Huff & Perlzweig (1942), though the experiments were not directly comparable. Nicotinuric acid was found to be split as observed by Huff & Perlzweig (1942), but not so completely as by dogs. Nicotinamide methochloride was eliminated unchanged but only to the extent of 63 %, confirming the findings of Ellinger (1947), Ellinger & Coulson (1944) and Perlzweig & Huff (1945) in man. The effect of methionine administered,

Table 6. *Response to extradietary nicotinamide derivatives by two strains of rats*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*				
		Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Nicotinuric acid	Total
		Albino				
Nicotinamide	20	23·7	0	9·3	0	33·0
	20 (+30 DL-methionine)	19·2	0	12·5	0	31·7
	50	31·6	0	15·0 [2]	0	46·6
Nicotinic acid	20	23·8	26·9	1·8	0	52·5
	20 (+30 DL-methionine)	20·4	49·5	1·0 [2]	0	70·9
	50	31·9 [2]	35·4	1·0 [2]	0	68·3
Nicotindiethylamide	20	36·7	0	9·8 [2]	0	46·5
	20 (+30 DL-methionine)	48·0	0	4·9 [2]	0	52·9
	50	38·8 [2]	0	3·4 [2]	0	42·2
Nicotinamide methochloride	17·5	0	0	71·0	0	71·0
Nicotinuric acid	33·9	13·0	2·1	3·2 [2]	72·8	91·0
		Hooded				
Nicotinamide	20	15·0	0	29·7	0	44·7
	20 (+30 DL-methionine)	16·5	0	59·7	0	76·2
	50	19·2	0	61·6 [2]	0	80·8
Nicotinic acid	20	24·1	27·7	16·0	0	67·8
	20 (+30 DL-methionine)	26·0	37·8	8·9 [2]	0	72·7
	50	25·4	19·4	5·7	0	50·5
Nicotindiethylamide	20	36·0	0	33·4 [2]	0	69·4
	50	34·4 [2]	0	13·7 [2]	0	48·1
Nicotinamide methochloride	17·5	0	0	63·2	0	63·2
Nicotinuric acid	33·9	11·4	2·0	3·1 [2]	62·2	79·6

[ ] indicates time in days over which elimination occurred, if more than one.
No trigonelline was eliminated.
* See note to Table 2*b*.

Rat. The two strains of rat examined differed mainly in the efficiency of the methylating mechanism. Rats, like dogs, eliminated only nicotinamide and nicotinamide methochloride (Table 3). The relative proportion of the latter to the former was 1·25 in the albino and 6·85 in the hooded strain. Relative to weight the output is high compared with that of cats; for the albino it was similar to that found by Huff & Perlzweig (1942) and for the hooded strain it was much higher. Both strains eliminated injected nicotinamide and nikethamide as nicotinamide and nicotinamide methochloride; when nicotinic acid was given it was eliminated partly unchanged (Table 6). The total response was greater in the hooded than in the albino strain. The values found for response to nicotinamide and nicotinic acid were

together with the nicotinamide derivatives on the formation of nicotinamide methochloride, was irregular. The elimination of nicotinic acid after administration of nicotinic acid was always increased by simultaneous administration of methionine. When large doses (100 mg.) of nicotinamide were administered the nicotinamide methochloride output was increased by rising doses of methionine; this indicates the exhaustion of methyl donors by methylation as shown for man by Ellinger & Hardwick (1947). In all cases the elimination of nicotinamide methochloride was far greater in the hooded than in the albino strains. On no occasion was nicotinamide deaminated or nicotinic acid formed from nikethamide. DL-Methionine proved to be toxic to rats. LD_{50} found was about 700 mg./kg. The hooded rats

died earlier and were more strongly affected by sublethal doses than the albino. Macroscopic post-mortem examination showed the kidneys congested with blood, confirming observations by Simmonds, Cohn & du Vigneaud (1947).

Young rats (Table 3), like adults, eliminated nicotinamide and nicotinamide methochloride but no nicotinic acid. This conversion of nicotinic acid into nicotinamide makes the observation of Handler & Dann (1942) that the growth of young rats is inhibited by nicotinamide but not by nicotinic acid even less explicable.

tinamide methochloride. It is concluded, therefore, that a substance is present in the urine giving the acetone but not the König reaction. A test for coenzymes which fulfils this condition gave negative results. The possibility has, therefore, to be considered that there is present an unknown factor which might be a metabolite of a nicotinamide derivative. It will be extremely difficult to isolate or identify it since it is present in minute quantities and no way has been found to increase its elimination markedly. It is possible that the 'F_2' which, according to Handler (1944), is eliminated by young

Table 7. *Average response to extradietary nicotinamide derivatives by rabbits*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*			
		Nicotinamide	Nicotinic acid	Trigonelline	Total
		Diet of cabbage			
Nicotinamide	100	2·9	3·3 [2]	5·1 [2]	11·3
	200	6·9	14·5 [3]	9·3 [3]	30·6
	400	7·5	18·6 [3]	9·4 [3]	35·5
Nicotinic acid	100	0	35·5 [2]	48·0 [2]	83·5
	200	0	63·4 [2]	33·9 [2]	97·3
Nicotindiethylamide	50	1·6	5·7	3·3	10·6†
	100	9·2	15·1	6·4	30·7†
	200	4·9	10·0 [2]	7·0 [2]	21·8†
	2 hourly doses of 100				
	600	7·5	21·7 [2]	2·7 [2]	30·9†
	6 hourly doses of 100				
		Diet of oats			
Nicotinamide	100	2·2	3·5 [2]	3·3	9·5‡
	200	7·5 [2]	13·0 [3]	6·5 [3]	27·0‡
Nicotinic acid	100	0	32·9 [2]	54·8 [2]	87·7
	200	0	52·4 [2]	29·8 [2]	82·2

[ ] indicates time in days over which elimination occurred, if more than one.
Neither nicotinamide methochloride nor nicotinuric acid were eliminated.
* See note to Table 2*b*.
† Indicates that after injection of nicotindiethylamide an unknown substance of high fluorescent efficiency was eliminated interfering with the application of the acetone method.
‡ Indicates that after injection of nicotinamide into rabbits fed on oats and possibly after that of nicotindiethylamide a substance was eliminated to a slightly increased extent giving a positive reaction with the acetone but not with the König (1904) method.

Rabbits (Table 3) independently of the diet, cabbage or oats, normally only eliminated nicotinic acid. In addition a substance was regularly eliminated, and to a slightly increased extent after injection of nicotinamide by rabbits fed on oats, which gave a positive reaction by the acetone method for nicotinamide methochloride. The amount was very small, just within the limits of the method, but the substance appeared to be always present. The König (1904) assay failed to show the presence of trigonelline or nicotinamide methochloride in the same urines. This might be due to insufficient sensitivity of the König reaction; however, this is improbable. The concentrations found with the acetone method were large enough to give positive results with the König method if the substance were nico-

rabbits and guinea pigs, but not increased after nicotinamide administration, and the nicotinamide methochloride found by Johnson *et al.* (1947) in the urine of young calves, which also is not increased by administration of nicotinamide, is in fact this unknown substance.

Extradietary nicotinamide and nikethamide were found to be deaminated to nicotinic acid which is methylated to trigonelline (Table 7). This observation contradicts the results of Komori & Sendju (1926) who, after feeding nicotinic acid to rabbits, isolated nicotinic acid and nicotinuric acid from the urine, but no trigonelline. The observation is also at variance with the assumption of Huff & Perlzweig (1943*a*) that rabbits are unable to carry out this methylation. The elimination of known metabolites

is low after ingestion of nicotinamide and nikethamide, but almost complete after the administration of nicotinic acid. The deamination might lead to a thorough disintegration of the pyridine ring. The type of diet seems to have very little influence on the qualitative and quantitative elimination of metabolites except for the increase in 'pseudo-nicotinamide methochloride' after administration of nicotinamide, which occurs only in rabbits fed on oats. The increased elimination of trigonelline following nicotinic acid injection is relatively higher after smaller than after bigger doses and indicates that the methylating mechanism is exhaustible.

The urine passed by rabbits after administration of nikethamide exhibits without any treatment a strong purplish blue fluorescence in the long ultraviolet which increases in intensity with rising nikethamide administration. The urine ceases to be fluorescent about 16 hr. after the injection. Some preliminary data of the isolation and properties of the substance responsible for this fluorescence have been obtained. The fluorescent substance is not extractable from neutral, acid or alkaline urine by ethyl acetate, benzene, *iso*butanol, light petroleum, chloroform or ether and is stable to boiling in neutral, acid or alkaline solution. It is not adsorbed on decalso or charcoal, but is adsorbed on Al_2O_3 (Brockmann) from dry ethanol solution. For its isolation the urine was acidified with HCl, filtered through a decalso column, and shaken with charcoal to remove as many of the other urine constituents as possible. The colourless filtrate was evaporated to dryness, extracted with hot dry ethanol and filtered through an Al_2O_3 column, the fluorescent material being completely adsorbed. The column was thoroughly washed with dry ethanol. Two fluorescent zones were seen on the upper part of the column, a narrow one of purplish blue fluorescence on the extreme top and a wider one of bright blue fluorescence clearly separated from it farther down. The top layer was cut off and both layers were eluted with 50% (v/v) ethanol for the top layer and 85% (v/v) ethanol for the other one. Both eluates were evaporated to a small volume *in vacuo* and treated with non-fluorescent acetone. In both cases part of the fluorescent material was precipitated and another part remained dissolved in acetone. The precipitates from the top layer (*A*) and from the lower layer (*B*) were filtered off, washed with dry ethanol and twice recrystallized from hot ethanol. The main fluorescent material (*C*) dissolved in acetone was brought to dryness by evaporation *in vacuo*, dried *in vacuo* over P_2O_5 and recrystallized three times from hot dry ethanol. The three substances had the following properties.

Substance *A*: m.p. 166·5–168·5°; ultraviolet absorption in water; no band between 260–380 mμ., general absorption from 280 to 220 mμ. with shoulder at 260 mμ., $E^{1\%}_{1\,cm.} = 2{\cdot}5$.

Substance *B*: m.p. 325° with decomposition and sublimation; ultraviolet absorption in water: similar to *A* with much smaller general absorption.

Substance *C*: very hygroscopic, colourless, turns brown when exposed to air. M.p. 96·5°; if heated to 108·5°, it does not resolidify on cooling; ultraviolet absorption in water: distinct band at 336 mμ., $E^{1\%}_{1\,cm.} = 4{\cdot}6$, with general absorption from 280 to 220 mμ., shoulder at 265 mμ., $E^{1\%}_{1\,cm.} = 3{\cdot}4$ and indications of a peak at 220 mμ., $E^{1\%}_{1\,cm.} = 17{\cdot}0$. In a cataphoretic experiment it formed a uniform band and moved slowly to the anode. It has not been possible so far to collect sufficient quantities of the fluorescent pigments for analysis and estimation of the mol.wt.

Nikethamide is toxic to rabbits and larger doses have to be divided; the total amount which can be administered is, therefore, small. Moreover, the mechanism involved in the production of the fluorescent pigments seemed to be quickly exhausted; the animals used have to rest for a considerable time before they can be used with advantage for a second collection. None of the substances seems to be identical with 1-methyl-2 (or 6)-pyridone-3-carbondiethylamides; these differ from the pigments by their fluorescence and ultraviolet absorption. Perhaps the pigments are derivatives of a dihydropyridine which, according to Warburg & Christian (1936), has a band at 340 mμ.

Guinea pigs differed from all other species examined by not eliminating any metabolite except 'pseudo-nicotinamide methochloride' (Table 3) and by not methylating any extradietary nicotinamide derivative (Table 8). Slight increase of the 'pseudo-nicotinamide methochloride' occurred after nicotinamide and nikethamide, but not after nicotinic acid administration. Nicotinamide was completely de-

Table 8. *Average response to extradietary nicotinamide derivatives by guinea pigs*

Compound administered	Dose* (mg.)	Metabolites eliminated (% of ingested)*			
		Nicotinamide	Nicotinic acid	Nicotinamide methochloride	Total
Nicotinamide	100	0	32·4	0*	32·4
	200	0	24·2 [2]	0* [2]	24·2
	400	0	38·9 [2]	0* [2]	38·9
Nicotinic acid	100	0	60·5 [2]	0	60·5
	200	0	82·2 [2]	0	82·2
	400	0	66·7 [2]	0	66·7
Nicotindiethylamide	25	12·9	12·7	0†	25·6
	50	10·3	20·4 [2]	0†	30·7

[ ] indicates time in days over which elimination occurred, if more than one.
Neither trigonelline nor nicotinuric acid were eliminated.
* See note to Table 2*b*.
† Indicates that after administration of nicotinamide or nicotindiethylamide a substance was eliminated to a slightly increased extent giving a positive reaction with the acetone, but not with the König (1904) method.

aminated to nicotinic acid. Of the ingested nicotinamide or nikethamide 25–38 % was eliminated and of the nicotinic acid about 60–80 %.

DISCUSSION

The most surprising result is that the two compounds described by other authors (Ackermann, 1913; Komori & Sondju, 1926; Linneweh & Reinwein, 1932*a*, *b*; Melnick *et al.* 1940 and Perlzweig *et al.* 1940) as the metabolites of nicotinic acid or nicotinamide in dogs, men or rats, viz. trigonelline and nicotinuric acid, are not eliminated by any of these species normally or after administration of the tested compounds. It is easy to understand that authors using the König (1904) method for assay have described the occurrence of trigonelline in the urine before nicotinamide methochloride had been established as a metabolite. The two compounds cannot be distinguished by the König method. However, it has been claimed that these two substances can be isolated from urine and analyses for the compounds or derivatives have been given. Ackermann (1913) e.g. analyzed the gold salt of a substance obtained from urine of dogs after feeding nicotinic acid for gold, carbon and hydrogen, but not for nitrogen, and claimed to have identified it as a salt of trigonelline. The theoretical values of gold, carbon and hydrogen are almost identical for the gold salts of trigonelline and nicotinamide methochloride, while the nitrogen value of the latter is about twice that of the former. The same omission explains the results of Komori & Sondju (1926) who only made an analysis for gold. The results of Linneweh & Reinwein (1932*a*, *b*), who have produced analytical values for carbon, hydrogen and nitrogen in agreement with trigonelline itself for a substance isolated from human urine, are more difficult to explain. This probably was pure nicotinamide methochloride. With regard to nicotinuric acid, Ackermann's (1913) results on dogs are inexplicable since injected nicotinuric acid is completely split by the dog and eliminated as nicotinamide, nicotinic acid and nicotinamide methochloride (Table 4). It cannot, therefore, be an end product of nicotinic acid metabolism in the dog. This breakdown to nicotinamide, however, explains the anti-blacktongue (Woolley, Strong, Madden & Elvehjem, 1938) and antipellagric activities (Elvehjem & Teply, 1943) of nicotinuric acid. The findings of Melnick *et al.* (1940) that man eliminates nicotinuric acid after ingestion of doses of 500 mg. and more of nicotinic acid have not been tested. It is probable that their method of assay is not suitable for separate determination of nicotinamide and nicotinuric acid.

The contradictory results of the many investigations are mainly due to the faults of the assay methods based on the König principle. The conditions of hydrolysis are of great importance for a clean separate determination of the metabolites as well as for securing low blanks. Melnick *et al.* (1940), Perlzweig *et al.* (1940), Sarett *et al.* (1942), Sarett (1942) and Huff & Perlzweig (1942) use for the hydrolysis of nicotinamide and nicotinuric acid N-hydrochloric acid and 5N-hydrochloric acid respectively. The latter produces strongly coloured hydrolysates and, consequently, such high blank values that correct absorption readings are almost impossible. This can be avoided by using N-sodium hydroxide for the hydrolysis of nicotinuric acid. Bandier & Hald's (1939) method for the removal of interfering pigments is satisfactory, while Wang & Kodicek's (1943) method is tedious and results in a strong yellow tint interfering with the assay. The modification of the method of Bandier & Hald (1939) by Carter & O'Brien (1945) with regard to pH and amount of metol is advantageous. By systematic study of the effect of pH and amount of metol used on the reproducibility and intensity of colour, the method has been further improved. Contrary to the findings of Bandier & Hald (1939), exposure to daylight, even direct sunlight, does not interfere with the colour intensity.

Considering the metabolism of nicotinamide derivatives, the mammalian species examined so far can be classified into two groups; man, dog, cat and rat which aminate nicotinic acid to nicotinamide, whilst rabbit and guinea pig deaminate nicotinamide to nicotinic acid. Before drawing any further conclusions more species have to be examined; but it is attractive to base on this and similar fundamental functions a classification of species on the basis of their biochemical properties. It has already been mentioned that some mammalian species such as rabbit and horse do not methylate nicotinic acid or nicotinamide whilst other species do so. Whether the type of diet (carnivore, omnivore or herbivore) is responsible for these differences is doubtful. It cannot play any role in the process of methylation since herbivores like rabbit and guinea pig differ in this respect. The mechanisms of methylation and amination of these compounds have been elucidated and their sites located in the liver (Perlzweig, Bernheim & Bernheim, 1943) and kidney and brain (Ellinger, 1946, 1948), respectively. It would be interesting to see whether the methylating enzyme is absent from guinea-pig liver and where and how the deamination occurs in rabbit and guinea pig. It is possible that aminating and deaminating enzymes are present in both types of species, the one being inhibited in normal conditions in the living animal as has been shown for the sulphonamide acylating and deacylating enzymes by Krebs, Sykes & Bartley (1947). The instability of nicotinamide in rabbit and guinea pig suggests that the nicotinamide moiety of the coenzymes might be replaced by nicotinic acid in these species.

The metabolism of nikethamide particularly in man, rabbit and guinea pig shows, as already suggested by Ellinger *et al.* (1947), that this compound is broken down by de-ethylation to nicotinamide followed, in rabbit and guinea pig, by deamination of the latter compound.

SUMMARY

1. The metabolism of nicotinamide derivatives in men, dogs, cats, rats, rabbits and guinea pigs has been studied under normal conditions and after administration of nicotinamide, nicotinic acid, nikethamide and, in some instances, of nicotinamide methochloride and nicotinuric acid. The metabolites tested for have been nicotinamide, nicotinic acid, nicotinuric acid, trigonelline and nicotinamide methochloride.

2. Under normal conditions men eliminate nicotinamide, nicotinic acid and mainly nicotinamide methochloride, dogs and rats nicotinamide and nicotinamide methochloride, cats only the latter compound, rabbits nicotinic acid and guinea pigs none of these compounds. No nicotinuric acid or trigonelline was found in the urine. Rabbits and guinea pigs, however, eliminate small amounts of an unknown substance, giving a positive reaction by the acetone method.

3. Extradietary nicotinamide was eliminated by men almost exclusively as nicotinamide methochloride, by dogs, cats and rats partly as nicotinamide, partly as nicotinamide methochloride, by rabbits as nicotinamide, nicotinic acid and trigonelline and by guinea pigs as nicotinic acid; in the last-named species the unknown compound giving a positive reaction with the acetone method was slightly augmented.

4. Nicotinic acid was eliminated by men mainly as nicotinamide methochloride and to a very small extent unchanged and as nicotinamide; by dogs, cats and rats in the form of all three metabolites, by rabbits partly unchanged, partly as trigonelline and by guinea pigs unchanged.

5. Nikethamide is broken down to nicotinamide and accordingly further metabolized by all species. In rabbits after the injection of nikethamide, purplish blue fluorescent pigments occur in the urine, three of which have been isolated.

6. Men, dogs, cats and rats aminate nicotinic acid; rabbits and guinea pigs deaminate nicotinamide; all species except guinea pigs methylate the metabolites to nicotinamide methochloride or trigonelline, respectively; nicotinuric acid is broken down by dogs and rats to nicotinic acid and nicotinamide and cannot, therefore, be an end product of metabolism, while nicotinamide methochloride is eliminated unchanged by rats.

7. DL-Methionine has no constant effect on the metabolism of the various derivatives in rats and is toxic to these animals in larger doses.

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REFERENCES

Ackermann, D. (1913). *Z. Biol.* **59**, 17.
Bandier, E. (1939). *Biochem. J.* **33**, 1787.
Bandier, E. & Hald, J. (1939). *Biochem. J.* **33**, 264.
Barton-Wright, E. C. (1944). *Biochem. J.* **38**, 314.
Benesch, R. (1945). *Lancet*, i, 718.
Carter, C. W. & O'Brien, J. R. P. (1945). *Quart. J. Med.* N.S. **14**, 197.
Coulson, R. A. & Ellinger, P. (1943). *Biochem. J.* **37**, xvii.
Coulson, R. A., Ellinger, P. & Holden, M. (1944). *Biochem. J.* **38**, 150.
Dann, W. J. & Huff, J. W. (1947). *J. biol. Chem.* **168**, 121.
Ellinger, P. (1946). *Biochem. J.* **40**, xxxi.
Ellinger, P. (1947). *Biochem. J.* **41**, 308.
Ellinger, P. (1948). *Biochem. J.* **42**, 175.
Ellinger, P & Abdel Kader, M. M. (1948). *Biochem. J.* **42**, xxxiii.
Ellinger, P., Abdel Kader, M. M. & Emmanuelowa, A. (1947). *Brit. J. exp. Path.* **28**, 261.
Ellinger, P., Benesch, R. & Hardwick, S. W. (1945). *Lancet*, ii, 197.
Ellinger, P. & Coulson, R. A. (1943). *Nature, Lond.*, **152**, 383.
Ellinger, P. & Coulson, R. A. (1944). *Biochem. J.* **38**, 265.
Ellinger, P. & Emmanuelowa, A. (1946). *Lancet*, ii, 716.
Ellinger, P., Fraenkel, G. & Abdel Kader, M. M. (1947). *Biochem. J.* **41**, 559.
Ellinger, P. & Hardwick, S. W. (1947). *Brit. med. J.* i, 672.
Elvehjem, C. A. & Teply, L. J. (1943). *Chem. Rev.* **33**, 185.
Handler, P. (1944). *J. biol. Chem.* **154**, 203.
Handler, P. & Dann, W. J. (1942). *J. biol. Chem.* **146**, 357.
Hochberg, M., Melnick, D. & Oser, B. L. (1945). *J. biol. Chem.* **158**, 265.
Huff, J. W. & Perlzweig, W. A. (1942). *J. biol. Chem.* **142**, 401.
Huff, J. W. & Perlzweig, W. A. (1943*a*). *Science*, **97**, 538.
Huff, J. W. & Perlzweig, W. A. (1943*b*). *J. biol. Chem.* **150**, 483.
Huff, J. W. & Perlzweig, W. A. (1947). *J. biol. Chem.* **167**, 157.
Johnson, B. C., Hamilton, T. S. & Mitchell, H. H. (1945). *J. biol. Chem.* **159**, 231.
Johnson, B. C., Wiese, A. C., Mitchell, H. H. & Nevens, W. B. (1947). *J. biol. Chem.* **167**, 729.

Knox, W. E. & Grossman, W. I. (1946). *J. biol. Chem.* **166**, 391.
Knox, W. E. & Grossman, W. I. (1947). *J. biol. Chem.* **168**, 363.
Komori, Y. & Sendju, Y. (1926). *J. Biochem., Tokyo*, **6**, 163.
König, W. (1904). *J. prakt. Chem.* **69**, 105.
Kosser, S. A. & Baird, G. R. (1944). *J. infect. Dis.* **75**, 250.
Krebs, H. A., Sykes, W. O. & Bartley, W. C. (1947). *Biochem. J.* **41**, 622.
Linneweh, W. & Reinwein, H. (1932*a*). *Hoppe-Seyl. Z.* **207**, 48.
Linneweh, W. & Reinwein, H. (1932*b*). *Hoppe-Seyl. Z.* **209**, 110.
Melnick, D., Robinson, W. W. & Field, H., jun. (1940). *J. biol. Chem.* **136**, 157.
Najjar, V. A. (1944). *Johns Hopk. Hosp. Bull.* **74**, 392.
Najjar, V. A. & Wood, R. W. (1940). *Proc. Soc. exp. Biol., N.Y.*, **44**, 386.
Perlzweig, W. A., Bernheim, M. L. C. & Bernheim, F. (1943). *J. biol. Chem.* **150**, 401.
Perlzweig, W. A. & Huff, J. W. (1945). *J. biol. Chem.* **161**, 417.
Perlzweig, W. A., Levy, E. D. & Sarett, H. P. (1940). *J. biol. Chem.* **136**, 729.
Pittman, M. & Fraser, H. F. (1940). *Publ. Hlth Rep., Wash.*, **55**, 915.
Rosen, F., Perlzweig, W. A. & Handler, P. (1948). *Fed. Proc.* **7**, 181.
Sarett, H. P. (1942). *J. Nutrit.* **23**, 35.
Sarett, H. P. (1943). *J. biol. Chem.* **150**, 159.
Sarett, H. P., Huff, J. W. & Perlzweig, W. A. (1942). *J. Nutrit.* **23**, 23.
Simmonds, S., Cohn, M. & du Vigneaud, V. (1947). *J. biol. Chem.* **170**, 631.
Wang, Y. L. & Kodicek, E. (1943). *Biochem. J.* **37**, 530.
Warburg, O. & Christian, W. (1936). *Biochem. Z.* **287**, 291.
Wooley, D. W., Strong, F. M., Madden, R. J. & Elvehjem, C. A. (1938). *J. biol. Chem.* **124**, 715.

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Niacin-Tryptophan Relationships in Man and Niacin Requirement

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PARTICIPATION in this Symposium honoring Dr. Virgil Sydenstricker is a real privilege and pleasure. It seems particularly suitable to discuss certain aspects of niacin metabolism as Dr. Sydenstricker and his associates have made many contributions to this field.

Knowledge of niacin-tryptophan relationships in man will be reviewed briefly in historical perspective before discussing current research. It is of considerable interest that astute clinical observations of 200 years ago have been validated and explained by recent scientific experiments.

In the first descriptions of pellagra in the eighteenth century, both Casal and Frapoli[1] noted the association of the disease with a poor diet in which corn (maize) was one of the principal foods. Casal[2] even described the good effects of a "milk diet." In the early nineteenth century, Fanzaga and Marzari[1] suggested that pellagra was due to protein inanition and that maize was deleterious because of its low nitrogen content. Roussel,[2] in his treatise on pellagra in 1845, emphasized the importance of diet in therapy. His rules "of the alimentary regimen of the pellagrous" included exclusion of maize of poor quality and bringing into the diet "a progressively increasing proportion of animal substances beginning with the milk diet."

Early in the present century Funk[3] suggested that pellagra was due to vitamin deficiency. Another etiologic concept at this time, held particularly by observers of pellagra in Egypt, was that this disease was related to lack of an essential amino acid, probably tryptophan.[3] In the course of Goldberger's classic investigations of the etiology of pellagra, he showed that the disease could be prevented by increasing the intake of fresh animal and leguminous protein foods.[4] Subsequently, he induced pellagra in 6 of 11 subjects who subsisted for seven months on a diet similar to that consumed by persons with endemic pellagra.[5] In continued search for the pellagra preventive factor, Goldberger[6] conducted experiments which linked tryptophan to the pellagra problem. One of the corn proteins, zein, had been known since the early 1900's to be of poor biologic value, being low in lysine and tryptophan. These amino acids were administered to pellagrous subjects and improvement followed tryptophan administration. At this time, Goldberger suggested that pellagra might be due to amino acid deficiency. However, further research with food sources of the pellagra-preventive factor made vitamin deficiency seem a more likely possibility and the idea of a relationship to protein received less attention.

Concurrent with the studies of Goldberger, Voegtlin[7] demonstrated that a proper diet containing milk, eggs and meat was an essential aspect of the treatment of pellagra. He assumed that there might be a deficiency of certain vitamins and a deficiency of certain amino acids in the pellagragenic diet.

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Subsequent to these studies, pellagra was treated with a good diet, yeast and, when it became available, with liver extract. Then, in 1937, Elvehjem and his associates[8] demonstrated that niacin and its amide cured "black tongue" in dogs, a condition previously shown to be the canine analogue of pellagra. Following this discovery, niacin was found to be effective in the treatment of pellagra by a number of investigators.[9] In 1938, Schmidt and Sydenstricker[10] attempted to prevent relapse of chronic pellagra with nicotinic acid, 100 mg being given twice weekly. This quantity proved insufficient and the importance of diet and other accessory factors in the prevention of the pellagra syndrome was emphasized.

Although niacin had been demonstrated to be the pellagra-preventive vitamin, certain aspects of the occurrence of pellagra remained unexplained. Diets in some areas of the world in which pellagra was rare were found to contain less niacin than did corn diets in areas in which pellagra was common. Furthermore, certain foods known to be effective in the prevention of pellagra, such as milk, were found to be low in niacin.

TRYPTOPHAN

In 1945, Krehl and associates[11] observed growth retardation in rats when corn was included in large amounts in a low protein ration. This retardation was corrected by the administration of niacin or of the amino acid, tryptophan. It had been shown previously that the rat could synthesize niacin and that the synthesis appeared to be related to the protein level of the diet. In 1946, Rosen and associates[12] reported that the administration of tryptophan to rats was followed by a marked increase in the urinary excretion of niacin metabolites. This was confirmed by Singal, Briggs, Sydenstricker and Littlejohn[13] who found that after tryptophan was given, there was an increased excretion of nicotinic acid, a methylated derivative of nicotinic acid and an unidentified substance which was converted to nicotinic acid by acid but not by alkaline hydrolysis. They suggested that this unidentified substance might be quinolinic acid. In 1947, Sarett and Goldsmith[14] and Perlzweig and associates[15] showed that administration of tryptophan to human subjects led to an increased excretion of N^1-methylnicotinamide (N^1-Me) in the urine. These experiments in rats and in man indicated that tryptophan might be an important precursor of niacin.

Since this time, tryptophan has been shown to be effective in preventing and curing nicotinic acid deficiency in many animal species.[16] Pellagra was found to respond satisfactorily to treatment with large doses of tryptophan by Sarett and Goldsmith[17] and by Vilter, Bean and their associates.[18] Administration of tryptophan to human subjects is followed by an increase in the excretion of N^1-Me, the pyridone of N^1-Me and quinolinic acid.[14–17, 19]

It was thought by some that tryptophan might exert its effect through the intestinal flora. However, further investigation showed that injection of tryptophan caused an immediate increase in the urinary output of niacin derivatives in the rat[20] and in man.[21] Formation of niacin from tryptophan was found to take place in the absence of the entire intestinal tract[22]; it also occurred in liver slices.[23]

TRYPTOPHAN CONVERSION

The mechanism of conversion of tryptophan to niacin was elucidated to a large extent by studies in mutant fungi.[24] Intermediates in this conversion in neurospora were found to be kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid. Henderson[25] found that administration of tryptophan or 3-hydroxyanthranilic acid to rats led to an increase in quinolinic acid excretion. He hypothesized that this substance was an intermediate in the conversion of tryptophan to niacin. However, the activity of quinolinic acid on a molar basis was found to be much lower than that of niacin or 3-hydroxyanthranilic acid. Accordingly, Krehl, Bonner and Yanofsky[26] suggested that quinolinic acid might be an alternate end product (Fig. 1). In human subjects, oral administration of quinolinic acid led to an increased excretion

of niacin metabolites but to a less extent than might have been anticipated, had it been in the main pathway of conversion of tryptophan to niacin.[19]

Heidelberger and associates[27] proved conclusively by isotope experiments that tryptophan was converted to niacin in the rat. They showed that carbon atom 3 in the indole ring of tryptophan became the carboxyl carbon atom of nicotinic acid. Henderson and Hankes[28] studied the metabolic fate of tryptophan labeled with C^{14} in the benzine ring or in the α carbon atom in adult rats. With ring-labeled tryptophan, the distribution of C^{14} in the quinolinic acid excreted in the urine was in good agreement with theoretical values for conversion through the sequence: kynurenine, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid. Urinary N^1-Me had a specific activity which suggested a 5-fold dilution with body pools of tryptophan, pyridine nucleotides and other precursors.

Another feature of the conversion of tryptophan to niacin is of interest. Pyridoxal phosphate functions as a coenzyme with kynureninase in the conversion of 3-hydroxykynurenine to 3-hydroxyanthranilic acid.[29] In vitamin B_6 deficiency, kynurenine is diverted from this pathway to the formation of xanthurenic acid. Snyderman and associates[30] reported impairment in the conversion of tryptophan to niacin compounds in experimentally induced vitamin B_6 deficiency in infants.

Studies of the extent of conversion of tryptophan to niacin in man have been dependent on measurement of urinary excretion of niacin derivatives after tryptophan administration. The principal niacin metabolites in human urine are N^1-methylnicotinamide (N^1-Me)[31] and N-methyl-2-pyridone-5-carboxamide (pyridone).[32] Administration of tryptophan leads to an increase in excretion of N^1-Me[14-17] and pyridone[33] that is roughly proportionate to the size of the dose.[16, 34] There is also an increase in quinolinic acid excretion.[17, 19] Price and associates[35] reported that the chief urinary metabolites of tryptophan in man are kynurenine, kynurenic acid and o-amino hippuric acid. Xanthurenic acid, acetylkynurenine and anthranilic acid glucuronide were relatively minor metabolites. Pyridone was excreted to the extent of 0.8 per cent of a single oral dose of 2 g of L-tryptophan.

Experiments were conducted in our laboratory[36] in 14 adult subjects on controlled diets, either high or low in niacin and tryptophan, and supplemented at intervals with 2 to 6 g of DL-tryptophan for periods of 10 days or more (1 subject received 1 g of L-tryptophan). The following percentages of administered tryptophan were excreted as metabolites: 0.4 per cent as N^1-Me, 1.5 per cent as pyridone and 0.4 per cent as quinolinic acid. In these studies, it was assumed that D-tryptophan was not converted to niacin compounds. Considerable evidence supports this assumption[17, 34] but it has not been proved.[37] The excretion of niacin metabolites after administration of 10 to 30 mg of niacinamide was also measured in these subjects. From these data, the per cent conversion of tryptophan to niacin on a molar basis was estimated. Conversion averaged 3.3 per cent with a range of 1.9 to 5.0 per cent. The amount of dietary tryptophan which appeared to be equivalent to 1 mg of niacin averaged 55.8 mg with a range of 33.7 to 86.3 mg. Horwitt and associates[38] estimated the quantity of tryptophan converted to niacin in several groups of subjects maintained for months on diets low in niacin and tryptophan. One group received a supplement of 100 mg L-tryptophan, another a supplement of 10 mg of niacin and two groups were unsupplemented. Calculation of the amount of tryptophan equivalent to 1 mg of niacin from urinary excretion of N^1-Me, for two weeks of these regimens, gave figures of 52 and 65 mg. During the study, one group of subjects received a supplement of 3 g of lactalbumin which furnished about 200 mg of tryptophan. Findings in this group indicated that approximately 60 mg of the tryptophan provided in lactalbumin was equivalent to 1 mg of niacin. The findings of Goldsmith and Horwitt in subjects receiving diets which varied greatly in tryptophan and niacin content agree remarkably well. Accordingly, it seems justifiable for practical purposes to assume a factor of

60 to 1 for estimation of the efficacy of dietary tryptophan as a niacin precursor.

HUMAN REQUIREMENTS OF TRYPTOPHAN

Prior to the discovery that tryptophan was converted to niacin compounds, it had not been possible to determine the human requirement of this vitamin. Dann[39] estimated from a review of evidence obtained in dietary surveys that the minimum requirement of niacin for a 70 kg man was probably less than 10 mg. Frazier and Friedemann[8] calculated the protein and niacin content of pellagra-producing and pellagra-preventive diets and concluded that with a marginal diet containing corn products, the minimal niacin intake which would prevent pellagra approximated 7.5 mg daily. On a diet without corn, or one containing corn which was made adequate in some respects by the addition of large quantities of milk or milk products, the minimum need appeared to be about 4 mg daily.

After it was found that tryptophan was a precursor of niacin in man, experiments were initiated in our laboratory to determine niacin requirement and to elucidate the role of corn diets in the production of pellagra. Estimation of minimum tryptophan requirement by Rose[40] made possible formulation of diets containing little tryptophan in excess of that needed for maintenance of nitrogen balance. Diets were devised which were low in niacin and tryptophan and contained either corn or wheat as the principal cereal. A total of 19 long-term studies have been conducted in 15 adult human subjects, twelve females and three males.[33b,41] Niacin deficiency was induced in 15 of these experiments, the first signs appearing after one to several months. In 10 subjects deficiency was severe, in five it was mild. Practically all of the clinical features of pellagra were noted during the course of these studies although some subjects showed few or minimal lesions. Although the diets were supplemented with B vitamins other than niacin, cheilosis, angular fissures and nasolabial seborrhea were observed occasionally and healed after niacin administration. Twelve of the subjects who developed deficiency received diets in which corn was the principal cereal, three, diets in which wheat was substituted for corn. Deficiency tended to develop more rapidly and to be more severe with the corn than with the wheat diets; deficiency was less readily induced in males than in females.

The diets which resulted in niacin deficiency furnished 3.4 to 5.4 mg of niacin and 151 to 207 mg of tryptophan daily (Table I). Assuming that 60 mg of tryptophan is equivalent to 1 mg of niacin, the total niacin furnished by these pellagra-producing diets, or the "niacin equivalent" of the diets, ranged from 5.9 to 8.8 mg. The "niacin equivalent" of the diets in four subjects who failed to develop deficiency ranged from 7.4 to 10.6 mg.

Horwitt and associates[33] also conducted studies designed to determine human niacin requirement. The diets used by this group provided 5.2 to 7.0 mg of niacin and 238 to 318 mg of tryptophan. The diets contained no corn although 6 g of zein was included. Fifteen subjects received these diets for from 38 to 87 weeks without developing any clinical evidence of pellagra. Calculation of the total niacin furnished by these diets, including that potentially formed from tryptophan, gives a range of 9.2 to 12.3 mg (Table I).

From these data the minimal niacin required appeared to be in the neighborhood of 9 mg daily. However, calculation of the "niacin equivalent" of the diets used by Goldberger in the production of pellagra gives a total of 12.2 mg, if the tryptophan content of the diet is estimated as 330 mg.[38] Goldberger's diet furnished about 3,000 cal, while diets used by Horwitt supplied 2,070 to 2,760 cal and those of Goldsmith, 1,325 to 2,150 cal. These findings suggest that niacin requirement is related to caloric intake. Horwitt[33] concluded from an analysis of available data that the minimal amount of niacin which would prevent pellagra, including that formed from tryptophan and assuming a conversion figure of 60 to 1, was 4.4 mg/1,000 cal except with diets which supplied less than 2,000 cal in which instance 8.8 mg was required (Table I).

Goldsmith and associates[41] noted a relationship between niacin requirement and body size (Table I). Of twelve subjects who

TABLE I

Niacin and Tryptophan Intake in Relation to Experimental Production of Niacin Deficiency

Investigator	Number subjects	Niacin deficiency	Niacin in diet mg	Tryptophan in diet mg	Niacin equivalent* of diet mg	NE/* 1,000 cal mg	NE*/kg of body weight mg
Goldsmith	10	Severe	4.1–5.4	151–197	6.6–8.6	3.7–4.9†	0.11–0.18‡
Goldsmith	5	Mild	3.4–5.4	152–207	5.9–8.8	4.3–4.9†	0.12–0.20
Goldsmith	4	None	4.2–5.4	193–264	7.4–10.6	4.0–5.4	0.13–0.19§
Horwitt	15	None	5.2–7.0	238–318	9.2–12.3	4.4	0.15–0.21
Goldberger	11	Present in 6	6.7	330 (estimated)	12.2	4.1	0.14–0.22

* Niacin equivalent = dietary niacin plus 1/60 of dietary tryptophan.

† Subjects with ratios of 4.4 or above received less than 2,000 cal(1,600 to 1,900).

‡ Only one subject received more than 0.14 mg/kg.

§ Only one subject received less than 0.16 mg/kg.

received less than 0.15 mg "niacin equivalent" per kg of body weight, nine developed severe and two mild niacin deficiency, while one showed no abnormal findings. Of seven subjects who received 0.15 mg to 0.20 mg "niacin equivalent" per kilogram, three showed no evidence of deficiency, three mild deficiency and only one severe deficiency. Horwitt's fifteen subjects received 0.15 to 0.21 mg niacin equivalent per kilogram of body weight per day and none became deficient.

In other studies of Goldsmith and associates,[41a] subjects were given corn diets which supplied 200 mg of tryptophan and supplements of niacinamide were added in increasing or decreasing amounts. A significant change in the percentage of dietary niacin excreted in the urine as metabolites was observed when the niacin content of the diet approached 8 to 10 mg daily, suggesting that this level of niacin intake might be considered adequate. If it is assumed again that 60 mg of tryptophan will supply 1 mg of niacin, the "niacin equivalent" of these diets was about 11 to 13 mg.

Only one study of niacin requirement has been conducted in infants and none in children. Holt[42] maintained infants on a synthetic diet free of niacin and found that requirements were met, as judged by excretion of N^1-Me, when 15 per cent of the calories was supplied by casein. If the casein content of the diet was reduced to 10 per cent of the calories, excretion of N^1-Me decreased to a minimal value. The "niacin equivalent" of the 15 per cent casein diet, calculated as described above, would be 6 mg, that of the low-casein diet 4 mg.

"Niacin equivalents" have been calculated for some of the diets used by investigators in inducing pellagra prior to implication of niacin or tryptophan in the disease and also for diets used in testing the pellagra-preventive value of foods (Table II).[2,9] Values for

TABLE II

Niacin Equivalents of Pellagra-Producing and Pellagra-Preventive Diets

Pellagra-producing diets	Niacin equivalents
Unsupplemented	8.9–14 mg
Supplemented—preventive	10.4–22 mg
Supplemented—semipreventive	6.6–12 mg
Supplemented—not preventive	6.8–11 mg

"niacin equivalents" of the pellagra-producing diets of Goldberger, Ruffin and Smith, Spies, and Sydenstricker ranged from 8.9 to 14 mg daily. Such figures are presumably too high as no allowance was made for loss of nutrients in food preparation. Furthermore, available data on the tryptophan content of many foods are meager and average values are often based on widely varying analytic figures.[43] It is of interest to note that most investigators observed recovery of some subjects on these pellagra-producing diets.[2,9] Calculations of

the "niacin equivalent" of Goldberger's diets which were supplemented with certain foods and found to be pellagra-preventive[2] give values of 10.4 to 22 mg. Diets with supplements which were found to be semi-preventive furnished about 6.6 to 12 mg "niacin equivalent." Diets with supplementary foods which failed to prevent pellagra furnished 6.8 to 11 mg "niacin equivalent." Dietary data in a study of niacin requirement by Briggs, Singal and Sydenstricker[44] were also used for calculation of "niacin equivalent." Two subjects with signs of mild niacin deficiency were observed for 9 and 42 weeks without progression of lesions. These diets furnished about 9.3 and 8.0 mg of "niacin equivalent," respectively. In view of the inaccuracy of dietary calculations, there is remarkable agreement of these data with recent findings of Goldsmith and Horwitt.

OTHER FACTORS

From these studies of niacin-tryptophan relationships and niacin requirement, it is apparent that the pellagragenic effect of corn diets may be explained in large part by low niacin and tryptophan content. Other factors may play a minor role, however. In 1951, Kodicek[45] reported the presence of "bound" niacin in corn which was unavailable to the rat unless the corn had been subjected to alkaline hydrolysis. Laguna and Carpenter[46] noted that the growth depression in rats induced by high corn diets could be diminished by treatment of corn with lime. It has been suggested that release of "bound" niacin from corn by lime treatment, prior to incorporation in the diet, may explain the relatively low incidence of pellagra in areas such as Central America in which corn is prepared in this manner. In the only clinical study in which this hypothesis has been tested, experimental pellagra was produced as readily with lime-treated as with untreated corn.[41b] In this study, corn products furnished only 15 to 20 per cent of the diet whereas in Central America, corn products supply about 80 per cent of the caloric intake. Lime treatment might have an influence in the latter situation but this has not been investigated. Other explanations for the low incidence of pellagra in areas where corn is treated with lime should be considered, particularly the niacin and tryptophan furnished by the remainder of the diet. A recent study in our laboratory[34] indicates that coffee contributes a significant amount of niacin to the diet, yet ingestion of this beverage has never been considered in evaluating dietary niacin intake. A cup of coffee may furnish 1 to 3 mg of niacin depending on darkness of roast, amount of coffee used and method of preparation.

Several other possibilities merit consideration in discussing the pellagragenic effect of corn. This cereal may contain some toxic or inhibitory factor, as noted by Wooley[47] in experiments in mice. Available data suggest that if this factor has a role in human pellagra, it must be a minor one. Amino acid imbalance has been shown to influence niacin-tryptophan metabolism in animal experiments.[48] Such imbalance in corn diets has not been excluded as a factor in the genesis of pellagra in man.

SUMMARY

Pellagra has been known to be associated with diets high in corn and low in animal protein since it was first described two centuries ago. Recent research had elucidated this relationship, clarified the etiology of pellagra and made possible the estimation of human niacin requirement. Niacin was shown to be the pellagra-preventive vitamin in 1937. Some years later, the amino acid, tryptophan, was found to be a precursor of niacin in many animal species and in man. Administration of tryptophan is followed by an increase in urinary excretion of niacin metabolites. Tryptophan, when given in large doses, is effective in the treatment of pellagra. The pathway of conversion of tryptophan to niacin was elucidated by studies in neurospora; intermediate substances were found to be kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid. Proof of a similar pathway of conversion in mammals was demonstrated by experiments with C^{14} labeled tryptophan.

Studies in normal adults have shown that an average of 3.3 per cent of administered

tryptophan is converted to niacin compounds. On a molar basis, approximately 60 mg of dietary tryptophan appears to be equivalent to 1 mg of niacin.

The minimum human requirement for niacin is about 9 to 12 mg daily in adults, including that formed from tryptophan. Requirement appears to be related to body size and to caloric intake. The close association of pellagra with diets high in corn can be explained in large part by the low niacin and tryptophan content of this cereal. Other factors may have a role in the pellagragenic effect of corn but appear to be of minor importance.

REFERENCES

1. Casal, Frapoli, Fanzaga and Marzari, quoted in Harris, H. F.: *Pellagra*. Macmillan, New York, 1919.
2. Casal and Roussel quoted in Frazier, E. I. and Friedemann, T. E.: Pellagra, a study in human nutrition. The multiple-factor principle of the determination of minimum vitamin requirements. *Quart. Bull. Northwestern Univ. M. School* 20: 24, 1946.
3. Funk, C.: *The Vitamins*. Williams and Wilkins, Baltimore, 1922.
4. Goldberger, J., Waring, C. H., and Willets, D. G.: The treatment and prevention of pellagra. *Pub. Health Rep.* 29: 2821, 1914.

5a. Goldberger, J. and Wheeler, G. A.: Experimental pellagra in the human subject brought about by a restricted diet. *Pub. Health Rep.* 30: 3336, 1915.

b. Goldberger, J. and Wheeler, G. A.: The experimental production of pellagra in human subjects by means of diet. *U. S. Hygiene Laboratory, Bull. No. 120*, Feb. 1920.

6. Goldberger, J. and Tanner, W. F.: Amino acid deficiency is probably the primary etiological factor in pellagra. *Pub. Health Rep.* 37: 462, 1922.

7a. Voegtlin, C.: Recent work on pellagra. *J.A.M.A.* 63: 1094, 1914.

b. Voegtlin, C.: The treatment of pellagra. *Pub. Health Rep.* 35: 1435, 1920.

8. Elvehjem, C. A., Madden, R. J., Strong, S. M., and Wooley, D. W.: Relation of nicotinic acid and nicotinic acid amide to canine black tongue. *J. Am. Chem. Soc.* 59: 1767, 1937.
9. Sydenstricker, V. P., Schmidt, H. L., Fulton, M. C., New, J. S., and Geeslin, L. E.: Treatment of pellagra with nicotinic acid. *South. M. J.* 31: 1155, 1938.
10. Schmidt, H. L., Jr. and Sydenstricker, V. P.: Nicotinic acid in the prevention of pellagra. *J.A.M.A.* 110: 2065, 1938.
11. Krehl, W. A., Teply, L. J., Sarma, P. S., and Elvehjem, C. A.: Growth retarding effect of corn in nicotinic acid low rations and its counteraction by tryptophan. *Science* 101: 487, 1945.
12. Rosen, F., Huff, J. W., and Perlzweig, W. A.: The effect of tryptophan on the synthesis of nicotinic acid in the rat. *J. Biol. Chem.* 163: 343, 1946.
13. Singal, S. A., Briggs, A. P., Sydenstricker, V. P., and Littlejohn, J. M.: The effect of tryptophan on the urinary excretion of nicotinic acid in rats. *J. Biol. Chem.* 166: 573, 1946.
14. Sarett, H. P. and Goldsmith, G. A.: The effect of tryptophan on the excretion of nicotinic acid derivatives in humans. *J. Biol. Chem.* 167: 293, 1947.
15. Perlzweig, W. A., Rosen, F., Levitas, N., and Robinson, J.: The excretion of nicotinic acid derivatives after ingestion of tryptophan by man. *J. Biol. Chem.* 167: 511, 1947.
16. Sarett, H. P. and Goldsmith, G. A.: Tryptophan and nicotinic acid studies in man. *J. Biol. Chem.* 177: 461, 1949.
17. Sarett, H. P. and Goldsmith, G. A.: Metabolism of L- and DL-tryptophan in normal man and in pellagrins. *J. Biol. Chem.* 182: 679, 1950.

18a. Vilter, R. W., Mueller, J. F., and Bean, W. B.: The therapeutic effect of tryptophan in human pellagra. *J. Lab. & Clin. Med.* 34: 409, 1949.

b. Bean, W. B., Franklin, M., and Daum, K.: A note on tryptophan and pellagrous glossitis. *J. Lab. & Clin. Med.* 38: 167, 1951.

19. Sarett, H. P.: Quinolinic acid excretion and metabolism in man. *J. Biol. Chem.* 193: 627, 1951.
20. Hundley, J. M.: Role of the gastrointestinal tract in the conversion of tryptophan to nicotinic acid. *Fed. Proc.* 8: 386, 1949.
21. Snyderman, S. E., Ketron, K. C., Carretero, R., and Holt, L. E., Jr.: Site of conversion of tryptophan into nicotinic acid in man. *Proc. Soc. Exper. Biol. & Med.* 70: 569, 1949.

22a. Henderson, L. M. and Hankes, L. V.: Effect of enterectomy on synthesis of niacin in the rat. *Proc. Soc. Exper. Biol. & Med.* 70: 26, 1949.

b. Hundley, J. M.: Influence of intestinal bacteria on synthesis of nicotinic acid from tryptophan. *Proc. Soc. Exper. Biol. & Med* 70: 592, 1949.

23. Hurt, W. W., Scheer, H. L., and Deuel, H. J.: The synthesis of niacin from tryptophan in rat liver slices. *Arch. Biochem.* 21: 87, 1949.

24a. Beadle, G. W., Mitchell, H. K., and Nye, J. F.: Kynurenine as an intermediate in the formation of nicotinic acid from tryptophan by neurospora. *Proc. Nat. Acad. Sc.* 33: 155, 1947.

b. Bonner, D. M.: The identification of a natural precursor of nicotinic acid. *Proc. Nat. Acad. Sc.* 34: 5, 1948.

c. MITCHELL, H. K. and NYC, J. F.: Hydroxyanthranilic acid as a precursor of nicotinic acid in neurospora. *Proc. Nat. Acad. Sc.* 34: 1, 1948.

25. HENDERSON, L. M.: Quinolinic acid excretion by the rat receiving tryptophan. *J. Biol. Chem.* 178: 1003, 1949.

26. KEHL, W. A., BONNER, D., and YANOFSKY, C.: Utilization of niacin precursors and derivatives by the rat and neurospora. *J. Nutrition* 41: 159, 1950.

27a. HEIDELBERGER, C., GULLBERG, M. E., MORGAN, A. F., and LEPKOVSKY, S.: Tryptophan metabolism. I. Concerning the mechanism of the mammalian conversion of tryptophan into kynurenine, kynurenic acid and nicotinic acid. *J. Biol. Chem.* 179: 143, 1949.

b. HEIDELBERGER, C., ABRAHAM, E. P., and LEPKOVSKY, S.: Tryptophan metabolism. II. Concerning the mechanism of the mammalian conversion of tryptophan into nicotinic acid. *J. Biol. Chem.* 179: 151, 1949.

28. HENDERSON, L. M. and HANKES, L. V.: The metabolism of DL-tryptophan-3a, 7a, 7-C^{14} and DL-tryptophan α C^{14} in the rat. *J. Biol. Chem.* 222: 1009, 1956.

29. Liver kynureninase activity and tryptophan metabolism in vitamin B_6 deficiency. *Nutrition Rev.* 11: 278, 1953

30. SNYDERMAN, S. E., HOLT, L. E., JR., CARRETERO, R., and JACOBS, K.: Pyridoxine deficiency in the human infant. J. CLIN. NUTRITION 1: 200, 1953.

31a. NAJJAR, V. A and HOLT, L. E., JR.: The excretion of specific fluorescent substances in the urine in pellagra. *Science* 93: 20, 1941.

b. HUFF, J. W. and PERLZWEIG, W. A.: N^1-methylnicotinamide, a metabolite of nicotinic acid in the urine *J. Biol. Chem.* 150: 395, 1943.

32. KNOX, W. E. and GROSSMAN, W. I.: A new metabolite of nicotinamide. *J. Biol. Chem.* 166: 391, 1946.

33a. HOLMAN, W. I. M. and DE LANGE, D. J.: Role of tryptophan and other amino acids in the metabolism of nicotinic acid by humans. *Nature* (London) 166: 468, 1950.

b. GOLDSMITH, G. A., SARETT, H. P., REGISTER, U. D., and GIBBENS, J.: Studies of niacin requirement in man. I. Experimental pellagra in subjects on corn diets low in niacin and tryptophan. *J. Clin. Investigation* 31: 533, 1952.

34. GOLDSMITH, G. A.: Unpublished data.

35. PRICE, J. M., BROWN, R. R., and ELLIS, M. E.: Quantitative studies of the urinary excretion of tryptophan metabolites by humans ingesting a constant diet. *J. Nutrition* 60: 323, 1956.

36. GOLDSMITH, G. A., MILLER, O. N., and UNGLAUB, W. G.: Efficiency of tryptophan as a niacin precursor. *Fed. Proc.* 15: 553, 1956.

37. PRICE, J. M. and BROWN, R. R.: Quantitative studies on human urinary metabolites of D-, DL-, acetyl-L and acetyl-D-tryptophan. *J. Biol. Chem.* 222: 835, 1956.

38. HORWITT, M. K., HARVEY, C. C., ROTHWELL, W. S., CUTLER, J. L., and HAFFRON, D.: Tryptophan-niacin relationships in man. *J. Nutrition* 60: Suppl. 1, October, 1956.

39. DANN, W. J.: The human requirement for nicotinic acid. *Fed. Proc.* 3: 159, 1944.

40. ROSE, W. C.: Amino acid requirements of man. *Fed. Proc.* 8: 546, 1949.

41a. GOLDSMITH, G. A., ROSENTHAL, H. L., GIBBENS, J., and UNGLAUB, W. G.: Studies of niacin requirement in man. II. Requirement on wheat and corn diets low in tryptophan. *J. Nutrition* 56: 371, 1955.

b. GOLDSMITH, G. A., GIBBENS, J., UNGLAUB, W. G., and MILLER, O. N.: Studies of niacin requirement in man. III. Comparative effects of diets containing lime-treated and untreated corn in the production of experimental pellagra. AM. J. CLIN. NUTRITION 4: 151, 1956.

c. GOLDSMITH, G. A.: Experimental niacin deficiency. *J. Am. Dietet. A.* 32: 312, 1956.

42. HOLT, L. E., JR.: The adolescence of nutrition. *Arch. Dis. Childhood* 31: 427, 1956.

43. ORR, M. L. and WATT, B. K.: Amino acid content of foods. *Home Economics Report No. 4.* U. S. Dept. Agriculture, Washington, D. C., 1957.

44. BRIGGS, A. P., SINGAL, S. A., and SYDENSTRICKER, V. P.: A study of nicotinic acid restriction in man. *J. Nutrition* 29: 331, 1945.

45. KODICEK, E.: The biological activity for the rat of the bound form of nicotinic acid present in maize. *Biochem. J.* 48: VIII, 1951.

46. LAGUNA, J. and CARPENTER, K. J.: Raw versus processed corn in niacin-deficient diets. *J. Nutrition* 45: 21, 1951.

47. WOOLEY, D. W.: The occurrence of a "pellagragenic" agent in corn. *J. Biol. Chem.* 163: 773, 1946.

48. Amino acid imbalance. *Nutrition Rev.* 10: 135, 1952.

J. Am. Med. Assoc. 194(2):167-173. 1965.

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Goldberger Award

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Niacin: Antipellagra Factor, Hypocholesterolemic Agent

Model of Nutrition Research Yesterday and Today

Grace A. Goldsmith, MD

Niacin, the antipellagra factor, which was found recently to be a hypocholesterolemic agent, serves well as a prototype of the trends in nutrition research in the present century. When Joseph Goldberger initiated his studies of the etiology of pellagra in 1914,[1-3] the concept that disease could be due to deficiency of a nutritional factor was relatively new and had not gained wide acceptance. His brilliant epidemiological studies, culminating in the experimental production of pellagra in a group of prisoners by dietary restriction, proved that pellagra was due to nutritional deficiency.[4-6] Search for the missing dietary factor required more than 20 years. Goldberger[7] participated in this search and suggested at one time that amino acid deficiency might be involved but later concluded that vitamin deficiency was probably responsible.

Nutrition research during the 25 years following Goldberger's early work was directed primarily toward determination of essential dietary substances for animals and man and delineation of the deficiency syndromes resulting from an inadequate supply of essential nutrients, particularly vitamins. The clinical and pathological changes in deficiency states were described, and, in the latter part of this period, attention was directed toward elucidation of the role of nutrients in metabolism. This evolution of nutrition research is illustrated by investigations leading to discovery of the antipellagra factor[8] (Table 1). A dietary-deficiency disease, known as blacktongue, that appeared to be the canine analogue of human pellagra, was produced in dogs. This experimental approach, used with other nutrients also, was of great assistance in the search for pellagra-preventive vitamin. In 1935, niacinamide was found to be a part of two coenzymes, one obtained from erythrocytes, triphosphopyridine nucleotide, and the other, a substance needed for the alcoholic fermentation of carbohydrate by yeast, diphosphopyridine nucleotide. Niacinamide was isolated from heart muscle and then from liver by Elvehjem and associates.[9,10] These workers administered niacin and its amide to dogs with blacktongue and found that it cured the disease. Shortly after this, niacin was administered to patients with pellagra by a number of investigators and shown to be therapeutically effective.

Table 1.—Highlights in Niacin Research, 1915-1940
Pellagra—A deficiency disease
Blacktongue in dogs—Canine pellagra
Niacin—A coenzyme and tissue constituent
Niacin—The antipellagra factor

The remarkable advances in biochemistry, particularly since 1940, were applied widely in nutrition research and made possible delineation of the exact role of many nutrients at the cellular and molecular levels. The use of radioisotopes permitted tracing of the metabolic pathways of nutrients from ingestion through utilization to breakdown and excretion. The requirements of a number of nutrients, especially vitamins, were determined. Niacin may again be utilized to illustrate these trends in research.

Our interest in niacin began in the early 1940's after this vitamin had been shown to be the antipellagra factor and when methods were being developed to assay some of the urinary exception products of niacin metabolism. At this time, it was thought that the problem of the etiology of pellagra had been solved completely. However, further studies uncovered findings that could not be explained satisfactorily. Diets in some parts of the world in which pellagra was not encountered contained less niacin than did corn diets which were associated with pellagra. Furthermore, certain pellagra-preventive foods, such as milk, were low in niacin. Investigations at the University of Wisconsin assisted in solving the problem. Krehl and as-

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sociates[11] observed that when rats were fed diets containing 40% corn, there was cessation of growth. Administration of either niacin or tryptophan restored growth to normal. The rationale for tryptophan administration was that one of the proteins in corn, zein, is low in this amino acid. Shortly after this, Rosen and associates[12] found that administration of tryptophan to rats led to a marked increase in the urinary excretion of the niacin metabolite, N¹-methyl nicotinamide (N¹-Me). The findings suggested that tryptophan might be a precursor of niacin (Table 2).

About this time we initiated studies in human subjects and found that the administration of tryptophan led to an increase in excretion of N¹-Me in the urine.[13] Similar findings were reported by Perlzweig and associates.[14] Subsequently, Vilter et al[15] and our group found that the administration of tryptophan in large amounts was effective in the treatment of pellagra. It appeared likely

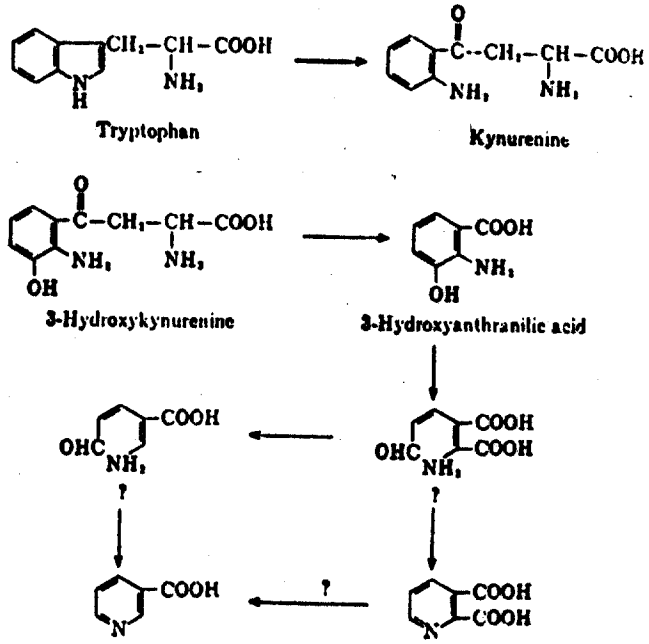
Table 2.—Highlights in Niacin Research, 1940-1955

Tryptophan—A niacin precursor
Human Niacin Requirement—4.4 mg/1,000 calories
Corn diets—Relationship to pellagra
Methods for evaluation of niacin nutrition
Metabolic functions of niacin

that tryptophan was converted in the body to niacin. Studies of many investigators using neurospora and several animal species elucidated the pathway of this conversion[8] (Fig 1).

At one time it was suggested that tryptophan might catalyze the synthesis of niacin by intestinal bacteria rather than being converted to niacin in the tissues. However, it was shown that in the enterectemized rat the administration of tryptophan was followed by an increased urinary excretion of niacin compounds. In human subjects we found that the conversion of tryptophan to niacin was not affected by oral administration of streptomycin in amounts that largely inhibited the growth of intestinal microorganisms. Finally, the conversion of tryptophan to niacin was demonstrated unequivocally by several groups of investigators using radioisotope techniques.[8] Administration of tryptophan labeled with radioactive carbon (^{14}C) was followed by recovery of niacin in the urine with the isotope in the carboxyl group. When the indole nucleus of tryptophan was labeled with tritium, the label appeared in the ring nitrogen of niacin derivatives in the urine. The conversion of tryptophan to niacin is a rather inefficient process. Data obtained in human subjects by Horwitt et al[16] and in our laboratory[17] indicated that an average of about 60 mg of tryptophan can be converted to 1 mg of niacin. Thus, two centuries after pellagra was first described by Casal in Spain, this disease was shown to be due to deficiency of a vitamin, niacin, and its precursor, the amino acid tryptophan.

In the 1940's, proteins and their constituent amino acids became a prominent area of nutrition research. Rose[18] determined minimum requirements of amino acids in rats and in man. The estimation of minimum tryptophan requirement for the maintenance of nitrogen balance made possible the formulation of diets containing little excess tryptophan and set the stage for determination of human niacin requirements. With this objective, studies were initiated in our laboratory[19,20] and in that of Horwitt and associates.[16] In our studies, niacin deficiency was induced in 15 of 19



1. Pathway of conversion of tryptophan to niacin.

long-term experiments in adult human subjects. Practically all of the characteristic manifestations of pellagra were observed. The diets that resulted in pellagra furnished 3.4 to 5.4 mg of niacin and 151 to 207 mg of tryptophan daily. Twelve of the subjects who developed pellagra received diets containing corn as the principal cereal, whereas three received diets containing wheat. In Horwitt's studies, none of 15 subjects developed evidence of niacin deficiency. His diets provided 5.2 to 7.0 mg of niacin and 238 to 318 mg of tryptophan. The diets contained no corn, although 6 gm of zein was included. The potential total niacin values of the diets furnished by Goldsmith and Horwitt and their associates can be calculated by assuming that approximately 60 mg of tryptophan is equivalent to 1 mg of niacin. Such calculations showed that diets that resulted in experimental pellagra furnished 5.9 to 8.8 mg of niacin equivalent, whereas the diets that did not induce deficiency furnished 9.2 to 12.3 mg. From these data, minimum niacin requirement for the prevention of pellagra appeared to be about 9 mg/day.

Calculation of the niacin equivalent of the diets used by Goldberger and Wheeler in 1915 in the production of pellagra indicated a value of about

12 mg. The caloric intake of Goldberger's diet was much higher than that of diets used by Horwitt or Goldsmith. Horwitt[16] analyzed all data available and concluded that the minimum amount of niacin that would prevent pellagra, including that formed from tryptophan and assuming a conversion factor of 60 to 1, was 4.4 mg/1,000 calories, except at low levels of caloric intake, when at least 8.8 mg was required.

Pellagragenic Effect of Corn.—Other studies in our laboratory, with diets containing a constant amount of tryptophan (200 mg) and varying amounts of niacin, indicated a significant change in the percentage of dietary niacin excreted in the urine as metabolites when the niacin content of the diet approached 8 to 10 mg daily.[21] Assuming that 60 mg of tryptophan will supply 1 mg of niacin, the total niacin furnished by these diets was 11 to 13 mg. These and other studies of niacin-tryptophan relationships and niacin requirement indicate that the pellagragenic effect of corn diets may be explained in large part by the low niacin and tryptophan content of corn. They also illustrate an area of interest in nutrition research in recent years, namely, interrelationships among nutrients. Another illustration of such interrelationships was the development of angular stomatitis and cheilosis in our subjects in whom experimental pellagra was induced. These findings are usually attributed to riboflavin deficiency. The diet contained adequate riboflavin, and the signs disappeared when niacin or tryptophan was administered.

Factors other than the niacin and tryptophan content of corn may play a role in the pellagragenic effect of this cereal. Most of the niacin in corn has been shown to be present in bound form which is unavailable to the experimental animal.[8] It can be made available by treatment with alkali. It was suggested that treatment of corn with lime, a practice common in Central America, might be a partial explanation for the relatively low incidence of pellagra in this area, in which corn supplies about 80% of the caloric value of the diet. Experiments in our laboratory indicated that pellagra could be produced as readily with lime-treated as with untreated corn.[22] However, corn products furnished only 15% to 20% of the caloric intake. In the process of treating corn with lime in Central America, there is an overall loss of niacin of about 20%. If release of bound niacin is responsible for a pellagra-preventive effect of lime-treated corn, the amount of niacin made available must be large enough to more than compensate for the overall loss. This might be the case.

Amino acid imbalance has been suggested as another factor in the relationship of corn diets to pellagra. Corn has a high leucine content as has another cereal, jowar (Indian millet). Gopolan and Srikantia[23] reported that administration of leucine caused an increase in the urinary excretion of N¹-Me. They suggested that excess leucine caused amino acid imbalance which resulted in loss of niacin from the tissues. Studies in our laboratory failed to confirm these findings.[24]

For many years it was thought that corn contained a toxic or inhibitory factor. Woolley[25] concluded from experiments in mice that such a substance was present in corn. In our investigations, we found that pellagra seemed to develop more rapidly and to be more severe with corn than with wheat diets of similar niacin and tryptophan content.[19-22] In addition, pellagra was induced more rapidly with whole corn than with degerminated corn. These findings might be explained by the presence of some inhibitory substance in corn, particularly in the bran and germ layers, which affects requirement or utilization of niacin. However, there are other possible explanations for the findings. If an inhibitory factor is present in corn, it appears to have a minor role in the development of human pellagra.

Methods for the evaluation of niacin nutrition by estimation of urinary excretion of niacin metabolites have been developed through studies of normal subjects and of patients with experimental and endemic pellagra. The two principal metabolites of niacin found in the urine are N¹-Me and the 6-pyridone of N¹-Me. In pellagra the combined excretion of these two metabolites in the urine is usually less than 2 mg in 24 hours. In mild deficiency, slightly larger quantities are excreted. Normal subjects receiving good diets excrete in the neighborhood of 5 to 8 mg of N¹-Me and 7 to 10 mg or more of pyridone daily.

Functions of Niacin.—The functions of niacin have been widely studied in recent years. Niacin or one of its derivatives is required by all living cells. It is an essential component of two coenzymes, diphosphopyridine nucleotide or coenzyme I (niacine adenine dinucleotide [NAD]) and triphosphopyridine nucleotide or coenzyme II (niacine adenine dinucleotide phosphate [NADP]). More than 40 biochemical reactions dependent on these enzymes have been identified. The major function of NAD and NADP is the removal of hydrogen from certain substrates in cooperation with dehydrogenases and the transfer of hydrogen or electrons to another coenzyme in the hydrogen-transport series or to another substrate which is correspondingly reduced.

The many reactions in which NAD and NADP are involved include glycolysis, pyruvate metabolism, pentose biosynthesis, and the process by which high-energy phosphate bonds are synthesized. They also function in lipid, amino acid, and protein metabolism and in photosynthesis. The exact reactions and mechanisms involved in many of these complex systems remain unknown.

Niacin Deficiency in Various Disease States.—In recent years, the effects of various diseases and of chemotherapeutic agents on the nutritional status of the patient has received increased attention (Table 3). Nutritional deficiency may occur as a complication of pathological states in which food

intake is restricted, in which there is interference with absorption or utilization of nutrients, or in which nutrient requirements are increased. Most of the pellagra in the United States at the present time occurs in association with chronic alcoholism. It may be encountered also in patients with cirrhosis of the liver, chronic diarrheal diseases, diabetes mellitus, neoplasia, prolonged febrile illnesses, and thyrotoxicosis or after parenteral feeding without niacin supplementations. Signs of lack of niacin have been reported in patients with malignant carcinoid tumors. In this instance, as much as 60% of the body's tryptophan may be converted to 5-hydroxytryptamine instead of a normal 1%. This may result in less tryptophan being available for synthesis of niacin.

Modern methods of therapy occasionally lead to the development of deficiency states. Pellagra has occasionally been observed during therapy with isonicotinic acid hydrazide which is a pyridoxine (vitamin B_6) antagonist and may cause pyridoxine deficiency. Pyridoxine is needed in one of the steps of the conversion of tryptophan to niacin and in severe deficiency this conversion may be curtailed.

Nutrition research has become concerned with inborn errors of metabolism. An hereditary disease characterized by a pellagra-like skin rash, severe but reversible cerebellar ataxia, and psychological disturbances has been described in families and termed Hartnup disease. Gross aminoaciduria of renal origin and abnormalities of tryptophan metabolism are characteristic. It has been suggested that there is defective transport of tryptophan across the cells of the jejunum and proximal renal tubules. Tryptophan is found in the feces, which is not the case in normal subjects. Kynurenine excretion in the urine is decreased. Presumably there is a decrease in the conversion of tryptophan to formylkynurenine. This would result in a decrease in the conversion of tryptophan to niacin. Niacin will relieve the pellagra-like symptoms of this disease.

Dietary Factors and Atherosclerosis.—Currently, there is wide interest in the role of nutrition in diseases that are not considered to be primarily nutritional in origin. Extensive investigation has indicated a relationship between a number of dietary factors and the development of atherosclerosis. Fats have received particular attention, but proteins, carbohydrates, vitamins, and minerals have been implicated as well. Some years ago, a causal relationship was postulated between dietary fat, serum cholesterol concentrations, and atherosclerosis on the basis of epidemiologic and clinical studies in man and investigations in several animal species. Many dietary manipulations, including changes in the amount and kind of dietary fat, have been shown to influence the levels of cholesterol and other lipids in the serum, but the role that serum lipids play in atherogenesis is still uncertain.

Effects of Niacin on Cholesterol Level.—Many pharmacological agents have been shown to influence serum lipid concentrations, among them niacin. In 1955, Altschul first observed that the administration of large doses of niacin lowered serum cholesterol levels in human subjects. Administration of the niacinamide was without effect. This observation was confirmed by Parsons et al and by investigations in our laboratory.[27,28] Our interests have been centered primarily on elucidation of mechanisms that control serum lipid concentrations and determination of the mode of action of various dietary factors and pharmacological agents. Serum lipids can be reduced by (1) decreasing the quantities supplied by the diet, (2) limiting absorption, (3) inhibiting tissue synthesis, (4) increasing degradation or excretion, or (5) affecting lipid transport or distribution with an increase in tissue lipids at the expense of those in the circulating blood. The concentration of serum cholesterol is known to be the result of the amount ingested and absorbed, plus the amount synthesized in the body, as related to the amount excreted in the bile as cholesterol or bile acids (to which cholesterol is degraded) and the amount utilized or stored in the tissues. Some of the bile acids and cholesterol are reabsorbed from the intestine and act as a feed-back mechanism influencing the amount of cholesterol synthesized and degraded. Details of the feed-back mechanism are being gradually elucidated.

Table 3.—Highlights in Niacin Research, 1955-1965
Niacin deficiency induced by disease
Niacin deficiency induced by drugs
Hereditary niacin—Tryptophan abnormalities
Niacin—A hypocholesterolemic agent

Niacin in large doses, 3 to 6 gm daily, causes a reduction in the concentrations in serum of cholesterol, both free and esterified fractions, triglycerides, and, to a lesser extent, phospholipids. In our investigations of the mechanism of action of niacin, the first hypothesis was that it might increase fecal excretion of lipids. Subjects were placed in a metabolism ward on controlled diets, high in saturated or unsaturated fat, and niacin was administered. Fecal excretion of fats, sterols, and bile acids was determined. Niacin was found to have no effect on excretion of these compounds. Subsequent studies showed that the action of niacin was not related to depletion of methyl groups in the body. Administration of methionine with niacin had no influence on its action in lowering serum lipid levels. Since both methionine and choline influence lipid transport, these data suggested that niacin did not influence lipid transport indirectly through methionine.

It appeared possible that the action of niacin might be related to an increased demand for the production of aminoacetic acid (glycine). Niacin is conjugated with aminoacetic acid to form nicotinuric acid, which is a major excretory product

The same type of condensation occurs in the case of bile acids which are excreted in conjugated form. Niacin might compete with bile acids for aminoacetic acid. To test this possibility, sodium benzoate, which also requires aminoacetic acid for detoxification, was administered to human subjects, being substituted for equimolar amounts of niacin. It was not effective in lowering serum lipid levels. In other studies, when niacin was given in association with diets high in unsaturated fat as compared with those high in saturated fat, smaller amounts of nicotinuric acid were excreted in the urine during the unsaturated-fat regimen. The excretion of methylated products of niacin was the same with both diets. Unsaturated fat may lower serum cholesterol in part by increasing the fecal excretion of sterols and bile acids,[29,30] although this remains controversial. The administration of unsaturated fat may have reduced formation of nicotinuric acid by the liver when bile acid excretion increased, as both substances require conjugation with aminoacetic acid. These data suggest a possible competition for aminoacetic acid. Although this does not explain the mechanism of action of niacin in lowering serum lipids, it might explain the retention of sulfobromophthalein (Bromsulphalein) that occurs in some patients receiving niacin. This substance also requires aminoacetic acid conjugation prior to excretion. When niacin is administered, large amounts of nicotinuric acid are excreted in the urine, whereas none is excreted when niacinamide is given. At one stage in our investigations, some data suggested that nicotinuric acid might be the metabolite of niacin responsible for lowering serum cholesterol concentration. Subsequent experiments failed to substantiate this hypothesis.

In experiments using rat-liver mitochondria, Kritchevsky and associates[31] reported that niacin caused an increased oxidation of cholesterol to bile acids by the liver and suggested this might be responsible for its hypocholesterolemic effect. This seems unlikely in view of our failure to find an increase in fecal excretion of bile acids. The most probable mechanism of action of niacin is an effect on the biosynthesis of cholesterol and perhaps of other lipids. It has been reported that liver slices from rats fed niacin converted more acetate ^{14}C to carbon dioxide and less to cholesterol and fatty acids than did liver slices from control rats.[32] Parson's studies in human subjects indicated that less acetate ^{14}C was converted to cholesterol when patients were receiving niacin. Studies in our laboratory showed that the decrease in total cholesterol esters during therapy with niacin was the result of proportionately equal lowering of cholesteryl linoleate, arachidonate, oleate, stearate, and palmitate.[28] This might be interpreted as indicative of a decreased synthesis of cholesterol, since the decrease in cholesterol esters resulting from administration of unsaturated fat or of neomycin did not result in proportionate lowering of cholesterol esters. If niacin inhibits cholesterol synthesis, the failure to find any other sterol in the serum of patients treated with niacin is consistent with the view that it inhibits the sequence of reactions prior to the cyclization of squalene to form lanosterol.

Studies in rabbits have shown that niacin therapy tends to protect against atherosclerosis or reduce its severity. Whether niacin has a similar influence in man remains unknown. Lipid deposits in the skin have disappeared in patients during niacin therapy.[26]

Niacin, when administered in large doses, has a number of side effects. These include cutaneous flushing, which may be severe but often disappears after a few weeks of therapy. The action of niacin in lowering serum lipids does not seem to be related to cutaneous vasodilatation, since the same effect is observed in the absence of the flush reaction. Niacin may cause gastrointestinal symptoms, dryness of the skin, and, in some instances, brown pigmentation. Hepatic dysfunction may be observed with impairment of sulfobromophthalein excretion, and an increase in alkaline phosphatase and glutamic-oxalacetic transaminase levels in serum, but histological findings on liver biopsy are usually normal. Prolonged use of niacin may occasionally result in histologic changes, including fibrosis and cholangiolitis. Glucose tolerance may decrease with niacin therapy, and there is a tendency for serum uric acid levels to rise slightly. Practically all of these findings are reversed rapidly when therapy is discontinued.

Effects of Neomycin Administration.—Another pharmacological agent that lowers serum lipid levels, neomycin, has been studied in our laboratory.[29,30] Neomycin was administered in amounts of 0.5 gm four times daily to subjects on controlled diets high in saturated or in polyunsaturated fat. When the diet was changed from saturated to unsaturated fat, a decrease in cholesterol, total esters, and phospholipids in serum was observed. In association with this decrease, we found an increase in the fecal excretion of bile acids and neutral sterols. There was also a change in the ratio of cholestane to coprostane compounds; the latter are indicative of the activity of the intestinal flora. The ratio changed from 1:8 when the diet furnished saturated fat to 1:4 when it furnished unsaturated fat. This decrease in conversion of cholestane to coprostane supported the thesis that the type of fatty acid furnished by the diet influenced the intestinal flora.

The administration of neomycin with either the saturated- or unsaturated-fat regimen caused a decrease in serum cholesterol concentration of 10% to 30%. This was accompanied by a several fold increase in fecal excretion of bile acids. The excretion of sterols was not increased, but only cholestane compounds were present in the feces. There was failure of conversion of cholic acid to desoxycholic acid. Neomycin has a profound effect on the intestinal flora but does not completely sterilize

the gut. In most instances, coliform organisms are absent or markedly reduced, as are other enteric organisms with the exception of enterococci and *Clostridium welchii*, which tend to become more abundant.[32] During neomycin administration, the taurine and glycine conjugates of bile acids are split to free acids. This action has been shown by Danielsson et al[34] to be carried out by clostridia. Cholic acid is usually the predominant bile acid found in the feces after oral administration of neomycin, but occasionally large amounts of 7-ketodesoxycholic acid are found. The conversion of cholic acid to this compound is accomplished by coliform organisms. The bacteria that convert cholesterol to coprosterol were inhibited by neomycin except in one instance. All samples have shown complete inhibition of the conversion of cholic acid to desoxycholic acid. The organism that converts cholic to desoxycholic acid has not been identified.

Little is known about the absorption of bile acids from the large intestine, but, since both lithocholic and desoxycholic acids have been shown to be formed by intestinal bacteria and both of these acids appear in significant amounts in the bile, absorption is obviously significant. It has been suggested that neomycin has its effect on serum lipids by causing a "malabsorption syndrome." In several studies in which large doses of neomycin (8 to 12 gm daily) were administered, this has been the case. In studies of Leveille et al[35] and in our laboratory,[33] fecal fat excretion increased slightly during administration of small doses of neomycin, ie, amounts up to 2 gm/day. The average in Leveille's series was a rise from 2.5 gm to 5.5 gm of fecal fat per day when 2 gm of neomycin was administered.

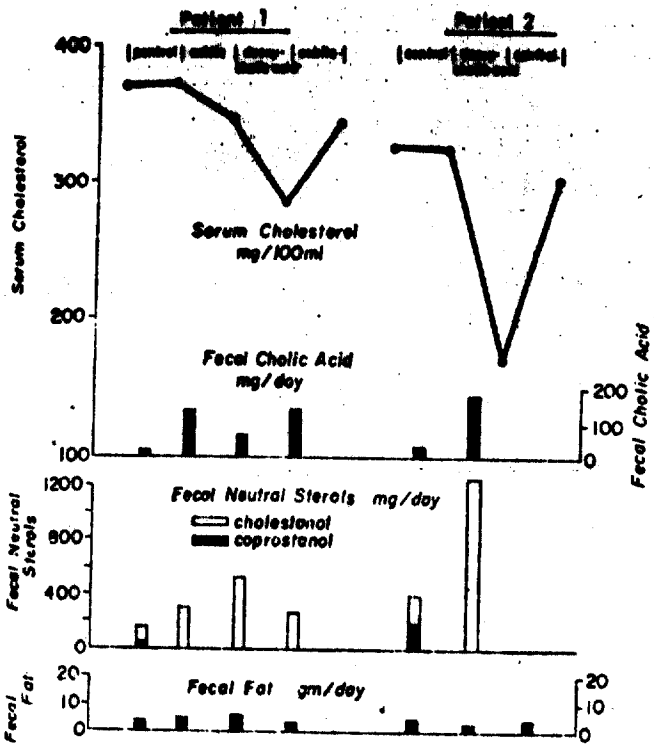
De Somer et al,[36] in a study of chicks, reported findings that support the hypothesis that basic substances such as neomycin interfere with intestinal absorption of fats, cholesterol, and bile acids by disturbing the emulsification of lipids in the intestine or by complexing bile acids. Although the mechanism by which neomycin lowers serum cholesterol is still the subject of some difference of opinion, findings in our studies and those of others indicate a reciprocal relationship between the amount of bile acids excreted and the level of serum cholesterol. This could be part of a mild "malabsorption syndrome," but such terminology is not very satisfactory. The malabsorption appears to be medically inconsequential, whereas the decrease in serum cholesterol is significant. The increase in fecal excretion of bile acids may be due to changes in the intestinal flora which in turn influence the structure of bile acids (and sterols), thus affecting their absorption. Cholesterol synthesis and degradation may be increased during meomycin administration, but there is an overall loss of cholesterol from the body. Neomycin is a useful tool in studying mechanisms that control serum lipid levels but is not advocated as a therapeutic agent in hypercholesterolemia.

Failure of desoxycholic acid formation during neomycin therapy prompted us to administer desoxycholic acid to a patient who was receiving neomycin. Serum cholesterol concentration decreased to still lower levels, and fecal excretion of cholic acid and cholesterol increased. There was a disappearance of coprostanol from the stools at first, but this was followed by a marked increase. In view of this response, desoxycholic acid was given alone in amounts of 1.5 to 3 gm daily to seven subjects who received constant diets consisting of ordinary foods or liquid formula and containing predominantly saturated fats. Serum cholesterol concentration decreased significantly in all subjects. Although diarrhea developed frequently, fecal fat excretion was not altered appreciably. The excretion of cholic acid and cholesterol in the stools increased markedly, almost no coprostanol was formed, and total neutral sterol excretion increased (Fig 2).

It was decided to compare the administration of desoxycholic acid with administration of ox bile concentrate, 3 gm daily (Fig 2). In three subjects who received the latter medication, there was slight or no depression of serum cholesterol, although fecal sterol excretion increased considerably and coprostanol was virtually absent. Both whole bile and desoxycholic acid appear to influence the intestinal flora and increase excretion of neutral sterols, largely cholesterol, whereas only desoxycholic acid markedly lowers serum cholesterol concentration. The mechanism of action of desoxycholic acid requires elucidation. Findings to date suggest that it may decrease the absorption of cholesterol and cholic acid. It may also, by a feed-back mechanism, influence cholesterol degradation or inhibit cholesterol synthesis or have an effect on both mechanisms. Fimognari and Redwell[37] have shown that certain bile salts inhibit biosynthesis of mevalonate, and hence of cholesterol, from acetate-$2^{14}C$ in normal rat-liver homogenates. Desoxycholate was more inhibitory on a molar basis than cholate or taurocholate. The evidence suggests that bile salts may be te cholesterol metabolites responsible for physiological regulation of cholesterol synthesis.

These studies of niacin and other hypocholesterolemic agents exemplify one of the current areas in nutrition research of great importance to human health, namely, the role of nutrition in the pathogenesis of atherosclerosis and its complications. This avenue of research has led to a great increase in knowledge of the metabolism of lipids. Today, nutrition research is delving into many unsolved metabolic problems and yet nutritional deficiency is of paramount importance in all of the developing countries of the world.

This brief review of niacin as an antipellagra factor and hypocholesteremic agent has attempted to point out trends in nutrition research in the past half centruy. The advance in nutrition knowledge since the time of Goldberger has been tremendous



2. Desoxycholic acid and ox bile effects on serum cholesterol concentration and fecal excretion of fat, cholic acid, and neutral sterols.

and, as information has accumulated, research has turned to new areas. The future is bright, with new tools and techniques and the imagination engendered by the space age. Nutrition is an integral part of the current molecular biological era of science. Yesterday, interest was concentrated on the description of disease and methods of diagnosis as well as the search for etiologic factors and understanding of pathogenesis. While this search continues, it is at a different level. Modification of molecular reactions and configurations may dominate the nutritional and medical horizon of tomorrow but always with the aim of improvement in human health.

References

1. Goldberger, J.: The Etiology of Pellagra: The Significance of Certain Epidemiologic Observations With Respect Thereto. *Public Health Rep* **29**:1683-1686 (June 26) 1914.

2. Goldberger, J.: The Cause and Prevention of Pellagra, *Public Health Rep* **29**:2354-2357 (Sept 11) 1914.

3. Goldberger, J.; Waring, C.H.; and Willets, D.G.: The Treatment and Prevention of Pellagra, *Public Health Rep* **29**:2821-2825 (Oct 23) 1914.

4. Goldberger, J., and Wheeler, G.A.: Experimental Pellagra in the Human Subject Brought About by a Restricted Diet, *Public Health Rep* **30**:3336-3339 (Nov 12) 1915.

5. Goldberger, J., and Wheeler, G.A.: Experimental Production of Pellagra in Human Subjects by Means of Diet, *US Hgy Bull* **120**:7-116 (Feb) 1920.

6. Goldberger, J., and Wheeler, G.A.: Experimental Pellagra in White Male Convicts. *Arch Intern Med* **25**:451-471 (May) 1920.

7. Goldberger, J., and Tanner, W.F.: Amino Acid Deficiency Is Probably the Primary Etiological Factor in Pellagra, *Public Health Rep* **37**:462-486 (March 3) 1922.

8. Goldsmith, G.A.: "The B Vitamins: Thiamine, Riboflavin, Niacin," in Beaton, G.H., and McHenry, E.W. (eds.): *Nutrition: A Comprehensive Treatise*, New York: Academic Press, Inc., 1964, vol 2, pp 161-198.

9. Elvehjem, C.A., et al: Relation of Nicotinic Acid and Nicotinic Acid Amide to Canine Black Tongue, *J Amer Chem Soc* **59**:1767-1768 (Sept 7) 1937.

10. Elvehjem, C.A., et al: The Isolation and Identification of the Anti-Black Tongue Factor, *J Biol Chem* **123**:137-149 (March) 1938.

11. Krehl, W.A., et al: Growth-Retarding Effect of Corn in Nicotinic Acid-Low Rations and Its Counteraction by Tryptophane, *Science* **101**:489-490 (May 11) 1945.

12. Rosen, F.; Huff, J.W.; and Perlzweig, W.A.: The Effect of Tryptophane on the Synthesis of Nicotinic Acid in the Rat, *J Biol Chem* **163**:343-344 (April) 1946.

13. Sarrett, H.J., and Goldsmith, G.A.: The Effect of Tryptophane on the Excretion of Nicotinic Acid Derivatives in Humans, *J Biol Chem* **167**:293-294 (Jan) 1947.

14. Perlzweig, W.A., et al: The Excretion of Nicotinic Acid Derivatives After Ingestion of Tryptophane by Man, *J Biol Chem* **167**:514-571 (Feb) 1947.

15. Vilter, R.W.; Mueller, J.F.; and Bean, W.B.: The Therapeutic Effect of Tryptophane in Human Pellagra, *J Lab Clin Med* **34**:409-413 (March) 1949.

16. Horwitt, M.K., et al: Tryptophan-Niacin Relationships in Man: Studies With Diets Deficient in Riboflavin and Niacin, Together With Observations on the Excretion of Nitrogen and Niacin Metabolites, *J Nutr* **60** (suppl 1):1-43 (Oct) 1956.

17. Goldsmith, G.A.; Miller, O.N.; and Ungiaub, W.G.: Efficiency of Tryptophan as a Niacin Precursor in Man, *J Nutr* **73**:172-176 (Feb) 1961.

18. Rose, W.C.: Amino Acid Requirements of Man, *Fed Proc* **8**:546-552 (June) 1949.

19. Goldsmith, G.A.: Experimental Niacin Deficiency, *J Amer Diet Assoc* **32**:312-318 (April) 1956.

20. Goldsmith, G.A.: Niacin-Tryptophan Relationships in Man and Niacin Requirements. *Amer J Clin Nutr* **6**:479-486 (Sept-Oct) 1958.

21. Goldsmith, G.A., et al: Studies on Niacin Requirements in Man: II. Requirement on Wheat and Corn Diets Low in Tryptophan, *J Nutr* **56**:371-386 (July) 1955.

22. Goldsmith, G.A., et al: Studies on Niacin Requirements in Man: II. Comparative Effects of Diets Containing Lime-Treated and Untreated Corn in the Production of Experimental Pellagra, *Amer J Clin Nutr* **4**:151-160 (March-April) 1956.

23. Gopalan, C., and Srikantia, S.G.: Leucine and Pellagra, *Lancet* **1**:954-957 (April 30) 1960.

24. Truswell, A.S.; Goldsmith, G.A.; and Pearson, W.N.: Leucine and Pellagra, *Lancet* **1**:778-779 (April 6) 1963.

25. Woolley, D.W.: The Occurrence of a "Pellagrogenic" Agent in Corn, *J Biol Chem* **163**:773-774 (June) 1946.

26. Parsons, W.R.: Treatment of Hypercholesteremia by Nicotinic Acid, *Arch Intern Med* **107**:639-652 (May) 1961.

27. Miller, O.N.; Hamilton, J.G.; and Goldsmith, G.A.: Investigation of the Mechanism of Action of Nicotinic Acid on Serum Lipid Levels in Man, *Amer J Clin Nutr* **8**:480-490 (July-Aug) 1960.

28. Miller, O.N.; Hamilton, J.G.; and Goldsmith, G.A.: On the Mechanism of Action of Nicotinic Acid in Lowering Serum Lipids, *Amer J Clin Nutr* **10**:285-296 (April) 1962.

29. Goldsmith, G.A.; Hamilton, J.G.; and Miller, O.N.: Lowering of Serum Lipid Concentrations, *Arch Intern Med* **105**:512-517 (April) 1960.

30. Goldsmith, G.A.: Mechanisms by Which Certain Pharmacologic Agents Lower Serum Cholesterol, *Fed Proc* **21**:81-85 (July-Aug) 1962.

31. Kritchevsky, D.; Whitehouse, M.W.; and Staple, E.: Oxidation of Cholesterol-26-C^{14} by Rat-Liver Mitochondria: Effect of Nicotinic Acid, *J Lipid Res* **1**:154-158 (Jan) 1960.

32. Perry, W.F.: Effect of Nicotinic Acid and Nicotinamide on Incorporation of Acetate into Cholesterol, Fatty Acids, and Carbon Dioxide by Rat-Liver Slices, *Metabolism* **9**:686-689 (July) 1960.

33. Hamilton, J.G., et al: The Effect of Neomycin on Cholesterol Metabolism, *J Amer Oil Chem Soc* **41**:760-762 (Nov) 1964.

34. Danielsson, H. et al: On the Turnover and Excretory Products of Cholic Acid and Chenodeoxycholic Acid in Man, *J Biol Chem* **238**:2299-2304 (July) 1963.

35. Leveille, G.A., et al: Effect of Orally and Parenterally Administered Neomycin on Plasma Lipids of Human Subjects, *Amer J Clin Nutr* **12**:421-426 (June) 1963.

36. De Somer, P.; Vanderhaeghe, H.; and Eyssen, H.: Influence of Basic Antibiotics on Serum and Liver Cholesterol Concentrations in Chicks, *Nature* **204**:1306 (Dec 26) 1964.

37. Fimognari, G.M., and Rodwell, V.W.: Cholesterol Biosynthesis: Mevalonate Synthesis Inhibited by Bile Salts, *Science* **147**:1038 (Feb 26) 1965.

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Genetically determined organ specific responses to the teratogenic action of 6-aminonicotinamide in the mouse†

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It is now well recognized that the frequency of malformations following treatment of experimental animals with a teratogen varies with the genetic constitutions of the mother and embryo (Kalter & Warkany, 1959; Fraser, 1962). Little attention has been paid, however, to the question of whether the genes involved act by altering the animal's general susceptibility to the given teratogen, or by producing variations in response of the specific organ systems showing the malformations.

Kalter & Warkany (1957), using maternal treatment with the riboflavin antagonist galactoflavin, found that cleft palate, absent oesophagus and open eye (as well as several other defects) occurred with different frequencies in the four inbred mouse strains DBA, 129, A/Jax and C57BL. In two strains (DBA and 129) relatively high frequencies of malformations were produced by doses which caused very few, if any, malformations in the other two, indicating that there is a genetically controlled difference in general susceptibility to the drug. At a higher dose level, the relative frequencies of the different malformations varied from strain to strain—for instance, the frequency of cleft palate was high in the DBA and low in the A/Jax strain, absent oesophagus was frequent in both the A/Jax and DBA strains, and the frequency of open eye was high in the A/Jax and low in the DBA strain. This shows that there are also genetic differences in response of specific organ systems to the teratogen.

The present study makes use of a teratogen, 6-aminonicotinamide, and a method allowing precisely timed exposure of the embryo, to provide further evidence that the genetic basis for a strain difference in frequency of induced malformations differs for different organs in animals of the same genotype, and to show that these differences are in part cytoplasmic.

6-aminonicotinamide is a structural analogue of nicotinamide and was shown to be a competitive inhibitor of nicotinamide by Johnson & McColl (1955, 1956) and Dietrich *et al.* (1958). Johnson & McColl (1955, 1956) also showed that nicotinamide, nicotinic acid and, to a lesser extent, tryptophan, protect against its lethal effects.

The teratogenic nature of 6-aminonicotinamide has been demonstrated in chickens (Landauer, 1957; Murphy, Dagg & Karnofsky, 1957; Dagg & Karnofsky,

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1958), in rats (Murphy, Dagg & Karnofsky, 1957; Dagg & Karnofsky, 1958), and mice (Pinsky & Fraser, 1959, 1960). When nicotinamide was injected at the same time no malformations were induced, suggesting that the analogue interferes with development by producing a relative deficiency of nicotinamide. Pinsky & Fraser (1960) demonstrated that the nature of the malformations induced varied sharply with the gestational stage at which the drug was given. By administering nicotinamide, in a quantity shown to prevent any further teratogenic action of 6-aminonicotinamide, 2 hr. after the initial dose of 6-aminonicotinamide, they were able to focus the teratogen on a very precisely defined stage of pregnancy.

1. MATERIALS AND METHODS

Mice of two highly inbred strains, A/Jax and C57BL/6J, subsequently referred to as A and C, were obtained from the Jackson Memorial Laboratory, Bar Harbor, Maine, at 6–7 weeks of age and maintained on Purina Lab Chow and water *ad libitum*, supplemented with milk, bread and lettuce once a week. The males were placed in cages with nulliparous females for one night. The females were examined for vaginal plugs and weighed the next morning, and examined for pregnancy by palpation on the day of treatment. The day on which a vaginal plug was found was called day 0.

The following types of mating were carried out, the female parent being written first in each case: intra-strain—A × A, C × C; inter-strain—A × C, C × A; and back-cross to the A strain—(AC) × A and (CA) × A. Pregnant females were treated on one of the following days of gestation: 8·5, 9·5, 10·5, 11·5, 12·5, 13·5, or 14·5. The treatment consisted of an intramuscular injection of 6-aminonicotinamide in aqueous solution (19 mg./kg.) followed 2 hr. later by an injection of nicotinamide in aqueous solution (7·3 mg./kg.) which had previously been shown to prevent further teratogenic action of the antimetabolite (Pinsky & Fraser, 1960). Control observations were made on the offspring of untreated females and on the offspring of females given an injection of water followed 2 hr. later by nicotinamide on day 9·5 in A × C and C × A, day 10·5 in A × A and day 12·5 in C × C (these were the days when the embryos were most susceptible to the teratogenic effects of the treatment). No differences were observed between the control series in litter size or malformation frequency; thus the experimental procedure had no teratogenic effect.

On day 18·5 the females were killed. The positions of the embryos and resorption sites in the uterus were recorded, the embryos were removed, and, after gross examination, most of them were cleared for skeletal staining with alizarin (modified from Dawson, 1926).

2. RESULTS

A variety of malformations were produced, depending on the day the treatment was given, and these will be reported elsewhere. The present paper will deal with only two of them—vertebral fusions and cleft palate.

(i) *Vertebral fusions*

Treatment on day 8·5 and on day 9·5, but not on any other day tested, resulted in fusions between vertebral bodies in the thoracic and lumbar region. The frequencies are presented in Table 1.

Table 1. *Frequencies of vertebral fusions (VF) following maternal treatment with 6-aminonicotinamide on day 8·5 or 9·5 of gestation*

Cross	Day treated	Numbers of females treated	Numbers of embryos		Percent of embryos with VF
			Resorbed	Alive	
1. A × A	8·5	9	75	7	0
	9·5	10	37	55	89
	Control	18	34	111	0
2. C × C	8·5	12	27	64	9
	9·5	12	20	73	56
	Control	12	19	72	0
3. A × C	8·5	10	61	14	14
	9·5	10	16	49 (65)†	45
	Control	10	24	52	0
4. C × A	8·5	5	1	32	37
	9·5	10	7	52 (67)†	67
	Control	10	13	65	0

† Only the numbers of mice cleared for the examination of the skeletons are included. The numbers in brackets refer to the total number of embryos.

In crosses involving strain A mothers (1 and 3) treatment on day 8·5 caused such a high frequency of resorptions that no conclusions about the frequency of malformations can be drawn. In crosses involving strain C mothers (2 and 4) the frequency of vertebral fusions is lower in the C strain (9%) than in the F_1(37%) the difference being highly significant ($p < 0{\cdot}001$).

After treatment on day 9·5 the frequency of vertebral fusions is higher in offspring of the A strain (89%) than of the C57BL strain (56%), at the 0·1% level of significance. A patroclinous reciprocal cross difference is noted in the F_1 hybrids—67% in the offspring of C × A and 45% in the offspring of A × C crosses ($p < 0{\cdot}05$).

(ii) *Cleft palate*

Figure 1 represents the frequency of cleft palate following a 2-hr. treatment with 6-aminonicotinamide on the various days of gestation. All four crosses show definite peaks on day 13·5 which is thus the critical period for cleft palate production with 6-aminonicotinamide.

The results of treatment at the critical period are presented in Table 2.

The frequency of induced cleft palate in the A × A embryos (76·1%) was higher than in the C × C embryos (10·8%), the difference being highly significant ($p < 0{\cdot}001$), and was also higher than that in the A × C embryos (36·3%; $p < 0{\cdot}01$).

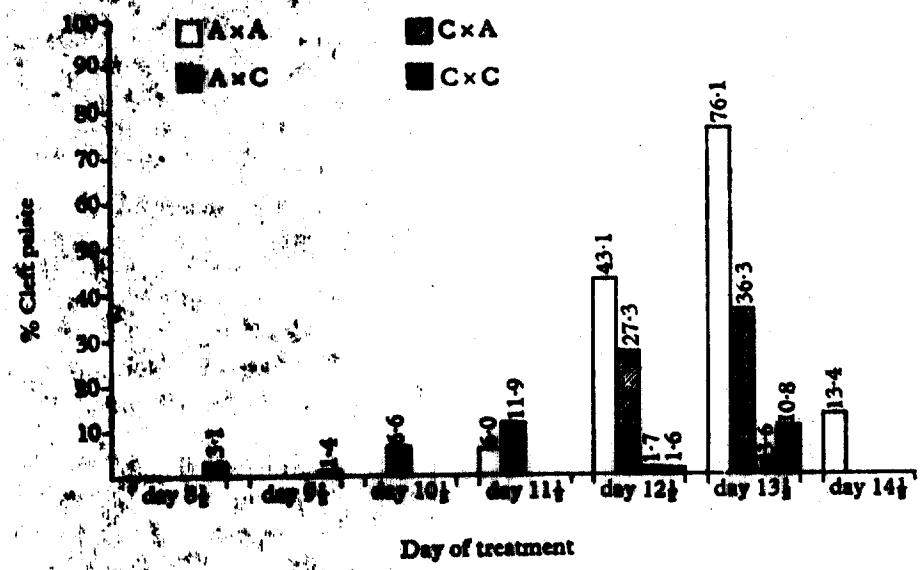

Fig. 1. Frequency of cleft palate following treatment on various days of gestation.

Table 2. *Frequencies of cleft palate (CP) following maternal treatment with 6-aminonicotinamide on day* 13·5 *of gestation*

Cross	Day treated	Number of females treated	Numbers of embryos: Resorbed	Numbers of embryos: Alive	Percent of embryos with CP
1. A × A	13·5	10	19	71	76·1
	Control	18	34	111	0
2. C × C	13·5	12	28	74	10·8
	Control	12	19	72	2·8
3. A × C	13·5	12	13	80	36·3
	Control	9	14	31	0
4. C × A	13·5	10	7	56	3·6
	Control	11	7	64	0
5. AC × A	13·5	9	1	76	23·7
6. CA × A	13·5	11	5	73	5·5

There was a matroclinous reciprocal cross difference in the F_1 hybrids, the A × C embryos having a higher frequency (36·3%) than the C × A embryos (3·6%; $p < 0{\cdot}001$). Such a maternal effect could be a reflection either of differences in the embryo's environment, or of strain differences in factors transmitted through the egg cytoplasm. To distinguish between these possibilities the two types of F_1

mothers (A × C and C × A) were backcrossed to strain A males, and treated with 6-aminonicotinamide on day 13·5. (These females had not been exposed to 6-aminonicotinamide when they themselves were embryos.) There was a significant difference in cleft palate frequency in the two types of backcross, with 24% for AC × A and 6% for CA × A, suggesting that the teratogenic response to 6-aminonicotinamide is influenced by factors transmitted through the egg cytoplasm.

3. DISCUSSION

A number of interesting features emerge from these data. Following treatment on day 9·5 of gestation the frequency of induced vertebral fusions is higher in the A strain (89%) then in the C strain (56%), showing that there are genetically determined differences in response to the teratogen. The complicated nature of these differences is revealed by the reciprocal cross difference in the frequency of induced vertebral fusions in the F_1 hybrids of crosses between the two strains. The frequency was higher in the C × A hybrids (67%) than in the A × C hybrids (45%); that is, the F_1 resembled the paternal strain. Since the genetic contributions of the parental strains to the F_1 (except for the Y chromosome) are presumably the same in the reciprocal crosses, the patroclinous effect may have been the result of (*a*) random variation, (*b*) a factor for resistance to the teratogenic effects of 6-aminonicotinamide transmitted by the sperm but not the egg—a highly unlikely interpretation—(*c*) a maternal uterine or cytoplasmic factor for resistance to the teratogenic effects of 6-aminonicotinamide, which was stronger in the A than the C strain, interacting with a genetic factor for resistance stronger in the C than in the A strain. Thus the A strain could be postulated to carry genes for relative susceptibility and a maternal uterus or cytoplasmic factor for relative resistance of the vertebral anlage to the effects of 6-aminonicotinamide, with the converse situation in the C strain. The F_1 hybrids would be genetically intermediate, but the maternal or cytoplasmic factors would result in a lower frequency of defects in the A × C than in the C × A offspring. The existence of cytoplasmic differences causing patroclinous reciprocal cross differences in vertebral number has been demonstrated by ova transplantation experiments in the mouse (Green & Green, 1959).

A fourth possibility (*d*) would be that the differences reflect differences in the rates of development of the two types of hybrid, as already demonstrated in the case of palate closure (Trasler & Fraser, 1958). If the C × A hybrids were being treated at, say, the point of maximum sensitivity of the vertebral anlage to the teratogen, and the A × C hybrids were developing a little faster, or (as in the case of the palate) slower than the C × A hybrids, so that they were being treated at some stage other than that of maximum sensitivity, they would have a lower frequency of defects. In this case the patroclinous nature of the difference, as measured by the frequency of vertebral fusion, might actually be a matroclinous effect (as with cortisone-induced cleft palate), when considered in terms of embryonic developmental rates.

Turning to the results of treatment on day 13·5 of gestation we find that the A strain embryos have a higher frequency of induced cleft palate than the C embryos,

and again there is a reciprocal cross difference in the F_1, but in this case it is matroclinous. The frequencies are: A × A, 76%; C × C, 11%; A × C, 36%; and C × A, 4%.

Since the A × A and A × C embryos both have A mothers but different genotypes, they have different frequencies of induced cleft palate, the embryo's genotype is important in determining its response to the teratogen. On the other hand, since the A × C embryos have a higher frequency of cleft palate than the C × A embryos, even though they are (except for the Y chromosome) genetically identical, the embryonal response is also influenced by the nature of the mother. In the backcross to the A strain, in which both the maternal and foetal genotypes are identical but any maternal cytoplasmic factors would be different, the (AC) × A embryos are significantly more susceptible to cleft palate (23·7%) than the (CA) × A embryos (6·9%) ($p = 0·01 - 0·001$). Since these crosses differ in the origin of their maternal cytoplasm, this suggests that there are factors in the A cytoplasm which increase the embryo's susceptibility to the teratogenic action of 6-aminonicotinamide on day 13·5.

An alternative, though less likely, interpretation is that the uterine environment provided by the mother is influenced by the uterine environment in which she herself developed. Additional backcrosses are being carried out to investigate this problem further. At present we shall assume, as a working hypothesis, that the differences are cytoplasmic in nature. This differs from the situation reported for cortisone by Kalter (1964), who found that the susceptibility to cortisone-induced cleft palate in the same two strains of mice was determined by an interaction between maternal and embryonic genotypes, but that maternal cytoplasmic factors were not involved. If the embryonic genotype and maternal cytoplasmic factors were the only determinants of susceptibility to cleft palate production by treatment on day 13·5, one would expect the cleft palate frequency to be higher in the (AC) × A embryos than in the A × C embryos since the former contain more genes from the susceptible strain than the latter. In fact, however, the cleft palate frequency is, if anything, lower in the (AC) × A cross (24%) than in the A × C cross (36%) though the difference is not significant ($p = 0·10–0·05$). Since the cleft palate frequency in the (AC) × A cross did not show the expected increase above the A × C value, it is concluded that the maternal constitution must also play a role in determining susceptibility to the treatment, i.e. the palate of an embryo appears to be more resistant to 6-aminonicotinamide when it is growing in an A × C uterus than in an A uterus.

The reciprocal cross differences demonstrated in malformation frequency induced by 6-aminonicotinamide were patroclinous in the case of vertebral fusions and matroclinous for cleft palate. Cytoplasmic factors influencing the embryos' response to the teratogen appeared to be active in the case of cleft palate, and may exist for vertebral fusions, but if so they must act in the opposite direction to the ones for cleft palate. In any case, the fact that the reciprocal cross differences were in opposite directions for vertebral fusions and cleft palates, respectively, shows that the genetic differences in response to the teratogen are organ-specific.

4. SUMMARY

1. A two-hour relative deficiency of nicotinamide, produced by maternal treatment with 6-aminonicotinamide, resulted in a maximum frequency of vertebral fusions following treatment on day 9·5 of gestation, and a maximum frequency of cleft palates following treatment on day 13·5.

2. Both defects appeared with higher frequencies in the A/Jax than in the C57BL/6J inbred strain.

3. The frequency of induced vertebral fusions in F_1 embryos from crosses between the strains was higher when the father was from the A/Jax strain than when the mother was—a patroclinous reciprocal cross difference.

4. The frequency of induced cleft palate in F_1 embryos from crosses between the strains was higher when the mother was from the A/Jax strain than when the father was—a matroclinous reciprocal cross difference.

5. Since the reciprocal cross differences in frequency of vertebral fusions and for cleft palates were in opposite directions, the hereditary factors influencing susceptibility to the teratogen appear to differ for the respective organ anlage. These differences appear to be, in part, cytoplasmic.

6. The frequency of induced cleft palate in the offspring of backcrosses of (untreated) F_1 female hybrids to A/Jax males differed according to the cytoplasmic origin of the F_1 mothers. Thus the susceptibility of an embryo to the teratogen appears to be influenced by factors transmitted through the cytoplasm.

REFERENCES

DAGG, C. P. & KARNOFSKY, D. A. (1958). Some effects of 6-aminonicotinamide in chick embryos. *Fed. Proc.* **17**, 361.

DAWSON, A. B. (1926). A note on the staining of the skeleton of cleared specimens with alizarin red S. *Stain Tech.* **1**, 123–124.

DIETRICH, L. S., FRIEDLAND, I. M. & KAPLAN, L. A. (1958). Pyridine nucleotide metabolism: mechanism of action of the niacin antagonist, 6-aminonicotinamide. *J. biol. Chem.* **233**, 964–968.

FRASER, F. C. (1963). Methodology of experimental mammalian teratology. *Methodology in Mammalian Genetics*, W. J. Burdette, Ed. Holden-Day Inc.

GREEN, E. L. & GREEN, M. C. (1959). Transplantation of ova in mice. An attempt to modify the number of presacral vertebrae. *J. Hered.* **50**, 108–114.

JOHNSON, W. J. & MCCOLL, J. D. (1955). 6-aminonicotinamide—a potent nicotinamide antagonist. *Science*, **122**, 834.

JOHNSON, W. J. & MCCOLL, J. D. (1956). Antimetabolite activity of 6-aminonicotinamide. *Fed. Proc.* **15**, 284.

KALTER, H. (1954). The inheritance of susceptibility to the teratogenic action of cortisone in mice. *Genetics*, **39**, 185–196.

KALTER, H. & WARKANY, J. (1957). Congenital malformations in inbred strains of mice induced by riboflavin deficient, galactoflavin containing diets. *J. exp. Zool.* **136**, 531–566.

KALTER, H. & Warkany, J. (1959). Experimental production of congenital malformations in mammals by metabolic procedures. *Physiol. Rev.* **39**, 69–115.

LANDAUER, W. (1957). Niacin antagonists and chick development. *J. exp. Zool.* **136**, 509–530.

MURPHY, M. L., DAGG, C. P. & KARNOFSKY, D. A. (1957). Comparison of teratogenic chemicals in the rat and chick embryos. *Pediatrics*, **19**, 701–714.

PINSKY, L. & FRASER, F. C. (1959). Production of skeletal malformations in the offspring of pregnant mice treated with 6-aminonicotinamide. *Biol. Neonat.* **1**, 103–112.

PINSKY, L. & FRASER, F. C. (1960). Congenital malformations following a two-hour inactivation of nicotinamide by its analogue, 6-aminonicotinamide, in pregnant mice. *Brit. med. J.* 2, 196–197.

TRESLER, D. G. & FRASER, F. C. (1958). Factors underlying strain, reciprocal cross, and maternal weight differences in embryo susceptibility to cortisone-induced cleft palate in mice. *Proc. X Int. Cong. Genet.* 2, 296–297.

WALKER, B. E. (1958). *Genetico-embryological studies in normal and cleft palates in mice.* Ph.D. Thesis (McGill University).

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THE ROLE OF NICOTINIC ACID (NIACIN) IN MENTAL HEALTH AND DISEASE

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SECTION A: THE AETIOLOGY AND PSYCHIATRIC MANIFESTATIONS OF PELLAGRA

1. Introduction:

The Vitamin B Complex and the Aetiology of Pellagra

Shortly before the end of the last century, Eijkman observed that fowl receiving a diet of polished rice developed a disease which he believed to be of the same nature as human beri-beri. It was subsequently shown that this condition in fowl (polyneuritis gallinarum), and beri-beri in man, could both be cured by the addition to the diet of rice polishings or an extract prepared from them. In 1911, Funk obtained from rice polishings a crystalline substance capable of preventing or curing beri-beri, which he named "vitamine" in view of its evident importance to life, and in the erroneous belief that it had the chemical structure of an amine. Four years later, McCollum and Davis demonstrated that at least two such dietary factors were necessary for growth in rats —"fat-soluble A" and "water-soluble B". Before long it was recognized that the latter factor had the properties of the antineuritic "vitamine", and a number of similar organic compounds were discovered, which were essential constituents of the diet in minute quantities, and for which the general term "vitamin" was agreed upon. For several years it was assumed that water-soluble vitamin B (contained in yeast, rice polish, liver, etc.) was a single entity, but in 1919 Mitchell noted that certain vegetables rich in the antineuritic principle had little power to promote growth, and in 1926 two fractions were distinguished, each essential for growth—thermolabile vitamin B_1, containing the antineuritic principle (thiamin), and thermostable vitamin B_2.

Now a disease known to the peasants of Lombardy as pellagra (from "pelle agra", meaning rough skin) was first recorded in medical literature by the Italian physician Frapolli in 1771. A Spaniard by the name of Casal had described this condition some years earlier under the term "mal de la rosa", and had attributed it to a poor diet, but it was not until 1915 that its dietary origin was conclusively demonstrated by Goldberger. At that time, pellagra was considered due to the "biological inferiority" of protein consumed (causing deficiency of essential amino-acids) and it was another ten years before it was shown to result from vitamin deficiency (as originally predicted by Funk). Not long after the latter discovery, it was postulated (1) that the pellagra-preventive factor was a single substance, vitamin B_2 (G), the thermostable fraction of the vitamin B complex, but in 1933 riboflavin was isolated, and other factors were subsequently separated from the vitamin B_2 complex, one of which was nicotinic acid (niacin).

Nicotinic acid was first derived from nicotine by the chemist Huber in

1867, and Funk (2) reported its presence in his extracts in 1911, but its physiological significance was still not apparent at that time. Some years later, Warburg (3) recognized its association with tissue respiratory enzymes, and appreciated its fundamental importance in the oxidative processes of the cell. Then in 1937 Elvehjem and his associates isolated nicotinic acid and its amide from liver, and proved that it cured and prevented "black tongue" in dogs, a condition analogous to human pellagra. A few months later, three independent groups of investigators (5–7) established its efficacy in the treatment of pellagra, but it soon became evident that this disease was a symptom-complex associated with deficiency of several vitamins. It was learned that the frequent polyneuropathy was caused by lack of thiamin, while ariboflavinosis was responsible for angular stomatitis, bulbar conjunctivitis and facial seborrhoea. Niacin and its amide were found to relieve mental symptoms, mouth and mucous membrane lesions, and dermatitis (8, 9).

The term pellagra has since been reserved by some authorities for the symptoms and signs resulting from nicotinic acid (amide) deficiency (10–12), but with full realization that the latter: (i) may be precipitated by diets deficient in the protein component tryptophane (v.i.), (ii) is usually associated with a deficiency of one or more other vitamins, particularly thiamin and riboflavin (v.s.). The mechanism of pathogenesis of this vitamin deficiency state will now be considered.

2. Factors that May Produce Nicotinic Acid Amide Deficiency (Pellagra)

(a) *Precipitating Factors*

The factors that may precipitate nicotinic acid amide deficiency are similar to those that may precipitate deficiencies of other vitamins, and may be classified as follows (modified after Leitner (13) and others (10, 14)):

(i) *Inadequate Amount of Niacin Available in Diet* ("*Primary Deficiency*"): The average daily adult requirement of nicotinic acid is about 12 to 20 mgm. (15). The fact that the diet available contains less than this basic amount of niacin (and may or may not contain adequate amounts of other essential substances) may result from either (a) *inability to procure an adequate diet* (e.g. on account of famine, or for socio-economic reasons), or (b) *choice of a nutritionally unbalanced diet*, usually rich in carbohydrates and fats, but low in proteins, minerals and vitamins (e.g. due to ignorance, individual preference, or prescription by a physician).

(ii) *Interference with Ingestion* may be caused by a wide variety of conditions both organic and "functional", which include the following: (a) any condition in which there is *anorexia or vomiting*, (b) *gastro-intestinal diseases*, (c) *psychiatric disorders* (e.g. psychoneuroses, both organic and functional psychoses, and addiction to alcohol or other drugs), (d) *neurological and traumatic disorders* that interfere with self-feeding, (e) *oral diseases* (e.g. sore mouth, or loss of teeth).

(iii) *Interference with Bio-synthesis*. Several of the constituents of the vitamin B complex, including nicotinamide, are known to be synthesized by the intestinal bacteria (16–20), and Ellinger *et al.*, have estimated that as much as 80 per cent. of the human requirement of niacin may be manufactured in the intestines. This normal synthesis may be impaired by several factors: (a) *inadequate intake of tryptophane*, which has been shown to counteract an induced need for nicotinic acid (21–24), and from which the

latter is believed to be synthesized (20), (b) *ingestion of structurally similar compounds* (which may inhibit the formation of niacin by substrate competition). Thus such substances as maize, gelatin, phenylalanine and adenine have been shown to exert a pellagrogenic action (25–28), (c) *destruction of the bacteria responsible for bio-synthesis*, as by the "sterilizing" sulphonamides (e.g. sulphaguanidine and succinyl sulphathiazole) or by other antibiotics (such as penicillin or aureomycin).

(iv) *Interference with Absorption* may result from such conditions as the following: (a) *absence of the normal digestive secretions* (e.g. achlorhydria, which is frequently found in pellagra (29), obstructive jaundice, etc.), (b) *intestinal hypermotility*, as in various types of diarrhoea, (c) *reduction of effective absorbing surface*, due to disease, or surgical removal, of part of the gastro-intestinal tract, (d) *administration of drugs*, such as mineral oil, cathartics, or colloidal adsorbents.

(v) *Interference with Utilization* may be effected by: (a) *generalized interference with cellular metabolism*, which may be brought about by cellular toxins (e.g. "toxamins", alcohol, general anaesthetics, etc.), or by a variety of metabolic disorders such as hypothyroidism, diabetes mellitus, or any type of anoxia (anoxic, anaemic, stagnant, or histotoxic), (b) *specific inactivation of nicotinic acid*. In addition to their inhibition of bio-synthesis, it is known that after absorption the sulphonamides exert an *anti-vitamin action* by substrate competition with *p*-amino-benzoic acid. There is some indication that there may be a similar competitive inhibition of nicotinic acid by closely related chemical substances (e.g. by some pellagrogenic agent that may be present in corn (23), or by isoniazid (30)).

(vi) *Interference with Storage*. While nicotinic acid compounds are widely distributed throughout the animal tissues, the concentration is highest in actively metabolizing tissues, particularly the liver. Hence any condition causing *impairment of liver function* may interfere with the amount of nicotinic acid retained in the body.

(vii) *Increased Excretion or Loss*: (a) *in the urine*. Nicotinic acid is normally excreted in the urine in the form of its methyl betaine (trigonelline), and in combination with glycine (nicotinuric acid) (110). The output by this route may be increased in such conditions as renal disease or diabetes (mellitus or insipidus). (b) *by other routes*. Substantial amounts of nicotinic acid and other vitamins may be lost during lactation, or with other body fluids (e.g. in serous exudates due to burns, or in severe loss of blood).

(viii) *Increased Nutritive Requirements* are present in a large number of conditions in which the metabolic rate is elevated above its usual level, amongst which are the following: (a) *hyperthyroidism*, (b) *periods of rapid growth*, (c) *pregnancy and lactation*, (d) *pyrexia*, from any cause, (e) any condition in which there is *increased muscular activity* (e.g. delirium), (f) several types of *treatment that may be prescribed by a physician* (e.g. high carbohydrate diets, or administration of glucose, insulin, thyroid, fever therapy, or stimulants such as caffeine or amphetamine).

(b) *Predisposing Factors*

The factors that predispose to the development of nicotinic acid amide deficiency ([illegible]–32) usually act by a combination of several of the mechanisms

that have just been outlined, and will now be discussed briefly. These predisposing factors may be classified according to whether they are predominantly biological, psychological or social in nature. However, the observation that a given factor may be placed in two or even all three of these categories serves to emphasize that the integration of the individual is essentially bio-psycho-social.

(i) *Biological Factors*. A wide variety of somatic disorders that may cause the development of *pellagra secondary to organic disease* have already been mentioned in the preceding section, concerning the factors that may precipitate niacin deficiency. The somatic disorders that most commonly lead to the onset of this deficiency state are probably the following: (a) *gastro-intestinal diseases* are first in importance, and may produce pellagra by several mechanisms—usually by interference with ingestion, bio-synthesis and/or absorption. Mann and Stare (33) state that "probably the most frequent contributing cause in nutritional deficiency is diarrhoea". In this connection, it is also interesting to note Hardwick's clinical deduction (34) that upper intestinal disorders are prone to result in thiamin deficiency, whereas lower intestinal disorders are more likely to lead to nicotinic acid deficiency, (b) *diseases causing increased nutritive requirements*, often only temporary in nature (particularly acute infections, and delirious states), (c) *surgical operations* are almost invariably accompanied by at least temporary interference with both ingestion and utilization (in cases receiving general anaesthesia), and may also be complicated by a number of other factors that may precipitate niacin deficiency.

(ii) *Psychological Factors*. Psychiatric disorders, both organic and functional in nature, frequently lead to the onset of a secondary vitamin deficiency due to ingestion of a nutritionally unbalanced diet, or to an overall interference with ingestion (e.g. on account of anorexia, or delusional ideation). However, psychological factors are also causally related both to somatic pathology ("psychosomatic disease") (35), and to social factors (such as the poverty and ignorance cited below) (36), and hence may indirectly contribute to the development of nutritional deficiencies by a wide variety of mechanisms.

(iii) *Social Factors. Famine, poverty and ignorance* are the factors held responsible for the development of endemic pellagra. In these cases, the main mechanism of production of the deficiency is the presence of an inadequate amount of the vitamin, or its precursor tryptophane, in the diet ("primary deficiency"—v.s.)—either through inability to procure an adequate diet, or choice of a nutritionally unbalanced diet, or both—but the lack of niacin may also result from interference with bio-synthesis by ingestion of pellagrogenic substances such as maize.

(iv) *Alcoholism*. The existence of a close association between alcoholism and pellagra was emphasized by Klauder and Winkelmann (37) in 1928. A few years later, in an analysis of 102 cases of pellagra, Boggs and Padget (38) found that about 30 per cent. were of the senile type (v.i.), 39 per cent. were postalcoholic, and in about 30 per cent. the disease had arisen as a complication of some other malady (v.s.). In patients developing *alcoholic pellagra* ("pseudo-pellagra"), there has almost invariably been prolonged inadequate nutrient intake (due to both ingestion of a nutritionally unbalanced diet, and to an overall reduction in intake), and probably also interference with bio-synthesis, absorption and/or storage (due to gastro-intestinal and hepatic dysfunction). However, in addition, a clinical

deficiency state may be precipitated by other mechanisms (e.g. an increase in nutritional requirements, when the alcoholism has been complicated by delirium tremens or organic disease—v.s.).

(v) *Senility*. Boggs and Padget (38), Gottlieb (69) and others have drawn attention to the frequent occurrence of pellagra, or aniacinosis, in senility. Mild degrees of vitamin deficiency are probably usual in elderly persons, for which there appear to be a number of reasons. Inadequate nutrient intake is common, and may be attributed to socio-economic factors, psychological dysfunction (on an organic or functional basis) and or somatic disease. In addition, there may be interference with absorption, utilization and/or storage, and a clinical deficiency state is often finally precipitated by some minor acute organic disease (v.s.).

3. The Neuro-pathology and Psychiatric Manifestations of Pellagra

Following a recent clinical and neuro-pathological study of 14 fatal cases of pellagra, and a review of the relevant literature, Leigh (39) concluded that the term "pellagra" was no more than a generic title, embracing several nutritional deficiency syndromes of differing aetiology. In the syndromes consisting of weight-loss, diarrhoea, dermatitis of exposed surfaces, and mental changes, a retrograde cell degeneration of the Betz cells was the only constant pathological finding. The cells of the pontine, dorsal vagal, gracile and cuneate nuclei also showed a similar change, but were less constantly affected than the Betz cells. Clinically, he observed that loss of weight (which was sometimes very marked) commonly preceded the onset of both diarrhoea and dermatitis. It has also been found that the mental signs of mild niacin deficiency, or *pellagra sine pellagra*, often occur in the absence of any dermatologic, mucous membrane, or gastro-intestinal symptoms (12, 13, 65–67, 81).

The mental signs of pellagra may be regarded as those of either an acute ("toxic") or chronic organic reaction (40, 41)—*primary signs of organic brain dysfunction* (varying degrees of impairment of intelligence, memory and consciousness; with disinhibition, emotional lability, disorientation, confusion, perseveration, confabulation, delirium or stupor, and a decreased tolerance to toxic substances)—and *secondary functional signs* due to exaggeration of previous personality characteristics (often depressive or paranoid tendencies), or to the release of overt symptomatology of a hitherto latent functional psychosis or psychoneurosis. Both the physical lesions of pellagra and the signs of organic brain dysfunction are frequently preceded by psychoneurotic symptoms of this type. McLester, Sydenstricker, Spies and others (8, 10, 13, 15, 42–46, 81) have described syndromes of neurasthenia and hypochondriasis, similar to those caused by thiamin deficiency (47–54), and characterized by such symptoms as fatigue, anorexia, insomnia, headaches, vertigo, palpitation, anxiety, apprehension and depression.

Of all the possible mental changes in pellagra, those most commonly recognized consist of three syndromes (10, 20, 55, 56), which may justifiably be designated "the three D's": *Depression* (with or without signs of organic brain dysfunction), *Delirium* (an acute, reversible, "toxic" reaction) and *Dementia* (a chronic, irreversible, organic reaction). However, the diverse and protean nature of mental disorders associated with pellagra has long been appreciated, and Singer (57) in 1915 separated them into the following groups: (*a*) disorders directly due to the pellagrous syndrome (symptomatic depressions, and delirious

to effect improvement are tabulated below, according to the postulated rationale for such improvement:

(a) *Psychiatric disorders attributed wholly to nicotinic acid deficiency*

(i) Pellagra, the characteristic mental changes progressing as follows:

$$\text{Depression} \xleftrightarrow{\text{reversible}} \text{Delirium} \xrightarrow{\text{irreversible}} \text{Dementia.}$$

(ii) Pellagra sine pellagra, mental changes occurring in the absence of physical changes (these mental changes consisting in mild cases of psychoneurotic syndromes).

(iii) Nicotinic acid deficiency encephalopathy, with specific neurological manifestations.

(b) *Psychiatric disorders with possible relative or associated deficiency of nicotinic acid, but in which part of the therapeutic effect of nicotinic acid has also been attributed to mass action and or vasodilatation*

(i) Atypical organic psychoses associated with malnutrition

(ii) Organic psychoses associated with alcoholism

(iii) Organic psychoses associated with senescence and senility.

(c) *Psychiatric disorders apparently unrelated to nutritional deficiency, in which the therapeutic effect of nicotinic acid has usually been attributed to vasodilatation*

(i) Organic brain dysfunction following cerebral trauma, and hypoxic episodes.

(ii) Organic brain dysfunction following somatic psychiatric therapies (e.g. E.C.T., prolonged insulin coma, lobotomy).

(iii) Apparently functional depressive and anxiety reactions.

Bibliography

1. Goldberger, J., *U.S.A. Pub. Hlth. Rep. No. 1174*, 1927.
2. Funk, C. J., *Physiologist*, 1911, **43**, 395.
3. Warburg, O., *Science*, 1925, **61**, 575.
4. Elvehjem, C. A., Madden, R. J., Strong, F. M., and Woolley, D. W., *J. Biol. Chem.*, 1938, **123**, 137.
5. Fouts, P. J., Helmer, O. M., Lepkovsky, S., and Jukes, T. H., *Proc. Soc. Exper. Biol. and Med.*, 1937, **37**, 405.
6. Smith, D. T., Ruffin, J. M., and Smith, S. G., *J.A.M.A.*, 1937, **109**, 2054.
7. Spies, T. D., Cooper, C., and Blankenhorn, M. A., *J.A.M.A.*, 1938, **110**, 622.
8. Spies, T. D., Aring, C. D., Gelperin, J., and Bean, W. B., *Amer. J. Med. Sci.*, 1938, **196**, 461.
9. Jolliffe, N., *J. Mt. Sinai Hosp.*, 1942, **8**, 658.
10. Spies, T. D., and Butt, H. R., *Diseases of Metabolism*, 1952, pp. 488–501. Edited by Duncan, G. G. 3rd Edition. Philadelphia: W. B. Saunders Company.
11. Darby, W. J., *Principles of Internal Medicine*, 1950, pp. 522–6. Edited by Harrison, T. R., *et al.* Philadelphia: Blakiston Company.
12. Youmans, J. B., *Handbook of Nutrition*, 1951, pp. 554–62. 2nd Edition, A.M.A. Philadelphia: Blakiston Company.
13. Lettner, Z. A., *Brit. med. J.*, 1948, **1**, 917.
14. Keys, A., *Diseases of Metabolism*, 1952, pp. 574–6. Edited by Duncan, G. G. 3rd Edition. Philadelphia: W. B. Saunders Company.
15. McLester, J. S., *Nutrition and Diet in Health and Disease*, 1949, pp. 77–8 and 318–2[illegible]. 5th Edition. Philadelphia: W. B. Saunders Company.
16. Najjar, V. A., and Holt, L. E., *J.A.M.A.*, 1943, **123**, 683.
17. Najjar, V. A., Johns, G. A., Medairy, G. C., Fleischmann, G., and Holt, L. E., *J.A.M.A.*, 1944, **126**, 357.

states), (*b*) disorders based on peculiarities in personal make-up, precipitated by pellagra (manic depressive psychoses, dementia praecox, and the psychoneuroses), (*c*) disorders due to definite brain changes, with pellagra as a complication (arteriosclerotic dementia, senile and presenile psychoses, and general paresis). Subsequent observations have indicated that pellagra and other nutritional deficiencies (i) may not only precipitate functional disorders, but also result from them (when they cause inadequate nutrient intake—v.s.), (ii) may be at least partly responsible for the development of certain of the organic psychoses enumerated above, as well as occurring as a complication of them (66, 70).

Pellagra in infancy and childhood. Pellagra is not uncommon in infancy and childhood (10, 15, 58–61), but the mental signs and symptoms differ slightly from those found in adults. Affected children lack the spontaneous laughter and tireless energy of normal children. They are listless, apathetic and tired, but are also usually irritable, easily frightened, apprehensive, fretful, and apt to cry frequently. In cases of any duration, there is both *physical and mental retardation* (with impairment of intelligence, memory and concentration), and in older children there is consequently a rapid decline in progress at school. In very severe cases confusion, hallucinations and delirium occur, as in adults, and may be followed by coma and death. Appropriate treatment causes the disappearance of the delirium, but in some cases the child thereafter remains permanently retarded (61). Carothers (62) has pointed out that "malnutrition in prenatal life and infancy may interfere with neurone development, and, in early childhood, may incapacitate the children at the very time when they should be most adventurous and curious; in either case, it is likely to result in a backwardness which cannot be readjusted later".

SECTION B: NICOTINIC ACID THERAPY IN PSYCHIATRIC DISORDERS—A CLINICAL REVIEW

1. Nicotinic Acid Therapy in the Psychiatric Manifestations of Pellagra

Since its first application to the treatment of human pellagra, considerable evidence has accumulated, confirming the initial reports that nicotinic acid effected prompt improvement both in psychotic and in psychoneurotic syndromes occurring in this deficiency state (8, 42–45, 63–65). Hardwick (66) and others have also drawn attention to the frequency of pellagra and related deficiency states in psychiatric practice.

In a review of vitamin B deficiency and nervous disease published in 1939, Aring and Spies (65) discussed the results of niacin therapy in over 300 such pellagrins having various psychiatric manifestations. In 70 patients with acute organic psychoses, that had been present from 1 to 83 days, nicotinic acid effected complete recovery. In 13 patients with chronic organic psychoses, uniform improvement was noted. No chronic pellagrous psychoses of many years duration wholly resolved, but something approaching a cure was achieved in two cases hospitalized for about nine months. In 225 mild pellagrins, symptoms typical of neurasthenia were completely relieved. These authors emphasized their observations that many persons develop mental signs of pellagra, at least to a mild degree, long before they show any other signs of the disease.

2. Nicotinic Acid Therapy in "Toxic" Psychoses Attributed to Nutritional Deficiency

In the same article (65), Aring and Spies recorded that niacin had effected prompt relief in 71 further cases, with mental changes ranging from psychoses to stupor, but with no clinical evidence of pellagra other than malnutrition (and in most cases a positive test for porphyrins or related substances in the urine). At about the same time, Cleckley, Sydenstricker and Geeslin (67) obtained beneficial results from the use of nicotinic acid in the treatment of 19 patients with comatose and stuporous states. These patients lacked the typical physical signs of pellagra, but showed evidence of toxicity or dehydration, and were regarded as having atypical psychotic states associated with malnutrition.

Two years later, however, Sydenstricker and Cleckley (68) reported a series of 29 cases, all having severe psychiatric symptoms of a confusional nature, and none having any of the physical signs of either pellagra or malnutrition. Only one had a previous history of pellagra, and in this case there had been no evidence of the disease for several years. Half of the cases in this series were lethargic or stuporous, but about a third were actively disturbed. It is interesting to note that about two-thirds were in the presenile or senile age range. The majority of these patients underwent prompt and often very impressive improvement after treatment with nicotinic acid, and the authors felt that, while these cases might ordinarily have been diagnosed as toxic psychosis or exhaustion delirium, the real cause was probably an avitaminosis sufficiently severe to produce a psychosis, but without any other indication of its presence. Seven patients underwent some degree of improvement only, one remaining psychoneurotic, while the other six showed persistent intellectual and emotional impairment, which was apparently related to cerebral arteriosclerosis, senility, or other factors. Even in these patients, it was felt that a deficiency of nicotinic acid was in part responsible for the psychiatric condition, and it was concluded that a therapeutic trial with nicotinic acid was indicated in toxic psychoses, exhaustion delirium, and other confusional psychoses of doubtful aetiology.

Gottlieb (69) in 1944 described five cases of mental confusion or stupor, occurring in middle-aged or elderly persons. These cases responded to niacin therapy, and he considered their condition to be one of "aniacinosis", emphasizing the following aetiological factors: senility (associated with inadequate nutrient intake, and following acute illness or surgical operations), chronic alcoholism (with anorexia, gastritis, and interference with absorption), and gastro-intestinal disturbances (both organic and functional). The following year, Musselman (70) reported that delirium, occurring in cases of deficiency disease when complicated by acute infections such as malaria or dysentery, was relieved by nicotinic acid and thiamin.

More recently, Foster (71) reviewed the results of therapy in 40 patients with "toxic psychosis" (an organic reaction, with memory defect and disorientation, etc.), who received nicotinamide and measures designed to correct hepatic insufficiency. Twenty of these patients were admitted to hospital because of the toxic psychosis, 11 were surgical patients who developed a toxic psychosis post-operatively, and the remaining 9 patients had functional depressions on which symptoms of a toxic psychosis were superimposed. It is noted that 23 of these 40 patients were over the age of 60. As a result of his investigation, the author reached (amongst others), the following conclusions: Toxic psychosis on a nutritional basis may occur without any physical signs of vitamin deficiency. If nicotinamide therapy is commenced immediately after the onset of the psychosis,

and adequate diet restored, the response may be very rapid and dramatic. In cases of longer duration, response to nicotinamide may be slow and may not occur until normal liver metabolism is restored, which may take some months. When the latter was restored, several patients recovered without massive doses of nicotinamide. All long-standing cases showed liver insufficiency, and the mental state did not return to normal until there had been improvement in liver function. In depressed patients with nutritional deficiency, E.C.T. was of no value until the deficiency had been corrected. The author also proposed the term "nutritional psychosis" for toxic psychosis accompanying deficiency disease.

3. Nicotinic Acid Therapy in Encephalopathies Commonly Associated with Alcoholism

Attention has already been drawn to the existence of a close association between alcoholism and pellagra (37), and the fact that 39 per cent. of the cases of pellagra recorded by Boggs and Padget (38) were postalcoholic. Biochemically, Dowan (72) has shown that nicotinic acid and riboflavin are essential for brain to metabolize alcohol, and niacin therapy has been felt to be of value in some cases of delirium tremens (68). The role of niacin will now be discussed in two syndromes which are closely related to each other—nicotinic acid deficiency encephalopathy, and Wernicke's encephalopathy. Both these syndromes: (i) have been frequently (though by no means invariably) associated with alcoholism, (ii) have been reported to respond favourably to niacin therapy (either with or without other therapeutic agents (73–77)), (iii) have been attributed, either wholly or partially, to deficiency of niacin (73–74). These encephalopathic states have been considered by some authorities to be identical (73–74), but Jolliffe and his associates (76–77), Spillane (81), and Hardwick (82) have regarded them as distinct entities.

(a) *Nicotinic Acid Deficiency Encephalopathy*

Jolliffe, Bowman, Rosenblum and Fein in 1940 reported 150 cases of a syndrome, which they termed "nicotinic acid deficiency encephalopathy" (75–76), and which was characterized by clouding of consciousness, cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes. Bender and Schilder (79), who had previously described its clinical picture, had included this syndrome as one of a group of five which they had called collectively "encephalopathia alcoholica". However, while most of their subjects were alcoholics, Jolliffe and his associates pointed out that their encephalopathic syndrome did not occur exclusively in alcoholic patients. It was observed in association with pellagra, polyneuropathy, scurvy, ariboflavinosis, delirium tremens or the Wernicke syndrome (76–77). Only half of their series of 150 cases showed other signs of nicotinic acid deficiency. When these patients were treated with routine diet and parenteral fluids, with or without additional thiamin therapy, 95 per cent. died. Mortality (from the condition itself) was reduced to 50 per cent. by feeding a vitamin rich diet, and giving concentrates of whole vitamin B complex, in addition to parenteral fluids. A further substantial reduction in mortality—to 15 per cent.—was brought about when patients were given only a basal diet and parenteral fluids, but these measures were supplemented by niacin therapy.

Sydenstricker (73) subsequently commented on having seen a number of instances of this encephalopathy, and confirmed the striking effects of nicotinic

acid in promoting rapid improvement. However, in spite of the dramatic reduction in mortality thus achieved, the recovery of mental function was found to be incomplete in a large proportion of these cases. Bowman and Wortis (80) drew attention to the fact that many patients who remained alive after receiving niacin therapy retained signs of permanent organic brain dysfunction. From these and similar observations, it has been concluded that reversible changes in cellular function of the brain ("*biochemical lesion*") may readily progress to irreversible structural changes ("*morphological lesion*") (10, 64, 67, 80–83, 98). Hence, "it does not necessarily follow that the failure of vitamin therapy to reverse a pathological process means that the disease is unrelated to deficiency of the vitamins" (82).

In his book on nutritional disorders of the nervous system, Spillane (81) remarks on the similarity between some of the case reports on acute encephalopathic states attributed to nicotinic acid deficiency and some of the older accounts of "typhoid pellagra". He goes on to speak of the dramatic response to nicotinic acid that he had observed in indigent Arabs in the Middle East, admitted to hospital unconscious, and having a variety of signs of neurological involvement including tetanic spasms of the body, tremors and rigidities of the limbs, grasping and groping movements, and writhing of the lips and tongue, sometimes with loud sucking sounds. While the immediate results of nutritional therapy in these cases was good, he considered the ultimate prognosis poor.

Spillane also mentions having seen stupor, delirium and acute psychotic symptoms in some of the German patients taken prisoner in the Channel Isles in 1945. These cases responded well to treatment, but since they received whole vitamin B complex, it was not possible to deduce a deficiency of niacin. Moreover, the majority apparently did not demonstrate the specific syndrome of neurological manifestations referred to by Jolliffe *et al.* as nicotinic acid deficiency encephalopathy.

(b) *Wernicke's Encephalopathy*

Wernicke (84) in 1881 described a syndrome characterized by clouding of consciousness, varying ophthalmoplegias, and ataxia, which was associated with acute superior haemorrhagic polio-encephalitis. In 1938, Alexander, Myerson and Pijoan (85) produced Wernicke's pseudo-encephalitis in the pigeon by feeding diets low in vitamin B_1 and high in other vitamins, a Alexander (86) subsequently showed the identity of these experimental lesi with the lesions of haemorrhagic polio-encephalitis occurring in chr alcoholism in man.

Campbell and Biggart (87) pointed out that a significant number of the cases occurred as a complication of conditions other than alcoholism, an Jolliffe, Wortis and their associates studied 34 cases of the Wernicke syndrome three of which were in non-alcoholics (77–78). The latter group found polyneuropathy, considered due to thiamin deficiency, to be present in all instances, and nicotinic acid deficiency encephalopathy in approximately a third of their cases. Whenever appropriate specific therapy (e.g. thiamin, or nicotinic acid) was given early enough, improvement or cure resulted. From their own observations, and a review of the literature, these authors reached (among others) the following conclusions: The syndrome originally described by Wernicke is probably a combination of several nutritional deficiencies affecting the nervous system. It is invariably associated with a deficiency of thiamin (78), but there is usually a lack of other nutritive essentials (one of these being niacin). The ophthalmoplegia is due to a thiamin deficiency, and is always preceded or

accompanied by peripheral neuropathy. The clouding of consciousness may be related to anything which interferes with proper cerebral metabolism (e.g. lack of carbohydrate, oxygen, thiamin, niacin or riboflavin). Delirium frequently precedes the onset of this syndrome, and in recovered patients the development of a Korsakoff syndrome is the rule.

A number of other contributions have since been made towards the further understanding of Wernicke's encephalopathy, but most of them fall outside the scope of the present article, whose concern with the latter syndrome is confined to the role of nicotinic acid in its causation or treatment. However, it may be relevant to mention here that Meyer (88) has drawn attention to an apparent negative correlation between the neuropathology of this syndrome and of pellagra. Currently accepted formulations on the aetiology of Wernicke's encephalopathy (74, 81–82) tend to concur substantially with that of Jolliffe, Wortis *et al.* (vide supra) in emphasizing the presence of thiamin deficiency, but in recognizing the likelihood of associated deficiencies (particularly of niacin or other members of the vitamin B complex).

4. Nicotinic Acid Therapy in Organic Psychoses Associated with Senescence and Senility

Reference has already been made to the fact that mild degrees of vitamin deficiency are probably usual in elderly persons, and to the observation of Boggs and Padget (38) that nearly a third of their cases of pellagra were of the senile type. In the past fifteen years numerous accounts have appeared of improvement in mental confusion and other signs of organic psychoses occurring in senility, following the administration of nicotinic acid and other metabolic agents.

Wexberg (89–90) in 1941 analysed in some detail the manifestations of neurometabolic deficiency in old age (for which he proposed the term "senile encephalomyelosis"). Evidence of brain involvement consisted of mental confusion, ranging from mere disorientation as to time to delirium with clouded sensorium, extreme restlessness, hallucinations, severe anxiety, and frequent paranoid delusions. The onset was acute or subacute, and often superimposed upon an already existing senile or arteriosclerotic dementia. It was found that improvement of the mental disorder or complete recovery under treatment with thiamin chloride, nicotinic acid, and liver extract, was sometimes very dramatic —being observed occasionally even in apparently moribund patients— and occurred in some cases of senile delirium in which no physical signs of deficiency were present.

Similar results were achieved the same year in a controlled experiment by Stephenson, Penton and Korenchevsky (91), who administered vitamins B and C to 40 patients suffering from senile dementia. Improvement in the mental condition was recorded in 25 of these patients, in that they were less incoherent and more intelligent in their talk, less depressed or less excited, brighter, more friendly and sociable, less quarrelsome, cleaner in their habits, recognized relatives and nurses, performed better work, and showed improvement in nocturnal insomnia and day sleeping.

Other authors have observed striking improvement in organic psychoses occurring in senescence or senility following the administration of nicotinic acid alone. Thus it has been noted earlier that about two-thirds of the cases in the series reported by Sydenstricker and Cleckley in 1941 (68) were in the presenile or senile age range, and Gottlieb's cases of "aniacinosis" (69) also

belonged to the same age group. Meyersburg (92), Shock (93), Schick (94) and others have pointed out that many of the psychiatric manifestations of the organic psychoses of senility are similar to those of nutritional deficiency, particularly pellagra ("pellagrous encephalopathy"), and that fatal results usually follow failure to institute appropriate therapy in the latter condition.

There has been considerable difference of opinion as to whether niacin therapy effects improvement in the psychoses attributed to cerebral arteriosclerosis and senile atrophy. Many physicians have felt that niacin is of value in such cases only when there is an associated or relative deficiency of this vitamin but this view has not been definitely established. Amongst authors who have recommended a therapeutic trial with niacin in cases with one or other of these diagnoses may be mentioned Sydenstricker and Cleckley (68), Caldwell and Hardwick (95), Strecker, Ebaugh and Ewalt (96) and Lehmann (83). These comparatively recent articles of relevance to this question are discussed below.

Moore, Morris, Smith and Lawson (97) in 1951 announced the development of a programme for the treatment of psychosis with cerebral arteriosclerosis, with special emphasis on the intravenous administration of histamine and nicotinic acid. These drugs were each administered on alternate days with the intention of effecting cerebral vasodilatation, and their preliminary report indicated very promising clinical results. Out of 24 patients with symptoms of organic brain disease, who were considered to have received adequate treatment, all but one improved. After the termination of intravenous therapy, an attempt was made to maintain this improvement by the use of oral nicotinic acid. The patients were subjected to re-evaluation of their condition at least ten months after the discontinuation of intravenous medication, and at this time it was found that 1 patient remained in hospital unchanged (he also had C.N.S. syphilis), 2 patients had improved but remained in hospital (now requiring general medical rather than psychiatric care), 5 patients had undergone improvement initially, and were at home but had remained essentially unchanged since leaving hospital, 3 patients were at home and had continued to improve after their return, 8 patients were at home showing marked clinical improvement or working part time, and 5 patients were at home, markedly improved, working full time. The authors also pointed out that, as the confusion and disorientation improved, a number of their cases became increasingly depressed, and E.C.T. was administered to a total of 9 out of the 24 cases evaluated above. In some of the latter cases there was a return of confusion, but further histamine-nicotinic acid therapy seemed to produce a rapid remission of the post E.C.T. confusion.

Gregory (98) administered large doses of nicotinic acid (300 mgm. 3 times a day by mouth, and 100 mgm. parenterally daily) to a series of patients of both sexes having organic psychoses of senility (senile psychosis, and psychosis with cerebral arteriosclerosis), immediately following their admission to a private mental hospital (when they were also receiving a highly nutritious diet containing liberal supplies of other vitamins). An attempt was made to evaluate the *degree of improvement* that might be anticipated in these cases, and the *proportion of patients* in which a given degree of improvement might be expected to occur. Systematic psychiatric examinations (with particular reference to orientation, memory, and secondary functional symptoms), supplemented whenever possible by psychological tests of intellectual function, were performed before the commencement of niacin therapy, and were repeated after maximal improvement (if any) had occurred. Every effort was made (by means of detailed enquiry from relatives, as well as relevant somatic investigations) to

establish the diagnosis beyond reasonable doubt, and particularly to exclude possible toxic aetiological factors. However, it was recognized that this is difficult in elderly subjects with confusional psychoses, since protracted cerebral decompensation may be precipitated by quite transient and minor disorders of metabolism (such as relatively mild infections, intoxications, anoxic episodes, or nutritional deficiencies).

Analysis of the results of therapy in these patients tended to corroborate certain empirical impressions derived from previous experience with much larger numbers of similar cases. The *proportion of patients* with psychoses of senility that underwent marked improvement during treatment bore a close relationship to their age. Out of 14 patients up to and including the age of 65, 8 showed either dramatic or significant improvement. Out of 40 patients over the age of 65, however, only 4 improved to a comparable degree. The *degree of improvement* observed was infinitely variable, being limited by residual signs of permanent organic brain dysfunction, similar to that described by Bowman, Worth and others (10, 65, 68, 80–83)—vide supra. It was concluded that the final level of intellectual function attained in these cases was related to two independently varying factors—namely, the initial intelligence, and the severity of the residual organic mental dysfunction (resulting from irreversible structural changes, or "morphological lesion"). After consideration of a number of possible factors involved in the causation of the latter, Gregory proposed certain *tentative criteria for the estimation of prognosis* in these cases (98). He postulated that the degree of improvement (or final level of intellectual function) in any individual case could frequently be predicted by assessment of the following (and possibly other) factors:

(i) former *intelligence* (the prognosis being better in those whose former intelligence was high),

(ii) *age* (the prognosis being better in younger patients),

(iii) *duration of psychosis* at commencement of therapy (the prognosis being better in cases of recent, and fairly rapid, onset),

(iv) a clinical *diagnosis* of "psychosis with cerebral arteriosclerosis" (carrying a more favourable prognosis than that of "senile psychosis"),

(v) a psychosis with pronounced *secondary* (*functional*) *signs*, particularly of depression (carrying a more favourable prognosis than a psychosis with only primary signs of organic confusion),

(vi) adequate dosage of niacin, and *administration* for a sufficient length of time.

It is interesting to apply these prognostic criteria in retrospect to the series of cases recorded by Moore *et al.* (97), which has been reviewed earlier. While the high proportion of cases in this series that underwent improvement may be attributed to differences in therapeutic technique (and possibly also diagnostic criteria) several of the above factors are applicable, and may have indicated a relatively favourable prognosis *ab initio*: (*a*) age—only two of these patients being over the age of 65, (*b*) diagnosis—all having a clinical diagnosis of "psychosis with cerebral arteriosclerosis", (*c*) secondary signs of depression. In one-third of these patients (8 out of 24) the psychosis was considered "predominantly affective", and 6 of this group (75 per cent.) were markedly improved following treatment. The remaining two-thirds of the patients (16 out of 24) were considered "predominantly cognitive", and only 7 of the latter group (approximately 45 per cent.) underwent marked improvement.

One further article concerning niacin therapy in the organic psychoses of senility is mentioned here, in view of its recency and some apparent variance with the two that have just been discussed. Levy (99) has published an account of the administration of various combinations of three drugs to 30 aged mental hospital patients, 21 having primary diagnoses of chronic brain syndrome with cerebral arteriosclerosis or senility, and the remainder being felt to have senile changes overshadowing their original mental disturbances. All were over the age of 60, and the average duration of hospitalization was 7 years, the shortest stay in hospital being 9 months. The three therapeutic agents consisted of cytochrome C, leptazol (metrazol) and nicotinic acid, and were chosen for their stimulatory, vasodilatory and enzymatic properties. Levy found that nicotinic acid alone, which he employed in doses of 100 mgm. orally 3 times a day with the intention of producing vasodilatation (although it must be noted that this dosage effects relatively little vasodilatation), was ineffective therapeutically, as were each of the other two drugs when administered singly. However, when the same doses of nicotinic acid and leptazol as had been given separately were prescribed in combination, he observed both objective and subjective improvement in these patients, with a marked improvement in behaviour and a definite (though less remarkable) increase in intellectual function (the average gain in the Wechsler-Bellevue intelligence quotient being 6 points). In this connection, the relatively minor improvement in the intellectual function of a large proportion of the patients in this series might have been predicted, in view of the diagnoses and duration of confusional symptomatology (and possibly also the dosage of drugs employed).

It remains to be pointed out that considerable further controlled research is indicated into the efficacy of various therapeutic agents in this important group of organic psychoses of senescence and senility—which constituted over 15 per cent. of the first admissions to Canadian mental institutions (exceeded only by schizophrenia) in a typical recent year (100). It would also be of interest to learn the relationship (in the causation and treatment of these disorders) of niacin to other enzymatic or vasodilator drugs, including niacinamide (which possesses the same vitamin properties, but does not produce vasodilatation—vide infra).

5. Nicotinic Acid Therapy in Psychiatric Disorders Apparently Unrelated to Nutritional Deficiency

Nicotinic acid deficiency of varying degree or duration has been held to be either wholly or partially responsible for the development of all psychiatric manifestations that have been ameliorated by administration of this substance —including all the disorders hitherto discussed. However Wexberg (90), Lehmann (83), and others have concluded that it is not justifiable to postulate such a deficiency merely on the basis of a successful therapeutic test with nicotinic acid, since the latter may exert a beneficial effect by means of other mechanisms or modes of action (vide infra).

Apart from some of the cases already reviewed, there have been several reports of favourable results from niacin therapy in cases of both organic and apparently functional disorders in which no evidence of nutritional deficiency was discovered. Thus Lehmann (101), in 1944, described a case of post-traumatic confusional psychosis that resolved completely following administration of massive doses of niacin. The patient was a forty-three year old man who had

suffered concussion in an accident, had remained in a state of confusion for the following nine weeks, and had undergone gradual mental deterioration in spite of several types of treatment. Careful enquiry into his previous history, together with thorough physical examination and laboratory investigation, failed to reveal any nutritional deficiency or other aetiological factor apart from cerebral trauma. In addition to establishing the diagnosis beyond reasonable doubt, special care was taken to ascertain whether the patient's improvement was really due to the administration of niacin, and was neither spontaneous and coincidental, nor resultant from other physical or psychological factors. He was examined several times daily, both psychiatrically and by means of psychological tests, throughout the course of treatment as well as for some time previously. The changes in his condition were dramatic and almost immediate. A definite improvement in memory was noted on the second day of niacin therapy, and all major symptoms of organic mental impairment resolved within a week. The patient had wholly recovered by the end of a month, and was able to leave hospital and resume his former employment as an accountant.

The same author has drawn attention to the use of nicotinic acid in combination with other drugs—and, to a lesser extent, alone—for sedating patients with organic brain disease and senile disturbances (102). By administering a preparation containing nicotinic acid and minimal doses of several sedative drugs, having different sites of elimination or detoxification and varying durations of action, it was found possible to avoid the marked and sometimes prolonged increase in mental confusion that commonly follows the administration of an effective dose of a single sedative to a patient of this type. At the same time, the overall sedative effect of the combination of drugs was rendered adequate through synergistic action of its components.

A further therapeutic application of niacin mentioned by Lehmann (83) is its administration to patients exhibiting more than the usual amnesia following electro-convulsive therapy. Its use in this syndrome has been corroborated by Parsons, and Moore *et al.* (97), amongst others, and niacin has also been considered of some value in cases of prolonged insulin coma (103) and in the confusional state that may follow the latter.

In many of the psychiatric disorders found by earlier workers to respond to niacin therapy, depression is frequently a prominent feature (e.g. organic psychoses occurring in classical pellagra, psychoneurotic syndromes due to mild niacin deficiency, organic psychoses of senescence and senility, and other toxic or organic reactions), but this substance has also been applied to the treatment of apparently functional depressions. In an article published in 1950, Wilkinson (106) described the use of nicotinic acid as a pharmacological adjunct to psychotherapy in patients with various types of depression, almost all functional in origin. Out of 29 patients receiving this treatment, the results in 14 (which included those believed to have a high degree of suggestibility) were considered inconclusive. The remaining 15 patients were all university students between the ages of 18 and 46. In this group, all but one showed a marked elevation in mood and activity-level within a few days of commencing niacin therapy, and some of them relapsed while taking the drug. Eleven of them required further treatment at a later date, but in each instance an improvement identical with the first occurred on repeating the medication. The author felt that no conclusion could be drawn from the improvement observed in this small group of patients, but that the results were of sufficient uniformity to render further investigation desirable.

Another article has since appeared, in which Thompson and Proctor (105)

recorded their experience in the use of nicotinic acid together with phenobarbital in the management of depressive and anxiety reactions. Initially they used nicotinic acid alone, but were not impressed with the response of depressive patients, and observed that those presenting a mixture of depressive and anxiety symptoms responded better. They then administered a combination of nicotinic acid with phenobarbital and selected for study the first 100 patients so treated, who ranged in age from 21 to 60. Tablets containing nicotinic acid 100 mgm. and phenobarbital 8 mgm. were given in doses of ½ or 1 tablet at 3 successive intervals before meals for 21 days. The results were based as objectively as possible on clinical observation and what the patients and their families reported, reliable follow-up histories being available in 91 of these cases. 34 per cent. of the cases studied showed "definite improvement" during treatment, being relieved of most of their symptoms, and requiring no further intensive treatment. A further 47 per cent. were considered to have undergone "some improvement" but required other treatment.

It would appear that further research is indicated into the administration of nicotinic acid to patients with functional psychiatric disorders, as well as the organic disorders discussed previously, but that such research would be rendered more valuable by comparison of the results with those obtained in similar series of untreated controls.

SECTION C: THE ACTIONS AND ADMINISTRATION OF NICOTINIC ACID

1. Pharmacology: Postulated Actions of Nicotinic Acid

Several possible modes of action will now be considered, by which niacin may effect improvement in various psychiatric disorders: (*a*) elimination of an existing vitamin deficiency, (*b*) mass action on cellular metabolism ("saturation effect"), (*c*) cerebral vasodilatation with increased blood supply to the brain, (*d*) other actions—physical and psychological.

(a) *Elimination of an Existing Vitamin Deficiency*

The normal metabolism of the nervous system (106) is dependent, among other things, on: (i) an adequate supply of oxygen, (ii) an adequate carbohydrate substrate, (iii) intact enzyme and coenzyme systems. Glucose is the main substrate utilized in the respiration of the grey matter, and studies have shown that 80 to 90 per cent. of the normal respiration of the brain can be accounted for by glucose consumption (107). The vitamins thiamin, riboflavin and nicotinic acid are essential constituents of certain of the tissue enzymes involved. Nicotinic acid is pyridine carboxylic acid, and its amide is present as a prosthetic group in the di- and tri-phosphopyridine nucleotides (DPN and TPN) known as coenzymes I and II (cozymase (108) and coferment (109)) respectively (110, 111). It has been established that these two coenzymes are involved in both glycolysis and respiration (112).

Now, although nerve fibres can contract a small oxygen debt, grey matter cannot do so, and is highly susceptible to deprivation of its supply of oxygen, glucose or essential vitamins (106). If there is a deficiency of one or more of these essential substances, reversible changes in cellular function occur ("biochemical lesion"), which may progress to irreversible structural changes ("morphological lesion"). Such disorders of function or structure of the brain are accompanied by evidence of disordered psychological functions (e.g. perception, ideation and

behaviour). The impairment of various psychological functions due to anoxia has been studied extensively (113), and it is known that similar manifestations result from hypoglycaemia, or from deficiency of one of the constituents of the enzyme or coenzyme systems, including nicotinic acid.

At least one action of nicotinic acid in any psychiatric disorder in which it is administered must be the elimination of any existing deficiency of this vitamin, and the restitution of disordered cellular metabolism. Some investigators have concluded that this is its only mode of action, and that there must be some relative or associated deficiency of nicotinic acid in every syndrome in which it is genuinely beneficial. However, several other possible mechanisms of action have been postulated, and are discussed below.

(b) *Mass Action on Cellular Metabolism* ("*Saturation Effect*")

It has been suggested that massive doses of niacin may produce their beneficial action, in syndromes where there is no deficiency of the vitamin, through some kind of "saturation effect" (83). In the latter instance, it would still be operating through a direct action on cellular metabolism, though not by replacement of a deficient factor. Certain evidence in support of this possible mode of action will now be considered.

It has already been noted that coenzymes I and II are involved in both glycolysis and respiration (112), and this is perhaps illustrative of the intimate functional interrelationships of the various substances essential for the metabolism of brain. Thus deficiency of one such essential substance may cause deficiency of another—hypoglycaemia, for example, has been shown to cause profound anoxia (114). Moreover, the impairment of function caused by deficiency of one such essential substance may be partially corrected by the administration of another such substance without the initial deficiency being corrected. Thus McFarland and others (113) found that the impairment of visual sensitivity caused by hypoglycaemia was counteracted by administration of oxygen, and conversely that administration of glucose tended to reduce the impairment in visual sensitivity brought about by anoxia.

It would be reasonable to suppose that a similar effect might occur following administration of nicotinic acid, and the results of several experiments tend to confirm this supposition. Mosell (115) in 1940 noted that nicotinamide produced an increase in the capacity for hard muscular exercise at sea level, and Frankau (116) in 1943 observed acceleration of co-ordinated muscular effort by the same substance.

Calder (117) in 1948 suggested on theoretical grounds that the enzymatic phases of cellular respiration might constitute a protective mechanism, useful in tiding the animal organism over a temporary period of reduced oxygen tension, and that this might well be the device by which the tissues were enabled to accumulate an "oxygen debt" during excessive muscular exercise. The effectiveness of this mechanism would depend on an adequate supply of oxidized coenzyme, and if part of the latter were trapped in the reduced state because of lack of oxygen, the administration of nicotinic acid might augment the available supply of coenzyme, and thus partly correct the induced deficiency. He therefore investigated the effects of nicotinic acid on anoxia in rats subjected to low barometric pressures. He found that rats treated with nicotinic acid or its amide were able to survive a greater degree of anoxic anoxia than untreated controls. Similarly, the tachypnoea developing at low barometric pressure (with diminished oxygen tension) was much less in treated than in untreated rats.

(e) *Cerebral Vasodilatation, with Increased Blood Supply to the Brain*

In addition to the two preceding actions on cellular metabolism—the former established and the latter hypothetical—niacin has a pronounced systemic action. Smith, Ruffin and Smith (6), together with other pioneers in its application to the treatment of pellagra, observed marked vasodilatation following the administration of niacin, but not niacinamide. Abramson, Katzenstein and Senior (118), using the venous occlusion plethysmograph, demonstrated that increased bloodflow occurred through the arm, and to a lesser extent through the leg, following oral or intravenous administration of nicotinic acid. There has since been considerable controversy as to whether this vasodilatation affects the cerebral vessels, and, in the latter event, whether the increased blood supply associated with such cerebral vasodilatation is responsible for the beneficial effects of niacin therapy in some psychiatric syndromes.

Moore (119) in 1940 reported that nicotinic acid caused an increase in cerebrospinal fluid pressure in humans, and dilatation of the pial vessels in the cat. The following year, Aring *et al.* (120) noted that nicotinic acid caused an increase in the rate of cerebrospinal fluid displacement, occurring during a standardized sudden brief compression of the veins of the neck, and concluded that it caused an equivalent increase in intracranial blood flow. However, Loman, Rinkel and Myerson (121) administered the drug by the intravenous, intrabrachial and intracarotid routes, and recorded the following findings: (i) the cerebrospinal fluid pressure was not significantly altered, (ii) the calibre of the retinal vessels was unaltered, (iii) the cerebral bloodflow, using changes in the arteriovenous differences in oxygen content as an index, was only slightly increased, while the bloodflow in the arm was moderately to markedly increased, (iv) nicotinic acid shortened the Raynaud-like response produced by epinephrine when both drugs were injected into the brachial artery.

The latter results are supported by those of a more recent study. Using the nitrous oxide method for measuring cerebral bloodflow, Scheinberg (122) in 1950 investigated the effects of nicotinic acid in 20 subjects. He concluded that "intravenous nicotinic acid in flushing doses produces no change in cerebral blood flow, arteriovenous oxygen and glucose difference, oxygen and glucose consumption, or vascular resistance". The comment may be made, however, that the findings as initially recorded would tend to indicate a considerable increase in cerebral blood flow in two cases, and a diminution in arteriovenous oxygen difference in four cases, but that the author attributed these findings to contamination of the internal jugular blood by extracerebral blood.

Opposed to the results of the latter two investigations, and in support of the earlier studies of Moore (119) and Aring *et al.* (120) are the findings of Furtado *et al.* (123), who investigated nicotinic acid and its derivatives for a number of years. In animals, they measured and photographed variations in calibre of the small vessels of the cortex and the retinal vessels, while in man they investigated the effects of intravenous injections on retinal vessels, ocular tension, C.S.F. pressure, blood pressure and skin temperature. They found that nicotinic acid and quinine nicotinate had a very marked vasodilating action on cerebral and retinal vessels, while nicotinic acid amide had not, except in very large doses. The characteristics of this vasodilatation were as follows: (i) it was more marked for the small vessels of the brain, particularly the arterioles, than for the large, (ii) the retinal vasodilatation was accompanied by cerebral vasodilatation, (iii) it could be obtained by retro-ocular injection of the nicotinic derivative, (iv) it was accompanied by a very moderate fall in blood pressure

and a certain increase in C.S.F. pressure, (v) its action was transient, vessels returning to their previous calibre within 15 to 20 minutes. It was also found that, as compared with other substances tried out under the same conditions (acetylcholine, histamine, aminophylline, nitroglycerine), the cerebral vasodilating action of these nicotinic derivatives was much stronger and almost without repercussions on the general circulation.

The latter investigations are the most extensive in the literature, but in view of the conflicting experimental evidence it may still be questioned whether nicotinic acid causes cerebral vasodilatation, with increased cerebral blood flow, in all instances. It may well be that niacin is better able to effect vasodilatation in individuals with mild cerebral arteriosclerosis (with functional rather than structural constriction of the cerebral vessels) than in those with normal vessels.

In this connection, it may be mentioned that Scheinberg's 20 cases were all chosen at random from the wards of a general hospital, that the oldest member of the group was aged 60, and that none were reported to be showing psychotic symptoms.

Pugsley, Woodward and Katy (124), using the nitrous oxide technique, have made quantitative measurements of cerebral blood flow and metabolism in patients with organic psychoses of senility. They concluded that these psychoses of senility were associated with, and probably the result of a significant reduction in cerebral oxygen utilization, on the basis of an increased cerebrovascular resistance and its resultant significant reduction in blood flow through the brain. It would be interesting to compare the effects of nicotinic acid on cerebral blood flow and metabolism in a similar group of patients having psychoses of senility, with these effects of nicotinic acid in a group of normal controls.

Inferences as to the occurrence of vasodilatation in the psychoses of senility could also be made from a comparison of the clinical effects of niacin and nicotinamide in such patients, it being agreed that the latter has no such effect.

(d) *Other Actions—Physical and Psychological*

For the sake of completeness two other possible actions of nicotinic acid may be recorded.

It has been suggested (85) that in some conditions niacin may act as a "physical alexipharmic", and that the repeated pronounced peripheral vasodilatation may be compared with the effects of physiotherapy which in most of its applications also produces vasodilatation.

It is also noted that the pronounced vasodilatation often makes a strong impression on the patient, and it may therefore exert some effect by rendering the patient more receptive to suggestion by the therapist.

2. The Administration of Nicotinic Acid

The mode of administration of this drug, and the dosage, depend on whether it is being given prophylactically or therapeutically.

(a) *The Prophylactic Administration of Nicotinic Acid*

The average daily adult requirement of nicotinic acid is about 12 to 20 mgm. (19). The presence of this quantity in the diet is ensured by informed food selection and by food enrichment. In a recent evaluation of the enrichment

programme in the United States, Sebrell (125) pointed out that in the 1920's and 1930's pellagra was the most serious deficiency disease in that country. For the past 25 years, however, the incidence of pellagra has shown a consistent downward trend. This is attributable in part to complex socio-economic factors, but also to a public health programme of nutritional education and enrichment. Enrichment of bread with niacin (and other nutrient essentials) was commenced on a voluntary basis in 1941, and made compulsory by Federal law from 1943 to 1946. Since this time more than half the States have passed laws making enrichment mandatory, and the programme has been largely continued on a voluntary basis in the remaining States.

In 1928, at the height of reported mortality in that country, there were approximately 6 deaths per 100,000 population from pellagra. By 1937, the year niacin was isolated and applied to the treatment of pellagra, the mortality was about 2·5 per 100,000. In 1943, two years after niacin-enriched foods appeared on the market, the rate was 1, and by 1950 it had dropped to 0·2 per 100,000 population. Mortality rates do not reflect the true health importance of pellagra (in a region of high prevalance, for example, at least 33 cases per death were found in 1917), but there has also been a corresponding reduction in the incidence of recognizable clinical pellagra reported from various centres. Even among chronic alcoholics, once commonly afflicted, clinical pellagra has become rare, in spite of the fact that there appears to have been no significant change in their economic status, alcoholic consumption, or eating habits, apart from the consumption of vitamin-enriched bread. Comparable declines have been noted in the incidence of both Wernicke's encephalopathy and the syndrome of "nicotinic acid deficiency encephalopathy" described by Jolliffe, which have also been attributed to the enrichment of bread and flour with thiamin and niacin respectively (126).

However, Sebrell recognizes that there remains the problem, the extent of which is uncertain, of borderline deficiencies of niacin and other nutrients. Such subclinical deficiencies are probably extremely common in alcoholism, senility and a number of other conditions—biological, psychological and/or social in origin. It has been suggested that some deficiency of niacin may well contribute to the production of the organic psychoses associated with senility (and alcoholism), and hence that administration of amounts in excess of the normal adult requirements may help to prevent or delay their onset. It is also necessary that the education of physicians shall make them aware of the great variety of functional and organic disorders in which vitamin requirements are increased (v. supra—section A, 2) so that they may prescribe adequate amounts of supplementary vitamins at such times.

(b) *The Therapeutic Administration of Nicotinic Acid in Psychiatric Disorders*

There are several aspects of the therapeutic administration of niacin that require consideration: (i) whether niacin is preferable to niacinamide or vice versa, (ii) whether other nutritional therapy should be administered concurrently in all cases, (iii) the route of administration, (iv) the size and frequency of dosage, (v) the duration of therapy.

(i) *Selection of niacin or niacinamide.* After taking an oral dose of 50 mgm. or more of nicotinic acid, particularly on an empty stomach, flushing of the face, neck and other parts of the body may occur within ten or twenty minutes. In larger doses, many patients complain of burning, itching, headache, palpitation, abdominal discomfort, or other subjective sensations resulting from vasodilatation. Niacinamide does not cause this vasodilatation, and may therefore

be preferred when only the metabolic actions of the vitamin are required. Some authorities have stated that the use of niacinamide is always to be preferred to that of niacin. However, at least part of the therapeutic effect of niacin in some psychiatric disorders has been attributed to cerebral vasodilatation, with increased blood flow to the brain (v. supra). Hence, *in the present state of our knowledge regarding its actions in psychiatric disorders, it is probably advisable to use nicotinic acid rather than its amide in all but clear-cut deficiency states* (83).

(ii) *Administration of other nutritional agents concurrently with niacin.* It has been pointed out that pellagra may be precipitated by diets deficient in tryptophane (believed to be the precursor from which niacin is synthesized in the intestines), and is usually associated with a deficiency of one or more other vitamins, particularly thiamin and riboflavin. Consequently, for the adequate treatment of pellagra, it is usually recommended (10–12, 32, 46, 127) that, in addition to specific therapy with niacin or its amide, a diet should be prescribed that is rich in protein (as well as foods containing niacin), and whole vitamin B complex should also be administered.

Moreover, it has been remarked (13, 81) that large doses of a single vitamin, especially of the B group, may precipitate latent deficiencies of other vitamins, and so cause unpleasant side-effects. In view of these considerations, *when nicotinic acid is administered in psychiatric disorders, it is probably advisable to administer other supplementary vitamins (particularly whole vitamin B complex) together with a high protein diet if there is any possibility of nutritional deficiency, and perhaps in all instances.*

(iii) *The Route of Administration* selected depends partly on the severity of the disorder present and partly on the rationale for therapy with niacin. The substance may be administered either orally or parenterally, but the latter route is nowadays rarely considered necessary in cases of deficiency disease unless the condition of the patient is critical, as in delirium or coma. In such cases parenteral administration is adopted during the initial phases of treatment.

The intravenous route has also been used by a number of investigators for the purpose of effecting rapid vasodilatation. However, it is not wholly devoid of risk, an occasional severe reaction with collapse having been observed. In any event, marked vasodilatation can be obtained readily, conveniently, and as often as desired, by the oral administration of adequate doses, particularly on an empty stomach.

(iv) *Size and Frequency of Dosage.* Different schedules of dosage recommended vary greatly, and again depend partly on the severity of the disorder present and partly on the rationale for this form of therapy. In cases of pellagra, maximal dosage is prescribed initially, the total amount varying from 200 to 1,000 mgm. daily according to the severity of the condition, 500 mgm. being generally as usually effective. This total amount is frequently administered in divided doses (e.g. 50 or 100 mgm., from four to ten times a day) for the purpose of maintaining the blood level. All or a part of this amount may be given parenterally initially, but administration is usually oral, and dosage is gradually reduced over a period of several weeks. However, it is sometimes recommended that, even when the patient has apparently fully recovered, a maintenance dose of 50 to 150 mgm. orally per day should be continued for prolonged periods, and perhaps indefinitely in senile patients.

Doses prescribed in order to effect vasodilatation have often been larger but less frequent—individual doses recorded being as high as 400 mgm. intravenously or 900 mgm. orally, but sometimes being administered only every

second day or at even longer intervals. However, a number of physicians have prescribed for this purpose several large doses daily by mouth. One such regime, which incidentally provides a convenient compromise between the divided doses suggested in deficiency disease and the relatively large doses desired for marked vasodilatation, is the administration of 300 mgm. three times daily ½ to 1 hour before meals.

(v) *The Duration of Therapy* depends again partly on the rationale, but also on the patient's response to therapy. In pellagra of acute onset there is usually a fairly rapid response over a period of a few days, and sometimes even a dramatic improvement within a few hours, but in cases of longer duration the response tends to be much slower and the recovery of function less complete. Probably a considerable proportion of the final recovery of function will have occurred within a week, and most within a month, of the commencement of maximal dosage. However, it should be noted that a three months' trial of therapy has been recommended in psychoneurotic syndromes believed due to mild niacin deficiency.

Similar responses to therapy have been observed in other organic mental disorders of less certain aetiology, in which niacin may have been acting by virtue of its metabolic properties or by means of vasodilatation or both. In cases in which the rationale of niacin therapy has been vasodilatation alone, it has been a common practice to place the patient on a therapeutic trial of about three or four weeks duration.

3. Conclusion: Rationale for Administration of Nicotinic Acid in Psychiatric Disorders

Nicotinic acid has been selected for consideration from amongst the other members of the vitamin B complex with full recognition of a number of factors that might argue against such special attention, including the following: (i) that there is an intimate functional interrelationship (biochemical and physiological) between the various members of the vitamin B complex, (ii) that deficiency of one member of the vitamin B complex is commonly associated with varying degrees of deficiency of the other members, (iii) that psychiatric manifestations of deficiency of one such member of the B complex may be very similar to those caused by deficiency of another member, (iv) that administration of one member of the vitamin B complex may precipitate latent deficiencies of other members, (v) that for all these reasons, administration of niacin should be accompanied by administration of other members of the vitamin B complex (though not necessarily in equivalent dosage).

Nevertheless, the literature on niacin specifically has appeared to merit individual consideration, for several reasons: (i) mild degrees of niacin and other vitamin deficiencies are probably much more common than generally realized, (ii) the first signs of niacin deficiency may be the development of psychiatric manifestations, (iii) the psychiatric manifestations of niacin deficiency may possibly be more pronounced than those of equivalent degrees of deficiency of other members of the vitamin B complex, (iv) if niacin deficiency remains uncorrected, these psychiatric manifestations may become irreversible, (v) improvement in certain psychiatric disorders following administration of niacin is attributed to vasodilatation, an action not possessed by niacinamide or other members of the vitamin B complex.

Finally, the psychiatric disorders in which nicotinic acid has been reported

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THE EFFECT OF EXCESSIVE NICOTINAMIDE FEEDING ON RABBITS AND GUINEA PIGS

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Slightly depressed growth and fatty livers were observed in animals fed moderate amounts of nicotinamide, while larger quantities completely inhibited growth (1, 2). The fatty livers were found to be susceptible to the action of choline, while only methionine was found to alleviate the growth inhibition. These phenomena were ascribed to the forced synthesis of trigonelline from nicotinamide with consequent diminution of the "labile methyl" supply, or, more specifically, the supply of methionine. It has since been demonstrated (3) that the methylated excretory product resulting from nicotinamide feeding is not trigonelline but N^1-methylnicotinamide (F_2). However, it was not determined whether the effects of nicotinamide feeding were due solely to the diminution in the "labile methyl" supply or to toxicity of the excess, unmethylated nicotinamide.

In the present work it has been found that the ingestion of large quantities of nicotinamide by young rabbits and guinea pigs does not impair their growth. Since neither of these species excreted extra N^1-methylnicotinamide after nicotinamide feeding, it is concluded that the toxic effects of nicotinamide in the rat are due entirely to the synthesis of N^1-methylnicotinamide and consequent depletion of available methionine.

EXPERIMENTAL

Rabbits—Two diets were employed in this series. Diet A was a commercial rabbit chow in pellet form[1] used as a stock feed for our colony. Nicotinamide was incorporated therein by spraying a shallow layer of pellets with the proper volume of a 10 per cent solution and then drying in a current of warm air. Diet B was a mixture of oats, rye, alfalfa, grass, and other dry vegetable matter and nicotinamide was added to this ration in the same manner. All animals were housed in individual cages and were offered hay *ad libitum* every 5th day. Weanling rabbits, average weight 1250 gm., were used and after 20 days the animals were sacrificed by decapitation and samples of liver taken for fat analysis. Urinary N^1-methylnicotinamide excretion was determined by the method of Huff and Perlzweig (4) on the pooled urines of three rabbits collected for 48 hours

[1] Purina chow, Ralston Purina Company, St. Louis, Missouri.

on the 15th and 16th days of the experiments. These measurements were very kindly performed by Mr. Jesse W. Huff of the Biochemistry Department. The results are summarized in Table I. It will be seen that the presence of nicotinamide in either diet had no significant effect on the animals' growth, liver fat content, or urinary N^1-methylnicotinamide excretion.

As controls, young rats were also fed Diet A. These results are also presented in Table I. They agree completely with the observations previously obtained with synthetic diets (1). No data are presented for the N^1-methylnicotinamide excretion of rats, as this has already been done in detail (1). For comparison with the results obtained herein with rabbits and guinea pigs it may be stated that under comparable circumstances the

TABLE I

Effect of Nicotinamide Feeding on Rabbits

Basal diet	Test animal	Supplement to basal diet	Weight change	Liver fatty acids	F_2 excretion
			gm. per day	*per cent*	*γ per day*
A	Rabbits	None	25.3	4.5	740
"	"	1% nicotinamide	22.1	4.3	790
"	"	2% "	20.9	3.9	800
"	Rats	None	2.9	5.2	*
"	"	1% nicotinamide	1.1	11.4	*
"	"	2% "	−0.6	3.1	*
B	Rabbits	None	21.0	3.5	1030
"	"	1% nicotinamide	17.3	3.9	970
"	"	2% "	22.5	3.6	1120

* Complete data have already been published (1).

presence of 2 per cent nicotinamide in rat diets produced an 80-fold increase in N^1-methylnicotinamide (thought to be trigonelline at the time) excretion.

Guinea Pigs—The basal diet used in this series was patterned after that of Woolley (5). The composition of Basal Diet 1 was as follows: casein 20, sucrose 45, cod liver oil 5, cottonseed oil 10, salt mixture (6) 5, and linseed meal 15. The linseed meal was extracted three times at room temperature with a 75:25 mixture of ether and alcohol to remove some of the choline, since seed meals have been reported to be a rich source of this substance (7). Each kilo of diet also contained thiamine 3 mg., riboflavin 5 mg., pyridoxine 3 mg., nicotinic acid 10 mg., pantothenic acid 25 mg., and ascorbic acid 100 mg. Basal Diet 2 was similar to this but contained in addition, 0.15 per cent of choline and of inositol. The animals were offered the experimental diets *ad libitum* 7 days after birth. Their average weight at the start of the experiment was 124 gm. N^1-Methylnicotinamide values

were calculated from determinations performed on the pooled urine of three guinea pigs collected for 48 hours on the 16th and 17th days of the experiment. The results are summarized in Table II. All the animals ate sparingly for the first 5 days on the experimental diets. Accordingly, the figures presented in Table II were determined for a period of 3 weeks following the 5 days of relative anorexia.

Again the presence of nicotinamide appeared to exert no toxic effect. No significant disparities in growth, liver fat content, or N^1-methylnicotinamide excretion were noted.

TABLE II

Effects of Nicotinamide Feeding on Guinea Pigs

Diet	Weight change	Liver fatty acids	F_2 excretion
	gm. per day	*per cent*	*γ per day*
Basal Diet 1	1.2	4.3	110
" " 1 + 1% nicotinamide	1.3	4.4	125
" " 2	1.8	3.6	155
" " 2 + 0.5% nicotinamide	1.4	4.1	
" " 2 + 1.0% "	2.2	4.0	185
" " 2 + 2.0% "	1.5	3.7	

DISCUSSION

It is apparent from these data that large amounts of nicotinamide in the diet of rabbits and guinea pigs are innocuous. Unlike the rat, these species do not synthesize and excrete extra N^1-methylnicotinamide under these conditions. Since the effects of nicotinamide on the rat are completely alleviated by the administration of methionine, and since nicotinamide is not toxic in the diet of the rabbit or guinea pig, it seems likely that the toxicity of this compound in the diet of the rat is due solely to the synthesis of N^1-methylnicotinamide with consequent depletion of the available methionine supply. This situation, then, affords an example of a process in which an essentially innocuous substance undergoes what has been considered a "detoxication" reaction and thereby produces deficiency of a necessary dietary component.

By elucidating the mechanism of nicotinamide toxicity, the present work confirms and amplifies the conclusion earlier reached concerning the essentiality of a diet capable of supporting growth in the production of fatty livers due to choline deficiency (1, 2, 8). This conclusion has been criticized by McHenry and Patterson (9) who attributed the results obtained with nicotinamide feeding to a non-specific toxicity of unknown mechanism. The present work, however, substantiates the original hypothesis that the

inclusion of nicotinamide in the rat diet is simply tantamount to feeding a methionine and, hence, choline-deficient diet. Since the objections of McHenry and Patterson appear groundless, the original conclusion remains valid. While small amounts of dietary nicotinamide permitted rat growth and induced fatty liver formation, large quantities completely inhibited growth and no fatty infiltration of the liver occurred (1, 2). The failure of fatty livers to appear in the concomitant presence of choline and thiamine deficiencies is probably, as in the case of nicotinamide feeding, an example of the general concept that the fatty livers otherwise associated with choline deficiency are not manifest when the basal diet is incapable of supporting growth.

However, it must also be stated that this conclusion applies only to short term experiments such as those which have been employed to study simultaneous choline and thiamine (10), riboflavin (11), and methionine (1) deficiencies. In experiments of longer duration[2] it has appeared that when the animals cease losing weight and the growth curves reach a plateau accumulation of fat in the liver does occur.

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BIBLIOGRAPHY

1. Handler, P., and Dann, W. J., *J. Biol. Chem.*, **146**, 357 (1942).
2. Handler, P., and Bernheim, F., *J. Biol. Chem.*, **148**, 649 (1943).
3. Huff, J. W., and Perlzweig, W. A., *J. Biol. Chem.*, **150**, 395 (1943).
4. Huff, J. W., and Perlzweig, W. A., *J. Biol. Chem.*, **150**, 483 (1943).
5. Woolley, D. W., *J. Biol. Chem.*, **143**, 679 (1942).
6. Drummond, J. C., and Watson, A. F., *Analyst*, **47**, 235 (1922).
7. Engel, R. W., *J. Nutr.*, **25**, 441 (1943).
8. Handler, P., *J. Biol. Chem.*, **149**, 291 (1943).
9. McHenry, E. W., and Patterson, J. M., *Physiol. Rev.*, **24**, 128 (1944).
10. McHenry, E. W., *J. Physiol.*, **89**, 287 (1937).
11. Engel, R. W., *J. Nutr.*, **24**, 175 (1942).

[2] Handler, P., unpublished data.

J.A.M.A. 204:1010-1011. 1968.

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Adverse Effects of Niacin In Emergent Psychosis

To the Editor:—Since 1962, several reports have described the apparently successful treatment of schizophrenia with repeated large doses (up to 3 gm daily) of niacin, either as niacin or niacinamide.[1-5] All of these studies used a reduction in length of hospitalization as the indicator of drug effect, and although the niacin-treated patients spent fewer days in the hospital, the use of only this one measure of outcome and the lack of replication by other investigators limit the general applicability of the studies. In the *New York Times* (March 31, 1966), there was a report of suc- [illegible] (acute and chronic) schizophrenic patients by administering orally 1 to 2 gm of nicotinamide adenine dinucleotide (NAD), better known as nadide. Subsequently there have been two published reports which fail to demonstrate any therapeutic effects of this compound.[6,7]

Even though the claims of successful niacin therapy in schizophrenia have not received independent support, there continues to exist a belief in its usefulness in some lay and professional circles. We have observed that patients sometimes request niacin be used in their treatment. These requests are little different than numerous other wishes for relief and can usually be successfully dealt with. Of more serious import are those instances where niacin is prescribed and used in an attempt to ward off impending psychosis. In these instances the false sense of security stemming from the belief in the prophylactic value of niacin may lead to serious consequences. In addition there is suggestive evidence that the pharmacologic effects of niacin (particularly the flush) interact and possibly potentiate the psychotic symptoms. The following two case reports illustrate these points.

Report of Cases.—This 25-year-old white man successfully completed college at age 23 but upon graduation began to experience "break-downs" consisting of intermittent and transient episodes of "apathy, depression, worthlessness, and loneliness." The patient felt apart from his environment, and was unable to "make contact with anyone or become emotionally involved." These episodes occurred with mildly increasing frequency during the two years between graduation and his eventual hospitalization. The patient was aware of the abnormality of these feelings and after reading of the alleged usefulness of niacin for "people with schizophrenic tendencies," he took approximately 1.5 gm of niacin within a one-half hour period. Shortly thereafter he experienced a marked flush which produced considerable anxiety and within a few hours the first of a series of uncontrollable crying spells occurred with continuous feelings of panic and the need for close physical contact. The following day the patient smoked marihuana. Whereas marihuana smoking had been pleasant on four previous occasions, this time he became terrified, felt that his mind was drifting away, and that he had lost his identity. In addition, the patient began to experience frighten-

dreams. These symptoms gradually increased in severity so that hospitalization was necessary five days later. In the hospital the patient was found to be extremely fearful and agitated, with involuntary tremors of his limbs. There were repeated crying episodes alternating with periods of control, and he reported mild perceptual distortions such as people looking distant and objects moving with irregular bursts of speed. The patient was well-oriented and had not formed hallucinations or delusions. Psychologic testing two months later demonstrated a borderline psychotic character.

CASE 2.—This 28-year-old unmarried writer had taken LSD in three unsupervised sessions over the year prior to his hospitalization. The reactions were very characteristic of LSD experiences and consisted of the usual sensory alterations and a mixture of pleasant and unpleasant feelings. There was some evidence that the unpleasant aspects of the experience were becoming more dominant with each use of LSD. Several weeks prior to hospitalization, a psychiatrist (who was also a friend) placed the patient on approximately 3 gm of niacin a day telling the patient that the niacin would help him "go way back into childhood traumas." The patient experienced a "kind of amphetamine effect" during this period. Four days prior to his hospitalization the patient took his fourth LSD "trip" in the presence of (and with) the same psychiatrist. The reaction consisted of sensations of increased sensory input, sudden increased insight into life, sensitivity to detail, and increased sensory vividness. These symptoms did not abate and there was a progressive formation of delusions which necessitated hospitalization four days later.

Comment:—Both cases illustrate the obvious point that uncritical acceptance of an unproven treatment generates a false sense of security which may delay or prevent proper medical attention. We view this as an "iatrogenic side effect" of all placebo medications. There is suggestive evidence that the pharmacologic effects of niacin potentiated the psychotic symptoms in the two cases presented here. In the first case, the flush caused considerable anxiety and was quite clearly followed by an increase in the severity of anxiety attacks and crying episodes, which eventually led to hospitalization. In the second case, the "amphetamine-like effect" experienced after niacin seemed to be a milder manifestation of the increased sensory input which followed the LSD and led to progressive delusion formation. In both cases, following niacin, drug experiences which had previously been mainly pleasant ones turned into frightening psychotic experiences. Clearly no conclusion can be based on data from only two cases since this may simply be a fortuitous relationship between drug use and emerging psychosis. However, until firm clinical evidence of benefit is available, we urge caution in the prophylactic and therapeutic use of niacin with psychiatric patients.

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1. Denson, R.: Nicotinamide in the Treatment of Schizophrenia, *Dis Nerv Syst* 23:167-172, 1962.
2. Hoffer, A.: *Niacin Therapy in Psychiatry*, Springfield, Ill: Charles C Thomas, Publisher, 1962.
3. Hoffer, A.: Nicotinic Acid: An Adjunct in the Treatment of Schizophrenia, *Amer J Psychiat* 120:171-173, 1963.
4. Hoffer, A., and Osmond, H.: Treatment of Schizophrenia With Nicotinic Acid, *Acta Psychiat Scand* 40:171-189, 1964.
5. Osmond, H.A.: Massive Niacin Treatment in Schizophrenia: Review of a Nine-Year Study, *Lancet* 2:316-319, 1962.
6. Gallent, D.M.; Bishop, M.P., and Steele, C.A.: DPN (NAD-Oxidized Form): A Preliminary Evaluation in Chronic Schizophrenia Patients, *Curr Ther Res* 8:542, 1966.
7. Kline, N.S., et al: Controlled Evaluation of Nicotinamide Adenine Dinucleotide in the Treatment of Chronic Schizophrenia Patients, *Brit J Psychiat* 113:731-742, 1967.

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Biochemistry of Nicotinic Acid and Nicotinamide

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Nicotinamide was the third member of the B class of vitamins to be identified and was known as Vitamin B-3. It is the amide of nicotinic acid. The body can easily change one to the other. The structure of these two vitamins and the coenzyme they form, nicotinamide adenine dinucleotide (NAD), is shown in Figure 1.

Although these pyridine chemicals are classed as vitamins they have no known role in the biochemistry of the body except as precursors of NAD. Pellagra is due to a deficiency of NAD, and it is conceivable that a patient may have normal quantities of nicotinic acid in the diet and have pellagra because of a failure to synthesize NAD. There is another precursor of NAD known as quinolinic acid which in turn comes from tryptophan. There is evidence that quinolinic acid is converted into nicotinic acid ribonucleotide more readily than is nicotinic acid. Graham (1966) suggested that nicotinic acid and nicotinamide are not classed properly as vitamins but should instead be looked upon as chemical intermediates between tryptophan and NAD. In fact, he suggested quinolinic acid might one day replace nicotinic acid as the anti-pellagra preventative agent.

According to Gholson (1966) nicotinic acid and nicotinamide participate in the pyridine nucleotide cycle as shown in Figure 2.

Gholson considers the pathway from tryptophan through quinolinic acid to NAD as the *de novo* pathway. It is the most important pathway for synthesizing NAD. Pyridoxine or Vitamin B6 controls this reaction and in its absence quinolinic acid piles up. Graham (1966) believes this pathway is more

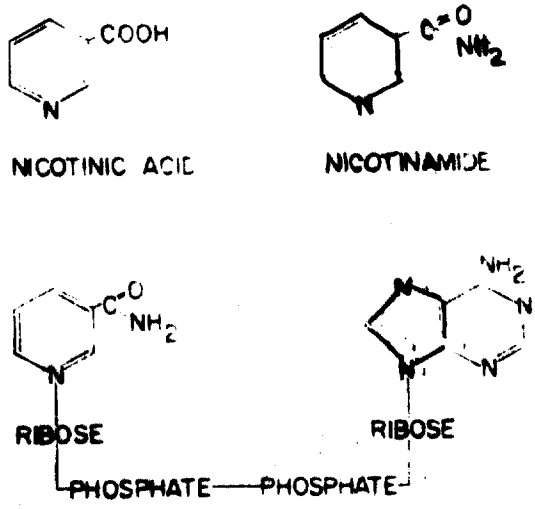

Figure 1. Structure of nicotinic acid nicotinamide and NAD.

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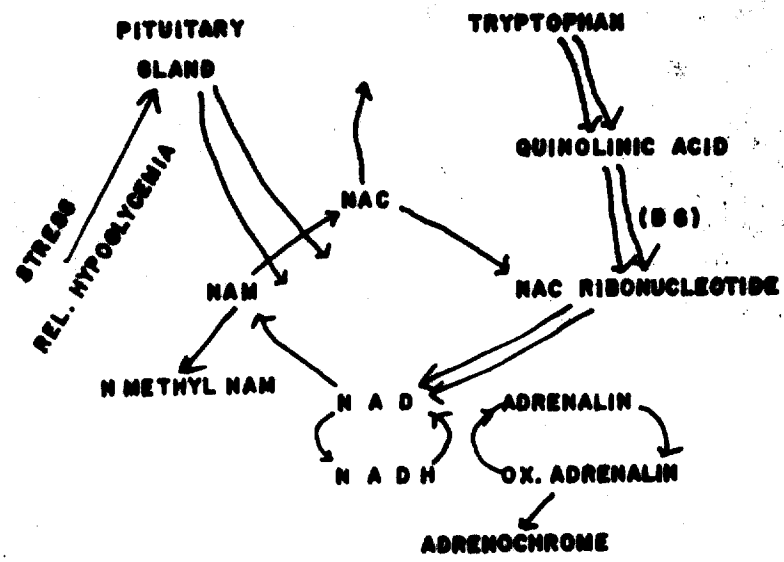

NAC = NICOTINIC ACID

NAM = NICOTINAMIDE

NAD = NICOTINAMIDE ADENINE DINUCLEOTIDE

Figure 2. Possible relationship between stress, the pyridine nucleotide cycle and schizophrenia.

important than the nicotinic acid precursor pathway for making NAD. When animals are fed nicotinic acid there is less increase in NAD than when they are fed tryptophan and pyridoxine. However, we do know this is a dose related problem and mega niacin doses can increase nucleotide levels in the body.

NAD is hydrolyzed rapidly. Brain tissue is especially rich in enzymes which hydrolyze NAD. There is, therefore, a salvage mechanism for reusing the pyridine molecule. The nicotinamide released from NAD is de-amidated to nicotinic acid which in turn is converted into nicotinic acid ribonucleotide and into NAD.

As you can see any reaction which pulls pyridine molecules out of the cycle will interfere in the synthesis of NAD. The best known pathway for losing pyridine molecules is by the methylation of nicotinamide to N methyl nicotinamide. This reaction is accelerated by methyl donors such as methionine and is inhibited by tranquilizer phenothiazines, but not by nontranquilizer phenothiazines. Buscaino (1966) found this reaction accelerated in acute schizophrenic blood *in vitro*. Another way of losing pyridine is by excessive conjugation of nicotinic acid with glycine to form nicotinuric acid. This reaction theoretically can be blocked by *para amino benzoic acid* (PABA) which is a competitor for glycine.

The pyridine nucleotide cycle also involves the adrenaline, oxidized adrenaline and adrenochrome cycle and several other substances including riboflavin and the coenzyme FAD ascorbic acid and dehydroascorbic acid. It also is under the control of the pituitary gland. When animals are hypophysectomized the deamidation of nicotinamide to nicotinic acid is greatly increased.

Elsewhere I proposed (Hoffer 1966) a relationship between hallucinogenic activity and the pyridine nucleotide cycle. In our opinion (Hoffer and Osmond 1967) there is an even closer relationship between schizophrenia and this coenzyme.

The scheme I have shown you provides a rational explanation for the therapeutic action

every chemical shown to be effective except insulin coma and ECT. Using this one can understand the rationale for relative hypoglycemic diet, for hormones such as thyroxin and progesterone to reduce overactivity, for nicotinic acid, nicotinamide and NAD, for mega ascorbic acid therapy, for tranquilizers. It suggests that methionine, PABA and quinolinic acid should be examined as therapeutic agents. It accounts for the toxic effect of methionine in worsening schizophrenic symptomatology.

However, I will consider in this paper only the pharmacology of nicotinic acid and nicotinamide because these two pyridine derivatives have proven to be so valuable in the treatment of schizophrenia.

The vitamin concept, very valuable many years ago, may have outlived its usefulness. Thus Stone (1965, 1966) has presented a very powerful argument that ascorbic acid is not a vitamin, but an essential metabolite which the human liver is unable to synthesize. He prefers the term hypoascorbemia and apparently we all suffer from this metabolic disorder. The use of high doses of ascorbic acid he terms mega ascorbic acid therapy. In the same way no man can make enough NAD from the tryptophan in the diet and must supplement it with nicotinic acid or nicotinamide. We all suffer from hyponadenia and we are well as long as we have sufficient nicotinic acid in our diet. In fact, using Stone's line of reasoning we all have pellagra, but it is arrested. Using this concept it is easy to conclude that some humans are able to convert tryptophan more effectively into NAD. According to our view schizophrenics come from that part of our population less able to convert efficiently tryptophan to NAD.

SIDE EFFECTS

Hereafter, I will consider only meganiacin and meganiacinamide therapy. The usual dose range is 3 to 18 grams per day. By side effects I refer to physiological changes which may make the patient uncomfortable, but they are not dangerous and they are easily controlled.

(a) Vasodilation or flush.—Nearly every person who takes these doses of nicotinic acid will have a marked flush. It usually begins in the forehead and travels down the face to the chest. Rarely it will flush the entire body. However, many elderly people and many schizophrenics have very mild flushes or do not flush at all. The patient is aware of a burning tingling sensation and may be very itchy. The flush comes on about ½ hour after the nicotinic acid is taken by mouth and lasts 30-60 minutes, then recedes. Rarely there is a moderate chill which follows. But as the medication is taken regularly the flush decreases in intensity until the patient may be unaware of it. I took 2 grams one hour before this lecture.

If patients are not told they will flush they may become terribly frightened. They must be advised what will happen. If the physician looks upon it as a nuisance, but no more, very few of his patients will object.

There is no flush with nicotinamide. I therefore, prefer it for very young patients. The mechanism of the flush is becoming known. According to Boyle (1966) it is due to a marked release of histamine from mast cells. Once they are depleted no more can be released and there is no further flush.

Robie (1966) found that 4 mg. of periactin sharply reduced the flush. This I have found also. If the flush remains troublesome and if one does not wish to use periactin then nicotinamide may be used. However, Robie believes nicotinic acid is much more effective for schizophrenia than nicotinamide. My experience is the same, especially for chronic schizophrenics.

(b) Headache.—A number of patients complain of frontal dull headaches on either nicotinic acid or nicotinamide. The best estimate is that about 10 per cent or less have this. However, even this group will continue to take the treatment since they prefer the headache to their previous schizophrenia. It is probably a histamine headache and is readily controlled using antihistamines, analgesics, etc. Eckley (1967) has evidence that headache, nausea and vomiting occurred especially in subjects who increased the consumption of milk and milk products. When they stopped eating these dairy products the symptoms cleared, but returned if they once more ate milk and its products.

(c) Nausea and Vomiting.—Nausea occurs just as frequently with both forms, but vomiting is rare on nicotinamide. It does occur on nicotinic acid. However, very few patients are intolerant of both forms. One should try first one, then the other. Periactin is helpful. Vogel (1966) found that tranquilizer suppositories were very helpful. I have already referred to the effect of milk. Some of the newer forms of nicotinic acid such as Xanthinol Niacinate* and Fructose Tetranicotinate** have produced no nausea or vomiting in a couple of subjects who could not tolerate nicotinic acid or nicotinamide and the flush was very moderate.

(d) A few subjects develop increased pigmentation on the flexor surfaces of arms. This appears to be due to increased deposition of melanin in the epidermis. The brownish skin peels off when wet as does a sun tan and the skin underneath is clear. Patients who complain of this should be advised to rub it off after the skin has been wetted some time in the bath.

TOXICITY

Altschul (1964) summarized the toxic reactions to nicotinic acid. Nicotinamide should be less toxic because it is not acidic. Toxicity is relative. Every chemical has toxicity, even water, especially if doses are too large. In every instance one must balance the toxicity of the chemical against the toxicity of the disease it must control. This is especially important when no other chemicals are available. In general one should use the chemical with the least toxicity provided it does the job. With this in mind it is clear that nicotinic acid and nicotinamide are less toxic than any barbiturate, any anti-tension compound, any tranquilizer and any anti-depressant.

The LD50 for animals in 4.5 grams per kg for mice by mouth and 2.5 grams per kg when given by vein. Dogs could tolerate 2 grams per kg IV.

In long term experiments it is equally safe. Rats tolerated 1 gram per kg for 40 days with no toxicity. There were no changes in the liver. Dogs tolerated 2 grams per kg for 35 days. In some experiments dogs were injured by nicotinic acid, but not by sodium nicotinate. Dogs seem especially sensitive to acidity.

In Saskatchewan over 400 patients have been on nicotinic acid, some since 1952. Two patients were given 25 grams per day for three months. There have been no deaths, very little toxicity and one case of jaundice.

(a) Liver Damage.—Handler and Dann (1942) reported that when nicotinic acid comprised 2 per cent of diet for rats the fatty acids in liver increased 4.2 to 11.8 per cent. It was prevented by choline. They assumed nicotinic acid stole methyl groups and produced fatty livers, but they did not examine the livers histologically. This observation resulted in the widespread belief that nicotinic acid can produce liver damage. Altschul duplicated these experiments in rats and rabbits and found no increase in fatty acids and when the livers were examined histologically found no fatty degeneration.

In humans there has been very little evidence for liver damage. I would guess less than one in a thousand will show liver changes. If they do occur, they are probably coincidental. In Saskatchewan I saw one case. A young schizophrenic boy who had recovered on nicotinic acid came down with severe infectious hepatitis. At the height of his fever his internist stopped the nicotinic acid. But a few days later when still feverish I restarted it as his psychosis had returned. He subsequently recovered from his infectious hepatitis and schizophrenia. Goldner and Vallan (1958) found normal liver tests in 5 patients treated ten weeks. Goldner (1960) observed no changes after three years. In fact, liver function tests which were abnormal prior to treatment did not get worse. Parsons (1962) after many years of careful study concluded that when abnormal liver tests occurred they were indicative of enzyme changes which are reversible and do not indicate liver damage.

(b) Reduced Glucose Tolerance.—In 195 I discovered that nicotinic acid markedly elevated the sugar levels in one schizophren

* Complamin—Available U.S.A.: Riker Laboratories, Inc., Northridge, California; Canada: Elliott-Marion Company Ltd., 4940 Fisher Street, Montreal 9, P.Q.

** Bradilan—Bracco, Italy.

patient during a glucose tolerance test, (Hoffer, 1963); but since then, I have used it freely in diabetics and have not seen any harmful effects. It has not increased insulin requirements. In my opinion every diabetic should be on nicotinic acid for his fatty acid and cholesterol levels will remain normal, and he will be less apt to suffer the dangerous sequelae of diabetes such as arteriosclerosis, retinopathy and peripheral vascular disease.

Six months ago a chronic young diabetic with schizophrenia was referred to me. She had been on tranquilizers (which tend to raise cholesterol levels) for three years and was a very difficult behavioral problem. She would not co-operate with a dietary program, was nearly blind in one eye from a cataract and was a severe problem to everyone. She required 50 units insulin per day. I started her on nicotinic acid 3 grams and later increased it to 6 grams. For the past four months her diabetes has been under excellent control. Her vision in her one good eye became normal. When I saw her a few days ago she was nearly normal mentally and reported she would go to work with her father in his shop. She had been unable to work for many years. She was advised not to measure sugar in urine, but to monitor her diabetes by her weight and her sense of well-being.

Gurian and Adlersberg (1959) treated five non-diabetic patients with nicotinic acid and found a decrease in tolerance to glucose. When nicotinic acid was discontinued it became normal. But in their diabetics nicotinic acid did not influence the glycemia and did not increase requirement for insulin.

(c) Robie (1966) reported two cases of bullous lesions on the skin. This was controlled or prevented in other cases by periactin. I have seen none in over 400 cases although I have seen severe urticarial rashes. I have wondered whether this was due to traces of free pyridine in the tablets. Many years ago some preparations had a distinct pyridine odor and had to be thrown away. Patients should be examined regularly for any skin lesions. The best treatment is to stop medication and start again with a different form.

(d) Toxic Amblyopia.—Harris (1963) reported toxic amblyopia in one patient who was taking 6 grams nicotinic acid per day to control his hypercholesterolemia. Three days after he stopped taking nicotinic acid his visual complaints disappeared.

There may be other effects, but they have been reported very rarely and were most likely coincidental. A similar large group of physically ill patients undoubtedly would report the same frequency of changes.

(e) Occasionally hypotensive reactions can occur. Boyle (1966) reported he had seen several cases. Herjanic (1964) reported one patient on 100 mg. Tofranil per day who was given nicotinic acid, 1 gram T.I.D. After the first three doses his blood pressure dropped to 70/50 with a pulse of 116. On IV glucose and water he was normal in 30 minutes. Later he was started on nicotinic acid again with smaller doses reaching 3 grams in two weeks. There were no side effects this time.

DISCUSSION

Nicotinic acid and nicotinamide are remarkably safe compared with the whole field of chemotherapy. I doubt whether anyone could commit suicide with it. Recently a subject just beginning treatment took about 90 grams nicotinic acid at one time. She later had a stomach ache, but there was no change in level of consciousness at any time. But no matter how safe a chemical may be, every patient taking it and every physician prescribing it must be aware that side effects and toxic effects can and will occur and must know how to deal with them.

I will close by reading a report on nicotinic acid from *The Medical Letter*, October 11, 1963, Vol. 5 #21—

"Flushing and itching of the skin are the most common side effects of nicotinic acid, and severe abdominal cramps often occur with the high doses used. Activation of peptic ulcer has also been reported. One case of bilateral amblyopia occurred in a patient taking 6 gm. of nicotinic acid daily for a year, but it was reversed when the drug was discontinued. With prolonged use, liver function may occasionally be impaired to the extent of causing cholestatic jaundice, but it returns to normal when the drug is stopped. Some patients have developed mild diabetes, also reversible. Serum uric acid usually rises, but

gout has not been noted. The hypotensive effects of ganglionic blocking drugs may be increased."

Those of you who have used nicotinic acid widely will disagree with the statement that abdominal cramps often occur. This was the case for some experimental slow release preparations, but they are not used anymore.

Graham (1966) in a recent review of its toxicity reported: "It's use has brought out side effects caused by large doses; gastrointestinal disorders, dry skin, brown pigmentation, hepatic dysfunction which may lead to fibrosis and cholangiolitis, decreased glucose tolerance and increased serum uric acid. Most of these manifestations are completely reversible when the vitamin is stopped."

BIBLIOGRAPHY

1. Altschul, R.: Niacin in Vascular Disorders and Hyperlipemia. Springfield, Ill.: C. C. Thomas, 1964.
2. Boyle, E.: *Personal Communication.* 1966.
3. Buscaino, G. A., Spadetta, V. and Carella, A.: *In Vitro Methylation of Nicotinamide: A Biochemical Test for Schizophrenia.* Madrid: International Congress Psychiatry, 1966.
4. Eckley, P. A.: *Personal Communication.* 1967.
5. Gholson, R. K.: The Pyridine Nucleotide Cycle. *Nature,* 212:933-934, 1966.
6. Goldner, M. G.: Uber Die Nikotinsaure-Behandling der Hypercholesterolamie. *Zeschr. f. Kreislaufforsch,* 49:251-255, 1960.
7. Goldner, M. G. and Vallans, L. E.: Marked and Sustained Blood Cholesterol Lowering Effect by Medication with Niacin and Pyridoxine. *Amer. J. Med. Sci.* 236:341-352, 1958.
8. Graham, G. G.: Johns Hopkins Conjoint Clinic on Vitamins. *J. Chron. Dis.* 19:1067-1081, 1966.
9. Gurian, H. and Adlersberg, D.: The Effect of Large Doses of Nicotinic Acid on Circulating Lipids and Carbohydrate Tolerance. *The Amer. J. Med. Sci.* 237:12-22, 1959.
10. Handler, Ph. and Dann, W. J.: The Inhibition of Rat Growth by Nicotinamide. *J. Biol. Chem.* 146:357-368, 1942.
11. Harris, J. L.: Toxic Amblyopia. *Amer. J. Ophthal.* 55:133-134, 1963.
12. Herjanic, M.: *Personal Communication.* 1964.
13. Hoffer, A.: Enzymology of Hallucinogens. From *Enzymes in Mental Health.* Ed. G. J. Martin and B. Kisch. Phil.: J. B. Lippincott, Co., 196[illegible]
14. Hoffer, A. and Osmond, H.: Nicotinamide adenine Dinucleotide (NAD) as a Treatment for Schizophrenia. *J. Psychopharm.* 2, (In Press) 1967.
15. Parsons, W. B., Jr.: Use of Nicotinic Acid to Reduce Serum Lipid Levels. *J. Amer. Ger. Soc.* 10, 850-864, 1962.
16. Robie, T.: *Personal Communication,* 1966.
17. Stone, I.: Studies of a Mammalian Enzyme System for Producing Evolutionary Evidence on Man. *Amer. J. Phys. Anthrop.* 23:83-86, 1965.
18. Stone, I.: Hypoascorbemia, the Genetic Disease Causing the Human Requirement For Exogenous Ascorbic Acid. *Perspectives in Biology and Med.* 10:133-134, 1966.
19. Vogel, M. J.: *Personal Communication,* 1966.

There are as many nights as days, and the one is just as long as the other in the year's course. Even a happy life cannot be without a measure of darkness, and the word "happy" would lose its meaning if it were not balanced by sadness.—Dr. Carl Jung

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Safety, Side Effects and Relat
Nicotinic Acid and Nicotinam

Abram Hoffer, M.D., Ph.D.

Nicotinic acid and nicotinamide are safe when used in vitamin dosages, and seem equally safe when used in megavitamin dosages (over 3 gm. per day) in adults. However, many physicians unfamiliar with the use of these substances at these dosage levels have been concerned about toxicity, especially hepatotoxicity. Since the use of these forms of vitamin B_3 to lower cholesterol levels,[1] for schizophrenia,[2] for alcoholism,[3] and for alcoholic schizophrenia[4] has increased at a very rapid rate, it is important to review the evidence relative to their side effects and toxicity.

Side Effects

The chief side effects of nicotinic acid and nicotinamide are (1) vasodilatation in the anterior part of the body accompanied by a sensation of heat and sometimes itching, (2) nausea occasionally followed by some vomiting, (3) rarely activation of peptic ulcers, (4) rarely dryness of skin, increased brownish pigmentation of flexor surfaces, or bullous lesions of the skin, and (5) headaches.

Flushing

Flushing (vasodilatation) usually begins in the forehead and spreads downward. The entire body, including the toes may be enveloped in the warmth of the flush, but usually the lower part of the body does not flush as much as the upper part. The flush is accompanied by a sensation of warmth or heat which most patients find innocuous. A few find it barely tolerable and some, especially elderly persons with arthritis, enjoy the sensation of warmth in their joints. Several of my patients have refused to take nicotinamide preferring to flush. Others will discontinue nicotinic acid for a day or so in order to have the flush when they resume medication. Pruritus may accompany the flush, but patients should be advised not to scratch, as this generally makes it worse. Fair-complexioned persons who do not tan easily usually have more difficulty with the nicotinic acid flush than do more darkly pigmented subjects.

As a rule, the first flush is the most intense. As each dose is taken, the intensity and duration of the flush decrease. As the patient accommodates to the flush the amount of the skin involved decreases until eventually only the forehead and face will show a faint reddening.

The intensity, duration and spread of the flush are related to the speed of absorption of the nicotinic acid. Intravenous injection produces the most severe flush. Any procedure that increases the rate of absorption from the gastrointestinal tract will increase the flush. Taking powdered nicotinic acid dissolved in water, along with a hot drink on an empty stomach, will produce a more intense flush. Thus, to moderate the flush one should take large tablets after a meal, followed by a cool drink—preferably milk.

Lack of Toxicity of

With 1 gm. tablets, the ratio of surface to volume is small and nicotinic acid is released more slowly. One 1 gm. tablet produces less flush than two 0.5 gm. tablets taken simultaneously. Of course, ten 100 mg. tablets taken at the same time will produce even more intense flushing.

There is no general agreement regarding the mechanism of the flush. Boyle's[5] explanation seems the most logical. He suggested that nicotinic acid releases histamine from storage sites such as the mast cells and that the flush is a typical histamine flush. After the flush recedes histamine slowly returns to the storage sites. When the next dose is given the same event occurs. If the next dose is given before the sites are replenished, less histamine is available to be released and the flush is less intense. When full dosage is achieved, these storage sites no longer become replenished and further flushing does not occur. However, if nicotinic acid is not taken for several days, the sites are filled and flushing can again occur.

No one has measured blood histamine levels during the flush. However, the following observations support Boyle's suggestion: (1) The nicotinic acid flush resembles the flush produced by injection of histamine in intensity, distribution and duration. In 1952 my colleagues and I routinely gave large doses of histamine to patients, and the resulting flush markedly resembled the flush from nicotinic acid. (2) In many patients, antihistamines will moderate the flush. (3) Phenothiazines, which have weak antihistamine properties, reduce flushing. (4) The flush is very sensitive to timing of the doses. Usually the most intense flush during the day occurs after an overnight fast. (5) Secretion of gastric juices is often increased after nicotinic acid is taken. The undesirable effect of nicotinic acid in some cases of peptic ulcer may be due as much to this histamine release as to the direct hydrogen ion concentration of nicotinic acid. (6) Schizophrenics usually flush less than other patients, which is explained by the presence of increased amounts of adrenochrome and adrenolutin. Adrenochrome is a weak antihistamine.

It is interesting that nicotinic acid has never been observed to produce a flush in either albino or normally colored animals.[6] Neither has it caused any apparent discomfort, nasal stuffiness or scratching reactions.

Several preparations produce much less flush than do nicotinic acid. Of these, the most effective is Hexanicotol®, an inositol nicotinate preparation. This seldom causes a flush and has none of the other side effects of nicotinic acid. However, it is more expensive. It should be used whenever a subject cannot tolerate either nicotinic acid or nicotinamide. Another preparation is xantinol nicotinate (Complamin®), but this agent does cause flushing in a considerable number of subjects. Both Hexanicotol® and Complamin® are equally as effective as nicotinic acid in all conditions in which the latter is helpful.[7]

Several methods have been devised for moderating the flush. Robie[8] used an antihistamine (4 mg. cyproheptadine hydrochloride [Periactin®]), given a few minutes after the flush began. I have also found this helpful. Other investigators have used other antihistamines. However, De Soldati, Stritzler, Balassanian and Bourguet,[9] Ost[10] and Iliescu, Iliescu, Roman, Iacobini, Constantinescu and Nutu[11] did not find antihistamines helpful. Goldner and Vallan[12] used tranquilizers to prevent or reduce the flush.

Pfeiffer[13] has given nicotinamide before nicotinic aicd to moderate the flush, but Ward[14] has not found this technique particularly helpful. There is probably a good deal of variation between patients in regard to the intensity of flushing.

Gastrointestinal Symptoms

These include nausea, vomiting, soft stools, diarrhea and foul-smelling stools. In many patients these symptoms disappear as treatment is continued. In others they quickly disappear when treatment is discontinued and do not reappear when the vitamin medication is resumed. Often when a patient who has taken nicotinic acid for years has a cold or influenza, these symptoms will appear. The incidence of nausea and vomiting may increase during influenza epidemics. As soon as patients recover, the symptoms disappear.

I had one patient who could not take even 1 gm. per day of either nicotinic acid or nicotinamide because of vomiting. Tranquilizers caused the same reaction. He took a series of electroconvulsant therapy and since has been able to take 6 gm. of nicotinic acid per day without nausea and vomiting.

Certain slow-release preparations used experimentally many years ago caused a good deal of nausea, vomiting and even abdominal cramps in patients who could take nicotinic acid with no difficulty. These products are not available today. Apparently, nicotinic acid is best released in its free form in the areas of the gastrointestinal tract accustomed to acidity. In cases in which the acidity generated by the nicotinic acid aggravates peptic ulcer, it is important to neutralize the acid or its effect. This is accomplished by the patient's drinking milk after taking the tablets; by use of antacids; by use of buffered nicotinic acid, in which an agent like sodium bicarbonate is added; or by use of sodium nicotinate. Nicotinamide is almost as effective in conditions such as arthritis or schizophrenia.

On the basis of findings that diabetics rarely have peptic ulcer, Buckley[15] suggested that hyperglycemia might protect or treat patients with ulcers. If this is true, nicotinic acid, which produces slight hyperglycemia, might have a beneficial effect on some peptic ulcers, especially if the agent is buffered.

Parsons[16] found that in a series of patients, peptic ulcer was activated in seven who were taking nicotinic acid. Two patients had had previous ulcers. Three had a deformed duodenum, and the remaining two had some proneness for ulcer. When a buffered solution of nicotinic acid was given, ulcer symptoms subsided promptly in all seven patients. Berge,[17] who treated a large number of patients for long periods did not observe one case of ulcer activation due to nicotinic acid.

Since 1952 I have given nicotinic acid or nicotinamide to over a thousand patients and have kept detailed records on 982. Gastrointestinal complications in these patients were as follow: Fourteen patients taking nicotinic acid had nausea and vomiting; these symptoms developed in three of these patients during an influenza epidemic. One of these three was able to take 20 gm. per day with no difficulty after recovering from the infection. One patient was receiving tranylcypromine (Parnate®) and nicotinic acid. When the Parnate® was

stopped, nausea and vomiting ceased even though the nicotinic acid was not discontinued. One patient had serious nausea and vomiting with nicotinamide, and one was unable to take either form of the vitamin for the same reason. One patient had abdominal cramps, one had abdominal pain, and one patient with a colostomy had diarrhea. Table 1 lists all side effects in this series of patients.

Table 1

SIDE EFFECTS IN 982 PATIENTS TREATED WITH NICOTINIC ACID OR NICOTINAMIDE SINCE 1952

Patients treated	Daily dosage (Grams) 1.5	3	6	Patients with side effects
	%	%	%	
351 (early in series)	4	90	6	9
232 (19 early in series)	6	86	8	2
399 (current)	5	50	45	14

Hawkins[4] does not consider the nausea that occurs with nicotinamide a side effect. Instead, he considers it a physiologic indicator of the optimum dose, which he defines as that dose which produces nausea, less 1 gm. per day. Thus, if 6 gm. daily produces nausea, the optimum dose is 5 gm. Hawkins' patients are instructed to increase the dosage until this optimum is reached. Vomiting with nicotinamide is very rare, and this agent does not aggravate or activate peptic ulcer.

Skin Reactions

Reactions from nicotinic acid manifested in the skin must be differentiated from the flushing previously discussed. Robie[8] described several cases of severe bullous lesions that were successfully treated with Periactin®. I have seen one severe rash from nicotinamide, one from nicotinic acid, and one case of bullous dermatitis that required cortisone medication.

Occasionally, a brown discoloration of flexor surfaces occurs that resembles a suntan wearing off. This is not dangerous. The pigmented outer epidermal layers easily peel off when the skin is wet, leaving normal skin. The discoloration may be present for several months or years, but then disappears.

Headaches

A small proportion of patients complain of headaches when taking either nicotinic acid or nicotinamide. These usually respond well to simple analgesics. On the other hand, patients who have had severe headaches from other causes for many years have found they have been relieved after several weeks of medication. The incidence and frequency of headaches among a population using these vitamins probably would be no greater than would be expected in a control population not taking them.

Other Side Effects

From time to time, other side effects will occur in patients taking nicotinic acid or nicotinamide. No medication is wholly free of them. However, they occur infrequently, and respond quickly to simple control measures.

Some side effects are caused by the ingredients in tablets used to bind the vitamins, either because the patients are allergic to the binding agents or because they are carbohydrate materials such as lactose or starch.

Occasionally, the nicotinic acid tablets deteriorate and have a pyridine odor. Fortunately, this has been very rare in the past few years. Pyridine is toxic, and whenever the tablets have this odor, they should be discarded.

Some side effects are beneficial. These are changes for the better in symptoms that were minor or about which patients had not complained, as well as major changes in symptoms that were not primarily the ones being treated. For example, if a schizophrenic under treatment discovers after a month that his acne is gone and his circulation improved, these developments would

be beneficial. A large number of such effects have been reported. Several clinicians have reported that patients taking nicotinic acid to lower cholesterol levels have experienced an inexplicable sense of well-being. Achor and Berge,[18] Bonfiglio and Proja,[19] Chazin,[20] Hunter,[21] Ljunggren, Grissler and Probst,[22] and Boyle[5,23] observed that this feeling in patients taking nicotinic acid was much greater than could be explained by the lowering of cholesterol levels. Other workers have reported disappearance of xanthelasma and xanthoma with this medication.[6]

Ward[24] reported that 13 of 262 patients given 3 gm. nicotinamide per day for 3 to 36 months (mean, nine months) were changed to nicotinic acid. Only two could not tolerate nicotinic acid Hexanicotol® or Nialex®. Jaundice or skin blebs did not occur. The nicotinamide was discontinued because of headaches (four patients), heartburn (one patient), nausea (two patients), other gastrointestinal complaints (two patients), sore mouth (one patient), hives (one patient), fatigue, exhaustion and lightheadedness (one patient) and inability to focus eyes, dry hair and tautness of face (one patient).

Cott[25] reported that of 400 patients given nicotinic acid, 30 had nausea and vomiting, four had headache, and five had severe itching. He considered these minor side effects.

Importance of Recognizing Side Effects

It is very important to know the side effects of nicotinic acid and nicotinamide so that other serious pathologic disorders will not be overlooked. Recently, MacLean[26] reported that a schizophrenic patient who had been improving on nicotinic acid was in an automobile accident. After the accident the patient complained of severe abdominal pain. His physician assumed this was due to the nicotinic acid and it was discontinued. The patient was readmitted to another mental hospital, where he died two days later because of a ruptured spleen.

Both nicotinamide and nicotinic acid produce side effects that may be irritating or annoying and in some cases frightening, especially if the patient has not been adequately prepared. Altschul,[6] after a thorough review of the literature, concluded: "After more than eight years' experience by numerous investigators, it appears that they [nicotinic acid and nicotinamide] are not harmful." In cases in which side effects have been possibly harmful, they have been reversed quickly by discontinuing the treatment.

Factors Influencing Side Effects

Physician's skill—Many factors influence the incidence and intensity of the side effects of nicotinic acid and nicotinamide. Physicians who have become skillful in using these vitamins generally report side effects in 5 percent or less of the patients. At a meeting of the Committee on Therapy, American Schizophrenia Foundation,[27] eight psychiatrists using megavitamin therapy for more than two years on 6,000 patients reported an overall incidence of side effects of less than 5 percent. None considered the side effects more than a minor problem easily dealt with.

Moses[28] has stated: "Physicians who give the drug with confidence and enthusiasm find their patients tolerate the side effects better than those with a less optimistic outlook." Goldsborough[29] prepared his patients by telling them they would flush and that this was desirable, expected and harmless. Berge[17] reported: "Reassurance that the severe flushing will subside rapidly with continued treatment has usually taken care of this problem, which has not seemed to warrant all of the attention it received."

When patients are not given accurate information, they may be terribly upset and

even panic. Recently in Detroit a patient was given a prescription for nicotinic acid, with no explanation of what to expect. Later in the evening when he flushed, he became very fearful, and believing he was poisoned, called a poison control center. On learning that the patient had taken 1 gm. of nicotinic acid, the physician who took the call exclaimed, "My God, you have taken a lethal dose," and ordered the patient to rush to by ambulance. By the time the patient arrived his flush had begun to recede.

Patient's age and condition—In general, older subjects have side effects less often and of less intensity than younger ones. Subjects under the age of 21 most often prefer nicotinamide since they find the flushing and flush more irritating. I usually give these patients nicotinamide; however, [illegible], they will accommodate to [illegible]. Older subjects often prefer [illegible] because of the sensation of [illegible] the flush. They seldom [illegible] of the flush and infrequently [illegible].

[illegible] generally have fewer side effects than [illegible] controls. When Altschul and [illegible] worked with medical students in 1955, we were impressed with the frequency of their complaints compared with those of our patients who had been given the same dosages of nicotinic acid over a three year period.

Galbraith, Perry and Beamish[31] noted that the [illegible] group complained [illegible] side effects but the control group of medical students were most vocal [illegible]. Altschul[8] concluded: "It seems [illegible] that the patients who [illegible] as a treatment for their [illegible] will bear any inconveniences better than the medical controls who lend themselves to the treatment either as a favor or for a relatively small fee." Schizophrenic patients are seldom distressed by these vitamins and if side effects do occur they are mild.

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Toxicity

Toxic reactions are severe reactions that lead to serious pathologic disorder or death. The lethal dose of nicotinic acid and of nicotinamide for man has never been determined. One of my young female patients took 100 gm. of nicotinic acid in one dose. She had no ill effect, but later complained of some mild abdominal distress. Table 2 shows the experimental median lethal doses that have been reported for nicotinic acid. Nicotinamide generally is twice as toxic as nicotinic acid.

Table 2

MEDIAN LETHAL DOSES OF NICOTINIC ACID IN ANIMALS

Authors	Animals	Median lethal dose (Grams per kilogram) Intravenous	Subcutaneous	Oral
Frontherz and Spiegelberg[15]	Mice	2.5	2.8	4.5
Unna[16]	Mice and rats	4 to 5		5 to 7
Brandi and Coulson[20]	Rabbits	2.5		
	Rats	5		

These animal doses are equivalent to over 250 gm. per adult male human, or at least 25 times the largest single dose given to patients.

A number of chronic studies using very high dosages, that is, 1 to 2 gm. per kilogram of body weight for up to several months in rats, mice and dogs, showed a few changes in some instances and no changes in others.[6]

Liver Toxicity

When Nath, Harper and Elvehjem[32] gave nicotinic acid to rats as 0.5, 1 and 2.5 percent of the diet for three weeks, they observed no toxic reactions. In contrast, Handler and Dann[33] gave this agent to rats as 2 percent of the diet and reported an increase in fatty acids from 4.2 to 11.8 percent. Addition of 0.4 percent choline chloride prevented this increase. Although Handler and Dann's finding was never corroborated and is contrary to subsequent reports, it generated a general belief that nicotinic acid and nicotinamide are hepatotoxic. In spite of massive evidence to the contrary, some physicians still have this erroneous belief.

In 1958 Altschul and I[34] replicated this experiment using a dosage in human terms of 54 gm. per day. This treatment produced no significant increase in liver fats. In rabbits given 0.5 gm. six times per week for 147, 158 and 170 days, the percentage of liver fat dry weight was 1.58, compared with 1.57 percent in controls.

Electron microscopic examination of the liver tissue from these animals showed no pathologic features. Parsons[35] referred to a study by W. F. Kremer, who gave rats 4 gm. per kilogram per day of nicotinic acid for one year and observed no changes in the liver. This is 90 times the starting dose of 3 gm. per day for humans. Janes[36] found no increase in liver fat in rats given 35 mg. nicotinic acid intraperitoneally for five days.

Not only is there no significant evidence that nicotinic acid causes liver toxicity in animals, but there is contrary evidence that this agent protects liver against other forms of toxicity. Gallagher and Simmonds[37] reported that 0.05 gm. of nicotinic acid per day given intraperitoneally to rats in two doses of 0.025 gm. for two to three days protected them against lethal doses of carbon tetrachloride. They concluded that increased concentration of nucleotides counteracted the toxic action of carbon tetrachloride on respiratory enzymes and on mitochondria. The dosage used was equivalent to 20 gm. per day for an adult man weighing 60 kilograms.

Altschul[34] found that in rabbits nicotinic acid inhibited fatty liver formation which is almost regularly produced by feeding cholesterol. Merrill and Lemly-Stone[38] and Cava, Achor, Berge and co-workers[39] reported similar results. Studies on humans carried out since 1949, support the conclusions gained from studies of animal toxicity.

The incidence of liver damage caused by nicotinic acid or nicotinamide as indicated by jaundice is very low. In my own series of 1,000 cases, infectious hepatitis, with very high fever, developed in one young schizophrenic patient who required 6 gm. nicotinic acid per day to remain well. When the patient was hospitalized, the nicotinic acid was discontinued, and in a few days he was severely psychotic. The same dosage of nicotinic acid was resumed, and he slowly recovered from the hepatitis and the schizophrenia. In another patient receiving both nicotinic acid and Parnate,® jaundice developed, but this cleared when the Parnate® was discontinued. I have seen no other cases of liver toxicity.

At a recent meeting of the Committee on Therapy, American Schizophrenia Foundation, only one other case of liver toxicity was reported out of a total of 6,000 cases in which nicotinic acid or nicotinamide was used. MacLean[26] found one case in which obstructive jaundice developed twice when either nicotinic acid or nicotinamide was given. Of the group of patients observed, most were either schizophrenic or alcoholic, and of course, in the latter group predisposition to liver damage would be expected.

Altschul[6] found only four cases of jaundice in a complete review of the literature on giving nicotinic acid and nicotinamide. Two of these patients were given slow-re-

lease preparations of nicotinic acid. In all four patients, liver function tests became normal several weeks after nicotinic acid was discontinued.

Because of the fear that nicotinic acid might cause liver damage, a large number of clinicians have conducted careful liver function tests. The Mayo Clinic group and Parsons[6] found that one or more of the usual tests became normal. Parsons and Flinn[16] performed 17 liver biopsies on patients who had received nicotinic acid for one year, and found that the tissue was normal. In three patients who had taken nicotinic acid for three years, biopsies showed fatty changes in one, a diabetic, cholangiolitis in one, and no changes in the third. Berge[17] reported that liver function tests were normal in 28 of 61 patients who had been taking nicotinic acid, and at least one test was positive in the remainder.

On the basis of six years' experience, Parsons[6] concluded that abnormal liver function tests do not indicate hepatocellular damage, but express changes in liver enzymes which are rapidly reversible when nicotinic acid is discontinued.

Effect on Carbohydrate Metabolism

In 1952 I[41] reported that nicotinic acid decreased glucose tolerance in some patients, while nicotinamide did not exert this effect. Animal studies in this respect have not been conclusive, some showing that nicotinic acid is hyperglycemic and others showing that it is hypoglycemic. However, it is generally agreed that nicotinic acid does elevate glucose tolerance in some humans.

In spite of this, nicotinic acid can be given to diabetics to lower cholesterol levels. In these cases the prevention or inhibition of the onset of some of the toxic cardiovascular effects of diabetes mellitus more than compensates for the decreased sugar tolerance.

Gurian and Adlersberg[42] noted a decrease in glucose tolerance in five nondiabetic psychiatric subjects on nicotinic acid. The curves became normal when the agent was discontinued. These workers also found that nicotinic acid did not increase the requirement for insulin in several subjects, although they later reported one case in which the insulin requirement was [illegible] creased. Eilersen and Hobolth[43] observ[illegible] one patient in whom diabetes became [illegible] dent while nicotinic acid therapy was [illegible] carried out. Goldner[44] found no chang[illegible] fasting sugar levels or insulin requireme[illegible] of diabetics. Davis, Beck, Bergal and [illegible] workers[45] found hyperglycemia in all of [illegible] cases, and Belle and Halpern[46] obs[illegible] one diabetic who became worse [illegible] tinic acid. Berge[17] found norm[illegible] sugar levels in 9 of 61 patients [illegible] exceeding 90 mg. per 100 milli[illegible] a maximum of 17 mg. per mil[illegible] patients. Glucose tolerance [illegible] in 8, equivocal in 5, and abnormal [illegible]

Although it is clear that gluco[illegible] tolerance curves are elevated in pati[illegible] ng nicotinic acid, it is very doub[illegible] that these changes are harmful. In fact, for many patients who have relative hypoglycemia (functional hyperinsulinism), it is quite beneficial, and many workers use nicotinic acid as an adjunct to the special diet used in relative hypoglycemia.

When nicotinic acid is given to diabetics, the risk of increasing insulin requirements must be balanced against the risk of serious toxic effects of diabetes (hypercholesterolemia, arteriosclerosis, visual changes, gangrene, etc.). I believe that the risk of the cardiovascular and cerebrovascular pathologic changes from diabetes alone is much greater than the risk of taking nicotinic acid. By lowering cholesterol levels, nicotinic acid decreases the risks of these vascular changes.

Schizophrenia and diabetes rarely coexist. I have treated one such patient. She was severely psychotic and was partially

controlled by heavy doses of tranquilizers. However, this patient did not become normal; she refused to follow the diet and insulin medication, and periodically was admitted in a severely psychotic state with the diabetes out of control. The patient was started on 6 gm. nicotinic acid per day and has been on it for three years. She became mentally normal in two months; she does not require tranquilizers and no longer allows her diabetes to become uncontrolled. Her insulin requirements have not changed.

Nicotinamide has no effect on glucose tolerance and may be preferred for some diabetics who become uncontrolled while taking nicotinic acid.

Effect on Uric Acid

Nicotinic acid increases the uric acid level in some subjects; however, the significance of this elevation is not known. Altschul[6] pointed out that most patients requiring nicotinic acid, i.e., patients with hypercholesterolemia, are prone to have high blood uric acid levels. To this group, I would add also elderly persons and alcoholics. In spite of the elevation, gout is not aggravated or produced.

Parsons[47] found hyperuricemia (over 6 mg. per 100 milliliter) in 22 of 30 patients given nicotinic acid for one to three years, but he stressed that these patients had no increase of uric acid in the urine, no gout, and no nephrolithiasis. Two patients who had had gout previously did not have any attacks while taking nicotinic acid. Berge[17] observed gouty attacks in two patients taking nicotinic acid. One patient had had gout previously, and only one attack occurred in the other. One of my patients, a man in his late seventies, has been taking 3 gm. nicotinic acid daily for 14 years. He has had three mild attacks of gout, which have cleared rapidly on specific therapy whether or not he has taken nicotinic acid. If he discontinues the nicotinic acid, severe pain develops in his feet, which reminds him he has not taken it regularly.

Effect on Embryos

Nicotinic acid and nicotinamide have not been reported to have any toxic effect on the embryo. Altschul[6] gave female rabbits large doses before mating them, and continued the nicotinic acid through gestation and lactation. None of the litter had any abnormalities. Altschul also reported on one pregnant woman who was given nicotinic acid during her pregnancy and whose baby was normal.

I have given nicotinic acid to pregnant women since 1952. I have no detailed breakdown of the number, but thus far every baby has been normal and there have been no miscarriages. Recent findings suggest that some fetal abnormalities are due to a deficiency of NAD and that large doses of nicotinic acid might prevent some forms of embryonal damage.

REFERENCES

1. Altschul, R., Hoffer, A., and Stephen, J. D.: Influence of nicotinic acid on serum cholesterol in man. Arch. Biochem. Biophysics. 54, 558-559, 1955.
2. Hoffer, A., Osmond, H., Callbeck, M. J., and Kahan, I.: Treatment of schizophrenia with nicotinic acid and nicotinamide. J. Clin. Exp. Psychopath. 18:131-[illegible], 1957.
3. Smith, R.: Personal communications, 1967.
4. Hawkins, D. R.: Treatment of schizophrenia based on the medical model. J. Schiz. 2:3-10, 1968.
5. Boyle, E., Jr.: Personal communication, 1967.
6. Altschul, R.: Influence of Nicotinic Acid (Niacin) on Hypercholesterolemia and Hyperlipemia and on the Course of Atherosclerosis. Niacin in Vascular Disorders and Hyperlipemia. Springfield, Illinois, Charles C Thomas, 1965.
7. Hoffer, A.: Comparison of complamin and nicotinic acid for treatment of schizophrenia. Schizophrenia. Vol. 1, No. 1, 24-37, 1969.
8. Robie, T. B.: Cyproheptadine. An excellent antidote for niacin-induced hyperthermia. J. Schiz. 1:135-139, 1967.
9. De Soldati, L., Strickler, G., Balasanian, S., and Bourguet, M. E.: Effect of nicotinic acid on blood lipids in arteriosclerotic patients. Cardiologia 5:[illegible]4 1959.
10. Ost, C. R.: Nikotinsyrebehandling vid arteriosclerosis och blodlipidrubbningar. Nord. Med. 64:1360, 1960.
11. Hiescu, C. C., Hiescu, M., Roman, L., Iacobini, V., Constantinescu, S., and Nutu, S.: Effect of nicotinic acid on blood lipids in atherosclerosis. Med. Intern. (Bucur) 15:39, 1963.
12. Goldner, M. G., and Vallan, L. E.: Marked and sustained blood cholesterol-lowering effect by medication with niacin and pyridoxine. Amer. J. Med. Sc. 236: 341, 1958.
13. Pfeiffer, C.: Committee on Therapy, American Schizophrenia Foundation, Brunswick Hospital Center, Long Island, New York, 1967.
14. Ward, J.: *Ibid.*
15. Buckley, R. F.: Induction of hyperglycemia as treatment for peptic ulcers. Lancet 2:497-499, 1967.

[illegible], W. B., Jr.: The effect of nicotinic acid on [illegible] lipids. Amer. J. Clin. Nutr. 8:471, 1960.

[illegible] in treat- [illegible] 1961.

[illegible] of hy- [illegible] of nicotinic acid. [illegible]

[illegible] 1957.

[illegible] acid on blood cho- [illegible]

21. Hunter, J. D.: [illegible] in patients with coronary [illegible] 1959.

22. [illegible] Treatment of [illegible] with nicotinic acid [illegible]

23. [illegible] levels in man, and [illegible] Soc. 10: [illegible] 1962.

24. Ward, J.: [illegible] 1962.

25. Cott, A. A.: [illegible]

26. MacLean, R.: [illegible]

27. [illegible] Foun- [illegible] California, [illegible]

28. [illegible] in the control of [illegible] 1962.

29. [illegible] in the treatment of [illegible] 1960.

30. [illegible] of nicotinic [illegible] 1959.

31. [illegible] R. E.: [illegible] Lancet 1:222, [illegible]

32. [illegible] C. A.: Diet [illegible] and nico- [illegible] 1959.

33. [illegible] of rat [illegible] 1942.

34. [illegible] of salts of nico- [illegible] Brit. Med. J. 2:713, [illegible]

35. [illegible] of hypercholesteremia by [illegible] acid. [illegible] 1961.

36. James, R. G.: Certain metabolic effects of niacin and pericoline. Amer. J. Physiol. 174:48, 1953.

37. [illegible], C. H., and Simmonds, R. W.: Prophylaxis of poisoning by carbon tetrachloride. Nature 184:1407, [illegible]

38. Merrill, J. M., and Lemley-Stone, J.: Effects of nicotinic acid on serum and tissue cholesterol in rabbits. Circ. Res. 5:617, 1957.

39. Cava, E. E., Achor, R. W. F., Berge, K. G., Wakim, K. G., Edwards, J. E., McKenzie, B. F., and Barker, N. W.: Effect of nicotinic acid on experimental atheromatosis of rabbits. Mayo Clin. Proc. 34:502, 1959.

40. Parsons, W. B., Jr., and Flinn, J. H.: Reduction of serum cholesterol levels and beta-lipoprotein cholesterol levels by nicotinic acid. Arch. Int. Med. 103:783, 1959.

41. Hoffer, A.: Niacin Therapy in Psychiatry. Springfield, Illinois, Charles C Thomas, 1962.

42. Gurian, H., and Adlersberg, D.: The effect of large doses of nicotinic acid on circulating lipids and carbohydrate tolerance. Amer. J. Med. Sci. 237:12, 1959.

43. [illegible], P., and Hobolth, N.: Behandling of hypercholesterolemia med nicotinsyre. Ugeskr. Laeg. 121: [illegible] 1959.

44. [illegible], M. G.: Uber die Nikotinsaure-Behandlung der Hypercholesterolamie. Z. Kreislaufforsch. 49:251, 1960.

45. Davis, O. F., Beck, Ch., Bergal, M., Sloan, N., and Levine, A. J.: Some observations on the relationships between atherosclerosis, hyperlipemia, and D-thyroxine. Amer. Heart J. 64:7, 1962.

46. [illegible], M., and Halpern, M. M.: Oral nicotinic acid for hyperlipemia. Amer. J. Cardiol. 2:449, 1958.

47. Parsons, W. B., Jr.: The effects of nicotinic acid on serum lipids. Amer. J. Clin. Nutr. 8:471, 1960.

48. Frankhorn, K., and Spiegelberg, H.: Pharmakologische Wirkungen des B-Pyridylcarbinols und verwandter B-Pyridylverbindungen. Helv. Physiol. Pharmacol. Acta 6:[illegible], 1948.

49. Unna, K.: Studies on the toxicity and pharmacology of nicotinic acid. J. Pharmacol. Exp. Ther. 65:95, 1939.

50. [illegible], F. G., and Coulson, R. A.: Toxicity of nicotinic acid and some of its derivatives. Proc. Soc. Exper. Biol. Med. 62:19, 1946.

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Vitamin B_3 Dependent Child

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Introduction

Since Dr. Humphry Osmond and I began the first double blind controlled studies in psychiatry in 1953 for testing the efficacy of vitamin B_3 for treating schizophrenia, we have explored various facets of what has been termed megavitamin therapy. It is better called orthomolecular therapy. I will not review the many studies we, and more recently many other psychiatrists, have recorded but it is essential I emphasize the following points.

The first is that orthomolecular therapy does not mean that only vitamins are used. It refers to a proper combination of nutrition, with megadoses of vitamin B_3 and, if necessary, of ascorbic acid, thiamine, pyridoxine, vitamin B_{12}, plus any other chemical currently used in psychiatry. These are tranquilizers, anti-depressants, stimulants and so on.

It also includes electro convulsive therapy for adults where necessary. In other words, the orthomolecular approach consists of treating patients with every known chemotherapeutic agent and increasing the intensity, variety and tempo of treatment depending upon the patient's response.

As a rule, treatment using chemicals normally not found in the body, i.e. tranquilizers, antidepressants, etc., is temporary and continued only until recovery can be maintained with vitamins, minerals and diet alone.

The second point is that without exception every psychiatrist who has used the orthomolecular approach as described has become very impressed. They were able to double their recovery rate. So far, there has been no attempt to run controlled experiments of the overall orthomolecular approach.

I think that I should list for you what we have claimed.

These are:

(1) That the addition of vitamin B_3 in an adequate dose substantially improves recovery rates.

(2) That relapses are decreased and that readmissons are fewer and for shorter periods of time.

We have never claimed that vitamin B_3 treatment is the only treatment for every possible schizophrenic in every possible circumstance.

There is no doubt that a major proportion of schizophrenics recover on vitamin B_3. Any psychiatrist who begins with a cohort of 100 acute schizophrenics and follows the orthomolecular approach for a sufficient period of time, say three years, will find that 90% of his patients are well, the rest are improved, none will be worse. Anyone who doubts this need only visit members of the Committee on Therapy, see their patients and records, and repeat the program on their own cases.

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I have studied the use of megadoses of vitamin B_3 chiefly with adult schizophrenics and have published my results. So far, I have not made any claims for the efficacy of this approach for schizophrenic children although I have treated nearly a hundred cases. Cott[1,2,3] and Hawkins[4] have, however, published their results. We are in agreement that the megavitamin approach here has very great promise.

It is difficult to work with children. Diagnosis of disturbed children is in a very chaotic state, there being close to 50 different diagnostic terms for hyperactive or hyperkinetic children. They range from perceptually disturbed children, to minimal brain disorders, hyperkinetic disorders, schizophrenia and autistic children.

It occurred to me four years ago that we might be able to classify these disturbed children by their response to megadoses of vitamin B_3. Is there a syndrome that could be labelled "the vitamin B_3 responsive syndrome." This could be done by giving a fairly large number of disturbed and sick children ample quantities of vitamin B_3. Children who became well would then be examined for some constant features which could become an indication for using vitamin B_3. In principal it is the same as labelling every person who recovers on vitamin doses of B_3 as having suffered from pellagra or subclinical pellagra.

To examine this question, I began a single blind placebo controlled study three and one half years ago on children under age 13 who were referred to me because of disturbed and disturbing behavior. Many had been treated by various psychiatrists before this. This study will soon be completed, but certain conclusions are now evident.

Design

All seriously disturbed children referred to me by family physicians were carefully examined in my office and later by a colleague, Dr. B. O'Regan. They were then placed upon nicotinamide or, rarely, on nicotinic acid if there was no response to nicotinamide. The dose was increased from 1½ to 6 gm. per day. They were also given ascorbic acid, 3 gm. per day and rarely very small doses of tranquilizers or antidepressants. They were then seen every three months to evaluate their progress. At no time were they given or were their parents given any dynamic psychotherapy.

As soon as the child recovered, whether it took three months or two years, he was taken off nicotinamide and given the same dose of equivalent placebo tablets. The ascorbic acid and other chemotherapy was not altered. The child was not aware of any change in medication. The mother was—as I consider it medically unethical for me to use any more double blind experiments with vitamin B_3.

As long as the child remained well he was kept on placebo. But as soon as the parents were convinced that the child had regressed to a substantial level, they stopped the placebo and started him back on the nicotinamide.

After three years I made a final evaluation of each child taking into account his performance in school, his relation to his family and the presence of any symptoms. They were also re-evaluated by Dr. O'Regan.

Each child was given a diagnosis but irrespective of this, they were placed into the research group.

Results

Of the 38 children entering the study six were terminated before they had completed their three years.

Of these, one, a mongoloid child whose father is a recovered schizophrenic did not respond after six months and there seemed then no point in carrying on with him.

A second child was making excellent improvement but would not keep her appoint-

ments. Her parents seemed quite disinterested and she was dropped from the study.

A third child would not take his medication. Whenever he was forced to take his vitamin he would begin to recover but the battle between he and his parents was too difficult and eventually he was sent to a home for disturbed children.

The remaining three children were the products of a schizophrenic, alcoholic father who killed himself, leaving a severely schizophrenic widow. It was impossible for her to ensure her children's cooperation, nor was she herself able to cooperate.

Twenty-four children went through the treatment-placebo-treatment cycle. In each cases he or she recovered on treatment, relapsed on placebo within one month, and recovered again on vitamin B_3. In many cases, recovery was slower after a placebo-induced relapse.

The remaining eight are still in the first phase of the study, are well or nearly well and will this year go onto placebo.

Thus, of 33 children who took medication as directed, only one was a failure.

I should emphasize that by "well" or "recovered," I mean they are free of symptoms and signs, are performing well in school, getting on well with their families and with the community. Some are now in their early teens and members of Schizophrenics Anonymous.

Twenty-seven families were included in this study. In 13 families, neither father or mother were ill. Of their 47 children, 16 were included in the group, i.e., 34% of their children were ill. Since they were target families with at least one sick child, this is close to what one would expect, assuming an average family size of around three.

In nine families one parent had been ill and had recovered from a vitamin B_3 responsive illness, usually schizophrenia.

Six had sick fathers and three had sick mothers. Out of 29 children, 13 or about 45% were ill.

In five families both parents had schizophrenia. From 22 children, 18 or 82% were ill.

Discussion

Most of the children who were given the medication regularly recovered but a few parents were too ill or too indifferent to cooperate and their children's recovery was too interrupted by failure to maintain medication. In other words, most of the children are vitamin B_3 responsive.

The main variable was vitamin B_3 for when this was replaced by placebo all children had relapsed within 30 days. There was no change in ascorbic acid, in other medication or in nutrition.

In every case good nutrition was emphasized. When vitamin B_3 was restarted, the children recovered again, although in many cases, more slowly.

Diagnosis of these children was as varied as with any group of disturbed children. The only thing in common was that they were ill, very disturbed and most were hyperactive. Diagnosis was no indicator of response.

Therefore, I must conclude that the condition which I term a vitamin B_3 dependent disease can manifest itself in a variety of forms. I consider it a vitamin B_3 dependent disease because they require 3 to 12 gm. per day of vitamin B_3 and because good diet alone has absolutely no effect upon them.

My data shows that vitamin B_3 dependency is inherited. In more than 100 families that I have examined in the past 10 years, I find that if one parent is vitamin B_3 dependent, one quarter of the children also will be. If both parents are vitamin B_3 dependent, one will expect more than ¾ of the children also to be vitamin B_3 dependent.

There has so far been no generation gap. One can trace this from one generation to

another. I have now in my care five patients including one mother, three of her nine children and one hyperkinetic grandchild, son of one of the three. The grandfather was a paranoid, depressed personality. Of his 10 children three including the mother of the nine were mentally ill with schizophrenia or retardation.

Another example comes from this controlled study and covers two generations. Peter and Mary are patients in this study.

Peter, 9 years old, was the first member of a vitamin B_3 dependent family who was referred to me for treatment. For over a month he had markedly changed from a happy, too quiet, obedient boy to one who was hostile, irritable and fearful. He was terribly worried he might give way to his murderous impulses against his parents or against himself. Thus, he was afraid to take a bath because he was afraid that he might drown himself. These fears had been present over one year but not at the same intensity. Peter described his life as a nightmare of visions, perceptual illusions and fears.

He was started on nicotinamide 1½ gm. per day, ascorbic acid 1½ gm. per day, and continued on Thorazine 50 mg. at bedtime.

After one month he was slightly better. After the third month he was even better. He reported hearing voices and a choir of voices singing church songs. His performance in school had improved substantially. He reported that rubbing his ears no longer masked out the voices the way it used to and he described a vision he had seen before starting on megavitamin therapy. He saw Christ sitting on a chair.

After 7 months he was normal. He was started on placebo while continuing with ascorbic acd and Thorazine. After two weeks he began to relapse and his behavior began to revert to his pre-treatment condition. He could no longer sleep, nightmares came back, objects seemed far away and he became fearful and disobedient. There was no doubt he had relapsed.

After one month of placebo he was placed back on nicotinamide and Thorazine was discontinued. Within a month he was well. When seen after three years I found him normal as did my colleague who had examined him earlier. He reported that Peter was "a normal 12 year old boy."

Peter's HOD scores were:

1968	Total	Perceptual	Paranoid	Depression
January	76	18	2	11
April	56	14	3	8
July	36	9	4	3
October	13	1	1	2

Peter's sister, Mary, age 7, was next referred. She was considered retarded. She had started to walk late and had learned to speak slowly. For two years she was a placid, quiet baby. Then she became disturbed; suffered many temper tantrums. In 1963 she was severely retarded but in 1961 she was classed as dull normal. She went to kindergarten but was too disturbing to the class and she was sent to a class for the retarded. She had not responded to tranquilizers.

When I saw her, I did not consider her retarded as she was very alert, perceptive, but was typically hyperactive. She was noisy, irritable, short-tempered. She had a marked epicanthal fold which gave her a mongoloid appearance. She was started on nicotinamide and ascorbic acid, the dose increasing to 4½ gm. per day of vitamin B_3. She was also on Thorazine and 200 mg. per day of Pyridoxine.

After six months there had been no improvement and the parents, in discouragement, stopped all medication. For one year she remained the same, but late in 1969 she began to hear voices and TV in her head. She was again started on nicotinamide 3 gm. per day, ascorbic acid 3 gm.

per day, glutamic acid 2 gm. per day and Pyridoxine 100 mg. per day.

Improvement was very slight. In July, 1970 she became violently psychotic. She heard voices telling her to kill, she was in a constant panic and terribly fearful. It appeared she would have to be treated in an institution.

As a last resort she was started on nicotinic acid 12 gm. per day, ascorbic acid 3 gm. per day and, as a sedative, Dilantin 150 mg. per day. For the next month this family lived through a nightmare in which they had to give Mary 24-hour nursing care. Then she began to improve slowly.

When seen on March 5, 1971 she had shown dramatic improvement. She was relaxed, at ease, no longer fearful, able to sleep alone, and getting on much better in school. It was very clear she was an intelligent girl slowly recovering from a very severe psychosis. If she maintains her present rate of improvement, she will be well by the end of 1971.

Peter's and Mary's father was referred next. He had been under psychiatric treatment for depression for two years. These episodes of depression had troubled him all his life. Medication had levelled out his mood to a chronic state of depression. He had read *How to Live With Schizophrenia* and concluded that he too suffered from schizophrenia.

When examined he was not very ill but he described having seen visions and other perceptual changes. He had also been paranoid in the past but his main complaint was depression and fatigue. As he was obese I ran the five hour glucose tolerance test and found he had relative hypoglycemia. After six months of orthomolecular treatment he was well. (His father had been very irritable and suspicious for 10-years before he died at age 65.)

His HOD scores were:

1968	Total	Perceptual	Paranoid	Depression
January 16	27	5	0	6
April 2	15	3	0	4

The next family illustrates another two generation transmission of vitamin B_3 dependency. Mr. J. D., born in 1933, was seen in 1967 because of severe marital disharmony. Their marriage was normal until their first baby died in 1957. Gradually the marriage deteriorated and was especially bad for the past five years. He had concluded that he and his wife must separate because he had no feeling toward her whatever and was sexually disinterested and impotent.

When examined he was very suspicious but admitted peculiar perceptual changes, complained that his memory was bad and was very depressed. He denied any paranoid ideas but these were reported to me by his wife. He also had a severe form of relative hypoglycemia.

He was started on vitamin B_3, 3 to 6 gm. per day, ascorbic acid 3 gm. per day, Elavil for one month and in three months was normal.

His HOD scores were down substantially:

	Total	Perceptual	Paranoid	Depression
Nov. 30, 1967	47	7	1	12
Dec. 14, 1967	62	14	3	6
Jan. 19, 1968	23	3	0	0

Early in January, 1968 the second child, a girl age 8, was brought in because her performance in school was so erratic, because of her violent temper, and because of a reading problem. Words moved on

the page, faces pulsated, she saw vivid hallucinations, heard voices, and complained of being tired.

She was started on nicotinamide and ascorbic acid, 1 gm. of each per day. By May, 1968 she was normal. She was started on placebo to replace the nicotinamide. She deteriorated to her pre-treatment level within four weeks.

She was started again on nicotinamide but responded very slowly. The dose of nicotinamide was increased to 4 gm. per day by February, 1969. However, by October, 1970 she was well again and the dose was reduced to 2 gm. per day. At the end of the three years she was still normal.

There is a well-known vitamin deficiency disease which is an excellent model. Unfortunately psychiatrists are no longer familiar with the clinical manifestations of pellagra. When the older literature is examined, it is clear that the best model of schizophrenia is pellagra. It is so good that for many years psychiatrists in mental hospitals could not distinguish between them.

The only certain diagnostic test was the therapeutic one, once crystalline vitamin B_3 became available. If the psychotic patient recovered in a matter of days on 1 gm. per day or less he was labelled pellagrin. If he did not he was retained in the diagnostic group "schizophrenia."

Both diseases are characterized by changes in perception, in thought and mood. The major difference has been in skin pigmentation. Pellagrins usually suffer symmetrical brown pigmentary changes while this was less common in schizophrenics. It is likely, however, this was an artifact resulting from the way the patients were cared for. Schizophrenics generally were locked up in mental hospitals and were not exposed to the sun, whereas pellagrins came in from the community and either recovered fairly quickly or died.

What is not as well known is that long before pellagrins became psychotic they suffered from tension, depression, personality problems, fatigue and every other change commonly seen in neurosis, psychopathies, depressions, etc. In other words, mild forms of pellagra modelled non-psychotic forms of mental disease and severe forms the psychotic varieties.

Green has treated a large number of disturbed children with nicotinamide. From the dramatic responses he has concluded they suffered from subclinical pellagra. His examination of the literature led him to the same conclusion as mine.

There is one major difference between pellagra and schizophrenia. It is entirely quantitative. Pellagrins require vitamin doses and schizophrenics require megavitamin doses. But even this distinction is not absolute. Chronic pellagrins, who should be compared with chronic schizophrenics, also require megadoses for long periods of time.

There is thus a quantitative continum from pellagrins who fail to ingest vitamin doses of vitamin B_3, say 50 mg. per day or less, to chronic pellagrins who require up to 1 gm. per day, to acute schizophrenics whose needs are 3 to 6 gm. per day to chronic cases who will require 6 to 30 gm.

The group who require 50 mg. per day or less will develop pellagra if their diet is deficient. The group requiring over 1 gm. per day will develop schizophrenia since no modern diet will provide this amount of vitamin B_3. What I do not know is how much vitamin B_3 per day given to this latter group will prevent them from developing schizophrenia. To be on the safe side I recommend 1 gm. per day for children of parents who are vitamin B_3 dependent. One could study this very easily by placing a large number of children from schizophrenic parents on various doses to see how much is required to prevent anyone from becoming ill.

Conclusion

In my opinion based upon this study

which I will report in detail later on, upon hundreds of other cases, my own and those reported by Cott and Hawkins, there is a syndrome in children arising from a vitamin B_3 dependency.

This syndrome is characterized by:

(1) Hyperactivity.
(2) Deteriorating performance in school.
(3) Perceptual changes.
(4) Inability to acquire or maintain social relationships.

Any child showing three or more of these features should be given a trial with the orthomolecular approach. In each case there should be a titering of dose until the child is exposed to the optimum dose. Once the child is recovered, it can be slowly reduced to a maintenance dose.

I do not know how long they will require vitamin B_3 but I suggest it not be discontinued until they have achieved their final physical growth. One schizophrenic girl has been taking vitamin B_3 for 17 years but will need it for the rest of her life. Another young man stopped his vitamin at age 16 and is still well two years later.

REFERENCES

COTT, ALLAN: Treatment of ambulant schizophrenics with vitamin B_3 and relative hypogylcemic diet. J. Schiz. 1:189-196, 1967.

COTT, ALLAN: Treating schizophrenic children. Schizophrenia 1:44-60, 1969.

COTT, ALLAN: The parenteral use of vitamins in the treatment of schizophrenia. Schizophrenia 2:177-179, 1970.

GREEN, R. G.: Subclinical pellagra; its diagnosis and treatment. Schizophrenia 2:70-79, 1970.

HAWKINS, D. R.: J. Schiz. 2:3-10, 1968.

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Schizophrenia: An Evolutionary Advance

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INTRODUCTION

Huxley, Mayr, Osmond, and Hoffer (1964) presented a hypothesis that schizophrenia is a genetic morphism (see Huxley, 1955). This is in general agreement with the proposition that all genetic characteristics which exist in a population at a frequency higher than can be maintained by mutation alone must be a morphism. The frequency of the morphic gene is the result of a balance between its selectively favorable and unfavorable properties. An advantage of a morphism is that it allows populations depleted by natural difficulties or disasters to reproduce rapidly when environmental conditions become favorable. A condition which remains a genetic morphism for a long time could eventually become universal if there was a major shift in factors favoring such a development. Hypoascorbemia (Stone, 1965, 1966) may originally have been a genetic morphism, but today after many million years no man can synthesize ascorbic acid and everyone has the orthomolecular condition hypoascorbemia.

Whenever reasonable statistics are available, they show a lifetime incidence of schizophrenia of about 1 to 2 percent in all racial and ethnic types in all geographical regions. A few studies have shown a higher incidence in lower socioeconomic strata, but if this is a real phenomenon it is not general. It will be shown later that this might be a true finding and related not to the stress of poverty from a psychological point of view, but to the malnutrition and perhaps increased consumption of bread and sugars which is a natural concomitant of poverty. The diet would also contain less of the more expensive high-protein and high-vitamin foods. Poverty was said to account for the higher incidence because of the psychological stress. In the same way many claims have been made that maternal deprivation causes growth retardation in infants. Whitten et al. (1969), in a carefully controlled experiment on underdeveloped infants, discovered that in spite of assurances from mothers they were feeding their infants adequately, they were not getting enough food. When the infants were provided proper meals in hospital or at home without disturbing the mother-child relationship, these infants rapidly gained weight. Emotional deprivation played no role in growth retardation. Maternal neglect of proper infant feeding was solely responsible. The 1 to 2 percent lifetime incidence, according to Wender (1969, may be an underestimate as it is based upon mental hospital admissions. It does not take into account patients seen in clinics and by private psychiatrists. An estimate of up to 3 percent may be much more accurate.

Another real possibility is that schizophrenic patients who do not recover find it difficult to compete with normal

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people. They must, therefore, work at jobs which pay less or survive on social welfare. This would force them into areas with lower living standards. In addition, unusual behavior may be more acceptable in the lowest income groups.

The evolutionary disadvantages of having schizophrenia are well-known.[1] If the disease strikes before puberty, males are less likely to marry and reproduce. This seems to be less important for females who, if left in the community, have reproduced more quickly. When the disease struck during the childbearing age, it used to effectively remove most of the patients from the community and prevent a normal reproductive life. The modern concept of treatment in the community makes these restrictive measures much less effective.

Another disadvantage is the high suicide rate which Osmond and Hoffer (1967) have estimated to be about 25 times higher than that in the general population.

In spite of the tremendous effort society has made to limit reproduction of schizophrenics by incarceration in institutions, by therapeutic abortions, and by sterilizations, the lifetime incidence of schizophrenia has remained constant. There is substantial evidence that the newer discharge policies have removed a major reproductive disadvantage and we should expect a real increase in the lifetime incidence; that is, if we combine the lifetime incidence of 1 to 2 percent with the lifetime incidence in offspring of parents now in the community who formerly were kept in institutions, it is inevitable that there will be a real and major increase. Erlenmeyer-Kimling et al. (1966) compared the reproductive rates of 1934 - 36 to 1954 - 56 admissions. The rate increased from 57 to 94 children per 100 patients. They concluded that "any selective disadvantage which schizophrenic illness may have in terms of its evolutionary history is now in the process of disappearing."

There are two main types of compensatory advantages:

1. Physiological

These are reviewed by Huxley et al (1964). They include resistance to surgical and wound shock, to visceral perforation, to high doses of histamine, insulin, thyroxine, and adrenalin, to pain, to arthritis, to many allergies and to many infections.

Carter (1968) examined the relatives of schizophrenics in comparison with similar relatives of nonschizophrenics in two geographically separate practices in England. Carter selected each schizophrenic patient in these two practices. The control case was the next same-sexed patient in the case files born in the same five-year period. They located 28 schizophrenics who had 64 relatives, and 29 controls who had 73 relatives. There was a definite deficit of virus infections (influenza, measles, mumps, chicken pox, rubella, herpes zoster, common cold, corneal ulcer, plantar warts, and enterovirus infections) among schizophrenic relatives – 58 compared to 95 among controls. There was no difference in the incidence of bacterial infections.

In one of the practices, schizophrenic relatives had a smaller accident rate than control relatives.

Carter also found evidence which supported earlier findings of a diminished susceptibility to allergies. Of great importance was Carter's finding that schizophrenic relatives had an increased pregnancy wastage (miscarriages, stillbirth, and neonatal death rates) and childhood mortality (sex not given); but this was more than compensated by a 30 percent increase in fertility. Fifty schizophrenic relatives had 131 children compared to 79 children on 40 control relatives.

Perhaps these factors accounted for the finding by Erlenmeyer - Kimling (1968) that female offspring of schizophrenic parents (male or female) had significantly lower mortality to age 15 than the population at large. They say "even a slim differential in the probability of reaching childbearing age would be important in the balance of selection relating to schizophrenia."

2. Reproductive advantages

Although schizophrenic males do not marry at the same rate as normal men, the increased fecundity of schizophrenic women and certain psychological advantages of the illness, in an evolutionary sense, more than compensate for this. Over the past two years I have been impressed with (1) the number of schizophrenic women who become pregnant before marriage because they wish to, in response to delusions or because they are not in control of their activities, do not adopt birth control measures, and who in seeking male companionship to break their loneliness will have relations which they do not enjoy as a way of retaining their male friends; (2) the number of adopted children who are schizophrenic brought in by their normal parents. I have the feeling that normal parents who adopt must find out whether either parent was schizophrenic so that if the child becomes ill they can take appropriate action. The prophylactic use of niacinamide, 1 gram per day, is indicated.

GENETICS OF SCHIZOPHRENIA

For many years clinicians, who have worked closely and for long periods of time with schizophrenics and their relatives, have been impressed with the frequency with which they find several members of the same family afflicted with this disease. I have been impressed over the past 18 years, on a case material of over 2000 schizophrenics, with the high degree of association. Not only was it obvious to me, but once the patients had recovered and became knowledgeable about schizophrenia, it was equally clear to them. I have dozens of examples of schizophrenic mothers correctly spotting their offspring who were showing the early signs and symptoms and who, on chemical assay, were found to have malvaria. Invariably, mothers brought in their sick children first for examination. I have numerous examples of young schizophrenic men and women who, upon recovery, brought in sometimes reluctant fathers or mothers who were and had been psychotic many years. I have a few examples where recovered patients brought in their schizophrenic spouses. In fact, it is rare to find families where only one member is ill. As early as 1685, Thomas Willis observed, "It is a common observation that men born of parents that are sometimes wont to be mad will be obnoxious to the same disease."

Genetic theories have shared the field with environmental theories with fashion rather than fact determining which will be most popular. The earliest environmental theories were the demoniac possession theories which gave way to medical theories when schizophrenia was removed from the sphere of influence of priests and taken over by physicians. During the height of enthusiasm for genetics, it once more was considered primarily somatic or genetic. But by the end of the last war, when psychoanalysis became so influential in the U.S., family theories once more became popular even though there was no new data to support this point of view. Family hypotheses which seemed plausible soon were assumed to be real, and large schools of family therapy sprang up in which the schizophrenic member was considered not the sickest member of a healthy family but the healthiest member of a sick family who had taken upon himself the role of sacrificial lamb. The proponents of this school vigorously attacked the geneticists by demanding a degree of purity and virtuosity of their methods and data hardly ever attained in any branch of medical research even though they had no hard data to support their own point of view.

However, their critique did encourage a series of well-planned studies which, while adding little new information to that gathered by men like Kallmann, Slater, Rudin, Luxenburger, and Schulz, did impress even hard-core environmentalist research centers like N.I.M.H. However, it is impossible to measure the total loss to schizophrenia research by the diversion of immense sums of money to this line of research which added so little new information.

Wender (1969) has summarized the evidence derived from genetic studies:

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(1) Consanguinity Studies - as a general rule the closer the biological affinity, the higher the concordance rate for schizophrenia. Rainer (1962) gave the following expectancy of schizophrenia amongst schizophrenic relatives.

	Percentage Expectancy
General Population	0.85
Half siblings	7- 8
Full siblings	5-15
Parents	5-10
Children (of one schizophrenic parent)	8-16
Children (of two schizophrenic parents)	53-68
Fraternal twins	14
Identical twins	86

(2) Family and Psychodynamic Studies - It has been shown that schizophrenics often come from disturbed families. But this fact does not help one decide whether the disturbance in the family resulted from having to live with a schizophrenic or whether it caused the schizophrenia. Wender concludes that this kind of data does not permit the evaluation of the relative contribution of heredity or environment. It is difficult to visualize a family which can avoid being disturbed when one of its close members is ill with schizophrenia, especially when parents are directly or obliquely accused of making their child ill. It is rare to find families who are not disturbed, but in nearly every case the independent variable is the schizophrenia in the sick member, and the dependent variable is family discomfort. As the schizophrenia subsides, so does the degree of family disturbance decrease until it regains its normal pattern when the patient has recovered.

Evidence which favors the major influence of heredity (and minimizes environmental factors) may be summarized as follows:

(a) Evidence that the illness can occur during early infancy when it is inconceivable the infant could perceive or respond to schizophrenogenic mothers:

Thus, Bender (1955), Bender and Helme (1953), Fish (1957), Fish and Alpert (1962) have been able to detect abnormal states of consciousness and muscle tone in infants age one month who later clearly were schizophrenic.

These studies begun in 1952 have shown that neurological changes are present as early as one month after birth. Many different changes were found, including a lag or a peculiar sequence of motor development, or confused proprioception and perception of form, or abnormal torpid or flaccid muscle tone. Fish and Alpert (1962) carefully followed development of states of consciousness and muscle tone in 13 infants born to schizophrenic mothers in state mental hospitals. Four showed marked apathy and irritability and three showed less extreme deviations from the norm. The quiet infants had decreased motor impulses, responded little to proprioceptive stimuli, and in extreme cases had flaccid muscle tone and irregular postural development.

Pollin et al. (1965) studied identical twins (three female pairs and two male pairs) of whom only one was schizophrenic. They found that the twin to become schizophrenic weighed less at birth, was perceived by parents as vulnerable, and therefore received more care and attention. Early development was slower, and this twin always tended to be more dependent and had greater difficulty achieving any degree of autonomy and separateness.

My conclusion differs from the authors who tended to see it as a defect in the mother as she reared her children. I believe the twin destined to become schizophrenic was in fact more vulnerable, that this was correctly perceived by the mother, who, as most mothers would, was forced to give this child more attention and received fewer compensating rewards. This is also true when a child, not a twin, becomes schizophrenic and is compared to normal sibs. I have many families where parents have shown similar solicitude and care for their sick children until the children recovered. After that the parent-child relationship became the same for the schizophrenic child as it had been for the other sibs.

Some, who give unusual prescience to babies, have fallen back on orphanage data to prove that even infants can detect rejection. But recently it has been shown that rejection and malnutrition often go hand in hand, and that marasmic babies properly recover very quickly without huge doses of love (unless of course they equate food and love, but then this is not how psychologists who believe in the importance of maternal rejection would see it).

Studies have been done to detect what were the early malignant influences and whether differential parental attitudes could be detected which would explain why a certain son or daughter became ill. In two investigations, it has been shown that the child who became schizophrenic was more dependent and the family had to make allowances for it. With identical twins, Pollin et al. (1965) observed that the lighter, physically less developed twin developed schizophrenia first.

In a recent study, Block (1969) compared the parents of schizophrenic, neurotic, asthmatic, and congenitally ill children. Block found no support for the idea that there was any psychogenic specificity between these groups of mothers. On the basis of clinical descriptions of so-called schizophrenogenic or asthmatogenic mothers, factors characteristic for each were compared in this empirical test. The mothers of asthmatic children did not differ significantly from mothers of the schizophrenic children. However, not surprisingly, there was an association between parental psychopathology and symptoms in the child. The correlation was 0.539 which means that the mothers' psychopathology could account for about one-quarter of the psychological symptoms in their children. This is significant, but hardly exciting, and suggests that even a complete removal of all psychiatric symptoms from mothers of schizophrenic children would not relieve their children's schizophrenia appreciably.

(b) **Adoption studies** seem particularly useful in sorting out genetic and environmental factors in the development of schizophrenia. There are four possible combinations, children from schizophrenic parents adopted by either schizophrenic or normal parents and children from normal parents adopted by either schizophrenic or normal parents. One would expect the highest incidence of schizophrenia and othe psychiatric problems amongst the group of children from schizophrenic parents adopted by schizophrenic parents, since not only would genetic loading act but also all the presumed stresses of adoption and separation from biological parents would interplay with the stress of being reared byschizophrenic parents. Next, in order of frequency, would be children from schizophrenic parents raised by normal parents. If there were in fact no significant differences between these two groups, this would be evidence against any major effect of environment in producing schizophrenia.

Children from normal parents raised by schizophrenic parents should have a low incidence of schizophrenia while in the last group one would expect the usual 1 or 2 percent lifetime incidence. If these latter two groups were not significantly different this would also be evidence against environmental causal factors.

1. **Children from schizophrenic parents adopted and reared by schizophrenic parents.**

Higgins (1966) selected 50 children out of 200 born from schizophrenic mothers. They were divided into two groups of 25 each using carefully matched variables. One group remained with their mothers their entire life. The other group was separated by age 1½ and was reared by normal mothers. Higgins had predicted that the group reared by schizophrenic mothers would show greater maladjustment. But the results of the study showed there was no difference between the two groups. The slight differences which were found suggested that rearing by a schizophrenic mother has less to do with the child's level of adjustment than with the direction of its basic orientation to the world. In other words, the mother had little to do

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with the fact of the presence of abnormality, but not surprisingly did have some effect on the content of the changes. The Higgins study does not provide data on children of schizophrenic parents adopted by schizophrenic parents but it is the closest to it of any study I have seen so far.

2. Children from schizophrenic parents reared by normal parents.

Karlsson (1966, 1967) selected a group of siblings of schizophrenic patients still in hospital with one parent having a history of mental illness. They had all been reared by normal parents. Out of 119 cases, 17 were schizophrenic. In a further study, Karlsson selected eight other cases who had been reared in a foster home. Karlsson then identified 29 biological sibs and 28 foster sibs. Out of 29 of the biological sibs, six were schizophrenic. None of the 28 foster sibs became ill.

Heston (1966, 1970) examined a series of children of schizophrenic mothers who were reared in foster or adopted homes. Out of 47 cases, five were schizophrenic and another eight were borderline. Thus, about one-third developed major pathology which is comparable to the proportion who develop similar pathology when reared by their own schizophrenic parents. In Heston's control group of children from normal parents reared by normal parents, there were no cases of schizophrenic or of borderline schizophrenic states. Heston also found that another 13 cases presented other psychiatric diagnoses. In the control group there were only nine cases with personality problems. Finally, Heston found that among index subjects who were mentally normal there were a large number of very talented people.

Rosenthal et al. (1968) found similar frequencies of abnormality. Out of 39 index cases, three became schizophrenic and 10 were borderline. Out of 47 control cases none became schizophrenic, but six were borderline. Karlsson (1967) has compared biological relatedness and whether cases were reared by schizophrenic or by normal parents.

His results are shown in Table 1.

Table 1

OFFSPRING OF SCHIZOPHRENIC PARENTS

Reared by Schizophrenic Parent	
Monozygotic twins (1)	Concordance very high
Two schizophrenic parents	Risk of developing schizophrenia 35%
Sibs of schizophrenia — one parent	Risk 12%
One schizophrenic parent	Risk 12%
Reared by Normal Parent	
Monozygotic twins (1)	Concordance very high
Two schizophrenic parents	Only one case found — he is schizophrenic
Sibs of schizophrenia — one parent	3 out of 9
One schizophrenic parent	11 out of 100

3. Children from normal parents reared by schizophrenic parents.

Kallmann (1946) found that step-children of schizophrenics did not show any elevated risk of becoming schizophrenic. I have been unable to find any other reports.

TWIN STUDIES

The largest series of twins with schizophrenia were studied by Kallmann (1946), which included 174 monozygotic twin pairs. The most striking findings were that expectancy rates were 14.5 percent for dizygotic twins and 86.2 percent for monozygotic twins. Similar results were reported by Inouye (1961) and Slater (1953). The Kallmann studies have been most extensively criticized but it was shown by Shields et al.(1967) that the criticisms were minor or invalid. Their final conclusion was that "he did not allow himself to be biased," and the data constituted an important source of information to all who would try to unravel the contributions of heredity and environ-

ment to the etiology and phenomenology of schizophrenia.

(1) Identical twins reared in separate homes from infancy.

Gottesman and Shields (1966) reviewed schizophrenia in twins over 16 years of consecutive admissions, and again found concordance rates to be much higher for monozygotic twins, but concordance was related to severity of the illness. Chronic patients residing in or admitted to long-stay hospitals showed the highest concordance.

One of the major criticisms of Kallmann's data by Rosenthal (1961) was that his data contained too few opposite-sexed twins. Generally one would expect an equal number of both types of twin pairs. In the five studies listed by Rosenthal the ratio of opposite sex to same sex varied from 1.54 to 1, to 0.75 to 1. But Kallmann's series included 517 pairs of twins as against 33 pairs in Luxenburger's study. Rosenthal suggested that Kallmann's data could be due to bias by hospital personnel in discovering twins (opposite-sexed twins would be missed) or in calling many pairs dizygotic when in fact they were monozygotic. Shields et al. (1967) re-examined Kallmann's data and methods of data collection and concluded these criticisms were not sound. This is not surprising since Rosenthal provided no experimental evidence for his speculations, i.e., that monozygotic twins in mental hospitals are less frequently missed.

There is an explanation for Kallmann's higher incidence of same-sexed twins. If Kallmann's series, because of its size or for other reasons, included a larger number of twins born to schizophrenic mothers who were ill, one might expect the differential effect of the mother's schizophrenia or sex of offspring to account for this. If in only 20 percent of the theoretical opposite-sexed twins the male was reabsorbed leaving only one female, one could expect an uneven distribution of opposite and same-sexed twins. The same effect would occur in male same-sexed twins and this should increase the ratio of female same-sexed twins to male same-sexed twins. In fact, except for the Gottesman and Shields (1966) study, most twin studies showed an excess of females over males.

Kallmann's unusual distribution of alike and opposite-sexed twins may therefore be the correct one.

Ancillary Evidence

Another line of evidence comes from conditions which are generally accepted as wholly genetic. If it can be shown that these conditions are highly correlated with schizophrenia, then it strengthens the evidence for the genetic basis of schizophrenia. Total finger ridge count is one of the few conditions which is almost wholly genetic.

Mellor (1967) compared finger ridge counts of normal and schizophrenic men and women. He found a significant difference between normal and schizophrenic males, but not between normal and schizophrenic women. There was a significant difference between normal men and women (men having higher counts), but not between schizophrenic men and women. Schizophrenic men had effeminate counts.

FAMILY STUDIES OF MALVARIA

In 1961, Irvine (1961), Hoffer and Mahon (1961) reported that a larger proportion of schizophrenics excreted a mauve-staining factor than any other group. Since then many thousand cases have been examined and the following proportion from various diagnostic groups have been found to be positive.

Group	*Percent Positive*
Schizophrenia	
(a) First attack	90%
(b) During any relapse	75%
(c) Chronic	50%
(d) Ill over 20 years and in state hospitals	10%
(e) Schizophrenics who have recovered	0%
(f) Depressions	25%
(g) Neuroses	25%
(h) Behavioral disorders and alcoholism	25%

(Table continued)

(i) Adult retarded population in a state hospital 65%
(j) Infantile Autism 0%
(k) Mentally normal and physically ill 11%
(l) Normal 5%

The mauve factor was not due to dietary factors and only one tranquilizer, mellaril, interfered. So far, there have been no reports failing to corroborate when our method was used as described.

In 30 families where one member was found to have the mauve factor, every other member of the family was tested and information on each person tested was obtained by clinical examination of every adult and by description of parents of their children's behavior. We have found that parents who are well are good observers and reporters.

From the first-order relatives of the index malvarian, 30 percent were also malvarian. This group included 26 schizophrenics, 29 other psychiatric illnesses, two retarded children, one physically ill child, and four who were normal. The nonmalvarian group contained four schizophrenics, eight other conditions, three retarded children, and 44 who were normal. These results are shown in Table 2.

Table 2

	Schizophrenia and Schizoid	Other Diagnosis	Well
Malvarian	26	31	5
Not malvarian	4	11	44
Offspring from schizophrenic parents	13	13	21
Offspring from normal parents	0	9	41

Mauve factor is kryptopyrrole (Irvine, Bayne, and Miyashita, 1969).

Comparison with Heston's data shows that the malvarian group, although selected differently, resembles his group of offspring from schizophrenic parents more than the other group while the nonmalvarian distribution is more like the offspring from normal parents *(1966)*.

From families with one parent malvarian, 40 percent of the children were malvarian. To test the ability of mothers to detect illness in their children, they were asked to bring in urine specimens first from the child they considered the sickest and last from the child they considered most normal. Of the 19 children first tested, 15 were positive. Of the 44 children brought in last, none were positive. If we compare the first three choices against the last four choices, Chi square is over 2.6.

We have been able to test two identical twin pairs. They were so alike physically that their parents often could not distinguish one from the other. All four were malvarian.

The A Twins (born 1939)

D.A. had been deeply depressed and anxious for two weeks. A previous depression in 1963 lasted six months, and responded to antidepressant medication. During this time, D.A. was paranoid, believing people were always watching him and talking about him because they knew he was mentally ill. He was also suspicious of his wife. His HOD scores were Total 49, Perception 9, Paranoid 4, Depression 16; and on the EWI (El-Meligi and Osmond, 1970), on a retrospective test, he showed a severe schizophrenic reaction with depression and paranoid ideas. He was started on nicotinamide 3 grams per day, ascorbic acid 3 grams per day, and an antidepressant. Two weeks later, he was nearly well and has remained well since on the vitamins. His HOD scores were Total 10, Perception 2, Paranoid 0, Depression 1, and on the EWI profile he was well.

E.A., his brother, was normal. When infants, his mother tied a ribbon on one so they could be distinguished. Both grew up with similar interests and hobbies. Both are married. E.A. had one convulsion in 1959. The EEG one week later was normal. He took anticonvulsant medication several

years. Between 1962 and 1967 he took dilantin and phenobarbital whenever he became very tense and excessively tired - about five times per year.

The B Twins (born 1951)

This family was discovered when the oldest son, a student at university, became schizophrenic in 1957. He recovered on nicotinamide 3 grams per day. Then he expressed concern about his psychotic father who had been treated several times in a mental hospital. He considered his twin sisters were well although they were having difficulty in school.

I.B. was the smaller of the twins. She resembled her sister but they were always distinguished by size. I.B. was a B average student in school but in grade 11 her performance dropped perceptibly as follows: December average, 52 percent, January average, 43 percent, and in April, 1968, 44 percent.

I.B. tried very hard to overcome her defect, but even though she worked very hard she could not learn. Apart from irritability and shyness, Irene appeared normal. She was started on nicotinamide 3 grams per day. Four months later, her mother reported that Irene had improved markedly. Irene wrote, "Since I have been taking them I found it easier to learn and understand the teachers. I wasn't as crabby as before. I find it easier to talk to people. In school I've improved in five out of eight subjects."

Miss B.B. was considered normal by her parents, but they had been concerned about a deterioration in performance at school. She was a B average student and was able to maintain this record, but had had to study longer hours and it was much harder for her. Both girls had nearly identical HOD scores as shown below.

	Total Score	*Perceptual Score*	*Paranoid Score*	*Total Score*
I.B.	13	2	0	2
B.B.	13	2	1	2

The HOD test is a simple card sort test developed by Hoffer and Osmond (1961), Kelm et al. (1967), for assisting in the diagnosis of schizophrenia. High scores indicate severe psychopathology. Normal scores are as follows: Total score, 0 - 30, Perceptual score, 0 - 3, Paranoid score, 0 - 3, Depression score, 0 - 3.

She was also started on nicotinamide 3 grams per day with no expectation of change. However, three months later her twin in a report wrote, "Before Bev started to take the pills she could hardly talk. She has improved in school and passed into grade 12."

The father had identified himself as a schizophrenic by reading up on it. Born in 1915, he was reasonably well until 1962 when he admitted himself to a mental hospital complaining of severe abdominal pain which he knew was cancer. He was very paranoid about his wife, believing she was having an affair with a neighbor, and he spent much time and energy searching for evidence. His second son, he was convinced, was not his. He was also very anxious and fearful of death. He had no insight and judgment was poor. One month later, he was discharged better, but readmitted a few weeks later for another short stay in hospital. He responded to tranquilizer medication which he continued to take as an outpatient. However, he remained irritable, hostile, unreasonable, and often paranoid, and this resulted in a perpetual marital discord leading to several separations. The hospital diagnosis vacillated between depression and schizophrenia.

The malvarian data resembles the family data reported by other investigators. However, the main error in this work is that the mauve factor may disappear when the schizophrenia becomes chronic, or it may appear only on certain days. If the two diagnostic groups, schizophrenia (a clinical diagnosis) and malvaria (a laboratory diagnosis), were to be combined, it is highly likely the study of the genetics of schizophrenia would be simplified. Our data suggests that malvaria detects borderline or incipient schizophrenia.

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Identical schizophrenic and malvarian twins, some of whom were treated with the megavitamin B3 approach. Several years ago, Burrell and Osmond (1959) suggested that identical twins ought to be used for clinical trials since this would both simplify and reduce costs of these trials. Beveridge (1950) had recommended this be done by using one twin as a control. In animal experiments involving butterfat yields, one pair of identical twin cows was as valuable as results obtained from two groups of 109 cows each. For measuring growth during the first year of life, one pair of identical calves gave results equivalent to at least 25 pairs of ordinary calves. When this suggestion was made, no therapeutic studies with twins had been reported nor have any appeared since. The statement made by Burrell and Osmond is still relevant today.

"This is a strange oversight, because it seems that twin pairs used in this way might be of even more relative value than in those animal experiments to which we have already referred. In pure breeds of livestock, one would expect that there would be a greater degree of genetic homogeneity than among humans and so relatively less benefit would be gained by the experimenters. Not only are humans inherently more variable, but also the type of inbreeding which is possible among cattle is socially prohibited, and so more control would be gained by twin studies involving humans. Naturally, this would have to be confirmed experimentally."

There is no direct evidence to show how many subjects per group in a controlled study would be equivalent to one identical twin pair, but by using animal data one could assume that it might be equivalent to 50 subjects per group. Since few clinical studies report more than 50 per group, due to costs and other factors, and since a comparison group of over 30 is usually sufficient to yield significant differences between treated and untreated groups if in fact the treatment is superior, it would follow that one identical twin pair in a therapeutic trial would be just as helpful and much more practical to study than the usual comparison groups.

In addition, if identical twins responded the same way to similar therapy, this would reinforce the genetic and biological view. If each twin pair represents a study equivalent to comparison groups of 50 subjects each, a series of twins would represent very substantial data equivalent to hundreds of patients.

I have been in direct contact with five pairs of twins of whom two were concordant. Because the patients were examined very early and were mostly young people, this is probably an underestimate. In the B pair, the twin considered well improved substantially on nicotinamide medication. The evidence is strong that had she not started she would have become ill like her sister. In the case of the K. twins, one was never seen but her history of dropping out of school, of stealing and lying was a mini version of the schizophrenic twin's behavior. Of all the seven pairs, four were concordant. From the four adult twin pairs, concordance was present in three pairs. A summary of the twins' history is shown in Table 3 and in the brief case histories which follow.

Mrs. M.G. (Born 1921)

The patient remained well until 1950 when three months after the birth of her first child, a girl, she developed severe schizophrenic psychosis and remained in hospital six weeks. Then she remained well for two years. After that, for the next 14 years, she had to return to hospital fifteen times, the last admission in 1946 when it was recommended that she have a lobotomy. Her average stay in hospital was about one month. She received standard therapy including psychotherapy, drugs, and ECT. Early in 1966, she consulted a family physician for pain in her back. He diagnosed her schizophrenia and started her on nicotinic acid 1 gram t.i.d. She responded quickly and has remained well. I saw her in September, 1966, when she had been well for six months. She was last seen in August, 1969, and was still well. This is the longest period of health since her first attack.

Mrs. M.G.'s son had always been considered retarded. He was started on nicotinamide and after a year was a B-average student in high school and had matured a lot.

Her twin sister, Mrs. L. G., became ill three months ahead of Mrs. M. G. and has suffered similar recurrent episodes of psychosis. She has required fewer admissions but each one has averaged three months. By fall, 1966, she had remained out of hospital five years but was living a sheltered, seclusive, withdrawn life with her husband.(1) Mrs. M. G. had made strenuous attempts to persuade her sister to take nicotinic acid but was blocked by her sister's psychiatrist who refused to consider it.

In fall, 1967, this twin again went to a hospital and after one month with no response was going to receive another series of ECT. Her normal sister wrote, "It just breaks my heart that even now they won't try this nicotinic acid."

As girls these twins were so alike it was impossible for friends and relatives to tell them apart.

Mrs. A. Ka (Born 1920)

Patient became schizophrenic in 1956, a few months after the birth of her last child, a boy. In 1960 she was admitted to a psychiatric ward where she displayed visual and auditory hallucinations, thought disorder, and marked apathy. She was given 20 ECT, tranquilizers, propylthiouracil, and nicotinic acid, 1 gram t.i.d. Upon discharge, the patient was much improved, showed little confusion, had no perceptual changes, and was more appropriate socially. She was placed on maintenance nicotinic acid, 1 gram per day, for two months. This is a totally inadequate maintenance dose.

She was admitted several times to another ward. On September 16, 1965, she was admitted for two weeks to start slow-release medication as she had been unable, because of her illness, to take medication. She has continued to function at home since, on home care, with a nurse making regular visits to give her injectable tranquilizer. Her present condition, chronic schizophrenia, improved but with recurrent attacks of agitation. There are many marital and home problems.

Mrs. M. Ka, the twin, has also been schizophrenic for many years and presented a picture similar to that of Mrs. A. Ka. She has been on home care many years and has received ECT and tranquilizers. However, she has remained a chronic schizophrenic — improved, with many family and marital problems.

The D twins (born June 14, 1949)

Linda, at birth, weighed 4 lb. 3 oz. and Lorraine 5 lb. 2 oz. For a long time, the parents could not differentiate the twins. They were slow to walk. At age nine months they began to speak a few words, but after having whooping cough, they both stopped talking to anyone else but to each other, babbling in what the parents called Chinese. Then they began to talk to others more clearly. Both have a peculiar lisp we have noted in several young schizophrenics. Both were slow in school and were considered retarded.

Linda completed grade seven, then quit. In 1959, she felt that she had rocks in her stomach. In 1965, she became disinterested in school, refused to study, and stopped reading because whenever she read she got severe pain in her head. She was admitted to a hospital for severely retarded patients for evaluation and training. There she was found to have a low normal intelligence and was referred to a psychiatric ward for two months. A year later she began to feel she was losing her mind. In 1969 she had a few perceptual changes, suffered thought disorder (blocking, paranoid ideas) and poor judgment, and she was very nervous and tired. She was admitted for a series of unilateral ECT and chemotherapy and was discharged five weeks later improved. Since then, she has continued to improve on nicotinamide 3 grams per day.

Lorraine had a very similar history. She

1 Over the past five years she required about 12 admissions

completed grade seven, but that year she became aware of her breathing and has since been unable to take her mind off this. She became very fearful of dying and for several weeks before admission was too frightened to fall asleep and stayed up continually. She suffered many perceptual changes including visions, feelings of unreality, a feeling her mind was floating away, and hyperawareness of her respiration. She had thought disorder including blocking, paranoid ideas, poor memory and concentration, and confusion. She was also depressed and suicidal. She received a series of unilateral ECT plus the megavitamin B3 therapy, and on discharge was improved.

The K twins (Born June 1950)

Miss A. K. did not believe that she was ill. She was referred because she was charged with stealing. In spring, 1967, while in grade 10, she dropped out of school in order to get married. Her sister Alice also dropped out for the same reason. A. K. hoped to get a job to earn money for her marriage. In the fall, she broke the relationship and became deeply depressed, but in March, 1968, she felt better. For several years, she had been shoplifting and lying to her parents as did her twin sister. She became unreliable, drank heavily, and swore at her parents. They described a character change from a good girl to her present personality. She denied perceptual changes, but on the HOD test admitted many. She also was paranoid, blocked, unreliable, showed poor judgment, and lacked insight. There was no improvement on medication and she was admitted for 5 ECT. March 27 to April 5, 1968, she was better on discharge. After this, she was seen several times and remained better. She left home, worked for awhile, but continued to have trouble with her parents. When last seen in August, 1969, she was on her way to Vancouver for a job, having been kicked out of her home by her parents. Since then, she has been in hospital several times, has continued to drink heavily and has not been replaced on megavitamin therapy.

The mother was seen several times and was the most likely transmitter of the schizophrenic genes. She was puritanical, rigid, hostile, eager to be rid of her children, and most reluctant to take them back.

The twin has not been seen but married recently.

HOD scores were:

	Total Score	*Perceptual Score*	*Paranoid Score*	*Depression Score*
March 5, 1968	53	15	4	14
May 8, 1968	100	21	6	11
June 9, 1968	68	14	2	8

The Bu Twins

Both boys were normal until October, 1963. Both were freshmen at university. In the fall, B. began to phone home frequently with great anxiety. He could not study and did not turn in his assignments. At midterms he made a B average. In January, 1964, B. ran away and tried to enroll in the navy (against his religion), but was persuaded to go back to college. In February, B. dropped out and began seeing a psychiatrist. B. remained somewhat better all summer and remained under psychiatric care. In the fall, it was decided that the twins were too dependent on each other and must be separated. It was stated that they suffered from an identity crisis. This was done and the other twin, R., was sent to live with a relative. By November, B. had deteriorated. He argued frequently with his father, told his mother he was in love with her. Later, he read the Merck manual on schizophrenia and told his mother this was what he had.

From January to May, 1965, B. could not keep a job as he fought with every employer. He continued to receive therapy. In May he was admitted to Sheppard Pratt hospital. In the hospital he became very hostile toward his parents and did not wish them to visit anymore. The psychiatrist in charge reported that this hostility was a sign of progress. In September he ran away, but was persuaded

to return. March, 1966, B. ran away again but was returned by the police. In April, 1966, B. would no longer speak to his father. In September, 1966, B.'s parents asked the hospital to start B. on niacin as their son R., after three months on megavitamin therapy, was much improved. This was refused. October, 1966, B. was taken home and he was started on megavitamin B3 therapy by another psychiatrist. Between January and March, 1967, B. began to improve and got a job delivering books and magazines. In April, 1967, B. developed infectious hepatitis. All medication was stopped and B. quickly regressed until he was violent and psychotic. He was admitted to a local hospital and given nicotinamide and a tranquilizer. Within 24 hours, he was rational and after awhile the tranquilizer was discontinued.

During the summer of 1967, B. was able to work regularly, but tired easily and required a lot of sleep. B. had no regression at any time and slowly continued to improve.

B. often denied that he was ill and would stop taking his medication, but his parents would persuade him to start and he would recover again. September, 1967, the dose was doubled to 6 grams per day and followed by a marked improvement. Last report, January, 1969, he was still improving and was a resident at a special hospital where he took courses.

R., the other twin, was well until March, 1964, when he began to sleep excessively and began to miss classes. He passed in May, but seemed withdrawn. He seemed to be in a daze. He was started on Elavil but remained depressed and dazed. In September, he became delusional and paranoid and was admitted to a hospital for ECT. This was stopped in October with no improvement. January, 1965, R. came home from the hospital, but was very sleepy and behaved irrationally at times and continued to hear voices. By January, 1966, R. seemed better. June, 1966, R. began to receive nicotinic acid 3 grams per day. He improved very quickly and remained much improved and by January, 1969, he was nearly normal. He had a job which he enjoyed. In the spring, 1967, he also developed infectious hepatitis. He was given nicotinamide up to 6 grams per day and did not relapse as had his brother B.

Table 3

Twins	Condition before Treatment	Treatment Given	Present Condition
Twins personality known to us			
A	III	Megavitamin B3	Normal
A	Well	None required	Normal
B	III	B3	Well
B	Well	B3	Improved compared to initial condition
D	III	B3	Much improved
D	III	B3	Much improved
M.G.	III	B3	Well
S.G.	III	Standard	III
K	III	B3	Well
K	Well	None	Well
Twins treated by others			
B	III	B3	Much improved
B	III	B3	Much improved
A.Ka	III	Standard	III
M.Ka	III	Standard	III

Of the seven twin pairs, 11 twins were schizophrenic. Of these 11, three received only standard treatment (tranquilizers and ECT) and remain chronic schizophrenics in the community and live in a family torn by marital discord, (Ka twins), or in a hospital enclave created by a devoted husband in their home. The other eight are well or much improved. One of the twins considered well when first seen was much better after three months on nicotinamide medication. Thus, in this small series of seven identical pairs, with no exception, the patients who were treated with the standard therapy were benefitted little, and those receiving megavitamin B3 therapy are well, recovered, or much improved. In each case, the twin first receiving megavitamin B3 therapy recovered first.

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EFFECT OF SCHIZOPHRENIC PARENTS ON CONGENITAL ABNORMALITIES AND ON SEX RATIO OF THEIR OFFSPRING

It is strange that several decades of research into genetics and familial aspects of schizophrenia have failed to recognize an amazing effect of maternal active schizophrenia on the offspring. Shearer et al. (1967) found that out of 343 babies born to schizophrenic women patients in Michigan's six state hospitals between 1925 and 1964, 148 were male and 186 were female. Even more remarkable was their observation that 14 females and no males were delivered to women whose schizophrenic symptoms came on within one month of the theoretical date of conception. The authors suggested that the mother carried a chemical which interfered with viability development of the Y-chromosome carrying sperm or the fertilized ovum but was not lethal later in gestation.

Taylor (1969) examined the sex of offspring resulting from 54 pregnancies in schizophrenic women admitted to Manhattan State Hospital. There were 49 full-term births — 20 male and 29 female. Of 13 women who became schizophrenic within one month of conception, all delivered female children. Taylor also suggested that the mothers had a toxic blood factor which caused reabsorption of the male fetus if it occurred during the first month, and caused the male fetus to develop abnormally or die slowly if it attacked during the second and third month. Taylor also found that of 13 women who became psychotic within two months after parturition, two delivered females and eleven males. He suggested that schizophrenia developing late in pregnancy is fended off by production of steroid sex hormones by the fetus. When the baby is born, this protective effect is gone and the psychosis is allowed to appear (as if a protective chemical [drug] were suddenly withheld).

This hypothesis suggested that a male fetus in the second and third trimester would prevent or ameliorate schizophrenia in the mother, i.e., that schizophrenic women carrying male fetuses would improve and that schizophrenia would occur in women primarily with female fetuses. This was tested by Taylor and Levine (1969) and found to be true. A study of charts at Metropolitan State Hospital (New York) showed that of 18 pregnancies associated with maternal psychosis, 17 were associated with birth of a female. In pregnancies in which maternal illness improved, all delivered male offspring; and in pregnancies in which the illness got worse, all delivered females.

Hoffer and Osmond (1960) had already suggested a relationship between pregnancy and schizophrenia. They described how some schizophrenic patients improved clinically during pregnancy especially during the last trimester. They had suggested this was due to increased formation of ceruloplasmin which would suddenly be withdrawn after parturition. Ceruloplasmin is able to bind toxic substances such as adrenolutin, etc. This could explain the sudden onset of puerperal schizophrenia. However, Taylor and Levine's observations suggest that ceruloplasmin plays a small role if any and that the steroid hormones probably are the effective chemicals.

As will be shown later, this effect of pregnancy on schizophrenia may have a profound effect on racial survival, for schizophrenic women who have experienced the feeling of well-being associated with being pregnant may seek to repeat this condition more often, and those mothers giving birth mainly to girls may continue to become pregnant until they give birth to a boy.

Rosenthal (1966) listed the offspring from three published studies: (1) by Kahn, (2) by Schultz, and (3) by Elsasser. There seems to be no apparent relationship between schizophrenia and sex ratio of the offspring. But if one divides the schizophrenic mothers into those first admitted at age 35 or earlier and into a group admitted at age 36 and older, there is a trend toward the same sex ratio found by Shearer et al. and by Taylor. The younger women are more apt to be both pregnant and schizophrenic while the older

group would be more apt to have their children before the onset of their schizophrenia. Out of about 70 babies born to the under-35 age group, about 30 were male and 41 were female. But from the over-36 age group, out of about 75 children, 45 were male and about 30 were female. If one examines the mean age of first admission of all women for the three studies, it is found that the mean age for the Kahn group was about 42 years, and for the Schultz group about 39. The mean age for the Elsasser group is about 33. One would, therefore, expect a similar sex ratio divergence between the Kahn, Schultz group on the one hand and the Elsasser group on the other. In fact, this is the case. In the latter group, only the women admitted under age 35 gave birth more often to females while the women over age 36 gave birth more often to males.

In the past two years, I have treated 121 women who were schizophrenic and who had given birth to at least one child. On a routine first interview the names, ages, and general condition of all the children born to the patients were listed. It was thus possible to relate in a crude way the onset of each attack of schizophrenia, if there were more than one, to the pregnancies and the sex of the children. The onset of schizophrenia, unless it is very sudden, can very rarely be accurately related to time, and in most cases there is a large error in the estimate. The sex ratios of the offspring were examined for offspring born before the first attack of schizophrenia, and after the disease had appeared. The results are shown in Table 4.

Table 4

SEX RATIO OF OFFSPRING BORN TO MOTHERS BEFORE AND AFTER DEVELOPING SCHIZOPHRENIA

	Offspring born before schizophrenia appeared	Offspring born after schizophrenia appeared	Total
Male	154	38	192
Female	91	76	167

The difference is significant (Chi square over 30). There are two major differences: (1) The increased proportion of females which supports the findings of Shearer et al. (1967), and Taylor and Levine (1969). This difference from the expected normal ratio is also very significant (Chi square over 6). (2) The increased proportion of males born to the women who had not yet become schizophrenic. This is significantly different from the expected even ratio (Chi square over 7). This unexpected finding is supported by the Elsasser data recorded by Rosenthal. It suggests that even before the woman becomes schizophrenic her body provides an environment chemically hostile to female fetuses (or female-producing sperm). Over the entire child-bearing years, there still remains a higher ratio of male to female than would be expected in a normal population.

A striking example from our series is one woman schizophrenic who, before she married, continually heard voices and saw visions until treated with megavitamin B3 therapy three years ago. She had seven girls. Of these one is severely retarded, one has epilepsy, and two have chronic schizophrenia.

Of the women seen, 11 were treated with megavitamin B3, and after recovery gave birth to 12 children, eight male and four female. One woman gave birth to one child during her schizophrenia and another child while on treatment with nicotinic acid.

The finding that women who are going to become schizophrenic give birth to more male babies is puzzling. Perhaps this is due to the protective effect of male fetuses and comparable to recurrent doses of preventive medication. A woman potentially schizophrenic becoming pregnant with a male fetus would be given a protective period which would decrease her chance of becoming schizophrenic for a period of time. If she had two or three successive male pregnancies, this would postpone the disease even more. But eventually the pressure for the disease would no longer be contained and the disease would occur.

The conclusions from the studies reviewed in this section are: (1) that women destined to become schizophrenic give birth to more boys than girls; (2) that women already schizophrenic give birth more often to girls; (3) that male fetuses protect mothers from and ameliorate any schizophrenia which may be present. Early medication with megavitamin B3 restores normal sex ratios among offspring of schizophrenic women.

It has been known for some time that the incidence of congenital abnormalities among offspring of schizophrenic women is about three times the normal incidence. Taylor found that out of 49 children born, six had birth defects (deafness, mutism, cerebral palsy, blindness, and retardation). If we consider the mute and retarded child to be infantile schizophrenics, it leaves a very high proportion of congenital defects.

RELATIONSHIP OF CONGENITAL ABNORMALITIES (teratogenic activity) TO NICOTINIC ACID OR NICOTINAMIDE

Landauer (1957) showed that 3-acetylpyridine, an antimetabolite of vitamin B3 (nicotinic acid or nicotinamide), is teratogenic for chicken embryos. It produced skeletal muscle hypoplasia. Nicotinamide given at the same time completely protected the embryo against the teratogenic effects of 3-acetylpyridine. This report initiated a series of studies on so-called nicotinamide antagonized teratogens. Caplan, Zwilling, and Kaplan (1968) found that 3-acetylpyridine produced degenerative effects of myoblast cultures and greatly stimulated production of cartilage in chondrogenic cell cultures. This was prevented by nicotinamide, which by itself inhibited cartilage formation. They suggested that nicotinamide may participate in differentiation of limb structure by sustaining muscle formation and inhibiting excessive cartilage formation. The teratogen 3-acetylpyridine acts, therefore, by interfering in the nicotinamide control of growth

Roger et al. (1964) found that the teratogenic effect in chick embryos of certain organophosphate insecticides was prevented by nicotinamide and several of its derivatives (like NAD) and analogues. As well as being teratogenic, these substances were also neurotoxic. As little as 30 mg of nicotinic acid and nicotinamide per egg protected the embryo. NAD was even more active. Tri-o-cresyl phosphate produced neurotoxic changes in adult hens including marked ataxia and debilitation. Nicotinamide and phenyl nicotinate prevented most of the changes.

Nicotinamide and analogues also protected chick embryos from teratogenic effects produced by eserine, insulin, 6-aminonicotinamide. The last compound produces behavioral changes in dogs such as hyperexcitability, hyperthermia,uncoordinated movements, and twitching of the ears and cheeks. It produced lesions in the anterior horn of the spinal cord and in the brain stem nuclei. Three-acetylpyridine also produces specific lesions in the hypothalamus (Hick, 1955). Nicotinic acid derivatives protected against neurotic effect of several substances (Chambers and Casida, 1967).

The best known teratogen is thalidomide which, according to Jarvik (1962), produced deformed babies in 20 percent of the women who took it. A few women also developed neuropathy. Frank et al. (1963) found that thalidomide inhibits growth of some protozoa and that this was counteracted by nicotinic acid, nicotinamide, and NAD. Six-aminonicotinamide resembled thalidomide in inhibiting growth and again this was prevented by nicotinic acid. Thalidomide in humans, as well as being teratogenic, produced polyneuritis and glossitis. Since nicotinic acid antagonists (antimetabolites) produced teratogenic changes, one might expect similar changes to occur when nicotinic acid is lacking as in pellagra. Fratta et al. (1964) reported that, in rats made pellagrin by vitamin B3-deficient diets, there was a high incidence of fetal death and resorption of embryos.

Hoffer and Osmond (1966) suggested that schizophrenia was an NAD-deficiency

disease. If true, it would not be surprising that schizophrenic women would give birth to more than the average number of congenitally abnormal children. One would have to postulate a differential effect of NAD deficiency on male embryos. This could be tested by examining the ratio of boys to girls in women who have pellagra. It is thus possible to partially account for the peculiar effect of schizophrenia on their offspring by assuming the NAD deficiency which is responsible for the schizophrenia. It may also be responsible for the schizophrenic effect on congenital abnormalities and perhaps on sex ratio.

Greengard et al (1966) found that adrenocortical steroids prevented and brought about remission in rats and dogs of nicotinamide-deficiency disorders. In rats, these hormones prevented fetal death and resorption common in pellagrous rats. According to Greengard et al. and Zak (1968) the steroid hormones would act by increasing availability of tryptophan for synthesis of NAD. Perhaps the female fetus is able to produce more corticosteroid hormones and therefore is better able to protect itself against the teratogenic effect of NAD deficiency.

If NAD deficiency is the main reason in producing increased congenital abnormalities and changes in sex ratio, then these phenomena should not be unique for schizophrenia. In any situation where populations suffer extensive malnutrition one would expect an increase in female births. Therefore, the following quotation from Brillat - Savarin (1960) is most interesting.

"Upon this physiological question I shall say no more; but I must not omit to mention an observation of my own, which can easily be verified.

"Some years ago now, I went to see a country house on the outskirts of Paris, situated to be more exact, in a village on the banks of the Seine, facing the island of Saint-Denis, and mainly consisting of eight fishermen's huts. I was struck by the number of children whom I saw playing there by the roadside.

"I expressed my surprise to the boatman who ferried me across the river.

"'Sir,' was his reply, 'there are only eight families of us, and we have fifty-three children, forty-nine of them girls and but four boys; of those four one is mine; see, there he is.' So saying, he stood up with an air of triumph, and showed me a little monkey five or six years old, sitting in the bows of the boat and enjoying a feast of raw crayfish. The name of that little village is _____.

"From this observation, which goes back more than ten years and from others which I cannot so easily describe, I have come to believe that the effect of ichthyophagy upon the sexes is stimulating, but not attended by the most substantial results; and my opinion is borne out by the fact that quite recently Doctor Baily proved, by a series of observations extended over nearly a century, that whenever the annual census of births contains a much larger number of girls than boys, the superabundance of females has invariably been due to debilitating circumstances; and in all probability this is the origin of the jokes which have from time immemorial been made at the expense of the husband whose wife gives birth to a daughter."

What is very interesting is that, in those times, when mankind was uncontaminated by modern sanitation, public health, and preventive medicine, it was possible to recognize a phenomenon of this kind.

The increased birth of girls would have a remarkable effect on rebuilding a population decimated by nutritional catastrophies.

A BIOCHEMICAL HYPOTHESIS WHICH MAY PROVIDE A MECHANISM FOR GENETIC TRANSMISSION OF SCHIZOPHRENIA

There are no biochemical tests specific for schizophrenia nor will there be until there is general agreement that a test which is positive in the majority of schizophrenics shall be used as the independent diagnostic variable. This kind of problem in diagnosis is not unique for schizophrenia.

Every disease which today is diagnosed by a laboratory test had to go through a similar

change in definition. Serological tests are specific because we say they shall be. In other words, we have all agreed that a positive serological test will be sufficient to establish the diagnosis. When this happens for schizophrenia, e.g., when test A positive by agreement indicates schizophrenia, even if present in clinical nonschizophrenia, that person will be diagnosed schizophrenic. It is, therefore, very difficult to claim specificity from an etiological position, and critics of any biological theory will be able forever to deny specificity.

It may be simpler to develop a hypothesis based upon biochemical therapy, especially if several chemotherapies can be shown to operate upon a biochemical mechanism known to be active in the body. I am convinced that vitamin B3, i.e., either nicotinic acid (niacin) or nicotinamide (niacinamide) alone or in combination with the tranquilizer phenothiazines, provide the most specific therapy for schizophrenia so far developed.

Hoffer et al.(1957) was the first to show that vitamin B3 in megadoses of 3 grams per day or more markedly improved the recovery rate when combined with ECT or standard chemotherapy. But before that, it had been used in doses of 2 grams per day or less for organic psychosis. Sydenstricker and Cleckley (1941) and Cleckley et al. (1939) reported recoveries when nicotinic acid was given to cases of stupor, lethargy, and what they termed atypical states. Some of their patients had been diagnosed schizophrenic, but when they recovered on nicotinic acid they were promptly rediagnosed as pellagra psychoses. This, of course, made it certain that no schizophrenic could be said to be treated successfully with nicotinic acid. The chronic schizophrenics who presumably did not recover were still labelled schizophrenic. They require doses up to 30 grams per day for many years combined with tranquilizers. Other organic psychoses which responded were senile psychosis (Gregory, 1952), acute brain syndrome (Martz, 1965), organic confusional states (Lehmann, 1944; Hoffer, 1965) and delirium tremens (Gould, 1953, 1954, 1958; Armstrong and Gould, 1955).

Wolberg et al.(1964) used a nicotinamide derivative, nicotinamide adenylate, and found significant improvement in a series of elderly confused subjects. Washburne (1950), Sherrill (1950), and Thompson and Proctor (1953) used nicotinic acid with good results for depressed patients. It has also been used as an antidote against LSD psychoses in man (Agnew and Hoffer, 1955, who reported it modified the psychoses). Apparently, some black market LSD is absorbed on nicotinic acid tablets and is sold as a product which yields a superior high. Nicotinic acid dampens down the perceptual component of LSD and reduces anxiety and depression so it could convert bad trips into good ones. It also antagonized the effect of LSD in dogs. Ivanova et al. (1964) had prevented the increase in oxidation of adrenalin in whole blood usually caused by LSD. According to Kanig (1966), nicotinamide antagonized the action of harmine and mescaline in rats and nicotinic acid antagonized the effect of mescalin in rats.

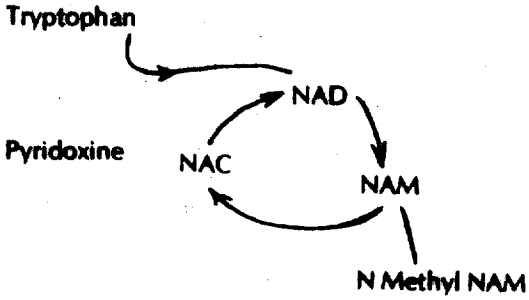
The treatment of schizophrenia with vitamin B3 in megadoses has been developed by five double-blind controlled studies plus a large number of clinical studies in several psychiatric centers. The references in alphabetical order are Ananth, Ban, Lehmann, and Bennett (1970), a double-blind study; Chinaglia (1965), Cott (1967, 1969), Denson (1962), a double-blind study; Foy (1970) Green (1969, 1970), Hawkins (1968, 1969), Hawkins et al. (1970), Herjanic et al. (1967), a double-blind study; Hoffer (1962), reference to two double-blind studies with the first run in 1952 — 53; also Hoffer (1963, 1966, 1966a, 1966b, 1966c, 1967, 1967a, 1967b, 1969, 1970a); Hoffer and Osmond (1960, 1962, 1963, 1963a, 1964, 1966, 1967); Hoffer et al.,(1957); Kowalson (1967); Maslowski (1967); Meiers (1967); Newbold (1970); Osmond (1967); Osmond and Hoffer (1962, 1967); Rimland (1973); Robie (1967); Szatmari et al. (1955); Ward (1967); Zelinskii (1956).

Nicotinamide adenine dinucleotide (NAD),

the coenzyme of vitamin B3, was found effective in treatment of acute and chronic noninstitutionalized schizophrenics by Hoffer and Osmond (1967). Kline et al. (1967) using deteriorated inadequately prepared NAD on a group of chronic deteriorated institutionalized schizophrenics, found no effect. Gallant et al. (1966), using better NAD, also found no effect on equally chronic institutionalized cases. There is a remarkable variability of commercial NAD (McComb and Gay, 1968), and some of the discrepancy may be due to a lack of stable reliable preparation.

At a recent meeting of the American Schizophrenia Foundation, the Committee on Therapy, 1956, reviewed nearly 9,000 cases treated since 1952. All the studies were corroborative. So far, no studies have been published where it has been found that megadose B3 therapy did not yield the same results as described by the authors listed above.

A substantial amount of data has accumulated which shows that the pyridine nucleotide cycle is involved in the genesis of schizophrenia. Gholson (1966) showed that this cycle consists of the following series of reactions.



We need only assume that there is a defect in the turnover of NAD levels which is lowered. It would follow that any substance which increases NAD synthesis or activity will be therapeutic, and any substance which decreases NAD synthesis will be hallucinogenic or aggravate schizophrenics or make them worse. Fortunately, their effect upon NAD levels is known.

Substances Which Influence NAD Levels

A. By effect on concentration of precursors, e.g., nicotinic acid and nicotinamide. Preiss and Handler (1957) found that nicotinic acid increased NAD levels in red blood cells. Niçotinamide does the same (Hayaishi, 1966). Many investigators have studied the effect of these precursors on NAD levels. Ijichi et al. (1966) found that in small doses nicotinic acid is a better precursor of NAD than nicotinamide but in large doses nicotinamide is better. Primarily nicotinamide served as a precursor to NAD for a prolonged period of time.

Tryptophan may be the most important precursor of NAD in most people. Pellagra which produces a psychosis often indistinguishable from schizophrenia is commonly found low in tryptophan, low in absorbable nicotinic acid or nicotinamide, and high in leucine. There is some evidence that the deficiency in tryptophan is responsible for the skin and gastrointestinal changes of pellagra. I view schizophrenia as a pure dependency state (a relative deficiency state) of vitamin B3 while pellagra is a multiple-deficiency state. It is likely some of the factors which perpetuated chronic schizophrenia in mental hospitals was the malnutrition and decreased protein intake patients suffered some years ago. Faurbye (1968) found that decreasing the intake of tryptophan in schizophrenics provoked a flare-up in hallucinations and delusicns.

B. Enzymes which effect conversion of substrates into NAD. Of these the best known is pyridoxine or vitamin B6 (Rosenberg, 1969). B6-dependency diseases include infantile convulsions, cystathioninuria, xanthurine aciduria and homocystinuria. Because it catalyzes conversion of tryptophan to NAD, a deficiency of B6 can also produce pellagra. Rosenberg (1969) defines a vitamin-dependency disease as a genetic disturbance that leads to specific biochemical abnormalities affecting only one reaction

catalyzed by the vitamin and that responds only to pharmacologic amounts (megadoses).

C. Substances which influence excretion of pyridine molecules. Any substance which increases excretion of pyridine molecules will decrease formation of NAD and should aggravate schizophrenia.

1. By increasing formation of N-methylnicotinamide. This substance can no longer participate in the pyridine nucleotide cycle and is excreted (Sebrell and Harris, 1954). In schizophrenic blood in vitro nicotinamide is methylated much more rapidly to N-methylnicotinamide than in normal blood (Buscaino et al., 1963; Buscaino et al., 1966; and Gentili and Borghisi, 1968). There are, therefore, enzymes or activators of methylferase in schizophrenic blood (or lack of an inhibitor).

2. By decreasing formation of N-methylnicotinamide. Burton (1960), Burton et al. (1958), Burton et al. (1960), Burton and Salvador (1962), Burton et al. (1962), Greengard et al. (1967), Greengard and Quinn (1962), Greengard (1966), Salvador and Burton (1965), Salvador et al. (1959), in a series of studies have shown that tranquilizer drugs like chlorpromazine, promazine, trifluoperazine and reserpine retard decrease of elevated NAD levels after administration of nicotinamide, whereas nontranquilizer phenothiazines and substances like ethanol, phenobarbital, meprobamate have no effect. Substances which were not sedatives had no effect. The effect of tranquilizers was dose related. These authors suggested that nicotinamide methylferase was inhibited, thus decreasing formation of N-methylnicotinamide.

In rats, hypophysectomy increases one-half life of nicotinamide partly due to decreased excretion of nicotinamide and of N-methylnicotinamide (Greengard et al. 1967). Greengard et al. (1966) found that adrenocortical steroids prevented the effects of nicotinamide deficiency in rats and dogs. They prevented the decrease in NAD levels due to diets deficient in nicotinamide. They also protected the animals against the toxic effect of the vitamin B3 antimetabolite, 6-aminonicotinamide. They suggested that adrenocorticoid hormones stabilized NAD levels in tissues both preventing a decrease in pellagrous animals and preventing an increase in hypophysectomized animals.

Woolley (1958) found that nicotinamide alone was a tranquilizer for mice. Perhaps it acts by elevating NAD levels.

3. By increasing excretion of N-methylnicotinamide.

Gopalan (1969), Gopalan and Srikantia (1960) have examined the relationship of vitamin B3 metabolism to pellegra. Pellagra, under control in North America, is still a problem in many parts of the world. The psychosis pellagra is often indistinguishable from schizophrenia when clinical criteria only are used. Gopalan (1969) reports that, in Hyderabad, 8 - 10 percent of admissions to mental hospitals during certain times of the year are pellagra.

Leucine precipitated psychotic changes in pellagrins and increased the excretion of N-methylnicotinamide. Subjects were given 10 grams of leucine per day and increased excretion of quinolinic acid, a precursor of NAD. Isoleucine counteracted these effects. Leucine also impaired synthesis of nicotinamide nucleotides. Erythrocytes contain nicotinamide mononucleotide (NMN), NAD, and NADH. In pellagra NMN was elevated 20 percent but NAD and NADH were lowered. In controls, only 2½ percent is present as NMN.

Leucine, 20 - 30 grams per day, produced a striking deterioration in mental condition in pellagrins after seven days. According to Sebrell and Harris (1954) testosterone decreased urinary excretion of N-methylnicotinamide. Maayan and Rosenberg (1968) found that 6-N propylthiouracil greatly increased NAD and NADH in the thyroid gland. On the other hand, alcohol increased the excretion of N-methylnicotinamide.

D. NAD Levels.

In increasing levels - administration of NAD ought to increase cellular levels. Other substances which affect levels (excluding the direct precursors already discussed) are d-amphetamine 10 mg per kg which decreased brain NAD levels by 20 percent. Chlorpromazine had no significant effect, but an inspection of data of Lewis and Pollock (1965) shows that highest mean brain NAD levels in rat brain occurred with 30 mg per kg of chlorpromazine.

According to Appelt et al. (1968), mescaline 100 mg per kg given to mice decreased the brain increase in NAD following intracerebral injection of NAD.

Ethionine is an antimetabolite of methionine which is required for transmethylation reaction. Ethionine lowers rat liver NAD and NADH (Clark and Pinder, 1966; Slater and Sawyer,)[1] probably by inhibiting hepatic ATP synthesis (Palma-Carlos et al. 1966). It also produced porphyria in rats.

Ethionine has not been given to patients. From its two effects (a) in decreasing NAD synthesis which should make schizophrenics worse; (b) as an antimetabolite of methionine which should improve them, it is not possible to predict what would happen. It could be tested in pellagrous animals. Large doses of methionine have made a few subjects more psychotic (Park et al. 1965).

Methionine sulfoximine, another antimetabolite of methionine, generally makes normal subjects psychotic which suggests that ethionine ought to do the same. The production of experimental porphyria in animals would tend to support this view since porphyria in humans is associated with psychotic changes. Perhaps in normal subjects, a decrease in NAD levels is the primary change. However, schizophrenics were temporarily benefitted by methionine sulfoximine suggesting that reduction in transmethylation was beneficial by reducing excretion of N-methylnicotinamide. But, in chronic trials (after 30 days), signs of organic mental disturbances appeared in schizophrenics.

Ethionine would decrease NAD synthesis and decrease methylation of nicotinamide. The net result on NAD levels is unpredictable. One would suspect that there would be a lowering of NAD in humans and thus a worsening of the clinical picture in the long run even though there might be a transient improvement.

METHODS OF ELEVATING NAD LEVELS AND RESULTS

1. Providing more substrate. Tryptophan, nicotinic acid, and nicotinamide in megavitamin doses are all therapeutic.
2. Increasing conversion of tryptophan to NAD by giving pyridoxine (vitamin B6) is therapeutic for infantile convulsions and some forms of retardation.
3. Phenothiazine tranquilizers which decrease formation of N-methylnicotinamide are the mainstay of the chemotherapy of schizophrenia. Reserpine is less effective but would be used if the more efficient tranquilizer had remained unknown. It also elevates NAD levels.

It will not be possible to use hypophysectomy as a therapy, but adrenocortical hormones may be helpful when combined with vitamin B3.

WHERE TO LOOK FOR THE GENETIC DEFECT

Pauling (1968) has shown how it can be advantageous to become more dependent upon external sources of essential nutrients such as vitamins. For example, very few species, excluding man, require external sources of ascorbic acid. The chemical enzymes essential to synthesize ascorbic acid have been dropped from human cells. If, therefore, inadequate levels of ascorbic acid are present in the diet, scurvy will be the result. The minimum level required to prevent scurvy will vary from person to person as it will from the optimum level.

Pauling has shown that there are additional biochemical advantages as ascorbic acid levels are increased much above the usual vitamin levels. In evolutionary terms,

the advantage in not having to make ascorbic acid, provided it is present in one's diet, is that biochemical machinery freed from this task can be diverted into other more essential processes.

The concept of vitamin-dependency disease, which has recently developed, suggests that the process of dropping enzymes and becoming totally dependent upon external sources may be incomplete in some animal species. A vitamin-deficiency disease appears in people whose needs for the vitamin are average, but whose intake is much below. But a much smaller number of the population has needs much greater than average and for these people average nutritional doses are inadequate. This is a dependency condition. About a dozen have been described. This means only that the optimal need for these nutrients varies over a much greater range than has been suspected, perhaps a hundred or a thousand-fold. It seems to be a skewed curve with most people having needs which cluster about the usual mean while a smaller number, with much greater needs, appear far from the mean. This latter smaller group will be the vitamin-dependent group.

Nicotinamide adenine dinucleotide (NAD) is made from two sources. It is made from tryptophan, an essential amino acid, and from vitamin B3 in food. The vitamin B3 can be present as nicotinic acid, nicotinamide, or as mono- or dinucleotides. Tryptophan is found in protein in much greater quantities than is B3 in foodstuff, but only a small proportion is converted into B3. It requires about 60 mg of vitamin B3. This estimate may be totally erroneous for certain groups of people. It might be advantageous if NAD could be made entirely from vitamin B3, and the enzymes involved in making it from tryptophan were no longer needed. If this did occur in some people, they would require much larger quantities of vitamin B3 from dietary sources. This could explain dependency conditions.

I suggest that in people who develop schizophrenia, this process has gone further than in most people, i.e., they are less able to make NAD from tryptophan and are more heavily dependent upon dietary NAD. If we are to discover where biochemical geneticists are to look, I suggest that this is a promising area. Using tagged tryptophan, one could discover how much is converted into NAD. According to this suggestion, this reaction will be less active on vitamin B3-dependent subjects. They can readily be located by testing schizophrenics.

Animal experiments have shown that long-continued deprivation of vitamin B3 converts them from a deficiency into a dependency state. When the animals were maintained on vitamin B3-deficient diets for a short time, they quickly became normal. However, if they were deprived for a long time, they no longer became normal with the same small vitamin doses but, thereafter, required megadoses to remain well. This suggests that enzymes, dependent upon NAD, somehow become permanently impaired and much larger quantities have to be available to the cell before these enzymes function efficiently again.

This is also the case with schizophrenia where it has been demonstrated that very early cases recover and remain well on low megadoses while chronic cases may require doses up to 10 times as great. It is likely that hyperkinetic children who have been shown by Green (1970) and Cott (1969) to be variants of pellagra respond very quickly to B3 if detected and treated early. Dr. Green, a general practitioner, sees these cases very early in its development. Most cases were well in one month. But by the time they are referred to orthomolecular psychiatrists they have been ill many years and require many months and years of intensive therapy.

I have recently, (Hoffer, 1970), reminded psychiatrists of the remarkable similarity between pellagra and schizophrenia. This was well-known to psychiatrists alive during the pellagra pandemics of the early 20th century. What our geneticist colleagues must do is to

investigate why some people require much larger quantities of B3, how this need is transmitted, and how it can be detected so that early treatment and prevention can be begun.

THERAPEUTIC TRIALS OF VITAMIN B3 WITH NO ATTEMPT TO REPRODUCE THE MEGAVITAMIN B3 OR ORTHOMOLECULAR APPROACH

A small number of studies have been reported where vitamin B3 was used as one component of the therapeutic program. No attempt was made to follow the total treatment program which has been given in detail many times and which has been followed by all the orthomolecular physicians who have obtained similar good recovery rates. I cannot understand why there has been no attempt by any research group or University Department outside of Saskatchewan to repeat the entire program.

Either this is due to the well-known conservatism of psychiatric departments who consider themselves part of the psychiatric paradigm and must defend it, or to the fact that investigators are not prepared to do their homework by reading the literature carefully or by personally inspecting the patients and studies of psychiatrists who are able to use the program effectively. Or it may be due to a reluctance to use ECT again, having given it up in favor of tranquilizers. Whatever the reason, there is no denying the fact that so far no attempt has been made to repeat our work surely one of the necessary elements of any corroborative study.

It is necessary to refer to these studies and show where they failed to reproduce the program so that others who wish to enter this field will not make the same error.

The orthomolecular program depends upon the following variables: (1) use of optimum dose of vitamin B3; (2) use of adequate time which ranges up to seven years; (3) other vitamins; (4) the use of ECT once or more often; (5) the use of the medical model; (6) the use of any one or combination of tranquilizers, antidepressants and other psychoactive drugs each in their optimum dose. Authors who did not use adequate doses include Ban and Lehmann (1970), Greenbaum (1970), O'Reilly (1955), and Ramsay et al. (1970). In addition, these authors used a fixed, rather brief trial, did not use other adjunctive vitamins, and did not use ECT. Rapp (1968) is a special case because he used Roniacol thinking it was the same as nicotinic acid. It has only very slight vitamin B3 properties. Rapp's paper merely makes a new claim, i.e., that Roniacol does not help alcoholics, but no one had ever claimed it did.

So far every physician who has used the orthomolecular megavitamin B3 approach has reported equally high recovery rates. Every failure has been due to a failure in methodology.

REFERENCES

AGNEW, N., and HOFFER, A.: Nicotinic acid modified lysergic acid diethylamide psychosis. J. Ment. Sc. 101: 12, 1955.

ANANTH, J. V., BAN, T. A., LEHMANN, H. E., and BENNETT, J.: Nicotinic acid in the prevention and treatment of methionine induced exacerbation of psychopathology in schizophrenics. Canad. Psychiat. Ass. J. 15: 15, 1970.

APPELT, G. D., WALKER, N. O., and BROWN, R. G.: Effect of mescaline on nicotinamide adenine dinucleotide synthesis in central nervous system. J. Pharmaceutical Sciences 57: 527, 1968.

ARMSTRONG, R. W., and GOULD, J.: The nature and treatment of delirium tremens and allied conditions. J. Ment. Sc. 101: 70, 1955.

BAN, T. A. and LEHMANN, H. E.: Nicotinic acid in the treatment of schizophrenics. Summary statement — Progress Report I, Canadian Mental Health Association collaborative study Canad. Psychiat. Ass. J. 15: 499, 1970.

BENDER, L.: Childhood schizophrenia. Amer. J. Orthopsychiat. 26: 499, 1955.

BENDER, L., and HELME, W. H.: A quantitative test of theory and diagnostic indicators of childhood schizophrenia. Archives Neurology and Psychiat. 70: 413, 1953.

BEVERIDGE, W. I. B.: The Art of Scientific Investigation. New York, New York: W. W. Norton and Co., 1950.

BLOCK, J.: Parents of schizophrenic, neurotic, asthmatic and congenitally ill children. Archives Gen. Psychiat. 20: 659, 1969.

BRILLAT-SAVARIN, J. A.: The Physiology of Taste. New York: Dover Books, 1960.

BURRELL, R. H., AND OSMOND, H.: Identical twins: an economy in clinical research. The Lancet 2: 291, 1959.

BURTON, R. M.: Alteration of tissue pyridine nucleotide levels and the central nervous system. Inhibition of the Nervous System and Gamma Amino Butyric Acid. E. Roberts Ed.: 249. New York: Pergamon Press, 1960.

BURTON, R. M., KAPLAN, N. O., GOLDIN, A., LEITENBERG, M., HUMPHREYS, S. R., and SODD, M. A.: Effect of reserpine and promazine on diphosphopyridine nucleotide synthesis in the liver. Science 127: 30, 1958.

BURTON, R. M., KAPLAN, N. O., GOLDIN, A., LEITENBERG, M., and HUMPHREYS, S. R.: Interaction of nicotinamide with reserpine and chlorpromazine III. Some effects on the diphosphopyridine nucleotide content in the liver. Arch. Int. Pharmacodyn 128: 268, 1960.

BURTON, R. M., and SALVADOR, R.: The effect of chlorpromazine on nicotinamide methylferase: an example of drug enzyme interaction at the molecular level. Ann. N. Y. Acad. Sciences 96: 353, 1962.

BURTON, R. M., SALVADOR, A., GOLDIN, A., and HUMPHREYS, S. R.: Interaction of nicotinamide with reserpine and chlorpromazine II. Some effects on the central nervous system of the mouse. Arch. Intern. Pharmacodyn 128: 253, 1960.

BURTON, R. M., SALVADOR, R., SMITH, K., and HOWARD, R. E.: The effect of chlorpromazine, nicotinamide, and nicotinic acid on pyridine nucleotide levels in human blood. Ann. N. Y. Acad. Sciences 96: 185, 1962.

BUSCAINO, G. A., STEFANACHI, L., SALLUSTO, L., SPADETTA, V., and COLUCCI, F.: Metilazione della nicotinamide nigli schizofrenici. Il Lavoro Neuropsichiatrico, 33: 1963.

BUSCAINO, G. A., SPADETTA, V., and CARELLA, A.: Possible applicazione del test di metilazione in vitro della nicotinamide alla diagnosi biochemica della schizofrenia. Acta Neurologica 21: 1, 1966.

CAPLAN, A. I., ZWILLING, E., and KAPLAN, N. O.: 3-acetylpyridine: Effects in vitro related to teratogenic activity in chicken embryos. Science 160: 1009, 1968.

CARTER, M.: A general practice investigation into possible biological advantages among schizophrenic relatives. Pers. Comm.: 1968.

CARTER, M., and WATTS, C. A. H.: Possible biological advantages among schizophrenics' relatives. Brit. J. Psychiatry 118, 453, 1971.

CHAMBERS, H. W., and CASIDA, J. E.: Protective activity of nicotinic acid derivatives and their 1-allsyl-2 and 1-allsyl-6-pyridines against selected neurotoxic agents. Toxicology and Applied Pharmacology 10: 105, 1967.

CHINAGLIA, L.: Sul trattamento della schizofrenia con amide nicotinica. Folia Psychiatrica 8: 123, 1965.

CLARK, J. B., and PINDER, S.: Control of nicotinamide adenine dinucleotide phosphate synthesis in the livers of rats treated with ethionine. Nature 210: 631, 1966.

CLECKLEY, H. M., SYDENSTRICKER, V. P., and GEESLIN, L. E.: Nicotinic acid in the treatment of atypical psychotic states. J.A.M.A. 112: 2107, 1939.

COTT, A. A.: Treatment of ambulant schizophrenics with vitamin B-3 and relative hypoglycemic diet. J. Schizophrenia 1: 189, 1967.

COTT, A. A.: Treatment of schizophrenic children. J. Schizophrenia 1: 44, 1969.

COTT, A. A.: The parenteral use of vitamins in the treatment of schizophrenia. J. Schizophrenia 2: 177, 1970.

DENSON, R.: Nicotinamide in the treatment of schizophrenia. Dis. Nerv. System 23: 167, 1962.

EL-MELIGI, A. M., and OSMOND, H.: EWI, Manual for the clinical use of the Experiential World Inventory. New York: Mens Sana Publishing Co., 1970.

ERLENMEYER-KIMLING, L.: Mortality rates in the offspring of schizophrenic parents and a physiological advantage hypothesis. Nature 220: 798, 1968.

ERLENMEYER-KIMLING, L., RAINER, J. D., and KALLMANN, F. J.: Psychopathology of Schizophrenia. New York: Grune and Stratton, 1966.

FAURBYE, A.: Role of amines in etiology of schizophrenia. Comp. Psychiat. 9: 155, 1968.

FISH, B.: The detection of schizophrenia in infancy. J. Nervous and Mental Disease 125: 1, 1957.

FISH, B., and ALPERT, M.: Abnormal states of consciousness and muscle tone in infants born to schizophrenic mothers. Amer. J. Psychiat. 119: 439, 1962.

FOY, J. G.: Gone is Shadow's Child. Watchung, New Jersey: Watchung Book Sales, 1970.

FRANK, O., BAKER, H., ZIFFER, H., AARONSON, S., HUTNER, S. H., and LEEVY, C. M.: Metabolic deficiencies in protozoa induced by thalidomide. Science 139: 110, 1963.

FRATTA, I., ZAK, S. B., GREENGARD, P., and SIGG, E. B.: Fetal death from nicotinamide deficient diet and its prevention by chlorpromazine and emipramine. Science 145: 1429, 1964.

GALLANT, D. M., BISHOP, M. P., and STEELE, C. A.: DPN (NAD oxidized form): a preliminary evaluation in chronic schizophrenic patients. Current Therapeutic Research 8: 542, 1966.

GENTILI, C., and BORGHISI, E.: Rilievi sue tasso delle transmetilasi en pazienti schizofrenici. Bollettino della Societa Italiana di Biologia Sperimentale 43: 1496, 1968.

GHOLSON, R. K.: The pyridine nucleotide cycle. Nature 212: 933, 1966.

GOPALAN, C.: Possible role for dietary leucine in the pathogenesis of pellagra. The Lancet 1: 197, 1969.

GOPALAN, C. and SRIKANTIA, S. G.: Leucine and pellagra. Lancet 1: 954, 1960.

GOTTESMAN, I. I., and SHIELDS, J.: Schizophrenia in twins: 16 years consecutive admissions to a psychiatric clinic. Brit. J. Psychiat. 112: 809, 1966.

GOULD, J.: Treatment of delirium, psychosis and coma due to drugs. The Lancet 1: 570, 1953.

GOULD, J.: The use of vitamins in psychiatric practice. Proc. Royal Soc. Med. 47: 215, 1954.

GOULD, J.: The enzymatic basis of certain psychoses. Recent Progress Psychiatry 3: 1, 1958.

GREEN, R. G.: Reading disability. Canad. Med. Ass. J. 100: 586, 1969.

GREEN, R. G.: Protein poor diet means pellagra. Canad. Family Physician 16: 88, 1970.

GREEN, R. G.: Subclinical pellagra: its diagnosis and treat-

ment. J. Schizophrenia 2: 70, 1970.

GREENBAUM, G. H. C.: An evaluation of niacinamide in the treatment of childhood schizophrenia. Amer. J. Psychiatry 127: 129, 1970.

GREENGARD, P., KALINSKY, H., MANNING, T. J., and ZAK, S.: Prevention and remission by adrenocortical steroids of nicotinamide deficiency disease. II a study of the mechanism. J. B. C.: 4216, 1968.

GREENGARD, P., PETRACK, B., and KALINSKY, H.: Effect of hypophysectomy on pyridine nucleotide metabolism. J. B. C. 242: 152, 1967.

GREENGARD, P., and QUINN, G. P.: Metabolic effects of tranquilizers and hypophysectomy. Ann. N. Y. Acad. Sc. 96: 179, 1962.

GREENGARD, P., SIGG, E. B., FRATTA, I., and ZAK, S. B.: Prevention and remission by adrenocortical steroids of nicotinamide deficiency disorders and of 6-aminonicotinamide toxicity in rats and dogs. J. Pharmacol and Experimental Therapeutics 154: 624, 1966.

GREGORY, I.: Nicotinic acid therapy in psychosis of senility. Amer. J. Psychiat. 108: 888, 1952.

HAWKINS, D. R.: Treatment of schizophrenia based on the medical model. J. Schizophrenia 2: 3, 1968.

HAWKINS, D. R.: Treatment of schizophrenia: The psychotherapy versus the chemotherapy controversy. Newsletter Amer. Schizophrenia Foundation: 1969.

HAWKINS, D. R.: World Medical News, Psychiatric Supplement: Nov., 1969.

HAWKINS, D. R., BORTIN, A. W., and RUNYON, R. P.: Orthomolecular Psychiatry: niacin and megavitamin therapy. Third Int. Congress of Psychosomatic Med., Buenos Aires. Psychosomatics 11: 517, 1970.

HAYAISHI, O.: Fifth International Symposium on regulation of enzyme activity and synthesis in mammalian tissues. Science 155: 1137, 1966.

HERJANIC, M., MOSS-HERJANIC, B., and PAUL, W. K.: Treatment of schizophrenia with nicotinic acid. J. Schizophrenia 1: 197, 1967.

HESTON, L. L.: Psychiatric disorders in foster home reared children of schizophrenic mothers. Brit. J. Psychiat. 112: 819, 1966.

HESTON, L. L.: The genetics of schizophrenic and schizoid disease. Science 167: 249, 1970.

HICK, S. P.: Pathologic effects of antimetabolites. Amer. J. Pathology 31: 189, 1955.

HIGGINS, J.: Effects of child rearing by schizophrenic mothers. J. Psychiat. Research 4: 153, 1966.

HOFFER, A.: Niacin Therapy in Psychiatry. Springfield, Illinois: C. C. Thomas, 1962.

HOFFER, A.: Nicotinic acid: an adjunct in the treatment of schizophrenia. Amer. J. Psychiat. 120: 171, 1963.

HOFFER, A.: Treatment of organic psychosis with nicotinic acid. Dis. Nerv. System 26: 358, 1965.

HOFFER, A.: The effect of nicotinic acid on the frequency and duration of rehospitalization of schizophrenic patients: a controlled comparison study. Int. J. Neuropsychiat. 2: 236, 1966.

HOFFER, A.: Enzymology of Hallucinogens. Philadelphia: J. B. Lippincott, 1966a.

HOFFER, A.: Malvaria and the law. Psychosomatics 7: 303, 1966b.

HOFFER, A.: Use of nicotinic acid and/or nicotinamide in high doses to treat schizophrenia. Canad. J. Psychiat. Nursing 7: 5, 1966c.

HOFFER, A.: Five California schizophrenics. J. Schizophrenia 1: 209, 1967.

HOFFER, A.: Biochemistry of nicotinic acid and nicotinamide. Psychosomatics 8: 95, 1967a.

HOFFER, A.: Treatment of schizophrenia with a therapeutic program based upon nicotinic acid as the main variable. Molecular Basis of Some Aspects of Mental Activity, p. 435. Ed.: Walaas, O., Vol. 2. New York: Academic Press, 1967b.

HOFFER, A.: A Program for Treating Schizophrenia and Other Conditions Using Megavitamin Therapy. Available from A. Hoffer. Saskatoon: Modern Press, 1967.

HOFFER, A.: Comparison of xanthine nicotinate and nicotinic acid as treatment for schizophrenia. J. Schizophrenia 1: 24, 1969.

HOFFER, A.: Adverse effects of niacin in emergent psychosis. J. Amer. Med. Ass. 207: 1355, 1969.

HOFFER, A.: Scientific Committee Reports. J. Schizophrenia 1: 9, 1969.

HOFFER, A.: Safety, side effects and relative lack of toxicity of nicotinic acid and nicotinamide. J. Schizophrenia 1: 78, 1969.

HOFFER, A.: Pellagra and schizophrenia. Third Int. Congress on Psychosomatic Medicine, Buenos Aires, Jan. 1970. Psychosomatics 11: 522, 1970.

HOFFER, A.: Childhood schizophrenia: a case treated with nicotinic acid and nicotinamide. J. Schizophrenia 2: 43, 1970a.

HOFFER, A., and MAHON, M.: The presence of unidentified substances in the urine of psychiatric patients. J. Neuropsychiatry 21: 331, 1961.

HOFFER, A., and OSMOND, H.: The Chemical Basis of Clinical Psychiatry. Springfield, Illinois: C. C. Thomas, 1960.

HOFFER, A., and OSMOND, H.: A card sorting test helpful in making psychiatric diagnosis. J. Neuropsychiat. 2: 306, 1961.

HOFFER, A., and OSMOND, H.: Some schizophrenic recoveries. Dis. Nerv. Syst. 23: 204, 1962.

HOFFER, A., and OSMOND, H.: Scurvy and schizophrenia. Dis. Nerv. Syst. 24: 273, 1963.

HOFFER, A., and OSMOND, H.: Malvaria: a new psychiatric disease. Acta Psychiat. Scand. 39: 335, 1963a.

HOFFER, A., and OSMOND, H.: Treatment of schizophrenia with nicotinic acid. Acta Psychiat. Scand. 40: 171, 1964.

HOFFER, A., and OSMOND, H.: How to Live with Schizophrenia. New Hyde Park, New York: University Books, 1966.

HOFFER, A., and OSMOND, H.: Nicotinamide adenine denucleotide (NAD) as a treatment for schizophrenia. J. Psychopharmacology 1: 79, 1966.

HOFFER, A., and OSMOND, H.: The Hallucinogens. New York: Academic Press, 1967.

HOFFER, A., OSMOND, H., CALLBECK, M. J., and KAHAN, I.: Treatment of schizophrenia with nicotinic acid and nicotinamide. J. Clin. Exper. Psychopath. 18: 131, 1957.

HUXLEY, J.: Morphism and evolution. Heredity 9: 1, 1955.

HUXLEY, J., MAYR, E., OSMOND, H., and HOFFER, A.: Schizophrenia as a genetic morphism. Nature 204: 220, 1964.

IJICHI, H., ICHIYAMA, A., and HAYAISHI, O.: Studies on the biosynthesis of nicotinamide adenine denucleotide. J. Biol. Chem. 241: 3701, 1966.

INOUYE, E.: Similarity and dissimilarity of schizophrenia in twins. Proc. Third World Congress in Psychiatry, Vol. 1, 524. Montreal: McGill University, 1961.

IRVINE, D.: Apparently non-indolic Ehrlich-positive substances related to mental illnesses. J. Neuropsychiat. 2: 292, 1961.

IRVINE, D., BAYNE, W., and MIYASHITA, H.: Identification of kryptopyrole in human urine and its relation to psychosis. Nature 224: 811, 1969.

IVANOVA, R. A., MILSTEIN, G. T., SMIRNOVA, L. B., and FANTCHENKO, N. D.: The influence of nicotinic acid on an experimental psychosis produced by LSD 25. J. Neuropathology and Psychiat. of C. C. Korsakoff (Moscow) 64: 1172, 1964.

JARVIK, L. F.: Congenital malformations attributed to sleeping pill (thalidomide). Eugenics Quarterly 9: 95, 1962.

KALLMANN, F. J.: The genetic theory of schizophrenia. Amer. J. Psychiat.: 103: 309, 1946.

KANIG, K.: Tierexperimentelle untersuchungen zur frage der wirkungsweise von niacin und niacinamid bei der therapie von psychosen. Proc. IV World Cong. Psychiatry, Madrid, Sept., 1966. Excerpta Medica International Congress Series No. 150.

KARLSSON, J. L.: The Biologic Basis of Schizophrenia. Springfield, Illinois: C. C. Thomas, 1966.

KARLSSON, J. L.: Evidence for hereditary transmission of schizophrenia. J. Schizophrenia 1: 239, 1967.

KELM, H., HOFFER, A., and OSMOND, H.: Hoffer-Osmond Diagnostic Test Manual. Saskatoon: Modern Press, 1967.

KLINE, N. S., BARCLAY, C. L., COLE, J. O., ESSER, A. H., LEHMANN, H., and WITTENBORN, J. R.: Controlled evaluation of nicotinamide adenine denucleotide. Brit. J. Psychiat. 113: 731, 1967.

KOWALSON, B.: Metabolic dysperception: its diagnosis and management in general practice. J. Schizophrenia 1: 200, 1967.

LANDAUER, W.: J. Exp. Zool. 136: 509, 1957.

LEHMANN, H.: Post traumatic confusional state treated with massive doses of nicotinic acid. Canad. Med. Ass. J. 52: 598, 1944.

LEWIS, J. J., and POLLOCK, D.: Effects of d-amphetamine and chlorpromazine on oxidized (NAD) and reduced (NADH2) nicotinamide adenine denucleotide levels in rat brain. Biochem. Pharmacol. 14: 636, 1965.

McCOMB, R. B., and CAY, R. J.: A comparison of reduced NAD preparations from four commercial sources. Clin. Chem. 14: 754, 1968.

MAAYAN, M. L., and ROSENBERG, I. N.: Pyridine nucleotides in the thyroid gland II effect of nicotinamide, nicotinic acid and 2 tryptophane administration. Endocrinology 82: 209, 1968.

MARTZ, D. M.: Acute brain syndrome secondary to niacin deficiency. Amer. J. Psychiat. 122: 215, 1965.

MASLOWSKI, J.: Nicotinic acid in treatment of chronic schizophrenia. Psychiatria Polska 1: 307, 1967.

MEIERS, R. L.: Relative hypoglycemia in schizophrenic reactions. J. Schizophrenia 1: 204, 1967.

MELLOR, C. S.: Finger prints in schizophrenia. Nature 213: 939, 1967.

NEWBOLD, H. L.: How one psychiatrist began using niacin. Schizophrenia 2: 150, 1970.

O'REILLY, P. O.: Nicotinic acid therapy and the chronic schizophrenic. Dis. Nerv. System 16: 67, 1955.

OSMOND, H.: Background to the niacin treatment. J. Schizophrenia 1: 125, 1967.

OSMOND, H., and HOFFER, A.: Massive niacin treatment in schizophrenia. Review of a nine-year study. Lancet 1: 316, 1962.

OSMOND, H., and HOFFER, A.: Schizophrenia and suicide. J. Schizophrenia 1: 54, 1967.

PALMA-CARLOS, A., PALMA-CARLOS, L., GAJDOS-TOROK, M., and GAJDOS, A.: Experimental porphyria induced in rats by ethionine. Nature 211: 977, 1966.

PARK, L. C., BALDESSARINI, R. J., and KETY, S. S.: Methionine effects on chronic schizophrenics. Arch. Gen. Psychiat. 12: 346, 1965.

PAULING, L.: Orthomolecular psychiatry. Science 160: 265, 1968.

PAULING, L.: Orthomolecular somatic and psychiatric medicine. Sonderdruck aus der Teitschrift Vitalstoffe-Zivilisationskrankheiten, 1: 1968.

PAULING, L.: Vitamin therapy: treatment for the mentally ill. Science 160: 1181, 1968.

POLLIN, W., STABENAU, J. R., and TUPIN, J.: Family studies with identical twins discordant for schizophrenia. Psychiat. 28: 60, 1965.

PREISS, J., and HANDLER, P. G.: Synthesis of diphosphopyridine nucleotide from nicotinic acid by human erythrocytes in vitro. Amer. Chem Soc. J. 79: 1514, 1957.

RAINER, J. D.: Expanding Goals of Genetics in Psychiatry. New York: Grune and Stratton, 1962.

RAMSAY, R. A., BAN, T. A., LEHMANN, H. E., SAXENA, M. A., and BENNETT, J.: Nicotinic acid as adjuvant therapy in newly admitted schizophrenic patients. Canad. Med. Ass. J. 102: 939, 1970.

RAPP, M. S.,: Use and abuse of drugs. Canad. Med. Ass. J. 98: 922, 1968.

RIMLAND, B.: The institute for child behavior research study of high dosage vitamins as a method of treating severely mentally ill children. Conference and annual meeting, National Society for Autistic Children. San Francisco, 1970.

RIMLAND, B.: High-dosage levels of certain vitamins in the treatment of children with severe mental disorders. Orthomolecular Psychiatry. Ed.: Hawkins, David R., and Pauling, Linus. San Francisco: W. H. Freeman and Company, 1973.

ROBIE, T. R.: Cyproheptadine: an excellent antidote for niacin induced hyperthermia. J. Schizophrenia 1: 133, 1967.

ROGER, J. C., CHAMBERS, H., and CASIDA, J. E.: Nicotinic acid analogues: Effects on response of chick embryos and hens to organophosphate toxicants. Science 144: 539, 1964.

ROSENBERG, L. E.: Inherited aminoacidopathies demonstrating vitamin dependency. The New England J. of Medicine 281: 145, 1969.

ROSENTHAL, D.: Problems of sampling and diagnosis in the major twin studies of schizophrenia. Psychiat. Res. 1: 116, 1961.

ROSENTHAL, D.: The offspring of schizophrenic couples. J. Psychiat. Res. 4: 169, 1966.

ROSENTHAL, D., WENDER, P. H., KETY, S. S., SCHULSINGER, F., WELNER, J., and OSTERGAARD, L.: Schizophrenics Offspring Reared in Adoptive Homes, 377. New York: Pergamon Press, Inc., 1968.

SALVADOR, R. S., and BURTON, R. M.: Inhibition of the methylation of nicotinamide by chlorpromazine. Biochem. Pharm. 14: 1185, 1965.

SALVADOR, R., BURTON, R. M., KAPLAN, N. O., GOLDIN, A., and LEITENBERG, M.: Effects of reserpine and chlorpromazine on pyridine nucleotide synthesis. 135th Meeting American Chemical Society. Boston, 1959.

SEBRELL, W. H., and HARRIS, R. S.: The Vitamins, Vol. 2, 449, New York: Academic Press, 1954.

SHEARER, M. L., DAVIDSON, R. T., and FINCH, S. M.: The sex ratio of offspring born to state hospitalized schizophrenic women. J. Psychiat. Res. 5: 349, 1967.

SHERRILL, D.: Nicotinic acid in the treatment of certain depressed states. J. Bowman Gray School Medicine 8: 137, 1950.

SHIELDS, J., GOTTESMAN, I. I., and SLATER, E.: Kallmann's 1946 schizophrenic twin study in the light of new information. Acta Psychiatrica Scand. 43: 385, 1967.

SLATER, E.: Psychotic and neurotic illnesses in twins. Med. Res. Council Special Report No. 278. London, 1953.

SLATER, T. F., and SAWYER, B. C.: Nicotinamide adenine denucleotides in acute liver injury induced by ethionine and a comparison with the effects of salecylate. B. J. 101: 24, 1966.

STONE, I.: Studies of a mammalian enzyme system for producing evolutionary evidence on man. Amer. J. Phys. Anthrop. 23: 83, 1965.

STONE, I.: Hypoascorbemia, the genetic disease causing the human requirement for exogenous ascorbic acid. Perspectives in Biol. and Med. 10: 133, 1966.

SYDENSTRICKER, V. P., and CLECKLEY, H. M.: The effect of nicotinic acid in stupor, lethargy and various other psychiatric disorders. Amer. J. Psychiat. 98: 83, 1941.

SZATMARI, A., HOFFER, A., and SCHNEIDER, R.: The effect of adrenochrome and niacin on the electroencephalogram of epileptics. Amer. J. Psychiat. 111: 603, 1955.

TAYLOR, M. A.: Sex ratios of newborns: associated with prepartum and postpartum schizophrenia. Science 164: 723, 1969.

TAYLOR, M., and LEVINE, R.: The effect of maternal schizophrenia on the sex of offspring. Soc. Biol. Psychiat.: May 2, 1969.

TAYLOR, M. A., and LEVINE, R.: Puerperal schizophrenia: a physiological interaction between mother and fetus. Biological Psychiat. 1: 97, 1969.

THOMPSON, L. J., and PROCTOR, R. C.: Depressive and anxiety reactions treated with nicotinic acid and phenobarbital. N. Carolina Med. J. 14: 420, 1953.

WARD, J. L.: Treatment of neurotics and schizophrenics using clinical and HOD criteria. J. Schizophrenia 1: 140, 1967.

WASHBURNE, A. C.: Nicotinic acid in the treatment of certain depressed states: a preliminary report. Ann. Int. Med. 52: 261, 1950.

WENDER, P. H.: The role of genetics in the etiology of the schizophrenias. Amer. J. Orthopsychiat. 39: 447, 1969.

WHITTEN, C. F., PETTIT, M. G., and FISCHOFF, J.: Evidence that growth failure from material deprivation is secondary to undereating. J. Amer. Med. Ass. 209: 1675, 1969.

WOLBERG, L. R. RIESSE, B. F., DI CYAN, E. D., and DAIN, H. J.: The "Curtain of Fog" syndrome. Mind 2: 75, 1964.

WOOLLEY, D. W.: Tranquilizing and antiserotonin activity of nicotinamide. Science 128: 1277, 1958.

ZELINSKII, S. P.: Chem. Abstracts 50: 1956.

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An Examination of the Double-Blind Method as It Has Been Applied to Megavitamin Therapy

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Introduction

Under my direction, the first double-blind experiments were conducted in psychiatry. With the first one we examined the efficacy of a yeast nucleotide preparation which had been claimed to be effective in treating chronic schizophrenic patients. None of the patients improved. With the second experiment we compared the efficacy of nicotinic acid, nicotinamide, and placebo in combination with the standard treatment of that day (electroconvulsive therapy, psychotherapy, and sedatives). The clinician in charge of each case decided whether or not to use ECT. Half from each of the three groups (usually the sickest patients) received ECT. Nicotinamide was used as a hidden control group to compensate for the vasodilation (flush) produced by nicotinic acid when the medication is started. None of the nursing or medical staff were aware of the nicotinamide group. The 30 patients were admitted from the community to a psychiatric ward and had not spent long periods of time in any institution. They were mainly acute and subacute. On the average they were in hospital about two months while going through the experimental program.

They were re-evaluated every three months after discharge and a final evaluation was made one year after discharge. The follow-up worker made his evaluations blind. Three grams per day of nicotinic acid or nicotinamide was used for 33 days while in hospital.

At the end of one year after discharge, one-third of the placebo group were well. However, two-thirds of the vitamin groups were well, there being no difference between nicotinamide and nicotinic acid. After that, three more double-blind experiments were completed in Saskatchewan. In each case, the results when vitamin B3 was used were superior to standard treatment only.

Since then, as a result of the work of physicians, now known as orthomolecular psychiatrists, many significant improvements have been made. The treatment today contains many additional variables and produces a greater number of recoveries. Orthomolecular therapy includes megadoses of vitamins as a main component but also includes attention to nutritional therapy, to tranquilizers, antidepressants, and to ECT. The best comprehensive outline is in *Orthomolecular Psychiatry* (Hawkins and Pauling, 1973)

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Only one other psychiatrist, Dr. H. Osmond, has had as much experience as I in conducting double-blind experiments, not in the number of trials, but in the number of years that trials have been conducted. Over the years we have become more and more aware of the inherent defects of this method, and in a series of papers we have drawn these difficulties to the attention of the medical world (Hoffer and Osmond, 1961, 1963; Hoffer, 1967). I have concluded that the double-blind method has so many imperfections that its use is limited, that it leads to a large number of serious errors, i.e., it would do so if clinicians took it seriously, and that its main function is to make it easier for government agencies to turn down new drugs. It seems to be most appreciated by groups who have access to unlimited funds and limited access to clinical curiosity and creativity. I have finally concluded that the observations and conclusions made from double-blind experiments have as little relevance to the therapy of patients as do observations on monkeys in a cage to their behavior in their native habitat. The beast seems to be the same, but there the resemblance ends.

The defects of the double-blind methodology are these:

(1) The basic assumptions behind the use of statistical analyses are ignored (Hogben, 1957). The design assumes that the comparison groups will be equivalent, will be homogeneous, and will be invariant. Over time a proper randomization may approximate equivalence but since psychiatric populations are very heterogeneous, it is impossible to obtain equivalent groups. This can be overcome by very large samples, but these are very rare in medical research. Nor can we assume the conditions are invariant. There is a natural historical drift in the nature and intensity of diseases due to factors only dimly understood. Therefore, according to Hogben, statistical analyses based upon probability theory is invalid.

(2) Little account is taken of the disease model being followed in most double-blind experiments. Diseases may be short-lived, like pneumonia, or may last most of one's life, like diabetes or schizophrenia. The same variability of models is inherent in any psychiatric population. Since chronic patients usually require chronic treatment, it is inappropriate to use short-term treatment for chronic patients. But chronic double-blind experiments are very difficult to control so they are seldom used. We therefore find that short experiments are applied to groups of patients whose duration of illness varies from several months to many years (Glick and Margolis, 1962).

(3) The three main components of the patient-doctor relationship are the status of patient and doctor tied together by the relationship. The patient is impelled to have some faith and trust that the physician will be able to help him. The greater the threat to the person, the greater is the drive to have faith. The physician, on the basis of his education and experience, will have a certain degree of confidence that he can help the patient, either to achieve a cure or to alleviate the discomfort. There is no generally accepted term for this complex relationship. Terms like placebo effect, psychotherapy, etc., have been used but do not quite get at the essential relationship. Placebo effect is generally described as a positive response in the patient due to his expectations, his faith in the doctor or in his medication. Negative placebo effects have been given less consideration.

Hoffer and Osmond (1961) presented the term **obecalp** to describe another aspect of the relationship. Inasmuch as a positive response to an inert substance is a placebo response, so a negative response to an active chemical is an obecalp reaction (placebo backward). This we defined as a reaction in which a compound of known potency produces no response in test subjects due to factors such as fear of medication, either in the subject or in the doctor and others involved in giving the drug, lack of faith, negative suggestion, and so on.

There are two phases in the placebo and obecalp reaction, the initial reaction when treatment is just underway, and the sustained reaction. Of these the sustained reaction is more rational and more important. During the initial phases, the patient is dependent upon the transaction with his doctor and has no way of directly experiencing whether he is being helped. However, once treatment has started he begins to experience changes in himself, good or bad, from which he draws conclusions which enhance his placebo or obecalp reaction. If a patient finds that his depression or his hallucinations become less troublesome, this increases his faith and trust in the medication and so enhances placebo response. A positive feedback develops which increases the level of placebo effect as more and more improvement is experienced. This is the optimum placebo effect which will remain high as long as improvement is sustained. The physician is also affected in the same way for, as he observes his patient's improvement, his faith in the treatment that he is giving goes up, which in turn is evident to his patient.

Generally there must be a sufficient placebo effect for the patient to start the treatment. This the doctor achieves by his manner of confidence in giving the diagnosis to his patient, in his explanations of it, and in describing the importance of the treatment and the outcome or prognosis. If the patient remains unconvinced, he will not even start the therapy unless he has a family who can persuade him to cooperate, and supervise the medication. If this is impossible, the patient will have to be hospitalized for treatment. The patient's initial faith may be zero, provided the family can ensure the program will be followed. Thus, patients have been given nicotinic acid or nicotinamide disguised in their food because they were violently opposed to taking any medication, and they have recovered. In the same way, a pellagrin given nicotinamide in his food will also recover whether or not he knows this is being done.

However, unless there is a sustained placebo effect, the recovery will not be maintained since the patient will discontinue medication. Fortunately, most psychiatric patients when well do not wish to relapse into their previous sick condition. Many schizophrenics who have been well for many years on the megavitamin therapy will discontinue medication but will in most cases resume medication if they become aware of a resurgence of symptoms.

In JAMA 224, 1584, 1973, Borda's report on patient evaluation of tranquilizers was reviewed. Borda studied over 15,000 patients in 10 hospitals of whom 25 percent had received at least one tranquilizer. There was a marked discrepancy between the patients' and their doctors' evaluation of efficacy. About 66 percent of the physicians reported good results but only 21 percent of the patients reported feeling better. With this major disagreement, it is simple to understand why patients are so reluctant to take them, and why there is such a development in slow-release, long-acting tranquilizers. Apparently tranquilizers, either because they are ineffective or because of undesirable side effects, do not sustain the placebo effect. A major problem in treating chronic schizophrenics is in keeping them on their tranquilizers. There must therefore be enough initial and sustained placebo reaction to ensure the medication will be taken.

In the normal situation the patient's personal physician attempts to set placebo effect at a very high level. However, in a double-blind experiment, if it remains truly blind, it is impossible for the physician to do so. Since he knows that the patient may receive an inert substance, he cannot honestly advise the patient that this will be helpful to him. The patient will detect his physician's reluctance to be a real physician to him. This is even more apt to occur in situations where double-blind experiments are run, i.e., in institutions, university wards, and so on, for in many cases the patient does

not have a physician or does not know who he is. I have seen large numbers of patients after discharge from these institutions who did not know who had been their doctor. They had been seen by medical students, interns, and residents, but very infrequently by the physician under whose name they had been admitted and who was finally responsible for treatment. By setting the placebo effect at a minimum, the double-blind destroys one of the essential components of the treatment. This is like measuring the rate of a chemical reaction, say an enzyme, which works best at 37°C, by setting the reaction at 0°C. There may be a reaction but it will not help the patient much. This is the main reason why double-blind results have little relevance to the real therapeutic effects of chemicals as commonly used by physicians.

(4) Perhaps the most serious criticism of the double-blind method is that it has not been established empirically. There is no data which shows that the double-blind method does control those factors which theoretically it was designed to control. We are therefore swept up in a technique which has received overwhelming approval by institutions and universities but which has never been subjected to the experimental test of whether it works. The discussion that I have presented so far indicates that when such a test is finally performed, it will show the double-blind not to be a useful method.

In science, a new technique is not used until it has been calibrated, i.e., compared to a current method. If it is more accurate, and more sensitive, it will supercede the older method. If it has not these advantages, it may still take over if it is more economical, quicker, and so on. But in the double-blind we find a method which is not established by experiment, not proven to be better, more difficult to run, and much more expensive, which has displaced usual clinical trials. Credit must be given to those research workers who have carried the field with enthusiasm and dedication for they had little else to bolster their position. They assumed that, because chemical treatments replaced each other, e.g., sulfonamides by penicillin, etc., and because double-blind experiments generally showed drugs considered active to be no better than placebo, this proved (1) double-blinds were superior, and (2) caused active drugs to replace inactive ones. This is a major fallacy. Better drugs have always displaced weaker drugs even before double-blinds became fashionable. If penicillin hadn't been developed we would still be using sulfonamides. Finally, the fact that double-blinds generally show active drugs to be inactive may be interpreted as showing that the technique is no good since it fails to detect therapeutic activity in compounds known to be active. Double-blinds enhance obecalp reactions.

Hogben and Wrighton, 1952, summarize their point of view in this way: (1) Hitherto it has been customary to assess the claims of therapeutic and prophylactic measures in statistical terms by recourse to tests which invoke a unique and so-called null hypothesis, namely that the procedures compared are equally efficacious. (2) This procedure has no bearing on the operational intention of the trial, viz., to find out how much advantage accrues from substituting one treatment for another. (3) Within its more restricted domain, the credentials of any significance test which takes within its scope only one hypothesis have now to meet the criticism that it takes into account only one sort of error, viz., that of rejecting the hypothesis when it is true. (4) A procedure which justifies assertions of so limited and conditional a scope may be a useful self-disciplinary convention; but its claims to rank as an instrument of statistical inference are no longer acceptable.

In spite of the mounting concern over the heavy reliance placed on results of double-blind experiments by men like Glick and Margolis (1962); Freyhan (1963) in his discussion of their paper; Bellak and Chasson (1964); Chasson (1957, 1959, 1960, 1961);

Plutchik, Platman, and Fieve (1969); Baird (1964, 1968); Cromie, (1963); Dalen (1969) (who questions the power of statistical tests. They are always used in double-blind experiments where the null hypothesis is used. This, according to Popper, is only a test of the null hypothesis for only that hypothesis is in danger of being refuted); Lasagna (1972); Feinstein (1970, 1971, 1972); Cotzias (1972). Many investigators will use no other technique and depend upon these questionable methods to resolve therapeutic controversy. They seem to be unaware that clinicians (doctors who work directly with patients) generally remain unconvinced by double-blind experiments. Double-blind experiments generally tend to prove active drugs to be inactive, i.e., yield obecalp responses. On the other hand, clinical trials in the older fashion may too often show inactive or slightly active drugs to be too active. I consider the latter error safer for medicine. If every drug used today had been forced to be double-blinded at its inception I doubt that we would have insulin, thyroid, aspirin, antihistamines, and other very valuable drugs. It has been claimed that the need to impress government agencies in the U.S.A. has substantially reduced the flow of new drugs onto the market. The government agencies will only accept double-blind studies.

The megadose vitamin B3 controversy is caught in the middle of this methodology controversy. It was established on the basis of the first double-blind experiments in psychiatry on acute and subacute schizophrenics treated with ECT, sedatives, and psychotherapy. The groups were randomized. One group received placebo. So far no one has attempted to reproduce this experiment using similar patients and similar treatment. We also reported that nicotinic acid alone did not benefit chronic patients such as are found in a mental hospital (see O'Reilly, 1955). This we reiterated in many of our reports.

However, in a series of studies over a five-year period, investigators seemed unaware of these conclusions and used subacute and chronic patients in mental hospitals without ECT. They concluded that nicotinic acid was not therapeutic for schizophrenia. Hoffer (1971) reviewed the reasons for their failure to obtain positive results.

In order to illustrate the inherent defects of the double-blind design, I will review several reports by Wittenborn, Weber, and Brown (1973), Wittenborn (1973), and DeLiz (1973), all bearing upon the same double-blind therapeutic trial.

Patients newly admitted to a mental hospital but ill at least 4.8 years on the average were randomized into two groups. The randomization was imperfect since the nicotinic acid group had been ill 4.8 years on the average and the control group had been ill for three years. The experimental group were given 3 grams per day of nicotinic acid with or without tranquilizers, depending upon the usual indications for giving tranquilizers. No ECT was used. The experiment was described as double-blind but no evidence is given that it was double-blind, nor were there suggestions that the code had been broken. Out of an initial group of 140, 75 completed two years of treatment. Out of 36 patients who dropped out of the experimental group, 20 or 58 percent were uncooperative. Out of 29 who dropped from the control group, 21 or 72 percent were uncooperative. Out of 83 who started on nicotinic acid, 24 percent dropped out while out of 57 on placebo, 37 percent were dropped because they did not cooperate. This suggests that more placebo patients were suffering from negative placebo effects and might be explained by the fact that some of them were aware of the fact that they were on placebo (DeLiz, 1973). Their general conclusion was that there was no therapeutic effect from the use of nicotinic acid.

In a more recent report, Wittenborn (1973) concluded that patients with certain descriptive indices did respond well to nicotinic acid. Each patient had been examined carefully before treatment was started. From

social data so obtained 12 factors (items) discriminated between placebo and nicotinic acid as the study progressed. He concluded, "These items appear to have a common implication for the description of the premorbid personality of patients who responded relatively well to the high dosage of niacin. Thus niacin was most effective for those patients for whom some features of definite interpersonal participation was found in the premorbid background."

The 12 items were combined into a predictor scale ranging from 0.00 to 1.00. The 75 patients who scored over 0.50 indicated easily evident pathology. The average scores indicated the experimental group had more pathology than the control group (consistent with the finding that they had been sick longer). Patients with high predictor scores generally responded better to therapy.

When high-score patients (over 0.6) were compared, the group on niacin responded better than the placebo group. For example, at 24 months the niacin group had half the depression of the placebo group. For schizophrenic excitement, the incidence of significant pathology was more than twice as great in the placebo group. Paranoia and hebephrenia were twice as prevalent in the placebo group. During the discussion after presenting this paper, Wittenborn reported that two-thirds of the niacin group were well compared to one-third of the placebo group. He concluded, "A high positive predictor score was associated with a clinical significant advantage for those patients who were treated with the high level of niacin medication."

"The items of the follow-up inquiry which showed the required consistency of relationship with the predictor score in the experimental group appear to be mutually consistent and describe the kind of person who participates in ordinary interpersonal interactions and who is approaching at least some of the tasks and challenges of his life constructively. The respective correlations based on the control sample displayed in Table 3 do not show a comparable or even an inverse set of relationships with the predictor scores. Thus it would appear that among the patients treated with high-dosage niacin those patients with a high positive predictor score have resumed the constructive quality of adjustment which the high positive predictor score implied for the premorbid status of these patients.

"The present **post hoc** treatment of the data reveals that persons whose premorbid history suggested a participatory life style tend to return to a participatory pattern of living after a year or more treatment with high levels of niacin. No such reconstructive trend was indicated for the control patients, however."

"There is a conceivable relationship between the fact that in the present sample patients with a high predictive score responded well to niacin and the fact that Hoffer and Osmond had claimed that niacin was more effective in relatively acute patients than in chronic patients. It is probable that patients who, in the present sample, had a high positive predictor score would have been classified by Hoffer and Osmond as acute schizophrenics. Perhaps in this way the differential effect observed by them could be in part explained."

"Why should a pretreatment disposition which has a favorable significance for patients treated with niacin have an unfavorable significance for patients not treated with niacin? One possible explanation for the paradoxical worsening in the control group draws upon observations that many patients with a favorable premorbid history are harmed by phenothiazine treatment in the sense that their remission is burdened."

Here is illustrated one of the main defects of the double-blind method — its inapplicability to heterogeneous groups. Since we had many times pointed out that early cases responded better and without need for as many other chemotherapies, there was no

need to use a mixture of early and well-developed cases. As a result, the double-blind by Wittenborn et al. yielded no significant difference. However, when the groups were purified (made more homogeneous) by using indications which sorted the early from late cases, the differences in the early cases became highly significant. The chronic cases should have been given ECT in combination with the vitamin if it had been desired to repeat our original double-blind experiments.

However, this is not the only problem. Recently Dr. DeLiz submitted a critique of the double-blind experiment run by Wittenborn. This is published in this Journal. The most serious charge is that the experiment was **not** double-blind. Patients on placebo discovered this and felt they were being deceived (as they were), and at least one and perhaps others tried to get niacin on their own. If the patients knew, so must have some of the staff. Since the preponderant feeling in most institutions is violently opposed to megavitamins, it is easy to understand that there would be immense negative pressure against niacin and positive pressure in favor of placebo. Obecalp would be strongly favored.

The findings from the second study are therefore even more significant, emerging from a study where a double-blind design was not adhered to and where obecalp reactions were favored by the staff. It is apparent that when treatment was matched to the right patients, i.e. nicotinic acid and tranquilizers to acute patients (phase one), the superiority of nicotinic acid over placebo was amply evident in a setting favoring obecalp responses. Two of the psychiatrists involved in the study eventually began to practice orthomolecular psychiatry after leaving the study.

The main opposition to the orthomolecular approach has come from these so-called double-blind experiments conducted by psychiatrists who accept only double-blinds as scientific evidence. The debate is not a debate between the physicians who have used similar treatment methods and have obtained conflicting results. This is the normal kind of scientific debate. It is between two sets of methodologies. It is clear that each group can reproduce each other's work. The orthomolecular psychiatrist using any method as well as double-blind gets similar results. The double-blind methodologists also confirm each other since they all use essentially the same method.

Fortunately, double-blinds are inherently unconvincing to clinicians and to their patients and will not long stand in the way of good clinical observations made by orthomolecular physicians, by their patients, their families, and by others who work with them.

In a personal communication, Dr. DeLiz reported that when relatives of patients on placebo complained, they were assured that this was untrue and that the patients were having fantasies. This would alienate patient from family. DeLiz wrote, "It is rather easy to see how the secondary symptoms, real reactions to a contaminated social and psychological environment as regards to niacin, were pervasive and might in their turn distort the totality of the psychiatric, social, and psychological rating procedures."

It is evident that the double-blind method does not solve the problem of proper trials and in fact is probably worse than usual clinical observations made by interested clinicians. Orthomolecular psychiatrists who value the welfare of their patients will be wise not to expose them to experiments of this kind. It is possible to run comparison experiments where one program is compared against another. The procedure is simple, relatively inexpensive, and the results would be decisive and convincing. But so far no one in any University or research setting has shown much interest in this kind of study. We will therefore have to depend on our clinical observations bolstered by psychological tests such as MMPI, HOD, and EWI, and by clinical tests of hair, blood, and urine (kryptopyrrole, for example)

REFERENCES

BAIRD, K. A.: Assessment of Drug Trials. Can. Med. Ass. J. 90, 1279 only, 1964.

BAIRD, K. A.: Medicines Domination by the Control Worshippers. Can. Doctor, 27 only, 1968.

BELLAK, L. and CHASSAN, J. B.: An Approach to the Evaluation of Drug Effect During Psychotherapy: A Double Blind Study of a Single Case. J. Nerv. Mental Dis. 139, 20-30, 1964.

CHASSAN, J. B.: On the Unreliability of Reliability and Some Other Consequences of the Assumption of Probabilistic Patient States. Psychiatry 20, 163-171, 1957.

CHASSAN, J. B.: On the Development of Clinical Statistical Symptoms for Psychiatry. Biometrics 15, 396-404, 1959.

CHASSAN, J. B.: Statistical Inference and the Single Case in Clinical Design. Psychiatry 23, 173-184, 1960.

CHASSAN, J. B.: Stochastic Models of the Single Case as the Basis of Clinical Research Design. Behavioral Science 6, 42-50, 1961.

COTZIAS, G. C.: Limitations of Controlled Double Blind Studies of Drugs. New Eng. J. Med. 287, 937 only, 1972.

CROMIE, B. W.: The Feet of Clay of the Double Blind Trial. The Lancet 2, 994-997, 1963.

DALEN, PER.: Causal Explanations in Psychiatry: A Critique of Some Current Concepts. Brit. J. Psychiatry 115, 129-137, 1969.

DeLIZ, A. J.: A Note of Criticism Concerning Wittenborn's Paper on an Experimental Double-Blind Research Design Dealing with the Action of Nicotinic Acid on Schizophrenia. J. Orthomolecular Psychiatry 2: 3, 1973.

FEINSTEIN, A. R.: What Kind of Basic Science for Clinical Medicine? New Eng. J. Med. 283, 847-852, 1970.

FEINSTEIN, A. R.: Clinical Biostatistics IX. How Do We Measure Safety and Efficacy? Clin. Pharm. and Ther. 12, 544-558, 1971.

FEINSTEIN, A. R.: The Need for Humanized Science in Evaluating Medication. The Lancet 2, 421-423, 1972.

FREYHAN, F.: Discussion of Paper by Glick and Margolis.

GLICK, B. S. and MARGOLIS, R.: A Study of the Influence of Experimental Design on Clinical Outcome in Drug Research. Am. J. Psychiatry 118, 1087-1096, 1962.

HAWKINS, D. R. and PAULING, L.: Orthomolecular Psychiatry. W. H. Freeman and Co., San Francisco, 1973.

HOFFER, A.: A Theoretical Examination of Double Blind Design. Can. Med. Ass. J. 97, 123-127, 1967.

HOFFER, A.: Megavitamin Therapy for Schizophrenia. Can. Psychiat. Ass. J. 16, 499-504, 1971.

HOFFER, A. and OSMOND, H.: Double Blind Clinical Trials. J. Neuropsychiatry 2, 221-227, 1961.

HOFFER, A. and OSMOND, H.: Some Problems of Stochastic Psychiatry. J. Neuropsychiatry 5, 97-111, 1963.

HOGBEN, L.: Statistical Theory: The Relationship of Probability, Credibility and Error. George, Allen and Unwin, Ltd., London, 1957.

HOGBEN, L. and WRIGHTON, R.: Quoted in Hoffer and Osmond (1963).

LASAGNA, L.: The Nature of Evidence: Triangle 11, 145-152, 1972.

O'REILLY, P. O.: Nicotinic Acid Therapy and the Chronic Schizophrenic. Dis. Nerv. System 16, 67-72, 1955.

PLUTCHIK, R., PLATMAN, M.B., and FIEVE, R. R.: Three Alternatives to the Double Blind. Arch. Gen. Psychiatry 20, 428-432, 1969.

WITTENBORN, J. R.: The Selective Efficacy of Niacin in the Treatment of Schizophrenia. N.I.M.H. Conference, Washington, 1973.

WITTENBORN, J. R., WEBER, E. S. P., and BROWN, M.: Niacin in the Long-Term Treatment of Schizophrenia, Arch. Gen. Psychiatry 28, 308-315, 1973.

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Effects of Excess Dietary Methionine and Niacinamide in the Rat. (23769)

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Excess dl-methionine in the diet inhibits growth and causes a marked loss of body fat, enlargement of the kidneys, increased excretion of creatinine and a small increase in liver fat in the immature rat(1,2,3). Excess dietary niacinamide also inhibits growth in the rat (4). Since these effects were observed in short term studies in rats maintained on basal diets, this study was designed to ascertain the effects of prolonged administration of excess dietary methionine and niacinamide on the growth rate and organ weights of rats maintained on a standard laboratory ration.

Methods. The effect of various dietary supplements on growth in the rat was determined in 2 series of experiments. In the first series, 5 groups of 12 male Holtzman rats, weighing 110-135 grams, were treated with various combinations of dl-methionine, niacinamide, and biotin for a period of 12 weeks. The rats were allowed food and water *ad libitum*. The food a standard rat chow, was finely ground and definite amounts of the nutrients being tested were added. The animals were weighed at weekly intervals and 4 rats of each group were sacrificed at the end of 2, 8 and 12 weeks of treatment. The adrenal glands, liver and kidneys were removed and weighed. In the second series, 4 groups of 10 rats were administered dietary supplements of malic acid, dl-methionine and niacinamide. The procedures used were the same as above except animals were sacrificed only at the end of 8 and 12 weeks of treatment. The results obtained from the 2 series of experiments were analyzed statistically using the Analysis of Variance Method. For this analysis all gland weights were expressed as a function of the body weight.

Results. All diets containing excess methionine inhibited the growth rate during the first 2 weeks of treatment ($P<0.01$) (Fig. 1). At the end of 8 and 12 weeks of treatment, only the animals receiving diets containing both 2% methionine and 0.1% niacinamide exhibited a significant retardation of growth ($P<0.01$). However the addition of 1% malic acid to the diet prevented the decrease in the growth rate. Niacinamide administered at the level of 0.1% of the diet for 8 weeks caused no significant change in the growth rate, but at the 0.2% level, growth was enhanced and at the 0.4% level, growth was inhibited ($P<0.05$) (Fig. 2). During the next 4 weeks of treatment the body weights of animals receiving 0.2% niacinamide in the diet returned to control levels but inhibition of growth by the 0.4% dosage became more marked ($P<0.05$). As shown in Table I, there is a transient enlargement of the kidneys during the first few weeks of treatment with all diets containing 2% methionine. In addition, a transient adrenal hypertrophy is observed in rats treated with methionine alone. There is a decrease in the liver size in rats receiving 2% methionine plus 0.1% niacinamide for 12 weeks but this is prevented by the ad-

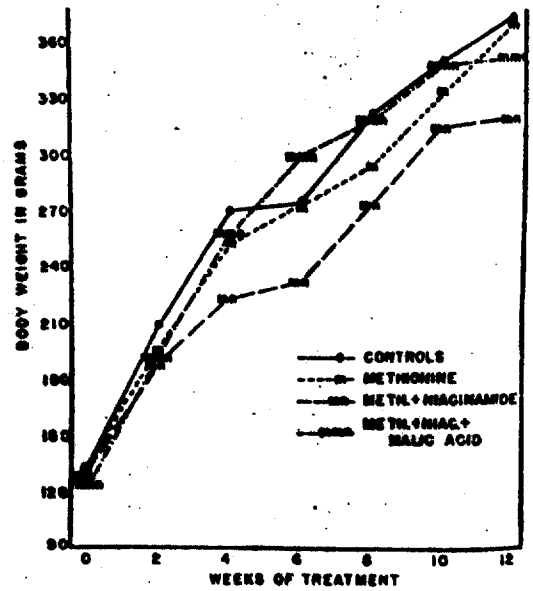

FIG. 1. Effect of excess dietary methionine, niacinamide and malic acid on growth rate of the rat.

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TABLE I. Effect of Excess Dietary Nutrients on Relative Weights of Liver, Kidney and Adrenal Glands of Rats.

Treatment†	Liver (g %)*			Kidney (g %)			Adrenals (mg %)		
	Weeks of treatment								
	2	8	12	2	8	12	2	8	12
Control	4.73	3.92	3.92	.96	.79	.79	17.0	15.6	13.9
2% M	5.04	3.74	4.10	1.17§	.83	.77	20.0‡	15.9	12.9
2% M .1% N	5.04	3.77	3.39§	1.12§	.84	.83	18.2	16.9	12.4
2% M .1% N .004% B	5.29	3.95	3.96	1.13§	.82	.80	17.5	14.6	13.2
2% M .1% N 1% MA		3.89	3.55§		.87	.85		13.7	13.1
2% M 1% MA		4.02	3.84		.89	.90		15.8	13.6
.1% N	4.84	3.67	3.82	1.03	.79	.69‡	15.2	15.1	12.9
.2% N		4.06	3.63‡		.74	.74		13.9	13.0
.4% N		4.10	3.67		.73	.84		17.4	15.5
.004% B	4.92	3.62	3.77	.99	.77	.81	17.0	12.0§	12.2
1% MA		3.83	4.05		.80	.83		14.7	13.7

* Gland wt/100 g of body wt. † M = Methionine; N = Niacinamide; B = Biotin; MA = Malic acid. ‡ Significant at the 5% level. § Significant at the 1% level.

dition of 0.004% biotin to the diet. The relative weight of the adrenal glands in rats receiving 0.004% biotin only is significantly decreased after 8 weeks ($P<0.01$) but not after 12 weeks of treatment.

Discussion. Handler and Perlzweig(5) suggested that excess dietary niacinamide causes a retardation of growth by inducing a secondary methionine deficiency. Niacinamide undergoes obligatory methylation prior to excretion and methionine appears to be the source of the labile methyl groups. The data presented here are not in agreement with this hypothesis since niacinamide was found to augment the effect of methionine on the growth rate rather than to inhibit it. However, the discrepancies between the data presented here and that obtained by Handler and Perlzweig are probably caused by the difference in the dosages and the basal diets that were used. The prevention of the effect of treatment with methionine and niacinamide on growth by malic acid suggests that growth is retarded *via* an action on carbohydrate metabolism at or preceding the tricarboxylic acid cycle. Since pyridoxine will counteract the effect of moderate amounts of methionine on growth in the rat(6), the addition of malic acid to the diet may compensate for a pyridoxine deficiency. It is interesting to note that malic acid prevents the inhibition of growth but not the decrease in liver size caused by the treatment whereas the reverse is seen when biotin is added to the diet. In general, the various

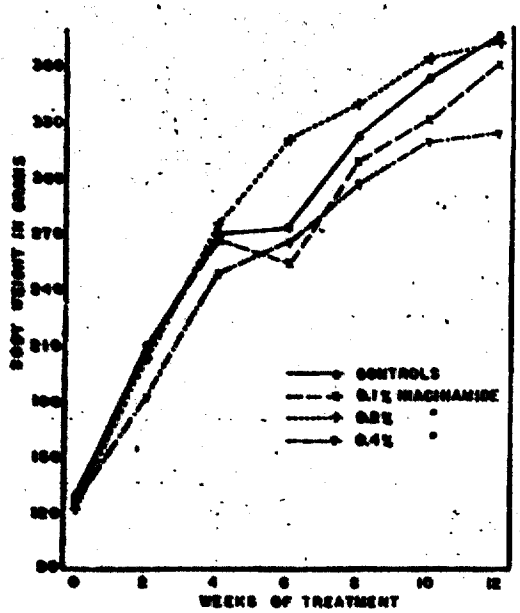

FIG. 2. Effect of various dosages of niacinamide on growth rate of the rat.

treatments are relatively non-toxic. There is a transient hypertrophy of the kidneys during the first few weeks of treatment with methionine but as prolonged treatment did not cause adrenal hypertrophy, it is doubtful that any of the regimens placed a severe stress on the animals.

Summary. The effects of prolonged administration of excess dietary dl-methionine and niacinamide on growth rate and on the relative weights of the liver, kidneys and adrenal glands of rats were determined. Although both methionine and niacinamide caused a decrease in the growth rate, a greater retardation of growth was obtained when both nutrients were administered together. The addition of 1% malic acid to the diet prevented the inhibition of growth by these substances. Although methionine caused a transient enlargement of the kidneys, none of the treatments appeared to place a severe stress on the animals.

1. Van Pilsum, J. F., Berg, C. P., *J. Biol. Chem.*, 1950, v177, 533.

2. Russell, W. C., Taylor, M. W., Hogan, J. M., *Arch. Biochem.*, 1952, v39, 249.

3. Allison, J. B., *Some Aspects of Amino Acid Supplementation*, Edited by W. H. Cole, New Brunswick: Rutgers Univ. Press, 1956, p69.

4. Handler, P., Dann, W. J., *J. Biol. Chem.*, 1942, v146, 357.

5. Perlzweig, W. A., *Ann. Rev. Biochem.*, 1945, v14, 617.

6. DeBey, H. J., Snell, E. E., Baumann, C. A., *J. Nutrition*, 1952, v46, 203.

Received September 9, 1957. P.S.E.B.M., 1958, v97.

Nord. Med. 16:3052-3053. 1942.

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NICOTINIC ACID AND ITS THERAPEUTIC USE

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It is interesting that nicotinic acid and therapeutic experiments with this substance are connected with the most rapidly occurring and absolutely staggering effect on pellagra.

In the Southern States, where endemic pellagra was widespread, and where the disease reached a degree in development which we hardly ever see in these latitudes, there is no evidence that nicotinic acid is missing in the treatment of this disease. With the introduction of nicotinic acid per os, there sets in, in the course of a few days, a definite improvement in the condition of the often deathly-ill person. Diarrhea ceases, stomatitis and glossitis vanish, the skin takes on once more its natural appearance, the patient is lucid and begins again to eat and take on weight, and improvement begins a new movement forward.

That a disease with such a complex symptomatology as pellagra can be completely cured with the introduction of a single, chemically well-defined substance, has naturally given an impulse to the value of intense study and research on the biological effects of this material.

After a short survey of nicotinic acid, a therapeutic experiment will be discussed which was conducted with the same substance.

Nicotinic acid, or more correctly, nicotinic acid amide, into which nicotinic acid is transformed in the body, enters into the B-vitamin complex, along with aneurin and riboflavin. In addition to this, a portion of another substance is involved, whose significance for human pathology has still not been fully clarified. The substance works like aneurin and riboflavin which are involved in intermediate metabolism, such as carbohydrate metabolism, as a real enzyme system, in this case co-dehydrogenase 1 and 2, which is a link in the destructive splitting of hydrogen from a carbohydrate chain. These enzymes are found in every cell where there is carbohydrate destruction, and it is necessary for its normal metabolism.

If there is an insufficient supply of nicotinic acid, the co-dehydrogenases may not be built up; the organism itself cannot synthesize nicotinic acid and metabolism is compromised. The reactions of the different tissues and body systems herein manifest themselves as disease phenomena, which affords an indication for treatment with nicotinic acid.

It appears from this that an increase in carbohydrate metabolism may release latent deficit symptoms. Pellagra symptoms are also observed to break out, for example, in unilateral glucose feeding or in other circumstances with increased combustion, as in diabetics, which rises abruptly with carbohydrate and insulin, in hyperthyreosis, fever, or pregnancy (Sydenstricker).

Nicotinic acid is a slightly toxic substance which is very easily resorbed, for which reason it can almost always be given per os, if a condition involving constant vomiting is not present. In animal experiments on mice, it is observed that its toxicity is much less than that of nicotine, by 5000 times. The most ~~trivial~~ secondary effect, even after therapeutic doses, is vascular dilation in the head, throat, and upper extremities, appearing as a flush and increase in temperature with a slightly burning sensation, a situation which is also in need of therapeutics. Occasionally there may arise a slight burning and sucking in the epigastrium. Re-

spiration, pulse, electrocardiogram, and blood pressure are not affected appreciably. Nicotinic acid works by stimulating stomach secretion and the mobility of the gastrointestinal tract. Nicotinic acid amide, which in regard to therapeutics otherwise acts as nicotinic acid, has none of the vascular effects mentioned. It should be said that from the Danish viewpoint, a good and accurate method has been worked out for determining nicotinic acid in blood and urine (Sandter).

Among the cases which present conditions for treatment with nicotinic acid, pellagra must be named first of all. This is a disease which is seen fairly rarely completely developed in this country. Even though primary treatment consists of nicotinic acid (300-100 mg daily), a fact which is now understood, the disease is seldom [illegible] a pure nicotinic acid deficiency, for which reason treatment must be supplied by another component in the B-complex.

Quite as important as completely developed pellagra, where the diagnosis, on the basis of the characteristic symptoms, is easy to report, is a large group of diseases with indefinite symptoms, involving the digestive tract, which can possibly be ascribed to hypo vitaminosis B, specifically a nicotinic acid deficiency. Much has been written about this sort of case (Condorelli, Siegel, Spies et al. Meyer, Geoffroy et al.) and the effect of nicotinic acid has been noted. This as a rule concerns patients with symptoms of enterocolitis, with alternation between constipation and diarrhea. Achylia is found most often, and now and then the patients complain of a slight burning sensation in the tongue, and the appetite is worse. The complaints may be vague and indefinite, and the patients given a neurasthenic impression. Possibly the onset of the dyspeptic symptoms is sustained by diet, which further accentuates the symptoms, as it sets up a vicious circle due to the vitamin-poor diet. If it is not possible, after careful research, to find another cause for the symptoms' appearance, it indicates a test is necessary to support the diagnosis of hypo vitaminosis B ex juvantibus, to give nicotinic acid or nicotinic acid amide in 300-500 mg tablets daily, supplemented by other components in the B-complex, and otherwise to take care that the patients have an ample and varied diet. This simple therapy often gives hood results in the case mentioned.

It should be pointed out that hypovitaminosis B may appear as a complication with pain in the digestive tract, where the stomach's function is incomplete, for example due to achylia, after stomach operations, or in a condition with constant vomiting, as in hyperemesis gravidarum. In mental patients who refuse to eat, there is a high chance of pellagra developing.

Another area should be mentioned hereafter, where nicotinic acid has been used with success from different points of view. It has been found that with pellagra, porphyrin is excreted in the urine in pathologic quantities, and this porphyrinuria disappears after nicotinic acid administration. This leads to consideration of the possibility of trying therapy with nicotinic acid in another condition where there is porphyrinuria. Good results have been observed in the annoying symptoms of nausea, vomiting, indisposition, and porphyrinuria which appear after X-raying, called radiation sickness (Graham). In addition, it is observed that in sulfonamide poisoning, where in some cases there is porphyrinuria, there is often a marked effect with nicotinic acid, as nausea, vomiting, and cyanosis disappear or decrease sharply, when administration of this

substance can be continued (McGinty, Siegel, Brown et al., Detweiler et al., Cottini).

Porphyrinuria in lead poisoning also disappears with the use of nicotinic acid.

Anemia in premature babies, as well as postinfectious anemias in infants, are treated with good results with nicotinic acid (in some cases with the addition of riboflavin) in 30-50 mg daily injection. It would take us too far afield to enter into an overview of this therapy (Gobell).

In a series of skin diseases, in which, according to some opinions, the effect of light plays a role similar to that in pellagra dermatosis, a good result has also been observed for nicotinic acid. This is valid for lupus erytematodes, erytema exsudativum multiforme, rosacea, acrodynia, and pernicis. One must also consider the previously mentioned vessel-dilating effect of nicotinic acid (Kuhnau, Schoenhoven van Beurden, Peseld).

On the basis of this dilation effect, in many cases patients with angiospastic headache, with or without hypertension, have been treated with good results with 30 mg of nicotinic acid as an injection 3 times a day (Condorelli).

Finally it should be mentioned that in some cases (above), an effect of nicotinic acid on nausea from various causes has been observed, specifically in the worst cancer patients who receive large doses of morphine.

As for the dosage of nicotinic acid for adults, one is on the safe side if 300-500 mg are given per os daily, in doses of 60-100 mg. In case a rapid and strong vascular effect is intended (for example, in angiospastic headache), a subcutaneous injection of 100 mg is appropriate.

References

Bauman, E.: Lihp. [illegible] 1940.
Bauman, W. G. & al.: J.A.M.A. 1940:[illegible]:1085.
Gottschalk, L.: [illegible]
Corson, G. R.: [illegible]
Lurwman, H. K. & al.: Arch.Int.Med. 1940:66:1146.
Graham, W.: J.A.M.A. [illegible]
Gruvroy, W. & al.: Münch.med.Wchrft. 1941:88:180.
Gänzle, P.: Klin.Wchrft. [illegible]
Kühnau, W. W.: Klin.Wchrft. [illegible]:1117.
Meyer, W.: Münch.med.Wchrft. [illegible]:707.
Pessler, K.: Münch.med.Wchrft. 1941:88:1374.
Schoenhoven van Beurden: Nederlandsch Tijdschrift voor Geneeskunde [illegible]:4793.
Sessa, A. K.: J.M.A.Georgia [illegible]:447.
Sure, T. D. & al.: J.A.M.A. [illegible]
[illegible], V. D.: [illegible]

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FÖR PRAXIS

Nikotinsyre og dens terapeutiske anvendelse.

Af

Læge Iversen, København.

Interessen for nikotinsyre og for terapeutiske forsøg med dette stof hænger sammen med den meget hurtigt indtrædende og rent ud forbløffende virkning overfor pellagra.

I Syderstaterne, hvor den endemiske pellagra var meget udbredt, og hvor sygdommen naaede en udviklingsgrad, som vi næsten aldrig ser paa disse breddegrader, betød gennembruddet af nikotinsyren som den manglende faktor en revolution i behandlingen af denne sygdom. Ved tilførsel af nikotinsyre per os, indtraadte der i løbet af faa dage en slørende bedring af disse, ofte dødssyge mennesker tilstand. Diarrhoerne ophørte, stomatitten og glossitten svandt, huden antog atter sit naturlige udseende, psykisk blæsedt patienterne op, begyndte igen at spise, tog paa i vægt, og bedringen skred nu rask fremad.

At en sygdom med en saa kompleks symptomatologi som pellagra kan fuldstændig helbredes ved tilførsel af et enkelt, kemisk veldefineret stof, har naturligvis givet stødet til, at der verden over arbejdes intenst med undersøgelser over dette stofs biologiske virkninger.

Efter en kort oversigt over nikotinsyrens skal de terapeutiske forsøg, der er gjort med den omtales.

Nikotinsyren — eller rettere nikotinsyreamidet, som nikotinsyren i organismen omdannes til — indgaar sammen med aneurin og riboflavin i B-vitaminkomplekset, hertil kommer en del andre stoffer, hvis betydning for den menneskelige patologi endnu ikke er fuldt opklaret. Stoffet fungerer, ligesom aneurin og riboflavin, som byggesten for et af de for det intermediære stofskifte, spec. kulhydratstofskiftet saa vigtige enzymsystemer, i dette tilfælde codehydrogenaserne 1 og 2, der som et led i nedbrydningen afspalter brint fra en række kulhydrater. Disse enzymer findes i enhver celle, hvor der sker en kulhydratnedbrytning, og er en nødvendighed for det normale stofskifte.

Hvis der foreligger et mangelfuldt tilbud af nikotinsyre, kan codehydrogenaserne ikke opbygges, da organismen ikke selv kan syntetisere nikotinsyre, og stofskiftet kompromitteres. De forskellige væv og organsystemers reaktion herpaa manifesterer sig som de sygelige fænomener, der afgiver indikation for behandling med nikotinsyre.

Det fremgaar heraf, at en forøgelse af kulhydratstofskiftet kan udløse latente deficitsymptomer, — man har da ogsaa set pellagrasymptomer opstaa f.ex. ved ensidig glukosetilførsel eller ved andre tilstande med øget forbrænding, f.ex. hos diabetikere, der pludselig stiger med kulhydrat og insulin, ved hyperthyreose, feber, eller graviditet (HYDEBSTRICKER).

Nikotinsyren er et lidet toxisk stof, der meget let resorberes, hvorfor det næsten altid kan gives per os, hvis der ikke netop foreligger tilstande med stadige opkastninger. Ved dyreforsøg paa mus har man vist, at toxiciteten er godt 5,000 gange mindre end nikotinens. En meget almindelig bivirkning, selv efter terapeutiske doser, er en karvidelation paa hoved, hals og overextremiteter, visende sig ved varme og hudestigninger med en let brændende fornemmelse — et forhold, som man ogsaa har udnyttet terapeutisk. Lejlighedsvis kan der opstaa en let brænden og sugen i epigastriet. Respiration, puls, elektrocardiogram og blodtryk paavirkes ikke mærkevædigt. Nikotinsyre virker stimulerende paa ventrikelsekretionen og mavetarmkanalens motilitet. Nikotinsyreamid, der i terapeutisk henseende ellers virker som nikotinsyre, har ikke den omtalte karvirkning. Det skal nævnes, at der fra dansk side er udarbejdet en god og nøjagtig metode til bestemmelse af nikotinsyre i blod og urin (BANDIER).

Blandt de tilfælde der frembyder indikation for behandling med nikotinsyre maa først nævnes pellagra. Det er en sygdom, der ret sjældent ses fuldt udviklet her i landet. Selv om hovedbehandlingen er nikotinsyre (500—1000 mg dgl.), er man nu klar over, at sygdommen sjældent kan opfattes som et rent nikotinsyredeficit, hvorfor behandlingen bør suppleres med de andre komponenter i B-komplekset.

Fuldt saa vigtig som den fuldt udviklede pellagra, hvor diagnosen, paa grund af de markante symptomer, er let at stille, er den store gruppe med ubestemte *symptomer fra fordøjelseskanalen*, der muligvis kan tilskrives en hypovitaminosis B, spec. nikotinsyredeficit. Der er beskrevet mange af den slags tilfælde (CONDORELLI, SIEGEL, SPIES & al., MEYER, GUGGEROY & al.), og virkningen af nikotinsyre har været udmærket. Det drejer sig som regel om patienter med enterokolitiske symptomer med veksien mellem obstipation og diarrhoe. Som oftest finder man achyli, og af og til klager patienterne over en let brændende fornemmelse i tungen, appetiten er dårlig; klagerne kan være vage og ubestemte, og patienterne gør et neurasthenisk indtryk; maaske har vedkommende efter de dyspeptiske symptomers indtræden holdt diæt, hvilket yderligere accentuerer symptomerne, idet der sættes en circulus vitiosus i gang paa grund af den vitaminfattige kost. Hvis det ikke — efter en nøje undersøgelse — er muligt at finde anden aarsag til symptomernes optræden, er det indiceret at prøve at stille diagnosen hypovitaminosis B ex juvantibus, ved at give nikotinsyre eller nikotinsyreamid i tabl. 300—500 mg dgl. evt. suppleret med de andre komponenter i B-komplekset, og iøvrigt sørge for, at patienterne faar en rigelig og varieret kost. Denne simple terapi giver ofte gode resultater i de nævnte tilfælde.

Det skal pointeres, at hypovitaminosis B kan optræde som komplikation ved lidelser i fordøjelseskanalen, hvor ventriklens funktion er ufuldstændig, f.ex. paa grund af achyli, efter ventrikeloperationer, eller ved tilstande med stadige opkastninger, f.ex. hyperemesis gravidarum. Hos sindssyge med spisevægring er der stor chance for udvikling af pellagra.

Der skal herefter nævnes en del andre områader, hvor man med held har anvendt nikotinsyre udfra forskellige

synapunkter. Man har erfaret, at der ved pellagra udskilles porfyrin i urinen i patologiske mængder, denne porfyrinuri svinder efter nikotinsyrebehandl. Dette førte tanken hen paa den mulighed, at forsøge terapi med nikotinsyre ved andre tilstande hvor der er porfyrinuri. Gode resultater er set ved de ubehagelige symptomer, kvalme, opkastninger, utilpashed og porfyrinuri, der opstraader efter røntgenbestraalinger, benævnt *røntgenskister* (Graham). Ligeledes ses ved *gasmaskemiddelforgiftningen*, hvor der i en del tilfælde er porfyrinuri, ofte en udmærket virkning af nikotinsyre, idet kvalme, opkastning og cyanose svinder eller aftager stærkt, saaledes at indgiften af disse stoffer kan fortsættes i tilfælde, hvor man ellers paa grund af kvalme og opkastning maatte sepenere dem (Mc Ginty, Siegel, Brown & al., Detweiler & al., Cottini — og flere andre).

Porfyrinurien ved *blyforgiftning* svinder ogsaa efter nikotinsyre.

Anæmi hos for tidligt fødte børn samt *postinfektiøse anæmier hos spædbørn* er med godt resultat behandlet med nikotinsyre (i nogle tilfælde med tilskud af riboflavin) 30—50 mg dgl. som injection; det vil føre for vidt her at komme ind paa de overvejelser, der fører til denne terapi (Gorell).

Ved en række hudsygdomme, hvor for nogles vedkommende en lymphoavirkning spiller en rolle ligesom ved pellagrodermatitsen, har man set god virkning af nikotinsyren; det gælder for *lupus erythematodes*, *erythema exsudativum multiforme*, *rosacea*, *acrodynia*, og *perniosis*, man man her ogsaa regne med den foremtalte kardilaterende virkning af nikotinsyren (Künnau, Schoonhoven van Beurden, Preold).

Paa grundlag af denne kardilaterende virkning har man i flere tilfælde med godt resultat behandlet patienter med *angiospastiske hovedpineanfald* — med eller uden hypertension — med nikotinsyre 30 mg som injection 3 gange dagligt (Condorelli).

Til slut skal nævnes, at man (forf.) i en del tilfælde har set virkning af nikotinsyre ved *kvalme* af forskellig aarsag, spe. hos meddagne cancerpatienter, der faar store doser morfin.

Hvad angaar doseringen af nikotinsyre til voksne, er man paa den sikre side, hvis man giver 300—500 mg per os dagligt, fordelt i doser paa 60—100 mg. I de tilfælde (f.ex. ved angiospastisk hovedpine) hvor man tilstræber en hurtig og kraftig karvirkning, vil subcutan injection af 100 mg være hensigtsmæssig.

LITTERATUR:

Bandier, E.: Disp. Kbhvn 1940.
Brown, W. H. & al.: J.A.M.A. 1940:*114*:1605.
Condorelli, L.: Med.Klin. 1940:*36*:131.
Cottini, G. B.: Dermatologica 1940:*81*:nr.283.
Detweiler, H. K. & al.: Arch.int.Med. 1940:*66*:1144.
Graham, W.: J.A.M.A. 1939:*113*:664.
Gueffroy, W. & al.: Münch.med.Wchrft. 1941:*88*:159.
Göbell, P.: Klin.Wschrft. 1939:*18*:1319.
Künnau, W. W.: Klin.Wschrft. 1939:*18*:1117.
Meyer, W.: Münch.med.Wchrft. 1941:*88*:707.
Preold, K.: Münch.med.Wchrft. 1941:*88*:1374.
Schoonhoven van Beurden: Nederlandsch Tijdschrift voor Geneeskunde 1940:*84*:4793.
Simon, A. E.: J.M.A.Georgia 1940:*29*:447.
Sebrell, T. D. & al.: J.A.M.A. 1939:*113*:931.
Sydenstricker, V. P.: Arch.int.Med. 1941:*67*:746.

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Nicotinic Acid and the Pellagra Problem

By E. Kodicek

Despite the fact that as early as 1937 nicotinic acid was found, by Elvehjem et al. (1937), to be the anti-pellagra vitamin, the incidence of endemic pellagra has not decreased as much as one would have hoped for. The problem of prevention and cure is clearly economic and sociological in nature and is not only dependent on the scientific "know how". The governing factors are the cost of enrichment or supplementation, the problems of distribution, of re-education of the population to overcome its conservatism in food habits, to overcome opposition or even suspicion towards new or enriched foods, or vitamin supplements. In general an improvement can be expected when the overall standards of living are raised and the economic status of the poorest section of the community is improved. This is nicely demonstrated in the rapid decline in endemic pellagra in the southern regions of the United States. Facing the problem of having more than 200,000 pellagrins and reported deaths exceeding 7,000 in 1929 (Harris, 1941; Sydenstricker, 1958), Public Health Authorities supported dietary measures based on the pioneer work of men like Funk, Osborne, Mendel, Goldberger and his colleagues, Sebrell and others. This was followed, after 1938, by an enrichment policy that introduced nicotinic acid in the diet. The result was a rapid drop of the incidence in pellagra as indicated by the decline of reported deaths from this deficiency to 2133 in 1940 and to only 70 in 1956 (Table 1). (Hundley, 1959).

The decline in the incidence of endemic pellagra in other countries has not kept pace with that in the United States. An exact survey is

Table 1

Total Deaths Reported in the United States from Several Nutritional Causes

	1929*	1935	1940	1945	1949	1956
Pellagra	7350	3543	2133	914	321	70
Beri beri	—	7	63	46	47	25
Scurvy	—	30	26	18	22	7

From HUNDLEY (1959).
* HARRIS (1941).

made difficult because the information is scattered over a great number of reports covering different years and because pellagra, not being a communicable disease and therefore not regularly reported to Health Authorities, is usually surveyed by teams gathered at random in various regions of the world. Table 2 shows the incidence as recorded by MITROVIC et al. (1958). In Europe, Yugoslavia, Roumania and Portugal report the occurrence of endemic pellagra. In Italy, a rapid decline in morbidity has been seen since 1912, due to certain changes in food habits of the affected population. In the province of Venice, there were, however, still 1153 pellagrins in 1938, but pellagra is now no longer a social problem (CALETTI, 1961). Spain experienced about 300,000 cases during the Civil War in 1936–1938. There appear to be regions in the U.S.S.R. where endemic

Table 2

Incidence of Pellagra in Various Countries

	Year	No. of pellagrins
Roumania	1935–1943	84000
Yugoslavia	1955	5800 in one district (70000)
Italy	1878–1912	30000–104000
	1938	1153 in province of Venice*
Spain	1936–1938	300000
Egypt	?	ca. 400000
South America	1916	175000
	1930*	250000

From MITROVIC et al. (1958).
* CALMETT (1941).

pellagra is or was rampant. EFREMOV et al. (1956) report that in 1929 30,000 people suffered from pellagra in West Gruzinsk and in 1930 about 15% of the population in the Senak region were affected. A new increase occurred between 1943 and 1947. However, efficient dietary measures seemed to have eliminated pellagra in West Gruzinsk by 1955.

In Asia, the countries of Asia Minor, Iran, India and China have still a pellagra problem. In Africa,—Egypt, Sudan, Basutoland and Southern Rhodesia are regions where endemic pellagra occurs (SCRIMSHAW, 1959). The majority of countries in Latin America and Puerto Rico report, since 1940, the occurrence of endemic pellagra (DARBY, 1957).

In most instances pellagra is associated with a high consumption of maize together with a diet low in animal protein and leguminous foods. Thus, according to MITROVIC et al. (1958), 90 out of 100 families consumed maize bread in regions of Serbia where endemic pellagra occurred, while none ate maize bread in regions with no pellagra. Where *sporadic* pellagra appeared, only 14 families consumed maize bread (Table 3). There is a seasonal variation in the incidence (Fig. 1). In the northern hemisphere the months of May–June are the worst, while in the Southern hemisphere the same Spring–Summer period of September and October shows the highest number of cases. This distribution may be connected with the amount of sunlight and/or with the eating habits of the inhabitants. In Basutoland, large amounts of maize are consumed during these months.

Table 3

Consumption of Basic Foods by 100 Families in Various Regions of Serbia (May–July 1955)

	Regions		
	No pellagra	Sporadic pellagra	Endemic pellagra
Meats	20–50	13–58	3.3
Dairy products	83	85	80
Potatoes	98	50	13–35
Pulses	85	93	22–51
Wheat bread	100	86	10
Maize bread	—	14	90

From Mitrovic et al. (1958).

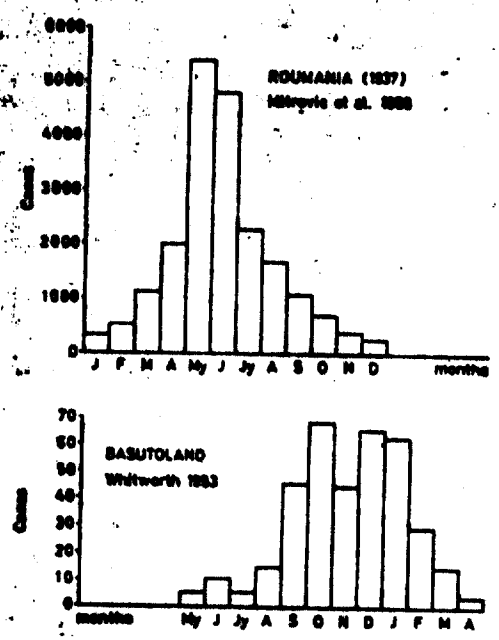

Fig. 1

Seasonal incidence of pellagra in the Nothern and Southern hemisphere, according to Mitrovic et al. (1958) and Whitworth (1953).

The pellagric syndrome often includes a number of secondary deficiencies of the vitamin B-group. The symptoms curable by nicotinic acid are produced by a combination of causes that can be enumerated as follows: low nicotinic acid and tryptophan intake, low protein nutriture combined with an imbalance of amino acids and finally, the occurrence of a bound form of nicotinic acid in cereals, particularly in maize, that makes the vitamin unavailable. The old theory of a toxic factor in maize had been given a new lease of life by the findings of Wooley (1946) that the cereal contains a toxic factor soluble in alkaline chloroform. Pearson, Valenzuela and Van Eys (1958) recently re-investigated this possibility, but were unable to confirm Wooley's results. In any case the non-availability of bound nicotinic acid, which constitutes 97–98% of the vitamin in maize, together with a low intake of tryptophan and an imbalance of amino acids can explain satisfactorily the pellagra-producing effect of maize without recourse to the "toxic factors" hypothesis. A low intake of tryptophan is, however, associated with the appearance of pellagra.

Table 4

Composition of Diets in Areas with Endemic Pellagra
(in % of calorific values)

	Roumania	Yugoslavia
Meats, fish, eggs, dairy products	1.8	6.9
Pulses and potatoes	21.1	2.9
Cereals: maize	61	72
other	16	14

From MITROVIC et al. (1958).

Thus, for instance, the high tryptophan content of millet is responsible for the low incidence of pellagra in populations consuming maize together with millet (MANGAY, PEARSON AND DARBY, 1957).

The contribution of cereals to the intake of nicotinic acid, if the vitamin were available, is substantial, particularly in regions where maize is consumed. Table 4 shows the composition of diets in Eastern Europe in areas with endemic pellagra, as reported by MITROVIC et al. (1958). As much as 61 to 72% of the calories are supplied by maize. This amounts to 600–800 g of maize. FLORES (1961) has recently given values for the average daily consumption of foods in areas of Central America (Table 5). Her figures agree well with those tabulated by a report of the Food and Agriculture Organization of the United Nations (1953). It can be seen that as much as 500 g maize products

Table 5

Average Daily Consumption of Certain Foods in Rural Areas of Central America

	Guatemala	Nicaragua	Costa Rica	Panama
Meats, fish, eggs, dairy products (g)	48	352	138	138
Pulses (g)	58	85	64	54
Cereals (g)	494 (Tortillas)	182 (Rice)	250	189 (Rice)
Nicotinic acid (mg)	12.2	9.5	6.9	10.2
Contribution from cereals	41%	19%	36%	19%
from pulses	8%	14%	15%	9%
Calories	2243	1623	1822	1927

From Pagnan (1961).

are consumed daily by one person in Guatemala. In terms of nicotinic acid intake, this amounts to 41% of the 12.2 mg consumed. Since the maize products were mainly *tortilla*, an alkali-treated maize, the bound nicotinic had been liberated and supplemented the otherwise meagre intake of nicotinic acid. In Nicaragua and Panama, the staple food is rice, but here the contribution to the available nicotinic acid supply would be nil, since rice seems to have its nicotinic acid also in bound form. However, the potential contribution by rice is small (19%), but it is compensated by its high tryptophan content and the larger amounts of meat, eggs and dairy products eaten in these areas.

It may be pointed out that pulses add a significant amount of nicotinic acid to the dietary intake (8–15%), since their nicotinic acid is free and fully available (KODICEK, 1951a). The contribution by leguminous vegetables which has been emphasized by SQUIBB et al. (1959), is however inferior to that of maize, if in the latter the vitamin is made available by treatment with lime-water, as in *tortilla*.

It would thus appear that a significantly large amount of available nicotinic acid could be supplied by *tortilla*, which may contribute as much as 80% of the calories of the rural Mexican diet (ANDERSON et al., 1948). This contribution of *tortilla* may be an important factor in the low incidence of pellagra in Mexico as has been originally pointed out by LAGUNA AND CARPENTER (1951). There is, however, the possibility that some "unconsidered trifles in the diet" (DRUMMOND AND MORAN, 1944), such as beverages, might add to the supply of

Table 6

Nicotinic Acid Content of Beverages
(KODICEK AND WILSON, 1959)

Beverage*	Nicotinic acid (mg/100 ml) Total	Available
Pulque	0.43	0.40
Coffee	0.63	0.63
Kaffir beer (pito)	0.34	0.20
Beer (Guinness)	0.87	0

* Pulque, from Mexico, 3% solids, fermented sap of Agave tree.
Pito, native Kaffir beer, freshly fermented from maize.
Beer, Guinness, 5.8% solids, tied by paper chromatographic assay all the nicotinic acid in bound form. The nicotinic acid content of coffee was calculated for an extract of 5 g coffee beans in 100 ml.

available nicotinic acid (Table 6). Thus *pulque*, a native Mexican drink, might supply as much as 4 mg/l, (KODICEK AND WILSON, 1959). Coffee is also a good source of available nicotinic acid (KODICEK, 1942; GOLDSMITH et al., 1959) and it has become a staple beverage in Central America (FLORES, 1961; BRESSANI AND NAVARRETE, 1959). Native Kaffir beer, drunk in Nigeria, on the other hand, has only a portion of its nicotinic acid free, presumably the part derived from the yeast in the freshly fermented brew. European beer has the vitamin in unavailable, bound form.

It is evident that the concept of a bound, unavailable form of nicotinic acids adds to the complexity of the pellagra problem, but it explains a number of facts which so far were puzzling the expert, for instance, the apparently high intake of nicotinic acid in some pellagric regions. The non-availability of the bound form explains this finding and emphasizes that the *total* nicotinic acid as determined chemically or even microbiologically is no criterion of the amount of the vitamin utilized by the organism. What then is the evidence for the existence of a bound form of nicotinic acid present in cereals and not available to mammals, birds and microorganisms?

Niacytin, the bound form of nicotinic acid

The occurrence of a bound form of nicotinic acid in cereal products was postulated about 20 years ago when aqueous and mild acid extracts of cereal grains were found by chemical means to contain little free nicotinic acid, whereas extracts of alkali-treated grains were good sources of the vitamin (KODICEK, 1940). Since then extensive studies have been made in our laboratory that showed that almost all the nicotinic in maize and other cereals is present in a bound form unavailable to the rat and pig and can be rendered available by hydrolysis with sodium hydroxide or with lime-water (CHAUDHURI AND KODICEK, 1950; KODICEK, 1951b; KODICEK, BRADDE, KON AND MITCHELL, 1956, 1959; KODICEK AND WILSON, 1959; KODICEK, 1960; CARPENTER, KODICEK AND WILSON, 1960; CHAUDHURI AND KODICEK, 1960.) These observations have been confirmed and extended to the dog, chick and duck (HARPER, PUNEKAR AND ELVEHJEM, 1958; LAGUNA AND CARPENTER, 1951; MASSIEU et al., 1956; PEARSON et al., 1957; SQUIBB et al., 1959; McDANIEL AND HUNDLEY, 1958; KREHL, ELVEHJEM AND STRONG, 1944; COATES et al., 1952; HEUSER AND SCOTT, 1953).

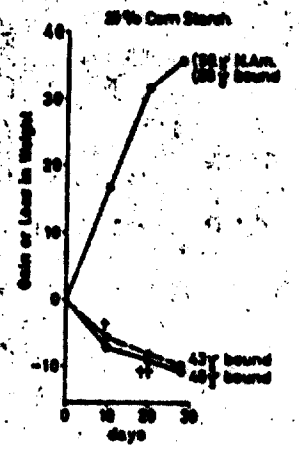

Fig. 4

Mean growth-curves of rats given unhydrolysed and NaOH-hydrolysed corn starch (Kodicek, 1960).

digestive gastric juices, obtained from human subjects also had no effect.

It became evident that the alkaline treatment affected beneficially material contained in bran. We assumed that the alkali-sensitive material was the bound form of nicotinic acid which is concentrated in this portion of the grain, but could not entirely rule out an effect of alkali on the protein moiety. An unexpected finding helped us at this stage. We obtained a batch of commercial zein (Glaxo Ltd.) that contained as a contaminant 100 μg bound nicotinic acid/g. Alkaline hydrolysis of this contaminated protein produced a pellagra-curative material while digestion of pure zein, even when fortified by five amino acids to correct the deficient protein (Kodicek, 1951 b, 1960) was ineffective. Fig. 5 shows a typical result. That a correction of an amino acid imbalance by alkaline hydrolysis was not responsible for the curative effect of alkali-treated maize was confirmed by the studies of Harper et al. (1958), and of Pearson et al. (1957).

There were disquieting reports that not all laboratories that attempted to reproduce the effect of lime-water treatment of maize, were successful. We have, therefore, re-investigated the lime-water procedure in detail in search of such differences as might lead to discrepant results. Mexican *tortilla* prepared by the original method of Castroviejo et al. (1945) was compared with a commercial prepara-

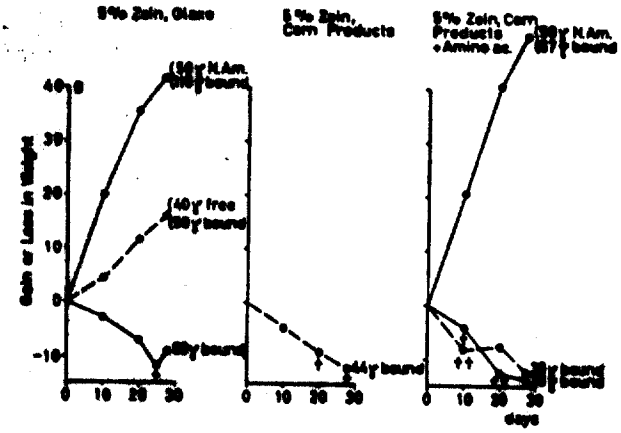

Fig. 5

Mean growth curves of rats given unhydrolysed and hydrolysed zein. Zein (Glaxo) contained 100 μg bound nicotinic acid as contaminant (KODICEK, 1951b).

tion *(masa harina)* of The Quaker Oats Co. of Chicago. The biological results are shown in Fig. 6. It was evident that while the Mexican *tortilla* cured the deficiency, the commercial sample showed only small curative properties (KODICEK AND WILSON, 1959). Further investigation revealed that the commercial sample had little free nicotinic acid. This was due to the way in which the *masa harina*

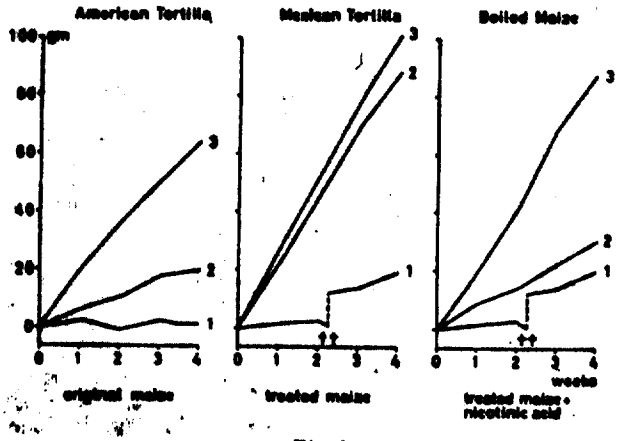

Fig. 6

Mean growth curves of rats given various preparations of *tortilla* or maize boiled in water for 5 h. The maize preparations constituted 40% of the diet (KODICEK AND WILSON, 1959; CARPENTER et al., 1960).

had been prepared. We then re-investigated the various stages of preparation of *tortilla* and found that the soaking and subsequent boiling of maize grains in 1% lime water liberated only partially the bound nicotinic acid and a complete liberation occurred only if the resulting alkaline *masa* was baked on girdles to prepare the *tortilla* cakes. The latter step was omitted in the commercial preparation and the alkali had been washed out to suit the taste of the American public.

PEARSON et al. (1957) reported that boiling maize for 4 h with water alone releases nicotinic acid from its bound form. This apparent instability of the bound form in aqueous solutions would tend to

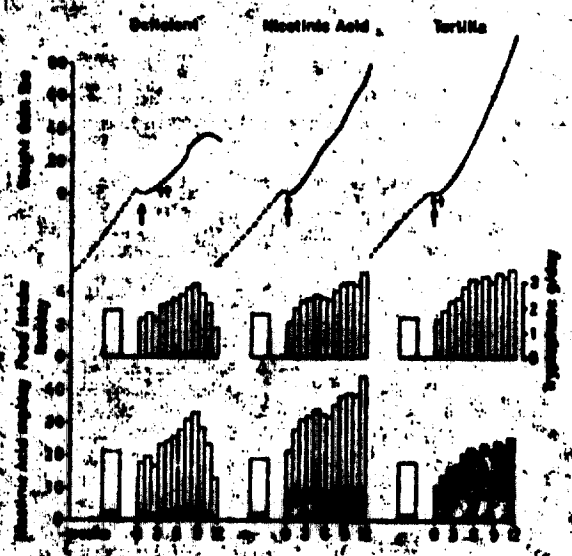

Fig. 7

Mean growth curves and daily intake of food, tryptophan and nicotinic acid of pigs deficient in nicotinic acid given various treatments for 10–12 weeks (reproduced from Kopeczik et al., 1959). Deficient control pigs (two pigs died); nicotinic acid group (pigs given 6 mg nicotinic acid daily; one pig died on 8th day of experiment proper); *tortilla* group (pigs given 79% of the diet as *tortilla*; two pigs died on last day of preliminary period); . . . preliminary deficiency period; —, experiment proper; A, beginning of experiment proper; +, died. Wide columns, mean daily intake of food, tryptophan or nicotinic acid for the whole preliminary period; narrow columns, mean daily intake during experiment proper calculated for periods of 1 week. Top columns, intake of food (lb/day) and of tryptophan (g/day); lower columns, intake of total nicotinic acid (mg/day); dark areas, free, available nicotinic acid (mg/day).

(reprinted by permission of the authors and the British Journal of Nutrition from Kopeczik et al. (1959) Brit. J. Nutr. 13, 363).

Table 7

Nicotinic Acid in Liver of Pigs

Group	Nicotinic acid µg/g
Deficient	66.2 ± 9.19
Nicotinic acid supplemented	90.1 ± 5.54
Tortilla	109.0 ± 1.33

KODICEK et al. (1959).

militate against the importance of lime-water treatment as an efficient pellagra-preventive measure. HARPER et al. (1958) and our laboratory (CARPENTER et al., 1960) were unable to confirm this finding (Fig. 6). Boiling with water for 1 h did not result in any detectable release of nicotinic acid and even after 5 h only about 14% of nicotinic acid was released from its bound form.

All these experiments were done with rats as the test animal. In view of the similarity of the nicotinic acid metabolism of the pig to that of man, experiments on the pig were undertaken in the hope that they might throw light on conditions in man (KODICEK et al., 1956, 1959). The results of these experiments confirmed the findings obtained with rats (Fig. 7). The curative effect depended on the degree of release of nicotinic acid from its bound form. Analyses of livers of the pigs showed that animals given a *tortilla* diet had as much or more nicotinic acid in their liver stores than pigs given a supplement of nicotinic acid (Table 7).

Isolation and purification of niacytin

We have succeeded in purifying the bound form of nicotinic acid contained in wheat bran and obtained a preparation homogenous by various measurements including electrophoretic studies and counter-current dialysis (KODICEK AND WILSON, 1960). The purity of the product is about 3–4 times greater than that described by DAS AND GUHA (1960). Our preparation contained the following components in per cent: nicotinic acid, 5; an aromatic amine, 5; glucose, 48.5; xylose, 8; arabinose, 4; phenolic esters (sinapic and ferulic acids), 27; and protein impurity, 2. It had a molecular weight of about 2400 based on the empirical formula and niacin content. Partial hydrolysis gave a number of fragments of the molecule of niacytin.

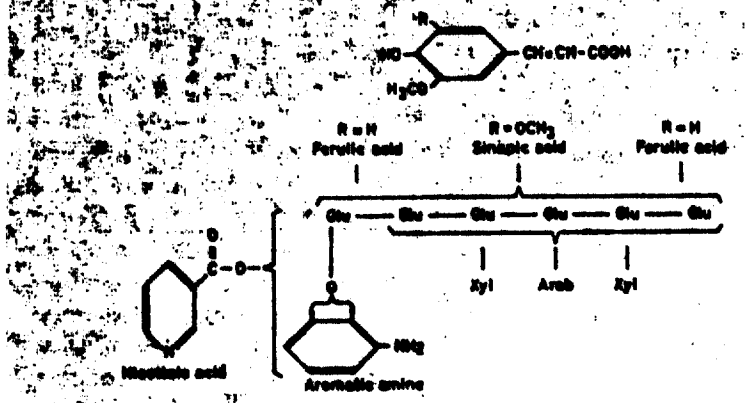

Fig. 8

Tentative structure of niacytin (bound nicotinic acid) (Kodicek and Wilson, 1960).

They were identified and led us to the tentative formula shown in Fig. 8. It can be seen that niacytin appears to contain 6 molecules of glucose, possibly in β 1:4 linkages, to which are attached two molecules of xylose and one molecule of arabinose, two ferulic and one sinapic acid molecule. On the first glucose, nicotinic acid appears to be linked by an ester bond and to the same glucose molecule appears to be attached an, as yet unidentified, aromatic amine. This latter chemical grouping may be responsible for the unavailability of the nicotinic acid. We have obtained a fragment by partial hydrolysis with *N*-HCl composed only of nicotinic acid, aromatic amine and two molecules of glucose. Even this relatively simple compound could not substitute as a source of nicotinic acid for *Lactobacillus casei*.

Implications for human nutrition

It remains for me to summarize the present status of our knowledge as far as they may apply to man. I can do no better than quote what we have said previously (Kodicek et al., 1956):

(1) If bound nicotinic acid is not available to man, the factor that would determine the pellagra-preventive potency of a cereal would be its tryptophan content, and possibly its amino-acid contribution to the balance of amino-acids in the whole diet. Thus cereals rich in tryptophan, such as wheat, rice, barley and rye, would owe

their nicotinic acid sparing activity to their tryptophan content and balance of amino-acids, and not to their bound nicotinic acid which is not available. Maize would be pellagragenic because of its lack of tryptophan and because of its specific amino-acid composition. These defects would not be compensated by its relatively high content of nicotinic acid, since this is present in an unavailable, bound form. There is therefore no need to postulate a toxic factor in maize to explain its pellagragenic properties. These considerations would explain the high incidence of pellagra on certain maize diets and the virtual absence of deficiency on rice diets; the reason for this difference was not explainable on the basis of their respective nicotinic acid contents, the maize diets being apparently richer in the vitamin than the rice diet (AYKROYD AND SWAMINATHAN, 1940). If, however, the nicotinic acid were not available in either cereal, the beneficial effect of the rice diet would doubtless be due to its higher tryptophan content.

(2) Attempts to breed maize with a high nicotinic acid content (RICHEY AND DAWSON, 1948, 1951; TEAS AND NEWTON, 1951; WILLIAMS, 1950; ANONYMOUS, 1950) are unlikely to lead to an improved nutritive value, since the increase would presumably also be in the bound form. A better way of enrichment is the addition of nicotinic acid (WILLIAMS, 1950). Alkali treatment, which liberates the bound nicotinic acid is a tempting possibility for 'enrichment' of cereals, particularly for countries where home-grown maize is consumed and where addition of nicotinic acid presents practical difficulties. Lime-water treatment, as practised in Mexico, is a possible way of preparation. Treatment with sodium bicarbonate will also liberate the niacytin, but the amount of the alkali that has to be used, makes the maize preparation unpalatable.

(3) The usual estimates of the nicotinic acid requirement of man and animals are based on the total nicotinic acid intake that includes the nicotinic acid present in cereals, which supply about 30–50% of the total intake. For instance, in Great Britain in 1957 (Ministry of Agriculture, Fisheries and Food; National Survey Committee, 1959) the daily intake of nicotinic acid was 13.8 mg/head. This figure includes the unavailable niacytin present in cereals, which contributes 17% of the daily intake. Since potatoes may also have their nicotinic acid in bound form, a further 15% of the daily intake may not be available to the organism. Thus the total consumption of the *biologically active* vitamin amounts to about 9 mg/day. An esti-

state of requirement based on the *total nicotinic acid* intake, a portion of which is unavailable, is too high and should be reduced (Braude et al., 1955). A correct estimate may be of particular importance in assessing the amount of nicotinic acid to be added to cereals in an 'artificial enrichment' policy.

Summary

Although nicotinic acid had been known for a long time as the anti-pellagra vitamin, pellagra still occurs in many countries of the world. The problem of prevention and cure is clearly economic and sociological in nature. In most instances the occurrence of pellagra is associated with a high consumption of maize. The pellagra syndrome includes a number of secondary deficiency diseases of the vitamin-B group. The symptoms curable by nicotinic acid are produced by a combination of causes, such as by a low nicotinic acid and tryptophan intake, by a low protein nutriture combined with an imbalance of amino acids and finally by the occurrence of a bound form of nicotinic acid in cereals, particularly in maize, that makes the vitamin unavailable. This bound form of nicotinic acid, called «niacytin», has now been purified and its constitution partially elucidated. On treatment of maize or other cereals with alkali, nicotinic acid can be liberated from niacytin and made fully available as a pellagra-preventive factor. This procedure has been used for a long time in Mexico, where lime-water treated maize in the form of *tortilla* is being consumed and where the incidence of pellagra is very low.

REFERENCES

Anderson, R. K.; Cravó, J.; Robinson, W. D.; Serrano, G. and Payne, G. C.: Nutrition appraisals in Mexico. Amer. J. publ. Hlth. *38:* 1126–1135 (1948).

Anonymous: Improvement of nutritive value of corn by plant breeding and selection. Nutr. Rev. *8:* 241–243 (1950).

Ayyeroyd, W. R. and Swaminathan, M.: The nicotinic acid content of cereals and pellagra. Indian J. Med. Res. *27:* 667–677 (1940).

Braude, R.; Kon, S. K.; Mitchell, K. G. and Kodicek, E.: Maize and pellagra. Lancet *269:* 898–899 (1955).

Brenani, K. and Navarrete, D. A.: Niacin content of coffee in Central America. Food Res. *24:* 344–351 (1959).

Caletti, G.: Experimental and clinical researches in pathogenesis and therapeutics of human pellagra. Proc. 3rd Internat. Congr. Dietetics, p. 218–219 (1961).

CARPENTER, K. J.; KODICEK, E. AND WILSON, P. W.: The availability of bound nicotinic acid to the rat. 3. The effect of boiling maize in water. Brit. J. Nutr. *14:* 25–34 (1960).

CHAUDHURI, D. K. AND KODICEK, E.: The biological activity for the rat of a bound form of nicotinic acid present in bran. Biochem. J. *47:* xxxiv (1950).

CHAUDHURI, D. K. AND KODICEK, E.: The availability of bound nicotinic acid to the rat. 4. The effect of treating wheat, rice and barley brans and a purified preparation of bound nicotinic acid with sodium hydroxide. Brit. J. Nutr. *14:* 35–42 (1960).

COATES, M. E.; FORD, J. E.; HARRISON, G. F.; KON, S. K.; SHEPHEARD, E. E. AND WILBY, F. W.: The use of chicks for the biological assay of members of the vitamin B complex. 2. Tests on natural materials and comparison with microbiological and other assays. Brit. J. Nutr. *6:* 75–89 (1952).

CRAVIOTO, R. O.; ANDERSON, R. K.; LOCKHART, E. E.; MIRANDA, F. DE P. AND HARRIS, R. S.: Nutritive value of the Mexican tortilla. Science *102:* 91–93 (1945).

DARBY, W. J.: Nutritional deficiency diseases today. J. amer. Dietetic Ass. *33:* 17–21 (1957).

DAS, M. L. AND GUHA, B. C.: Isolation and chemical characterization of bound niacin (niacinogen) in cereal grains. J. biol. Chem. *235:* 2971–2976 (1960).

DRUMMOND, J. C. AND MORAN, T.: Unconsidered trifles in our diet. Nature, Lond. *153:* 99–100 (1944).

EFREMOV, V. V. AND BERULAVA, I. T.: Elimination of pellagra in Gruzinsk SSR. Vop. Pitan. *15:* 26–31 (1956).

ELVEHJEM, C. A.; MADDEN, R. J.; STRONG, F. M. AND WOOLLEY, D. W.: Relation of nicotinic acid and nicotinic acid amide to canine black tongue. J. amer. Chem. Soc. *59:* 1767 (1937).

FLORES, M.: Food patterns in Central America and Panama. Proc. 3rd Internat. Congr. Dietetics, p. 23–27.

Food and Agriculture Organization of the United Nations: Maize and maize diets, FAO Nutritional Studies, No 9, Rome (1953).

GOLDSMITH, G. A.: Vitamins of the B complex. Food. The Yearbook of Agriculture, p. 139–149 (U.S. Dept. of Agriculture, Washington, D.C. 1959).

GOLDSMITH, G. A.; MILLER, O. N.; UNGLAUB, W. G. AND KERCHEVAL, K.: Human studies of biological availability of niacin in coffee. Proc. Soc. exp. Biol. *102:* 579–580 (1959).

HARPER, A. E.; PUNEKAR, B. D. AND ELVEHJEM, C. A.: Effect of alkali treatment on the availability of niacin and amino acids in maize. J. Nutr. *66:* 163–172 (1958).

HARRIS, L. J. AND KODICEK, E.: Quantitative studies and dose-response curves in nicotinamide deficiency in rats. Brit. J. Nutr. *4:* xiii (1950).

HARRIS, S.: Clinical Pellagra, p. 35 (Henry Kimpton, London 1941).

HAUSER, G. F. AND SCOTT, M. L.: Studies in duck nutrition. 5. Bowed legs in ducks, a nutritional disorder. Poult. Sci. *32:* 137–143 (1953).

HAWDLEY, J. M.: Statistics of health. Food. The Yearbook of Agriculture, p. 175–180 (U.S. Dept. of Agriculture, Washington, D.C. 1959).

KODICEK, E.: Estimation of nicotinic acid in animal tissues, blood and certain foodstuffs. 1. Method. 2. Application. Biochem. J. *34:* 712–723; 724–735.

KODICEK, E.: Biochemical studies on nicotinic acid. Ph. D. Thesis: University of Cambridge (1947).

KODICEK, E.: Biochemistry. 3. Nicotinic acid. Ann. Rep. Chem. Soc. *48:* 276 (1951a).

KODICEK, E.: The biological activity for the rat of the bound form of nicotinic acid present in maize. Biochem. J. *48:* viii (1951b).

KODICEK, E.: The availability of bound nicotinic acid to the rat. 2. The effect of treating maize and other materials with sodium hydroxide. Brit. J. Nutr. *14:* 13–24 (1960).

KODICEK, E.; BRAUDE, R.; KON, S. K. AND MITCHELL, K. G.: The effect of alkaline hydrolysis of maize on the availability of its nicotinic acid to the pig. Brit. J. Nutr. *10:* 51–67 (1956).

KODICEK, E.; BRAUDE, R.; KON, S. K. AND MITCHELL, K. G.: The availability to pigs of nicotinic acid in *tortilla* baked from maize treated with lime-water. Brit J. Nutr. *13:* 363–384 (1959).

KODICEK, E. AND WILSON, P. W.: The availability of bound nicotinic acid to the rat. 1. The effect of lime-water treatment of maize and subsequent baking into *tortilla*. Brit. J. Nutr. *13:* 418–430 (1959).

KODICEK, E. AND WILSON, P. W.: The isolation of niacytin, the bound form of nicotinic acid. Biochem. J. *76:* 27 P. (1960).

KARRER, W. A.; ELVEHJEM, C. A. AND STRONG, F. M.: The biological activity of a precursor of nicotinic acid in cereal products. J. biol. Chem. *156:* 13–19 (1944).

LAGUNA, J. AND CARPENTER, K. J.: Raw versus processed corn in niacindeficient diets. J. Nutr. *45:* 21–28 (1951).

MANGAY, A. S.; PEARSON, W. N. AND DARBY, W. J.: Millet *(Setaria italica)*: its amino acid and niacin content and supplementary nutritive value for corn (maize). J. Nutr. *62:* 377–393 (1957).

MASSIEU, H. G.; CRAVIOTO, D. Y.; CRAVIOTO, R. O.; GUZMAN, G. J. AND SUAREZ SOTO, M. DE L.: New findings on the effect of maize and tortillas on the growth of rats fed on diets low in tryptophan and nicotinic acid. Ciencia, Mex. *16:* 24–30 (1956).

MCDANIEL, E. G. AND HUNDLEY, J. M.: Alkali-treated corn and niacin deficiency. Fed. Proc. *17:* 404 (1958).

Ministry of Agriculture, Fisheries and Food: National Food Survey Committee (1959). Domestic Food Consumption and Expenditure, 1957. London: H.M. Stationary Office.

MITROVIC, M.; ATANACKOVIC, V.; YOVANOVIC, V.; PETROVIC, D. AND CLAUDIAN, J.: Pellagra. Nutrition *1:* 1–12 (1958).

PEARSON, W. N.; STEINFEL, S. J.; VALENZUELA, J. S.; UTLEY, M. H. AND DARBY, W. J.: The influence of cooked is raw maize on the growth of rats receiving a 9% niacin ratio. J. Nutr. *62:* 445–463 (1957).

PEARSON, W. N.; VALENZUELA, J. S. AND VAN ETS, J.: The influence of dietary fat upon the niacin requirement of the mouse. J. Nutr. *66:* 277–290 (1958).

RICHEY, F. D. AND DAWSON, R. F.: Possibilities and methods of breeding high-niacin corn. Plant Physiol. *23:* 238–254 (1948).

RICHEY, F. D. AND DAWSON, R. F.: Inheritance of niacin in corn. Plant Physiol. *26:* 475–483 (1951).

SCRIMSHAW, N. S.: Progress in solving world nutrition problems. J. amer. Dietetic Ass. *65:* 441–448 (1959).

SQUIBB, R. L.; BRAHAM, J. E.; ARROYAVE, G. AND SCRIMSHAW, N. S.: A comparison of the effect of raw corn and tortillas (lime-treated corn) with niacin, tryptophan or beans on the growth and muscle niacin of rats. J. Nutr. *37:* 351–361 (1959).

SYDENSTRICKER, V. P.: The history of pellagra, its recognition as a disorder of nutrition and its conquest. Amer. J. Clin. Nutrit. *6:* 409–414 (1958).

TEAS, H. J. AND NEWTON, A. C.: Tryptophan, niacin, and indoleacetic acid in several endosperm mutants and standard lines of maize. Plant Physiol. *26:* 494–501 (1951).

WHITWORTH, C. W.: Seasonal incidence of pellagra in Basutoland. Ann. Med. Rep., Basutoland (1953).

WILLIAMS, R. R.: Progress in cereal enrichment. Int. Z. Vitaminforsch. *22:* 35–44 (1950).

WOOLLEY, D. W.: The occurrence of a "pellagragenic" agent in corn. J. biol. Chem. *163:* 773–774 (1946).

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Brief Communications

Nicotinic Acid-6-^{14}C Metabolism in Man[1,2]

K. W. Lee, ph.d.,[3] D. M. Abelson, m.d.,[4] and Y. O. Kwon, m.s.[5]

Nicotinic acid metabolites have been identified in urine and tissues of several species (1). This report describes the fate of a tracer dose of nicotinic acid in man, using the ring-labeled compound to avoid possible decarboxylation (2).

A normal male subject weighing 71.4 kg was given 9.3 μc (0.04 mg) of nicotinic acid-6-^{14}C (Nuclear Chicago Corp.; >97% pure; specific activity 26.2 mc/mmole) intravenously. Blood was drawn six times the 1st hour, then at hourly intervals. Plasma and red cell fractions were separated. All urine was collected for 19 days. Aliquots of urine and plasma were counted in a Packard liquid scintillation counter according to the method of Solomon et al. (3), except that plasma was used instead of serum. Half-milliliter portions of trichloroacetic acid (TCA) red cell extracts were counted in 15 ml of Bray's solution (4). Counting efficiency and quenching were determined by internal standardization and the counts converted to disintegrations per minute (dpm).

Figure 1 shows the radioactivity in the plasma and red cell extracts. Radioactivity in the plasma 1.5 min after the injection was only 337 dpm/ml, and after 12 min it was too low to measure. On the other hand, the radioactivity in the red cell fraction was 4,960 dpm/ml 1.5 min after injection. Assuming a red cell mass of 30 ml/kg, 50% of the injected dose was in the red cells 1.5 min after injection. Radioactivity in the red cell fraction dropped rapidly to 2,900 dpm/ml at 8 min after which it leveled off and remained nearly constant for the next few hours. Six hours after injection the radioactivity was 2,000 dpm/ml.

Figure 2 shows the urinary excretion rate of the radioactive metabolites. This is characterized by three stages: an early sudden drop during the first 12 hr (from 186,000 dpm/hr during the 1st hour to less than 25,000 dpm/hr for the 8- to 12-hr interval), a period of fluctuation between

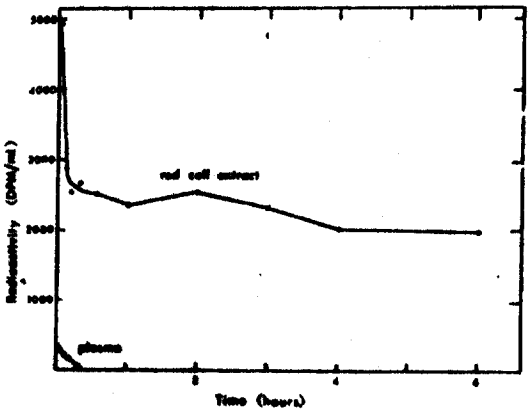

Fig. 1. Radioactivity in blood following intravenous nicotinic acid-6-^{14}C.

[1] From the Department of Internal Medicine, Graduate Hospital, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Supported by a grant from the John A. Hartford Foundation.

[3] Research Investigator in Medicine. [4] Associate Professor of Medicine. [5] Technician.

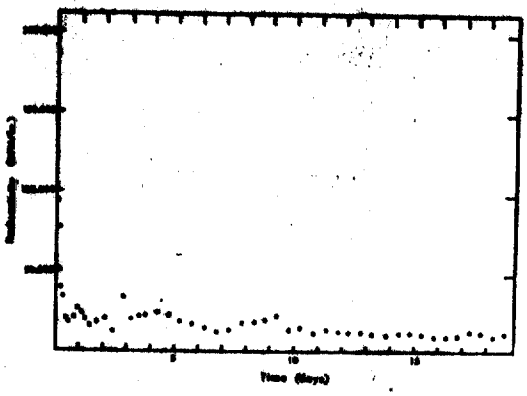

FIG. 2. Urinary excretion of nicotinic acid-6-^{14}C metabolites.

the 1st and 11th day, and a final phase of constant excretion from the 11th day until the end of the experiment (19 days).

Figure 3 shows the cumulative urinary excretion of nicotinic acid metabolites. Between the 1st and 5th day 5% of the injected dose was excreted each day. After the 10th day only 1.5% of the injected dose was excreted daily. After 19 days 38% of the injected dose had been recovered as urinary metabolites.

Aliquots of urine were partitioned as follows: *1*) alkaline extract. The urine was made alkaline and extracted with chloroform-isopropanol (19:1), which is known to remove nicotinamide and the pyridones from alkaline urine, as well as from plasma (5); *2*) acid extract. The aqueous layer was now acidified and reextracted, preliminary experiments having shown

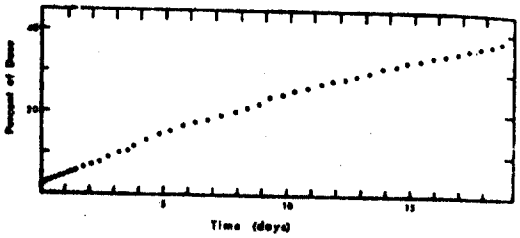

FIG. 3. Cumulative urinary excretion of nicotinic acid-6-^{14}C metabolites. The total counts excreted during each time interval were added to those of the previous intervals and expressed as a percentage of the injected dose.

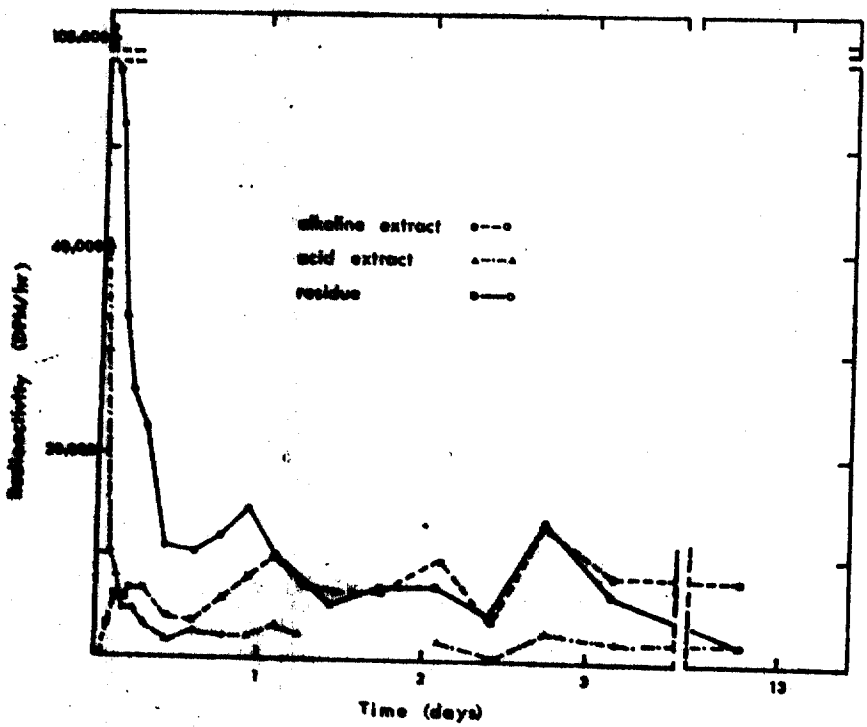

FIG. 4. Distribution of radioactivity.

that chloroform-isopropanol removes about 90% of nicotinic acid from an acidified solution; and 3) residue. The final aqueous layer, or residue, was counted. The alkaline and acid extracts were flash evaporated, taken up in water, washed with chloroform, and also counted.

Figure 4 shows the distribution of radioactivity in the three extracts. The sum of the radioactivity in the three fractions was 90% (average of 16 determinations) of the counts in the original aliquot. In the first few hours following the injection most of the radioactivity was found in the residue and very little in the alkaline extract. By the 12th day, however, most of the radioactivity was in the alkaline extract. The radioactive constituents of these three major fractions are presently being studied.

The biphasic excretion pattern shown in Fig. 4 suggests that tracer doses of nicotinic acid are metabolized in man by at least two distinct routes. We propose that nicotinic acid is first taken up by red cells and rapidly transported to tissue cells. It then enters one of two metabolic pools. One pool cycles through pyridine nucleotides (6). In the other (which may or may not involve pyridine nucleotides) metabolites are rapidly formed, released, and excreted.

REFERENCES

1. Petrack, B., P. Greengard and H. Kalinsky. On the relative efficacy of nicotinamide and nicotinic acid as precursors of nicotinamide adenine dinucleotide. *J. Biol. Chem.* 241: 2867, 1966.
2. Leifer, E., L. J. Roth, D. S. Hogness and M. H. Cohen. The metabolism of radioactive nicotinic acid and nicotinamide. *J. Biol. Chem.* 190: 595, 1951.
3. Solomon, L. M., H. E. Wentzel and E. Tulsky. The physiological disposition of C^{14}-norepinephrine in patients with atopic dermatitis and other dermatoses. *J. Invest. Dermatol.* 43: 193, 1964.
4. Bray, G. A. A simple efficient liquid scintillator for counting aqueous solutions in a liquid scintillation counter. *Anal. Biochem.* 1: 279, 1960.
5. Abelson, D. M., and A. Boyle. Spectrophotometric determination of plasma pyridones in man following nicotinamide administration. *Clin. Chim. Acta* 14: 483, 1966.
6. Gholson, R. K. The pyridine nucleotide cycle. *Nature* 212: 933, 1966.

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METABOLISM OF NICOTINIC ACID AND NICOTINAMIDE IN RATS

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Oklahoma State University, 1969

Adviser: Robert K. Gholson

SCOPE AND METHOD OF STUDY: To study the metabolites of nicotinic acid and nicotinamide in the liver and the urine of normal and hypophysectomized rats following the intraportal and intraperitoneal injection of nicotinic acid and nicotinamide.

FINDINGS AND CONCLUSION: Nicotinic acid was rapidly incorporated into nicotinamide adenine dinucleotide (NAD^+) following the intraportal injection of nicotinic acid (75 mμ moles, and 210 mμ moles). The newly formed NAD^+ was also rapidly degraded to nicotinamide by NADase. The nicotinamide formed from degradation of NAD^+ increased with increasing dosage of nicotinic acid. This suggests that NADase plays a role in control of NAD^+ concentration in liver. Nicotinamide was rapidly incorporated into N'-methylnicotinamide following intraportal injection of nicotinamide (210 mμ moles) and then rapidly excreted from the liver. Only a small amount of nicotinamide was incorporated into NAD^+ in both normal and hypophysectomized rats. The normal rats excreted more N'-methylnicotinamide and nicotinuric acid in the urine following intraperitoneal injection of nicotinic acid or nicotinamide, also the rate of excretion of the injected vitamins in normal rats was greater than that in hypophysectomized rats. This finding provides an explanation for the increase in the magnitude and duration of the elevation of hepatic NAD^+ in hypophysectomized (as compared to normal) rats following the administration of of nicotinamide and nicotinic acid. Two new urinary metabolites of nicotinamide were isolated and identified by mass, ultraviolet, and infrared spectrometric methods as 6-hydroxynicotinic acid and 6-hydroxynicotinamide. Further study of the metabolism of nicotinamide and nicotinic acid in germ free rats demonstrated that these new metabolites are formed in the rats' tissue rather than by the intestinal flora.

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Isolation and Identification of Two New Nicotinamide Metabolites*

(Received for publication, Feburary 17, 1969)

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SUMMARY

Two previously unreported metabolites of nicotinamide have been discovered as urinary excretion products of rats following intraperitoneal injection of nicotinamide-7-^{14}C or nicotinic acid-7-^{14}C. These compounds have been identified as 6-hydroxynicotinamide and 6-hydroxynicotinic acid by comparison of ultraviolet, infrared, and mass spectra and behavior on chromatography and electrophoresis with that of the authentic compounds. These compounds are also formed from nicotinamide and nicotinic acid by germ-free rats, indicating that they are produced in the tissues rather than by the intestinal flora. From 0.6 to 1.2% of the injected dose of either nicotinic acid or nicotinamide is excreted as 6-hydroxynicotinic acid and 6-hydroxynicotinamide.

The urinary metabolites excreted by rats and mice following injection of nicotinic acid-^{14}C and nicotinamide-^{14}C have been studied by several groups of investigators (1–6). In the most recent studies in mice (4) and rats (5, 6) five urinary metabolites of nicotinamide-7-^{14}C and nicotinic acid-7-^{14}C have been reported: $N^{\prime}$-methylnicotinamide, nicotinuric acid, nicotinamide-N-oxide, $N^{\prime}$-methyl-2-pyridone-5-carboxamide, and $N^{\prime}$-methyl-4-pyridone-3-carboxamide. These same metabolites are formed from both nicotinic acid and nicotinamide although the proportions differ with the compound administered and the size of the injected dose. During the course of studies on the influence of hypophysectomy on pyridine nucleotide metabolism in rats, we have discovered two additional nicotinamide metabolites which have been identified as 6-hydroxynicotinic acid and 6-hydroxynicotinamide. 6-Hydroxynicotinic acid is a known intermediate in the oxidation (7) and fermentation (8) of nicotinic acid by certain bacteria. However, to our knowledge, the occurrence or formation of 6-hydroxynicotinamide has not been previously reported in any biological system.

Since 6-hydroxynicotinic acid is a known bacterial metabolite, germ-free rats were used to establish whether the 6-hydroxylation of nicotinic acid and nicotinamide is due to the intestinal flora or is proceeding in mammalian tissues.

EXPERIMENTAL PROCEDURE

Materials—Nicotinamide-7-^{14}C and nicotinic acid-7-^{14}C (12.4 mCi per mmole) were purchased from Calbiochem and were purified before use by descending paper chromatography in butanol-1 saturated with 3% ammonia. 6-Hydroxynicotinic acid was purchased from Aldrich. 6-Hydroxynicotinamide was synthesized by refluxing 11 g of 6-hydroxynicotinic acid with 10 ml of thionyl chloride for 1 hour. The reaction product was slowly poured, with vigorous stirring, into 50 ml of concentrated ammonia in an ice bath. The product was collected by filtration and recrystallized twice from hot water. The product melted at 285° with decomposition. Cellulose powder for the preparation of thin layer plates was purchased from Microchemical Specialties Company, Berkeley, California. Hypophysectomized male rats were obtained from Hormone Assay Laboratories, Chicago, Illinois.

Methods—Male Holtzman rats weighing from 200 to 350 g were maintained on Purina laboratory chow and were injected intraperitoneally with nicotinamide-7-^{14}C or nicotinic acid-7-^{14}C. The rats were placed in all glass metabolism cages, and the urine was collected in a vessel surrounded by Dry Ice. Radioactive areas on paper chromatograms and thin layer plates were detected by a 4 π Nuclear Chicago Actigraph III. Ultraviolet spectra were measured on a Beckman DB spectrophotometer. Infrared spectra were determined with a Perkin-Elmer 457 grating infrared spectrophotometer in KBr pellets prepared with a microsampling kit. Mass spectra were determined with the prototype (9) of the LKB-9000 gas chromatograph-mass spectrometer with the use of the direct inlet probe. Radioactivity was determined with a Tri-Carb liquid scintillation spectrometer.

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Germ-free rats were maintained in the Gnotobiotic Laboratory at Fitzsimons Army Hospital and were tested weekly for germ-free status by fecal smears on nutrient agar plates.

RESULTS

The first evidence for a hitherto unidentified metabolite of nicotinamide was obtained during attempts to develop a thin layer chromatographic procedure for the quantitative determination of these metabolites. When urine from rats injected with nicotinamide-7-^{14}C (500 mg per kg) was chromatographed on cellulose thin layer plates developed with butanol-1 saturated

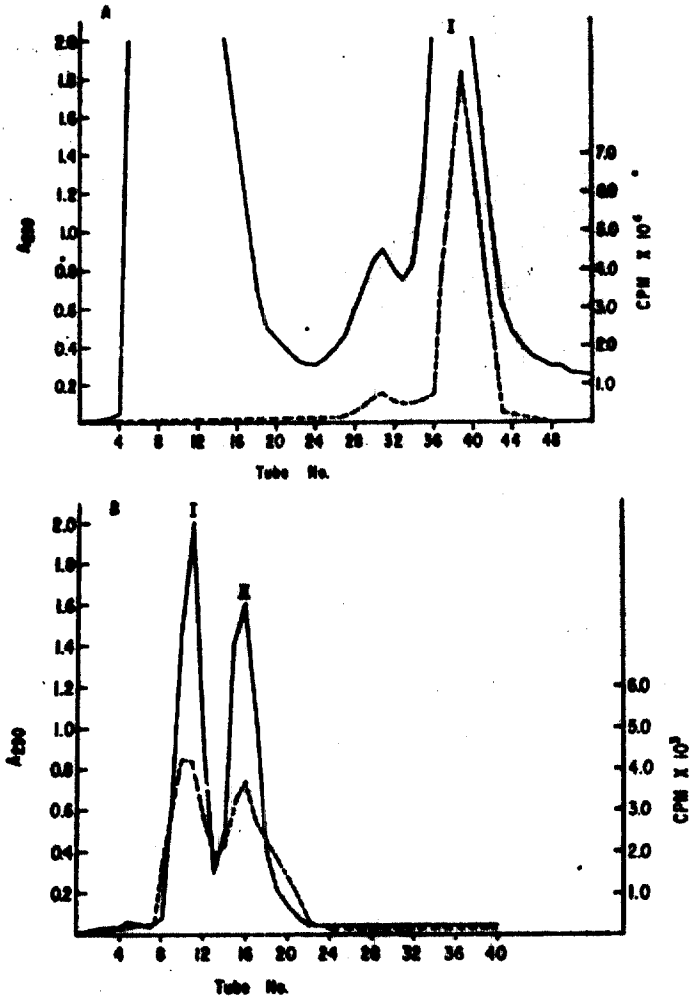

FIG. 1. Isolation of the unknown metabolite by ion exchange chromatography. *A*, Dowex-50 chromatography. Ten milliliters of a water solution of urine solids were placed on a column of Dowex 50 in the H^+ form (2.5 × 20 cm). The column was eluted with water, and 10-ml fractions were collected. Radioactivity was determined on 0.1-ml aliquots by liquid scintillation counting, and the absorbance at 290 mμ was measured with a Beckman DU spectrophotometer. Radioactive Peak I contained a mixture of *N'*-methyl-2-pyridone-5-carboxamide and the unknown compound. Fractions 34 to 43 were pooled and concentrated to 15 ml under vacuum. *B*, Dowex-1 formate chromatography. The solution obtained in *A* was applied to a Dowex-1 formate column (2.5 × 20 cm). The column was eluted with water, 10 ml fractions were collected, and the radioactivity and absorbance were measured as above. Peak I: *N'*-methyl-2-pyridone-5-carboxamide contaminated with a small amount of unknown. Peak II: unknown compound contaminated with a small amount of the pyridone. ——, A_{290}; - - -, radioactivity.

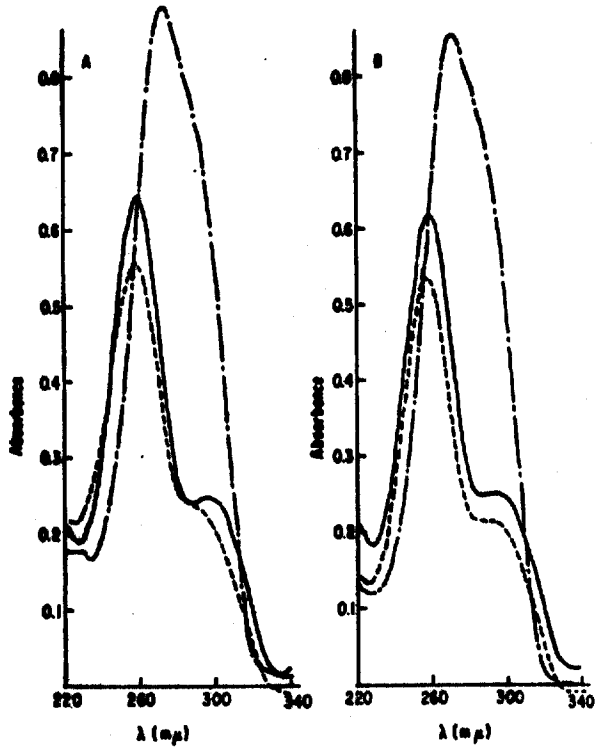

FIG. 2. Ultraviolet spectra of authentic 6-hydroxynicotinamide (*A*) and the material isolated from rat urine (*B*) measured on a Beckman DB spectrophotometer. Compound dissolved in H_2O (——); in 1 N HCl (- - -); in 1 N NaOH (-·-·-). The concentration of 6-hydroxynicotinamide was 4.7 × 10^{-5} M.

with 3% ammonia, poor resolution of nicotinic acid and nicotinamide *N*-oxide was obtained. Both compounds migrated close together at an R_F of 0.25 to 0.35. This area was therefore eluted with water, and the solution was subjected to high voltage paper electrophoresis (Savant Instrument Company, Hicksville, New York), 2000 volts, for 1 hour in 0.05 M sodium borate, pH 9.3. After electrophoresis, three radioactive areas were observed: nicotinic acid at +18 cm; nicotinamide *N*-oxide at −3 cm; and, at −1 cm, a compound which was not nicotinamide or one of its known metabolites. This compound was isolated from the pooled 24-hour urines of six 350-g rats injected with nicotinamide as described above. The urine was taken to dryness under reduced pressure at 50°, and the residue was dissolved in 50 ml of water. Ten milliliters of this solution were subjected to ion exchange chromatography with the results shown in Fig. 1. Fractions 13 to 20 from the Dowex-1 column were pooled and evaporated to dryness. This residue was dissolved in 2 ml of water and the solution streaked on Whatman No. 1 paper which was developed (descending) in 1-butanol saturated with 3% ammonia. Under ultraviolet light a major quenching spot was observed at R_F 0.28 to 0.30, which coincided with the major radioactive location as determined by paper strip counting. This area was eluted with water and used for identification after recrystallization from hot water. Since the unknown compound behaved like 6-hydroxynicotinamide on electrophoresis and column and paper chromatography, it was compared with this compound by ultraviolet, infrared, and mass spectrometry.

Fig. 2 shows a comparison of the ultraviolet absorption spectra of authentic 6-hydroxynicotinamide and the isolated unknown compound. The spectra in H_2O, HCl, and NaOH are almost

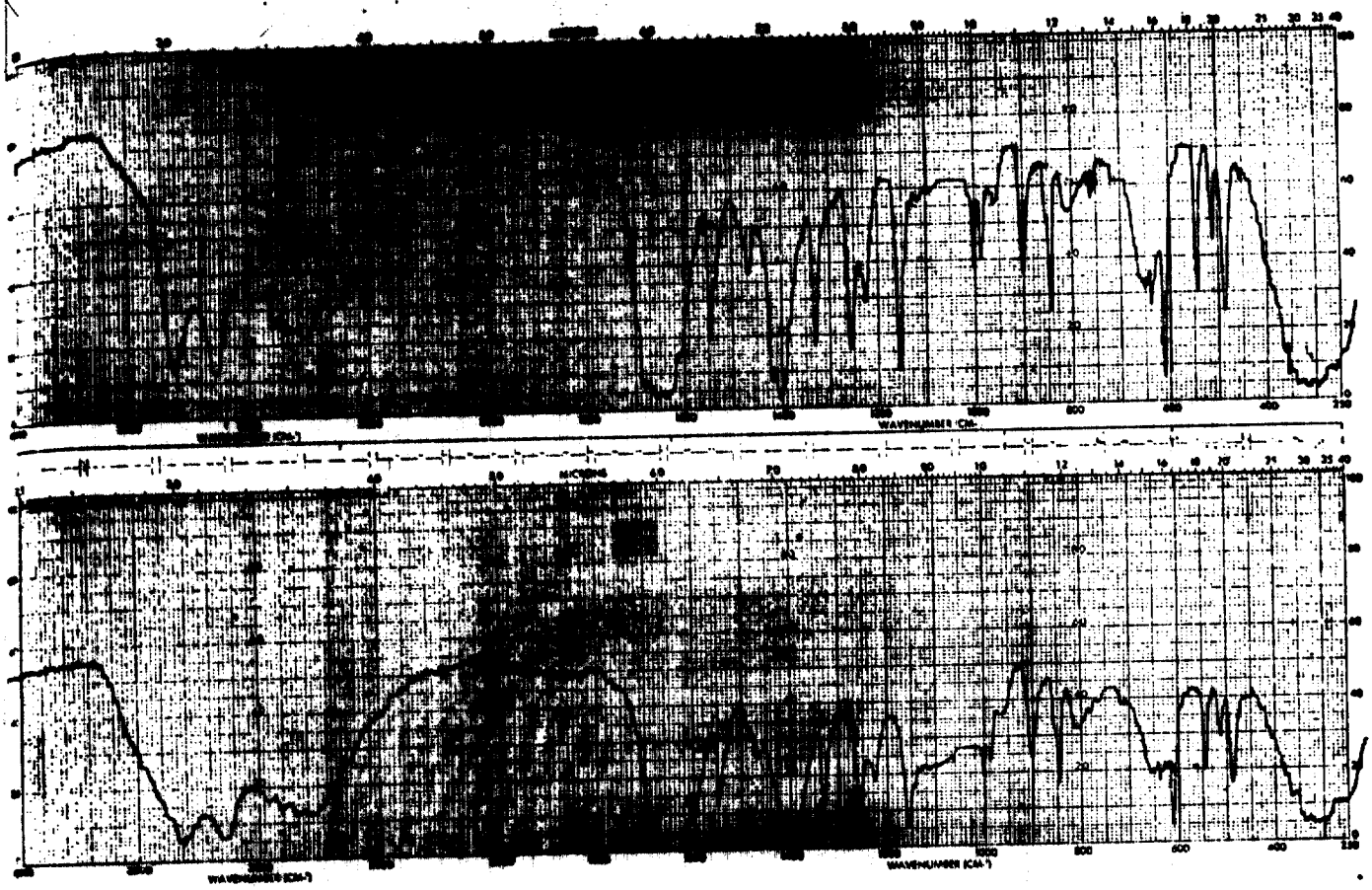

FIG. 3. Infrared spectra of authentic 6-hydroxynicotinamide (*upper*) and the compound isolated from rat urine (*lower*). Spectra were determined with a Perkin-Elmer 457 grating infrared spectrophotometer in a KBr pellet prepared with a microsampling kit.

identical. Further evidence for the identity of the unknown compound with 6-hydroxynicotinamide is provide by the infrared spectra shown in Fig. 3. The mass spectra in Fig. 4 are also nearly identical for 6-hydroxynicotinamide and the compound isolated from urine.

Fig. 5 shows the proposed partial fragmentation pattern. The parent peak is 138. Loss of the CO group would account for *m/e* 110 and the subsequent loss of NH_3 and CO would give *m/e* 94 and *m/e* 66. The ion at *m/e* 66 could also be formed by the successive loss of NH_3 to form *m/e* 122; CO, to form *m/e* 94; and, finally, CO to form *m/e* 66.

A second metabolite of nicotinic acid not previously reported in animals was first observed following intraperitoneal injection of nicotinic acid-7-^{14}C at a level of 5 mg per kg to a hypophysectomised rat. This compound cochromatographed with nicotinuric acid in the butanol saturated with 3% ammonia solvent system used by most workers to separate niacin metabolites by paper chromatography (3, 4). However, this compound could be separated from nicotinuric acid by thin layer chromatography on cellulose plates with the same developing solvent. Comparison of the chromatographic behavior of this compound with known nicotinic acid derivatives led to its tentative identification as 6-hydroxynicotinic acid.

In order to identify positively this unknown compound, it was isolated from the pooled 24-hour urines of three 200- to 300-g normal rats which were injected intraperitoneally with 5 mg of 7-^{14}C-nicotinic acid per kg. The pooled urines were placed on a Dowex-50 H^+ column (2.5 × 30 cm) which was eluted with water The first radioactive peak emerging from the column contained the unknown compound together with N'-methyl-2-pyridone-5-carboxamide. The unknown was further purified by paper chromatography with butanol-1 saturated with 3% ammonia followed by paper chromatography with butanol-1-acetic acid-water (4:1:2, v/v/v) as the developing solvent. Finally the isolated compound was crystallized from hot water and compared with authentic 6-hydroxynicotinic acid by ultraviolet, infrared, and mass spectrometry.

Fig. 6 shows a comparison of the ultraviolet absorption spectra of authentic 6-hydroxynicotinic acid and the compound isolated from urine. The spectra in H_2O, 1.0 N HCl, and 1.0 N NaOH are almost identical. Further evidence for the identity of the unknown compound with 6-hydroxynicotinic acid is provided by the infrared spectra shown in Fig. 7. The mass spectra shown in Fig. 8 are also identical for authentic 6-hydroxynicotinic acid and the compound isolated from urine of nicotinic acid-7-^{14}C-injected rats.

Quantitative studies have shown that approximately 0.7 to 0.8% of an injected dose (500 mg per kg) of nicotinamide is excreted as 6-hydroxynicotinamide in 24 hours following injection, by both normal and hypophysectomised rats.

The hypophysectomised rat in which 6-hydroxynicotinic acid was first discovered excreted about 6% of a 5 mg per kg intraperitoneal dose of nicotinic acid-7-^{14}C as this metabolite in 24 hours. However, this appears to be an exceptional case since

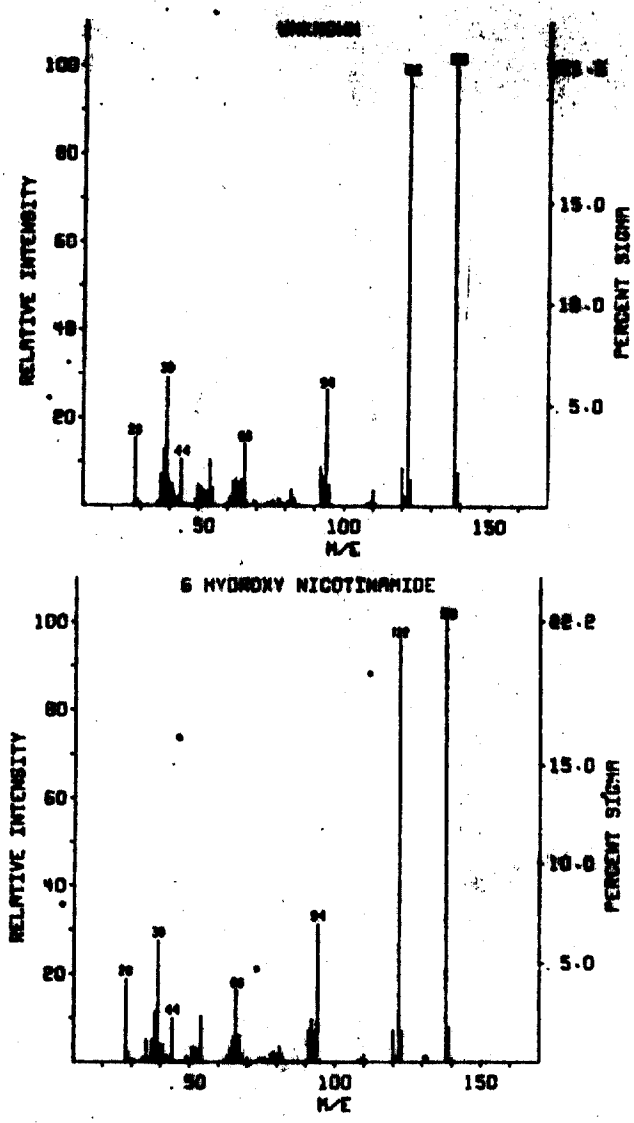

FIG. 4. Mass spectra of authentic 6-hydroxynicotinamide and the compound isolated from rat urine. Mass spectra were determined with the prototype (9) of the LKB-9000 gas chromatograph-mass spectrometer with the use of the direct inlet probe. The ion source temperature was [illegible], ionization current was 65 μamps, probe temperature was [illegible], electron energy was 70 e.v., and acceleration voltage was 3.5 volts.

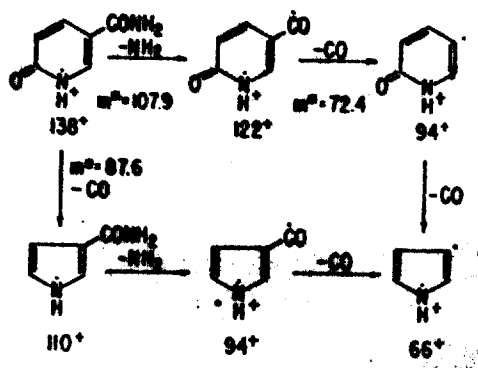

FIG. 5. Proposed partial fragmentation pattern of 6-hydroxynicotinamide under electron impact.

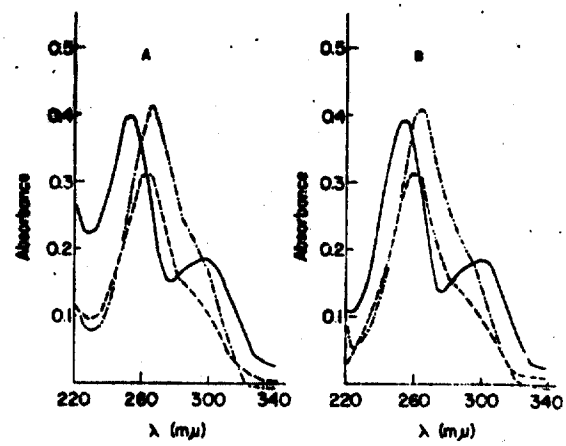

FIG. 6. Ultraviolet spectra of authentic 6-hydroxynicotinic acid (*A*) and the material isolated from rat urine (*B*) measured with a Beckman DB spectrophotometer. Compound dissolved in H_2O (——); in 1 N HCl (- - -); in 1 N NaOH (-·-·-). The concentration of 6-hydroxynicotinic acid was 2.6×10^{-5} M.

in other rats (both normal and hypophysectomized) which we have examined only about 1% or less of such a dose is excreted as 6-hydroxynicotinic acid in 24 hours.

The results presented above clearly indicate that 6-hydroxynicotinamide and 6-hydroxynicotinic acid are metabolites of nicotinamide and nicotinic acid in normal rats. However, the known production of 6-hydroxynicotinic acid by bacteria (7, 8) suggests that these metabolites might be produced by the intestinal flora rather than in the animal's tissues. Therefore, germ-free rats were used to resolve this question. Nicotinamide-7-^{14}C was given by aseptic intraperitoneal injection at a level of 500 mg per kg to a germ-free rat, and the 24-hour urine was subjected to Dowex 50 column chromatography as described above. The first radioactive peak eluted with water was chromatographed on paper with butanol saturated with 3% ammonia as the developing solvent. Fig. 9 shows the strip counter recording of this chromatogram. Radioactive spots corresponding to both 6-hydroxynicotinamide and 6-hydroxynicotinic acid were observed. To establish further the identity of these compounds, they were eluted from paper; 40 mg and 20 mg of carrier, respectively, were added; and the compounds were recrystallized five times. As shown in Table I, the specific activity of both compounds remained essentially constant after the second recrystallization. Table II shows a comparison of the percentages of the two 6-hydroxy derivatives excreted by individual normal and germ-free rats injected with 5 or 500 mg of nicotinamide-7-^{14}C or nicotinic acid-7-^{14}C per kg. Normal and germ-free animals excreted approximately the same percentage of each metabolite. When nicotinic acid was injected, a higher percentage of 6-hydroxynicotinic acid than of 6-hydroxynicotinamide was excreted than when nicotinamide was the precursor. A hundred-fold increase in dose level had little effect on the percentage of injected compound converted to each metabolite except in the two germ-free animals receiving 500 mg of nicotinic acid per kg. In this case the percentage of injected nicotinic acid excreted as 6-hydroxynicotinamide was considerably reduced from that observed following injection of nicotinic acid at 5 mg per kg.

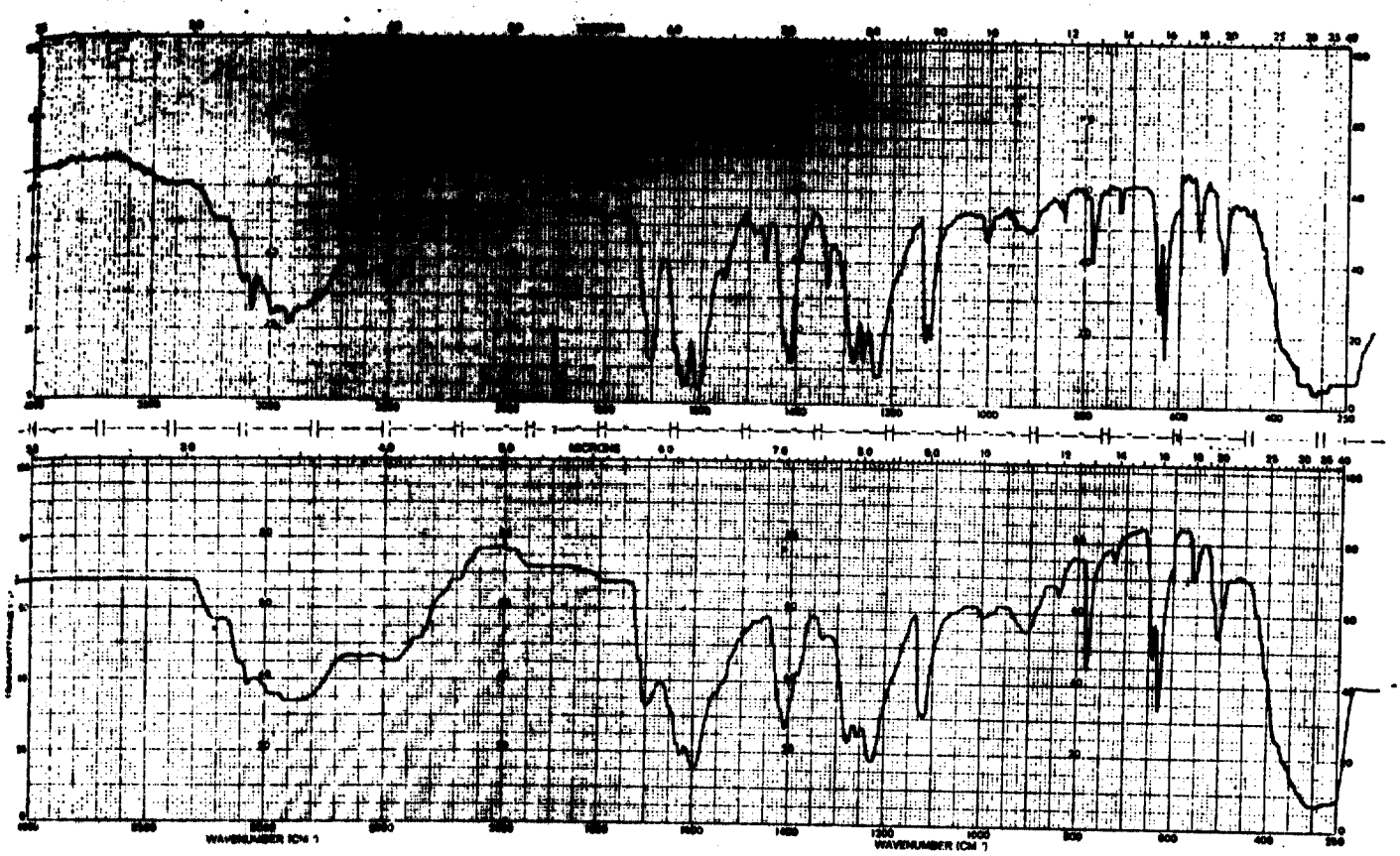

FIG. 7. Infrared spectra of authentic 6-hydroxynicotinic acid (*upper*) and the compound isolated from rat urine (*lower*). Spectra were determined as described for Fig. 3.

TABLE I

Recrystallization of urinary 6-hydroxynicotinic acid and 6-hydroxynicotinamide to constant specific activity

The compounds identified as 6-hydroxynicotinic acid and 6-hydroxynicotinamide were eluted with water from the chromatogram (shown in Fig. 9); 20 mg and 40 mg of authentic compound were added, respectively, and the compounds were recrystallized five times from hot water.

Peak	Carrier	Specific activity following recrystallization			
		2nd	3rd	4th	5th
		cpm/mg			
I	6-Hydroxynicotinic acid	107	119	119	102
II	6-Hydroxynicotinamide	165	136	149	155

DISCUSSION

The results presented above show that 6-hydroxynicotinamide and 6-hydroxynicotinic acid are urinary metabolites of nicotinamide and nicotinic acid in the rat and that these metabolites are formed in the tissues rather than by the intestinal flora. The failure of previous workers to identify these metabolites may be due to the fact that they are excreted in relatively small amounts and that in the [illegible]-water (3) and [illegible]-ammonia (4–6) solvent systems most commonly used for paper chromatography

TABLE II

Excretion of 6-hydroxynicotinamide and 6-hydroxynicotinic acid by individual normal and germ-free rats following injection of nicotinic-acid-7-^{14}C or nicotinamide-7-^{14}C

Male rats (normal and germ-free) weighing 200 to 350 g were injected intraperitoneally with nicotinamide-7-^{14}C or nicotinamide-7-^{14}C diluted with carrier to the dose levels indicated. The 6-hydroxy compounds were isolated from aliquots of 24-hour urines, and the radioactivity was determined as described in the text.

Status	Compound injected	Dose		Percentage of dose excreted as	
				6-Hydroxynicotinamide	6-Hydroxynicotinic acid
		mg/kg	*μCi*		
Normal	Nicotinamide	5	5.6	0.6	0.3
Normal	Nicotinamide	500	5.6	0.8	0.4
Normal	Nicotinic acid	5	5.6	0.2	1.0
Normal	Nicotinic acid	500	5.6	0.2	0.7
Germ-free	Nicotinamide	5	4.1	0.7	0.3
Germ-free	Nicotinamide	5	4.1	0.7	0.4
Germ-free	Nicotinamide	500	4.7	0.6	0.4
Germ-free	Nicotinamide	500	4.7	0.7	0.2
Germ-free	Nicotinic acid	5	9.9	0.2	0.7
Germ-free	Nicotinic acid	5	9.9	0.3	0.9
Germ-free	Nicotinic acid	500	10.3	<0.1	0.6
Germ-free	Nicotinic acid	500	10.3	<0.1	0.5

of nicotinamide metabolites 6-hydroxynicotinic acid has approximately the same R_f as nicotinic acid.

The physiological significance of these 6-hydroxylated compounds remains obscure. They may be produced by a non-specific hydroxylating system (10) and thus may represent products of a generalized detoxication mechanism. The excretion of both 6-hydroxylated compounds from either nicotinamide or nicotinic acid (and especially the formation of 6-hydroxynicotinamide from nicotinic acid) lends added support to the concept of a functioning pyridine nucleotide cycle in mammals (11).

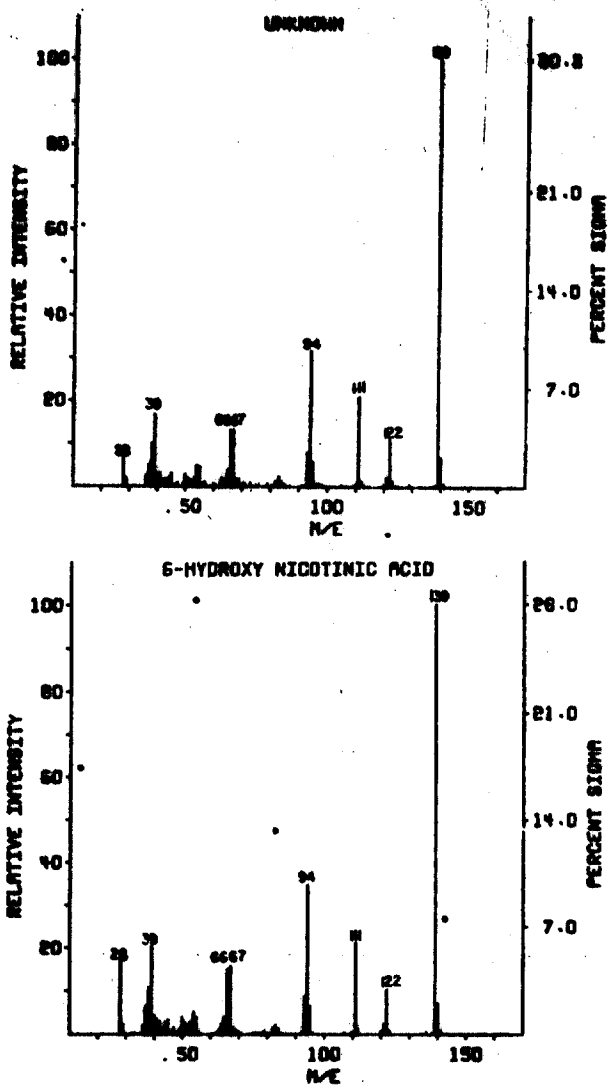

FIG. 8. Mass spectra of authentic 6-hydroxynicotinic acid and the compound isolated from gut urine. Mass spectra were determined as described for Fig. 4.

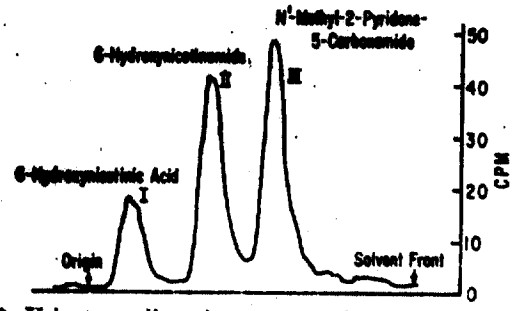

FIG. 9. Urinary radioactive compounds formed from nicotinamide-7-^{14}C in germ-free rats. Strip counter recording of a paper chromatogram after preliminary purification of the urinary compounds on Dowex 50. Experimental details are given in the text.

Acknowledgments—We wish to thank Dr. George R. Waller for his useful consultation during the course of this work, and Mr. Keith Kinneberg for determining the mass spectra.

REFERENCES

1. LEIFER, E., ROTH, L. J., HOGNESS, D. S., AND CORSOM, M. H., *J. Biol. Chem.*, **190**, 595 (1951).
2. CHANG, M. L. W., AND JOHNSON, B. C., *J. Biol. Chem.*, **234**, 1817 (1959).
3. BONAVITA, V., NARROD, S. A., AND KAPLAN, N. O., *J. Biol. Chem.*, **236**, 936 (1961).
4. CHAYKIN, S., DAGANI, M., JOHNSON, L., AND SAMLI, M., *J. Biol. Chem.*, **240**, 932 (1965).
5. PETRACK, B., GREENGARD, P., AND KALINSKY, H., *J. Biol. Chem.*, **241**, 2367 (1966).
6. GREENGARD, P., PETRACK, B., AND KALINSKY, H., *J. Biol. Chem.*, **242**, 152 (1967).
7. HUGHES, D. E., *Biochem. J.*, **60**, 303 (1955).
8. TSAI, L., PASTAN, I., AND STADTMAN, E. R., *J. Biol. Chem.*, **241**, 1807 (1966).
9. WALLER, G. R., *Proc. Okla. Acad. Sci.*, **47**, 271 (1968).
10. MITOMA, C., POSNER, H. S., REITZ, H. C., AND UDENFRIEND, S., *Arch. Biochem. Biophys.*, **61**, 431 (1956).
11. GHOLSON, R. K., *Nature*, **212**, 984 (1966).

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THE METABOLISM OF RADIOACTIVE NICOTINIC ACID AND NICOTINAMIDE*

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(Received for publication, December 4, 1950)

The metabolism of nicotinic acid and nicotinamide has been repeatedly investigated, and some of their metabolites in the urines of different animal species have been isolated and identified (1–3). In addition to the acid and amide forms of the vitamin, the presence of N^1-methylnicotinamide, nicotinuric acid, and N^1-methyl-6-pyridone-3-carboxylamide has been established in the urine of animals fed either nicotinic acid or nicotinamide. Much of the work described in the earlier literature regarding trigonelline (3, 4) was shown actually to pertain at least in part to N^1-methylnicotinamide (5, 6). Recently Huff and Perlzweig (7) and Ellinger and Abdel Kader (2) could not demonstrate the presence of trigonelline as a metabolite of either nicotinic acid or nicotinamide.

The synthesis of radioactive nicotinic acid and its amide labeled with C^{14} in the carboxyl position (8) has made possible the study of the urinary metabolites in high dilution by means of radioautographs of filter paper chromatograms.

In this paper the presence of six and the identity of five metabolites are recorded for the following animal species: dog, rat, mouse, and hamster. Respiratory $C^{14}O_2$ previously reported for the mouse (9) has been extended to include the other three species.

EXPERIMENTAL

Female mice of the CF1 strain, weighing approximately 25 gm., male rats of the Sprague-Dawley strain, weighing 100 to 125 gm., and hamsters weighing 50 to 60 gm. were injected intraperitoneally with 20 mg. per kilo of radioactive nicotinic acid or nicotinamide having a specific activity of 40 μc. per mg. The animals were placed in all-glass metabolism cages for the collection of urine, feces, and CO_2 samples (9). The stock animals had been maintained on standard diets of Purina laboratory chow in pellet form. In addition, lettuce and greens were given *ad libitum* to the hamsters. No evidence of any avitaminosis was present in the animals

* Work done under the auspices of the Atomic Energy Commission.

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studied. In order to maintain urine of high concentration, no water was given during the 24 hour experimental period. A female dog, weighing 10.4 kilos, was injected with 25 mg. of non-radioactive nicotinic acid intramuscularly 2 days before the experiment to insure against any nicotinic acid deficiency, although no symptoms were apparent. Just prior to the experiment an indwelling bladder catheter was inserted, and the animal was kept restrained. The bladder was evacuated and 20 mg. of C^{14}-nicotinic acid were administered by intravenous injection. Specimens of the urine were collected frequently by catheterization during the next 24 hours. 4 minute samples of exhaled CO_2 were obtained at frequent time intervals after the injection. The samples were collected over water with a modified United States Army gas mask. 8 days after the nicotinic acid experiment, 25 mg. of non-radioactive nicotinamide were injected into the same animal, and 2 days after this preliminary dose 20 mg. of radioactive nicotinamide were injected intravenously. Samples of urine and respiratory CO_2 were collected as described above.

Chromatographic Methods—Approximately 3000 disintegrations per second, corresponding to 0.01 to 0.1 ml. of fresh radioactive urine containing the mixture of metabolites, were placed in a transverse band on a strip of Whatman No. 1 filter paper 2 × 42 cm. Chromatograms were developed in *n*-butanol saturated with water. Radioautographs of the strips were prepared by placing the chromatograms in contact with "blue brand" x-ray film in cassettes for a 6 day period to allow the β-rays of C^{14} to expose the film. Preliminary radioautographs of pooled mouse urine indicated a maximum of six radioactive metabolites following an injection of labeled nicotinic acid (corresponding to Bands 1 to 6 in Fig. 1). Injection of nicotinamide showed predominantly Bands 1, 3, 4, 5, and 6 with the occasional appearance of Band 2 in low concentration. In order to eliminate the possible existence of more than the six metabolites found with the butanol-water system, each band was eluted and subjected to individual chromatographic analysis with the following solvent systems: (*a*) hexanol-ethanol (2:1) saturated with water, (*b*) *n*-butanol saturated with 3 per cent ammonium hydroxide, (*c*) *n*-butanol-acetone (3:1) saturated with water, (*d*) *s*-collidine saturated with water. None of the six bands was resolved into more than one component, thus indicating the presence of only six radioactive metabolites in the urine of animals injected with carboxyl-labeled nicotinic acid or nicotinamide.

Identification of Metabolites—Identification of the various metabolites of nicotinic acid and nicotinamide and the corresponding position of their radioactive bands on the chromatographic strips were established as follows:

An inert compound suspected of being a metabolite was added to radioactive urine and a chromatogram with a corresponding radioautograph

then made of the solution. After development, the filter paper strip was cut transversely into 5 mm. sections, each of which was eluted with water and analyzed qualitatively for the added compound (7, 10, 11). In this way the position of the inert compound on the filter paper strip was com-

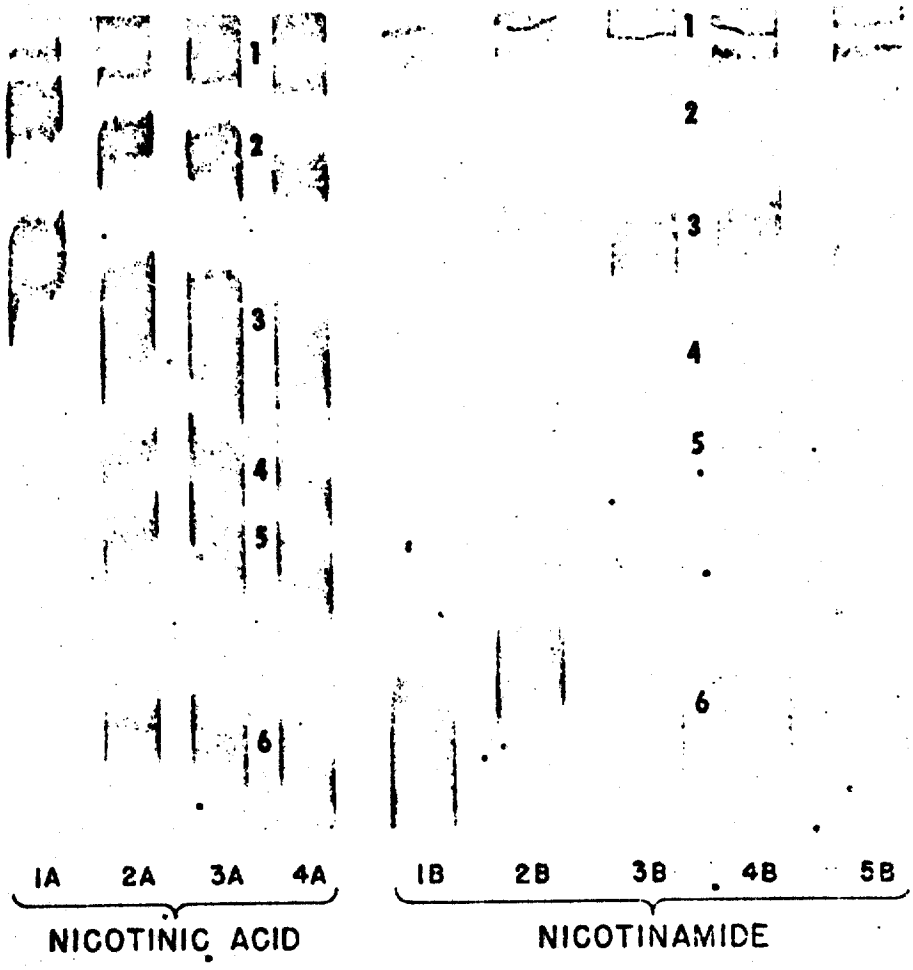

FIG. 1. Radioautographs of chromatographic strips, showing the appearance of urinary metabolites in mouse urine during various time intervals after intraperitoneal injection of C^{14}-nicotinic acid and C^{14}-nicotinamide. *1A*, 0 to 1 hour; *2A*, 1 to 9 hours; *3A*, 9 to 12¼ hours; *4A*, 13¼ hours after injection. *1B*, 0 to 1 hour; *2B*, 1 to 2¼ hours; *3B*, 2¼ to 11¾ hours; *4B*, 11¾ to 21¼ hours; *5B*, 21¼ to 24¼ hours after injection. Band 1, N^1-methylnicotinamide; Band 2, nicotinuric acid; Band 3, nicotinic acid; Band 4, unknown; Band 5, N^1-methyl-6-pyridone-3-carboxylamide; Band 6, nicotinamide.

pared with those of the bands on the radioautograph. Band 1 was therefore identified as N^1-methylnicotinamide, Band 2 as nicotinuric acid, Band 3 as nicotinic acid, Band 5 as N^1-methyl-6-pyridone-3-carboxylamide, and Band 6 as nicotinamide (Fig. 1). Spot tests made on duplicate chromatograms also demonstrated visually the correspondence of the positions of the added compounds to those of the bands on the radioautograph. Identification of nicotinic acid (Band 3) was further established by two other methods. (*a*) A filter paper chromatogram was cut into 4 cm. sections and placed on the surface of agar "pour plates" containing *Lactobacillus arabinosus* and a nicotinic acid-deficient basal medium (12). Growth occurred only around Band 3. (*b*) Radioactive nicotinic acid was added in large excess to the urine containing the radioactive metabolites. Radioautographs of chromatograms developed with this urine showed a marked increase in intensity, corresponding to the position of Band 3. Similarly, addition of radioactive nicotinamide to the above urine markedly increased the intensity of Band 6.

The identity of the compound corresponding to Band 4 is unknown at present. Addition of inert trigonelline to radioactive urine failed to establish Band 4 as that of trigonelline. Its position on the chromatogram was found to be between Bands 1 and 2, with some superimposition when identified by its colorimetric reaction with 12 N KOH. In none of these experiments was trigonelline shown to be produced from either nicotinic acid or nicotinamide.

Kinetics of Urinary Metabolite Excretion—Samples of urine collected during various time intervals after injection of C^{14}-labeled nicotinic acid and nicotinamide were assayed for total activity. Aliquots of each sample equivalent to 300 counts per second were placed on filter paper strips and chromatograms developed in a butanol-water system as described previously. Radioautographs were made of each strip, the exposure and developing times and conditions being kept constant. The relative per cent abundance of the various metabolites excreted during the various time intervals studied was determined as follows:

The first method consisted of visual comparison of the relative densities of the exposure bands of the radioautographs corresponding to the various metabolites. The results are shown in Fig. 1.

The second method consisted of cutting out the corresponding areas on the filter paper chromatogram strip and counting the corresponding activities with a Geiger counter. The data in Table 1 show the relative distribution of radioactivity among the various metabolites in the urine of the dog, rat, hamster, and mouse during the 12 to 24 hour period following the injection of C^{14}-nicotinic acid and nicotinamide.

Respiratory CO_2—Samples of respiratory CO_2 were collected from all

species. The CO_2 was converted to $BaCO_3$, which was plated onto oxidized copper disks, counted with a Geiger-Müller tube, and the results corrected for absorption by the method of Yankwich *et al.* (13). Total CO_2 was collected for all species except the dog. For the dog the values reported were obtained by taking six 4 minute CO_2 samples between 1 minute and 24 hours after injection and integrating under the curve to obtain the total $C^{14}O_2$ output during a specific time interval. The total per cent of administered activity excreted as CO_2 following the administration of labeled nicotinic acid to mice, rats, hamsters, and a dog is shown graphically in Fig. 2. The $C^{14}O_2$ output following administration of labeled nicotinamide to the same dog is also given.

TABLE I

*Relative Per Cent Distribution of Radioactivity among Urinary Metabolites of C^{14}-Nicotinic Acid and C^{14}-Nicotinamide 12 to 24 Hours after Injection**

Chromatogram band No. and metabolite	C^{14}-Nicotinic acid				C^{14}-Nicotinamide			
	Dog	Rat	Hamster	Mouse	Dog	Rat	Hamster	Mouse
1. N^1-Methylnicotinamide	94	56	23.6	13.6	94	73.5	35	20
2. Nicotinuric acid	1	10.5	2.8	21.8	0.5	0	0	0.5
3. Nicotinic acid	0.3	6.3	24.5	37.2	1	5.5	17	36.2
4. Unknown	0	11.9	13.0	7.0	1	3.6	13	9
5. N^1-Methyl-6-pyridone-3-carboxylamide	2	11.9	10.6	11.6	2.5	12	10	20
6. Nicotinamide	2.4	3.5	25.5	6.1	1	5.6	25	14.3

* The results represent averages from one dog, three rats, two hamsters, and four mice.

DISCUSSION

Although none of the metabolites was isolated from the urine following the injection of labeled nicotinic acid and nicotinamide into the various species, application of filter paper chromatograms made the identities of N^1-methylnicotinamide, nicotinuric acid, nicotinic acid, N^1-methyl-6-pyridone-3-carboxylamide, and nicotinamide quite certain. An unknown metabolite (Band 4) has not been identified. However, it was shown not to be trigonelline. The occurrence of trigonelline as a metabolite of nicotinic acid and nicotinamide could not be demonstrated. This is in conformity with the recent work of Huff and Perlzweig (7) and Ellinger and Abdel Kader (2). The proximity of the unknown compound to the 6-pyridone (Band 5) in all solvent systems raises the possibility of its being the 2-pyridone of N^1-methylnicotinamide described by Holman and de Lange (14). The exact identity of this compound, however, has not been established.

Following the injection of nicotinic acid, the relative densities of the exposure bands (Fig. 1) showed that nicotinuric acid (Band 2) was formed as a rapid detoxification product. The amount of nicotinuric acid decreased rapidly with increasing time after injection, as did the relative amount of nicotinic acid (Band 3). However, the relative amounts of N^1-methyl-6-pyridone-3-carboxylamide (Band 5) and nicotinamide (Band 6) increased. Following the injection of nicotinamide, the relative amounts of nicotinic acid and N^1-methyl-6-pyridone-3-carboxylamide in-

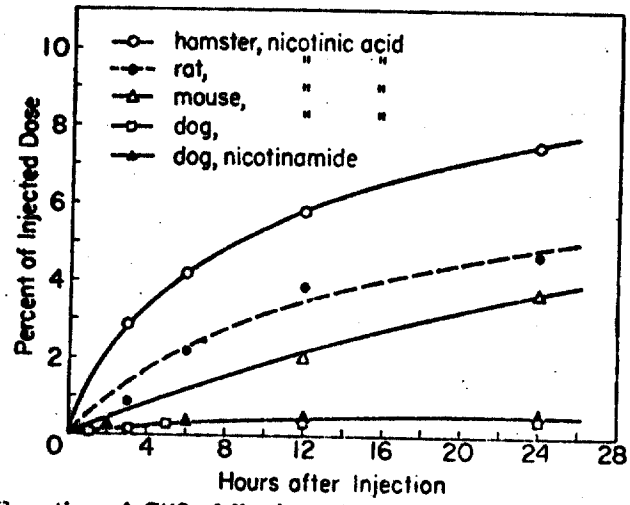

FIG. 2. Excretion of $C^{14}O_2$ following administration of C^{14}-nicotinic acid and C^{14}-nicotinamide to various species. Mouse, average of nine animals; rat, average of seven animals; hamster, average of six animals; dog, one animal.

creased with time, while nicotinamide decreased with time and nicotinuric acid was absent.

For all species the first urine collected after the injection of nicotinic acid contained a relatively high per cent of nicotinuric and nicotinic acids and only a small per cent of the other urinary metabolites. The amount of nicotinuric acid in the urine decreased rapidly with time and after 24 hours less than 5 per cent of the total radioactivity was excreted in this form. This finding is contrary to that of Ellinger and Abdel Kader (2), who could not demonstrate the presence of nicotinuric acid after administration of nicotinic acid to animals. Huff and Perlzweig (3) showed that very little if any nicotinuric acid was found in the urine of rats fed either nicotinic acid or nicotinamide.

The injection of nicotinamide into the various species was followed by a more rapid appearance of the various urinary metabolites, nicotinuric

acid appearing in only trace amounts (less than 0.5 per cent). Otherwise the products formed were identical with those following nicotinic acid injection.

There is a quantitative difference among the species examined as to the distribution of radioactivity in the various compounds appearing in the urines of the dog, rat, hamster, and mouse 12 to 24 hours after the intraperitoneal injection of C^{14}-nicotinic acid and nicotinamide. Qualitatively, however, all species produced the same known metabolites and thus may be assumed to have the same enzyme systems. The factors determining the proportions of the various metabolites are unknown.

Although there was a quantitative variation in the production of $C^{14}O_2$, it was found to be present in the expired air of all species studied (Fig. 2). Carbon dioxide therefore must be added to the list of known metabolites of nicotinic acid and nicotinamide.

SUMMARY

Six urinary metabolites were demonstrated after the injection of radioactive nicotinic acid or its amide by the technique of filter paper chromatography. Five of the compounds were identified as N^1-methylnicotinamide, nicotinuric acid, nicotinic acid, N^1-methyl-6-pyridone-3-carboxylamide, and nicotinamide. The sixth metabolite, corresponding to Band 4 of the chromatograms, is unknown but does not correspond to trigonelline.

There was a quantitative, but not a qualitative, difference in the relative distribution of these compounds in the urines of the dog, rat, hamster, and mouse as a function of time after injection. All species produced $C^{14}O_2$ from carboxyl-labeled nicotinic acid and nicotinamide, although CO_2 production by the various species differed quantitatively.

We are indebted to the late Dr. William A. Perlzweig of Duke University for the sample of nicotinuric acid, and to Dr. Jesse W. Huff of the Medical Division of Sharp and Dohme, Inc., and Dr. W. Eugene Knox of Northwestern University for samples of N^1-methyl-6-pyridone-3-carboxylamide used in these studies.

The authors wish to express their appreciation to Mrs. Betty Rogers and Mr. George Woodward for technical assistance.

BIBLIOGRAPHY

1. Perlzweig, W. A., Rosen, F., Leder, I. G., Hunter, S., and Pearson, P. B., *Federation Proc.*, **8**, 236 (1949).
2. Ellinger, P., and Abdel Kader, M. M., *Biochem. J.*, **44**, 77 (1949).
3. Huff, J. W., and Perlzweig, W. A., *J. Biol. Chem.*, **142**, 401 (1942).
4. Ackermann, D., *Z. Biol.*, **59**, 17 (1912).

5. Huff, J. W., and Perlzweig, W. A., *Science*, 97, 538 (1943).
6. Sarett, H. P., *J. Biol. Chem.*, 150, 159 (1943).
7. Huff, J. W., and Perlzweig, W. A., *J. Biol. Chem.*, 167, 157 (1947).
8. Murray, A., Foreman, W. W., and Langham, W., *Science*, 106, 277 (1947).
9. Roth, L. J., Leifer, E., Hogness, J. R., and Langham, W. H., *J. Biol. Chem.*, 176, 249 (1949).
10. Bandier, E., and Hald, J., *Biochem. J.*, 33, 264 (1939).
11. Rosen, F., Perlzweig, W. A., and Leder, I. G., *J. Biol. Chem.*, 179, 157 (1949).
12. Snell, E. E., *Physiol. Rev.*, 28, 255 (1948).
13. Yankwich, P. E., Norris, T. H., and Huston, J., *Anal. Chem.*, 19, 439 (1947).
14. Holman, W. I. M., and de Lange, D. J., *Biochem. J.*, 45, 559 (1949).

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A STUDY OF THE TOXICITY OF CERTAIN VITAMIN PREPARATIONS IN AN EXPERIMENT

G. N. Tipkan, Kiev

Vitamins are a group of compounds which have been widely studied. However in the literature available to us we encountered only isolated works touching on the toxicity of these biologically active substances (A. M. Timofeyeva and G. A. Tsofina, 1943; Ya. B. Maksimovich, 1963; Yu. M. Ostrovskiy et al., 1968; Winter et al., 1967).

We studied the toxicity, in acute experiments, of several water-soluble vitamins of the B group, ascorbic acid, a preparation of vitamin P - rutin, and galascorbine, which possesses C and P vitamin activity. The experiments were conducted on white rats which had been placed on the usual diet. Toxicity was determined using a probe-analysis method proposed by Litchfield and Wilcoxson (M. L. Belen'kiy, 1959). In all the experiments, the vitamin dosage was determined which caused the death of all the experimental animals, as well as the size of the dose which caused no deaths. Five animals were used for testing each dose. Solutions of the preparations were made immediately before administration in distilled water. The incompletely soluble substances were administered in the form of a suspension. Death of the animals was calculated over 2-3 days. The data obtained are reflected in Tables 1 and 2.

Of all the preparations we studied, vitamin B_1 and folic acid had a relatively high toxicity with intraperitoneal administration. The phosphorylated form of thiamine, co-carboxylase, under the experimental conditions, was approximately 5 times less toxic than vitamin B_1 itself.

In clinical practice, the pharmacodynamic effect of vitamin preparations is even more widely utilized. However increased doses of vitamins are often used without sufficient experimental grounds resulting from empirical observations and conclusions, while only isolated attempts in some way or other occur on which to base the possible application of increased doses of the citamins with the aim of therapeutics. Z. T. Malkin (1952) concluded that in order to

Table 1. Acute Toxicity of Vitamin Preparations with a Single Intraperitoneal Administration to Rats (mg/kg)

Preparation	Max. Tolerab. Dose (LD_0)	LD_{16}	LD_{50} & its Reliab. Lim. for p = 0.05	LD_{84}	Abs. Leth. Dose (LD_{100})
Vitamin B_1 (thiamine)	300	335	390 (342-445)	475	500
Co-carboxylase	1600	1655	1955 (1746-2190)	2300	2300
Vitamin B_2 (riboflavin)	3000	-	4000	-	-
Nicotinic acid	700	820	1080 (900-1296)	1400	1500
Vitamin B_6 (pyridoxine)	1600	1675	1925 (1750-2118)	2195	2200
Folic acid	500	610	720 (600-864)	850	900
Orotic acid	1500	1875	2200 (1880-2574)	2810	3000

Table 1 concluded

Ascorbic acid	2100	2200	2499 (2251-2774)	2810	3000
Rutin	15,000	-	20,000	-	-
Galascorbine	2800	2850	3120 (2943-3307)	3450	3500

obtain the pharmacodynamic effect of the vitamin preparations, it is necessary to use doses 10-20 times greater than the physiological doses, which reflect man's requirements for these vitamins. If you start with the physiological norms of man's daily requirement of these vitamins, established in 1960 by the Ministry of Health Protection in the USSR (N. S. Yarusov, 1961) and with the calculation principle presented above for doses of vitamin preparations having a pharmacodynamic effect, then for a man weighing 70 kg on the average, the curative doses are within the limits of 20-60 mg for vitamin B_1, 25-70 mg for vitamin B_2, 1000-2400 mg for vitamin C, 150-500 mg for nicotinic acid, and 20-40 mg for vitamin B_6. According to P. I.

Table 2. Acute Toxicity of Vitamin Preparations with a Single Subcutaneous Administration to Rats (mg/kg)

Preparation	Max. Tolerab. Dose (LD_0)	LD_{16}	LD_{50} & its Reliab. Lim. for p = 0.05	LD_{84}	Abs. Leth. Dose (LD_{100})
Vitamin B_1 (thiamine)	700	760	840 (785-899)	930	1000
Co-carboxylase	4000	4250	4650 (4346-4976)	5170	5200
Vitamin B_2 (riboflavin)	5000	-	8000	-	-
Nicotinic acid	2000	2050	2550 (2179-2984)	3125	3200
Vitamin B_6 (pyridoxine)	2600	2750	3130 (2653-3693)	3600	3800
Folic acid	3200	3250	3550 (3318-3799)	3950	4000
Orotic acid	3000	3300	3990 (3500-4519)	4750	5000
Ascorbic acid	3500	3850	4100 (3832-4387)	4400	4500
Rutin	25,0000	-	30,000	-	-
Galascorbine	3800	4050	4320 (4037-4622)	4650	4800

Shilov and T. I. Yakovlev (1964), in proposing a requirement for folic acid of 1-2 mg and for vitamin P of 50 mg, the therapeutic doses of these vitamins are, consequently, 10-40 mg and 500-1000 mg, respectively. Comparing the results obtained with those presented above, it must be noted that the therapeutic vitamin dosages are significantly less than their toxic doses. Thus, for vitamin B_1, the maximum therapeutic dose (1 mg/kg weight) is altogether 0.3% of the LD_{50} obtained in the experiment, for vitamin B_2 0.025%, nicotinic acid 0.65%, vitamin C 1.37%, vitamin B_6 0.029%, folic acid 0.079%, galascorbine 0.45%, and rutin 0.07%. In calculating these figures we used the LD_{50} of the vitamins for their intraperitoneal administration. Even if you take the maximum amount of the vitamins which shows a pharmacodynamic effect, for an average effective dose,

the therapeutic coefficient (ratio of the average lethal dose to the average effective dose) will in all cases exceed 100 (with the exception of ascorbic acid), which confirms the wide range of the therapeutic effect of vitamins. In addition, these data indicate the possibility of using vitamins for therapeutics in large doses.

In order to establish the optimal amount of vitamins for therapeutic application, the biological study of the effect of increased doses of these preparations is necessary above all. It is expedient to investigate the effect of significant doses of vitamins on the course of various pathological processes in the organism which are caused by extreme reactions. In this relation, the work of the Italian scientists is representative. In experiments on dogs, Barusco et al. (1968) formed conclusions about the usefulness for neuroleptanalgesia of thiamine and its monophosphoric ester, which have a narcotic effect in high dosages. Manami et al. (1968) administered thiamine internally in doses up to 250 mg/kg to patients at the time of narcosis and to healthy subjects - up to 350 mg/kg. Sauly et al. (1968) administered thiamine internally, on the average of 20 g to a man, in a 10% solution with the addition of 0.6 g of Pentothal. According to the data of Violani et al. (1968), 20 hours after administering 12-13 g of thiamine, it was not found in the blood.

According to our data, the doses of thiamine used by the Italian investigators are within the zone of toxic effect and could cause significant secondary effects.

The use, in anesthesiology, of thiamine, which has significant toxicity, inidcates the possibility of increasing the therapeutic doses of other less toxic vitamin preparations within the zone of their nontoxic pharmacodynamic effect. However the use of increased doses of vitamin preparations must be substantiated on all sides.

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ИЗУЧЕНИЕ ТОКСИЧНОСТИ НЕКОТОРЫХ ВИТАМИННЫХ ПРЕПАРАТОВ В ЭКСПЕРИМЕНТЕ

Г. Н. Липкан. Киев

Витамины относятся к всесторонне изученным соединениям, однако в доступной нам литературе мы встретили лишь единичные работы, касающиеся изучения токсичности этих биологически активных веществ (А. М. Тимофеева, Г. А. Цофина, 1963; Я. Б. Максимович, 1963; Ю. М. Островский и соавт., 1963; Winter и соавт., 1967).

Нами изучена токсичность в острых опытах некоторых водорастворимых витаминов группы В, аскорбиновой кислоты, препарата витамина Р — рутина и галаскорбина, обладающего С- и Р-витаминной активностью. Опыты проведены на белых крысах, находившихся на обычном рационе виварня. Токсичность определяли при помощи метода пробит-анализа, предложенного Литчфильдом и Вилкоксоном (М. Л. Беленький, 1959). Во всех опытах определяли дозу витаминов, вызывающую гибель всех подопытных животных, и величину дозы, не вызывающей гибели. Для испытания каждой дозы брали 5 животных. Растворы препаратов готовили непосредственно перед введением на дистиллированной воде. Плохо растворимые вещества вводили в виде взвеси. Гибель животных учитывали в течение 2—3 дней. Полученные данные отражены в табл. 1 и 2.

Из всех изученных нами препаратов относительно высокой токсичностью обладает витамин B_1 и фолиевая кислота при внутрибрюшинном введении. Фосфорилированная форма тиамина — кокарбоксилаза в условиях опыта примерно в 5 раз менее токсична, чем сам витамин B_1.

В клинической практике все более широко используется фармакодинамическое действие витаминных препаратов. Однако повышенные дозы витаминов часто применяются без достаточных экспериментальных обоснований, исходя из эмпирических наблюдений и выводов, причем встречаются лишь единичные попытки каким-либо образом обосновать возможность применения повышенных доз витаминов с терапевтической целью. З. Н. Малкин

Таблица 1. Острая токсичность витаминных препаратов при однократном внутрибрюшинном введении крысам (*мг/кг*)

Препарат	Максимально переносимая доза ($ЛД_0$)	$ЛД_{16}$	$ЛД_{50}$ и ее доверительные границы при $p = 0{,}05$	$ЛД_{84}$	Абсолютно смертельная доза ($ЛД_{100}$)
Витамин B_1 (тиамин)	300	335	390 (342 ÷ 445)	475	500
Кокарбоксилаза	1600	1655	1955 (1745 ÷ 2190)	2300	2300
Витамин B_2 (рибофлавин)	3000	—	>8000	—	—
Никотиновая кислота	700	820	1050 (900 ÷ 1236)	1250	1300
Витамин B_6 (пиридоксин)	1600	1675	1925 (1750 ÷ 2118)	2195	2200
Фолиевая кислота	500	610	720 (600 ÷ 864)	850	900
Оротовая кислота	1500	1875	2200 (1850 ÷ 2574)	2675	3000
Аскорбиновая кислота	2100	2200	2459 (2151 ÷ 2774)	2810	3000
Рутин	15 000	—	>20 000	—	—
Галаскорбин	2800	2850	31200 (2943 ÷ 3307)	3450	3500

(1952) считает, что для получения фармакодинамического эффекта витаминных препаратов необходимо применять дозы, в 10—20 раз больше физиологических, отражающих потребность человека в этих витаминах. Если исходить из физиологических норм суточной потребности человека в витаминах, утвержденных в 1960 г. Министерством здравоохранения СССР (Н. С. Ярусова, 1961), и вышеприведенного принципа расчета доз витаминных препаратов, обладающих фармакодинамическим эффектом, то для человека со средним весом 70 *кг* лечебные дозы находятся в пределах 20—60 *мг* для витамина B_1, 25—70 *мг* — для витамина B_2, 1000—2400 *мг* — для витамина С, 150—500 *мг* — для никотиновой кислоты, 20—40 *мг* — для витамина B_6. По П. И. Шилову и

Таблица 2. Острая токсичность витаминных препаратов при однократном подкожном введении крысам (*мг/кг*)

Препарат	Максимально переносимая доза ($ЛД_0$)	$ЛД_{16}$	$ЛД_{50}$ и ее доверительные границы при $p = 0{,}05$	$ЛД_{84}$	Абсолютно смертельная доза ($ЛД_{100}$)
Витамин B_1 (тиамин)	700	760	840 (785 ÷ 899)	930	1000
Кокарбоксилаза	4000	4250	4650 (4346 ÷ 4976)	5170	5200
Витамин B_2 (рибофлавин)	5000	—	8000	—	—
Никотиновая кислота	2000	2050	2550 (2170 ÷ 2981)	3125	3200
Витамин B_6 (пиридоксин)	2000	2750	3130 (2653 ÷ 3693)	3600	3600
Фолиевая кислота	3200	3250	3550 (3318 ÷ 3799)	3850	4000
Оротовая кислота	3000	3500	3990 (3500 ÷ 4549)	4750	5000
Аскорбиновая кислота	3700	3850	4100 (3832 ÷ 4387)	4400	4500
Рутин	25000	—	30000	—	—
Галаскорбин	3800	4050	4320 (4037 ÷ 4622)	4650	4800

Т. И. Яковлеву (1964), предположительная потребность в фолиевой кислоте — 1—2 *мг* и в витамине Р — 50 *мг*, следовательно, терапевтические дозы этих витаминов составляют соответственно 10—40 и 500—1000 *мг*. Сравнивая полученные данные с приведенными выше, следует отметить, что терапевтические дозы витаминов значительно меньше их токсических доз. Так, для витамина B_1 максимальная терапевтическая доза (1 *мг/кг* веса) составляет всего около 0,3% от $ЛД_{50}$, полученной в эксперименте, для витамина B_2 — 0,025%, никотиновой кислоты — 0,65%, витамина С — 1,37%, витамина B_6 — 0,029%, фолиевой кислоты — 0,079%, галаскорбина — 0,45%, рутина — 0,07%. При расчетах этих цифр мы пользовались $ЛД_{50}$ витаминов при их внутрибрюшинном введении. Если принять даже максимальные количества витаминов, оказывающие фармакодинамическое действие, за среднеэффективную дозу, терапевтический коэффициент (отношение среднесмертельной дозы к среднеэффективной) будет во всех случаях превышать 100 (за исключением аскорбиновой кислоты), что свидетельствует о большой широте терапевтического действия витаминов. Кроме того, эти данные указывают на возможность применения витаминов с терапевтической целью в больших дозах.

Для того, чтобы установить оптимальные количества витаминов для применения их с терапевтической целью, прежде всего необходимо биологическое изучение действия повышенных доз этих препаратов. Целесообразно исследовать влияние значительных доз витаминов на течение различных патологических процессов в организме, вызываемых экстремальными воздействиями. В этом отношении показательны работы итальянских ученых. В опытах на собаках Barusco и соавт. (1968) сделали вывод о пригодности тиамина и его монофосфорного эфира, обладающих в высоких дозировках наркотическим действием, для нейролептанальгезии. Manani и сотр. (1968) вводили тиамин внутривенно в дозе до 250 *мг/кг* больным во время наркоза внутривенно и здоровым испытуемым — до 350 *мг/кг*. Sauly и сотр. (1968) вводили внутривенно тиамин в среднем 20 *г* на человека в 10% растворе с добавлением 0,6 *г* тиопентала. По данным Violani и соавт. (1968), через 20 часов после введения 12—13 *г* тиамина последний в крови не обнаруживается.

По нашим данным, используемые итальянскими исследователями дозы тиамина находятся в зоне токсического действия и могут вызывать значительные побочные эффекты.

Применение в анестезиологии тиамина, обладающего значительной токсичностью, указывает на возможность повышения терапевтических дозировок других, менее токсичных витаминных

препаратов в зоне их нетоксического фармакодинамического действия. Однако использование повышенных доз витаминных препаратов должно быть всесторонне обосновано.

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A NEWER METHOD OF NICOTINIC ACID THERAPY IN HEADACHE OF THE VASOCONSTRICTIVE TYPE*

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In a preliminary report read before the American Therapeutic Society in Chicago in June 1952, I reported 5 patients with vasoconstriction headache, who were improved or well. The use of nicotinic acid therapy for the treatment of some types of headaches was suggested by the fact that nicotinic acid relieved post-spinal cephalgia and various depression states.

Fifty cases are presented in this paper, and descriptive details are listed in Table 1. These patients are of particular interest because all of them had previous treatment for their headaches without relief. Forty-five received ergotamine tartrate at one time or another, with unsatisfactory results; in fact, in a few instances the headache was intensified following the use of this drug. It is important to emphasize that in nearly every instance the patient presented some form of depression state. The results obtained following nicotinic acid therapy were very satisfactory in 44 of the 50 cases.

It is of interest to note, in a perusal of the literature, that there are many reports of relief of the migraine syndrome in emotionally unstable individuals following nicotinic acid therapy. Crosby (1) pointed out good results with the use of nicotinic alcohol (Roniacol tartrate), which is slowly converted into nicotinic acid in the body. Loman, Rinkel and Myerson (2) showed that nicotinic acid, in some unknown manner, causes an increase in brain volume, and it is exactly this action which is desired in the treatment of post-spinal and post-pneumoencephalographic headache.

Moore (3) had demonstrated a rise in cerebrospinal fluid pressure in 2 patients and dilatation of the pial blood vessels in cats following the administration of nicotinic acid, but Loman, Rinkel and Myerson were unable to find any change in the cerebrospinal fluid pressure, cerebral arterio-venous oxygen difference, or the size of retinal blood vessels following the injection of large doses of monoethanol amine nicotinate. Friedman (4) and his associates pointed out that in approximately 25 per cent of migraine patients and in 55 per cent of tension patients the headaches were improved to some extent by administering a placebo but, in general, this type of treatment is ineffective.

The tension type of headache is usually caused by changes in the size of the cranial vessels as well as by an increase in tonicity or spasm of the skeletal muscles of the neck and head, since both vascular and muscular influences seem to be present. Peters (5) asserts that between the typical tension headache and the typical migraine headache there are all degrees and combinations. The patient

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TABLE 1

*Differential Diagnosis of Migraine and Tension Headaches**

	Migraine	*Tension Headache*
Age of patient at onset	Begins before age of 20	Begins in early decade of life
Sex of patient	Female, 60%	Female, 70%
Familial history	Present in 65%	Present in 40%
Frequency	Daily headaches infrequent	Often more or less constant, with exacerbations
Prodromata	Present in 75%	Rarely, if ever, present
Type of pain	Throbbing	Dull, constrictive, or throbbing
Location of pain	Unilateral; often supraorbital	Bilateral; often begins in occipital region
Effect of ergotamine	Relief (usually)	No relief; often made worse
Followed by depression	Lassitude, but not depression	Usually followed by depression
Duration of headache	Often a few hours; rarely more than three days	Often lasts for several weeks, with few periods free from discomfort
Patient aware of cause of pain	Rarely	Usually
Associated symptoms	Visual and gastro-intest. irregularities; disturbances of psyche and autonomic nervous system (more severe)	Anxiety, depression, nausea, photophobia (less severe)
Condition during headache	Patient is ill and in marked distress; unable to work	Patient not very ill; able to work most of the time.

* Part of this table was taken from an article by Friedman and Von Storck (4).

will often remark "I have two kinds of headache" and will describe 1) the dull, constant bilateral more or less daily type, and 2) the usually unilateral, throbbing type, associated with ocular and gastro-intestinal symptoms, which occurs once or twice each month.

It has been pointed out that migraine patients are very prone to show severe emotional states which are provoked by a clearly defined condition. Wolfe (6) and many others have called attention to this fact, and have noted that such periods are associated with an increase in the intensity and frequency of the attacks. Pfeiffer (7) finds there are no consistent changes in the levels of blood electrolytes during relaxation or migraine headache, but that the attack is accompanied by a relative hemoconcentration. There are many other known factors which can be correlated with changes in blood volume and peripheral vascular tone.

More recently Friedman and Von Storck and others have attempted to distinguish between the ordinary migraine headache and the so-called tension headache. Their views are in accord with ours, based on results obtained with the forms of therapy suggested. They believe that tension headaches occur in direct relation to constant or periodic emotional conflicts of which such patients are usually only partially aware. These emotional states may provoke a headache by producing changes in the caliber of the cranial vessels and concomitant spasm of the skeletal muscles of the head and neck.

CRITERIA FOR THE USE OF NICOTINIC ACID

In the treatment of tension headache, it is important to be guided by certain factors. In order to obtain satisfactory results from the use of nicotinic acid therapy, we have postulated four criteria for differentiating tension headache from migraine. These criteria are as follows: 1) there is no aura, 2) the patient knows what causes the headache, 3) the headache is followed by some degree of depression, and 4) the patient is not relieved or is made worse following the administration of ergotamine or dihydroergotamine.

1. *Aura*

There is usually a striking absence of prodromata or pre-headache symptoms. Of our 50 cases of tension headache, in only 2 instances did prodromal symptoms occur. The patient is often awakened with the headache, which is described as a dull, throbbing or constrictive. The headache is ordinarily bilateral and often lasts for several hours or even days. In fact, upon close questioning, the patient will describe it in many instances as more or less constant but with exacerbation of a more severe pain at intervals.

On the other hand, in migraine headache, prodromata occur in about 75 per cent of the cases, manifested by such signs as scotoma, gastro-intestinal upsets, or disturbances of the autonomic nervous system. The pain is usually unilateral occurring frequently in the supraorbital region, and often described as throbbing. The patient is actually ill, seeks a dark room, wishes to be alone, and is unable to carry on his normal duties. After a variable period of time the pain disappears and in the interval between the attacks the patient is entirely normal.

2. *Cause of headache*

In the vast majority of cases the patient seems to know the cause of his headache. The factors producing the headache in our 50 cases were as follows: diet in 1 case, excitement in 10, overwork in 17, premenstrual tension in 7, occupational tension in 1, worry in 1, dislike of employer in 1, Ménière's disease in 5, mother-in-law trouble in 1, and unknown cause in 6 cases. Emotional factors are usually easily found. These may be constant (in which case the headache is usually constant) but are more often intermittent (then the headache is intermittent).

The headache may be due to living conditions, as in the case of one woman who was afflicted only when entertaining some unwelcome guest. Working conditions may be the cause; for instance, a patient may dislike his occupation or a fellow worker, or may resent being asked to work overtime by an employer toward whom he entertains a feeling of hostility.

3. *Depression*

Depression symptoms are the most commonly noted. They occurred in 34 of our 45 cases. It is remarkable how often the patient will volunteer the information that the attack is followed by a sense of depression which may last from one hour to several hours.

The migraine sufferer on the other hand is often tired but usually does not feel depressed.

4. *Effect of ergotamine*

I have had no success with nicotinic acid in those cases which are relieved by ergotamine tartrate (Gynergen). This is another reason for believing that tension headache is due to a vasoconstriction of the vessels. None of our cases was helped by ergotamine therapy. In 4 instances the headache was made worse.

During the past year, nicotinic acid was not used unless the patient fulfilled at least three of the four criteria postulated.

Many authors are of the opinion that nicotinic acid is indicated in various depressed states. Notably, Sydenstricker and Cleckley (8) believe that factors other than dietary disturbances play an important role in vitamin deficiency and that some unknown factor may also influence the failure of the neurones to receive and utilize an adequate supply of vitamins. According to Cleckley (9), it is probable in some cases that the beneficial effect observed is the result of vasodilatation rather than the correction of a deficiency state. Aring (10) concludes that there is an increase in the cerebral blood flow following the use of nicotinic acid. Goldzieher and Popkin (11) recommend its use in the treatment of severe celiopathic migraine. Crosby suggests the use of nicotinic alcohol (Roniacol tartrate) in the treatment of post-pneumoencephalographic headache and reports good results in a few cases: his recommendation is based on the good vasodilating action of this drug in the extremities. With these views in mind, it seems justifiable to use nicotinic acid in those cases not helped by ergotamine, since it is believed that in tension headache the pain is caused by vasoconstriction of the cerebral arteries rather than by dilatation of the extracerebral arteries.

Although the use of nicotinic acid is not new, the oral route of administration and insufficient dosage led to poor results and thus to its discontinuance in the treatment of headache. Washburne (12) published encouraging results with this drug in certain depressed states. The general outline of treatment which he recommended was followed in our cases of tension headache. In addition, we utilized the combined intravenous and oral routes, and administered a larger dosage of nicotinic acid.

In an exhaustive search of the literature, no contraindications to the use of nicotinic acid could be found.

RESULTS

The relief afforded following nicotinic acid therapy is always in proportion to the intensity of the vasomotor reaction, which is characterized by bright red flushing of the face, spreading rapidly over the entire trunk and often accompanied by tingling of the fingers, and lower extremities and with a marked sensation of heat. However, this reaction usually subsides in about ten to fifteen minutes, and there has never been any complaint if it was explained to the patient before the treatment was begun. Often, if the patient sits up too

soon, there is a sensation of dizziness due possibly to postural hypotension; this can always be obviated by placing the patient in a prone position and having him remain in the bed until the flush has subsided.

As nicotinic acid sometimes causes constriction of the splanchnic vessels, it was noted in a few instances that the patient complained of severe abdominal pain, which was quickly relieved by giving some form of atropine, or by hypodermic administration of methylamino-methylheptene (Octin) in 1-cc. dosage. Although there is the possibility of this rare side-effect, it does not lessen the effectiveness of the drug in relieving the headache, probably because it usually occurs late.

After frequent injections, occasionally it is impossible to get into the vein. If this occurs, the drug is given intramuscularly, using 200 mg. (100 mg. in each arm). This method causes a great deal of local pain, and the results are not as good. The pain can often be relieved by the application of an ice cube, wrapped in a small towel, applied to the site of the injection.

One of the best recommendations for the use of nicotinic acid orally and hypodermically (sterile technic) is that it is a perfectly safe procedure, and there are no contraindications, regardless of the age or physical condition of the patient. No patient has ever refused to take the treatment; they usually come in and ask for it.

In cases of premenstrual headache in which the usual drugs are of no avail, nicotinic acid therapy offers excellent results and should be given about twenty-four hours before the onset of headache. After a few periods of intravenous medication, oral administration is usually all that is necessary, provided the patient takes the drug orally for about six to eight months.

This type of treatment has also been used in persons with a tendency to Ménière's disease associated with endolymphatic hydrops. It seems to give as much relief as the use of histamine and is much less hazardous. Williams (13) recommends its use, and Porter (14) of Baltimore is very enthusiastic about it.

METHOD OF ADMINISTRATION

Intravenous administration: It is important to emphasize that the treatment should begin with nicotinic acid administered by the intravenous route. In all instances this should be immediately followed by oral administration. A solution of nicotinic acid (100 mg. in 10 cc. of sterile water) is injected intravenously, usually at the rate of 20 to 30 drops per minute. The rapidity of injection is determined in each case by the degree of flushing and warmth which ensues. The time required is usually about ten minutes. The intravenous therapy is continued as follows: for a two week period, three times a week; for another two-week period, twice a week; for another two week period, once a week; then once every other week for two doses, once every three weeks for two doses, once every four weeks for two doses, once every six weeks for two doses, and once every two months thereafter when necessary. At the conclusion of the first treatment, when the patient leaves the office, a prescription is given for two hundred 50 mg. tablets of nicotinic acid together with a typed schedule of instructions for its oral use; the first oral dose is to be taken preceding the next meal.

Oral administration: The schedule of oral administration is as follows: (a) For the first two days, three 50-mg. tablets are to be taken at 15-minute intervals preceding each meal. Example—if breakfast hour is 8:00 a.m., the first tablet is taken at 7:15, the second at

7:30, and the third at 7:45 a.m. (b) If no headache or nausea occurs, the dosage is increased on the third and fourth days as follows: four 50-mg. tablets are taken before each meal, according to the 15-minute schedule, the extra tablet being added to the first dosage. Example: 100 mg.—50 mg.—50 mg. (c) On the fifth and sixth days, five 50-mg. tablets are to be taken before each meal, the extra tablets being added to the first and second dosages. Example: 100 mg.—100 mg.—50 mg. (d) On the seventh and eighth days, six 50-mg. tablets are to be taken according to the 15-minute schedule before each meal, two tablets being taken together. Example: 100 mg.—100 mg.—100 mg. Thus, by the eighth day, the total daily dosage is 900 mg., and additional amounts may be given if necessary. The patient is maintained on the maximum dosage for a period of from seven to ten days, at the end of which time the dosage is decreased at the same rate at which it was increased. The average period for administration of nicotinic acid thus varies from two to six weeks, after which most patients are given 100 mg. three times a day, depending upon their reaction and condition.

As has been previously stated, the rapidity of the initial relief following the use of nicotinic acid is always in proportion to the intensity of the vasomotor reaction. After the second or third injection, side reactions if they occur, gradually become less severe. It must be emphasized again that the drug should be given slowly at first, but fast enough to get a definite flush.

DISCUSSION

Experimental and clinical observations point to a better understanding of the fundamental differences between migraine and tension headaches.

Giffin (15) asserted that tension states seem to be related to current situations, whereas migraine seems to be related to early psychogenetic factors. In tension headache patients have a feeling of insecurity, which leads to a sense of hostility to themselves and others with whom they associate and work. A sense of frustration often limits the individual in adjusting to his surroundings and manifests itself in a desire for affection and love.

The migraine individual on the other hand is not able to adjust to surroundings, whether the reaction be emotional, metabolic or allergic. Migraine headache has certain specific characteristics, whereas tension headache shows less of a set pattern.

Nicotinic acid therapy should be used only when there is a long-standing, more or less constant headache, usually not preceded by an aura, and followed by a sense of depression. The method of administration is of considerable importance and is commensurate with the good results obtained.

SUMMARY

Fifty cases of tension (vasoconstriction) headache are presented.

Four criteria for differentiating between migraine and tension headache are outlined.

Migraine is best treated with ergotamine, whereas tension headache is best treated with nicotinic acid.

For successful nicotinic acid therapy of vasoconstriction headache, the method of administration (intravenous plus oral) is highly important.

The favorable results obtained in this form of long-standing headache would appear to be due to the vasodilating effect of nicotinic acid.

REFERENCES

1. Crosby, R. M. N.: Treatment of post-pneumoencephalographic headache with 3 pyridyl carbinol tartrate (Roniacol tartrate), *Am. J. M. Sc.* **225**: 61, 1953.
2. Loman, J.; Rinkel, M., and Myerson, A.: Intracranial peripheral vascular effects of nicotinic acid, *Am. J. M. Sc.* **202**: 211, 1941.
3. Moore, M. T.: Treatment of multiple sclerosis with nicotinic acid and vitamin D, *Arch. Int. Med.* **65**: 1, 1940.
4. Friedman, A. P., and Von Storck, T. J. C.: Studies on vascular headache, *South. M. J.* **46**: 1127, 1953.
5. Peters, G. A.: Migraine: diagnosis and treatment with emphasis on the migraine tension headache; provocative tests and use of rectal suppositories, *Staff Meet., Mayo Clin.* **28**: 679, 1953.
6. Wolfe, H. G.: Psychobiologic aspects of migraine, *Arch. Neur. & Psychiat.* **37**: 895, 1937.
7. Pfeiffer, C.; Dreisbach, R. H.; Roby, C. C., and Glass, H. G.: The etiology of the migraine syndrome—physiologic approach, *J. Lab. & Clin. Med.* **28**: 1219, 1943.
8. Sydenstricker, V. P., and Cleckley, H. M.: The effect of nicotinic acid in stupor, lethargy, and various other psychiatric disorders, *Am. J. Psychiat.* **93**: 83, 1941.
9. Cleckley, H. M.: *Ibid.*, p. 92.
10. Aring, C. D.; Ryder, R. W.; Roseman, E.; Rosenbaum, M., and Ferris, E. B., Jr.: Effect of nicotinic acid and related substances on the intracranial blood flow of man, *Arch. Neurol. & Psychiat.* **46**: 649, 1941.
11. Goldzieher, J. W., and Popkin, G. L.: Treatment of headache with intravenous sodium nicotinate, *J. A. M. A.* **131**: 103, 1946.
12. Washburne, A. G.: Nicotinic acid and the treatment of certain depressed states, *Ann. Int. Med.* **32**: 261, 1950.
13. Williams, H. L.: Ménière's Disease. Springfield, Illinois, Charles C Thomas, Publisher, 1952.
14. Porter, Harry: Personal communication.
15. Giffin, M. E.: Some psychiatric aspects of migraine, *Staff Meet., Mayo Clin.* **28**: 691, 1953.

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Nicotinic Acid Side Effects and Toxicity: A Review

BY LOREN R. MOSHER, M.D.

The author reviews the literature on the possible toxicity of nicotinic acid, whose therapeutic value in the treatment of schizophrenia is still in dispute. While the drug appears to be relatively harmless, caution in prescribing it is advised, especially for women of childbearing age and for patients with a history of ulcer, gout, diabetes, or liver disease.

NICOTINIC ACID and nicotinamide have been reported to be both efficacious and harmless when used in high doses (up to 8-10 gm./day) as a treatment for schizophrenia, but the therapeutic effectiveness of the vitamin in this disorder remains a controversial, unresolved issue. Studies that report positive results(13, 20-25, 35) are offset to some extent by several negative ones(15, 27, 28, 31). The theoretical rationale for the use of this water-soluble B vitamin stems from a postulated defect in the transmethylation of nor-epinephrine to epinephrine (26). The drug is used in high doses (average daily requirement equals approximately 20 mg. [16]) to provide excess diphosphopyridinenucleotide (DPN) or nicotinamide-diphosphopyridine (NAD), its metabolically active end product, a methyl acceptor. In turn, the presence of excess methyl acceptors is thought to competitively inhibit the postulated aberrant transmethylation process(es).

This report will not attempt to validate or refute the claims made for nicotinic acid in the treatment of schizophrenia. Instead, it will review the relatively neglected literature on the possible toxicity of this "harmless" compound when used in massive doses. It is important to note that the vitamin, when used in these large doses, has effects that are never seen when it is given in the dose necessary to meet minimum daily requirements. It therefore should be called a *drug* at the dose levels advocated for the treatment of schizophrenia. Clinical reports of toxicity stem, in the main, from its use (because of its cholesterol-lowering effect) in the treatment of atherosclerosis.

Animal Studies

The dose at which 50 percent of animals given the drug die ($L.D._{50}$) for orally administered nicotinic acid in mice and rats ranges between 5 and 7 gm./kg.(47). Nicotinamide has been found to be two to three times as toxic as the acid(8). This finding is of some importance, as nicotinamide is said to be as effective in schizophrenia as the acid. Because it does not produce the flash associated with the latter compound, it may come into wide use.

Various derivatives of nicotinic acid have been given to several species of experimental animals for varying periods of time with—as might be expected—contradictory results. The experiments with rats, mice, and rabbits have yielded generally negative results(3, 9, 33, 47). Reports by Handler and Dann(18) and Rikans and associates(41) that a diet high in nicotinic acid (2 percent and 0.1 percent respectively) produces fatty livers in rats are the only reports of toxicity in these animals. Similar studies by Nath and associates (33) and Altschul and Hoffer(3) failed to produce fatty livers in rats. The extrapolation from these studies to long-term high-dose nicotinic acid use in humans is difficult because the preparations, dosages, and duration—21(41) to 170(4) days—were different from those commonly used with human subjects. There is no study presently available on these animals in which an oral dose of nicotinic acid equivalent to the

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3 gm./day recommended for schizophrenic patients has been administered for a prolonged period of time (i. e., a year or more).

Studies of nicotinic acid in birds (chickens and pigeons) have also given somewhat contradictory results: Unna(47) reported that five chickens fed sodium nicotinate for 21 days showed no ill effects, whereas Tomita and associates(46) found it to cause paralysis in two pigeons and chickens treated for ten days in a dose about three times that used by Unna.

Studies of nicotinic acid in dogs indicate that it may be toxic in this species. Chen and associates (9), Elvehjem and associates (14), and Chiu(10) report toxicity varying from weight loss(10) to bloody feces, convulsions, and death with associated gastrointestinal (erosions and petechiae) and central nervous system (shrunken, deeply stained cells in the cortex, hippocampus, and basal ganglia) pathology on autopsy (9). However, studies by Unna(47), Norcia and associates(34), and Ackermann(1) failed to demonstrate toxicity in dogs. Furthermore, only the two dogs in Chen's investigations that received 2 gm./day of nicotinic acid were so adversely affected. The four who received 1 gm./day and less gained weight. Two showed traces of albumin and one sugar in their urine. Chiu's(10) experiments seem particularly relevant to the long-term use of the drug as the two animals (the total number treated is not reported) that lost weight did so at the end of eight and 32 months of 100 mg./kg./day of nicotinic acid. This dose range (equivalent to 7 gm./day in a 70 K. human) is close to that used in humans (the drug has been used in doses up to 10 gm./day in schizophrenia), and the duration seems sufficient to relate it to long-term use in humans.

Animal studies of the effect of niacin in high dose on conception and gestation are rare. Altschul(2) reports that rabbits treated with 0.3 gm./day of nicotinic acid from before mating through lactation had no deformed offspring (including even those that did not survive). He gives no figures for survival rates of the treated vs. an untreated group. Several congeners of nicotinic acid, notably 6-amino nicotinamide and N-ethylnicotinamide have been widely used as experimental teratogens(12, 29, 40, 45). These studies have demonstrated that nicotinic acid operates to protect laboratory animals from the teratogenic effects of its congeners. It is thought that compounds like 6-amino nicotinic acid act by replacing nicotinamide in DPN, thereby inactivating it(18).

The report by Landauer and associate (29) contains the following disturbing quote: "It was also noted however, [in describing the protective effect of nicotinamide] that above the protecting level nicotinamide itself tends to act as a teratogen" (p. 199). The evidence for this apparently stems from an earlier study(30) in which nicotinamide protected chicks from insulin-induced rumplessness but caused an increased incidence of beak defects. The author was unable to locate any other studies of this possible teratogenic effect of high-dose nicotinamide. One must conclude that at this time there is little evidence either positive or negative with regard to the possible teratogenic effects of nicotinic acid.

Studies in Man

The reports of the use of high-dose niacin in schizophrenia in the psychiatric literature do not contain any evidence as to side effects or toxicity(13, 15, 20-25, 27, 28, 32). Two take up the issue directly(15, 20); the remainder give no specific information about whether blood tests were performed, nor do they contain clear statements about the number of patients who experienced side effects. Hoffer(20) cites a series of 12 patients who had been on 3 gm./day or more of niacin for a minimum of one year on whom bromsulfalein (BSP) tests were performed. Two of 12 patients had increased BSP retention. Three others were not on the drug during the test. This latter fact is important as the abnormal liver function tests associated with nicotinic acid's use usually revert to normal on cessation of the drug. Gallent and associates' study(15) of ten patients given DPN (the metabolically active end product of nicotinic acid) for 49 days specifically tested for blood, liver, and urinary abnormalities. None are reported, but as will be seen later, this period of time is probably not sufficient for abnormalities of liver function to appear.

The medical literature contains a number of reports that give in some detail the side effects and toxicity of niacin. Before turning

TABLE 1 – Nicotinic Acid Side Effects and Toxicity

AUTHOR AND YEAR	SAMPLE (NO. OF MALES)	AGE		DURATION	DOSE (gm./d)		SKIN				G.I.			
							FLUSH		PRURITIS		MINOR*		ULCER	
		MEAN	RANGE	RANGE	MEAN	RANGE	No	%	No.	%	No.	%	No.	%
Belle and Halpern 1958	48(31)	**	35-70	1-10 months	3	1-4	"all"		12	25	19	40	2	4
Parsons & Flinn 1959	44(30)	50	33-66	24-58 weeks	3	**	24 4-10ds	55	13	30	"frequent"		**	
							14 chronic	32						
Parsons 1962	68 **	**	**	1-3 years	4	3-6	"occurred"		**		"present" (no figs.)		9	13
Berge 1961	59(43)	47	7-66	10>1 year	3.5	3-6	"all"		**		13/66 1st 2 weeks	20	0	
				32>1-2 years			8/61 "moderate" after 2 weeks	13						
				19>2 years			36/61 "mild chronic"	59			11/61 prolonged	28		
Christensen and associates 1961	28(10)	51	30-72	all>1 year	3.3	**	"all"		1	4	1	4	**	

*Minor = nausea, vomiting, or diarrhea.
**No data given.

to those the point should be made that it is generally agreed the sustained-release preparations of the vitamin are more toxic than the regular or buffered preparations. As they do not ameliorate the gastrointestinal side effects, as originally intended, they probably should *not* be used.

Three studies, comprising five separate articles, report their findings in sufficient detail to allow comparison(6, 7, 11, 38, 39). The two reports by Parsons and those of Berge and Christensen and associates contain some of the same patients but are listed separately. Thus, some duplication occurs when reading table 1. A more detailed consideration of these reports is found in this table. Only the side effects found with use of *ordinary nicotinic acid* are summarized. Futhermore, *only* nicotinic acid was used in these studies, as the amide does not reduce serum cholesterol levels.

The table is self explanatory. The major findings will be summarized below.

Skin. An initial flush is experienced by essentially all patients who receive nicotinic acid. The figures for a chronic mild flush vary from 30 percent(39) to 59 percent(7). The figures for itching vary similarly. Two cases of hyperpigmentation(11) and two of acanthosis nigricans(39) have been reported. These skin effects disappeared on withdrawal of the drug.

Gastrointestinal. Some type of G. I. distress (heartburn, nausea, vomiting, or diarrhea), exclusive of ulcer, is reported in between 20(11) and 40 percent(8) of patients in the two large series that give precise data on its occurrence. Parsons reported nine ulcers in his series of 68 patients, and Belle reported two in his series of 48. Of his ulcer patients Parsons said: "In most instances the patients had previous ulcer symptoms or severe emotional trauma (p. 855)." In his earlier detailed report of seven cases Parsons(37) found the ulcers to be duodenal; they occurred after 96-130 weeks of 3-7.5 gm./day nicotinic acid therapy. In two cases there was a previous history of ulcer, one had previous symptoms of ulcer, two had other G. I. symptoms, and two had suffered severe emotional trauma.

Hepatic. Reports of abnormal liver function tests vary from "none"(6) to 45 percent (7, 11). As a rule these were abnormalities of BSP excretion or enzyme tests and reverted to normal either spontaneously or on withdrawal of the drug. Three cases of jaundice and one case of severe hepatic dysfunction have been reported secondary to prolonged nicotinic acid therapy. The two cases of jaundice reported by Christensen and associates(11) were with sustained-release preparations. The third, reported by Rivin(42), occurred after 70 weeks of plain

(only plain nicotinic acid included in the table)

AUTHOR AND YEAR	LIVER ABN. B.S.P. NUMBER	LIVER ABN. B.S.P. PER-CENT	LIVER ABN. ENZYME NUMBER	LIVER ABN. ENZYME PER-CENT	CARBOHYDRATE ABN. F.B.S. NUMBER	CARBOHYDRATE ABN. F.B.S. PER-CENT	CARBOHYDRATE ABN. G.T.T. NUMBER	CARBOHYDRATE ABN. G.T.T. PER-CENT	URIC ACID ABNORMAL NUMBER	URIC ACID ABNORMAL PER-CENT	MISCELLANEOUS
Belle and Halpern 1958	• •		• •		"1 case diabetes worse"				• •		6 "nervous" 2 "panic" 1 hypothyroidism
Parsons and Flinn 1959	"0/17 tested" "0/17 biopsied"				"No change in 3 diabetics"				29/40	72	2 cases acanthosis nigricans
Parsons 1962	11/131 tests	8	33/502 tests	7	Present (no figs.)				Present (no figs.)		"Heartburn" (no figs.)
Berge 1961	"23/52 or 45 percent had at least one abnormal test"				20/30 tested	67	14/27 "abn." 5/27 "equiv."	50 18	16/26 2 cases gouty arthritis	62	1 case esophagitis 2 cases brown pigmentation
Christensen and associates 1961	"45 percent with one abnormal test"		2/15	13	5/10	50	6/7	86	4/8	50	

nicotinic acid therapy and had a cytopathologic picture of intrahepatic cholestasis (like that found with chlorpromazine). In addition, Pardue(36) reported one case of severe functional hepatic impairment with ordinary niacin. The patient manifested generalized edema, reversed albumin/globulin ratio, abnormal BSP, cephalin flocculation, alkaline phosphatase, SGOT, and prothrombin time. This case, as did those with jaundice, cleared up within a month after cessation of the drug.

Carbohydrate metabolism. Hyperglycemia has been reported in 50(37) to 66 percent(7) of nondiabetics taking nicotinic acid. The percent of abnormal glucose tolerance tests closely parallels the reported incidence of increased fasting blood sugars. Molnar(32) found, in a careful metabolic study of six diabetic patients given 1-3 gm./day of niacin for five to six months, that all six showed increased glycemia, glycosuria, ketone bodies, free fatty acids, and insulin requirement. Gurian and Adlersberg(17) gave 3 gm. of niacin per day to ten mental hospital patients, three of whom were diabetic, and found abnormal fasting blood sugar in three (none of them diabetics) and abnormal glucose tolerance tests in two. They also stated that their diabetic patients required no additional insulin. Parsons and Flinn(39) also reported this, but Belle and Halpern(6) found that one patient's diabetes was exacerbated by the drug.

Uric acid. Berge(7) and Parsons and Flinn(39) both report an extraordinary percentage of increased serum uric acid levels in the patients tested (62 and 72 percent respectively). Berge's series contains two cases of acute gouty arthritis, one a recurrence and the second not previously diagnosed.

Miscellaneous. Belle and Halpern(6) reported a ten percent incidence of "nervousness," two "panic" states, and one case of hypothyroidism. The hypothyroidism improved when the drug was stopped. Berge's(7) series, which looked closely at thyroid function in a number of the patients, could not demonstrate any consistent abnormality. In addition, Henninger and Bowers (19) have recently reported the precipitation of incipient psychosis by nicotinic acid.

There are no reports of birth defects associated with use of nicotinic acid. It should be noted, however, that the major carefully reported series of patients have mean age ranges between 45 and 50 and contain a predominance of males (2 to 3 to 1 [see table 1]).

Discussion

In terms of toxicity the available evidence on niacin does indeed seem to indicate it is *relatively* harmless. But duodenal ulcer and hepatic damage can both be life-threatening if the agent responsible is not promptly withdrawn. For this reason, the psychiatric community should be cognizant of these poten-

tially dangerous effects of niacin. This is especially true if the recent publicity it has received as a treatment for schizophrenia means that more high-dose niacin will be prescribed.

To be on the safe side one must also urge caution in the prolonged use of this drug, as with any that has profound effects on several metabolic systems, the mechanisms of which remain to be elucidated. That is, high-dose niacin causes a significant fall in serum cholesterol and rises in blood sugar and uric acid. In addition, the hepatic toxicity of the sustained-release preparations appears to be related to prolonged activity of the drug on liver cells(11), which means of course (in conjunction with the abnormal tests found with the ordinary acid) that the function of liver cells can be impaired by the drug. Electron microscopic investigation of the drug's effect on liver cells seems to be warranted in view of these findings in conjunction with negative biopsy studies utilizing the light microscope(39). Recent evidence of direct hepatotoxic effect of alcohol as shown by the electron microscope(43, 44) makes such studies important in compounds that have metabolic effects but show no liver changes on study with the ordinary microscope. Caution would seem to be in order, especially when the drug's therapeutic effectiveness in schizophrenia is still under investigation. Even greater caution should be exercised if the drug is to be used in patients with a history of duodenal ulcer, diabetes, gout, or liver disease.

The drug has a number of annoying side effects which, although "harmless," resulted in up to one-third of patients in the medical series stopping the treatment, usually because of the flush. The possibility that niacin is teratogenic in large dose is in need of further study; it must be given serious consideration if the drug is to be prescribed for women of child-bearing age, as is the case with most schizophrenic women. Those who advocate the use of niacin in schizophrenia presently view it as especially helpful as adjunctive to phenothiazines in discharged schizophrenic patients. Thus, the drug may increasingly be given to women who are likely to become pregnant. Therefore, studies of its possible teratogenicity in animals would seem to be imperative.

Finally, the animal evidence that nicotinamide is two to three times as toxic as the acid (8) must be given due consideration. This point is stressed because nicotinic acid and nicotinamide have been reported to be equally effective in schizophrenia. Because the amide gives little or no flush (a bothersome, frequent side effect of the acid) it may come into wide use. The major reports of side effects and toxicity reviewed here used only the acid. Because of its possible increased toxicity one may not be justified in generalizing these results to the use of the amide. Additional comparative studies of the two compounds are necessary before a more precise answer can be given to their relative toxicities.

One must wonder why the medical investigations report so many side effects while the psychiatric do not (a recent unpublished study by Ananth and associates[5] *does* report distinct side effects in seven of 20 schizophrenic patients given nicotinic acid). Several possible explanations suggest themselves. The medical patients as a group are older (45-50 mean age vs. 30 for the psychiatric patients) and are being treated because of a medical illness, which in turn might make them more susceptible to side effects of toxicity (e. g., their livers might be already slightly damaged due to atherosclerosis or hypercholesterolemia). The younger psychiatric patients are usually, in contrast, medically "well."

Another explanation might relate to the intensity of scrutiny given the two groups. For example, the use of liver function tests in the medical series was far greater than in the psychiatric reports; only Gallent(15) reports using them routinely. Thus, potentially serious side effects could go unnoticed if they were not asked about unless laboratory tests are used routinely. This relates to a final possible explanation: In general, the physician's expectations affect both the occurrence and reporting of side effects. Thus, someone who strongly believes in the drug's usefulness might present it in such a way as to lead the patient to disregard or suppress side effects and might not inquire carefully as to their occurrence; this could result in the low rates reported.

As of this writing the Food and Drug Administration has not approved a New Drug

Application for niacin in the doses recommended for the treatment of schizophrenia. The criterion used in this regard is whether or not the drug has been shown to be safe and effective at the dose level recommended for the condition it is designed to treat. An Investigational New Drug permit is presently required for its study.

Summary

Studies of high-dose nicotinic acid treatment of animals and man are reviewed. Niacin, even in very high dose, appears to be a *relatively* harmless drug. There is, however, some evidence of toxicity in animals, a high incidence of annoying side effects, and a low but important incidence of toxicity (peptic ulcer, hepatic impairment, etc.) associated with its use in high dose in humans. The evidence from animal studies on its potential teratogenicity is inadequate to permit any definitive conclusions. In the doses recommended (3 gm./day and up) the vitamin has significant effects on several metabolic systems (carbohydrate, cholesterol, and uric acid), the mechanisms of which are poorly understood but which may be related to the impaired hepatocellular function indicated by the frequent association of abnormal liver function tests with its use.

At present, niacin's efficacy in schizophrenia remains an unresolved question. Because of these considerations as well as the need for additional studies in several areas of possible toxicity and a paucity of experience in its long-term use, caution would seem to be advised. It is recommended that prescription of the drug during pregnancy or for women of childbearing age, and for patients with a history of ulcer, gout, diabetes, or liver disease, be weighed very carefully.

REFERENCES

1. Ackermann, D., Fuchs, H. G., and Brandes, E.: Zur Wirkung der Nicotinsäure bei verschiedenen Anämien; Klin. Wchschr. author 18:348-350, 1939.
2. Altschul, R.: Unpublished study in Altschul, R., ed.: Niacin in Vascular Disorders and Hyperlipemia. Springfield, Ill.: Charles C Thomas, 1964, p. 69.
3. Altschul, R., and Hoffer, A.: Effects of Salts of Nicotinic Acid on Serum Cholesterol, Brit. Med. J. 2:713-714, 1958.
4. Altschul, R., and Hoffer, A.: Unpublished study in Altschul, R., ed.: Niacin in Vascular Disorders and Hyperlipemia. Springfield, Ill.: Charles C Thomas, 1964, p. 65.
5. Ananth, J. V., Ban, T. A., Lehmann, H. E., and Bennett, J.: Nicotinic Acid in the Prevention and Treatment of Methionine Induced Exacerbation of Psychopathology in Schizophrenics, presented at the annual meeting of the Canadian Psychiatric Association, Toronto, June 11-14, 1969.
6. Belle, M., and Halpern, M. M.: Oral Nicotinic Acid for Hyperlipemia, Amer. J. Cardiol. 2:449-452, 1958.
7. Berge, K. G.: Side Effects of Nicotinic Acid in the Treatment of Hypercholesteremia, Geriatrics 16: 416-422, 1961.
8. Brazda, F. G., and Coulson, R. A.: Toxicity of Nicotinic Acid and Some of its Derivatives, Proc. Soc. Exp. Biol. Med. 62:19-20, 1946.
9. Chen, K. K., Rose, Ch. L., and Robbins, E. B.: Toxicity of Nicotinic Acid, Proc. Soc. Exp. Biol. Med. 38:241-245, 1938.
10. Chiu, G. C.: Mode of Action of Cholesterol-Lowering Agents, Arch. Intern. Med. 108:717-732, 1961.
11. Christensen, N. A., Achor, R. W. P., Berge, K. G., and Mason, H. L.: Nicotinic Acid Treatment of Hypercholesteremia, J.A.M.A. 177:546-550, 1961.
12. Curley, F. J., Ingallas, T. H., and Zappasodi, P.: 6-Aminonicotinamide Induced Skeletal Malformations in Mice, Arch. Environ. Health, 16:309-315, 1968.
13. Denson, R.: Nicotinamide in the Treatment of Schizophrenia, Dis. Nerv. Syst. 23:167-172, 1962.
14. Elvehjem, C. A., Madden, R. J., Strong, F. M., and Woolley, D. W.: The Isolation and Identification of the Anti-Black Tongue Factor, J. Biol. Chem. 123:137-149, 1938.
15. Gallent, M., Bishop, M., and Steele, C.: DPN (NAD oxidized form): A Preliminary Evaluation in Chronic Schizophrenic Patients, Annals of Therapeutic Residency 8:542, 1966.
16. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics. New York: Macmillan Co., 1955.
17. Gurian, H., and Adlersberg, D.: The Effect of Large Doses of Nicotinic Acid on Circulating Lipids and Carbohydrate Tolerance, Amer. J. Med. Sci. 237: 12-22, 1959.
18. Handler, P., and Dann, W. J.: The Inhibition of Rat Growth by Nicotinamide, J. Biol. Chem. 146: 357-368, 1942.
19. Henninger, G., and Bowers, M.: Adverse Effects of Niacin in Emergent Psychosis, J.A.M.A. 204:1010-1011, 1968.
20. Hoffer, A.: Niacin Therapy in Psychiatry. Springfield, Ill.: Charles C Thomas, 1962.
21. Hoffer, A.: Nicotinic Acid: An Adjunct in the Treatment of Schizophrenia, Amer. J. Psychiat. 120:171-173, 1963.
22. Hoffer, A.: The Effect of Nicotinic Acid on the Frequency and Duration of Rehospitalization of Schizophrenic Patients, a Controlled Comparison Study, Int. J. Neuropsychiat. 2:234-240, 1966.
23. Hoffer, A., and Osmond, H.: Some Schizophrenic Recoveries, Dis. Nerv. Syst. 23:204-210, 1962.
24. Hoffer, A., and Osmond, H.: Treatment of Schizophrenia with Nicotinic Acid; A 10-Year Followup, Acta. Psychiat. Scand. 40:171-189, 1964.
25. Hoffer, A., Osmond, H., Callbeck, M., and Kahan, I.: Treatment of Schizophrenia With Nicotinic Acid and Nicotinamide, Journal of Clinical and Experimental Psychopathology 18:131-158, 1957.

26. Kety, S.: Current Biochemical Approaches to Schizophrenia, New Eng. J. Med. 276:325-331, 1967.
27. Kline, N. S., Barclay, G. L., Cole, J. O., Esser, A. H., Lehmann, H., and Wittenborn, J. R.: Controlled Evaluation of NAD in the Treatment of Chronic Schizophrenic Patients, Brit. J. Psychiat. 113:731-742, 1967.
28. Kline, N.S., Barclay, G.L., Cole, J.O., Esser, A.H., Lehmann, H., and Wittenborn, J.R.: Diphosphopyridinenucleotide (DPN) in the Treatment of Schizophrenia, J.A.M.A. 200:881-882, 1967.
29. Landauer, W., and Wakasugi, N.: Problems of Acetazolamide and N-Ethylnicotinamide as Teratogens, J. Exp. Zool. 164:499-516, 1966.
30. Landauer, W.: The Effect of Nicotinamide and Alpha-Ketoglutaric Acid on the Teratogenic Action of Insulin, J. Exp. Zool. 199:283-290, 1949.
31. Meltzer, H., Shader, R., and Grinspoon, L.: The Behavioral Effects of Nicotinamide Adenine Dinucleotide in Chronic Schizophrenia, unpublished paper.
32. Molnar, G.D., Berge, K.G., Rosevear, J.W., McGuckin, W.F., and Achor, R. P.: The Effect of Nicotinic Acid in Diabetes Mellitus, Metabolism 13:181-190, 1964.
33. Nath, N., Harper, A. E., and Elvehjem, C. A.: Diet and Cholesteremia. Four Effects of Carbohydrate and Nicotinic Acid, Proc. Soc. Exp. Biol. Med. 102:571-574, 1959.
34. Norcia, L. N., Brown, H. J., and Furman, R. H.: Non-Hypocholesterolemic Action of Nicotinic Acid in Dogs, Lancet 1:1255, 1959.
35. Osmond, H., and Hoffer, A.: Massive Niacin Treatment of Schizophrenia: Review of a 9-Year Study, Lancet 1:316-319, 1962.
36. Pardue, W. O.: Severe Liver Dysfunction During Nicotinic Acid Therapy, J.A.M.A. 175:137-138, 1961.
37. Parsons, W. B., Jr.: Activation of Peptic Ulcer by Nicotinic Acid, J.A.M.A. 173:1466-1470, 1960.
38. Parsons, W. B., Jr.: Use of Nicotinic Acid to Reduce Serum Lipid Levels, J. Amer. Geriat. Soc. 10:850-864, 1962.
39. Parsons, W. B., Jr., and Flinn, J. H.: Reduction of Serum Cholesterol Levels and Beta-Lipoprotein Cholesterol Levels by Nicotinic Acid, Arch. Intern. Med. 103:783-790, 1959.
40. Pinsky, L., and Fraser, F. C.: Congenital Malformations After the Inactivation of Nicotinamide in Pregnant Mice, Brit. J. Med. 2:195-197, 1960.
41. Rikans, L. L., Arata, D., and Cederquist, D.: Fatty Livers Produced in Albino Rats by Excess Niacin in High Fat Diets, J. Nutr. 85:107-112, 1965.
42. Rivin, A. U.: Jaundice Occurring During Nicotinic Acid Therapy for Hypercholesteremia, J.A.M.A. 170:2088-2089, 1959.
43. Rubin, E., and Lieber, C. S.: Early Fine Structural Changes in the Human Liver Induced by Alcohol, Gastroenterology 52:1-13, 1967.
44. Rubin, E., and Lieber, C. S.: Effect of Alcohol on Liver, New Eng. J. Med. 279:46-47, 1968.
45. Schardein, J. L., Woosley, E. T., Peltzer, M. A., and Kaum, H. A.: Congenital Malformations Induced by 6-Aminonicotinamide in Rabbit Kits, Exp. Molec. Path. 6:335-346, 1967.
46. Tomita, M., Komori, Y., and Sendju, Y.: Beiträgezur zur Kenntnis der Avitaminose, Zeitschrift fur Physikalische Chemie 158:80-89, 1926.
47. Unna, K.: Studies on the Toxicity and Pharmacology of Nicotinic Acid, J. Pharmacol. Exp. Ther. 65:95-103, 1939.

Who reads incessantly, and to his reading brings not a spirit and judgment equal or superior (and what he brings what needs he elsewhere seek?), uncertain and unsettled still remains, deep-versed in books and shallow in himself.

—JOHN MILTON

Newbold-'70
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LETTERS TO THE EDITOR

Niacin and the Schizophrenic Patient

SIR: I very much enjoyed reading Dr. Mosher's article, "Nicotinic Acid Side Effects and Toxicity: A Review". (March 1970 issue of the *Journal*). You will note that the title indicates it is a review, presumably a review of the literature. After reviewing the literature, Dr. Mosher takes it upon himself to advise other psychiatrists regarding the use of niacin, apparently in spite of the fact that he has had little experience in the vitamin's use in megavitamin doses. Dr. Mosher notes: "The reports of the use of high-dose niacin in schizophrenia in the psychiatric literature do not contain any evidence as to side effects or toxicity." I am afraid that Dr. Mosher has missed Dr. Abram Hoffer's article that appeared about one year ago in *Schizophrenia*(1). Dr. Hoffer devotes the entire article to the toxic side effects of niacin.

Dr. Mosher subdivides the toxic effects of niacin into several categories. The first category he discusses is the toxic effect on the skin in which he only mentions a flush. It is true that most patients flush with the medication, but if the flush is bothersome, it can usually be controlled with antihistamines. He fails to mention that patients develop a pigmentation of the skin or a dermatitis while taking the medication.

Under gastrointestinal reaction he notes that nicotinic acid may produce heartburn, nausea, diarrhea, or may activate an ulcer. This is certainly true. However, he fails to state that most experienced psychiatrists using niacin substitute niacinamide when treating a patient with an ulcer. He also fails to mention that the medication comes in many forms, i.e., the regular niacin tablet has a binder that is often the offending agent. Many patients who are unable to take the tablet are able to take the plain powder put up in capsule form. The niacin also comes in a buffered tablet, which many patients tolerate better than the plain tablet. These may seem to be small points, but they can certainly make the difference between success and failure where gastrointestinal symptoms are present.

Dr. Mosher correctly reports that liver function tests may be abnormal with the administration of niacin. However, these tests quickly revert to normal. I might also point out that other medications that lower blood cholesterol also frequently give false positive liver tests, and no one seems to get terribly excited about them.

Under carbohydrate metabolism, he mentions hyperglycemia as having been reported in 66 percent of nondiabetics. Many schizophrenics suffer from hypoglycemia, so the relative blood sugar elevation resulting from niacin is a very desirable feature. It is true that persons with diabetes must be closely watched after being started on niacin, since this may increase their blood sugar. On the other hand, one must keep in mind that the cholesterol level is lowered remarkably with the niacin administration, this factor alone may make it worthwhile to regulate the diabetic so that he can continue on niacin and possibly increase his life span with the lowered cholesterol level. Also, it is true that uric acid may be elevated. I have two patients who suffered from gout shortly before going on niacin; neither one has had his gout activated by the niacin.

It is interesting that there is a report of nervous panic states and the activation of a psychosis as a side reaction of niacin administration. Those of us who administer niacin are well aware of this fact and know that if excitement appears it can readily be held down, preferably by the use of diazepam (Valium). I administer anywhere from 40 to 100 mg. of diazepam daily and gradually decrease the level. With this technique this side effect can be rather easily managed.

I might add that some patients who cannot psychologically or physiologically tolerate niacin can be carried quite well on niacinamide, although Dr. Hoffer(2, 3) says that niacin and niacinamide are interchangeable as far as their psychological effects on schizophrenia are concerned. There are certainly exceptions to this statement, as Dr. Hoffer now agrees. Some persons suffering from schizophrenia react favorably to niacin and others react favorably to niacinamide. As far as the long-term effects are concerned, niacin in megavitamin doses has been used regularly since 1945. Dr. Hoffer has had more than 2,000 patients on niacin therapy.

Letters to the Editor are welcomed and will be published, if found suitable, as space permits. Please submit two copies (typewritten, double spaced), the length, if possible, not to exceed 500 words. Letters will be subject to the usual editing.

dating back to 1952. He states that none of them have sustained clinical liver damage.

Dr. Mosher also fails to mention the edema that sometimes follows niacin use.

It seems a mystery to me why there is so much controversy over the use of niacin in treating schizophrenia. I have an extraordinarily stable practice of schizophrenics (many of whom I have followed for eight to ten years) and have had them on numerous forms of medication. During the past five months I have had approximately 200 schizophrenic patients on niacin and have been quite impressed with the results. I have patients who, for one reason or another, have been taken off of niacin for short periods of time, and each almost invariably developed a full-blown picture of schizophrenia that disappeared once the niacin was resumed. It is true that niacin does not help all patients with schizophrenia, and many must be maintained on it for a long time.

If the National Institutes of Health wish to study niacin, they should not go about it by placing some schizophrenics on niacin and some on other medications; rather they should study patients with schizophrenia regulated by niacin. They should do psychological tests and clinical observations on these patients, withdraw the niacin for a period of time, and repeat the observations, after which they should place the patients back on niacin, making more observations and psychological tests. If such a research plan were carried out, there is no question whatsoever in my mind that niacin would be found vital to the well-being of many schizophrenics.

The references are:

1. Hoffer A: Safety, side effects and relative lack of toxicity of nicotinic acid and niacinamide. Schizophrenia 2:78, 1969
2. Hoffer A: Niacin Therapy in Psychiatry. Springfield, Ill, Charles C Thomas, 1962
3. Hoffer A, Osmond H: How to Live With Schizophrenia. New Hyde Park, NJ, University Books, 1966

H. L. Newbold, M.D
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Dr. Mosher Replies

Sir: I am pleased to see Dr. Newbold's response to my article since I think it is important that methods that can be used to avert or moderate the side effects of niacin therapy become widely known. I am also pleased with the letter because it substantiates, to some extent, my contention that there is considerable underreporting of niacin's adverse side effects in the psychiatric, as compared to the medical, literature.

I shall not respond to each of Dr. Newbold's criticisms, since in most cases he is only reiterating points contained in my article. For example, he states that in my section on skin I mention only the flush produced by niacin; however, the hyperpigmentation Dr. Newbold believes I overlooked is, in fact, pointed out on page 1292. I should like to note that since the paper's publication a number of practitioners have informally reported to me that they have found hyperpigmentation in up to one-third of their patients taking niacin in high doses.

I do want to apologize to Dr. Hoffer for not including his article in the review. Unfortunately, as I am sure Dr. Newbold knows, the time lag between a manuscript's preparation and its appearance in print is such that Dr. Hoffer's article appeared after the submission of my manuscript.

I think it is important to restate my article's purpose, since it seems that Dr. Newbold interpreted it differently than I had intended. I was not attempting to assess niacin's efficacy in the treatment of schizophrenia; rather I was attempting to make more widely known the literature available on its side effects and toxicity. In so doing I had hoped to provide practicing psychiatrists with information that might be important if they prescribed niacin in high doses. As I noted, Dr. Newbold's response seems to indicate that this compound's side effects, although present, have largely gone unnoticed or unreported.

Clearly, Dr. Newbold feels niacin is an important agent in the treatment of schizophrenia, and I cannot argue with clinical impressions derived from his personal experience. Nonetheless, I think it should be stressed (a point Dr. Newbold also makes) that nicotinic acid is not good for *all* schizophrenics. There is a need for research designed to delimit and define a subgroup of niacin responders.

Finally, let me thank Dr. Newbold again for doing a service to the readership of the *Journal* by citing methods of circumventing niacin's adverse side effects. It was not my intention to provide such information, and I appreciate his filling the gap.

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O'Reilly-'58
Bib No. 3221

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SOME CLINICAL ASPECTS OF NICOTINIC ACID THERAPY IN HYPERCHOLESTEROLÆMIA

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OVER THE PAST YEARS the relationship of lipid metabolism to the problem of atherosclerosis has been the source of intensive research. Nutritional,[9] dietary[1] and biochemical[4] studies have established an important relationship between lipid metabolism and the development of arteriosclerosis. In the psychiatric field the problem of arteriosclerosis leading to psychosis with cerebral arteriosclerosis is a steadily mounting one. Persons suffering from brain syndromes associated with cerebral arteriosclerosis constitute approximately 22% of first admissions to New York State psychiatric hospitals.[10] It is therefore necessary for the psychiatrist to concern himself with, and to promote research in, this field. Recent investigations of administration of nicotinic acid (niacin) to rabbits[5] and humans[3, 7, 8] have shown that nicotinic acid lowers serum cholesterol levels. The purpose of this study is (a) to investigate further this lowering property of nicotinic acid on cholesterol level, and (b) to study the clinical effects of prolonged administration of nicotinic acid in two cases.

METHOD

In a previous study[7] in which three groups were involved, nicotinic acid in a dosage of 3 grams daily over a 6-week period lowered serum cholesterol level by 20.4% in the non-arteriosclerotic group and 18.3% in the arteriosclerotic group. From these two groups 10 patients were selected who showed the greatest drop in cholesterol level. This group consisted of three subjects with a diagnosis of psychosis with cerebral arteriosclerosis. Diagnosis was based on the presence of a chronic syndrome, characterized by memory loss, periodic confusion, emotional lability and disorientation. History of a cerebral accident, headaches, dizziness and signs of peripheral arteriosclerosis, arteriosclerotic retinopathy and arteriosclerotic heart disease were taken into account. Their respective ages were 67, 63 and 61 years. The other seven members of the group were non-arteriosclerotic and consisted of six schizophrenics and one mental defective. Their ages ranged from 27 to 56 years with an average of 40.5 years. The average age of the whole group was 47.5 years.

TABLE I.

No.	Before niacin	On niacin for 6 weeks	Off niacin for 4 weeks	On niacin for 1 week	On niacin for 4 weeks	Diagnosis	Age
1	190.0	121.5	150	150	122	Schizophrenia	41
2	264.0	179.0	190	175	185	Psychosis with cerebral arteriosclerosis	67
3	288.0	243.0	290	232	215	Schizophrenia	56
4	200.0	110.0	265	175	120	Schizophrenia	31
5	208.0	149.0	220	210	120	Schizophrenia	52
6	209.0	132.5	235	156	115	Psychosis with cerebral arteriosclerosis	63
7	245.0	135.0	215	221	185	Mental deficiency	27
8	239.0	155.0	190	148	115	Schizophrenia	31
9	472.6	190.0	305	302	120	Schizophrenia	46
10	265.0	200.0	215	221	120	Psychosis with cerebral arteriosclerosis	61
Total	2580.6	1615.0	2265	1990	1417		
Mean	258.06	161.5	226.5	199.0	141.7		

PROCEDURE

At the beginning of the experiment, the fasting total serum cholesterol was determined for each

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subject by the Sperry-Schoenheimer method. The group were then given one g. of nicotinic acid by mouth three times daily for three months. One week after and six weeks after the start of the experiment, the serum cholesterol levels were again determined. At the end of the three-month period the nicotinic acid therapy was discontinued for a period of four weeks, at the end of which a serum cholesterol level was again determined for each subject. After this determination, the subjects were again given nicotinic acid, one gram three times daily, for period of four weeks and serum cholesterol levels were again estimated at the one-week and four-week periods. Table I shows the results obtained.

TABLE II.—CRITICAL RATIOS

	B On niacin for 6 weeks	C Off niacin 4 weeks	D On niacin 1 week	E On niacin 4 weeks
A Before niacin	8.33 (P = <.01)	1.77	1.967 (P = <.10> .05)	4.077 (P = <.01)
B On niacin 6 weeks		4.864 (P = <.01)	(P = <.10> .05)	1.121
C Off niacin 4 weeks			1.301	4.478 (P = <.01)
D On niacin 1 week				2.87 (P = <.05> .01)

1. Differences in means of cholesterol estimations from stage A (before niacin) to stages B (on niacin for 6 weeks) and E (on niacin 4 weeks) were significant at the .01 level; from stage A to intermediate stages C and D not significant.

2. Differences in means of cholesterol estimations from stage B (on niacin for 6 weeks) to stage C (niacin discontinued 4 weeks) were significant at the .01 level; from stage B to subsequent stages D and E not significant.

3. Differences in means of cholesterol estimations from stage C (niacin discontinued 4 weeks) to stage E (on niacin 4 weeks) were significant at the .01 level; from stage C to stage D (on niacin 1 week) not significant.

4. Differences in means of cholesterol estimations from stage D (on niacin 1 week) to stage E (on niacin 4 weeks) were significant at the .05 level.

CASE STUDIES

CASE 1.—A 62-year-old farmer was admitted to a general hospital for the treatment of cardiac failure. He was diagnosed by an internist as a case of arteriosclerotic hypertensive cardiovascular disease with diabetes mellitus. His diabetes was adequately controlled by a diet consisting of 200 g. of carbohydrate, 80 g. of fat, 150 g. of protein and 15 units of protamine zinc insulin daily. His cardiac condition was treated by Digoxin 0.25 mg. four times a day for the first two days and twice a day thereafter and a mercurial diuretic (Salyrgan) 2 c.c. every second day. On the third day of admission the patient became psychotic and was referred to the Saskatchewan Hospital, North Battleford, on November 16, 1954.

Physical Examination:

Cardiovascular system.—Heart enlarged to the left. Apex beat diffuse, gallop rhythm and duplication of the second sound. An occasional premature beat. Blood pressure 175/110 mm. Hg. with slight degree of pitting edema of both legs. *Respiratory system:* Multiple crepitations at both bases. *Eye grounds:* Optic discs normal. Irregular arteries with nipping in several places. *Peripheral vessels:* Generalized arteriosclerosis. *Electrocardiogram:* Left axis deviation.

Diagnosis: (1) Arteriosclerotic heart disease. (2) Mild diabetes mellitus.

Psychiatric examination revealed the patient to be mildly confused with pressure of speech, restlessness and euphoria. He was disoriented as to time and place. He had no insight into his condition and his judgment was impaired. *Diagnosis:* Psychosis associated with arteriosclerosis.

Treatment program.—The cardiac condition was treated by Digoxin 25 mg. tablets—one tablet four times a day for the first two days and one tablet twice a day thereafter, and Salyrgan 2 c.c. every second day. Condition improved.

The diabetes mellitus was controlled by the regimen previously prescribed. *Psychiatric treatment.*—The patient was given 1 g. nicotinic acid three times daily, and general care and management. After one week of this treatment he was no longer confused or disoriented and his euphoria had disappeared.

TOTAL SERUM CHOLESTEROL ESTIMATION

The serum cholesterol was determined before and after the taking of nicotinic acid. The estimation was carried out at 9 a.m. (fasting) and followed by a further estimation at 1:30 p.m. on the Monday and Friday of each week. A series of four serum cholesterol estimations were carried out before the start of treatment as a control. Nicotinic acid 1 g. tablets were given at 9:30 a.m., 1:45 p.m. and 4:00 p.m. daily. Investigation extended over a ten-month period from November 16, 1954, to September 12, 1955.

The serum cholesterol estimation as carried out is shown in Fig. 1.

Examination of Fig. 1 shows that from a serum cholesterol reading of 288 mg. % on November 22 (before therapeutic trial) the cholesterol level decreased to 180 mg. % on December 13 on a dosage of 3 g. nicotinic acid a day. The patient's physical and mental condition being improved, nicotinic acid was discontinued on the morning of December 14; serum cholesterol on December 20 before discharge on trial leave was 205 mg. %. The patient returned home on this date, having achieved a social remission, and was able to make a fair adjustment in the community. On May 16, 1955, when he once again became confused, retarded and depressed, hospitalization was again necessary. After 18 days on controlled diet, during which time no change was noted in his mental condition, the serum cholesterol level on June 3 was 305 mg. %. Three g. of nicotinic acid a day was prescribed once again. Having once again achieved a social remission he was discharged on trial leave on June 22. On that day his serum cholesterol level was decreased to 155 mg. %. He was given a maintenance dose of 1 g. nicotinic acid twice a day for an indefinite period. A follow-up study showed that on July 21, 1955, the serum cholesterol level was 198 mg. % and on September 12, 215

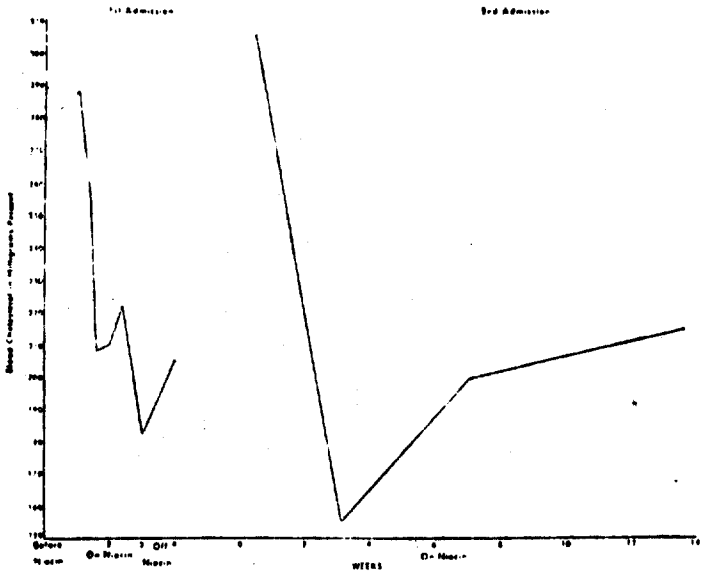

Fig. 1

mg. %. After his discharge from probation, contact was lost with the patient.

Electroencephalogram (E.E.G.) Investigations

A series of four E.E.G.'s were taken before and during the treatment period in order to evaluate any effect of nicotinic acid on the electrical pattern of the brain.

Before administration of nicotinic acid, over 50% of the E.E.G. records showed marked slow wave activity at 5 per second, with increased voltage in all areas of the head. When he was on nicotinic acid, the E.E.G. showed a remarkable improvement of the electrical patterns, and the marked slowing was not now evident in the recordings. The electrical patterns were now a stable 10 per second rhythm of moderate voltage in all areas of the head.

Side reactions.—Side reactions consisted of marked flushing and pruritus. These side reactions diminished and had disappeared on the third day of treatment.

Summary of Case 1.

A case of psychosis with cerebral arteriosclerosis was studied over a ten-month period. Administration of 3 g. of nicotinic acid a day resulted in a marked lowering of serum cholesterol level. E.E.G. tracings showed that normalization of the electrical pattern of the brain occurred. From a psychiatric viewpoint, nicotinic acid treatment resulted in a remission of the psychotic features of the case.

Case 2.—A professional man 55 years old had been diagnosed as a case of essential hypercholesterolemia. His serum cholesterol reading before treatment was 570 mg. %. He was given a rigid diet and his cholesterol level fell to 348.2 mg. % over a five-year period. He offered himself as a volunteer for nicotinic acid trials and he underwent a treatment regimen from November 20, 1956, to June 1, 1957, a total of six months.

Physical Examination:

He was slenderly built, height 5' 6". He had a peripheral arteriosclerosis and marked xanthoma of both lower eyelids. Lateral radiographs of the abdominal aorta showed a fairly marked calcification.

Work Tolerance:

He was able to walk only a short distance because he developed intermittent claudication in his lower limbs and fatigue, and was unable to drive in a car any distance as he developed carpo-pedal spasms. This necessitated the employment of a chauffeur for his automobile trips. From a psychological viewpoint this led to irritability, tenseness and anxiety as a reaction formation to his physical illness. He began 1 g. nicotinic acid 3 times a day on November 20, 1956, after investigation of his cholesterol level. Cholesterol levels were estimated on six occasions and the results are demonstrated in Fig. 2.

Results:

Over the six-month period certain beneficial effects of the nicotinic acid therapy were noted. The patient's work tolerance increased markedly. He was now able to walk as much as his work required. The cramps in his lower extremities were markedly decreased. He was also able to drive his car considerable distances without the onset of carpo-pedal spasms. His xanthoma of both lower eyelids showed a decrease in size. There was a marked reduction in anxiety, tension and irritability. This effect may have been due (1) to the effect of the nicotinic acid and (2) to the change in morale of the volunteer. Serial radiographs of the abdominal aorta over the six-month period showed no significant change in the extent of the calcification.

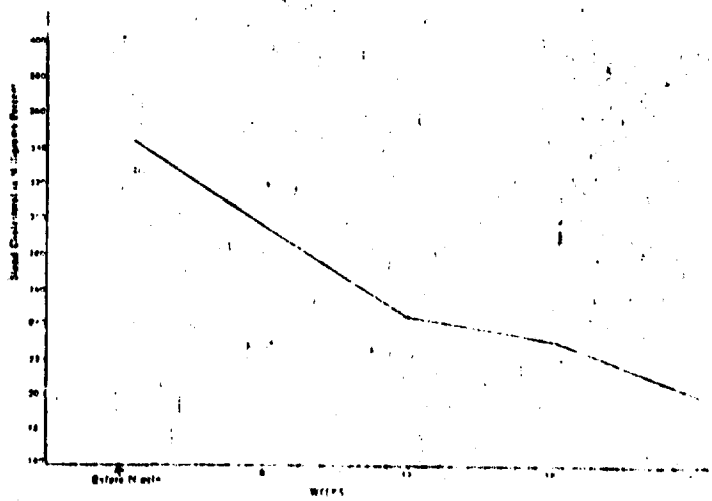

Fig. 2

Side Reactions:

Four weeks after the start of treatment the patient developed extrasystoles; the nicotinic acid was discontinued for four days and the condition cleared up. Resumption of treatment did not cause a recurrence.

Blood Cholesterol Level:

Over the six-month period the blood cholesterol fell markedly from 3 15.2 mg. % to 200 mg. % on a dosage of three g. of nicotinic acid daily.

Summary of Case 2:

A man with essential hypercholesterolaemia was given 3 g. of nicotinic acid daily over a six-month period. Beneficial effects noted were (1) increased work tolerance, (2) decrease in carpopedal spasm, and (3) lowering of cholesterol level to normal limits.

Discussion

The above findings confirm the serum cholesterol-lowering activity of nicotinic acid. The beneficial clinical effects are demonstrated in the two case studies. It seems pertinent therefore to study the role of nicotinic acid in lipoprotein metabolism. Our knowledge of the specific metabolic function of lipoprotein at the present time is limited. The "clearing" of alimentary lipaemia is attributed by Korn[5] to the enzyme "lipoprotein lipase" which catalyzes the biochemical reaction involved in the hydrolysis of triglyceride. Korn[5] has also shown that heparin or a similar compound is actually an intimate part of lipoprotein lipase molecule or complex. The parenteral administration of heparin and a few other compounds causes the enzyme activity to appear quickly in the plasma, where hydrolysis occurs. Preliminary investigations[5] suggest that nicotinic acid may have an anticoagulant effect. This effect may be due to a release of heparin by the nicotinic acid, thus leading to an increased activity on the part of lipoprotein lipase. This hypothesis would explain the action of nicotinic acid. Nicotinic acid itself on the other hand may have a direct action on the lipoprotein lipase similar to heparin.

Summary

This study confirms the serum cholesterol-lowering activity of nicotinic acid at the 1% level of confidence, i.e., there is only one chance in a hundred that the differences found were not true differences but due to chance. Two case studies are presented showing the effects of nicotinic acid in (a) a case of psychosis with cerebral arteriosclerosis, and (b) in a case of essential hypercholesterolaemia over a prolonged period of time. The possible action of nicotinic acid is briefly discussed.

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References

1. Ahrens, E. H. Jr. *et al.*: *J. A. M. A.*, 164: 1905, 1957.
2. Altschul, R.: *Circulation*, 14: 494, 1956.
3. Altschul, R., Hoyer, A. and Stephen, J. D.: *Arch. Biochem.*, 54: 588, 1955.
4. Fredrickson, D. S.: *J. A. M. A.*, 164: 1895, 1957.
5. Korn, E. D.: *J. Biol. Chem.*, 215: 1, 1955.
6. Kotlowski, K., and O'Reilly, P. O.: Unpublished observations, 1957.
7. O'Reilly, P. O., Demay, M. and Kotlowski, K.: *A.M.A. Arch. Int. Med.*, 100: 797, 1957.
8. Parsons, W. B. Jr. *et al.*: *Circulation*, 14: 495, 1956. *Idem*: *Proc. Staff Meet. Mayo Clin.*, 31: 377, 1956.
9. Stark, F. J. *et al.*: *J. A. M. A.*, 164: 1920, 1957.
10. Malzberg, B.: *Psychiat. Quart.*, 19: 122, 1945.

Résumé

Le contrôle de l'athérome et partant, de ses complications, semble lié au taux de cholestérol du sang, et parmi les diverses méthodes proposées pour abaisser la cholestérolémie, l'administration d'amide nicotinique semble prometteuse. L'auteur s'est proposé de l'appliquer à trois malades mentaux dont les troubles semblaient relever de l'artériosclérose cérébrale et à sept autres qui ne montraient pas d'atteinte vasculaire. Tous ces sujets reçurent un gramme de vitamine P.P. trois fois par jour pendant trois mois. La thérapie fut interrompue pendant quatre semaines et reprise pendant quatre autre semaines. On observa une chute probante du cholestérol sanguin chez chacun d'eux tant que fut administré ce médicament. Un de ces malades dont l'evolution est rapportée ici dans ses grandes lignes accusa une amélioration sensible au point de vue psychiatrique. Cette amélioration coïncida avec un retour de l'électroencéphalogramme vers la normale. Les faits cliniques d'un autre malade atteint d'hypercholesterolémie essentielle qui s'était soumis à cette cure avec avantage, sont aussi présentés dans le texte.

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Special Articles

MASSIVE NIACIN TREATMENT IN SCHIZOPHRENIA

Review of a Nine-year Study

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OUR interest in niacin began at the end of 1951 when exploring ideas developed with Dr. John Smythies (Osmond and Smythies 1952). We thought that schizophrenia might be caused by a disorder of adrenaline metabolism in which the body produced a substance with psychological effects like those of mescaline or *d*-lysergic acid diethylamide. These ideas have since been called the adrenaline metabolite theory of schizophrenia, and the adrenochrome hypothesis is a special example of that theory.

From time to time we asked ourselves what, supposing we were on the right track, would be an ideal treatment for schizophrenia. If our adrenaline metabolite idea was correct, then anything which reduced adrenaline production should help. We decided to try niacin because it might compete for methyl groups and so prevent more noradrenaline being methylated to adrenaline.

The introduction of a new treatment depends on a few cases responding favourably at the start. We had such luck with half a dozen cases early in 1952, the most dramatic being that of a boy of 17 admitted in February with acute schizophrenia:

A few days earlier he had become excited, overactive, silly,

TABLE I—FIRST DOUBLE-BLIND STUDY

Group	Number	Number on E.C.T.	Adjustment * of group	Mean number of months	
				Follow-up	Well
Placebo ..	9	6	9·2	29	11
Niacin ..	10	7	14·0	26	23
Nicotinamide	11	7	15·0	27	26

Statistical analysis:

	Well	Not well
Placebo	11 ..	12
Vitamin	49 ..	4

$\chi^2 = 16$ $P < 0{\cdot}001$.

* Described by Hoffer et al. (1957).

deluded, and sometimes hallucinated. He improved briefly with electroconvulsive treatment (E.C.T.), but subsequent insulin-coma treatment had to be stopped because of facial palsy. During the next three weeks his condition became much worse. Towards the end of May he was lying naked in bed, hallucinating, talking incomprehensibly, urinating and defaecating where he lay.

Since we could do nothing else for him at this time, on May 28 we started him on 5 grammes of niacin with 5 grammes of ascorbic acid daily, divided into four doses added to his tube-feeds. Next day tube-feeding was discontinued and ten days later he was described as "almost normal". When he went home on July 21 his family said he was "just as he'd always been". He was still well five years later, and he has not been in a mental hospital since.

A SMALL DOUBLE-BLIND TRIAL

Our first comparison study started in September, 1952, with 30 patients from the psychiatric ward of a general hospital who were diagnosed as schizophrenic by the psychiatric staff. These patients were divided at random into three groups, one receiving placebo, one niacin, and one nicotinamide. The dose was 3 g. a day, in 1 g. doses, for thirty-three days. The results (Hoffer et al. 1957), are summarised in table I. The placebo group did worst: they were followed up for nearly two years after discharge and on the average they were well only half the time. Patients who had niacin or the amide were followed up for just over two years, and they were well most of the time.

TABLE II—EFFECT OF TREATMENT IN 1952–55

Group	Number	Number of days in hospital mean	Number on E.C.T.	Number certified after discharge	Number of suicides
Niacin ..	73	63	34	7	0
No niacin ..	98	50	47	47	4

Statistical analysis:

	Number readmitted	Number not readmitted
Niacin	7 ..	66
Other treatment ..	47 ..	51

$\chi^2 = P < 0{\cdot}001$.

On the other hand, when O'Reilly (1955) gave niacin to a group of 11 chronic, regressed, deteriorated schizophrenics for eight weeks, only 3 improved in behaviour; and subsequently niacin, given in much larger doses for many months on end, did not benefit other chronic schizophrenics, even when combined with E.C.T.

Further Trials

We now began a larger investigation. Table II gives information about all the patients treated for schizophrenia in Saskatchewan in 1952–55. At the end of 1959 these patients were re-examined, and table III shows how many had been readmitted since they began treatment.

Of the 73 who received niacin while in hospital, 13 continued to take it into the follow-up period; 3 stopped in 1957, 2 in 1958, and 4 in 1959. Between 1952 and 1955 the cumulative readmissions increased more steeply for the group not receiving niacin (or amide). Over the next four years the readmission-rate was slightly higher in those who had been given the vitamin—most of whom were no longer receiving it. It seems from this that niacin kept the disease in check; but one can hardly expect such a protective action to continue indefinitely. As schizophrenia is not a transient infection like lobar pneumonia, a brief treatment cannot be expected to control it for ever. On the other hand, because it does not fluctuate as quickly as diabetes, continuous medication may not always be required. It lies somewhere in between. Most schizophrenics probably need chemical support for many years, and some may need it for a lifetime.

Table IV shows the effect of niacin and other treatments on the time spent in hospital. One way of summarising this table would be to say that, during the four-year follow-up, patients who had never had nicotinic acid spent two-fifths of a year in hospital, while for those who received it the average was only a sixth of a year.

TABLE III—CUMULATIVE READMISSIONS OF PATIENTS RECEIVING PLACEBO OR NIACIN

Group	Number	Year of readmission *		
		1952–55	1956–57	1958–59
Other treatment ..	98	47	53	56
Niacin	73	7	13	21
χ^2	..	30	23	14
P	..	<0·001	<0·001	<0·001

* Each patient requiring one or more readmissions was counted as one readmission.

VALUE OF LONG-TERM STUDIES

As already reported by one of us, a special study was made of 82 patients who had completed a second double-blind study (Hoffer 1961).

43 patients received placebo and 39 niacin. The two groups were similar as regards signs and symptoms, age, number receiving E.C.T., and mean days in hospital, but the placebo group had more females. All patients were followed up for two to six years and the results are shown in table V.

Patients were not considered "well" unless they were free from signs and symptoms and getting on satisfactorily with their family and in the community. They were "much improved" if getting on well in the community and with their family, but still having some residual symptoms. "Improved" patients were those who, though they were maintaining themselves out of the hospital, were doing so only because of the care and understanding of their family.

In analysing our data, we have used the term community-year, which means that the patient has been in the community one year. The group of 62 patients therefore were in the community a total of 241 community-years—i.e., a mean period of nearly four years.

TABLE IV—NUMBER OF DAYS IN HOSPITAL 1956–59

Group	Total	Patients re-admitted	Number of re-admissions	Total years' hospital stay per group	Days' stay per patient
Niacin	73	18	28	12·5	165
Other treatment	98	29	65	38	210

The clinical condition for each year is summarised in table V. The best results were among patients who not only received niacin in hospital but also took it for a long time after discharge. The second best were in those who did not get niacin in the hospital but had it after discharge.

TABLE V—PROGRESS IN THE COMMUNITY AFTER DISCHARGE

Group	Number	Total community years[1]	Community years		Readmitted		Five-year cures	Medication in year in which readmission occurred	
			W+M.I.	I+U	Patients	Admissions		Niacin	Placebo or none
Other treatment[2] ..	20	56	12	17	7	21	2	1/6[3]	20/49
Niacin[4]	62	241	109	73	24	45	19	6/112	39/127

1. One patient in community for 2 years equals 2 community years.
2. All other standard treatments as desired by therapist and placebo.
3. One patient admitted during calendar year when on nicotinic acid from a total of 6 community years.
4. Nicotinic acid in hospital and at least one year after discharge.
W = well. M.I. = much improved. I = improved. U = unimproved.

The third best were those who got niacin only when in hospital, while those who never received niacin at all ran a poor fourth. This supports our contention that patients taking niacin when well or much improved tend not to relapse. We infer from this that the vitamin protects them against schizophrenia in some way that is not yet understood. The time spent in hospital by the two groups, in the two to six years after their first discharge is shown in table VI.

TABLE VI—SECOND DOUBLE-BLIND GROUP: NUMBER OF DAYS IN HOSPITAL AFTER DISCHARGE

Group	Total	Patients re-admitted	Number of re-admissions	Total years' hospital stay per group	Days' stay per patient
Other treatment	20	7	16	9·1	207
Niacin ..	62	20	38	11·3	106

To exclude the possibility that our enthusiasm was somehow conveyed to our patients, we studied a number of schizophrenic patients who received niacin while in the hospital from doctors who were disinterested, or even sceptical, about its efficacy. We did not see these patients at all, but simply provided the vitamins and studied their progress from records while in hospital. We then checked our findings by consulting the senior doctor in charge of each patient. Those who received neither E.C.T. nor niacin fared worst (table VII). But the fact that they were in hospital for an average of only twenty-six days may account for their poor showing. The other two groups are comparable as regards the time they spent in hospital, and though no difference was noted on discharge, nearly five years later the niacin patients showed a clear advantage. This study underlines the need for careful and long-continued follow-up; for it was only after a lapse of years that the benefit of this treatment could be clearly demonstrated.

Norris (1959) found a follow-up period of two years sufficient to show what happened to schizophrenic patients five years after admission. From her studies in London she concluded that "the prognosis of schizophrenia is still gloomy . . . of those patients who recover enough to leave the mental hospital over one third will be admitted once again within the ensuing four years". Schizophrenics treated in Saskatchewan without niacin or nicotinamide had an equally gloomy prognosis (table III): over half were readmitted at least once within five years of discharge. But of those receiving this vitamin only about a sixth required readmission during the same period. ($\chi^2 = 23$, $P < 0{\cdot}001$).

FIVE-YEAR CURES

Any patient who has been out of hospital continuously for five years and is functioning satisfactorily (i.e., "well" or "much improved") is called a five-year cure.

The figures we give in section A of table VIII differ from those in table V because over a year has passed in checking the results and many more patients have become five-year cures. In the double-blind group over half of the niacin patients are five-year cures, and many others are already well into three or four years. Less than a quarter of the placebo group are five-year cures, but several more will also reach this point. This difference is significant at better than 1% probability, using a one-tailed test.

Section B refers to patients treated much earlier. The results are statistically better because the number of five-year cures is greater. ($\chi^2 = 7{\cdot}0$, $P < 0{\cdot}01$). Thus niacin seems to have had a curative effect for several years after treatment stopped.

TABLE VIII—NUMBER OF PATIENTS WELL FOR FIVE YEARS OR MORE

A. *Second Double-study*

Treatment	Total	Number well 5 years	5-year cure (%)
Niacin	62	34	55
Other treatment	20	4	20

$\chi^2 = 6{\cdot}0$ $P < 0{\cdot}01$ (one-tailed test).

B. *All other patients from Hoffer et al. 1957*

These include patients treated before the second double-blind trial was started.

Treatment	Total	Number well 5 years	5-year cure (%)
Niacin	58	45	78
Other treatment	90	34	38

$\chi^2 = 22{\cdot}0$ $P < 0{\cdot}001$.

Table VII (as previously mentioned) shows results in patients not treated by us. These treatments were started in September, 1955, for the E.C.T.-plus-niacin and for the control group, and in January, 1956, for the E.C.T. only group. At follow-up in 1961, there were already some five-year cures from the E.C.T.-niacin group, but none in the other two.

TABLE VII—TREATMENT RESPONSE OF PATIENTS NOT TREATED BY THE RESEARCH GROUP FOUR AND ONE-HALF YEARS AFTER FIRST PATIENT WAS TREATED

Group	Number	Mean age (age)	Mean days in hospital	Status at follow-up		Community status			Number of suicides
				(W+M.I.)	(I+U)	Re-admitted	In community		
							W	U	
Other treatment	22	37	26	1	21	13	2	6	1
E.C.T. only	26	35·5	65·5	5	21	13	10	1	1
E.C.T. and niacin	30	29·6	65·5	7	23	6	24	0	0

INDEPENDENT STUDIES

Apart from the unsuccessful trial of niacin by O'Reilly (1955), we know of only one test of the method by others. Denson (1961) in Saskatchewan found that of 17 schizophrenics treated with E.C.T. and nicotinamide, only 1 was still in hospital after two months. Of 19 controls who had received E.C.T. and placebo, 8 were still in hospital. On the average patients on nicotinamide spent 106·4 days in hospital during two years, compared with 177·5 for those on placebo.

TREATMENT WITH NIACIN AND NICOTINAMIDE

Niacin may be obtained in 0·5 g. tablets either alone or with various additives such as aluminum, acid buffers, or effervescents.

The sodium and potassium salts of niacin are also to be had. Some preparations contain other vitamins. Nicotinamide is not generally available in tablets but these can be made from the crystalline substance, which is easily obtainable from several manufacturing chemical firms. Niacin has a sour though not unpleasant taste but nicotinamide is very bitter and if given in solution should be dissolved in a flavoured carrier.

Niacin produces a flush but the amide does not. The flush (see Hoffer 1961) is readily tolerated by schizophrenics, by elderly patients, and by those with hypercholesterolæmia who know it will benefit them. As a rule, within a few days the flush is no longer noted.

We have not encountered the liver dysfunction which has been described in patients taking niacin. Occasionally there have been gastric and bowel disturbances, but we have not seen any patient who was intolerant of both niacin and nicotinamide.

There is no particular advantage in working the doses up slowly. A few days may be gained by starting on the full dose immediately.

The treatment, being safe and simple, can be combined with any other that the psychiatrist cares to use. In early or mild schizophrenia, when the patient is cooperative and does not need to be in hospital, 3–6 g. of niacin or nicotinamide are given every day. If he improves in three months this dose should be continued for a year. At the end of this time he may discontinue the vitamin; but if symptoms return the vitamin should be started again and given for another five years. This can be done continuously or sometimes intermittently, depending on the speed at which the symptoms return. We make a point of teaching our patients to recognise early symptoms.

We have found that while *supportive* psychotherapy is useful (Federn 1953) attempts at uncovering are harmful. Schizophrenics have to learn to live with what may be a chronic and severe illness, and like other patients they need help, encouragement, and clear medical direction. We have found our simple card-sort test (Hoffer and Osmond 1961) often helpful in following treatment, and this may in future be combined with the malve-factor urine test of Irvine (1961) or tests for the unknown urinary substances of Hoffer and Mahon (1961).

If the patient shows no improvement in three months he should be admitted to hospital and then treated as other patients who have had to come in because of their behaviour. Sedatives and tranquillisers can be used with niacin, but the effect of the phenothiazines may be potentiated (Burton et al. 1960). These adjuncts are needed only to reduce great anxiety or apprehension and should be stopped when they have done so; but the niacin should be continued.

When patients in hospital have not responded to niacin or its amide, we have found that a course of 8–20 E.C.T., combined with niacin, often brings much improvement. The patient should remain in hospital for two weeks after the last E.C.T. and then should continue as an outpatient on niacin or its amide.

A NEGLECTED REMEDY?

Niacin has some though not all the qualities of an ideal treatment: it is safe, cheap, and easy to administer, and it uses a known pharmaceutical substance which can be taken for years on end if necessary. But in spite of our intentions to the contrary, it is still an empirical remedy. It does not seem to affect the more chronic illnesses, and even in acute illneses its action is often less dramatic than that of some of the phenothiazines. Its protective qualities, continuing long after patients have stopped taking it, are puzzling. These would never have been observed had we used designs for our studies extending over only a few weeks or a few months.

Why then have these benefits passed almost unheeded? Partly perhaps because we have so far published only one paper (Hoffer et al. 1957) on the effects of niacin in schizophrenia. But another reason may be the extraordinary proliferation of the phenothiazine derivatives since 1954. Unlike these, niacin is a simple well-known vitamin which can be bought cheaply in bulk and cannot be patented, and there has been no campaign to persuade doctors of its usefulness. A third reason may be the still potent influence of Adolf Meyer whose notion that schizophrenia is a way of life rather than an illness has had many subtle effects on psychiatry. A sedative or tranquilliser can certainly alter a way of life; but a vitamin which is neither suggests dangerously that schizophrenia may be a disease. Whatever the reasons, interest in niacin treatment has been very small. If others confirm our work, then many sufferers from schizophrenia will spend longer out of hospital, in better shape than they do now, at negligible cost.

We still do not know whether niacin reduces the methylation of noradrenaline to adrenaline in the body, which led us to use it in schizophrenia. But Udenfriend et al. (1959) have found that methoxylation of noradrenaline is significantly reduced by nicotinamide. It has been proved to reduce the level of cholesterol in the blood. It seems to benefit some deliria not obviously associated with vitamin lack, and is claimed to improve many cases of intractable rheumatism. Moreover, this extraordinary vitamin is known to cure pellagra and the mental changes which accompany it.

In our view it is a useful adjunct in the treatment of schizophrenia, both for acute cases and to reduce the chance of relapses; and we hope it will be tested on a fairly large scale, with a carefully designed follow-up. At the worst, nothing would be lost.

For with niacin and its amide, unlike the waters of Jordan, one can always try the Abanas and Pharpars of the drug companies at the same time.

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REFERENCES

Burton, R. M., Kaplan, N. O., Goldin, A., Leitenberg, N., Humphries, S. R. (1960) *Arch. int. Pharmacodyn.* 128, 260.
Denson, R. (1961) Paper in Press. Diseases of the Nervous System 1962
Federn, P. (1953) *in* Ego Psychology and the Psychosis (edited by E. Weiss). London.
Hoffer, A. (1961) Niacin Therapy in Psychiatry. Springfield, Ill.
— Mahon, M. (1961) *J. Neuropsychiat.* 2, 331.
— Osmond, H. (1961) *ibid.* p. 306.
— — Callbeck, M. J., Kahan, I. (1957) *J. clin. exp. Psychopath.* 18, 131.

References continued overleaf

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Southern Med. J. 56:427-433. 1963.

Use of Nicotinic Acid to Reduce Serum Cholesterol and Remove Tissue Cholesterol*

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To quote from the author,*—"the use of nicotinic acid in large doses, like any form of therapy for hypercholesterolemia, must be considered experimental until the ultimate effect on human atherosclerosis can be assessed."

THE STATISTICAL RELATIONSHIP between hypercholesteremia and the incidence and mortality of coronary artery disease has long been recognized. Inclusion of hypercholesteremia as one of the factors being evaluated in epidemiologic studies, as in the Albany and Framingham studies, has further emphasized the fact that it is one of the 5 factors having an important bearing on the occurrence of myocardial infarction and death from coronary atherosclerosis,—the others are obesity, hypertension, smoking, and lack of physical exercise.

It has not yet been established that reduction in levels of serum cholesterol will retard or prevent the development of new atheromatous plaques or will remove plaques which have already formed.* Although proof is lacking, the consensus of informed opinion has swung more and more to the view that it is better to have a normal cholesterol level than an elevated one, and that some form of therapy is advisable. Some would say, as I have in the past, that both the physician and the patient should understand that they are participating in a clinical experiment. Today I would point out that a doctor interested in preventing coronary disease in his patients must take note of the factors listed above and decide what recommendations he will make about each of them. A decision to do nothing about any one or more of the factors might be difficult to justify on the basis of presently available statistics. This is especially true for any patient in whom two or more of the factors are abnormal, placing him in a high risk group.

In reducing levels of serum cholesterol, one may employ dietary measures, chemotherapy, or both. In the past decade the great emphasis has been on diet, first to the restriction of total calories and fat, and in the past several years toward restriction of saturated fats and the addition of unsaturated fats. In the past I have predicted that the ultimate treatment for hypercholesteremia would be chemotherapy, and I would now add that in 10 years we will remember the experimental dietary programs of the late 1950's and early 1960's only as a matter of historic interest and not as a major contribution to the long term care of most patients having hypercholesteremia.

Here it is important to distinguish between treatment of obesity and treatment of hypercholesteremia. If a patient is overweight, caloric restriction, which implies restriction of fats (most of which are saturated fats in the average American diet), is a necessity for weight reduction. On the other hand, if an individual's weight is not excessive, either dietary manipulation or chemotherapy may be utilized for hypercholesteremia. If diet is to be considered, it must be recognized that many programs which are highly effective in the metabolic unit or other short-term study in a research center are neither practical for home use nor acceptable to the patient as a way of life. As in diabetes, many patients with hyper-

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*Because of the many patients required to achieve statistical significance in 5 to 10 years, such a study is beyond the scope of any single institution. Only a nation-wide cooperative study can accomplish this evaluation, and would be a monumental undertaking. Preliminary committee work to consider the feasibility and estimate costs of such a study involving chemotherapeutic agents has been done at the request of the National Heart Council, but a decision to proceed with further planning has not been reached.

cholesteremia have a metabolic defect which is too severe to permit normalization of the serum level by dietary measures, at least by any which are practical in the home. These patients are candidates for chemotherapy, which might also be chosen for others because of its convenience and reliability. I customarily tell an obese patient with hypercholesteremia that he should first bring his weight to normal by caloric restriction, after which the serum cholesterol level may be normal. If it is still elevated on a diet which maintains ideal weight, he is offered nicotinic acid.

Manipulation of the composition of fats in the diet is only a means of altering lipid synthesis by the human body, and a relatively weak method at that as compared with chemotherapy. My reservation in predicting the complete shift of emphasis away from diet in 10 years is based on the large number of individuals who have spent years of their lives in research programs based on a dietary approach. However, some of the more courageous investigators in the field of atherosclerosis already are taking a long look at diet research and deciding that the noteworthy achievements have been in improved understanding of lipid metabolism and not in the care of patients.

In reviewing the effect of nicotinic acid on serum cholesterol and certain tissue deposits, I do not imply that in some individuals the elevated levels of serum triglycerides or other abnormalities in the lipid spectrum might not be of equal or greater importance. Happily, one working with nicotinic acid does not need to enter into controversies regarding cholesterol versus other lipid parameters, since nicotinic acid therapy results in reduction in all types of lipids which together constitute the total lipids of serum, as well as changing the lipoprotein fractions in the manner usually considered favorable from the standpoint of atherogenesis.

Nicotinic Acid Therapy

"What about the flush?" Probably the most frequent question asked when I present the nicotinic acid story is, "How can you get people to take such a large dose? Don't they have an awful flush?" When nicotinic acid is first administered (1 Gm. after each meal) all patients flush. The larger doses are given during or immediately following meals so complete absorption will be somewhat delayed. The flush appears to be no more severe than that produced by 50 mg. of nicotinic acid taken on an empty stomach. Furthermore, all investigators experienced with this form of treatment agree that the flush disappears in the early stages of treatment in most patients and constitutes no problem in long-term therapy. The average time for disappearance of the flush is the third or fourth day. The patient can be assured that the flush will be worst on the first day, will diminish daily thereafter, and is almost certain to have disappeared by the end of the first week of treatment. Blood pressure and cardiac rate are not affected by the flush. Nicotinic acid therapy neither precipitates nor aggravates angina pectoris.

At present there is a product commercially available (aluminum nicotinate*) which considerably reduces the incidence and severity of flushing, although it does not completely eliminate it. Both this product and plain nicotinic acid are available in 500 mg. tablets.

Reduction of Serum Cholesterol. In most individuals with hypercholesteremia, the level is reduced promptly by 1 Gm. of nicotinic acid taken three times daily—my usual starting dose. In many patients both the total cholesterol level and the beta-lipoprotein cholesterol fraction are normal in 2 to 4 weeks. If either of these values is still elevated after 12 weeks of therapy, the dose is increased to 4.5 Gm. daily and, if necessary, to 6 Gm. Higher doses have been used but do not appear to improve the results. For investigative purposes, I substitute nicotinamide for 12 weeks, from the 30th to 42nd week, both to illustrate by its placebo effect that the patient's response has not been related to factors other than nicotinic acid and also to permit certain special studies during this period in some patients.

Table 1 shows the average values for cholesterol, beta-lipoprotein cholesterol (BLC), and the beta/alpha$_1$-lipoprotein cholesterol ratio in our first 50 patients to complete one year of therapy. The failure of nicotinamide to maintain the lower levels achieved by nicotinic acid is well illustrated, with a return to lower levels when nicotinic acid was again used.

When the responses of individuals during most of their treatment periods are considered,

*Niclex—Walker Laboratories.

TABLE 1

RESPONSE OF SERUM CHOLESTEROL LEVELS TO NICOTINIC ACID THERAPY

	Pretreatment Average	Nicotinic Acid 0-12 Weeks	Nicotinic Acid 12-30 Weeks	Nicotinamide 30-42 Weeks	Nicotinic Acid 42-56 Weeks
Group 1 (26 pts.) Cholesterol*	323	263	248	320	240
Group 2 (24 pts.) Cholesterol*	304	239	223	306	216
Beta-lipoprotein cholesterol*	216	164	155	220	110
Beta/alpha ratio	6.1	3.1	3.1	5.5	3.8

*mg./100 ml.

(Each figure represents the average of individual patients' values, which in turn represent the average of all determinations made in each period.)

80% of the same 50 patients showed normal cholesterol levels and normal BLC fractions during most periods. Another 6% showed normal beta fractions and significant reduction* in serum cholesterol levels but not to normal. Still another 12% showed significant reduction* but not to normal in both total serum cholesterol and BLC levels. In only 2% (one patient) was there no significant reduction in either total cholesterol levels or the BLC fraction, and there was some doubt that he took his medication faithfully.

Table 2 shows the relationship of dosage to response in several groups of patients. The improvement in response by doses of 4.5 or 6 Gm. per day in patients failing to respond to smaller doses is shown. The patients in Groups B and C are also included in Group A, explaining why the Group A average on 3 Gm. of nicotinic acid per day is in the upper part of the normal range.

When we began to use aluminum nictotinate as the starting drug in many patients, it became apparent that the percentage of patients who needed larger doses after 12 weeks was reduced almost to zero, compared to about 50% for plain nicotinic acid (36 of 72 patients in Group A, Table 2). This, coupled with reports of others that 1.5 Gm. of aluminum nicotinate per day was an effective clinical dose in many patients (which had not been true of plain nicotinic acid), led to trials of the 1.5 Gm. dosage level for both drugs. (The data for most of these studies have not yet been compiled, which explains the small numbers available when table 2 was prepared.) Comparison of the two averages (Table 2) in these few cases lead to two working hypotheses: (1) Although 1.5 Gm. of either nicotinic acid or aluminum nicotinate per day may reduce serum cholesterol in some patients, the individual reductions and average reductions are greater when twice this amount is used. (2) Aluminum nicotinate may be somewhat more effective in reducing cholesterol levels than plain nicotinic acid, if these averages are verified in a much larger number of patients serving as their own controls.

Removal of Tissue Cholesterol. Although several groups have shown reduction in atherosclerotic lesions in cholesterol-fed rabbits by nicotinic acid, its effect on human atherosclerosis cannot yet be stated. However, the gradual disappearance of visible cholesterol deposits in skin and tendons leads to the hope that similar changes may occur in early atherosclerotic plaques and other por-

*Significant reduction is arbitrarily defined here as a reduction in average values of 40 mg./100 ml. or greater.

TABLE 2

RESPONSE OF SERUM CHOLESTEROL LEVELS* TO SEVERAL DOSES OF NICOTINIC ACID AND ALUMINUM NICOTINATE

	Dose Gm./day				
	0	1.5	3	4.5	6
Nicotinic Acid					
Group A (72 pts.)	311		311		
Group B (15 pts.)	308		2[illegible]	[illegible]	
Group C (21 pts.)	310		281	282	252
Group D (6 pts.)	301	253	[illegible]		
Aluminum Nicotinate					
Group E (7 pts.)	298	278			
Group F (8 pts.)	305		291		
Group G (4 pts.)	308	276	18[illegible]		

*mg. 100 ml.

tions of arterial walls which readily exchange cholesterol with that of the serum. Reduction in xanthoma tuberosum in two of my patients has been illustrated elsewhere.[1]

Mechanism of Action. My studies of the incorporation of radioactive acetate into cholesterol in hypercholesteremic patients, during nicotinic acid therapy and during control periods, have recently been reported to the Council on Arteriosclerosis of the American Heart Association.[2] The considerable differences shown in specific activity of serum cholesterol, cholesterol esters, and erythrocyte cholesterol probably indicate a marked decrease in cholesterol synthesis during administration of the drug. It is not certain whether this fully explains the drug's action. Perhaps increased oxidation of previously formed cholesterol, suggested by results of one series of animal experiments, also occurs.[3]

Gastrointestinal Side Effects. Early in treatment, a small percentage of patients have irritation of the upper gastrointestinal tract, usually consisting of heartburn or mild nausea, sometimes accompanied by vomiting. This effect occurred more frequently when we used several preparations which provided sustained release of nicotinic acid in the intestinal tract. The high incidence of gastric irritability and of alterations in hepatic function led to abandonment of these preparations, none of which were ever marketed.

Aluminum nicotinate, which should be designated as an "intermediate-release" preparation to distinguish it from those just described, also causes somewhat more nausea than plain nicotinic acid in doses of 3 Gm. per day or more. The 1.5 Gm. per day dose seldom causes nausea but, as previously noted, is not as effective as larger doses. (I have had no experience with doses of 2.0 or 2.5 Gm. per day.) It should be possible to reduce or eliminate nausea by appropriate pharmaceutical modification of this preparation, which otherwise appears satisfactory for clinical use.

If heartburn or nausea, often with vomiting, begins after months or years of treatment with nicotinic acid, the possibility of peptic ulceration exists. Several of the 9 instances of this complication observed in my series (the first 7 reported in detail elsewhere) have presented in this way.[4] Either previous symptoms or severe emotional trauma were present in most of the patients with activation of ulcers, but the possible role of nicotinic acid merits further study. In all patients the use of buffered nicotinic acid and an ulcer regimen have permitted continuation of therapy without deleterious effects.

Abnormalities in Liver Function Tests. In most patients receiving nicotinic acid, all tests of hepatic function remain at normal levels throughout treatment. In a minority of patients, one or more tests are abnormal at some time during therapy. The dysfunction is almost exclusively limited to tests depending on enzymic reactions (BSP., SGOT., SGPT., LDH., and occasionally alkaline phosphatase), whereas the serum bilirubin, serum protein fractions, cephalin flocculation, and thymol turbidity tests are rarely abnormal.

Our present policy of following these determinations in patients receiving nicotinic acid has gradually evolved over the past 6 years. The BSP. test, SGOT., SGPT., LDH., and alkaline phosphatase determinations are performed at the end of 6 months of therapy and every 6 months thereafter unless abnormal results are obtained. If the BSP. test is abnormal at any time, it is repeated one or two weeks later (along with the entire battery of tests named in the preceding paragraph). Needle biopsy of the liver is performed if the second BSP. result is abnormal also. If any abnormalities have ever occurred in a patient, the BSP. and other enzyme tests are performed at 3 month intervals, with the same determinations each month except that the BSP. test is omitted. This procedure has shown that the most frequent abnormalities are in the SGOT. and SGPT. determinations, but that none of the tests can be used to predict future BSP. retention.

All available evidence suggests that alterations in hepatic function tests represent temporary functional abnormality in enzymatic reactions rather than hepatic damage in the usual sense. (This is not surprising in view of the probability that the inhibition of cholesterol synthesis results from enzymatic changes, possibly competition for coenzyme A.) The evidence can be summarized as follows: (1) The abnormal results occur almost exclusively in tests depending on enzymatic function. (2) The abnormalities occur much more frequently during use of "sustained-release" nicotinic acid preparations, probably because of more continuous assault on hepatic

TABLE 3

RESULTS OF BSP. TESTS* DURING THERAPY WITH NICOTINIC ACID IN 68 PATIENTS

	Normal (0-10%)	Borderline (10-15%)	Elevated (15%)	Total
Plain nicotinic acid	120	6	5	131
Sustained-release preparations	11	7	11	29
Aluminum nicotinate	27	2	3	32
Total	158 (46 pts.)	15 (10 pts.)	19 (12 pts.)	192

*5 mg./kg.—45 minutes

enzyme systems. (3) The abnormal results are rapidly reversible when the drug is stopped or even when plain nicotinic acid is substituted in equal dosage. (4) Needle biopsies of the liver have failed to demonstrate any consistent pattern of histologic abnormality, with other factors incriminated when microscopic abnormalities were found. (5) The same patients can tolerate subsequent therapy with plain nicotinic acid or aluminum nicotinate without ill effects.

Table 3 shows the results of 192 BSP. determinations performed in 68 patients who had completed 6 months to more than 5 years of therapy, divided as follows: more than 5 years—3 patients; 4 to 5 years—14 patients; 3 to 4 years—7 patients; 2 to 3 years—15 patients; 1 to 2 years—19 patients; and 6 months to 1 year—10 patients. The increased incidence of abnormal tests during "sustained-release" therapy is noteworthy.

Table 4 shows the results of 296 SGOT. determinations in the same patients. The higher incidence of abnormality on "sustained-release" preparations is again illustrated, but it is also apparent that SGOT. values between 50 and 100 units can be expected in a minority of patients, occurring more frequently with

TABLE 4

RESULTS OF SGOT. DETERMINATIONS DURING THERAPY WITH NICOTINIC ACID IN 68 PATIENTS

	Normal (0-50 Units)	50-100 Units	>100 Units	Total
Plain nicotinic acid	173	13	1	187
Sustained-release preparations	17	13	7	37
Aluminum nicotinate	48	23	1	72
Total	238 (43 pts.)	49 (25 pts.)	9	296

TABLE 5

RESULTS OF ALKALINE PHOSPHATASE DETERMINATIONS DURING THERAPY WITH NICOTINIC ACID IN 68 PATIENTS

	Normal (0-12 U.*)	Slightly Elevated (12-20 U.*)	Definitely Elevated (20 U.*)	Total
Plain nicotinic acid	172	9	0	181
Sustained-release preparations	31	2	2	35
Aluminum nicotinate	66	2	0	68
Total	269 (57 pts.)	13 (9 pts.)	2 (2 pts.)	284

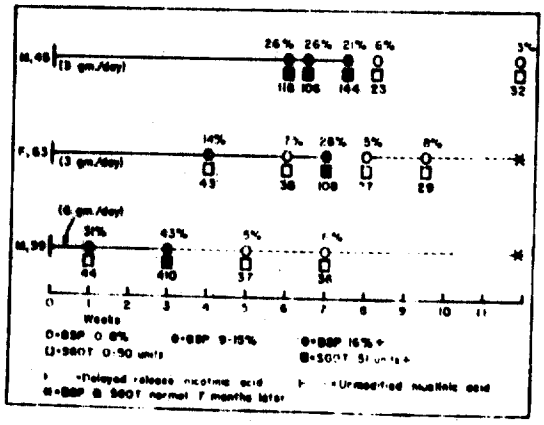
*King-Armstrong units.

aluminum nicotinate than with plain nicotinic acid. (As previously stated, the "sustained-release" drugs formerly used in the study are not commercially available.)

Table 5 shows the results of 284 determinations of alkaline phosphatase in the same patients. In comparison with the BSP. and SGOT. tests, the abnormalities are few, with only two instances of levels exceeding 20 King-Armstrong units, both occurring during "sustained-release" nicotinic acid therapy and associated with abnormalities in other tests in both patients.

Figure 1 shows the decidedly abnormal results of blood tests in 3 patients who were taking a "sustained-release" preparation of nicotinic acid ("K-B"). As with other such preparations I have used, these tablets reduced the incidence of flushing but produced a greater incidence of nausea and vomiting, necessitating a change to another preparation in several patients.

FIG. 1



The first patient took 3 Gms. of "K-B" daily for 7½ weeks. After 6 weeks he showed 26% retention of BSP and SGOT. activity of 118 units. Four days later the results were almost identical. To test the hypothesis that the abnormal BSP. retention might result from depletion of glycine by nicotinic acid (part of which is conjugated by glycine to form nicotinuric acid), an excess of glycine was administered for one week in addition to the previous program. However, this failed to alter the abnormal findings (BSP. 21%, SGOT. 144 units). Stopping medication for one week resulted in return of the tests to normal levels (BSP. 6%, SGOT. 23 units).

The second patient showed borderline or slightly elevated BSP. and SGOT. levels after 4 weeks of treatment with "K-B." Normal values were obtained at 6 weeks, but at 7 weeks the BSP. retention was 28% and SGOT level 108 units. Stopping the drug for only one week led to return of both tests to normal (BSP. 5%, SGOT. 27 units). Resumption of treatment with plain nicotinic acid failed to cause any abnormality in tests performed 10 days later and 7 months later.

The third patient showed 31% BSP. retention and 44 units of SGOT. after only one week on "K-B"; after 3 weeks the results were 43% and 410 units, respectively. Needle biopsy at this point showed normal liver tissue. When "the" drug was replaced (without interrupting therapy) by plain nicotinic acid, tests 2 weeks and 4 weeks later gave normal results, as did tests 7 months later.

As reported in detail elsewhere, needle biopsies of the liver have been performed in 5 patients who have shown two consecutive sets of abnormal results in the BSP. test as well as with other tests.[5] These cases are summarized in table 6. All 5 patients received "sustained-release" preparations when the abnormal results were obtained and biopsies performed. Factors which were present in these patients and are known to be associated at times with hepatocellular changes include diabetes mellitus (newly discovered and uncontrolled), prochlorperazine, carbon tetrachloride, and alcohol. All of these patients except one have subsequently taken plain nicotinic acid for periods of one year or longer without any clinical or laboratory evidence of hepatic dysfunction. The patient of Case 3, whose biopsy suggested early cirrhosis and who had been exposed to carbon tetrachloride, was not treated further because his serum cholesterol levels remained lower than 250 mg./100 ml.

Comment

A Committee on Clinical Trial of Anti-atherosclerotic Drugs, serving in an advisory capacity to the National Heart Council, considered the possibility of a nation-wide cooperative study and estimated the costs. Two types of studies were considered, both contemplating the use of three drugs and a control group. For a "secondary prevention" study in individuals who had experienced a previous myocardial infarction, it was estimated that 3,700 patients would be required (either remaining in the study for 5 years or suffering a second infarction). Assuming that it would take 8 years to accumulate this number of patients and follow them for 5 years, cost estimates were in the range of 2 to 3 million dollars annually over an 8 year period. For a "primary prevention" study, using individuals without previous vascular complication but with serum cholesterol levels above 300 mg./100 ml., it was estimated that 30,000 patients would be required on the same basis with an annual cost of 6 to 9 million dollars for 8 years. If these figures seem large or

TABLE 6

LIVER DISFUNCTION ON NICOTINIC ACID THERAPY—5 PATIENTS

	Case 1 (M-64)	Case 2 (M-58)	Case 3 (M-62)	Case 4 (M-54)	Case 5 (M-36)
BSP. retention—45 min.	31%, 31%	27%, 20%	26%, 20%	22%, 18%	31%, 43%
SGOT. (units)	70, 200	22, 86	118, 106	60, 38	44, 410
Alkaline phosphatase (King-Armstrong units)	18, 50	20, 9	12	9.9	6, 25
Needle biopsy	Fatty	Cholangitis?	Cholangitis? Cirrhosis?	Cloudy swelling	Normal
Other factors	Diabetes DRNA*	Prochlorperazine, diabetes, ulcer DRNA*	Carbon tetrachloride, DRNA*	Alcohol DRNA*	Ulcer DRNA*
Next BSP.	Normal	Normal	Normal	Normal	Normal
SGOT., alkaline phosphatase (post-treatment)	(1 mo)	(1 mo.)	(1 yr.)	(2 mo.)	(1 yr. — plain NA)

*Delayed-release nicotinic acid.

even prohibitive, consider them in relation to the figure of 4 million dollars for only the repairs of the launching pad following last week's launching of a Saturn missile, or contrast the costs of the medical study with the estimated 40 billion dollars for the program to land a man on the moon (which may not include the costs of his return trip).

The chemotherapeutic agents for hypercholesteremia which have received most attention in recent years are nicotinic acid, triparanol, and thyroid analogues. Of these, nicotinic acid has been studied longer, has proved more effective in providing prompt and sustained reduction in cholesterol levels, and appears most likely to prove free of serious side effects. If the increased incidence of nausea can be eliminated from aluminum nicotinate, it may be the most satisfactory preparation for widespread clinical use, but plain nicotinic acid or buffered nicotinic acid (the latter not commercially available now) provide versatility by being better suited to some patients.

Since the recent observation of the production of cataracts by triparanol in several patients, it is probable that this preparation will no longer be seriously considered for long-term administration.[6] Even before this development, the concern about the atherogenicity or other possible deleterious effect of the desmosterol in serum and tissues during triparanol administration led many investigators, including myself, to avoid its use.*

Of the several thyroid analogues studied in an effort to minimize the calorigenic effect while maintaining the cholesterol-reducing effect, d-thyroxine appears to be the only one worthy of further study. Unfortunately, the possibility of aggravation of angina or occurrence of sudden death remains a possibility when this agent is used to reduce cholesterol levels, and its use hardly seems justified except in a research setting at present.

Summary and Conclusions

(1) If treatment for hypercholesteremia is desired because of its statistical relationship to coronary artery disease and atherosclerosis in general, dietary methods or chemotherapy may be selected.

(2) If an individual is obese, caloric restriction should be prescribed until the excessive weight has been lost; if, however, a patient has hypercholesteremia without excessive weight, he may be treated by diet or pharmacologic agents or both.

(3) Nicotinic acid (3 to 6 Gm. per day) provides prompt reduction in serum cholesterol which is sustained as long as an effective dose is continued. Triglycerides and other lipid fractions are similarly reduced.

(4) Cutaneous flushing usually disappears early in treatment and constitutes no problem in long-term therapy. This effect is minimized by using aluminum nicotinate instead of plain nicotinic acid.

(5) Heartburn, nausea, and vomiting occur in a minority of patients taking nicotinic acid, and peptic ulcers have become active in a few patients. Nausea occurs more frequently when aluminum nicotinate is used.

(6) Available evidence indicates that alterations in tests of hepatic function during nicotinic acid therapy represent temporary functional abnormality in enzymatic reactions rather than hepatocellular damage in the histologic sense.

(7) Radioacetate incorporation studies suggest that nicotinic acid inhibits cholesterol synthesis in humans with hypercholesteremia.

(8) Gradual disappearance of visible cholesterol deposits (in skin or tendons) leads to the hope that atherosclerotic lesions may be similarly affected, either by decreased appearance of lipid in the plaques or by removal of lipid from early lesions.

(9) A large cooperative study is needed to determine the ultimate effect of nicotinic acid therapy on the incidence and mortality of myocardial infarction and other atherosclerotic complications in hypercholesteremic individuals.

*On April 17, 1962, The Wm. S. Merrell Co. sent a circular letter to the doctors of the country that it had withdrawn the drug from the market.

References

1. Parsons, W. B., Jr.: Treatment of Hypercholesteremia by Nicotinic Acid, Arch. Intern. Med. [illegible], 1961.
2. Parsons, W. B., Jr.: Reduction in Hepatic Synthesis of Cholesterol from C^{14} Acetate in Hypercholesteremic Patients by Nicotinic Acid, Circulation 24:1099, 1961 (Abstract).
3. Kritchevsky, D., Whitehouse, M. W., and Stapp, E.: Oxidation of Cholesterol-26 C^{14} by Rat Liver Mitochondria. Effect of Nicotinic Acid, J. Lipid Res. [illegible], 1960.
4. Parsons, W. B., Jr.: Activation of Peptic Ulcer by Large Doses of Nicotinic Acid. Report of Five Cases, J.A.M.A. 173:1466, 1960.
5. Parsons, W. B., Jr.: Studies of Nicotinic Acid Use in Hypercholesteremia, Arch. Intern. Med. [illegible], 1961.
6. Achor, R. W. P., and Bergen, K. G.: Personal Communication.

Parsons 57
Bib No. 3299

J. Am. Med. Assoc. 165:234-238. 1957.

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REDUCTION IN ELEVATED BLOOD CHOLESTEROL LEVELS BY LARGE DOSES OF NICOTINIC ACID

PRELIMINARY REPORT

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and
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Prompt and sustained reduction of blood cholesterol levels was obtained in nearly all of the hypercholesteremic patients who received large doses of nicotinic acid. Daily doses higher than 3 Gm. of nicotinic acid were required in more than 50% of the patients and in some cases 6 Gm. daily were needed to consistently reduce the blood cholesterol level. No dietary restrictions were imposed in this study. The mechanism by which nicotinic acid produces the observed changes in blood lipids remains obscure.

Previous studies by one of us (W. B. P.) and associates at the Mayo Clinic showed that significant reductions of levels of blood cholesterol and total lipids followed administration of large doses of nicotinic acid (niacin) in persons with hypercholesteremia.[1] The ratio of beta-lipoprotein cholesterol to alpha-lipoprotein cholesterol was also reduced by therapy with nicotinic acid. Phospholipids remained essentially unchanged, resulting in lowering of the cholesterol-phospholipid ratio. Substitution of a placebo resulted in return of cholesterol levels and the lipoprotein fractions to pretreatment levels. Further administration of nicotinic acid re-

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sulted in reduction of the lipid constituents similar to the initial response.[16] The effect of nicotinamide (nicotinamide) was not studied.

The present study was undertaken to confirm the results of the Rochester group, to obtain further experience with different doses of nicotinic acid, and to begin to evaluate the effect of nicotinamide on blood lipids. Blood cholesterol levels only were determined, omitting the total lipid and lipoprotein determinations, which had varied in the same direction and in about the same magnitude as the cholesterol levels in the earlier studies.[1] The results are so impressive that we consider a preliminary report to be justified at this time.

TABLE 1.—*Mean Cholesterol Levels at Intervals During Therapy with Nicotinic Acid*

	Mean Cholesterol Levels, Mg. per 100 Cc.		
Duration, Wk.	Group 1 8 patients	Group 2 16 patients	Groups 1 & 2
0	334	320	325
2	270	269	269
4	251	259	257
6	269	262	264
8	275	268	267
10	271	269	270
12	266	261	263
14	259		
16	241		
18	275		
20	273		
22	285		
24	272		
26	257		
28	225		
30	252		

Material and Methods

Patients were selected for study if the blood cholesterol level was consistently higher than 260 mg. per 100 cc. on at least two determinations before therapy. The average pretreatment level was 270 mg. per 100 cc. or higher in all patients.

Cholesterol determinations had originally been performed in these patients for a variety of reasons. Nine patients had survived myocardial infarctions. Three others suffered from angina pectoris, and two patients had arteriosclerosis obliterans with claudication. Two patients had survived cerebral infarctions. Two had diabetes mellitus. Xanthelasma of the eyelids had been noted in five patients, xanthoma tendinosum in one, and premature arcus senilis in two. Five patients gave a history of hypercholesteremia and/or atherosclerotic disease in members of their families but showed no evidence of these clinical states themselves.

Nicotinic acid was administered initially in doses of 3 Gm. daily in the form of capsules each containing 500 mg. Two capsules were given three times daily after meals to minimize side-effects. This dose was continued for 12 weeks in all patients. Then, if the blood cholesterol was normal (less than 250 mg. per 100 cc.), the same dose was continued, or, in a few patients, a maintenance dose of 1.5 Gm. per day was tried. In patients whose cholesterol levels remained above normal after 12 weeks, the daily dose was increased to 4.5 Gm. and later to 6.0 Gm. in some cases, depending on the response. After 30 weeks of therapy with nicotinic acid, nicotinamide was substituted in a dose equal to the most effective dose of nicotinic acid.

All patients were urged to continue eating exactly as they had before the study, so that the only variable introduced was the administration of nicotinic acid. Except in one patient (case 9) on a low-fat diet and two diabetic patients (cases 2 and 14) on special diets, all patients can be considered to have been eating an average American diet.

Blood samples were drawn at two-week intervals for cholesterol determinations by the method of Drekter.[2] Determinations of sulfobromophthalein (bromsulfalein) clearance and blood nonprotein nitrogen and urinalysis were performed after 8 to 32 weeks of therapy in 19 patients.

Results

Changes in Cholesterol Levels.—Twenty-four patients have thus far been followed for 12 weeks or longer. Of these, eight patients (group 1) have completed 30 weeks of therapy with nicotinic acid and 4 to 12 weeks of nicotinamide, permitting some preliminary observations regarding the latter drug. The remaining 16 patients (group 2) have completed 12 to 30 weeks of therapy with nicotinic acid.

Table 1 shows mean cholesterol levels for both groups of patients at two-week intervals. The prompt reduction effected by nicotinic acid is shown in the mean decrease of 56 mg. per 100 cc. in the first two weeks of therapy. The effect of the initial dose (3 Gm. daily) is shown by a mean reduction of 68 mg. per 100 cc. in group 1 and 59 mg. per 100 cc. in group 2 in the first 12 weeks. The effect of larger doses is shown by a further mean reduction of 14 mg. per 100 cc. in the subsequent 18 weeks in group 1.

TABLE 2.—*Average Cholesterol Levels During Therapy with Nicotinic Acid and Nicotinamide (Group 1)*

		Av. Cholesterol Levels, Mg. per 100 Cc.			
Case No.	Age and Sex	Before Therapy	0-12 Wks.	12-30 Wks.	Nicotinamide Therapy
1	56, M	480	291	264	342
2	54, F	305	241	252	280
3	41, F	308	241	205	284
4	58, F	337	231	249	349
5	56, M	272	276	246	301
6	38, F	315	269	260	318
7	61, M	298	269	219	326
9	50, F	360	290	292	254
Av.		334	267	258	319

As shown in table 1, the eight patients of group 1 showed a reduction in mean cholesterol level of 64 mg. per 100 cc. in the first two weeks of therapy, from 334 mg. to 270 mg. per 100 cc. At the end of 30 weeks of therapy, the mean cholesterol level had been reduced further to 252 mg. per 100 cc.

because of irritable bowel symptoms, and the latter after several weeks because of dryness of the eyes and blurring of vision with no objective findings when examined by an ophthalmologist before and after use of nicotinic acid. No side-reactions were observed in patients taking nicotinamide.

Sulfobromophthalein tests of liver function, determinations of blood nonprotein nitrogen levels, and urinalyses revealed no abnormality in 19 patients after 52 weeks of therapy.

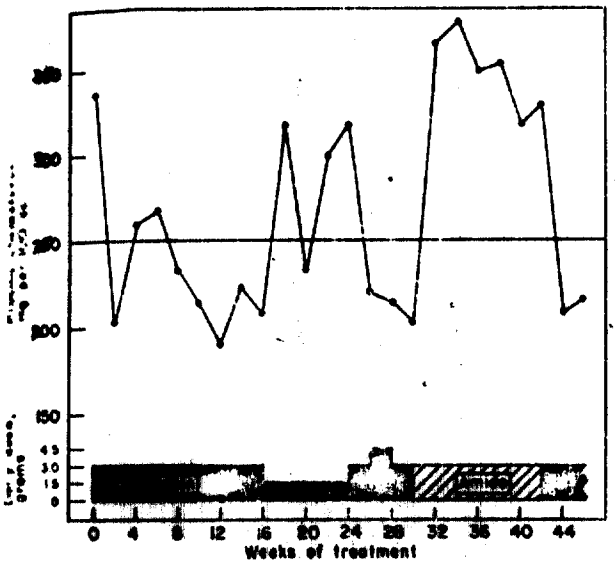

Fig. 1 (case 4).—Illustration of reduction of blood cholesterol levels by administration of 3 Gm. of nicotinic acid (niacin) daily, return to elevated levels during the use of 1.5 Gm. of nicotinic acid daily, reduction to normal levels when a daily dose of 3 Gm. of nicotinic acid was resumed, return to elevated levels when nicotinamide (niacinamide) was substituted, and reduction to normal levels when use of nicotinic acid was again resumed.

Comment

Prompt and sustained reduction of blood cholesterol levels after large doses of nicotinic acid in nearly all of the patients studied confirms the previously reported results of the Mayo Clinic group.[1] The greater reduction in cholesterol levels and larger percentage of cases showing reduction to normal values in our series can be attributed to more liberal use of doses of 4.5 or 6 Gm. per day. As further experience has been obtained, it has become apparent that 50 to 70% of patients require doses of this order to reduce cholesterol levels to normal. It also seems clearly established that continuous therapy at the same dosage is necessary to maintain the reduced levels, since substitution of a placebo or of nicotinamide resulted in prompt return of blood cholesterol to the pretreatment range of values. With very few exceptions, a dose of 1.5 Gm. of nicotinic acid per day has also proved to be ineffective or to give suboptimal results.

Figures 1, 2, and 3 show typical cases which illustrate individual variations in response to the various doses of nicotinic acid and the lack of effect of nicotinamide. Figure 1 shows the prompt reduction to normal cholesterol levels in case 4 on the initial dose of 3 Gm. daily. When the dose was reduced to 1.5 Gm. daily, the cholesterol levels again rose. Resumption of the original dose resulted in reduction to normal levels again. When nicotinamide was substituted at the end of 30 weeks, blood cholesterol levels rose to values as high as those observed before treatment. After 12 weeks of administration of nicotinamide, nicotinic acid was again given in the original dose, followed by prompt reduction of blood cholesterol level to normal.

Figure 2 shows the failure of the patient in case 7 to respond to the initial dose of 3 Gm. per day but reduction to consistently normal cholesterol levels after use of 4.5 Gm. daily. Substitution of nicotinamide in the same dose was followed by an abrupt rise in cholesterol levels to well above the normal range. When administration of nicotinic acid was resumed, blood cholesterol levels fell to normal and have remained consistently normal.

Figure 3 shows the failure of the patient in case 6 to respond to doses of 3 Gm. daily or 4.5 Gm. daily but reduction to consistently normal cholesterol levels after

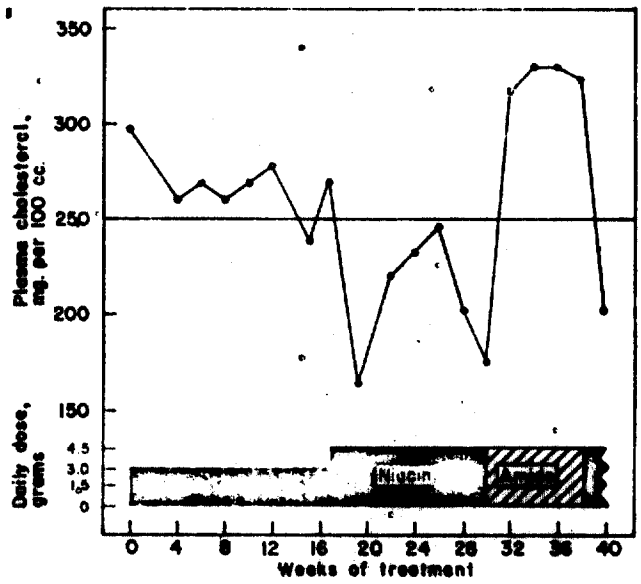

Fig. 2 (case 7).—Illustration of reduction of blood cholesterol levels to normal by administration of 4.5 Gm. of nicotinic acid (niacin) daily, return to elevated levels when nicotinamide (niacinamide) was substituted, and reduction to normal levels when use of nicotinic acid was resumed.

use of 6 Gm. daily. When nicotinamide was substituted in equal dosage, cholesterol levels returned to values as high as those observed before treatment.

The rapid disappearance of the flush which nicotinic acid produces and the absence of other significant side-reactions or toxic effects in the experience to date suggests that this method is practical for clinical use.

Since no dietary restrictions were imposed either in the present study or in the Mayo Clinic series, it is apparent that nicotinic acid reduces cholesterol and beta-lipoprotein cholesterol levels in spite of the use of an average American diet by persons with hypercholesteremia.

The mechanism by which nicotinic acid produces the observed changes in blood lipids remains obscure. The apparent failure of nicotinamide, which had an effect similar to that of the placebo employed by the Rochester group, may provide a clue to the mechanism of action because of the slight chemical difference between the two drugs. These observations may, in fact, open a new avenue of investigation regarding the mechanism which establishes the total blood cholesterol and its several lipoprotein fractions at normal or abnormal levels. The lack of cholesterol-reducing effect of nicotinamide agrees with the observations of Altschul and associates.[3]

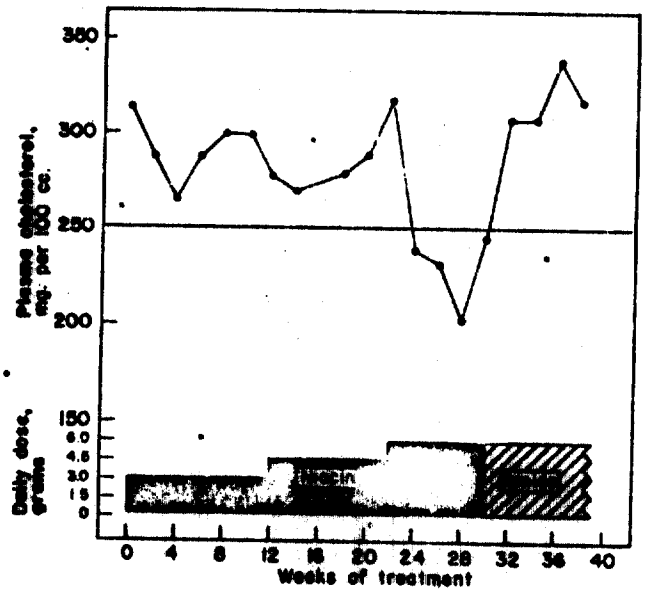

Fig. 3.—Illustration of the reduction of blood cholesterol levels to normal by administration of 6 Gm. of nicotinic acid (niacin) daily, with the return to elevated levels when nicotinamide (niacinamide) was substituted.

The accumulated experience in the Rochester and Madison series indicates, we believe, that nicotinic acid is the most effective and practical agent yet introduced for reduction of elevated levels of blood cholesterol and beta-lipoprotein cholesterol. The observed changes in blood lipids are those which have been the objective of many therapeutic programs because of the increased incidence of atherosclerosis in individuals with hypercholesteremia and elevated ratios of beta-lipoprotein to alpha$_1$-lipoprotein cholesterol. However, in spite of the well-known statistical relationship, we do not mean to imply that these changes will necessarily prevent atherosclerosis or arrest its progress. Evidence of such benefit can be obtained only by treating a large number of patients for many years and comparing the results with an untreated control group. This study is now in progress. It should be mentioned, however, that Altschul's studies on rabbits showed inhibition or prevention of atheroma formation in animals fed nicotinic acid and cholesterol in comparison to a control group fed cholesterol without nicotinic acid.[3b]

Summary

Administration of nicotinic acid (niacin) orally in large doses (3 to 6 Gm. daily) to 24 patients with hypercholesteremia resulted in significant reduction in blood cholesterol levels in 16 (66.7%). Normal levels were attained in 6 of 8 patients followed for 30 weeks or longer and in 7 of 16 additional patients followed for at least 12 weeks.

Doses higher than 3 Gm. of nicotinic acid daily were required in more than 50% of patients. Significant reduction in blood cholesterol occurred with doses of 6 Gm. daily in four of five patients whose levels had remained above normal after smaller doses, suggesting the possibility of future improvement in seven additional patients who have thus far failed to respond to a daily dose of 4.5 Gm.

Substitution of nicotinamide in equal dosage after 30 weeks of therapy with nicotinic acid in eight patients was followed by prompt return of blood cholesterol to pretreatment levels in every instance.

Flushing and pruritus, which occur after ingestion of nicotinic acid, subsided within the first week of therapy in nearly all cases. No serious side-reactions or toxic effects have been observed which can be attributed to nicotinic acid. Nicotinic acid proved to be effective in lowering cholesterol levels despite continuation of the patients' customary diets.

30 S. Henry St. (3) (Dr. Parsons).

References

1. Parsons, W. B., Jr., and others: (*a*) Changes in Concentration of Blood Lipids Following Prolonged Administration of Large Doses of Nicotinic Acid to Persons with Hypercholesterolemia: Preliminary Observations, Proc. Staff Meet. Mayo Clin. **31**:377-390 (June 27) 1956; (*b*) Effect of Large Doses of Nicotinic Acid on Plasma and Serum Lipids of Human Beings with Hypercholesterolemia, Presented to the American Society for the Study of Arteriosclerosis, Chicago, Nov. 12, 1956.

2. Drekter, I. J.: New Method for Direct Determination of Cholesterol, Bull. New York M. Coll. **6**:138-141 (Oct.) 1943.

3. (*a*) Altschul, R.; Hoffer, A.; and Stephen, J. D.: Influence of Nicotinic Acid on Serum Cholesterol in Man, Letter to the Editor, Arch. Biochem. **54**:558-559 (Feb.) 1955. (*b*) Altschul, R.: Die Beeinflussung des Blutcholesterinspiegels und der experimentellen Atherosklerose durch Nikotinsäure, Ztschr. Kreislaufforsch. **45**:573-576 (Aug.) 1956.

The capsules of nicotinic acid were supplied by the Eli Lilly Company. Each capsule contained 0.450 Gm. of nicotinic acid and 0.050 Gm. of lactose. For ease of calculation, the approximation of 500 mg. of nicotinic acid per capsule was used.

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COMPARATIVE STUDIES IN NIACIN METABOLISM. THE FATE OF NIACIN IN MAN, RAT, DOG, PIG, RABBIT, GUINEA PIG, GOAT, SHEEP AND CALF [1]

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In 1946 the salient facts concerning the fate of niacin administered in large doses to various animal species were as follows: In man, rat and dog the chief metabolite excreted in the urine was N^1-methylnicotinamide (Huff and Perlzweig, '42, '43; Huff, '45; Sarett, Huff and Perlzweig, '42; Sarett, '42b). But only in the dog was complete saturation (close to 100% excretion) observed in terms of this metabolite, plus a small amount of unchanged niacin (Sarett, Huff and Perlzweig, '42; Sarett, '42b). In man and the rat, only 30 to 40% of the dose could be recovered as N^1-methylnicotinamide in the urine, even after prolonged feeding of niacin (Huff and Perlzweig, '42, '43; Huff, '45). As observed in the present study, the pig excreted not more than 10% of ingested niacin as N^1-methylnicotinamide. In the two common laboratory species of herbivorous animals, the rabbit and guinea pig, it was observed that with the rather sensitive and

[1] A preliminary report of this work was presented at the meetings of the Federation of American Societies for Experimental Biology, Detroit, 1949 (Fed. Proc., *8:* 236, 1949).

[2] Deceased December 10, 1949.

[3] Nutrition Foundation, Inc., Fellow. The data in this paper were taken from the Ph.D. thesis submitted by this author, Duke University, 1949.

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specific method available to us it was not possible to establish the excretion of N^1-methylnicotinamide, even after saturation with large doses of niacin either orally or parenterally administered (Huff and Perlzweig, '46; Handler, '44). The same was true for the horse (Huff, Pearson and Perlzweig, '46).

It should be further pointed out that the amount of niacin excreted, either unchanged or in forms measurable by microbiological assay with *L. arabinosus* (which include, in addition to nicotinic acid, the amide, nicotinuric acid, pyridine nucleosides and coenzymes I and II), did not account for more than 10% of the ingested doses in man, rat, dog, or guinea pig (the rabbit and horse excrete large amounts of unchanged nicotinic acid). Thus, it appeared that a large portion of ingested niacin was metabolized to other products than those which could be determined. Furthermore, it was observed that N^1-methylnicotinamide itself, when administered to man, rat, rabbit, and horse, was largely "destroyed" and could not be recovered in the urine (Perlzweig and Huff, '45; Perlzweig, Huff and Rosen, '46; Huff and Perlzweig, '46).

Knox ('46) demonstrated the presence in rabbit liver of an enzyme capable of oxidizing N^1-methylnicotinamide. Shortly thereafter, Knox and Grossman ('46) were able to isolate the oxidation product from the urine of a human subject ingesting large amounts of nicotinamide, and to identify it as the 6-pyridone of N^1-methylnicotinamide (hereafter referred to as the 6-pyridone). It became apparent that this oxidation product might account for the hitherto unaccounted for portion of the metabolized niacin in man, and possibly in the other species. However, the lack of a suitable quantitative method for estimating the amount of 6-pyridone in the urine delayed this study until the current year, by which time such a method was elaborated and found adequate for these purposes (Rosen, Perlzweig and Handler, '48; Rosen, Perlzweig and Leder, '49). With the aid of this method, niacin balance studies were carried out in man, rat, dog, pig, rabbit,

guinea pig, sheep, goat and calf. These also included studies on the fate of N^1-methylnicotinamide and of the 6-pyridone in these species. Some of the data on the herbivora are taken from our previously published studies (Huff, Pearson and Perlzweig, '46; Pearson, Perlzweig and Rosen, '49).

In this paper comparative data will be presented on the metabolism of niacin in man and 8 other mammalian species. It will be shown that the 6-pyridone is a major end-product of niacin metabolism in man, but not in the other species.

METHODS

The analytical methods employed were: niacin and related compounds active for *L. arabinosus* were determined by a microbiological procedure (Krehl, Strong and Elvehjem, '43); N^1-methylnicotinamide by the fluorometric procedure of Huff and Perlzweig ('47); and the 6-pyridone of N^1-methylnicotinamide by the method of Rosen, Perlzweig and Leder ('49).

EXPERIMENTAL

Ten, healthy young human subjects were employed. Urine samples (24-hour) were collected during a control period during which the subjects ate freely of diets of their own choice. The urines so collected, and all other urines in this study, were preserved with 3 ml of 50% acetic acid and toluene and were kept in a refrigerator. Subsequently two of the subjects were given 500 mg of nicotinamide daily for 5 days. After a lapse of one week, they were each given 224 mg of N^1-methylnicotinamide daily for three days. One week later, they received a single dose of the pyridone.

Two adult, female dogs were housed in individual wire metabolism cages and fed 20 gm per kilogram per day of a commercial chow.[5] Nicotinamide and its derivatives were given in single oral doses.

Five male rats, whose initial weights varied from 175 to 213 gm, were fed a complete "synthetic" ration. They were housed in individual metabolism cages and given single oral

[5] Purina Checkers.

doses of the experimental materials as desired. Two young pigs were used. They were fed stock rations and control urines were collected for two days. On each of the next three days, 2 gm of nicotinamide were given orally in gelatin capsules. After a 5-day interval, the procedure was repeated with N^1-methylnicotinamide and 5 days later with the pyridone.

The two guinea pigs were fed a mixture of raw cabbage, oats and a commercial chow,[6] while the two rabbits were fed cabbage and carrots only. Nicotinamide was given in single oral doses on 4 consecutive days. After a lapse of one week, equivalent doses of N^1-methylnicotinamide were given for two days and urine collected for 6 days. Urine was collected for 48 hours after dosage with the pyridone.

Details of the experimental procedures used for sheep, goats and calves have been described in detail elsewhere (Pearson, Perlzweig and Rosen, '49).

RESULTS AND DISCUSSION

Man

Of the known derivatives of nicotinic acid, only nicotinuric acid (Sarett, '42a) and N^1-methylnicotinamide (Huff and Perlzweig, '43) were established as constituents of human urine prior to the isolation of the 6-pyridone by Knox and Grossman ('46). Acid-hydrolyzable derivatives of nicotinic acid, including nicotinuric acid, constitute approximately 10% (0.5 to 1.5 mg as niacin) of the measurable metabolites in normal urine. Trigonelline does not appear to be a normal end-product of nicotinic acid metabolism, and its presence in the urine can be traced to the coffee and leguminous food in the ordinary diet (Huff, '45). Huff found that the daily excretion of N^1-methylnicotinamide in normal adult subjects on an average diet ranged between 4 and 12 mg, with an average of 7 mg. Hochberg et al. ('45) reported a daily output of 3.3 to 9 mg of N^1-methylnicotinamide in 6 normal subjects whose diet contained 23 mg of nicotinic acid.

[6] Purina "Rabbit Chow."

The data describing the excretion of N^1-methylnicotinamide and its pyridone by 10 healthy humans on average diets is summarized in table 1.

The range of values for N^1-methylnicotinamide in this small group of subjects is of the same order of magnitude as that found by Huff ('45) in 67 adults. The daily excretion of 6-pyridone in this group ranged between 3.6 and 12 mg

TABLE 1

Twenty-four-hour excretion of N^1-methylnicotinamide and 6-pyridone by healthy individuals on a normal diet

SUBJECT	SEX AND WT.	NM[1]	6-PYRIDONE	RATIO: 6-PYRIDONE / NM	TOTAL
	kg	*mg*	*mg*		
J. C.	M,79	7.8	9.2	1.18	17.0(14.3)[2]
A. D.	M,61	5.9	5.9	1.0	11.8(10.0)
F. R.	M,63	6.1	10.0	1.6	16.1(13.4)
I. L.	M,74	10.2	12.0	1.18	22.2(18.8)
M. E.	M,86	6.4	11.8	1.84	18.2(15.1)
H. K.	M,66	6.8	10.9	1.6	17.7(14.8)
S. H.	F,59	3.0	3.6	1.2	6.6(5.44)
R. S.	F,56	5.0	10.8	2.18	15.8(13.2)
B. P.	F,52	6.6	3.8	0.52	10.4(8.9)
F. P.	F,55	5.3	6.1	1.53	13.4(11.2)
Average		6.3	8.6	1.37	14.9(12.5)

[1] N^1-methylnicotinamide.

[2] The values in parentheses represent an equivalent amount of nicotinamide. To this amount should be added approximately 1 mg of niacin excreted as derivatives determinable by *L. arabinosus* assay.

with an average of 8.6 mg. The ratio of 6-pyridone to the N^1-methylnicotinamide excreted in 8 of the normal subjects varied from 1.0 to 1.8; a value of 0.52 was obtained in one subject and 2.18 in another. When converted to an equivalent amount of nicotinic acid, the total average excretion of 6-pyridone and N^1-methylnicotinamide was 12.5 mg. The average American diet has been estimated by Cheldelin and Williams ('43) to contain 17 mg of nicotinic acid per 2,500

cal. Thus, the combined excretion of both derivatives, plus 0.5 to 1.5 mg of niacin and derivatives determined by *L. arabinosus* assay, can be assumed to account for a large part (80%) of the nicotinic acid consumed daily by the average American adult.

TABLE 2

The excretion of niacin and its derivatives in two adults following the ingestion of nicotinamide, N^1-methylnicotinamide and 6-pyridone. (Values are in milligrams per 24-hour urine)

URINE	N^1-METHYL-NICOTINAMIDE		6-PYRIDONE		NIACIN		TOTAL	
	F.R.	I.L.	F.R.	I.L.	F.R.	I.L.	F.R.	I.L.
			Control — no supplement					
1	6	9	10	12	0.9	1.1	17 (14)[1]	22 (19)
			Supplement — 500 mg nicotinamide					
2	130	185	221	280	7.1	5.3	358(282)	470(394)
3	161	165	376	279	7.5	3.7	544(451)	448(374)
4	214	278	278	271	5.6	4.5	498(418)	554(470)
5	262	245	246	238	6.1	4.7	514(436)	508(429)
6	263	191	280	228	7.4	4.4	550(465)	433(357)
			Supplement — 224 mg N^1-methylnicotinamide					
12	57	35	45	41			102	76
13	70	48	37	24			107	72
14	47	34	40	48			87	82
			Supplement — 25 mg 6-pyridone					
15			22	23			22	23

[1] Values in parentheses represent an equivalent amount of nicotinamide.

In a recent preliminary report, Dean and Holman ('49) have applied a method for the determination of 6-pyridone to urines from adults and new-born children. The details of the method were not given. The normal values for 24-hour specimens obtained from 4 adults ranged between 10.8 and 14.9 mg; 4 infants excreted from 1.0 to 2.1 mg during the first 72 hours of life. An average value of 1.4 was obtained for the ratio of 6-pyridone to the N^1-methylnicotinamide excreted by the adult subjects.

Huff ('45) and Sarett ('42a) have previously studied the pathway of nicotinic acid metabolism in the human by meas-

uring various metabolites in the urine after the ingestion of nicotinic acid and its derivatives. Huff found that only 30 to 40% of an ingested dose of nicotinamide could be recovered in the urine as N^1-methylnicotinamide and the acid-hydrolyzable derivatives. Approximately 75% of an oral dose of N^1-methylnicotinamide could not be accounted for in the urine. Since large amounts of 6-pyridone have been isolated from human urine after the ingestion of nicotinamide (Knox and Grossman, '46), it seemed probable that the excretion of this derivative would explain the fate of a large portion of the nicotinamide and N^1-methylnicotinamide unaccounted for in this species.

Table 2 shows the results of studies on the relationship of the 6-pyridone to the metabolic fate of administered nicotinamide and N^1-methylnicotinamide. Calculated as an equivalent amount of nicotinamide, the combined excretion of N^1-methylnicotinamide, 6-pyridone and nicotinic acid accounted for 82 and 89% of the total amount of nicotinamide ingested during the test period. After the ingestion of nicotinamide, values ranging between 1.0 and 2.3 were obtained for the 6-pyridone: N^1-methylnicotinamide ratio; this range is of the same order as that observed in normal urines.

The results obtained when N^1-methylnicotinamide was given orally were unexpected. Of the total dose, only 30 to 40% was recovered in urine as N^1-methylnicotinamide and 6-pyridone. The fate of 180 mg of N^1-methylnicotinamide given subcutaneously was tested in one subject (F. R.). In the following 72-hour urine, 58% of the dose was recovered as unchanged N^1-methylnicotinamide and 33% as 6-pyridone; a total of 91% of the dose. Previously, Perlzweig and Huff ('45) had shown that 67% of a dose of N^1-methylnicotinamide administered intravenously could be recovered as such in the urine; the 6-pyridone, then unknown, was not determined.

From 88 to 92% of a single dose of the 6-pyridone was recovered in the next 48-hour urine unchanged, which indicates that the further metabolism of this compound in the body is unlikely.

Dog

Sarett ('42b) presented a thorough study of the metabolic fate of nicotinic acid and its derivatives in the dog. When this species is saturated with niacin or its amide, from 80 to 100% of the total dose can be recovered in the urine as N^1-methylnicotinamide, niacin and nicotinuric acid. N^1-methylnicotinamide, measured as "trigonelline" by Sarett ('42b), represents 75 to 95% of the total excretion. Since almost all of the ingested vitamin can be accounted for in the urine, it may be presumed that the dog is unable to oxidize N^1-methylnicotinamide to form the 6-pyridone. In the experiments described herein, the metabolism of nicotinic acid in the dog was re-evaluated with respect to the fate and excretion of N^1-methylnicotinamide and the 6-pyridone.

On the basis of the data presented in table 3, the 6-pyridone does not seem to be a normal end-product of niacin metabolism in the dog. None of this metabolite was excreted following a dose of nicotinamide, and only very small amounts after the ingestion of N^1-methylnicotinamide. One of the 24-hour control urines contained 2 mg of substances reacting as 6-pyridone with the method of analysis used. The identity of these substances is not certain, however, in view of the limitations of the analytical method.

The results obtained when N^1-methylnicotinamide was given orally are difficult to interpret. Since the excretion of N^1-methylnicotinamide accounts for almost all of an ingested dose of nicotinic acid, an oral dose of this compound was expected to be excreted unchanged in the urine. Failure to absorb the compound when given orally seemed to be the most likely explanation for the low recovery shown in table 3. This was tested in both dogs by the subcutaneous administration of the same amount of N^1-methylnicotinamide as was given orally. Whereas dog B excreted, unchanged, as much as 85% of a subcutaneous dose, dog A excreted but 2%. Hydrolysis of N^1-methylnicotinamide to trigonelline might also explain the poor recovery of N^1-methylnicotinamide when given

TABLE 3

Metabolism of nicotinamide, N^1-methylnicotinamide and 6-pyridone in the dog, rat and pig

Species	Supplement fed		Excreted in urine [1]				
	Compound	Amount	N^1-methylnicotinamide	6-Pyridone	Nicotinuric acid [2]	Total: Acct'd. for	Total: Unacct'd. for
		mg/kg					
Dog	Nicotinamide	10	80	0 [3]	8	88	12
	N^1-methylnicotinamide	11	20	2 [3]		22	78
	6-Pyridone	2.5–4.0		69		69	31
Rat	Nicotinamide	100–200	50	3	15	68	32
	N^1-methylnicotinamide	100	50	3		53	47
	6-Pyridone	30–50		80		80	20
Pig	Nicotinamide	75–80	7	10	9	26	74
	N^1-methylnicotinamide	10	15	20		35	65
			(3.27)	(31.9)		55	45
	6-Pyridone	1		55			

[1] Values given as per cent of total dose excreted in the urine in 24 hours.
[2] Nicotinuric acid and derivatives as measured by *L. arabinosus* assay after 1 N HCl hydrolysis of the urine.
[3] Significance questionable due to low concentration.

orally. Samples of urine after oral ingestion of N^1-methylnicotinamide were analyzed for trigonelline according to the general method for estimating N^1-methyl derivatives of nicotinic acid in urine (Sarett, '43). The values for total methyl derivatives agreed very well with those previously obtained for N^1-methylnicotinamide, indicating that N^1-methylnicotinamide is not converted to trigonelline by the dog. The large percentage (69%) of unchanged 6-pyridone recovered in the urine after an oral dose of this compound indicates that the dog has a limited capacity for the further metabolism of this substance.

The excretion of 6-pyridone by the rat

Prior to the present studies on the excretion of 6-pyridone by the rat, the metabolism of niacin in this species was thought (with but one minor exception) to be similar to that observed in man. In contrast to man, nicotinuric acid was found to be hydrolyzed by the rat and to yield extra N^1-methylnicotinamide in the urine (Huff and Perlzweig, '42).

It was considered likely that the excretion of the 6-pyridone by the rat, as by man, would comprise a large portion of the hitherto unaccounted-for fraction after the ingestion of nicotinamide or N^1-methylnicotinamide. However, only 3% of an oral dose of nicotinamide or N^1-methylnicotinamide was excreted as the 6-pyridone. The significance of this small but definite amount of 6-pyridone formed from nicotinamide or N^1-methylnicotinamide is not clear. When 5 mg of 6-pyridone were given orally to these rats, 80% was recovered in the urine within 24 hours. Similar results were obtained when another group of rats were given these compounds intraperitoneally, thus eliminating the factor of absorption. On the basis of these results, it is unlikely that the rat does oxidize any appreciable quantity of N^1-methylnicotinamide to form the 6-pyridone. However, it should be added that, in preliminary studies, Hunter and Perlzweig ('49) have shown that rat liver slices are capable of oxidizing

small amounts of N^1-methylnicotinamide to the 6-pyridone. The present data do show, however, that N^1-methylnicotinamide is further metabolized in this species via another pathway. In this connection, Roth et al. ('48) have recently reported that nicotinic acid, labeled with C^{14} in the carboxyl group, or one of its metabolites, is decarboxylated by the mouse and that approximately 15% of an ingested dose of nicotinic acid can be recovered as respiratory carbon dioxide.

Attempts to measure the amount of 6-pyridone contained in normal rat urine were unsuccessful. It can be estimated, however, that less than 100 μg are excreted in 24 hours by rats kept on a purified diet containing 15% protein.

Pig

Although the requirement of the pig for nicotinic acid has been observed by many workers (Braude, Kon and White, '46; Hughes, '43; Powick, Ellis, Madsen and Dade, '47), the fate of nicotinic acid and its derivatives in this species has not been studied. N^1-methylnicotinamide has been established as an end-product of nicotinic acid metabolism in this species by Luecke et al. ('48), who have measured this derivative in the urine of pigs subsisting on purified rations containing various levels of casein.

The data presented in table 3 show that N^1-methylnicotinamide and the 6-pyridone are excreted by the pig following a dose of nicotinamide. However, the combined excretion of both derivatives and niacin accounts for only 26% of the total dose. It is difficult to evaulate the figures obtained for the chief metabolites excreted after the ingestion of N^1-methylnicotinamide, since they vary so widely (see values in parentheses, table 3). Only 55% of an oral dose of 6-pyridone was recovered, indicating that this derivative is further metabolized by the pig.

On the unsupplemented stock ration an average of 6 mg of N^1-methylnicotinamide was excreted in the 24-hour urine. In the control urine of one pig, 7.7 mg of 6-pyridone were

found, but none of this derivative could be detected in the control sample of the other animal.

Herbivora

In general, the behavior of the horse (Pearson and Luecke, '46; Huff, Pearson and Perlzweig, '46), rabbit (Handler, '44), and guinea pig (Handler, '44) in regard to nicotinic acid metabolism is unlike that of man, dog, pig and rat. These herbivora differ from other species in that they fail to excrete appreciable amounts of N^1-methylnicotinamide after the ingestion of nicotinic acid or its amide. In common with man, rat, dog, and pig, however, these species were found to be capable of "destroying" N^1-methylnicotinamide. On the basis of these observations it could not be stated whether herbivora methylate nicotinic acid and its amide, and the methylated derivative is further metabolized so rapidly that only small amounts are excreted, or whether niacin is metabolized via some other pathway. Since the N^1-methylnicotinamide-oxidizing enzyme was originally observed in rabbit liver, it seemed quite likely that the 6-pyridone would be a normal metabolite of niacin metabolism in this species and perhaps in other herbivora. To determine whether the 6-pyridone is an important end-product of niacin metabolism in herbivora, the fate of nicotinic acid and its derivatives was studied in 5 species of herbivorous animals; the rabbit and guinea pig, and the ruminants goat, sheep and calf.

The data in table 4 show that there is a small but significant increase in the excretion of 6-pyridone following the administration of nicotinamide to the rabbit and guinea pig. Only traces of a substance whose identity with the 6-pyridone is uncertain were found in the urine of the other herbivora (sheep, goat and calf) after the ingestion of nicotinamide. With the exception of the rabbit, the other species were capable of "destroying" from 84 to 96% of the orally administered N^1-methylnicotinamide. After the oral ingestion of N^1-methylnicotinamide, the rabbit continued to excrete significant

TABLE 4

Metabolism of nicotinamide, N^1-methylnicotinamide and 6-pyridone in the rabbit, guinea pig, goat, sheep and calf

Species	Supplement fed		Excreted in urine [1]				
	Compound	Amount	N^1-methylnicotinamide	6-Pyridone	Nicotinuric acid [2]	Total	
						Acct'd. for	Unacct'd. for
		mg/kg					
Rabbit	Nicotinamide	90–100	0.5 [3]	3	43 [3]	46.5	53.5
	N^1-methylnicotinamide	100	17	25		42	58
	6-Pyridone	11–15		90		90	10
Guinea pig	Nicotinamide	150–200	0.5 [3]	5	8	13.5	86.5
	N^1-methylnicotinamide	160–200	0.5 [3]	4		4.5	95.5
	6-Pyridone	40–50		40		40	60
Goat	Nicotinamide	70–100	0.5 [3]	0.5 [3]	14	15	85
	N^1-methylnicotinamide	10	12	4		16	84
	6-Pyridone	1		35		35	65
Sheep	Nicotinamide	30–60	0.5 [3]	0.3 [3]	30	31	69
	N^1-methylnicotinamide	10	1 [3]	3		4	96
	6-Pyridone	1		11		11	89
Calf	Nicotinamide	30–70	0.6 [3]	0 [3]	35	36	64
	N^1-methylnicotinamide	10	2 [3]	3		5	95
	6-Pyridone	1		58		58	42

[1] Values given as per cent of total dose excreted in the urine in 24 hours.
[2] Nicotinuric acid and derivatives as measured by *L. arabinosus* assay after 1 N HCl hydrolysis of the urine.
[3] Significance questionable due to low concentration.

amounts of this derivative and the 6-pyridone during the next 5 days. This observation, and the fact that N^1-methylnicotinamide is excreted in relatively small amounts after the ingestion of nicotinic acid, would seem to imply that N^1-methylnicotinamide is not a normal metabolite of niacin metabolism in the rabbit. That large amounts of nicotinamide are not methylated by the rabbit and the guinea pig can be inferred from the studies of Handler ('44), who showed that these two species are not depleted of "labile methyl groups" when large amounts of nicotinamide (2%) are included in the diet for three weeks.

Additional evidence that N^1-methylnicotinamide is not a normal metabolite in this species was obtained when almost all of an oral dose of 6-pyridone was recovered as such in the urine. In the other herbivora studied, only 11 to 58% of the ingested dose of 6-pyridone was accounted for in the urine. Therefore, with respect to the guinea pig, sheep, calf, and goat the possibility remains that part of the ingested nicotinamide is metabolized via N^1-methylnicotinamide and 6-pyridone, and that the latter compound is further metabolized.

It was not possible to detect any appreciable quantity of 6-pyridone in the control urines of the calf, goat, and sheep. Both the guinea pig and rabbit excreted approximately 0.3 mg of this derivative in a normal 24-hour urine. The average 24-hour control excretion of N^1-methylnicotinamide in the various herbivora were: sheep, 2.8 mg; goat, 2.5 mg; calf, 4.1 mg; guinea pig, 0.1 mg; and rabbit, 1.1 mg.

SUMMARY

Metabolism studies were conducted in 9 mammalian species (man, dog, rat, pig, calf, sheep, goat, guinea pig and rabbit) on normal diets and after the ingestion of nicotinamide, N^1-methylnicotinamide and the 6-pyridone of the latter.

In a group of 10 healthy human subjects on a normal diet, from 3.6 to 12.0 mg of the 6-pyridone were excreted in 24 hours, with an average of 8.6 mg. The ingestion of large amounts of nicotinamide by two male subjects for a period

of 5 days resulted in the excretion of 35 to 45% of the dose as 6-pyridone and 30 to 40% as N^1-methylnicotinamide; thus, 82 to 89% of ingested nicotinamide could be accounted for in the urine as niacin, N^1-methylnicotinamide, and the 6-pyridone. Only 30 to 40% of an oral dose of N^1-methylnicotinamide was recovered in the urine of these two subjects as 6-pyridone and N^1-methylnicotinamide. Parenteral administration of N^1-methylnicotinamide led to a recovery of 91% in the urine as N^1-methylnicotinamide plus the 6-pyridone. Ingested doses of the 6-pyridone were almost completely excreted unchanged.

In the rat, only 3 to 5% of an oral dose of nicotinamide or of N^1-methylnicotinamide is excreted as the 6-pyridone. This animal excretes unchanged 80 to 90% of a dose of the 6-pyridone. N^1-methylnicotinamide accounts for 40 to 50% of an oral or intraperitoneal dose of N^1-methylnicotinamide or nicotinamide in this species.

In the dog, in which N^1-methylnicotinamide accounts for almost all of the ingested niacin at saturation, no 6-pyridone could be detected in the urine after the administration of nicotinamide and only small amounts after doses of N^1-methylnicotinamide. The 6-pyridone, when given orally to dogs, was largely recovered in the urine.

In the urine of the pig, N^1-methylnicotinamide accounted for 7% and 6-pyridone for 10% of an oral dose of nicotinamide. Almost half of the dose of 6-pyridone administered to the pig was not recovered in the urine.

The rabbit excreted less than 4% of a total dose of nicotinamide as N^1-methylnicotinamide and the 6-pyridone. However, in response to an oral dose of N^1-methylnicotinamide, 17% appeared in the urine as N^1-methylnicotinamide and 25% as 6-pyridone. This indicates that N^1-methylnicotinamide is not a normal metabolite of niacin in this species. No appreciable amounts of 6-pyridone are "destroyed" by the rabbit when given orally.

Relatively small amounts of 6-pyridone and N^1-methylnicotinamide are found in the urine of the guinea pig, sheep, calf, and goat, normally and after large doses of nicotinamide

and N^1-methylnicotinamide. From 42 to 89% of an oral dose of the 6-pyridone could not be recovered in the urine of these species. Only 4 to 16% of an oral dose of N^1-methylnicotinamide could be accounted for in the urine of these herbivora.

Apparently, in man, dog, rat and pig (and possibly other omnivora and carnivora?) excesses of niacin are largely disposed of by methylating processes. On the other hand, in the herbivora (rabbit, guinea pig and the polygastric species) niacin is probably disposed of by pathways other than those involving methylation.

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LITERATURE CITED

BRAUDE, R., S. K. KON AND E. G. WHITE 1946 Observations on the nicotinic acid requirements of pigs. Biochem. J., *40:* 843.

CHELDELIN, V. H., AND R. R. WILLIAMS 1943 Studies of the average American diet. J. Nutrition, *26:* 417.

DEAN, R. F. A., AND W. I. M. HOLMAN 1949 Metabolism of nicotinic acid by infants. Nature, *163:* 97.

HANDLER, P. 1944 The effect of excessive nicotinamide feeding on rabbits and guinea pigs. J. Biol. Chem., *154:* 203.

HOCHBERG, M., D. MELNICK AND B. L. OSER 1945 Chemical determination and urinary excretion of the metabolite N^1-methylnicotinamide. Ibid., *158:* 265.

HUFF, J. W. 1945 Ph.D. thesis, Duke University.

HUFF, J. W., P. B. PEARSON AND W. A. PERLZWEIG 1946 Further studies on the metabolism of nicotinic acid and related compounds in the horse. Arch. Biochem., *9:* 99.

HUFF, J. W., AND W. A. PERLZWEIG 1942 Studies in nicotinic acid metabolism. J. Biol. Chem., *142:* 401.

——— 1943 N^1-methylnicotinamide, a metabolite of nicotinic acid in the urine. Ibid., *150:* 395.

——— 1946 Unpublished data.

——— 1947 The fluorescent condensation product of N^1-methylnicotinamide and acetone. J. Biol. Chem., *167:* 157.

HUGHES, E. H., 1943 The minimum requirement of nicotinic acid for the growing pig. J. Animal Sci., *2:* 23.

HUNTER, S., AND W. A. PERLZWEIG 1949 Unpublished data.

KNOX, W. E. 1946 The quinine-oxidizing enzyme and liver aldehyde oxidase. J. Biol. Chem., *163:* 699.

KNOX, W. E., AND W. I. GROSSMAN 1946 A new metabolite of nicotinamide. Ibid., *166:* 391.

KREHL, W. A., F. M. STRONG AND C. A. ELVEHJEM 1943 Determination of nicotinic acid. Ind. Eng. Chem., Anal. Ed., *15:* 471.

LUECKE, R. W., W. N. MCMILLEN, F. THORP, JR., AND C. J. TULL 1948 Further studies on the relationship of nicotinic acid, tryptophan and protein in the nutrition of the pig. J. Nutrition, *36:* 417.

PEARSON, P. B., AND R. W. LUECKE 1946 Further studies on the metabolism of niacin in ruminants (sheep, goats and calves). Arch. Biochem., *22:* 191.

PEARSON, P. B., W. A. PERLZWEIG AND F. ROSEN 1949 The metabolism of niacin in ruminants. Ibid., *22:* 191.

PERLZWEIG, W. A., AND J. W. HUFF 1945 The fate of N^1-methylnicotinamide in man. J. Biol. Chem., *161:* 417.

PERLZWEIG, W. A., J. W. HUFF AND F. ROSEN 1946 The effects of CCl_4 poisoning on the fate of N^1-methylnicotinamide in the rat. Fed. Proc., *5:* 149.

POWICK, W. C., N. R. ELLIS, L. L. MADSEN AND C. N. DADE 1947 Nicotinic acid deficiency and nicotinic acid requirements of young pigs on a purified diet. J. Animal Sci., *6:* 310.

ROSEN, F., W. A. PERLZWEIG AND P. HANDLER 1948 A fluorometric assay for N^1-methyl-6-pyridone-3-carboxylamide. Fed. Proc., *7:* 181.

ROSEN, F., W. A. PERLZWEIG AND I. G. LEDER 1949 A fluorometric method for the determination of the 6-pyridone of N^1-methylnicotinamide in urine. J. Biol. Chem., *179:* 157.

ROTH, L. J., E. LEIFER, J. R. HOGNESS AND W. H. LANGHAM 1948 Studies on the metabolism of radioactive nicotinic acid and nicotinamide in mice. Ibid., *176:* 249.

SARETT, H. P. 1942a Ph.D. thesis, Duke University.

——— 1942b Studies in nicotinic acid metabolism. II. The fate of nicotinic acid in normal and blacktongue dogs. J. Nutrition, *23:* 35.

——— 1943 A direct method for the determination of N-methyl derivatives of nicotinic acid in urine. J. Biol. Chem., *150:* 159.

SARETT, H. P., J. W. HUFF AND W. A. PERLZWEIG 1942 Studies in nicotinic acid metabolism. J. Nutrition, *23:* 23.

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An outbreak of food poisoning due to sodium nicotinate in meat is reported. The effects of the drug are discussed, other outbreaks are mentioned, and recommendations are made to avoid such occurrences.

FOOD "POISONING" DUE TO SODIUM NICOTINATE

REPORT OF AN OUTBREAK AND REVIEW OF THE LITERATURE

Edward Press, M.D., M.P.H., F.A.P.H.A., and Leona Yeager, M.D.

MODIFICATIONS in the physical and chemical composition of nature's food supply have been practiced almost as long as the records of modern civilization go. Modification, for example, of meat, by heating, salting, smoking, drying, by addition of preservatives and flavoratives of various types have been practiced for years. When properly used these have the advantage of extending and improving basic food supplies and making them available to more people for longer times. The addition of a wide variety of chemicals to our food and water supply has been practiced for generations and from the over-all standpoint, the benefits far outweigh the dangers. Nevertheless appreciable hazards may be involved through the addition of any substance and this is true for relatively harmless additives as well as more potentially hazardous ones. In order to maintain a positive balance between the benefits and the dangers of additives in food processing and distribution, it is essential to have a thorough scientific knowledge of the type, extent, and effects of all food additives and to provide for effective continuous monitoring of any extraneous substances. This paper is designed to supplement our knowledge of the extent and effect of one of these additives that is added to millions of pounds of meat annually in the United States, namely, sodium nicotinate.

Report of an Epidemic

About 15 to 20 minutes after the start of the evening meal at one of the sorority houses at Northwestern University in Evanston, Ill., early in November, 1960, the sudden onset of a diffuse feeling of warmth and heat accompanied by itching of the skin, redness and flushing of the face, neck, extremities, and trunk was noted among 44 of the students. There was no vomiting or diarrhea and the onset was so sudden that several of the persons who had not yet started their dessert were involved.

Of the 121 persons dining there, 39 female students and five male student waiters developed symptoms. Most of those afflicted noted the symptoms within 20 to 40 minutes after they began to eat; however, the time of onset ranged from about 10 to 60 minutes. In addition to the above mentioned symptoms there were a few who developed swelling of the knees, lips, or extremities and several that complained of dryness in the mouth. Some typical descriptions of symptoms were as follows:

Itching and burning on my face, back of neck and arms, and a hot feeling.

Felt funny as though I were under an oven lamp.

My ears stung and turned red.

Felt hot and itched all over.

My ears tingle, my neck and cheeks are hot and prickly, and my elbows and knees itch.

Got pain in my stomach five minutes after dinner, chilled immediately after the pain started and then I turned red and my face felt as if sandpaper were being rubbed against my face. My knees were very hot and red, my eyes burned, and my elbows itched.

Physical examinations revealed signs of generalized vasodilatation, especially marked in the blond, light skinned girls. Some of the patients manifested slight puffiness or swelling of the face and knees. The blood pressure ranged from systolic pressures of 80 to 160 (only one student with 160) and diastolic pressures of from 58 to 80. The pulse varied from 64 to 96. Most of the patients were given 25 or 50 mg of benadryl and reported gradual improvement after 20 to 40 minutes. However, those who did not receive the benadryl showed similar improvement. Two of the more seriously affected patients were hospitalized overnight and these, as well as all the others involved, recovered with no apparent residual effects within a few hours. In general the symptoms lasted only 30 to 40 minutes with a range of from 15 minutes to three hours.

An analysis of the menu and questioning of all persons developing symptoms and some of those who did not develop symptoms revealed that the only food item in common to those who became ill was Swedish meat balls made from ground beef (one of those affected denied eating any of the beef, but on later requestioning admitted taking "one teeny bite"—her only symptoms were a feeling of generalized warmth which disappeared in 15 minutes). Other items included in the menu were: water, ice cubes, noodles, broccoli, rolls, butter, green olives, celery, coffee, sugar, cream, salt and pepper, and a chocolate roll.

A careful review of the food storage, preparation, and service procedures was made with special effort given to the possibility of the inadvertent (or advertent —this being pledge week at the university) addition of some chemical contaminant, it being considered unlikely that a bacterial or virus agent would produce such prompt symptoms. Special attention was given to a search for galvanized or cadmium-lined utensils and the presence of insecticides, rodenticides, disinfectants, and so forth, but none were found.

Specimens of each of the food items served were taken for analysis and in view of the unusual nature of the symptoms, additional consultation[1] was sought as to the type of chemical contaminant that might be present. The following morning, despite initial denial, careful inspection and questioning at the meat purveying firm involved revealed that sodium nicotinate had been added to the ground beef delivered to the sorority house. Chemical tests of identification as described in the current U. S. Pharmacopeia were performed (by the Chicago Board of Health Laboratory) on some of the ground meat remaining from the evening meal and were negative; however, later microbiological assay tests[2] on another sample of the ground meat served gave a concentration of 225 mg of sodium nicotinate per 100 grams of cooked meat ball. Several blood and urine specimens taken from two or three of the patients were negative to chemical (USP) tests for sodium nicotinate or nicotinic acid. It was later learned that approximately 2 oz of powdered sodium nicotinate had been sprinkled on the ground meat directly following the first coarse grind and prior to the second fine grind. It was felt that the relatively uneven dispersion that ensued, together with varying susceptibility of the individuals, accounted for the fact that only 41 out of 121 persons concerned noted symptoms.

Discussion

History of Nicotinic Acid as Related to Pellagra

Nicotinic acid was first prepared by Huber[3] who obtained it by the oxidation of nicotine in 1867. However, it was not until 1912 that Suzuki and associates[4] isolated it from rice polishings. In 1913 Funk reported isolating it from yeast also.[5] By 1926, Goldberger and his associates[6] had clearly shown that pellagra was a deficiency disease and that the protective factor was associated with the more heat stable fraction of the vitamin B Complex. Although naturally occurring clinical pellagra in human beings is only rarely a monoavitaminosis, as the deficient diet usually lacks other components of the B Complex also, nevertheless it soon became apparent that nicotinic acid was the specific factor involved in pellagra.

In 1960, the American Medical Association Council on Drugs,[6] under dosage for nicotinic acid, stated that the recommended intake is 4 mg daily for infants, from 13 to 17 mg daily for those between 13 and 20 years of age, and 12 to 18 mg daily for adults. The recommendation during pregnancy and lactation is 15 mg daily. They indicate that the dose for the treatment of pellagra varies with the severity of the deficiency and perhaps with other still unknown factors and recommend doses of up to 500 mg per day given in doses of 50 mg each.

Both chemical and microbiological methods are available for the quantitative determination of nicotinic acid in plant and animal foods. Kidney, liver, and yeast are among the foods with the highest natural content of nicotinic acid, although brown rice, bran, and peanut butter also represent good sources. A report by Teply and associates[7] gives some representative values. These include the following in mg per cent: for dried meats: pork kidney 45.5, pork loin 23.5, pork ham 28.0, fried beef liver 38.0, veal liver 41.0, veal hind quarter 29.0, light chicken 29.0. For fresh fruit the following selected values given in mg per cent: apple, peeled 0.50, apple peelings 1.13, banana 0.61, wax beans 0.76, carrots 1.47, dates 2.18, white potato (peeled) 1.18, sweet potato peeled 1.29. For cereals and miscellaneous items: oats 1.13 mg per cent, barley 4.70, polished rice 0.90, brown rice 6.90, rice polishings 96.6, rye 1.03, yellow corn 1.56, whole wheat 5.0, bran 28.7, wheat germ 3.4, milk 0.48 (human milk 0.26), brewer's yeast 40.0-60.0, baker's yeast 40.0-50.0, white bread 0.95, whole wheat bread 1.80.

Nicotinic Acid in the Therapy of Conditions Other than Pellagra

The beneficial effect of nicotinic acid, sodium nicotinate, and nicotinic acid amide in pellagra is related to its effects on carbohydrate metabolism. It and its coenzymes are involved in the intermediate metabolism of dextrose and deficiencies of these enzymes (only small amounts of which are required) interfere with the cellular metabolism in such a way as to result in the clinical and physiological manifestations of pellagra. One of the regular side effects that occurs following doses of from 50 to 100 mg of nicotinic acid or sodium nicotinate (but not nicotinamide) is a generalized vasodilatation. This results in the subjective sensation of itching and burning of the skin, the lips, and the pharynx. The generalized flushing reaction which may occur in some individuals with as little as 25 or 30 mg of nicotinic acid, particularly if given on an empty stomach, has been used indirectly for a variety of miscellaneous clinical disorders. These include the following: migraine and other headaches; Bell's palsy, trigeminal neuralgias, Meniere's syndrome, asthmatic paroxysms (when patients do not react to epinephrine), arthritis, and so forth.

Although there is no question about the prompt appearance of a sensation of heat and evidence of flushing of the skin following the use of nicotinic acid, the mechanism of this vasodilatation, its extent centrally, in addition to its peripheral manifestation and its effect on oscillometric readings of pulsations in the extremities and skin and body temperature have been variable.[9,10]

The vasodilatory effects have been compared to those following histamine; however, Goldsmith and Gordill[10] do not believe that it results from stimulation of the parasympathetic nervous system. In spite of this, doses of from 100 to 120 mg are reported to cause an increase in the secretion of hydrochloric acid by the stomach of the same order as are produced by 1.0 mg of histamine phosphate, according to Sydenstricker.[11]

Skin temperature, body temperature and blood pressure have been noted to have a variable reaction following the vasodilatation effects of nicotinic acid. In general, these effects that occur after single doses of from 25 to 100 mg are transitory and disappear in from 20 minutes to one or two hours. There have been occasional reports of adverse effects from these regular doses, such as a single case of anaphylactic shock (Fineberg[12(a)]); a case of leukoplakia that might have been associated with a history of taking vitamin B Complex daily over a period of several years (Moehlig[13]); temporary peripheral leucopenia (Bassen, et al.,[14]); and decreased arteriolar pulsations in pregnant women (Odello[12(b)]). Nevertheless, in general, there have been no confirmed instances of permanent adverse effects following the use of nicotinic acid in doses of from 25 to 100 mg two or three times a day.

Use of Massive Doses of Nicotinic Acid for Hypercholesterolemia

For the past five or six years a substantial number of persons have been placed on daily doses of from 3 to 6 grams (3,000 to 6,000 mg) of nicotinic acid daily for periods of years in order to lower their serum cholesterol levels.[15-21] Practically all patients receiving these large doses (from 3 to 6 grams daily) of nicotinic acid manifested the cutaneous flushing reaction often associated with a feeling of heat and pruritus. For many of these patients after the first week or two the symptoms disappeared or diminished considerably, even though the nicotinic acid was still being taken during or after meals. However, between a quarter and a third or more continued to exhibit these symptoms during the entire course of treatment even though it lasted for years.

A smaller number amounting to 10 or 15 per cent of the patients, in addition to the above cutaneous reaction, showed symptoms of anorexia, nausea, vomiting, or combinations thereof. Usually these symptoms were mild, as only 5 or 10 per cent of the patients discontinued treatment because of them.

Tests of hepatic function were carried out by several groups of investigators and in general showed occasional transient impairment of liver function which, in most cases, became normal when the nicotinic acid was dropped. In a few instances this was serious enough to result in discontinuation of the nicotinic acid treatment. One of the most detailed and complete analyses of the toxic reactions in a series of 66 patients followed over a period of years has been compiled by Berge and associates.[22]

Berge stated that 23 of the 66 patients exhibited at least one abnormal test of hepatic function and that in 12 of these patients the abnormal results returned to normal. In only three of the 66 patients were persistently abnormal tests of hepatic function obtained. Nine patients who happened to have died while they were under treatment (death due to other causes) had

studies of their liver tissue made at necropsy. "Mild fatty change was noted in two cases in which death occurred during treatment with nicotinic acid. In addition, small focal areas of necrosis were noted in one and passive congestion in the other. In the other seven cases necropsy was done five weeks to one year after treatment with nicotinic acid. Fatty changes were graded as mild in five, moderate in one other, and absent in one. One person in this group, who died five weeks after cessation of treatment with nicotinic acid, also exhibited focal necrosis of hepatic cells."[22]

Rivin[24] reported a patient with familial hypercholesterolemia and levels of over 370 mg per cent of serum cholesterol who responded well (lowered to 225 mg per cent) to nicotinic acid therapy but who developed jaundice during the 72nd week of therapy. Rivin made no comment on whether or not this jaundice might have been related to a coincidental infectious hepatitis.

Berge[22] obtained glucose tolerance tests on 27 persons of his series of 66, and in 14 of these he obtained abnormal results (and in five additional, equivocal results). In three of those with abnormal glucose tolerance tests the results were still equivocal after an interval of two, three, and four months, respectively, without nicotinic acid treatment, but in most of the others the glucose tolerance tests returned to normal after nicotinic acid was discontinued. They also tested 26 patients on nicotinic acid for serum levels of uric acid and 16 of the 26 revealed values of over 6.0 mg per 100 ml of serum. Five of this group had subsequent normal levels of uric acid without stopping nicotinic acid treatment. Two persons experienced single episodes of acute gouty arthritis during treatment with nicotinic acid, although one had had attacks of gout prior to starting nicotinic acid therapy. The other patient had her first attack 21 months after initiation of therapy, but has had no subsequent attacks although therapy had been continued without interruption for an additional 21 months.

Parsons and Flinn[21] stated that 13 of their patients who had been on nicotinic acid for long periods of time noted dryness of the skin and that two also had a brown rash in the axilla and at pressure points somewhat resembling acanthosis nigricans. They also did needle biopsies of the liver in 17 patients after receiving nicotinic acid for one year and found no significant fatty metamorphosis or other morphologic abnormality on these biopsies.

Nicotinic Acid as a Meat Additive

Two United States patents have been issued[23] covering the use of nicotinic acid including its water soluble salts, particularly sodium nicotinate and several of its organic esters and also ascorbic acid and its salts, in such animal materials as meat and blood. These substances act to preserve the bright red color in meat by the following mechanism. The purplish red myoglobin and hemoglobin form a loose association with nicotinic acid or sodium nicotinate resulting in a red reaction product which appears the same as oxymyoglobin and oxyhemoglobin. Further oxidation of oxymyoglobin and oxyhemoglobin changes them in turn to a grayish brown metamyoglobin and to methemoglobin which is also grayish brown in color. The ascorbic acid in the presence of oxygen reduces the metamyoglobin and methemoglobin back to bright red oxymyoglobin and oxyhemoglobin.

A Chicago manufacturing chemical firm, under the provisions of these patents, formulates two products that utilize sodium nicotinate and ascorbic acid and its salts. One of these is a powder that contains approximately 5 per cent sodium nicotinate together with salts of ascorbic acid. The other product

which is primarily a seasoning substance contains under 1 per cent of sodium nicotinate together with other materials. Instructions furnished with these products clearly indicate that the percentage of the ingredients that should be added to various cuts of fresh and processed meats shall be added in such amounts that the total concentration of sodium nicotinate in the final products does not exceed 30 mg per pound of meat, which is approximately the concentration present in fresh liver. Officials of the concern holding these patents have indicated that they have received approval from the State Health Department or State Department of Agriculture for the use of sodium nicotinate in either fresh or processed meats from some states in the United States, although the following states and the cities of New York and Chicago prohibit its use: California, Colorado, District of Columbia, Florida, Georgia, Indiana, Kansas, Michigan, Minnesota, Nebraska, North Carolina, Ohio, Oklahoma, and West Virginia. In Illinois it is said to be approved for use in processed meats but not in fresh meats, and it is not approved at all in the city of Chicago.

Although the company that currently owns the use patent for sodium nicotinate formulates only two products in which this substance is used, four other companies are licensed under the patent to use sodium nicotinate.

Thus, in some of the states in the United States it is apparently legal to add nicotinic acid or sodium nicotinate to fresh or processed meats. The extent of such additions cannot be determined exactly inasmuch as the number of chemical firms manufacturing nicotinic acid and sodium nicotinate and the extent and amount of their production that are channeled into the field of meat additives is not precisely known. One of the basic chemical companies, the major one that produces sodium nicotinate for meat additives uses, was unofficially estimated to produce between 20,000 and 40,000 pounds annually of sodium nicotinate for this use. Assuming a rate of distribution and use of this product at 2 oz of the 5 per cent powder per 100 lb of meat (the dosage recommended currently by the Chicago firm) there would be enough available to modify 320 million lb of meat per year if the production were 20,000 lb. Inasmuch as the meat consumption in the United States is estimated at about 140 lb per capita, per year, this would represent under 1 per cent of the total meat consumption. The basic manufacturing firm estimates that if all of their production of sodium nicotinate is used for such additives, it would be enough for under 0.1 per cent of the total meat production in the United States. In any event millions of pounds of meat annually are involved in many states. Moreover, the amount of sodum nicotinate purchased directly by companies and added to meat without regard to the patent privilege is not known and this may be substantial.

In view of the likelihood that these millions of pounds of meat are consumed in the United States annually with added sodium nicotinate it would be anticipated that if this were not carefully added to the meat, in proper amounts, with uniform dispersion, there would be more outbreaks similar to that reported above at Northwestern University.

A review of the literature supplemented by some general inquiries reveals the following episodes briefly described below.

Other Episodes of Food "Poisoning" Due to Nicotinic Acid

Omaha, Neb.

Lyman[25] reported 83 individuals in 38 families developing symptoms of cutaneous flushing, sensation of warmth,

itching, nausea (but no vomiting) following the consumption of meat purchased from the same butcher shop over a 13-day period in 1956. This butcher had been adding a proprietary substance containing nicotinic acid to the beef, veal, and pork that he had sold in order to maintain a bright red color in the meat. The 38 families concerned included 145 individuals. Of the 88 who became ill, 68 did so after one meal of meat, seven after each of two meals, and 13 after the second of two meals. The ages and sex range of the persons involved included males and females ranging in age from one year up through adulthood and were approximately evenly distributed between male and female. Tests of six samples of the meat involved gave results that ranged from 14 mg per ounce of nicotinic acid to 105 mg per ounce. In all instances the symptoms subsided with no apparent ill effects within a period of a few hours.

Lockport, N. Y.

Oldham[26] reported four persons becoming ill with symptoms of cutaneous flushing, extreme warmth, and blotchy red rash, and so on, in March of 1958, in each instance following meals that consisted of either hamburger or cube steak to which a compound containing nicotinic acid, ascorbic acid, and dextrose had been added. The persons involved were two adult males and two adult females. Two were treated with cortisone and the other two received no special treatment. In all four instances the symptoms subsided within an hour or two.

Fremont, Ohio

Dern[27] and Wentworth[28] reported an outbreak in which 17 members of three separate families, all of whom had eaten either meat loaf or chop suey prepared with ground beef to which a proprietary product containing nicotinic acid had been added, became ill about 10 to 20 minutes following the ingestion of the meat. The symptoms were those of flushing of the skin of the face and body and a sensation of heat and itching; there was no nausea or vomiting. Recovery was complete with no evidence of complications or sequelae. Analysis of the proprietary product from an unopened 2-oz package indicated that the material contained about 14 per cent of nicotinic acid and 7 per cent of ascorbic acid. Analysis of one of the samples of ground meat in the chop suey to which some of the product had been added revealed 17.5 mg of nicotinic acid per ounce of the chop suey.

Oregon

Meador[29] reported that five persons in two families developed sudden flushing and burning of the skin while eating fried ground beef patties. Reactions lasted from 16 to 60 minutes and involved all of the family members eating the ground beef. The history of meat preparation suggested the possibility that the symptoms may have been due to the presence of a food additive containing both nicotinic acid and ascorbic acid. Laboratory tests for ascorbic acid indicated the presence of this, but tests were not available for nicotinic acid.

Evanston, Ill.

In addition to the episode at the Northwestern University sorority involving 44 out of 121 persons, questioning brought out that a nearby fraternity that obtained meat from the same supplier reported that three out of 51 male students partaking of a meal at about the same time had similar symptoms of cutaneous flushing and a sensation of warmth following consumption of meat. These symptoms, however, disappeared within 20 to 30 minutes and were recalled only after the students had learned of the widespread outbreak in the sorority described above.

East Stroudsburg, Pa.

Two adult females in the household of a physician in East Stroudsburg, Pa. (Leitner[20]), became ill shortly after eating some hamburger to which a proprietary product containing sodium nicotinate had been added. Shortly after eating some of this hamburger, the wife of the physician developed an alarming generalized erythema, palpitation, and dryness of the mouth and throat; she then became progressively more uncomfortable, developed some puffiness of her eyelids, had difficulty catching her breath, and her pulse rate rose to over 100. After checking with the butcher, who finally admitted that he had used the proprietary product in question and that he had added a "handful" of the material (designed to preserve a bright red color to the meat) to the 10 pounds of ground meat purchased for the physician's household. (The instructions furnished recommended adding only 2 oz to each 100 lb of meat.) Shortly after the first person became ill a maid in the same household that had also eaten the hamburger became ill with similar but less intensive symptoms. In both cases the flush disappeared spontaneously in two or three hours, but both patients felt quite weak for at least one additional day.

Summary

There is a rather widespread use in many states of the soluble sodium salt (sodium nicotinate) of nicotinic acid as an additive for both fresh and processed meats in order to help preserve the red color. In spite of the likelihood that the practice is widespread involving millions of pounds of meat annually, only a relatively small number of episodes with adverse symptoms of sudden cutaneous vasodilatation have come to light and seven of these have been described above. Although there has been no evidence to show that any permanent harmful effects, complications, or sequelae followed these symptoms (and thus the term food poisoning may not be literally correct), nevertheless the sudden onset of apparently unexplained acute flushing of the skin with sensation of warmth and itching is alarming to the patient and of concern to the physician. Moreover, long sustained doses of 3 to 6 grams daily of nicotinic acid have been shown, at times, to be associated with impaired liver function, abnormal carbohydrate metabolism (as reflected by glucose tolerance tests), elevated blood uric acid levels and recurrent unpleasant vasodilatation and occasionally gastric symptoms.

A wide variety of additives, preservatives, vitamin supplements, flavoratives, coloring agents, and so forth, have been added to food for many years. In general, most of these additives appear to be beneficial and, indeed, if it were not for the use of many chemical fertilizers, insecticides, herbicides, etc., our food supply could be seriously threatened. The principles of the addition to food, both fresh and processed, of preserving or fortifying agents in amounts that can be shown not to be harmful is a sound one. However, in the opinion of the authors, the use of such additives should be properly controlled and regulated in order to avoid misuse, and the product in which it has been used should be properly labeled or some other method of making the consumer aware of the additive should be utilized. When properly used, the concentrations in the final products should not exceed 20 to 30 mg per pound of meat.

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REFERENCES

1. G. M. Dack, M.D., professor of microbiology and director of the Food Research Institute of the University of Chicago, suggested the possibility of a nicotinic acid compound having been added.
2. Performed by the American Meat Institute Foundation in accordance with procedures outlined in "Official Methods of Analysis of the Association of Official Agricultural Chemists."
3. Huber, C. Vorläufige Notiz über einige Derivate des Nicotins. Liebigs Annalen Chem. u Pharm. 141:271, 1867 (quoted by Elvehjem, C. A. The Biological Significance of Nicotinic Acid. Bull. New York Acad. Med. 16:173-189 (Mar.), 1940).
4. Suzuki, U.; Shimamura, T.; and Odake, S. Über Oryzanin, ein Bestandteil der Reiskleie und seine Physiologische Bedeutung. Biochem. Ztschr. 43:89, 1912 (quoted from Elvehjem. Ibid.).
5. Funk, C. Studies on Beri-Beri: Chemistry of the Vitamin-Fraction from Yeast and Rice Polishings. J. Physiol. 46:173, 1913 (quoted from Elvehjem. Ibid.).
6. New and Non-Official Drugs (1960 ed.). Evaluated by AMA Council on Drugs.
7. Teply, L. J.; Strong, F. M.; and Elvehjem, C. A. The Distribution of Nicotinic Acid in Foods. J. Nutrition 23:417-423 (Apr.), 1942.
9. Popkin, Roy J. Nicotinic Acid: Its Action on the Peripheral Vascular System. Am. Heart J. 18:697-704 (Dec.), 1939.
10. Goldsmith, Grace A., and Cordill, Shirley. The Vasodilating Effects of Nicotinic Acid (relation to metabolic rate and body temperature). Am. J. M. Sc. 205:204-208 (Feb.), 1943.
11. Sydenstricker, V. P., et al. Treatment of Pellagra with Nicotinic Acid. South. M. J. 31:1155, 1938 (quoted by Sydenstricker, V. P. The Present Status of Nicotinic Acid. A.M.A. Arch. Int. Med. 67:746-754 (Apr.), 1941).
12 (a). Fineberg, S. K. Anaphylactic Shock Due to Nicotinic Acid. New York J. Med. 48:635-636 (Mar. 15), 1948.
(b). Odello, V. Stimulation of Vascular Reactions in Normal Pregnancy and in Toxicosis. Pathologica 51:569-572 (Nov.-Dec.), 1959.
13. Moehlig, Robert C. Leukoplakia of Oral Mucous Membrane, Tongue and Anal Region: Nine Year Ingestion of Vitamin B Complex as a Possible Etiologic Factor. J. Michigan M. Soc. 52:282-283 (Mar.), 1953.
14. Rossen, Frank A.; Etess, David A.; and Rosenthal, Robert L. Leukopenia Following Administration of Nicotinic Acid. Blood 7:623-630 (June), 1952.
15. Altschul, R.; Hoffer, A.; and Stephen, J. D. Influence of Nicotinic Acid on Serum Cholesterol in Man. Arch. Biochem. 54:558, 1955.
16. Altschul, Rudolph, and Hoffer, Abram. The Effect of Nicotinic Acid on Hypocholesterolemia. Canad. M. A. J. 82:783-785 (Apr. 9), 1960.
17. Altschul, Rudolph. Nicotinic Acid and Cholesterol Metabolism. GP 21:115-118 (Jan.), 1960.
18. ———. Personal communication.
19. Berge, K. G. Personal communication.
20. Achor, Richard W.; Berge, Kenneth G.; Barker, Nelson W.; and McKenzie, Bernard F. Treatment of Hypocholesterolemia with Nicotinic Acid. Circulation 17:497-504 (Apr.), 1958 (Part 1).
21. Parsons, William D., and Flinn, John H. Reduction of Serum Cholesterol Levels and Beta-Lipoprotein Cholesterol Levels by Nicotinic Acid. A.M.A. Arch. Int. Med. 103:783-790 (May), 1959.
22. Berge, Kenneth G.; Achor, Richard W.; Christensen, Norman A.; Mason, Harold L.; and Barker, Nelson W. Hypercholesteremia and Nicotinic Acid: A Long-Term Study. Am. J. Med. 31:24-36 (July), 1961.
23. Patent No. 2,491,616 Dec. 20, 1949, and 2,541,572 —Feb. 13, 1951.
24. Rivin, Arthur U. Jaundice Occurring During Nicotinic Acid Therapy for Hypocholesterolemia. J.A.M.A. 170:2088-2089 (Aug. 22), 1959.
25. Lyman, E. D.; Potthoff, Carl J.; and Jacobi, Herbert P. Food Poisoning Due to Nicotinic Acid in Meat: Report of an Outbreak. Nebraska Med. J. 42:243 (May), 1957.
26. Oldham, J. Revitt. Personal communication. Morbidity and Mortality—Weekly Rep. National Office of Vital Statistics, Public Health Service, U. S. Department of Health, Education, and Welfare, Vol. 7, No. 14 (Apr. 11), 1958.
27. Dern, Richard. Morbidity and Mortality—Weekly Rep. National Office of Vital Statistics, Public Health Service, U. S. Department of Health, Education, and Welfare, Vol. 19 (May 22), 1959.
28. Wentworth, Frederick, H., assistant director of health, Ohio State Department of Health, Columbus, Ohio. (Personal communication.)
29. Meador, Thomas L. Morbidity and Mortality—Weekly Rep. National Office of Vital Statistics, Public Health Service, U. S. Department of Health, Education, and Welfare, Vol. 9, No. 1 (Jan. 15), 1960.
30. Leitner, M. J. Personal communication, Dec. 28, 1960.

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Gas-Liquid Chromatography of Niacin and Niacinamide

By A. R. PROSSER and A. J. SHEPPARD

A procedure has been developed for the qualitative and quantitative determination of niacin and niacinamide by gas-liquid chromatography. Niacin was determined as its ethyl ester (ethyl nicotinate) or as *N*-ethylnicotinamide. Niacinamide was determined as niacinamide or converted to either ethyl nicotinate or *N*-ethylnicotinamide. An immobile biphase of 2.5 percent NPGS–10 percent SE-30 was the most satisfactory immobile phase evaluated. The results revealed that, in general, this sensitive gas-liquid chromatographic method could detect 5, 8, and 10 ng. of ethyl nicotinate, *N*-ethylnicotinamide, and niacinamide, respectively, using the hydrogen flame-ionization detector. The β-argon ionization detector (Ra_{226}) detected 15, 20, and 25 ng. of each compound, respectively. It was found that increasing quantities of ethyl nicotinate, *N*-ethylnicinamide, and niacinamide gave linear responses.

NIACIN (nicotinic acid) and its analog niacinamide (nicotinic acid amide) are important members of the B-complex vitamins. Niacinamide is included as an ingredient in decavitamin capsule and tablet composition requirements of the USP (1).

Chemical and biological methods are now widely used. The 10th edition of "Official Methods of Analysis" of the A.O.A.C. (2) includes both a chemical and biological method; the USP method (1) is based on a chemical technique. The chemical methods generally utilize the König reaction (3, 4) in which pyridine and its derivatives react with cyanogen bromide and an aromatic amine. In this reaction polymethine dyes are formed and are measured spectrophotometrically at 450 mμ. However, the chemical method is undesirable because the color development is pH sensitive and has low stability, which makes it difficult to reproduce results.

Biological methods provide the most specific quantitative assay presently available. The dog and chicken have been used for biological assay for total niacin activity. However, microbiological methods have been more popular and are far more practical from the standpoint of sensitivity, time, and expense. The A.O.A.C. method (2) uses *Lactobacillus plantarum*, which measures total niacin activity and can be used to specifically assay nicotinic acid in the presence of nicotinamide if the latter is first converted to 3-aminopyridine (6). Johnson has used *Leuconostoc mesenteroides* to measure nicotinic acid (5).

A polarographic method (7) and a thin-layer chromatographic method (8, 9) are available but have not been widely accepted.

Although a number of satisfactory methods are available for their separation and identification, a more rapid and simple method specific for niacin and niacinamide is needed. Since previous work from this laboratory (10, 11) has shown that vitamin B_6 of the water-soluble vitamin series is amenable to gas-liquid chromatography (GLC), it was felt that niacin and its analogs could also be measured by GLC. The present report is a summary of the feasibility of utilizing the gas chromatograph for the analysis of niacin and niacinamide.

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EXPERIMENTAL

Instrumentation—A model 5000 series Barber-Colman gas chromatograph (Barber-Colman, Rockford, Illinois) fitted with a high temperature hydrogen flame-ionization detector (FID) and a β-argon ionization detector (AID) with a 56 μc Ra_{226} foil was used with a 5-mv., 2-sec., 28-cm.-(11-in.) strip-chart recorder.

Materials—Niacin, niacinamide, and ethyl nicotinate were purchased from Eastman Organic Chemicals, Distillation Products Industries, Rochester, New York. *N*-Ethylnicotinamide was purchased from Aldrich Chemical Co., Milwaukee, Wisconsin. Pure grade *n*-hexane was obtained from Phillips Petroleum Co., Special Products Division, Bartlesville, Oklahoma. All other reagents were A.R. grade and used without further purification. Whatman No. 4 filter paper was used for all filtrations.

Preparation of Derivatives—Ethyl nicotinate was prepared by two methods (12): (*a*) direct action of ethanol and sulfuric acid on either niacin or niacinamide; (*b*) interaction of niacin with thionyl chloride followed by the reaction of the nicotinyl chloride hydrochloride product with ethanol and subsequent neutralization. Two methods of preparing niacinamide were used: (*a*) treatment of ethyl nicotinate with concentrated ammonia (12); (*b*) action of thionyl chloride on niacin followed by treatment of the resulting acid chloride with ammonia (13). *N*-Ethylnicotinamide was prepared by the following reactions: (*a*) action of thionyl chloride on niacin and treatment of the resulting acid chloride with ethylamine hydrochloride; (*b*) direct action of ethylamine on niacin in the presence of phosphorus pentoxide; (*c*) action of an aqueous solution of ethylamine on ethyl nicotinate.

Standard Solutions—Niacinamide and *N*-ethylnicotinamide were dissolved in enough ethanol and ethyl nicotinate in enough *n*-hexane so that a constant injection volume of 2 μl. was maintained throughout the investigation. Calibration standards were prepared from commercially obtained materials.

Gas–Liquid Chromatography—Three different column packings were used in this study. Column

1: 183 cm. × 3 mm. i.d. packed with a biphase mixture of 2.5% neopentyl glycol succinate (NPGS) and 10% SE-30 (w/w) on 100/120 mesh Gas Chrom P (silanized). Operating conditions: ethyl nicotinate: column, 180°; detector, 230°; flash heater, 220°; carrier gas, 50 ml./min. Niacinamide and *N*-ethylnicotinamide: column, 230°; detector, 280°; flash heater, 270°; carrier gas, 50 ml./min. Column 2: 244 cm. × 3 mm. i.d. packed with 5% NPGS (w/w) on 100/120 mesh Gas Chrom P (silanized) for the analysis of ethyl nicotinate. Operating conditions: column, 180°; detector, 260°; flash heater, 250°; carrier gas, 60 ml./min. Column 3: 244 cm. × 4 mm. i.d. packed with 2% neopentyl glycol sebacate (NPGSeb) (w/w) on 100/120 mesh Gas Chrom P (silanized) for the analysis of niacinamide and *N*-ethylniacinamide mixtures. Operating conditions: column, 210°; detector, 250°; flash heater, 230°; carrier gas, 60 ml./min.

All columns were U-shaped Pyrex glass and were preconditioned 24 hr. at 235° with carrier-gas flow rate of 60 ml./min. Argon was used as the carrier gas throughout the study. Compressed air and hydrogen flow rates were 460 and 36 ml./min., respectively, with the FID. A d.c. cell voltage of 900 was used at all times with the AID. Electrometer output was 1×10^{-14} amp. when FID was used and 3×10^{-9} amp. when the AID was used. The electrometer output is stated as full-scale output into a 5-mv. recorder unless otherwise stated in the text. Peak areas were determined by triangulation (width at half-height × height = peak area).

RESULTS AND DISCUSSION

The applicability of gas chromatography to niacin is limited by the presence of an acid group in the niacin molecule, its insolubility in most organic solvents, and the fact that niacin sublimes. It was therefore necessary to convert niacin to a derivative volatile enough for GLC. Ethyl nicotinate and *N*-ethylnicotinamide were chosen because of their relatively low boiling points, ease of preparation, and stability. Although niacinamide has an amide group, it is soluble in some organic solvents, has a low melting point, and is suitable for GLC analysis.

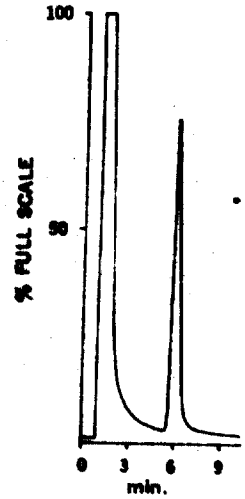

Fig. 1—Chromatograms of 1.0 mcg. ethyl nicotinate in n-hexane on a 2.5% NPGS–10% SE-30 biphase column at 180°.

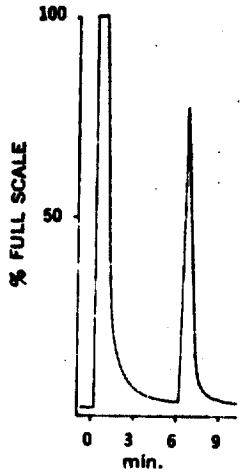

Fig. 2—Chromatogram of 2 mcg. niacinamide in ethanol on a 2.5% NPGS–10% SE-30 biphase column at 230°.

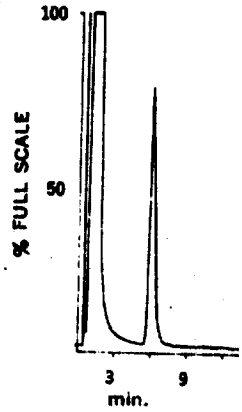

Fig. 3—Chromatogram of 1.25 mcg. ethyl nicotinate in n-hexane on a 5% NPGS column at 180°.

Derivative Preparation Efficiency—The yields of three derivatives were in good agreement with existing literature values (12, 13). GLC scans of the prepared derivatives indicated no contaminants present. The structures of the reaction products were confirmed by IR and UV spectroscopy.

Effect of Immobile Phase—The elution peaks of the three niacin analogs were typical adsorption isotherms on SE-30, QF-1, and biphase mixtures of NPGS-SE-30 when the ratio of NPGS to SE-30 was less than 1:4. The preceding immobile phases were rejected on the basis of their tailing adsorption isotherms. The 2.5% NPGS–10% SE-30 column at 180° gave a satisfacory elution peak for ethyl nicotinate (Fig. 1). When the temperature was increased to 230°, niacinamide produced a usable elution peak exhibiting slight tailing (Fig. 2). On this column, *N*-ethylniacinamide was found to precede niacinamide. The results suggest that by varying the column temperature and carrier solvents, GLC may be a potential means of screening for analogs of the vitamin.

Ethyl nicotinate exhibited a nearly symmetrical elution peak on the 5% NPGS immobile phase column (Fig. 3) whereas the other two analogs gave

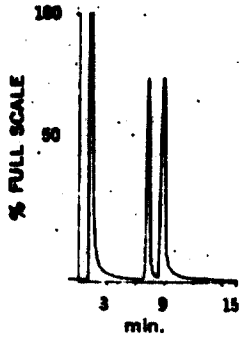

Fig. 4—Chromatogram of a mixture of 1.0 mcg. N-ethylniacinamide (7.6 min.) and 1.2 mcg. niacinamide (9.3 min.) on a 2% NPGSeb column at 210°.

broad tailing elution peaks at much longer retention times. The 2% NPGSeb column eluted *N*-ethylnicotinamide ahead of niacinamide (Fig. 4). At 210°, ethyl nicotinate was eluted along with the carrier solvent. This column will resolve all three niacin analogs at 180° but the retention times for *N*-ethylniacinamide and niacinamide are extended and the elutions peaks were quite broad and were, therefore, less desirable for quantitative analysis.

Effect of Quantity Injected—Response data for ethyl nicotinate, *N*-ethylnicotinamide, and niacinamide using the biphase column of 2.5% NPGS and 10% SE-30 are given in Table I. It can be seen from these data that as the quantity of compound increased the response was linear. The response lines for *N*-ethylnicotinamide and niacinamide are almost identical but the response line for ethyl nicotinate was not closely related to those of the other two analogs.

Sensitivity—The GLC method for niacin and niacinamide is very sensitive. By using the FID, an attenuator setting of 1, an electrometer output of 1×10^{-10} amp., and a 0-1-mv. recorder, 5 ng. of ethyl nicotinate and 10 ng. of niacinamide were detectable. The AID, with an attenuation of 1 and an electrometer output of 3×10^{-9} amp., detected 15, 20, and 25 ng. of ethyl nicotinate, *N*-ethylnicotinamide, and niacinamide, respectively. Quantitation at these low levels, however, is difficult because of the noise-to-signal ratio and because there is less control over the quantity injected.

CONCLUSIONS

It has been established that it is possible to detect and analyze three analogs of the vitamin niacin, *i.e.*, nicotinic acid as the ethyl ester, nicotinamide, and *N*-ethylnicotinamide. Studies are currently underway on applying the GLC analysis to pharmaceuticals containing niacin and niacinamide. Preliminary results indicate that the GLC analysis of the vitamin niacin is adaptable to pharmaceutical products.

TABLE I—RESPONSE OF ETHYL NICOTINATE, *N*-ETHYLNICOTINAMIDE, AND NIACINAMIDE[a]

	Peak Area,[b] mm.[2]		
mcg.	Ethyl Nicotinate	*N*-Ethyl-Nicotinamide	Niacinamide
0.5	25.0 ± 0.4	18.9 ± 0.5	9.8 ± 0.2
1.0	40.0 ± 1.4	31.3 ± 0.8	21.3 ± 0.2
2.0	70.0 ± 1.5	62.1 ± 1.3	45.0 ± 1.0
5.0	190.0 ± 2.5	124.2 ± 1.4	117.2 ± 1.3
10.0	384.0 ± 3.4	250.3 ± 2.9	245.4 ± 3.1
15.0	572.5 ± 4.4	362.5 ± 4.3	364.0 ± 2.7
20.0	757.5 ± 4.2	473.2 ± 4.7	477.8 ± 3.8

[a] 10 × attenuation, electrometer output of 1×10^{-10} amp. hydrogen flame detector, and a 2.5% NPGS–10% SE-30 column. [b] Mean of six analyses ± standard deviation.

REFERENCES

(1) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1960.
(2) "Official Methods of Analysis," The Association of Official Agricultural Chemists, 10th ed., Washington, D. C., 1965.
(3) König, W. J., *Prakt. Chem.*, 69, 105(1904).
(4) *Ibid.*, 70, 19(1904).
(5) Johnson, B. C., *J. Biol. Chem.*, 159, 227(1945).
(6) Atkin, L., Schultz, A. S., Williams, W. L., and Frey, C. N., *J. Am. Chem. Soc.*, 65, 992(1943).
(7) Strohecker, R., and Henning, H. M., "Vitamin Assay Tested Methods," Verlag Chemi GMBH, Weinheim/Bergstr, Germany, 1965.
(8) Nurnberg, E., *Dtsch. Apotheker-Ztg.*, 101, 142(1961).
(9) Bolliger, H. R., "Thin-Layer Chromatography," Stahl, E., ed., Springer-Verlag, Berlin, Germany; Academic Press Inc., New York, N. Y., 1965.
(10) Prosser, A. R., and Sheppard, A. J., *Federation Proc.*, 25, 669, 2711(1966).
(11) Prosser, A. R., Sheppard, A. J., and Libby, D. A., *J. Assoc. Offic. Anal. Chemists*, 50, 1318(1967).
(12) Vogel, A. I., "A Text-Book of Practical Organic Chemistry," 3rd ed., Longmans, Green and Co., Inc., New York, N. Y., 1956, pp. 849–850.
(13) "The Merck Index of Chemicals and Drugs," 6th ed., Merck & Co., Inc., Rahway, N. J., 1952, p. 674.

Keyphrases

Niacin—analysis
Niacinamide—analysis
Ethyl nicotinate, *N*-ethyl nicotinamide—derivatives
GLC—analysis

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Metabolism of Nicotinic Acid and Related Compounds in Man and Rat

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The earliest attempts to study the fate of ingested nicotinic acid were confined to the isolation of various metabolites from urines (Ackerman, 1912; Komori & Sendju, 1926). It is now accepted that N^1-methylnicotinamide (Huff & Perlzweig, 1943; Najjar, White & McNair Scott, 1944) and N^1-methyl-2-pyridone-5-carbonamide (Knox & Grossman, 1946, 1947; Holman & de Lange, 1949) are important excretory products of nicotinic acid metabolism. The excretion of tertiary nicotinyl compounds, which give a colour by König's reaction (1904), has also been repeatedly reported, but the data were obtained by techniques based on complicated differentiation procedures (Melnick, Robinson & Field, 1940; Perlzweig, Levy & Sarett, 1940; Huff & Perlzweig, 1941; Sarett, Huff & Perlzweig, 1942; Johnson, Hamilton & Mitchell, 1945; Ellinger & Kader, 1949). Recently, more refined and accurate techniques were used by Johnson & Lin (1951) and by Leifer, Lloyd, Hogness & Corson (1951) who gave labelled nicotinic acid and nicotinamide to rats and partitioned the metabolites in the urines by paper chromatography. This procedure, however, is difficult to apply to man.

The present communication deals with the differentiation and estimation of various metabolites of nicotinic acid and related compounds in the urines of man and the rat, by employing chromatographic techniques recently developed in this laboratory for both tertiary and quaternary nicotinyl compounds (Kodicek & Reddi, 1951). No attempt has been made to determine the N^1-methyl-2-pyridone-5-carbonamide, which the above mentioned procedure cannot detect.

MATERIALS AND METHODS

Human subjects

Four healthy male subjects on a normal diet were selected for these studies.

Collection of urines. The subjects were given various nicotinyl compounds (Table 1) in turn at weekly intervals, together with 400 ml. of water, and their urines were collected for 3 hr. The dose was administered after breakfast, except in the case of the second dose of nicotinic acid which was given before breakfast to induce maximum flushing of the skin.

The control urines from the undosed subjects were collected in the same way after giving 400 ml. of water. The urines were stored at 4° under toluene.

Rats

Sixteen male piebald rats, weighing 55–60 g., were divided into two groups and housed in individual cages. One group received the low-protein maize diet of Harris & Kodicek (1950), which is deficient in nicotinic acid, and the other group received an adequate synthetic diet containing 18% casein.

Low-protein maize diet (Harris & Kodicek, 1950). Casein (Genatosan, vitamin-free) 3·5, sucrose 51·4, maize meal 40, salt mixture 3 (Kodicek & Carpenter, 1950), cotton-seed oil 2, cystine 0·1.

Synthetic casein diet. Casein (Genatosan, vitamin-free) 18, sucrose 73·85, salt mixture 5, cotton-seed oil 3, cystine 0·15.

Each kg. of diet also contained: choline chloride 2 g., thiamine 3 mg., riboflavin 3 mg., pyridoxin 3 mg., calcium D-pantothenate 20 mg., biotin 0·1 mg.

In addition, each rat received *per os*, once a week, 0·5 mg. tocopherol acetate, 0·1 mg. 2-methyl-1:4-naphthaquinone and 0·1 g. Radiostoleum (British Drug Houses Ltd.) containing 1500 i.u. vitamin A and 300 i.u. vitamin D.

The rats were maintained on these diets for 19 days during which time the deficient group on the low-protein maize diet gradually decreased in weight. At the end of this period they were transferred to metabolism cages. Two rats were placed in each cage and their urines were collected for 48 hr. while they were maintained on the diets. The animals were then given various nicotinyl compounds, listed in Table 2, on palettes for 2 days and the urines were again collected.

Estimation of nicotinyl compounds

Total alkali-hydrolysable tertiary nicotinic acid derivatives, which include nicotinic acid, nicotinamide and nicotinuric acid (nicotinylglycine), were estimated chemically according to the method of Wang & Kodicek (1943). The estimation of N^1-methylnicotinamide was carried out by the method of Carpenter & Kodicek (1950).

In view of certain differences between the chemical and chromatographic data, human urines (see Table 1) were also studied by using the microbiological procedure of Clegg, Kodicek & Mistry (1952). Chromatograms of the urine from an undosed subject (no. 2) were also tested microbiologically by using a technique similar to that described by Leifer, Langham, Nye & Mitchell (1950). These estimations were kindly carried out by Miss K. M. Clegg.

Separation of nicotinyl compounds in urines by paper chromatography and their estimation

The chromatographic procedures for the separation of tertiary and quaternary nicotinyl compounds (Kodicek & Reddi, 1951) were applied to urines, and the concentrations of the tertiary nicotinyl substances were evaluated by visual

comparison of the coloured spots by a procedure similar to that described by Berry, Sutton, Cain & Berry (1951).

Procedure. 10 ml. of urine were evaporated to dryness under reduced pressure at 55–60°. The residue was extracted with 1 ml. of distilled water and centrifuged. The clear supernatant was used for chromatographic studies, in which 10 μl. were placed on Whatman filter paper no. 1 and descending chromatograms were run overnight. In some cases, where the quantity of substance to be detected was very low, four spots of 10 μl. each were placed one over the other after drying each spot thoroughly. Pure nicotinyl compounds, in amounts ranging from 0·1 to 2·0 μg., were run on the same paper along with the urines.

Tertiary nicotinyl compounds. For these compounds *n*-butanol saturated with water was found to be the best solvent system. After development, the papers were dried at room temperature. The dry papers were placed in a closed glass tank for 1 hr. at room temperature over CNBr, prepared according to the method of Wang & Kodicek (1943). They were then sprayed with 2% *p*-aminobenzoic acid (2 g. of *p*-aminobenzoic acid dissolved in 75 ml. 0·75 N-HCl and made up to 100 ml. with 96% ethanol). The different compounds could be identified by their colours and R_F values (Kodicek & Reddi, 1951). All the spots fluoresced bright yellow under ultraviolet light, and quantities as low as 0·1 μg. could be detected under these conditions. Since within a range of 0·1–2·0 μg. the area of the spots remained the same, the gradation of the colour intensity, especially when viewed in ultraviolet light, allowed a fairly accurate comparison with the standards. The most suitable concentration for evaluation was within the range of 0·25–0·5 μg., and by averaging the estimates of two independent observers a difference of 0·1 μg. could be detected. Duplicate chromatograms sprayed only with the *p*-aminobenzoic acid reagent, without exposing them to CNBr, served as controls to eliminate non-specific colour spots which were found to be present both in dosed and undosed urines. In the present studies it was not found necessary to adjust the pH of the urinary concentrate to neutrality, since the R_F values of the metabolites corresponded well with those reported earlier on pure substances (Kodicek & Reddi, 1951). However, it may be advisable in general to control the pH of the urinary concentrates to eliminate the possibility of shifts of R_F values.

The results obtained by the above procedure are given in the last three columns of Tables 1 and 2.

Quaternary nicotinyl compounds. The solvent system *n*-propanol-water (60:40) was found to be the best for developing chromatograms of quaternary nicotinyl compounds. The dry papers after development were placed over a mixture of ethyl methyl ketone and NH_3 (1:1) for 1 hr. in a closed glass tank at room temperature. The relative positions of various compounds could be detected by their bluish white fluorescence, and quantities as low as 0·05 μg. (nicotinic acid equivalents) could be detected.

Detection of tryptophan metabolites in urines of humans dosed with L-tryptophan

Urinary concentrate (10 μl.) was placed on Whatman filter paper no. 1 and developed in *n*-butanol-acetic acid-water (50:10:40) overnight and dried at room temperature. The chromatograms of urines from both dosed and undosed subjects were viewed under ultraviolet light and the R_F values of the fluorescent metabolites determined (Fig. 1). 3-Hydroxyanthranilic acid and kynurenic acid were identified by running pure samples on the same papers. Tryptophan and kynurenine were identified by spraying with the *p*-dimethylaminobenzaldehyde reagent (0·5 g. *p*-dimethylaminobenzaldehyde, 1 ml. conc. HCl and 100 ml. absolute ethanol), and by their behaviour on exposure to vapours of conc. HCl (Tabone, Robert, Thomassay & Mamounas, 1950). The R_F values of other metabolites were compared with those reported by Dalgliesh, Knox & Neuberger (1951).

RESULTS

Man

The urines from undosed subjects, collected for a period of 3 hr., contained 0·5–0·6 mg. of N^1-methylnicotinamide, with an average of 0·53 mg. (Table 1). The total content of tertiary alkali-hydrolysable derivatives of nicotinic acid, as determined chemically, ranged from 0·2 to 0·3 mg. within the 3 hr. period. However, no tertiary nicotinyl derivatives could be detected on chromatograms. In view of this discrepancy, microbiological estimations were carried out on urinary concentrates hydrolysed with N-sodium hydroxide. The microbiological values (Table 1) were much lower than those determined chemically, ranging from 0·04 to 0·12 mg. of nicotinic acid/3 hr. Similar results were obtained when the urines were tested without a prior alkaline hydrolysis.

When urine from undosed subjects, concentrated 10 times, was chromatographed and the strips were analysed microbiologically for nicotinic acid activity, according to the procedure of Leifer *et al.* (1950), the R_F region corresponding to nicotinamide showed some activity. The concentration of nicotinamide amounted to 40% of the total nicotinic acid derivatives as determined microbiologically. The rest of the activity remained at the place of application of the spots (40 μl.) and spread to a distance of 3 cm. from the origin.

Dosing with nicotinic acid. After doses of 100 mg. nicotinic acid the excretion of alkali-hydrolysable nicotinic acid derivatives and of N^1-methylnicotinamide increased to 6·0–14·6 mg. and 2·8–5·7 mg./3 hr., respectively (Table 1). The chromatographic results showed that the major metabolite in the urines was nicotinuric acid, forming 92–99% of the alkali-hydrolysable derivatives; the rest could be accounted for by a small amount (1–4%) of nicotinamide.

There was no free nicotinic acid in the urines except in one subject (no. 3) who had intense flushing of the skin soon after the ingestion of nicotinic acid. This individual had, incidentally, the highest excretion of tertiary nicotinyl compounds and the lowest of N^1-methylnicotinamide. The vasodilatory effect of nicotinic acid, especially when taken ante-prandially, is well known. It was of interest to verify whether the appearance of free

Table 1. *Excretion of nicotinyl compounds in human urines and their distribution*

Subject	Age (years)	Dose	Excretion (mg./3 hr.): N^1-Methylnicotinamide determined chemically	Total alkali-hydrolysable nicotinic acid derivatives determined: Chemically	Total alkali-hydrolysable nicotinic acid derivatives determined: Microbiologically	Approximate relative distribution of tertiary nicotinyl compounds (%)*: Nicotinic acid	Nicotinamide	Nicotinuric acid†
1	29	None	0·5	0·3	0·12	Nil	Nil	Nil
2	43		0·5	0·2	0·04	Nil	Nil	Nil
3	32		0·5	0·2	0·04	Nil	Nil	Nil
4	20		0·6	0·2	0·06	Nil	Nil	Nil
1	29	100 mg. nicotinic acid (after breakfast)	4·5	7·3	—	Nil	4	96
2	43		3·7	6·0	—	Nil	2	98
3	32		2·8	14·6	—	7	1	92
4	20		5·7	8·6	—	Nil	1	99
1	29	100 mg. nicotinic acid (before breakfast)	5·4	40·3	—	10	0·5	89·5
2	43		2·7	17·3	—	5	0·5	94·5
1	29	100 mg. nicotinamide	16·2	1·5	—	Nil	100	Nil
2	43		16·6	1·8	—	Nil	100	Nil
3	32		6·9	1·8	—	Nil	100	Nil
4	20		15·6	0·9	—	Nil	100	Nil
2	43	3 g. L-tryptophan	1·0	—	0·09	Nil	Nil	Nil
3	32		0·7	—	0·04	Nil	Nil	Nil
4	20		1·0	—	0·05	Nil	Nil	Nil

* Determined by paper chromatography (Kodicek & Reddi, 1951).
† The values for nicotinuric acid were obtained by difference.

nicotinic acid in the urine after a dose of nicotinic acid was associated with flushing and the other vasodilatory symptoms. Therefore, two individuals (nos. 1 and 2), who normally did not experience any flushing, were given before breakfast 100 mg. nicotinic acid and the urines, collected for 3 hr., were analysed in the usual way. Both subjects experienced intense flushing which was more pronounced in subject no. 1. As will be seen from Table 1, the urinary excretion of N^1-methylnicotinamide did not show any appreciable change, but that of the tertiary nicotinyl compounds increased considerably, to 40·3 and 17·3 mg. respectively. In addition to the usual appearance of nicotinuric acid (89·5–94 %) and of nicotinamide (0·26–0·5 %), free nicotinic acid also appeared in the urines in amounts of 5–10 % of the total tertiary nicotinyl compounds excreted.

Dosing with nicotinamide. After the ingestion of 100 mg. nicotinamide, there was a large increase in the excretion of N^1-methylnicotinamide, which varied from 6·9 to 16·6 mg./3 hr. The small rise in the tertiary nicotinyl derivatives (0·9–1·8 mg.) was solely due to nicotinamide, since no other nicotinyl compound could be detected on the paper chromatograms.

Dosing with tryptophan. After the ingestion of 3 g. L-tryptophan, there was an increase in the excretion of N^1-methylnicotinamide. The tertiary nicotinyl compounds, tested microbiologically, did not increase. On chromatograms tested by chemical means no nicotinyl compounds except N^1-methylnicotinamide were observed.

Tryptophan metabolites. When 10 times concentrated urines, obtained after dosing with tryptophan, were chromatographed using *n*-butanol-acetic acid-water (40:10:50), a number of tryptophan metabolites could be identified by their fluorescence and also by spraying with the *p*-dimethylaminobenzaldehyde reagent (Fig. 1). Spots 4 and 6 were identified as kynurenic acid and 3-hydroxyanthranilic acid, respectively, by running the pure substances side by side on the same paper. Spot 3 was identified as kynurenine. It corresponded to the spot *F* (kynurenine) of Dalgliesh *et al.* (1951). Spraying with *p*-dimethylaminobenzaldehyde produced an orange spot (S_2) which faded on exposure to fumes of concentrated hydrochloric acid. This behaviour was in keeping with the observations of Tabone *et al.* (1950). It was placed immediately above tryptophan (spot S_3) whose yellow colour turned violet on exposure to concentrated hydrochloric acid. The R_F values of spots S_2 and S_3 in *n*-butanol-water were 0·26 and 0·28, respectively, which agreed well with values reported by Tabone *et al.* (1950) for kynurenine and tryptophan. Spots 1, 2 and 5 had R_F values similar to those of spots *C*, *E* and *I* of Dalgliesh *et al.* (1951).

Spot S_1 turned bright yellow on spraying, and there was no change in colour on exposure to con-

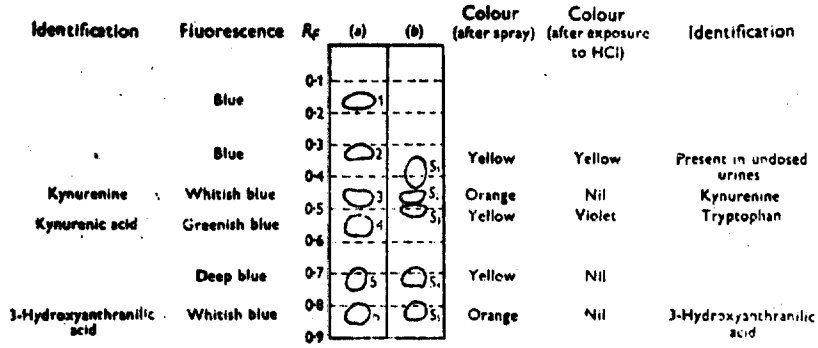

Fig. 1. Diagram showing the approximate R_F values of tryptophan metabolites in human urines after ingestion of L-tryptophan. (Solvent system: n-butanol-acetic acid-water, 40:10:50.) (*a*) Fluorescent spots obtained by chromatographing 10 times-concentrated urines; (*b*) colour spots of the same after spraying with *p*-dimethylaminobenzaldehyde.

centrated hydrochloric acid. However, a similar spot was observed in the urines from undosed subjects. It cannot therefore be considered a metabolite derived from tryptophan.

Rats

It will be seen from Table 2 that rats given a maize diet deficient in nicotinic acid excreted a very small amount of N^1-methylnicotinamide, nicotinic acid and nicotinamide, while those given an adequate casein diet excreted daily 0·24 mg. N^1-methylnicotinamide and 0·04 mg. total tertiary nicotinyl compounds per rat. Both deficient and normal rats excreted nicotinic acid and nicotinamide in equal proportions.

Dosing with nicotinic acid. After dosing with 2·5 mg. nicotinic acid, the deficient rats excreted 37 % and the normal animals 90 % of the dose in the form of N^1-methylnicotinamide, nicotinuric acid, nicotinic acid and nicotinamide. In the deficient animals, the major excretion products, N^1-methylnicotinamide and nicotinuric acid, were in equal proportions, each being about 16 % of the dose. There was a definite rise in the excretion of nicotinic acid, but only a small rise in nicotinamide, about 3·5 and 0·3 % of the dose respectively. In the normal animals, the main excretion products in descending order were N^1-methylnicotinamide 41 %, nicotinuric acid 23 %, nicotinic acid 12·2 %, and nicotinamide 2·5 % of the dose (Fig. 2). As will be seen from Table 2, nicotinuric acid formed 81 and 63 % of the total tertiary nicotinyl compounds found in the urines of deficient and normal animals respectively.

Dosing with nicotinamide. After dosing with 2·5 mg. nicotinamide, the deficient and normal rats excreted 52 and 95 % of the dose respectively. N^1-Methylnicotinamide, nicotinamide and nicotinic acid, but no nicotinuric acid, could be found on the chromatograms. The relative distribution of the tertiary nicotinyl compounds, namely nicotinamide and nicotinic acid, was in both groups in a ratio of 3 : 1

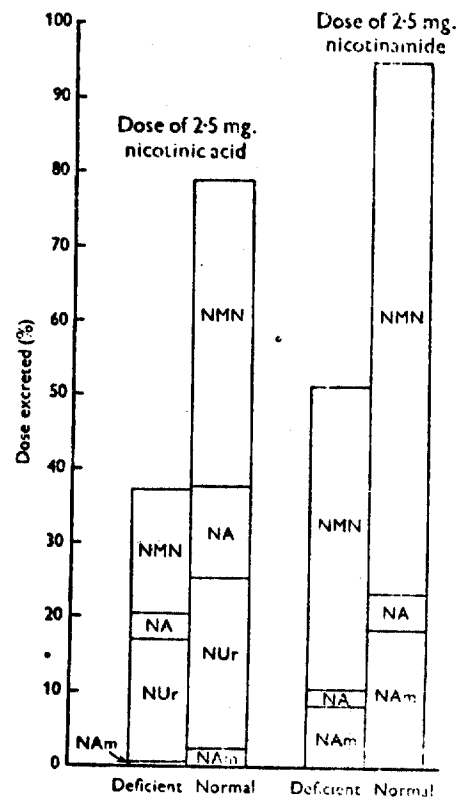

Fig. 2. The percentage of ingested nicotinic acid and amide excreted by nicotinic acid-deficient and normal rats. NMN, N^1-methylnicotinamide; NA, nicotinic acid; NUr, nicotinuric acid; NAm, nicotinamide.

(Table 2). The major excretion product was N^1-methylnicotinamide, forming in the deficient group 40 % and in the normal group 70 % of the dose.

Table 2. *Excretion of nicotinyl compounds in urines of normal and deficient rats before and after dosing with nicotinic acid and related substances*

Group	Diet	No. of rats	Average wt. (g.)	Dose	Average daily excretion per rat (mg.)			Approximate relative distribution of tertiary nicotinyl compounds (%)*		
					N^1-Methyl nicotinamide	Total alkali-hydrolyable nicotinic acid derivatives		Nicotinic acid	Nicotin-amide	Nicotinamide acid
1 (deficient)	Low-protein maize (Harris & Kodicek, 1950)	8	78	None	0·01	0·01		43	57	[illegible]
		2	78	2·5 mg. nicotinic acid	0·42	0·53		17	2	[illegible]
		2	87	2·5 mg. nicotinamide	1·03	0·27		26	74	[illegible]
		2	74	100 mg. quinolinic acid	0·01	0·01		46	54	[illegible]
		2	88	100 mg. L-tryptophan	0·10	0·03		71	29	[illegible]
2 (normal)	Synthetic casein diet	8	139	None	0·24	0·04		49	51	[illegible]
		2	147	2·5 mg. nicotinic acid	1·27	0·96		31	6	[illegible]
		2	210	2·5 mg. nicotinamide	2·03	0·62		25	75	[illegible]
		2	132	100 mg. quinolinic acid	0·57	0·14		86	14	[illegible]
		2	130	100 mg. L-tryptophan	1·74	0·20		90	10	[illegible]

* Determined by paper chromatography (Kodicek & Reddi, 1951).

Nicotinamide was excreted in significant amounts, namely 8 % of the dose in the deficient animals and 18·6 % in the normal rats. The excretion of nicotinic acid was only about 2·5 and 4·6 % of the dose respectively (Fig. 2).

Dosing with quinolinic acid. After dosing with 100 mg. quinolinic acid the deficient animals showed no rise in the excretion of N^1-methylnicotinamide, and an insignificant increase in the tertiary nicotinyl compounds. The distribution of nicotinic acid and amide was the same as in urine obtained before dosing, namely 46 and 56 %. In the normal group the excretion of N^1-methylnicotinamide increased from 0·24 to 0·57 mg. and that of the tertiary nicotinyl compounds rose from 0·04 to 0·14 mg./day/rat. This rise was mainly due to an increased excretion of nicotinic acid, which formed 86 % of the total tertiary nicotinyl compounds (Table 2).

Dosing with L-*tryptophan.* After dosing with 100 mg. L-tryptophan, there was, in the deficient rats, a slight increase in the excretion of N^1-methylnicotinamide and of tertiary nicotinyl compounds. A similar but more pronounced rise of these substances was found in the normal group. The increase in the tertiary nicotinyl compounds, both in the deficient and normal rats, was mainly due to a rise in nicotinic acid, which formed in the deficient group 71 % and in the normal rats 90 % of these derivatives (Table 2).

DISCUSSION

The paper-chromatographic technique used for partitioning nicotinic acid derivatives, besides being simple and easily performed, has many advantages over the chemical methods employed by earlier workers (Melnick *et al.* 1940; Perlzweig *et al.* 1940; Huff & Perlzweig, 1941). Especially in the case of the tertiary nicotinyl compounds, the estimations based on König's colour reaction may be interfered with by unspecific colour formation in the urines which has to be corrected by the use of proper blanks. In the chromatographic procedure, one compares the colour of pure compounds separated on the chromatograms and thus eliminates errors due to interference by other substances. It was found advantageous to spray a duplicate chromatogram with the *p*-aminobenzoic acid reagent alone, without the cyanogen bromide treatment, and to distinguish in this way several coloured non-specific spots which usually appear on the chromatograms. One other advantage of the procedure is the possibility of employing it in elucidating the fate of ingested nicotinyl compounds in man, where one could not easily use radioactive substances employed successfully in the rat (Johnson & Lin, 1951; Leifer *et al.* 1951). The method is sufficiently sensi-

tive to detect amounts of importance, although in certain cases one has to take recourse to the more sensitive microbiological technique (Leifer *et al.* 1950), as will be discussed below. One drawback of the method is that it could not be used for the detection of N^1-methyl-2-pyridone-5-carbonamide which is of particular importance in human urines. Furthermore, the method does not detect quinolinic acid.

The fluorescent procedure for detecting quaternary nicotinyl compounds is highly sensitive and would allow the differentiation of a number of compounds besides N^1-methylnicotinamide, should they appear in the urines. It is interesting that in no case could any other quaternary nicotinyl derivative, such as the pyridine nucleotide coenzymes or N^1-methylnicotinuric acid betaine, be found.

Metabolites in normal urine

In urine from undosed human subjects, no nicotinyl compound other than N^1-methylnicotinamide could be detected on the chromatograms. The high values of the total alkali-hydrolysable nicotinyl derivatives obtained by chemical methods may have been due to interfering substances which the blank did not correct. This is supported by the relatively low values found microbiologically. No such interference in the chemical method was found in the urines after dosing because of the small amount of urine used for assay. The analysis of chromatograms by the microbiological procedure showed the presence of a small amount of nicotinamide, of the order of 0·075 μg./ml. of urine. This concentration was below that detectable by the spraying procedure. The rest of the microbiological activity remained at the origin of the chromatograms and we were unable to identify these unknown active substances. Since large amounts of urine concentrate had to be applied to the paper to obtain a satisfactory microbiological response, and since the original spots spread to the region where normally nicotinuric acid appears, we could not eliminate the possibility of an occurrence of small amounts of nicotinuric acid; however, no nicotinic acid seemed to be present. Perlzweig *et al.* (1940) and Sarrett *et al.* (1942) reported the presence of small amounts of nicotinuric acid, while Melnick *et al.* (1940) could not find any in normal urine. Ellinger & Kader (1949) reported the presence of both nicotinic acid and nicotinamide. These discrepancies may be due to defects inherent in chemical methods. In contrast to the human urines, the urines both of the nicotinic acid-deficient and normal rats, which were not given any doses, contained detectable amounts of nicotinic acid and nicotinamide, in addition to small amounts of N^1-methylnicotinamide. These metabolites were present in a significantly higher concentration in the normal group.

Metabolites of nicotinic acid

The ingestion of nicotinic acid by man is followed within the first 3 hr. by the excretion of a glycine conjugate, nicotinuric acid, and of the N^1-methylated nicotinyl derivatives, of which N^1-methylnicotinamide could be detected in these studies. It is interesting to find a small rise in the excretion of nicotinamide, indicating not only that amidation has taken place, but also that a portion of this metabolite is being lost to the organism. It appears from our results that free nicotinic acid is not a normal constituent in the human urine after dosing, but is found only under certain conditions, associated with the known pharmacological effects of this compound. It seems that it is due to a sudden occurrence in the organism of a high concentration of nicotinic acid which cannot be dealt with satisfactorily by the normal metabolic mechanisms. The large excretion of nicotinic acid was particularly pronounced when the dose was taken on an empty stomach. It seems probable that the liver is mainly concerned with the formation of the glycine conjugate, and if it cannot perform this function free nicotinic acid circulating in the blood causes the vasodilatory symptoms and is ultimately excreted in the urine. The appearance of free nicotinic acid in the urine may possibly be a test for the efficiency of liver function, although the effect on the vessels of the kidney may be a complicating factor. A distribution of metabolites similar to that in man was found in the rat, but in this case nicotinic acid appeared consistently in appreciable amounts in the urines. This may have been due to the relatively large dose administered to the animals. The deficient animals excreted a smaller amount of nicotinyl metabolites than the normal group, but the excretion pattern did not change. It would be of interest to see if similar results were obtained in human deficiency.

Our results on human urines are in keeping with those of Holman & de Lange (1950*a*) who found that ingestion of nicotinic acid resulted in a greater excretion of non-methylated derivatives of nicotinic acid than after ingestion of nicotinamide. In either instance 76–80 % of the dose could be accounted for, when the excretion of N^1-methyl-2-pyridone-5-carbonamide was included. The presence of free nicotinic acid in the urines of individuals dosed with nicotinic acid, was reported by Ellinger & Kader (1949) who, on the other hand, could not find in human and rat urines any nicotinuric acid which in our studies formed the main excretory product. Our results on rat urines are in good agreement with those of Johnson & Lin (1951) and Leifer *et al.* (1951) who fed radioactive nicotinic acid to rats.

Metabolites of nicotinamide

The spectrum of metabolites appearing in human urines after dosing with nicotinamide was different from that found after ingestion of nicotinic acid. N^1-Methylnicotinamide appeared to be the major excretion product after dosing with nicotinamide, but we have no data for N^1-methyl-2-pyridone-5-carbonamide which is known to be an important metabolite (Knox & Grossman, 1946, 1947; Holman & de Lange, 1949). Of the tertiary nicotinyl compounds only nicotinamide was found in the urine. It thus seems that no appreciable deamidation occurred, sufficient to cause an excretion of free nicotinic acid or its glycine conjugate. Our results differ from those of Johnson *et al.* (1945) who found, by microbiological methods, free nicotinic acid in the urines. Ellinger & Kader (1949) could detect chemically only an increase in N^1-methylnicotinamide. Our results are based on direct evidence from chromatograms and are therefore more specific than those obtained by indirect methods.

In contrast to man, both deficient and normal rats excreted nicotinamide and a relatively smaller amount of nicotinic acid as well as N^1-methylnicotinamide. No nicotinuric acid was found, suggesting that also in the rat conjugation with glycine does not play any role in the disposal of nicotinamide. Our findings are in good agreement with data obtained from the isotope experiments of Leifer *et al.* (1951). On the other hand, Johnson & Lin (1951) by tracer techniques, and Perlzweig, Rosen & Pearson (1950), reported the presence of nicotinuric acid in rat urines after dosing with nicotinamide.

While only 50% of the dose of nicotinamide appeared in urines of deficient rats, almost the entire dose was recovered in the normal animals, the major part as N^1-methylnicotinamide. Similarly, a higher proportion of the dose of nicotinic acid was excreted by the normal than the deficient group. It would appear that in the presence of sufficient dietary tryptophan the rat either has preference for the tryptophan-nicotinic acid conversion or the ingestion of nicotinyl compounds may influence favourably this conversion of tryptophan. This may be the reason why in normal rats such a high recovery of the dose of nicotinic acid or amide was observed. This is in agreement with the findings of Spector (1948).

Metabolites of L-tryptophan

In man, after ingestion of tryptophan, an increased excretion of N^1-methylnicotinamide was found, but not of other nicotinyl derivatives. Similar observations were earlier reported by Sarrett & Goldsmith (1947, 1949, 1950) and by Sarrett (1950*a*). Perlzweig, Rosen, Levitas & Robinson (1947) observed by microbiological methods a small increase in the excretion of nicotinyl compounds. The excretion of N^1-methyl-2-pyridone-5-carbonamide, which rises significantly after administration of tryptophan (Holman & de Lange, 1950*b*), and of quinolinic acid, which forms a major excretion product in rats (Henderson, 1949*a*), and in man (Sarrett, 1950*a*), was not determined since these substances could not be identified on paper chromatograms with the present procedures.

In the rat, possibly due to its more efficient conversion of tryptophan to nicotinic acid, there was a small but definite increase in the excretion of nicotinic acid, while that of nicotinamide did not rise. This was the case both in the deficient and normal rats, but the latter excreted more of the nicotinyl metabolites than the deficient ones. The finding of nicotinic acid rather than the amide could be taken as circumstantial evidence that tryptophan is converted primarily into nicotinic acid. This is in keeping with the conclusions of Heidelberger, Abraham & Lepkovsky (1948, 1949) who showed the conversion by rats of labelled tryptophan into N^1-methylnicotinamide.

Sarrett (1950*a*, *b*) found an increase in the excretion of xanthurenic acid (4:8-dihydroxyquinoline carboxylic acid) in man after administration of tryptophan and of an ether-soluble tryptophan-like metabolite which seemed to be derived from D-tryptophan (Sarrett & Goldsmith, 1950). So far as we are aware, no other metabolites have been reported in the urine of humans dosed with tryptophan. In the present study, 3-hydroxyanthranilic acid, kynurenic acid and kynurenine have been found in the human urines. It seems, therefore, that the conversion of tryptophan in man follows the same pathway as was found for the rat (Heidelberger *et al.* 1949). An appearance of tryptophan in the urines was not unexpected, but there were several other tryptophan metabolites which could not be definitely identified. It was only possible to compare them with published paper-chromatographic data recently reported by Dalgliesh *et al.* (1951) and there is not sufficient evidence for a definite identification.

Metabolites of quinolinic acid

Dosing with large amounts of quinolinic acid in normal rats resulted in an increased excretion of N^1-methylnicotinamide and of nicotinic acid. This is in keeping with the findings of Henderson (1949*a*, *b*) and would indicate that the rat can convert quinolinic acid into nicotinic acid. However, no such effect was observed in deficient rats, but the declining growth of the rats was reversed and they increased in weight by 17 g. within 13 days after a single dose of 100 mg. quinolinic acid. It is possible

that the conversion into nicotinic acid was of such low order that all the vitamin was retained by the deficient animal and none was available for excretion. We would agree with Krehl, Bonner & Yanofsky (1950) that the metabolism of quinolinic acid is of the order of a side reaction rather than forming a keystone in the nicotinic acid turnover.

SUMMARY

1. The excretion of metabolites by man and the rat after administration of nicotinic acid, nicotinamide and tryptophan has been studied by paper-chromatographic techniques. The procedure did not allow for the detection of N^1-methyl-2-pyridone-5-carbonamide.

2. After a dose of 100 mg. nicotinic acid to man, the main nicotinyl metabolites in the urine were, in decreasing order, nicotinuric acid, N^1-methylnicotinamide and nicotinamide. Nicotinic acid appeared in the urine only when flushing of the skin and other vasodilatory symptoms occurred. In the rat, nicotinic acid appeared consistently in the urines, but otherwise the pattern of excretion remained the same as in man.

3. The administration of 100 mg. nicotinamide to human subjects caused only an increased excretion of N^1-methylnicotinamide and of nicotinamide. Rat urine contained, in addition, an increased amount of nicotinic acid. Nicotinuric acid was not excreted by either of the species.

4. After ingestion of 3 g. L-tryptophan, human urines showed an increase in the excretion of N^1-methylnicotinamide, while rat urines had in addition an increased output of nicotinic acid. In human urines, a number of tryptophan metabolites, namely kynurenic acid, 3-hydroxyanthranilic acid, kynurenine and tryptophan, were identified.

5. Administration of 100 mg. quinolinic acid to normal rats resulted in an increased excretion of N^1-methylnicotinamide and nicotinic acid, while rats deficient in nicotinic acid showed no such rise.

6. The differences in the excretion patterns between nicotinic acid-deficient and normal rats after dosing with the various substances have been discussed.

7. In urines from undosed human subjects, microbiological techniques instead of the chemical procedure had to be used to detect on chromatograms the tertiary nicotinyl compounds because of the small amounts of nicotinyl derivatives present. The urines contained a small amount of nicotinamide and of N^1-methylnicotinamide. Urines from undosed rats, both deficient and normal, contained N^1-methylnicotinamide, nicotinamide and nicotinic acid.

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REFERENCES

Ackermann, D. (1912). *Z. Biol.* **59**, 17.
Berry, H. K., Sutton, H. E., Cain, L. & Berry, J. S. (1951). *Univ. Tex. Publ.* no. 5109, 22.
Carpenter, K. J. & Kodicek, E. (1950). *Biochem. J.* **46**, 421.
Clegg, K. M., Kodicek, E. & Mistry, S. P. (1952). *Biochem. J.* **50**, 326.
Dalgliesh, C. E., Knox, W. E. & Neuberger, A. (1951). *Nature, Lond.*, **168**, 20.
Ellinger, P. & Kader, M. M. A. (1949). *Biochem. J.* **44**, 77.
Harris, L. J. & Kodicek, E. (1950). *Brit. J. Nutr.* **4**, xiii.
Heidelberger, C., Abraham, E. P. & Lepkovsky, S. (1948). *J. biol. Chem.* **176**, 1461.
Heidelberger, C., Abraham, E. P. & Lepkovsky, S. (1949). *J. biol. Chem.* **179**, 151.
Henderson, L. M. (1949*a*). *J. biol. Chem.* **178**, 1005.
Henderson, L. M. (1949*b*). *J. biol. Chem.* **181**, 677.
Holman, W. I. M. & Lange, D. J. de (1949). *Nature, Lond.*, **164**, 844.
Holman, W. I. M. & Lange, D. J. de (1950*a*). *Nature, Lond.*, **165**, 604.
Holman, W. I. M. & Lange, D. J. de (1950*b*). *Nature, Lond.*, **166**, 468.
Huff, J. W. & Perlzweig, W. A. (1941). *J. biol. Chem.* **142**, 401.
Huff, J. W. & Perlzweig, W. A. (1943). *Science*, **97**, 538.
Johnson, B. C., Hamilton, T. S. & Mitchell, H. H. (1945). *J. biol. Chem.* **159**, 231.
Johnson, B. C. & Lin, P. (1951). *Fed. Proc.* **10**, 203.
Knox, W. E. & Grossman, W. I. (1946). *J. biol. Chem.* **166**, 391.
Knox, W. E. & Grossman, W. I. (1947). *J. biol. Chem.* **168**, 363.
Kodicek, E. & Carpenter, K. J. (1950). *Blood*, **5**, 522.
Kodicek, E. & Reddi, K. K. (1951). *Nature, Lond.*, **168**, 475.
Komori, Y. & Sendju, Y. (1926). *J. Biochem., Tokyo*, **6**, 163.
König, W. (1904). *J. prakt. Chem.* **69**, 105.
Krehl, W. A., Bonner, D. & Yanofsky, C. (1950). *J. Nutr.* **41**, 159.
Leifer, E., Langham, W. H., Nye, J. F. & Mitchell, H. K. (1950). *J. biol. Chem.* **184**, 589.
Leifer, E., Lloyd, R. J., Hornness, D. S. & Corson, M. H. (1951). *J. biol. Chem.* **193**, 595.
Melnick, D., Robinson, W. D. & Field, H., jun. (1940). *J. biol. Chem.* **136**, 131, 145.
Najjar, V. A., White, V. & McNair Scott, D. B. (1944). *Johns Hopk. Hosp. Bull.* **74**, 378.
Perlzweig, W. A., Levy, E. D. & Sarett, H. P. (1940). *J. biol. Chem.* **136**, 729.
Perlzweig, W. A., Rosen, F., Levitas, N. & Robinson, J. (1947). *J. biol. Chem.* **167**, 511.

Perlzweig, W. A., Rosen, F. & Pearson, P. B. (1950). *J. Nutr.* 40, 453.
Sarett, H. P. (1950*a*). *J. biol. Chem.* 182, 671.
Sarett, H. P. (1950*b*). *J. biol. Chem.* 182, 691.
Sarett, H. P. & Goldsmith, G. A. (1947). *J. biol. Chem.* 167, 393.
Sarett, H. P. & Goldsmith, G. A. (1949). *J. biol. Chem.* 177, 461.
Sarett, H. P. & Goldsmith, G. A. (1950). *J. biol. Chem.* 182 679.
Sarett, H. P., Huff, J. W. & Perlzweig, W. A. (1942) *J. Nutr.* 23, 23.
Spector, H. (1948). *J. biol. Chem.* 173, 659.
Tabone, J., Robert, D., Thomassay, S. & Mamounas, N. (1950). *Bull. Soc. Chim. biol., Paris.* 32, 529.
Wang, Y. L. & Kodicek, E. (1943). *Biochem. J.* 37, 530.

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Hypercholesterolemia

Use of Niacin and Niacin Combinations in Therapy

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• Niacin or niacin combinations were administered in dosage of 1.0 to 6.0 gm. to 31 hypercholesterolemic patients for periods up to three years. Eighty per cent were able to continue medication for long periods without significant side effects. Jaundice, apparently due to nicotinic acid, occurred in one patient. Liver toxicity will probably be a hazard in the use of this therapy.

Significant and maintained serum cholesterol depression was achieved in 80 per cent of the patients who were able to take adequate dosage. Reduction in xanthomata was observed with cholesterol reduction. In some cases, when larger doses were not tolerated or were unsuccessful, combining 1.5 gm of niacin with small doses of estrogen or triparanol achieved the desired effect. Aluminum nicotinate had no important advantage over plain niacin.

NIACIN ADMINISTERED in daily dosage of 3 to 6 grams brings about a definite reduction in serum cholesterol in most subjects. The precise mechanism of this effect remains to be explained. Both increased and decreased hepatic synthesis have been reported, depending on the experimental animal used and the conditions of the study.[8,11,18,19] In man there does not appear to be any increase in bile acid or sterol excretion in the stool.[6] It has been suggested that in rats and rabbits nicotinic acid achieves its results only by inducing anorexia.[5] The clinical usefulness and potential toxicity of long-term treatment are still in doubt.

This is a report concerning 31 patients treated for periods up to three years with niacin, aluminum nicotinate,* or combinations of aluminum nicotinate and estrogen† or triparanol.‡

METHODS AND MATERIALS

Patients were all male Veterans Administration out-patients or private patients who had cholesterol levels before treatment greater than 270 mg. per 100 cc. of blood. The age range was from 6 to 62 years. Twenty-three had had myocardial infarction while the others had cholesterol deposits in the skin or tendons, or were known to have familial hypercholesterolemia.

In light of known vagaries in determination of serum lipids,[17] measurements were performed at least three times, each time in duplicate, over at least a two-month period to establish the level before treatment—the control level. Because of the great variability in lipid levels in the two months following myocardial infarction,[16] no control measurements were included for this period. Determinations of lipids were carried out again at 2 to 6 week intervals after the start of therapy.

The Kingsley technique[10] was used for total serum cholesterol measurement. At present we achieve a reproducibility of ± 3 mg. of 100 cc. with this method. A comparison of this method with the Abell method on 50 samples over a wide range indicated that the amount as determined by the Kingsley method averages 11 per cent higher. A modification of the Jencks and Durrum[9] technique was used for electrophoresis and staining.[16] Except for the two patients noted, diets were stable during the treatment period. Also, with one exception, weight did not vary more than 5 per cent during the study period.

RESULTS

A. Niacin alone

Nineteen patients were given plain niacin in 3 gm. to 6 gm. doses daily. Sixteen of them were able to continue the drug in adequate dosage with the following results:

1. *Lipid changes.* Thirteen subjects maintained reductions of serum cholesterol of 20 per cent or more below the control level, six having reductions greater than 30 per cent. It should be emphasized that these are persisting decrements and that the lowest single cholesterol level achieved during the therapy was often more than 50 per cent below the control. When niacin was temporarily discontinued in four patients there was a return to control levels in one month. Of the three unresponding patients, one had idiopathic hyperlipemia, one

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*Aluminum nicotinate supplied as Nicalex® by Walker Laboratories, Inc., Mt. Vernon, N. Y.

†Estrogen supplied as SC 9263 (which is 16-alpha-chloro-1,3,5-estratien-17-one-) by G. D. Searle Co., Chicago.

‡Triparanol supplied as MER/29® by Merrell Co., Cincinnati.

*Tables containing specific data may be obtained from the author.

familial hypercholesterolemia and the other had had an uncomplicated myocardial infarct.

Ten of the 13 patients who had favorable cholesterol effect also had changes to normal in their alpha:beta lipoprotein ratio, either by increased alpha, decreased beta, or both.

2. *Xanthomata.* Six patients had xanthoma tuberosum, tendinosum or xanthelasma at the start of therapy. In one, the xanthelasma completely disappeared and in two there was measurable reduction of the tendon deposits. One man had xanthomata removed before therapy was begun and at last report, after nearly two years, there had been no return.

3. *Angina, intermittent claudication and peripheral pulses.* There was no change in the single patient with absence of leg pulses even though cholesterol was maintained below 200 mg. per 100 cc. for two years. Although a decrease in angina was reported by a few patients, no convincing evidence of change was noted.

B. Aluminum nicotinate

Thirteen patients were given this medication. Three patients who could not tolerate niacin because of nausea and vomiting were also unable to tolerate aluminum nicotinate. Eight subjects were able to maintain therapy. Of these, four had maintained cholesterol depressions of greater than 20 per cent, along with favorable lipoprotein alteration. Three of the nonresponders were children of a hypercholesterolemic family who were unable to tolerate more than 1 gm. daily.

No effect on the peripheral pulses or exercise tolerance of one peripheral atherosclerotic patient was noted despite good cholesterol depression.

C. Aluminum nicotinate plus estrogen (designated SC 9263, which is 16-alpha-chloro-1,3,5,-estratrien-17-one-)

Two patients were started on this combination as their initial therapy; five were so treated when the full dose of niacin was not tolerated or when niacin alone either failed to reduce the cholesterol or to increase the alpha:beta lipoprotein ratio. Dosage of aluminum nicotinate was 1.5 gm. or 3 gm. daily, and of SC 9263 .5 mg. daily. Four patients had persisting cholesterol reductions of more than 20 per cent and 5 had lipoprotein shifts.

D. Niacin plus triparanol (MER/29®)

Two patients were given MER/29®, 250 mg. daily with niacin 1.5 gm. daily. This was done when an effective niacin dose could no longer be tolerated and after it was determined that MER/29 alone (250 mg. for two months) was without effect. In both cases, successful reduction in cholesterol occurred.

E. Side Effects

1. *Nausea and Vomiting.* Three patients were unable to take more than a few doses of niacin because of this symptom. Nor could they tolerate the medication when aluminum nicotinate was substituted for niacin. Doses of 500 mg. were tolerated but were ineffective. In two men nausea and vomiting developed later, in one after three weeks and in the other after 84 weeks of therapy. Again the aluminum salt was not better tolerated.

2. *Flushing.* Flushing of mild to severe intensity occurred in all patients during the first week. Thereafter, the flushing was mild and intermittent and in no case was it a cause for discontinuing treatment. Aluminum nicotinate administration produced only slightly less flush than niacin. Taking the medication without food resulted in severe flushing from one to three hours later. If the evening meal was small, patients were occasionally awakened at night with flushing.

3. *Epigastric burning* occurred in three patients, two of whom had a history of duodenal ulcer and one of whom was an alcoholic. Distress was not controllable with antacids and in one case was severe enough to lead to discontinuing medication.

4. *Jaundice.* In one of the early patients in the series jaundice developed at 70 weeks. This was believed to be owing to drug-induced intrahepatic cholestasis and was reported upon in detail elsewhere.[15] Because of this experience, SGO-transaminase and alkaline phosphatase were measured every three to four months in all patients. No abnormalities were noted. Bronsulfonphthalein determinations were not done, nor was liver biopsy carried out.

5. *Typical hives* developed in one patient after two doses.

With two exceptions, diets were stable during the treatment period. Most of the patients were on standard, American, high-fat diets, and the medication was as effective in these patients as it was in patients on restricted diet. One patient changed from restricted saturated fat to regular diet during treatment without negating the niacin effect. Another, however, had a sharp rise in cholesterol upon liberalization of diet, with a rapid gain of 18 pounds in body weight.

Aluminum nicotinate had the same cholesteropenic effect as equivalent doses of niacin. Patients intolerant to niacin because of nausea, vomiting or epigastric burning were also intolerant of the aluminum salt. There appeared to be slightly less flushing with aluminum nicotinate. Although a 1.5 gm. dose was tolerated when a 3 gm. dose was not, this smaller amount was ineffective except in one in-

stance. When 1.5 gm. of niacin was combined with either a small dose of estrogen or MER/29 (neither of which alone was effective) a lipolytic effect was achieved in five of six trials.

DISCUSSION

The decision as to the wisdom of using niacin therapy turns on the question of serious toxicity. Will important liver damage occur?

The case in which jaundice occurred in the present series, and the reports of other investigators regarding overt jaundice and abnormal liver function tests,[8,12,13] call for caution. While it is true that in each case the jaundice was reversible, and that in many cases enzymatic abnormalities of liver function appeared without histologic abnormality on liver biopsy, in at least one biopsy considerable parenchymal damage was seen.[4] We used only the alkaline phosphatase and SGO transaminase as screening procedures and detected no abnormalities in our other patients. These liver changes suggest, of course, that niacin is effective by virtue of some interference with liver synthesis of cholesterol. Such findings, plus the failure to observe reduced appetite or weight loss in patients, makes the Friedman suggestion[5] of anorexia as the mechanism of niacin-induced hypocholesterolemia, untenable for man.

Apparently clinically insignificant abnormalities in sugar tolerance and uric acid levels have been noted by other investigators.[3,7,13]

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REFERENCES

1. Altschul, R.: Niacin (nicotinic acid) and serum cholesterol, J.A.M.A., 166:822, Feb. 15, 1958.

2. Altschul, R., Hoffer, A., and Stephen, J. D.: Influence of nicotinic acid on serum cholesterol in man, Arch. Biochem., 54:558, 1955.

3. Berge, K. G., Achor, R. W. P., Christensen, N. A., Mason, H. L., and Barker, N. W.: Hypercholesterolemia and nicotinic acid, Am. J. Med., 31:24, July 1961.

4. Christensen, N. A., Achor, R. W. P., Berge, K. G., and Mason, H. L.: Nicotinic acid treatment of hypercholesterolemia, J.A.M.A., 177:546, Aug. 26, 1961.

5. Friedman, M., and Byers, S. O.: Evaluation of nicotinic acid as an hypocholesteremic and antiatherogenic substance, J. Clin. Invest., 38:1328, 1959.

6. Goldsmith, G. H., Hamilton, J. G., and Miller, O. N.: Investigation of mechanisms by which unsaturated fats, nicotinic acid and neomycin lower serum lipid concentrations. Excretion of sterols and bile acids, Trans. Assn. of Am. Physicians, 72:207, 1959.

7. Gurian, H., and Adlersberg, D.: The effect of large doses of nicotinic acid on circulating lipids and carbohydrate tolerance, Am. J. Med. Sci., 237:12, Jan. 1959.

8. Hardy, R. W. F., Gaylor, J. L., and Bauman, C. A.: Biosynthesis of sterols and fatty acids as affected by nicotinic acid and related compounds, J. of Nutrition, 71:159, 1960.

9. Jencks, W. P., and Durrum, E. L.: Paper electrophoresis as a quantitative method: The staining of serum lipoproteins, J. Clin. Invest., 34:1137, 1955.

10. Kingsley, G. R., and Schaffert, R. R.: Determination of free and total cholesterol by direct chloroform extraction, J. Biol. Chem., 180:315-328, Aug. 1949.

11. Merrill, J. M.: Effect of nicotinic acid on the incorporation of radiocarbon into cholesterol, Circulation Research, 6:482, 1958.

12. Pardue, W. O.: Severe liver dysfunction during nicotinic acid therapy, J.A.M.A., 175:137, 1961.

13. Parsons, W. B., Jr.: Treatment of hypercholesterolemia by nicotinic acid, Arch. Int. Med., 107:71, May 1961.

14. Parsons, W. B., Jr., and Flynn, J. H.: Alteration in serum cholesterol and lipoprotein cholesterol by nicotinic acid, Circulation, 28:765, Oct. 1958.

15. Rivin, A. U.: Jaundice occurring during nicotinic acid therapy for hypercholesteremia, J.A.M.A., 170:2088-2089, Aug. 22, 1959.

16. Rivin, A. U., and Wong, H.: Lipid measurements in coronary artery disease. Comparison with an age-matched normal control group, Am. J. of Cardiology, 5:731, 1960.

17. Rivin, A. U., Yoshino, J., Shickman, M., and Schjeide, O. A.: Serum cholesterol measurement: Hazards in clinical interpretation, J.A.M.A., 166:2108-2111, April 26, 1958.

18. Schade, H., and Saltman, P.: Influence of nicotinic acid on hepatic cholesterol synthesis in rabbits, Proc. Soc. Exper. Biol. and Med., 102:265, Nov. 1959.

19. Schon, H.: Effect of nicotinic acid on the cholesterol contents of rat livers, Nature, 182:531, 1958.

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Letters to the Editor

NICOTINIC ACID IN ANGINA PECTORIS

SIR,—In the last few years there has been a well-marked increase in cardiovascular disease among the age-groups usually affected—i.e., males of 45 and over. The probable reasons are many, among which late reactions of the last war, and the physical and emotional stresses of this war, rank as primary causes.

The relief of angina with nicotinic acid given by intravenous drip was described by Neuwahl (*Lancet*, 1942, ii, 419) but this is only possible in hospital. The following modification has given successful results in a series of 15 cases with one failure where there was a strongly positive Wassermann. Both private and hospital patients are included. Improvement was most rapid when the retinal arteries showed the least arterio-sclerotic changes.

Neuwahl pointed out that administration by mouth in whatever dosage seems to produce little or no effect, but as Moncrieff noted (*Ibid*, 1942, i, 633) the earliest symptoms may in some cases be controlled by oral medication, 50 mg. being taken twice a day immediately after a meal to reduce the liability to produce flushing. Thus a middle-aged man with persistent substernal discomfort, not necessarily associated with effort, may obtain immediate relief and the condition will not progress towards true angina.

Treatment in the earlier cases was started in July, 1943, and all have been moderately severe. Few reactions have been observed except blanching of the face and a temporary slowing of the pulse. Most patients have felt generally improved, but there is one very real danger, for if anginal attacks do occur they are likely to be severe, although the effect of nitroglycerin seems to be more rapid and prolonged after nicotinic acid treatment. The attack is usually precipitated as a result of over-confidence, when the patient in spite of warning persists in continued effort, as in one moderately severe case when after digging in heavy soil a farmer had a sharp attack.

Six daily doses of intravenous nicotinic acid amide are given in 2–5 ml. of sterile water, starting with one dose of 25 mg., the remaining five being 50 mg. each. These can be obtained in ampoules ready for use. For the next 2 weeks six doses are given on alternate days, and subsequently at gradually increasing intervals until a maintenance dose is reached at 4–8 week intervals, which is usually sufficient to keep the symptoms in check.

This treatment may be carried out in the consulting-room or at outpatients. The injections are administered slowly, using either the sitting or lying position, and the patient is kept quiet for a few minutes afterwards. No other medication of any sort has been given except that patients are advised to keep nitroglycerin at hand and are instructed to increase steady walking exercise up to a point where symptoms show signs of returning. This gives an indication of the rate of improvement.

Four cases of coronary thrombosis have also been treated but it is too early to assess results, although they appear encouraging. In this condition as well as in angina I am of the opinion that the body has lost its capacity to absorb the necessary quantity of vitamin taken by mouth. This is most marked in alcoholics and even moderate indulgence appears in some patients to have the same effect.

Worcester. H. C. ROOK.

Sarett-'42
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STUDIES IN NICOTINIC ACID METABOLISM

I. THE FATE OF NICOTINIC ACID IN MAN [1]

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A large number of publications have appeared within the last 3 years (reviewed by Lepkovsky, '40, and Morgan, '41) presenting quantitative data on the excretion of "nicotinic acid" in the urine of man and animals under a variety of conditions. Obviously, the figures and their interpretation depend almost entirely upon the specificity of the given methods and upon the relative yield of color reacting substances from techniques employed in the splitting or the transformation of the various nicotinic acid derivatives into nicotinic acid itself.

In considering the question of specificity, pyridine and its derivatives, including nicotine in the urine of smokers, demand attention. In the majority of reports in which the original König color reaction with CNBr and aniline was used, the relatively high daily outputs of 10 to 30 mg. of "nicotinic acid" in human urine could be traced to the presence of variable amounts of nicotine and of other pyridine derivatives in the urine.

[1] The data in this article are taken from a thesis to be presented by Herbert P. Sarett in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Arts and Sciences of Duke University.

A preliminary report was made by the authors before the meeting of the American Society of Biological Chemists at Chicago, April, 1941.

[2] Upjohn Fellow in Biochemistry.

Of the known nicotinic acid derivatives, only nicotinuric acid and trigonelline have been well established as constituents of human and dog urine (Ackermann, '12; Linneweh and Reinwein, '32 a and '32 b; Perlzweig, Levy and Sarett, '40; Melnick, Robinson and Field, '40). Euler and Schlenk ('39) and H. Kohn and P. Handler (personal communication) have found the concentration of coenzyme in urine to be below the sensitivities of their methods. Calculated from Kohn's data, not more than 4% of the acid hydrolyzable nicotinic acid derivatives could be in the form of coenzyme. Our own studies indicate that free nicotinic acid and nicotinamide could account for only 25 to 40% of the acid hydrolyzable nicotinic acid derivatives in normal urine, and even a smaller proportion after the administration of relatively large doses of nicotinic acid or amide (see below). The two derivatives which predominate in human and in dog urine, both normally and after the administration of either nicotinic acid or the amide, are nicotinuric acid and trigonelline. Trigonelline, which constitutes over 90% of the measurable nicotinic acid derivatives in normal urine (the remainder comprising the acid hydrolyzable fraction) also accounts for 60 to 95% of these derivatives after the administration of either nicotinic acid or the amide. Although the acid hydrolyzable nicotinic acid derivatives make up a small fraction of the total excretion in normal urine, over one-half of this fraction, as judged from the data in table 2, appeared to be in the form of nicotinuric acid. This is contrary to the statement of Melnick, Robinson and Field ('40) that no nicotinuric acid is found in normal human urine.

Recognizing these facts, all techniques and methods employed for the determination of nicotinic acid and its derivatives in urine must be so designed and the conditions so defined as to ensure the quantitative measurement of all of these nicotinic acid derivatives and not of any extraneous pyridine compounds. Since with these color reactions nicotinamide and nicotinuric acid yield variable intensities of the same color as obtained with nicotinic acid, they must first be completely

hydrolyzed to nicotinic acid by boiling with strong acid. Trigonelline can only be measured quantitatively after a strong alkali-urea hydrolysis following the acid hydrolysis.

Furthermore, since trigonelline is a normal constituent of a number of plant tissues and foods, notably coffee and the leguminous seeds (Maier-Bode and Altpeter, '34), the intake of these in the diet must either be excluded or controlled in metabolism experiments.

In the investigations reported in this and in the subsequent communication (Sarett, '42) we have been guided by the above considerations, while being fully aware of the fact that the measurement of the nicotinic acid derivatives mentioned above may not yet yield a complete picture of the fate of nicotinic acid in the human and animal organisms, as will be apparent from the presented data.

This communication deals with a study of the fate of nicotinic acid in normal man under controlled dietary conditions, before and after the administration of various nicotinic acid derivatives.

EXPERIMENTAL

The experiments reported here are divided into three parts. One series consists of the experiments performed on three normal individuals (the authors) who were maintained on a rigorously controlled diet consisting of trigonelline free foodstuffs. Levels of daily excretion of nicotinic acid and trigonelline on this diet and after oral doses of nicotinic acid derivatives were determined (table 1).

The second series of experiments was a set of analyses of the urines of thirty-three medical students, who were on various diets low in trigonelline, and of three fasting students (table 3).

The third series was a set of saturation tests with nicotinamide on six normal young adults (table 4).

All urines analyzed were 24-hour specimens which were collected under toluene and kept in the refrigerator. The acid hydrolyzable nicotinic acid fraction (NA) and trigonelline

were determined by the previously described method (Perlzweig, Levy and Sarett, '40). Since publication it has undergone the following minor modification and improvement:

After boiling a suitable urine sample [3] with 10 cc. of 7 *N* HCl and 0.25 cc. of concentrated HNO_3 over a microburner for 1 hour, there is very little charring and the pigments are largely decolorized. The nitric acid, however, produces a light yellow color in urine which is not removed by the subsequent procedures. This difficulty is overcome by extracting the acid digests, in 25 ml. glass stoppered graduated cylinders, with two or three 5 cc. portions of ether. The ether portions, containing most of the yellow pigments, are pipetted off; the ether remaining in solution in the digests is removed by immersing the cylinders into a beaker of warm (40-50°C.) water; after cooling, the solutions are adjusted to a convenient volume in the cylinders. This extraction with ether results in excellently low blank values in the final stage of the colorimetric determination. The ether extraction was shown not to cause any losses of nicotinic acid or of trigonelline. The rest of the analytical procedure as previously described remains unaltered.[4]

NA and trigonelline excretion after administration of nicotinic acid and derivatives

On a low trigonelline diet consisting of meats, white bread, rice, corn, milk, milk products and fruits, three subjects excreted 1.1 to 1.5 mg. of NA per day and 9 to 13 mg. of trigonelline per day (table 1).

[3] In the presence of relatively large amounts of nicotinuric acid, correspondingly smaller aliquots of urine were taken and the boiling continued for 90 minutes. If the nicotinuric acid is not completely hydrolyzed to nicotinic acid by the acid digestion, it will be split in the alkali urea hydrolysis of trigonelline, and will be erroneously measured as trigonelline.

[4] The most uniformly reproducible results in the final color reaction were obtained by using a 3% solution of crystalline CNBr (Eastman). This solution keeps well in dark amber glass in the refrigerator for at least 3 weeks and possibly longer.

TABLE 1

Excretion of NA and trigonelline by three subjects, on a "trigonelline free" diet, after ingested doses of nicotinic acid compounds.

	DAYS	SUBJECT H NON-SMOKER			SUBJECT S MODERATE SMOKER			SUBJECT P HEAVY SMOKER		
		NA [1]	Trig.	Total [2]	NA [1]	Trig.	Total [2]	NA [1]	Trig.	Total [2]
		mg.	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*
Control	1	1.4	12.2	12.4	1.1	13.0	12.8	1.4	12.0	12.2
	2	1.2	9.0	9.3	1.5	12.2	12.7	1.4	11.0	11.3
After 200 mg. dose of nicotinic acid	3	13.5	27.9	38.6	6.9	39.3	42.3	21.0	38.3	55.5
	4	1.0	19.1	18.2	1.2	18.2	17.6			
After 200 mg. dose of nicotinamide	9	1.3	51.0	47.3	1.6	68.0	62.6	2.0	45.0	42.5
	10	1.4	22.7	21.8	1.1	24.5	23.1	1.5	17.8	17.5
After 200 mg. dose of trigonelline	11	1.2	181.0		1.2	170.0		1.9	196.0	
	12	1.0	18.5		1.1	19.4		1.4	26.0	

[1] NA includes all nicotinic acid derivatives hydrolyzable by boiling with 7 N HCl.
[2] Total represents the total excretion of nicotinic acid and trigonelline, calculated in terms of nicotinic acid.

These data were substantiated by the values of 8 to 12.6 mg. of trigonelline excreted per day by three individuals after 3 days of starvation (table 3) and show that the dietary trigonelline was reduced to a minimum. The figures for NA given here and in the other tables represent HCl-HNO_3 acid hydrolyzable derivatives of nicotinic acid as described above, and include the nicotinic acid, nicotinamide, coenzyme and nicotinuric acid which may be present in the urine.

The daily dietary nicotinic acid intake of the three subjects was kept at a fairly constant level of about 30 to 40 mg.[5] Test doses of nicotinic acid derivatives were equally divided between breakfast and lunch and were taken orally at the end of these meals.

Two hundred milligram doses of nicotinic acid, taken on the third day (table 1) resulted in the added excretion of 35

[5] An average daily diet included 300 gm. of meats containing about 60 to 70 μg. NA per gram, and 2 kg. of cereals, breads and vegetables, which contained roughly about 8 to 10 μg. NA per gram.

to 44 mg. of total NA and trigonelline in the next 2 days.[6] The average for the days of the control period served as a base line for these calculations. This added excretion represented only 17 to 22% of the ingested dose. Of the total extra excretion 55 to 84% was in the form of trigonelline. The remaining 16 to 45% was entirely nicotinuric acid. This was demonstrated in the following manner.

Nicotinuric acid was completely hydrolyzed by the 7 *N* HCl–HNO_3 mixture which was used for nicotinic acid determinations. After treatment of nicotinuric acid in a water bath for 1 hour with 1 *N* HCl, the Bandier color reagents (Bandier and Hald, '39) gave only 35% of the color of the equivalent amount of nicotinic acid. Nicotinamide, on the other hand, was completely hydrolyzed by 1 *N* HCl or the 7 *N* HCl–HNO_3 treatment. Two equations have been set up:

$$\text{Nicotinuric acid} + \text{other nicotinic acid derivatives} = 7\ N\ \text{HCl value}$$

$$0.35(\text{nicotinuric acid}) + \text{other nicotinic acid derivatives} = 1\ N\ \text{HCl value}$$

Upon subtraction there was obtained the equation:

$$0.65\ (\text{nicotinuric acid}) = 7\ N\ \text{HCl value} - 1\ N\ \text{HCl value}$$

Typical figures for the partition of the NA fraction of normal urines and those obtained after doses of nicotinic acid are given in table 2.

TABLE 2

Partition of NA fraction in normal urines and after dose of nicotinic acid, by 1 N HCl and 7 N HCl hydrolyses. Explanation in text.

	NICOTINIC ACID			NICOTINURIC ACID
	After 1 *N* HCl	After 7 *N* HCl	As nicotinuric acid	
	µg./cc.	*µg./cc.*	*µg./cc.*	%
Normal urines	0.7	1.4	1.1	78
	0.9	1.5	0.9	60
	0.9	1.8	1.4	78
Urines after dose of nicotinic acid	13.0	41.0	43.0	105
	26.4	72.0	70.0	97
	7.2	19.2	18.4	96

[6] It is to be noted that while the NA fractions returned to a normal level on the second day after each dose of nicotinic acid or the amide, the trigonelline was more slowly excreted, maintaining a higher level in the urine for several days.

Since nicotinuric acid is the glycine conjugate of nicotinic acid, and since trigonelline is a methylated derivative of nicotinic acid, the effects of administrations of 2 gm. of glycine and of 400 mg. of choline in combination with 200 mg. nicotinic acid on the relative proportions of urinary trigonelline and nicotinuric acid were tried. No demonstrable effects of these additions were observed in the partition of the nicotinuric acid and trigonelline fractions in the urine in all three subjects. Likewise upon repeating these experiments in dogs (Sarett, '42) but using much larger amounts of glycine and choline no effect was observed.

Of the 200 mg. of nicotinamide taken on the ninth day, 18 to 30% could be accounted for by the added trigonelline excretion of the following 2 days. Distinctly different from the excretion after a dose of nicotinic acid was the lack of any increase in the NA fraction. To show that the question of absorption of nicotinic acid or nicotinamide from the gastrointestinal tract did not control these results, nicotinamide was given intravenously, with the same resultant excretion as that obtained after the oral dose.

Trigonelline ingested in 200 mg. doses was almost completely excreted (80–90%) in the following 2 days. Nicotinuric acid taken orally in 100 mg. doses by the three subjects was excreted, in unchanged form, to the extent of 56, 60 and 65%, with no concomitant increase in the trigonelline fraction. The utilization of nicotinuric acid by man thus appears to be doubtful, but because of its relative insolubility the complete absorption from the gastrointestinal tract is questionable. A more definite solution is being sought by means of parenteral administration of nicotinuric acid.[7]

Levels of nicotinic acid and trigonelline excretion of thirty-three medical students

In the course of their metabolic experiments on the effects of various dietary regimes upon the composition of the urine,

[7] Since this paper has gone to press it has been determined that nicotinuric acid given intravenously in 100 mg. doses to three subjects was excreted to the extent of 96, 94 and 97%.

thirty-three medical students who did not drink coffee were asked to abstain from leguminous foods. These regimes included normal, high protein, high carbohydrate-low protein diets, high water intake and starvation. The range and averages of NA and trigonelline excretions are shown in table 3.

TABLE 3

Daily excretion of NA and trigonelline by young normal adults on low trigonelline diet and in starvation.

	NA		TRIG.	
	Range	Average	Range	Average
	mg.	*mg.*	*mg.*	*mg.*
Various diets				
33 subjects (see text)	0.7–2.2	1.2	5–25.4	15.1
Starvation—Subject 1		1.1		9.3
Subject 2		2.0		12.6
Subject 3		1.4		8.2

The diets of these students could not be as rigorously controlled as were the diets of the first three subjects, and this resulted in several (seven) cases of high levels of trigonelline excretion. The average trigonelline excretion, omitting these questionable values was 15.1 mg. per day. The average for the more rigorously controlled diet (table 1) was 11 mg. trigonelline per day. The difference was due to the diet. The 8 to 12.6 mg. of trigonelline (average, 10 mg.) excreted by three individuals on the third day of fasting was an excellent check of the validity of the above values.

In this group of thirty-three students the NA excretion ranged from 0.7 to 2.2 mg. per day with an average daily excretion of 1.2 mg. Normal urines analyzed by our method have always given values in this range, in smokers as well as non-smokers. In the six habitual smokers in this group the NA values ranged from 1.0–2.2 mg., average 1.2; the trigonelline values ranged from 10.4 to 15.5, average 12.8 mg. These values do not differ in any significant manner from those obtained on the group as a whole.

The 24-hour urine of a 7-week-old premature baby weighing 3.1 kg., who was on a trigonelline free diet of milk and lactose, contained 0.14 mg. NA and 2.5 mg. of trigonelline.

On the basis of body weight the levels of NA and trigonelline excretion were much higher than those in the adult.

Saturation tests with nicotinamide

In all of the above experiments test doses of nicotinic acid and nicotinamide had been administered to normal individuals in a good nutritional state. Of the 200 mg. of nicotinic acid or amide ingested only 12 to 45% (average 22%) was accounted for by the added urinary NA and trigonelline. There were wide individual variations.

The ingested nicotinic acid which could not be recovered in the urine either went through another metabolic pathway or was taken up by the tissues which were not fully saturated. In dogs, which had been saturated with nicotinic acid, all of the extra administered nicotinic acid could be recovered in the urinary NA and trigonelline (Sarett, '42). In man this has not been possible to achieve thus far, as shown in the following experiment.

Six medical students were given 500 mg. of nicotinamide orally for 6 successive days. They abstained from trigonelline containing foods during this time. The urines of the first and sixth days were collected and analyzed. The results are summarized in table 4. The control urines were the normal urines collected in the preceding part of the experiment.

TABLE 4

Saturation tests on six individuals receiving 500 mg. nicotinamide per day for 6 days on low trigonelline diet.

SUBJECT NUMBER	CONTROL URINE			URINE OF FIRST DAY AFTER 500 MG. NICOTINAMIDE				URINE ON SIXTH DAY			
	NA [1]	Trig.	Total [1]	NA [1]	Trig.	Total [1]	Per cent recovery [2]	NA [1]	Trig.	Total [1]	Per cent recovery [2]
	mg.	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*	%	*mg.*	*mg.*	*mg.*	%
32 B	0.8	12.8	12.3	5.4	105	100	18	7.3	182	171	32
32 C	0.9	8.5	8.5	10.0	104	104	19	8.0	233	218	42
14	1.2	16.4	15.9	4.9	103	98	17	4.6	163	151	28
40	2.2	12.5	13.4	4.2	110	103	18	7.6	164	155	28
48	1.1	39.4	36.5	10.3	142	138	21	11.8	240	228	40
50	1.6	20.7	20.2	1.0	50	46	5	6.4	169	158	27

[1] See table 1.

[2] Per cent recovery refers to the portion of the 500 mg. dose of nicotinamide accounted for by the extra total excretion of NA and trigonelline.

In all cases, both on the first and sixth days, trigonelline comprised over 90% of the added total excretion. Of the remaining NA fraction only 65 to 80% was nicotinuric acid. This differs from the results obtained after the administration of nicotinic acid, in which the NA fraction was proportionately larger and was composed entirely of nicotinuric acid.

On the first day 17 to 21% of the ingested dose could be accounted for in the urines of five of the subjects, but only 5% in the urine of subject no. 50. On the sixth day, it was possible to account for 27 to 42% of the dose in this way.[8] Although this showed an increase in nicotinic acid saturation of the individuals, it also indicated that another pathway for nicotinic acid metabolism may exist in man.

The small output of NA and trigonelline by subject 50 after the first dose of 500 mg. of nicotinamide indicated the possibility of a deficiency in nicotinic acid. This was tested by giving 500 mg. of nicotinamide to ten more normal people all of whom responded with an excretion of NA and trigonelline of at least 17 to 20% of the test dose. In nutritionally deficient hospital patients, however, only a small portion (0 to 5%) of the nicotinamide could thus be accounted for, and in some of these patients several large doses of nicotinamide were necessary before any increase in NA and trigonelline could be detected.

Further results obtained on thirty unselected patients upon admission to the hospital indicate that it is possible to establish a test on this basis as a means for detection of nicotinic acid deficiency in man. This work is now in progress.

SUMMARY

Trigonelline and nicotinuric acid are the two known end products of nicotinic acid metabolism found in human urine.

For a study of normal trigonelline excretion in man, a diet free of coffee, peas, beans and other legumes is necessary. On

[8] After the daily intake of 500 mg. nicotinamide for 30 days, three normal subjects excreted no more than 40% of the ingested dose.

such a diet, rigorously controlled, three individuals excreted 9 to 13 mg. of trigonelline per day. On less rigorously controlled diets, twenty-six students excreted an average of 15 mg. of trigonelline per day. Three individuals, after 3 days of fasting, excreted 8 to 12.6 mg. trigonelline per day.

The normal daily excretion of acid hydrolyzable nicotinic acid derivatives (NA) by thirty-six subjects on different diets and under fasting conditions was 0.7 to 2.2 mg. This level was not affected by smoking.

There is a constant loss of at least 10 mg. of known nicotinic acid derivatives in the urine daily, regardless of diet.

Of 200 mg. oral doses of nicotinic acid, 25 to 90 mg. could be accounted for by the increase in urinary trigonelline and nicotinuric acid. Trigonelline accounted for 55 to 84% of this increase. The remainder was nicotinuric acid. The feeding of glycine and choline with 200 mg. doses of nicotinic acid did not change the proportions of trigonelline and nicotinuric acid excreted.

Of 200 mg. doses of nicotinamide, 36 to 60 mg. could be accounted for by the increase in urinary trigonelline. There was no increased excretion in the acid hydrolyzable nicotinic acid fractions.

Trigonelline is not utilized by man when taken orally, and is excreted almost completely as such. Nicotinuric acid when ingested is excreted to the extent of about 60%, unchanged, and without an accompanying increase in trigonelline.[9]

After six daily doses of 500 mg. of nicotinamide the urinary excretion of NA and trigonelline in six subjects accounted for 27 to 42% of the ingested dose, compared to 5 to 21% which could be accounted for after the first day. Over 90% of this added excretion was in the form of trigonelline. Of the remaining NA fraction, 65 to 80% was nicotinuric acid.

The extra excretion of NA and trigonelline after a test dose of nicotinamide may serve as an indication of the nutritional status of an individual with respect to nicotinic acid.

[9] See footnote 7, page 29.

LITERATURE CITED

ACKERMANN, D. 1912 Über das Vorkommen von Trigonellin und Nikotinursäure im Harn nach Verfütterung von Nikotinsäure. Z. f. Biol., vol. 59, p. 17.

BANDIER, E., AND J. HALD 1939 A colorimetric reaction for the quantitative estimation of nicotinic acid. Biochem. J., vol. 33, p. 264.

VON EULER, H., AND F. SCHLENK 1939 Nicotinsäureamid und Co-zymase im Blut. Klin. Woch., vol. 18, p. 1109.

LEPKOVSKY, S. 1940 The Water Soluble Vitamins. Ann. Rev. Biochem., vol. IX, p. 394, Stanford Univ. Press.

LINNEWEH, W., AND H. REINWEIN 1932 a Über das Vorkommen von Pyridinderivaten in normalen Harn. Z. physiol. Chem., vol. 207, p. 48.

——— 1932 b Über das regelmässige Vorkommen von Pyridinderivaten in normalen Harn. II. Z. physiol. Chem., vol. 209, p. 110.

MAIER-BODE, H., AND J. ALTPETER 1934 Das Pyridin und seine Derivate. See p. 223. Wilhelm Knapp, Halle.

MELNICK, D., W. D. ROBINSON AND H. FIELD, JR. 1940 Urinary excretion of nicotinic acid and its derivatives by normal individuals. J. Biol. Chem., vol. 136, p. 145.

MORGAN, A. F. 1941 The Water Soluble Vitamins. Ann. Rev. Biochem., vol. X, p. 352, Stanford Univ. Press.

PERLZWEIG, W. A., E. D. LEVY AND H. P. SARETT 1940 Nicotinic acid derivatives in human urine and their determination. J. Biol. Chem., vol. 136, p. 729.

SARETT, H. P. 1942 Studies in nicotinic acid metabolism. II. The fate of nicotinic acid in normal and black tongue dogs. J. Nutrition, vol. 23, p. 35.

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Partial Regression of a "Solid" Tumor with Multi-Compound Chemotherapy*

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Cancer chemotherapy studies in this laboratory have been directed toward exploiting the quantitative biochemical differences existing between normal and tumor tissues by the administration of combinations of selected antimetabolites (5–11). It has been postulated in these reports that compounds which, by themselves, are capable of inducing only carcinostasis will, when properly combined, summate in tumor regression with minimal toxicity to the host.

In conjunction with studies of an antimetabolite (9), the effects of the metabolite, itself, on tumor growth have been investigated. Nicotinamide, in high dosage, has been found to be carcinostatic. Further, this report documenting the results of combining these high doses of nicotinamide with three other chemical compounds, all of which, alone, are merely carcinostatic, shows that proper combination of these drugs can produce partial regression of a mouse breast carcinoma.

MATERIALS AND METHODS

The 755 mammary adenocarcinoma was implanted, by the usual trocar technic, into the axillary region of C57BL mice, 2-4 months old and weighing 18–22 gm. The mice were housed in plastic cages in an air-conditioned, constant-temperature room (74° F.) and had constant access to Rockland pellets and water.

Nicotinamide and deoxypyridoxine, dissolved in saline, were administered intraperitoneally twice a day at a 4-hour interval; 8-azaguanine, in weakly alkaline solution, was administered intraperitoneally once a day at the time of the second injections of nicotinamide and deoxypyridoxine; testosterone, in oil, was injected intramuscularly once a day at the time of the first injections of these two compounds. Injections were begun 14 days after tumor transplantation in all experiments employing combinations of compounds and 4–10 days following tumor transplantation in experiments with nicotinamide alone. See tables for dosages.

The tumors were removed the day following the termination of therapy, and wet weights were determined to the nearest milligram. To evaluate the presence or absence of an antitumor effect, the data were analyzed statistically, and the results were considered to have a probability of chance variation of 1 per cent or less when:

$$\frac{m_1 - m_2}{\sqrt{(\sigma m_1)^2 + (\sigma m_2)^2}} = 2.5 \text{ or greater},$$

where m_1 and m_2 are the average tumor weights of the two groups being compared. In all experiments with combinations of compounds, a group of the animals was sacrificed on the day treatment was begun. This group is labeled "sacrificed controls," and its mean tumor weight constitutes a reference point for evaluating tumor inhibition or regression induced by the chemotherapy.

Oxidized pyridine nucleotide determinations. The animals were killed by decapitation, the tumors immediately removed, weighed, prepared for analysis according to the procedure of Jederkin and Weinhouse (2), and assayed for oxidized diphosphopyridine nucleotide (DPN^+) according to the alcohol dehydrogenase method of Racker (4). Total oxidized pyridinium ion (PN^+) was assayed by the cyanide method of Colowick *et al.* (1).

RESULTS

Effect of nicotinamide.—In large doses (600 mg/kg or more twice daily) this vitamin was found to inhibit tumor growth (Table 1). Lower doses were ineffective despite a more prolonged period of treatment. At the highest dose of the drug alone (1250 mg/kg twice daily, Exp. 1), a marked degree of tumor inhibition occurred, but drug administration had to be discontinued after only 6 days of injections because of host toxicity. It is to be noted that even this toxic dose was incapable of producing tumor regression, as can be ascertained by comparing the average tumor weight of the treated group with that of the sacrificed control group (Table 1, Exp. 1).

Nicotinamide in combination tests. Nicotinamide, at a level of 600 mg/kg twice daily, was tested for its effectiveness in combination with 8-azaguanine, deoxypyridoxine, and testosterone

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(Table 2). The consistent 755 mammary tumor-inhibitory effect of 8-azaguanine (6), the lack of augmentation of this effect by the addition of testosterone (6, 10), the synergistic action of deoxypyridoxine and testosterone, and the additive effect of the latter two compounds to the carcinostatic activity of 8-azaguanine have been reported previously (10).

The triple combination of 8-azaguanine, testosterone, and nicotinamide resulted in cessation of tumor growth, as can be ascertained by comparison with the sacrificed control group (Table 2). However, the four-compound combination of 8-azaguanine, deoxypyridoxine, testosterone, and nicotinamide consistently resulted in statistically significant tumor regression as compared with the sacrificed control group. The above data have been graphically summarized in Chart 1.

In general, administration of the four compounds for from 6 to 8 days of treatment produced occasional deaths and a host weight loss of from 6 to 9 per cent. In four groups of twenty animals each observed for 1 week or longer after cessation of therapy, the mortality ranged from two out of twenty to seven out of twenty, with complete recovery of the remaining animals. Continuation of

TABLE 1

EFFECT OF LARGE DOSES OF NICOTINAMIDE ON 755 TUMOR IN MICE*

Exp. no.	Sex	Group†	Dose (mg/kg)	Days of inj.	Mean tumor wt. ±S.E. (mg.)	No. animals dead/total	Per cent change in body weight
1	♂	Sac. control			24 ± 3	0/19	
		Saline		6	831 ± 87	0/20	+ 7
		Nic.	1250	6	105 ± 16	4/20	− 6
		Nic.	1000	6	207 ± 28	0/19	− 5
2	♂	Saline		11	1003 ± 90	0/19	+ 6
		Nic.	600	11	506 ± 81	0/19	− 3
3	♀	Saline		14	1310 ± 186	0/20	+ 6
		Nic.	600	14	508 ± 82	0/20	− 2
4	♂	Saline		16	1960 ± 318	1/18	+15
		Nic.	600	16	1143 ± 115	0/21	+12

* Therapy was begun on 4–10-day-old 755 mammary adenocarcinomas grown in C57BL mice. Treated animals were sacrificed on the day following the last injection.

† Sac. control = animals sacrificed when injections of other groups begun; Nic. = nicotinamide administered intraperitoneally (I.P.) twice daily; saline at 0.85 per cent administered I.P. daily.

TABLE 2

SOLID TUMOR* REGRESSION WITH A FOUR-COMPOUND COMBINATION

Exp. no.	Sex	Group†	Mean tumor wt. ±S.E. (mg.)	No. animals dead/total	Per cent change in body weight
1	♂	Sac. control	198 ± 29	0/17	+ 5
		A+T	341 ± 44	0/18	+ 2
		A+T+D	352 ± 56	1/17	+ 1
		A+T+N	243 ± 44	4/19	− 5
		A+T+D+N	118 ± 14	4/19	− 9
2	♂	Sac. control	412 ± 52	0/18	+ 2
		A+T	541 ± 44	0/19	+ 6
		A+T+D	448 ± 48	0/19	+ 1
		A+T+D+N	212 ± 25	0/19	− 7
3	♀	Sac. control	461 ± 44	0/20	+ 5
		A+T	935 ± 87	0/19	+13
		A+T+D	748 ± 76	0/20	+ 6
		A+T+N	489 ± 44	1/19	− 2
		A+T+D+N	196 ± 30	1/21	− 8
4	♀	Sac. control	379 ± 46	0/20	+ 4
		A+T	555 ± 57	0/20	+ 7
		A+T+D	490 ± 58	0/20	+ 5
		A+T+N	334 ± 32	0/20	− 2
		A+T+D+N	193 ± 18	2/21	− 6

* Therapy was begun 14 days after transplantation of 755 mammary adenocarcinoma in C57BL mice. Treated animals were sacrificed on the day following the last injection.

† Sac. control = animals sacrificed when injections of other compounds begun; D = deoxypyridoxine at 80 mg/kg and N = nicotinamide at 600 mg/kg, both administered I.P. twice daily at a 4-hour interval; A = 8-azaguanine at 50 mg/kg administered I.P. daily; T = testosterone at 25 mg/kg administered intramuscularly (I.M.) daily. All groups received injections for 6–8 days.

treatment in the attempt to produce complete tumor regression resulted in serious host toxicity before the goal of "cure" could be reached.

Effect of nicotinamide on DPN+ synthesis.—The total cellular DPN+ content of mammary tumors 755 obtained from animals 4 hours after being injected with a high dose of nicotinamide was measured. The results as documented in Table 3 reveal no apparent effect on DPN+ level under these conditions.

DISCUSSION

The data clearly demonstrate the fact that selectively increasing the number of agents simultaneously administered can progressively augment the antitumor effect from inhibition of tumor growth, to arrest of tumor growth, to actual regression of a "solid" tumor. None of these compounds administered alone or even in triple combination, regardless of the dosage employed, was capable of producing more than inhibition or cessation of tumor growth. It required all four of these compounds to effect regression. This antineoplastic progression is graphically demonstrated in Chart 1. On the basis of these data, the feasibility of complete tumor eradication by larger chemical combinations appears to gain added strength. The recorded mortality with this particular multi-compound combination is more than is desirable. Nevertheless, the survivors, which constitute by far the majority of the treated animals, furnish strong biologic data supporting the validity of the principle of employing agents to effect simultaneous injury to multiple metabolic

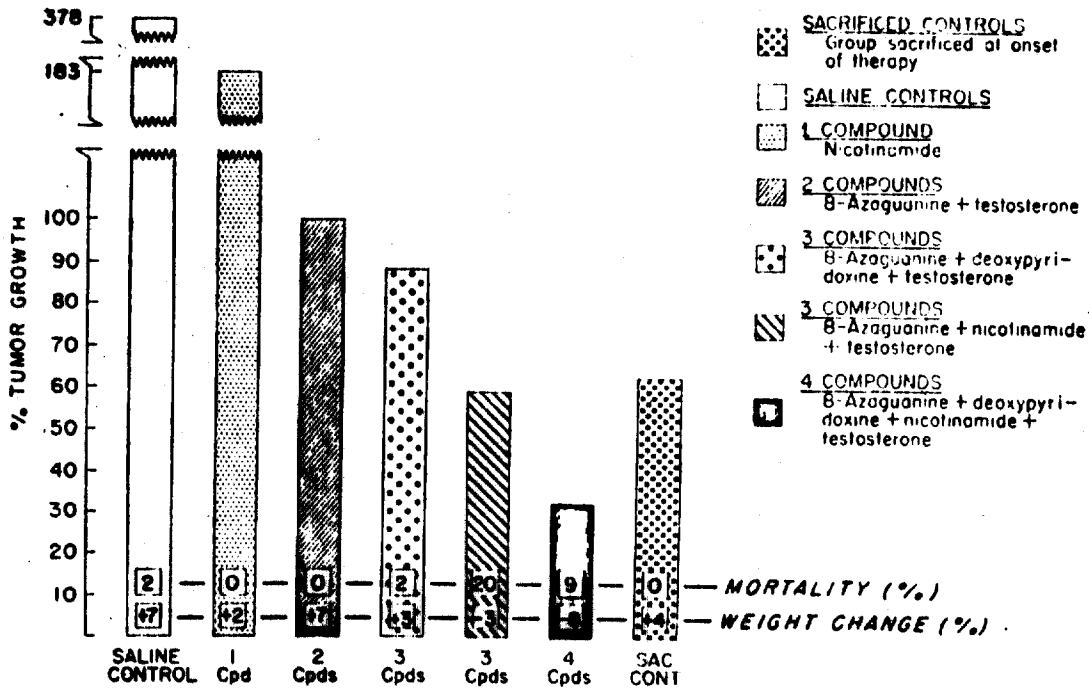

CHART 1.—Solid tumor regression with a four-compound combination

TABLE 3

EFFECT OF NICOTINAMIDE ADMINISTRATION ON DPN+ AND PN+ SYNTHESIS IN THE 755 TUMOR*

TREATMENT	DPN+	PN+
	μmoles/gm tissue wet wt	
None	0.22 (0.14–0.27)	0.38 (0.32–0.47)
Nicotinamide (1000 mg/kg)	0.30 (0.18–0.39)	0.49 (0.38–0.70)

* Grown in C57BL ♂ mice. Animals were sacrificed 4 hours after receiving nicotinamide injection. The range of values is in parentheses. Results are the average of three control animals and twelve treated animals. All determinations were run in duplicate. DPN+ and PN+ stand for oxidized diphosphopyridine nucleotide and oxidized pyridinium ion, respectively.

pathways so as to summate in tumor regression.

It has been previously demonstrated that increasing the number of agents in combination can result in increased antineoplastic effect within a shorter time period (8). Therefore, it seems reasonable to expect that further chemical augmentation of a partially regressing antitumor drug combination may result in complete eradication of the neoplasm within a time period too short to permit the appearance of serious cumulative toxicity on the host.

The tumor regression resulting from the administration of this drug combination is considered to be specific and not caused by the subsequent host weight loss of from 6 to 9 per cent. Although some 755 tumor *carcinostasis* will occur with a host mouse weight loss of 15 per cent or greater, unpublished studies in this laboratory have demonstrated that severe restriction of caloric intake (20–30 per cent host weight loss) will not produce regression of a well established 755 tumor.

The action of high doses of nicotinamide in the inhibition of tumor growth raises the interesting question as to the mechanism involved. One possibility is that the large amount of nicotinamide (which is methylated in the body and excreted as N^1-methylnicotinamide) imposes a severe drain on the pool of one-carbon compounds or their precursors. Another possibility is that nicotinamide stimulates excessive DPN^+ synthesis in the tumor cell, creating an intracellular imbalance leading to toxicity at the cancer cell level. Kaplan *et al.* (3) have reported increases in the concentration of DPN^+ in a number of experimental tumors following the administration of large amounts of nicotinamide. Our studies on the 755 tumor indicate that the administration of nicotinamide did not stimulate DPN^+ synthesis in this neoplasm. This, however, does not preclude the possibility that such changes do occur in the subcellular components, particularly in the mitochondria. Unpublished studies with a niacin antagonist (6-aminonicotinamide) show that, after chronic administration of this compound, there is no appreciable change in total cellular DPN^+ concentration but that a marked drop of DPN^+ concentration occurs in the mitochondria.[1] Therefore, it is conceivable that significant increases may occur in mitochondria after the administration of nicotinamide without causing obvious changes in over-all DPN^+ content.

SUMMARY

Nicotinamide administered in large doses (600 mg. or more/kg twice daily) inhibited the growth of the 755 mammary adenocarcinoma in C57BL mice.

The three-compound combination of 8-azaguanine, testosterone, and nicotinamide caused cessation of 755 tumor growth. The four compounds, 8-azaguanine, deoxypyridoxine, testosterone, and nicotinamide, concomitantly administered, produced significant tumor regression. It is emphasized that the presence of all four compounds was necessary to effect regression and that lesser combinations, in no matter what dosage, were incapable of other than arrest of tumor growth.

Large amounts of nicotinamide did not affect the total cellular concentration of DPN^+ in this tumor.

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REFERENCES

1. Colowick, S. P.; Kaplan, N. O.; and Ciotti, M. M. The Reaction of Pyridine Nucleotide with Cyanide and Its Analytical Use. J. Biol. Chem., **191**:447, 1951.
2. Jederkin, L. A., and Weinhouse, S. Metabolism of Neoplastic Tissue. VI. Assay of Oxidized and Reduced Diphosphopyridine Nucleotide in Normal and Neoplastic Tissue. J. Biol. Chem., **213**:271, 1955.
3. Kaplan, N. O.; Goldin, A.; Humphreys, S. R.; Ciotti, M. M.; and Stolzenbach, F. E. Pyridine Nucleotide Synthesis in the Mouse. J. Biol Chem., **219**:287–98, 1956.
4. Racker, E. Crystalline Alcohol Dehydrogenase from Baker's Yeast. J. Biol. Chem., **184**:313, 1950.
5. Shapiro, D. M. Combination Chemotherapy of Cancer Based upon Quantitative Biochemical Differences. Surgical Forum, **5**:646–50, 1954.
6. ———. Combination Chemotherapy with 8-Azaguanine and Sex Hormones on a Mouse Mammary Carcinoma. Cancer Research, **12**:713–15, 1952.
7. ———. Quantitative Biochemical Differences as a Basis for Multi-Combination Cancer Chemotherapy. Radiology (in press).
8. Shapiro, D. M.; Dietrich, L. S.; and Shils, M. E. Quantitative Biochemical Differences between Tumor and Host as a Basis for Cancer Chemotherapy. II. Riboflavin. Cancer Research, **16**:575–80, 1956.
9. ———. Quantitative Biochemical Differences between Tumor and Host as a Basis for Cancer Chemotherapy. V. Niacin and 6-Aminonicotinamide. *Ibid.*, **17**:600–604, 1957.
10. Shapiro, D. M.; Shils, M. E.; and Dietrich, L. S. Quantitative Biochemical Differences between Tumor and Host as a Basis for Cancer Chemotherapy. I. Vitamin B_6. Cancer Research, **13**:703–8, 1953.
11. Shapiro, D. M.; Shils, M. E.; Fugmann, R. A.; and Friedland, I. M. Quantitative Biochemical Differences between Tumor and Host as a Basis for Cancer Chemotherapy. IV. Niacin and 2-Ethylamino-1,3,4-thiadiazole. Cancer Research, **17**:29–33, 1957.

[1] L. S. Dietrich and D. M. Shapiro, unpublished studies.

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9783

Effect of Yeast and Nicotinic Acid on Porphyrinuria.*

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It has been shown by Beckh, Ellinger and Spies[1] that pellagrins have increased amounts of coproporphyrin I or III in their urine which disappear following the successful treatment of the pellagra by means of large amounts of yeast or liver extract. Since nicotinic acid had been shown to be effective in curing the mucous membrane lesions of pellagra,[2] it seemed desirable to determine whether or not it would decrease the porphyrinuria of pellagra and other diseases.

Specimens of urine were obtained from 4 groups of people (Table I). Group I included a patient with gonorrheal arthritis who had sulphanilamide treatment, a patient with diabetic coma, one with catarrhal jaundice, and one with alcoholic cirrhosis and ascites. Group II included 2 patients, one with barbital intoxication, and one with hypertensive heart disease, congestive heart failure, and an enlarged, tender liver. Group III included 2 cases of pellagra, one very severe, and the other mild. In Group IV were 6 normal persons who ate large quantities of a well-balanced diet.

The studies were conducted in such a manner that the source of the specimen of urine for analysis was unknown to the person examining it. Whenever positive tests were obtained, repeated observations were performed, usually by more than one examiner. After increased porphyrinuria had been demonstrated repeatedly, yeast or nicotinic acid was administered and the urine collected and examined as before. As indicated in the table, nicotinic acid, in doses of 500 mg., was administered to the persons in Group I and Group III, and yeast, in 50 gm. amounts, was given to the 2 patients in Group II. After the yeast or nicotinic acid had been given, and the test for porphyrinuria had become negative, the yeast or nicotinic acid was discontinued without any other changes. Subsequent urine

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[1] Beckh, Walter, Ellinger, Philipp, and Spies, Tom D., *Quar. J. Med.*, New Series, 1937, 6, 305.

[2] Spies, Tom D., Cooper, Clark, and Blankenhorn, M. A., *The Use of Nicotinic Acid in the Treatment of Human Pellagra*, read before the Central Society for Clinical Research in Chicago, Illinois, November 5, 1937.

TABLE I.
Summary of Data.

Case		Clinical Diagnosis	Days 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
											Group I																
1	C.M.	Gonococcal arthritis	+	+	+	+↑	—	—	—	—	+	+↑	—	—	—	—	+	+↑	—								
2	C.S.	Diabetic coma	+	+	+	+↑	—	—	—	+	+↑	—	—														
3	R.M.	Catarrhal jaundice	+↑	—	—	+	+↑	—	—	—																	
4	C.R.	Alcoholic cirrhosis with ascites	+		+	+	+		+	+		+	+	+	+	+	+	+↑	—	—	—	—	—	—	+↑	—	—
											Group II																
5	F.B.	Barbital intoxication	+↑	—	—								—	—	—												
6	M.B.	Hypertensive heart disease with congestive failure	+	↑	+	—	—↑	↑	—↑	—↑	—↑	—↑	—↑	—↑	—												
											Group III																
7	G.S.	Pellagra	+↑	+↑	↑	↑	+↑	↑	↑	↑	+↑	↑	—↑	—↑													
8	P.L.	Mild pellagra	+↑	—																							

+ = Positive test for porphyrinuria.
— = Negative test for porphyrinuria.
↑ = 500 mg. nicotinic acid in Groups I and III.
↑ = 50 gm. Brewers' Yeast (Harris) in Group II.

samples were examined. The method used for testing the urine was the same as that described by Beckh, Ellinger and Spies[1] for the estimation of ether-soluble porphyrin in small amounts in the urine.

As shown in the table, all persons with increased porphyrinuria gave a negative test for porphyrinuria following the administration of either nicotinic acid or yeast. The test for porphyrinuria became negative in 7 of the patients within 24 hours after the administration of either nicotinic acid or yeast. In the case of severe pellagra the porphyrinuria steadily decreased from the time the nicotinic acid was administered, but the test remained positive for several days. In the case of mild pellagra the test became negative over night following the administration of nicotinic acid. The urine specimens from the 6 persons who ate large amounts of a well-balanced diet always gave negative tests for porphyrinuria.

The present study confirms the observations of Beckh, Ellinger and Spies[1] that pellagrins have increased porphyrinuria. In addition these studies show that the administration of yeast was followed by the disappearance of porphyrin in the urine of a case of barbital intoxication and of another case with cardiac decompensation. Also, it has been shown in these studies that nicotinic acid likewise remits porphyrinuria in pellagra and in certain other diseases. Since there is a similarity between the clinical symptoms of pellagra and those of acute porphyrinuria, the presence of an excessive amount of porphyrin in the body of pellagrins might explain some of the clinical symptoms. If the increased porphyrin of the urine of pellagrins proves to be coproporphyrin I, we must consider the possibility of a complete new synthesis of porphyrin as suggested by Fischer and Duesberg.[3] If, on the other hand, it is coproporphyrin III, we may assume a connection with an abnormal hemoglobin metabolism. In the functionally impaired liver bilirubin eventually may be broken down into coproporphyrin III. It seems to the authors that the latter explanation is the most probable one, and it is consistent with the observation[1] that patients dying from pellagra frequently show anatomical changes in the liver. We must admit, however, that there are many discrepancies between anatomical and functional liver changes.

Summary and Conclusions. 1. These studies confirm the previous observations of Beckh, Ellinger and Spies[1] that porphyrinuria is a frequent finding in pellagra and disappears following the adminis-

[3] Fischer, H., and Duesberg, R., *Arch. f. exp. Path. u. Pharm.*, Berlin, 1932, **166**, 95.

tration of yeast. 2. The present study shows that nicotinic acid, a substance which has been shown to be curative for the mucous membrane lesions of pellagra, likewise produces a decrease of porphyrinuria in pellagrins. 3. In addition, the present study shows that the porphyrinuria associated with a number of diseases other than pellagra likewise is promptly decreased following the administration of either yeast or nicotinic acid.

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THE EFFECT OF NICOTINIC ACID IN STUPOR, LETHARGY AND VARIOUS OTHER PSYCHIATRIC DISORDERS[1]

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Psychosis has long been recognized as a frequent and prominent feature of pellagra(1, 2). In the recent literature attempts have been made to distinguish and classify various psychiatric pictures which develop in frank pellagra(3, 4). Prompt improvement in the psychosis of pellagra by treatment with nicotinic acid has been reported frequently(3, 5, 6). It has also been noted that other patients, lacking definite evidence of pellagra, but complaining of malaise, mild gastrointestinal disturbances and nervousness, often show rapid and impressive improvement or recovery when given nicotinic acid(3, 7). These cases, referred to by Spies and his coworkers(3) as "subclinical and mild pellagrins," are described as having had definite signs of pellagra in the past and as suffering from vague complaints strongly suggestive of neurasthenia or hypochondriasis. In this paper Spies and his associates do not refer to any subclinical cases (that is to say cases without physical signs of manifest pellagra) showing gross personality disturbances such as actual coma, delirium or frank psychosis; nor is there a reference to the neurotic complaints described having been treated in any patients without previous histories of pellagra.

Other observers(8) subsequently reported the prompt and complete relief of comatose and stuporous states in patients lacking signs regarded as necessary for the diagnosis of pellagra. Most of the cases in this series had no history of a previous illness that could be interpreted as pellagra. Most of them showed a mild glossitis consisting of dryness and abnormal redness but without papillary atrophy, a type of tongue generally considered as indicative of toxicity or dehydration rather than of pellagra. In some there was no glossitis and none showed dermatitis or diarrhea. They were without evidence of what could be classified by the ordinary criteria as even a mild pellagra. Their mental symptoms were profound, many having been entirely unconscious for days. These patients could not properly be referred to as subclinical cases for, in some instances, they appeared to be moribund. Weinberg(9) has recently reported the prompt recovery of a patient suffering from severe psychotic confusion after coramine was administered as a cardiac stimulant. The diagnosis of avitaminosis was made only in retrospect, no evidence of pellagra having been present. Jolliffe and his coworkers(10) have reported patients with marked clouding of consciousness, some of whom showed definite neurologic signs, who were greatly benefited or cured by the administration of nicotinic acid. Many of these patients also were free from the recognized signs and symptoms of pellagra.

Spies and his associates have reported(3) that nicotinic acid even in large doses and over long periods failed to bring about any improvement in a series of 26 cases of psychosis not associated with pellagra. Among the psychoses in this series delirium tremens is listed. Mainzer and Krause(11) on the other hand report the prompt and spectacular recovery of a patient with delirium tremens treated with a large dose (500 mg.) of nicotinic acid. This patient is reported to have had stomatitis, glossitis and diarrhea.

The present report is based on a series of 29 cases, all showing severe psychiatric symptoms (Table I). None of these patients had signs or symptoms that would have justified the diagnosis or even a serious suspicion of pellagra. Only one (No. 17) had a history of pellagra in the past, and in this case no signs of pellagra had been present for several years. In contrast to the

[1] Read at the ninety-sixth annual meeting of The American Psychiatric Association, Cincinnati, Ohio, May 20-24, 1940.

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TABLE I

Patient		Race Age Sex	Mental status	Duration of psychosis	Complications	Tongue	Other signs of avitaminosis	Additional	N.A. before result	Time before result	Result
1.	J.J.	W 78 M	Semistupor.	Several days.	Prostatic resection. Myocardial damage. Arteriosclerosis.	Coated.	None.	N.P.N. 32 mg.	700 mg. orally.	48 hours.	Clear. Rational.
2.	D.E.	W 26 F	Hysteria. Lethargy.	Several days.	None.	Normal.	None.	.....	200 mg. I.V.	24 hours.	Alert, still hysterical.
3.	S.H.	W 65 F	Semistupor. Disoriented.	Undetermined.	Arteriosclerosis. Hemiplegia.	Red, not slick.	None.	.....	600 mg. I.V.	48 hours.	Alert, but disoriented.
4.	M.H.	W 67 F	Semistupor.	Several days.	Diabetes mellitus. Fractured femur.	Red.	None.	.....	100 mg. I.V.	24 hours.	Clear. Rational.
5.	L.P.	W 57 F	Stupor.	1 day.	Arteriosclerosis. Myocardial degeneration. Conduction deafness.	Red, not slick.	Achlorhydia.	.....	300 mg. I.V.	24 hours.	Clear. Rational.
6.	S.M.	C 82 M	Comatose.	2 days.	Prostatic resection. Arteriosclerosis. Myocardial damage.	Red, coated, not slick.	None.	.....	200 mg. I.V.	10 hours.	Clear. Rational.
7.	J.C.	C 65 F	Semistupor. Confusion.	Several weeks.	Arteriosclerosis. Severe amblyopia.	Coated, slick at edges.	None.	.....	600 mg. I.V.	48 hours.	Clearer. Relevant.
8.	L.S.	W 68 M	Stupor.	5 days.	Prostatic resection. Arteriosclerosis. Myocardial damage.	Normal.	None.	N.P.N. 28 mg.	150 mg. orally. 300 I.V.	34 hours.	Clear. Rational.
9.	C.C.	W 34 M	Confusion. Disoriented.	3 days.	Peptic ulcer.	Coated.	None.	Had been on sippy diet 9 weeks.	3000 mg. orally. 900 I.V.	72 hours.	Clear. Insight poor.
10.	J.K.	C 49 M	Delirium. Semistupor.	3 days.	Arteriosclerosis. Arteriosclerotic heart disease.	Coated, red, not slick.	None.	.....	300 mg. I.V.	24 hours.	Clear. Rational.
11.	F.H.	W 60 M	Stupor. Delirium.	3 days.	Prostatic resection. Arteriosclerosis. Nephrolithiasis.	Coated.	None.	N.P.N. 28.5 mg.	150 mg. I.V.	8 hours.	Clear. Rational.
12.	R.S.	W 46 M	Lethargy.	Several weeks.	Headache. Dizziness.	Red, slick in middle.	None.	.....	900 mg. orally.	72 hours.	Clear. No complaints.
13.	B.D.	W 47 M	Typical delirium tremens.	6 hours.	Strangulated hemorrhoids.	Normal.	None.	C.S.F. pressure 100 mm. H_2O.	300 mg. I.V.	24 hours.	Clear. Good insight.
14.	L.D.	W 60 F	Stuporous. Incontinent.	2 days.	Arteriosclerosis. Nephritis.	Dry.	None.	.....	1200 mg. I.V.	96 hours.	Clearer.
15.	F.J.	W 12 M	Hebetude.	Several weeks.	Carcinoma of esophagus.	Coated, red, slick.	None.	Obvious malnutrition.	600 mg. I.V.	48 hours.	Clear. Rational.

TABLE I—CONTINUED

Patient		Race Age Sex	Mental status	Duration of psychosis	Complications	Tongue	Other signs of avitaminosis	Additional	N.A. before result	Time before result	Result
16.	M.B	W 34 F	Delusional. Confused.	7 days.	None.	Normal.	None.	Alcohol in the past.	900 mg. orally.	72 hours.	Clear. Rational.
[illegible]	W.H	W [illegible]	Irrational. Confused.	3 years.	None	Red, not slick.	None.	Alcoholism. Bromidism in past.	30 gm. orally.	6 weeks.	Clear. Rational.
18.	E.W.	W 44 M	Delirium tremens. Disturbed.	1 day	Drainage perirectal abscess.	Normal.	None.	.....	300 mg. I.V.	12 hours.	Clear. Good insight.
19.	J.K.	W [illegible] M	Hebetude Confusion.	1 week.	Hypertension. Arteriosclerosis.	Normal.	Alae Nasi Scaly.	Dysphagia on admission.	900 mg. I.V.	72 hours	Clear.
20.	M.J.	W 62 F	Stupor Delirium.	2 months.	Arteriosclerosis. Coronary disease.	Dry, red.	None.	.....	600 mg. I.V.	48 hours.	Clear Rational.
21	G.H	W [illegible] M	Semistupor Confusion	Several days	Prostatic resection Arteriosclerosis. Hypertension.	Coated.	None.	N.P.N. 75 mg.	300 mg I V	24 [illegible]	Clear Rational
22	[illegible]	W [illegible]	Lethargy Confusion	Several days	Prostatic hypertrophy. Arteriosclerosis.	Coated	None	N.P.N. 50 mg.	300 I V 750 mg orally	24 [illegible]	Clear Rational
23	[illegible]	W 66 M	Manic Confusion	4 hours	Sciatica	Coated, edges red	Sciatica	.....	100 mg I V (ap prox)	15 minutes	Clear Rational
24	B S	W 72 M	Semistupor	1 week	Fractured femur Arteriosclerosis	Red, not slick	None		225 mg orally	72 hours	Clearer
25	L.H.	W 40 M	Manic Confusion Disoriented	Several days	Compound fracture of femur Infection	Coated	None		500 mg orally	36 hours	Clear Rational
26	J J	W 73 M	Disoriented Confusion	4 days	Pneumonia Arteriosclerosis	Geographic	None	Geographic tongue cleared under treatment	800 mg I V	72 hours	Clear Rational
27	W C	W 73 M	Confusion Lethargy	4 days	Arteriosclerosis Pneumonia	Coated	None		800 I V 1800 mg orally	96 hours	Clear Rational
28	J A	W 77 M	Stupor	Undetermined	Arteriosclerosis	Dry, slick	None		4500 mg orally	72 hours	Clearer
29	J E	W 41 M	Delirium tremens	1 week	None	Normal	None		300 mg	12 hours	Clear Rational

patients cited in our previous report (8), all of whom showed stupor as the most prominent symptom, many of the cases now reported showed active psychotic reactions. Some (9, 13, 16, 17, 18, 23, 25, 26, 29) were not lethargic at all but were on the contrary, actively disturbed. Manic excitement, delusions, hallucinations and disorientation were prominent. Other cases (1, 5, 6, 8, 14, 15, 28) were typical of those described in our previous report. The three cases of delirium tremens in our series, unlike the case reported by Mainzer and Krause, showed no symptoms suggestive of pellagra.

Many of these patients were admitted to the hospital after coma or psychosis had developed. Others became psychotic or stuporous while in the hospital for surgical treatment. The duration of the psychosis prior to treatment varied from several years (No. 17) to a few hours (No. 23). Usually the response to nicotinic acid was prompt, often it was spectacular. In most instances hypertonic glucose and other treatment for dehydration and toxæmia had been administered before nicotinic acid was used. It might be argued that some of the patients, particularly the three cases of delirium tremens (Nos. 13, 18, 29) would have made a similarly prompt recovery without the treatment given. While this, of course, is possible, it scarcely seems likely, particularly in view of the fact that all three of the patients were growing rapidly worse at the time nicotinic acid was given. The recovery from psychosis was much more prompt and complete than any we have observed before in patients with delirium tremens treated according to the usual methods (12, 13, 14). Some of the patients had also been given thiamin chloride in large doses and without apparent effect on the psychosis or stupor. In our previous report we cited one such case who received thiamin chloride not only intramuscularly but also intrathecally without response.

In an effort to lessen subjectivity as well as to enhance concreteness in estimating degrees of improvement we have recently used forms which are checked daily by a member of the house staff (Table II). It is, of course, difficult to design a form of this sort sufficiently elastic to permit registration of all degrees and aspects of consciousness or alertness. Though this record represents only a tentative effort and is open to modification, it has been found helpful.

TABLE II

DAILY OBSERVATIONS OF NUTRITIONAL CASES SHOWING MENTAL SYMPTOMS

Excr.	Incont. always. Bow. Bl.	Incont. sometimes. Bow. Bl.	Uses bed pan but does not ask for it.	Asks for bed pan.
Food	Tube fed.	Hand fed.	Needs encouragement to eat.	Eats spontaneously.
Consc.	No response to stimuli. (Coma.)	Confused response to stimuli. (Stupor.)	Some relevance to stimuli or questions. Dull when alone. (Lethargy.)	Clear.
Verbal	None.	Irregular and irrelevant.	Regular response with some confusion.	Open and alert.
Eyes	Constantly closed. Not open to stimuli.	Open to stimuli. Not when addressed.	Opened when addressed (Staring.)	Open and alert.
Attention	Not obtained.	Obtained with difficulty.	Obtained easily but indifferent when alone.	Active interest in surroundings.
Conation	No response to requests.	Confused response to requests	Relevant response to requests.	Spontaneously talks and makes requests
Insight	No awareness that he is ill.	Vague awareness of confusion.	Fair idea of past. Confusion.	Accurate appreciation of past confusion.
Affect	None evident.	Inconsistent or minimal.	Dulled or disproportionate the appropriate.	Relevant and keen.
Face	Blank.	Dull.	Responsive.	Alert.
Delirium	Actively disturbed.	Delusional, restless, hallucinated.	Restless.	Quiet.
Orient.	Name.	Place.	Date.	
Memory	Knows what food was eaten at last meal. Gives name of examiner.			

Patient ..... Date .....

CASE 23.—J. R., a white man aged 66, was admitted to the University Hospital December 13, 1930, in a state of manic confusion which had developed suddenly several hours earlier. Eight months before admission he had begun to complain of abdominal distention, belching, malaise and pain in the right leg. He went to a physician who made the diagnoses of diabetes mellitus and sciatica. He was treated with insulin and dietary restriction and also given symptomatic medication for the sciatic pain. About a month before admission he came under the care of another physician who discontinued insulin and instituted vitamin therapy with nicotinic acid, 100 mg., thiamin chloride 10 mg. and riboflavin 2 mg. daily by mouth. The patient improved slightly and regained 5 pounds of 30 pounds he had lost, but continued to suffer with sciatic pain. He complained also of restlessness, malaise and constipation up to the onset of his psychosis.

On admission the patient was disoriented, agitated and entirely irrational. He was unable to interpret his surroundings, tried to leap out of bed, shouted in broken sentences, was constantly and purposelessly hyperactive. No definite or consistent delusional trend appeared. The patient's confusion was profound. Sodium nicotinate, 150 mg. in 300 c.c. of physiological saline, was given by venoclysis. About 15 minutes after the administration was begun and while the solution was still flowing into the vein the patient became quiet and cooperative. His confusion and agitation disappeared almost immediately. He spoke rationally and relevantly and showed no evidence of the psychosis which had been so prominent a few minutes earlier.

Temperature was 98.6, pulse 84, respiratory rate 20 and blood pressure 142 systolic, 102 diastolic. The tongue was coated and the edges were red but glossitis in the ordinary sense was not present. There was tenderness over the right sciatic nerve and some tenderness in the muscles of the right leg and thigh. Laboratory examinations showed the blood sugar 182 mg.; but no sugar was found in the urine. Sodium nicotinate, 300 mg. intravenously, was continued until December 19 when oral administration was substituted.

The patient remained free from any signs of psychosis or confusion. His sciatic pain persisted. On December 26 saline injected into the sacral canal gave the patient considerable relief. He was dismissed December 27. The failure of thiamin chloride therapy to relieve the sciatic pain in this case suggests that this symptom was probably not the expression of neuropathy due to avitaminosis (thiamin chloride).

CASE 6.—S. M., a colored man aged 82, was admitted to the University Hospital February 23, 1930, giving a history of urgency, frequency and difficulty in voiding for the past year. On admission the temperature was 98° F., pulse 60, respiratory rate 20, blood pressure 130 over 70. The prostate was moderately enlarged and there was urinary retention. Severe arteriosclerosis and arteriosclerotic heart disease were evident. Laboratory examination showed pus cells and *B. coli* in the urine. The non-protein nitrogen was 30 mg.; P.S.P. output was 35 per cent. The sensorium was clear and the patient was alert and rational. On March 4, under spinal anesthesia, a transurethral prostatic resection was performed. After the operation the temperature rose to 104.4° F. Under treatment for urinary infection and administration of hypertonic glucose solution intravenously symptoms were promptly controlled and the patient improved physically. After the operation a marked change in his mental status was immediately noted. Consciousness was seriously clouded and the patient was entirely irrational and disoriented.

Despite the rapid physical improvement the patient's stupor deepened. Usually he did not respond to moderate stimuli at all and strong stimuli elicited only vague, blundering, negativistic reactions such as twisting or pulling away. Sometimes the patient grunted or muttered inarticulate words or word fragments. On March 9, when seen by the psychiatric consultant, the patient was in a definite coma. He lay inert, with eyes closed or blankly staring, and did not respond to words or ordinary stimuli. Tube feeding had become necessary and the patient was incontinent. The tongue was coated, dry and more red along the edges than normally but no true glossitis as seen in pellagra was present.

Sodium nicotinate, 100 mg. intravenously, was administered on the morning of March 9, and repeated during the same afternoon. Within two or three hours after the first injection the coma seemed less deep. Ten hours after the first nicotinic acid the sensorium was entirely clear, the patient spoke rationally and was cooperative. The treatment was continued for seven days during which the patient was alert and rational at all times. Intravenous administration was discontinued on March 16, and 25 mg. of nicotinic acid three times daily by mouth was begun. On May 18, having recovered from his operation, in good physical condition and in a normal mental status, the patient was dismissed. No further disturbance of consciousness had been noted.

CASE 18.—E. W., a white man aged 44, was admitted to the University Hospital August 21, 1930, for surgical treatment of a perirectal abscess. There was an odor of alcohol about the patient and, though rational and cooperative, he showed moderate evidences of intoxication. Both the patient and his family stated that, except for moderate amounts of whiskey during the three days prior to admission, he had stopped drinking entirely for a period of six weeks. Before that time he had drunk to excess, consuming between a pint and a quart (approximately) daily. He had sold, however, but one drunk enough to be disabled and stated that he had not suffered from hallucinations or any noticeable amnesia. His wife confirmed his statement that he "very rarely became drunk." He worked regularly and was regarded by his employers as an able and valuable man despite his drinking. He had not missed more than a few days from work because of drink over a period of many years.

Operation for perirectal abscess was performed August 22. Condition after operation was excellent.

This patient remained rational and without any signs of a personality disorder until August 23, when, during the night, he began to see monkeys and little Negro boys dancing on the transom. At first he seemed to realize that these apparitions were imaginary, but soon becoming disturbed and uncooperative he began to believe they were real. Next day he insisted on leaving the hospital against medical advice and went home.

When seen at his home during the afternoon of August 23, he was in constant action. No sooner could he be induced to take to his bed than he would spring up frantically again and, seizing the broom or a fly swatter, belabor the bare walls with uncommon vigor and assiduity. "Those damn bugs, they're three feet long," he shouted repeatedly. He described great multicolored bugs, grotesquely formed, which he saw advancing along the wall in phalanxes, spitting at him and hissing as they came. It was in effort to repel these hallucinatory monsters that he strove. When his attention could be gained he was well oriented and not grossly irrational about general matters. Efforts at examination were, however, interrupted each moment by wild scrambling about the room in which the patient leaped over beds and chairs yelling curses at his imaginary attackers and offering vivid descriptions of what he saw. Although he seemed at times to be alarmed, he was not actually terrified but seemed rather to be enthralled with interest though determined to drive off the dragon like bugs, snakes, monkeys, spiders and other chimeras that threatened. There was no definite tremor.

He was returned to the hospital. In order to achieve sedation which was urgently needed, sodium amytal, gr. 7½, and sodium luminal, gr. 15, were given intravenously at 5.30 p. m. These drugs were administered slowly and it was not until he had received the full amount that he became calm enough to stay in bed. He was also given 50 cc. of 50 per cent glucose intravenously. Despite this extremely large amount of sedative drugs the patient became disturbed again at 9.30 p. m. Paraldehyde, 12 drams, was given by mouth during the night, the last dose being at 2.30 a. m. At 11.30 p. m. he had received nicotinic acid, 150 mg. intravenously.

When the patient woke up next morning the sensorium was entirely clear, he was rational and completely free from hallucinations. Nicotinic acid was continued, 300 mg. intravenously, daily until August 28, when the patient was dismissed without recurrence of any personality disorder.

Case 17. W. H., a white woman, aged 46 years, was seen in her home August 10, 1939. Four or five years previously this patient had frank pellagra with dermatitis, glossitis, gastrointestinal disturbances and psychosis. She was treated and recovered after a few weeks of illness. She had used alcohol to excess for many years. For two years preceding the present instance (August 10, 1939) marked personality disorders had been prominent. During this period the patient remained well oriented most of the time but was restless and complained of anxiety as well as of vague and varied somatic distresses. Frequently, however, she became definitely confused and disoriented, expressed fragmentary delusional ideas and was irrational in her behavior. She often spoke of people coming into her room at night to harm her and sometimes at night she sprang from the bed shouting that people or animals were after her. She took bromides and barbiturates as well as considerable amounts of alcohol over this period of two years and twice suffered a typical bromide intoxication psychosis. During these illnesses she was hospitalized and the blood bromide was found to be 500. She recovered from the bromide intoxications but her almost constant restlessness, her periods of acute confusion, delusions and hallucinations persisted. Sometimes these periods lasted only a few hours but at other times they continued for several days or a week. Even when she was prevented from taking alcohol, bromides or barbiturates, she still had these psychotic periods. When free from the drugs her sensorium was clear most of the time and her irrationality was less marked. Her judgment could not, however, be relied upon for, becoming confused, she would begin again and again to use drugs.

On August 10, 1939, she was well oriented and cooperative, but showed little insight into her condition. For weeks she had been confused during the day time and at night she disturbed the household by her turbulent and irrational behavior. Physical and neurologic examination showed nothing significant except a tongue redder than normal. No true glossitis, dermatitis or other sign of frank pellagra was present.

Nicotinic acid, 600 mg. daily by mouth, was begun. Within five days the appearance of the tongue had become normal. The patient's psychotic spells were less frequent and less severe but they still occurred. Even when not frankly psychotic she was moody, irritable and showed defective judgment and insight. Nicotinic acid in this amount was continued for 30 days with no additional improvement. The patient's mental status continued definitely better than before treatment had been started however.

On September 9, nicotinic acid was increased to 1500 mg. daily by mouth. After six days the patient became entirely clear. She no longer suffered from periods of confusion or delusional episodes. Her judgment and insight showed marked improvement. After two weeks the dose of nicotinic acid was reduced to 900 mg. by mouth daily. The patient is still taking 900 mg. daily. She has shown no evidence of psychosis during this time, a period of over nine months, and she has been able to avoid bromides, barbiturates and excessive drinking. She does her house work satisfactorily and is making a good adjustment.

Discussion

The changes noted in the mental status of these patients were no less impressive than those mentioned in our previous report(8) on a series of 19 cases all of whom showed

varying degrees of stupor. Fourteen cases (1, 2, 3, 4, 5, 6, 8, 12, 14, 15, 19, 24, 26, 27) in the present series showed a similar psychiatric picture in which clouding of consciousness was the sole feature. In five cases (7, 11, 20, 21, 22), however, misinterpretation of the surroundings, irrational excitement, purposeless behavior and fleeting delusions were prominent although consciousness was distinctly clouded. Six cases (9, 16, 17, 23, 25, 26) showed little or no hebetude but were actively psychotic. In all of these patients delusions, hyperactivity, disorientation and grossly irrational behavior constituted the psychosis. They were typical cases ordinarily diagnosed as toxic psychosis(15), exhaustion delirium(16), or perhaps, psychosis, type undetermined. Such patients are familiar to all physicians who have had experience in psychiatric hospitals and are not rare in the general hospital. Not infrequently one finds it difficult to determine what toxic agent or what stress is responsible for the psychosis. We have seen many such cases, diagnosed as *toxic psychosis* or exhaustion delirium in which no adequate cause could be named. We have also seen many similar cases classified as psychosis, type undetermined, and treated only by symptomatic measures. Among the six patients now under discussion peptic ulcer (9), fracture of the femur (25) and mild pneumonia (26) might be regarded as complications. The response to nicotinic acid would seem, however, to leave little doubt that the real cause of the psychosis was an avitaminosis, sufficiently severe to produce a psychosis but without other indication of its presence. Two other cases (16, 17) had no complications at the time, though both had used alcohol to excess in the past and one (17) had formerly suffered from pellagra. Case 23 had a mild sciatica which might be considered as indicating an avitaminosis (thiamin chloride). The sciatica did not, however, improve on treatment with the appropriate vitamin. Case 23 developed a psychosis while taking considerable amounts of nicotinic acid (600 mg. daily by mouth) yet made sudden and spectacular recovery when sodium nicotinate was administered intravenously. Case 17 remained psychotic despite the administration of 600 mg. of nicotinic acid daily but recovered when given 1500 mg. daily.

The prompt and striking recovery of three cases showing the typical psychosis of delirium tremens (13, 18, 29) would seem to leave little doubt that the psychosis in these instances was due primarily to avitaminosis. Whether or not more than one vitamin deficiency is responsible in such cases is another question.

Seven of the cases (2, 3, 7, 9, 14, 24, 28) listed showed improvement only. The nicotinic acid therapy did not furnish a complete and permanent solution for their psychiatric problem. One remained (2) psychoneurotic, others showed persistent intellectual and emotional impairment which apparently was related to cerebral arteriosclerosis, senility or other factors. Even in these patients, however, one can scarcely escape the conviction that a nicotinic acid deficiency was in part responsible for the psychiatric condition. In the other 22 cases the chief psychiatric problem was solved by the vitamin therapy.

Many of the patients in this series were taking diets which supplied nicotinic acid and other vitamins in amounts ample for the average person. It has already been mentioned that one (23) developed a psychosis while taking nicotinic acid in amounts larger than those usually necessary to cure active pellagra. One is therefore led to the conclusion that in the illness of patients here discussed factors other than dietary deficiency played important rôles. It is a matter of common knowledge(17) that failure to absorb vitamins from the gastrointestinal tract and failure to store and utilize vitamins, such as occurs in disorders of the liver may lead to avitaminosis even when large amounts of vitamins are ingested. The need for all vitamins which have to do with carbohydrate metabolism is naturally increased in febrile conditions, during periods of extraordinary exertion and under all circumstances which augment metabolic activity. Other factors yet undetermined and perhaps unsuspected may also influence the failure of the nuclei to receive and utilize an adequate supply of vitamin.

Summary and Conclusions

Thirty-eight patients in stuporous states or in active psychoses without evident cause

showed prompt and often very impressive improvement after treatment with nicotinic acid.

The usual criteria for the clinical diagnosis of pellagra or of other deficiency syndromes were absent.

This experience leads us to believe that many patients whose psychiatric status suggests the diagnosis of toxic psychosis or exhaustion delirium may be relieved of their symptoms by the administration of nicotinic acid. It is believed that in such cases and in cases who show unexplained clouding of consciousness a therapeutic trial of nicotinic acid is the only means available by which one can determine whether or not the psychosis is due to avitaminosis.

In some exceptional cases, even when clinical evidence of pellagra is absent, extremely large amounts of nicotinic acid are necessary to obtain satisfactory results.

BIBLIOGRAPHY

1. Noyes, A. P.: Modern clinical psychiatry. W. B. Saunders Co., 1939.

2. Strecker, E. A., and Ebaugh, F. G.: Clinical psychiatry. P. Blakiston's Son and Co., 1935.

3. Spies, T. D., Aring, C. D., Gelperin, Julius, and Bean, W. B.: The mental symptoms of pellagra. Am. J. M. Sc., 196: 461-475, 1938.

4. Frostig, J. P., and Spies, T. D.: The initial nervous syndrome of pellagra and associated deficiency diseases. Am. J. M. Sc., 199: 268-274, 1939.

5. Matthews, R. S.: Pellagra and nicotinic acid. J. A. M. A., 111: 1148-1153.

6. Sydenstricker, V. P., Schmidt, H. L., Jr., Fulton, M. C., New, J. S., and Geeslin, L. E.: The treatment of pellagra with nicotinic acid. South. M. J., 31: 1155-1163, Nov. 1938.

7. McLester, J. S.: Borderline states of nutritive failure. J. A. M. A., 112: 2110-2114, May 27, 1939.

8. Cleckley, H. M., Sydenstricker, V. P., and Geeslin, L. E.: Nicotinic acid in the treatment of atypical psychotic states associated with malnutrition. J. A. M. A., 112: 2107-2110, May 27, 1939.

9. Weinberg, M. H.: Case of subclinical pellagra—psychotic type—treated successfully with coramine (nicotinic acid). Am. J. Psychiat., 96: 701-704. Nov., 1939.

10. Jolliffe, N., Bowman, K. M., Rosenblum, L. A., and Fein, H. D.: Nicotinic acid deficiency encephalopathy. J. A. M. A., 114: 307-312.

11. Mainzer, F., and Krause, M.: Nicotinic acid in the treatment of delirium tremens. Brit. M. J., 2: 331-332, Aug. 12, 1939.

12. Piker, P., and Cohn, J. V.: The management of delirium tremens. J. A. M. A., 108: 345-349, Jan. 30, 1937.

13. Bowman, K., Wortis, H., and Keiser, S.: The treatment of delirium tremens. J. A. M. A., 112: 1217-1219, April 1, 1939.

14. Thomas, J. M., Semrad, E. V., and Schwab, R. S.: Observations on the use of fluids and lumbar puncture in the treatment of delirium tremens. Ann. Int. Med., 12: 2006-2009, June, 1939.

15. Henry, G. W.: Essentials of psychiatry. Williams & Wilkins Co., 1938.

16. Cheney, C. O.: Outlines for psychiatric examinations, p. 117. State Hospitals' Press, Utica, N. Y.

17. Sydenstricker, V. P.: Changing concepts of deficiency diseases. J. M. A. Alabama, 9: 105-109.

DISCUSSION

CHARLES D. ARING, M. D. (Cincinnati, Ohio).—Sebrell and Butler (Experiments on riboflavin deficiency in man, U. S. Pub. Health Reports, 1939, 54, 2121-2131) have suggested that in order to avoid further confusion, the diagnosis of pellagra should be confined to that syndrome which responds to nicotinic acid. If this thesis is followed, and if one uncritically accepts the literature on the subject, the field of the vitamin deficiencies will widen to include nearly all of medicine, and most of neurology. I would like to suggest why this thesis cannot be followed even though all the clinical writings on the vitamins be valid.

I shall confine my remarks chiefly to the effect of nicotinic acid on the cerebral circulation. When one injects nicotinic acid into an arm vein in man, and measures the cerebral blood flow before and after this procedure, it is found that there results a marked increase in the cerebral blood flow after the injection. This response has been obtained in seven cases. The increased cerebral blood flow lasts for at least 15 minutes with intravenous doses of 20 to 40 mg. To date we have not determined the maximum duration of this effect. In measuring cerebral blood flow in man by the plethysmographic method of Ferris (Relative intracranial blood flow in man, J. of Clinical Investigation, 1940, Proc. Soc. of Clin. Research, in press), we have found that the increase averages approximately 20 per cent in individuals without evident nicotinic acid deficiency. This finding may be correlated with that of Moore (Treatment of multiple sclerosis with nicotinic acid and vitamin B1, Arch. Int. Med., 1940, 65, 1-20) who noted that the pial arteries in the brain and spinal cord of a cat dilated after the intravenous injection of 48 mg. of nicotinic acid.

No change in the systemic blood pressure results from the injection of nicotinic acid in man. Neither is there a rise in the body temperature nor in respiratory rate. If cerebral blood flow increases and dilatation of the pial arteries occurs, and there is no alteration in systemic blood pressure, it seems reasonable to assume that cerebral function may improve if the cerebral symptoms are due to deficient cerebral circulation. This would hold whether the patient was suffering from a nicotinic acid de-

ficiency or not. Surely we believe that the relief of temporary circulatory disturbances of the brain results in profound change in neurological behavior. The syndrome known as "hypertensive encephalopathy" might be cited as an example. According to our work a reduction of cerebral blood flow occurs in patients suffering from so-called "hypertensive encephalopathy." We know how often these patients may "compensate," so to speak, and apparently recover from their abnormal cerebral manifestations. Although the physiological effect of an increase in carbon dioxide on the cerebral circulation is comparable to that of nicotinic acid, we do not postulate a carbon dioxide deficiency because of its cerebral action. Therefore one should thoroughly evaluate the pharmacological aspects of the vitamins before attributing their action to a deficiency of the same in the body.

The psychiatric service of the Cincinnati General Hospital is extremely interested in delirium tremens and has had a vast experience with this material. In recent studies by Rosenbaum and his group it was found that the average duration of the acute psychotic episode in 234 cases of delirium tremens was 2½ days. Sixty-five of a total of 234 patients on routine treatment, without the use of vitamins, cleared within 24 hours of the time they were first observed. They have used nicotinic acid (by mouth or parenterally) in 18 cases without shortening the duration of the psychotic episode, or the length of the entire course of delirium tremens. They are not impressed with the efficacy of nicotinic acid in other psychotic states not associated with pellagra, nor in stupor associated with the psychoses.

In consideration of the studies made by Drs. Sydenstricker and Cleckley it would seem to be a good policy to administer nicotinic acid to the type of case that they have described. Physiological consideration tends to encourage this policy. It will probably be wise to refrain from attributing these disorders to avitaminosis until more evidence is at hand.

HERMAN WORTIS, M. D. (New York City).—Drs. Sydenstricker and Cleckley have reported on the nicotinic acid treatment of 28 psychotic patients whose predominant symptoms were stupor and delirium. It is noteworthy that none of these cases showed any of the manifestations of pellagra, which we usually associate with a deficiency in nicotinic acid.

At the Bellevue Psychiatric Hospital, Dr. Norman Jolliffe and his associates have recently reported 150 cases of an encephalopathic syndrome which they believed to be a nicotinic acid deficiency. The syndrome is rather clear-cut and is characterized by clouding of consciousness, cogwheel rigidities and uncontrollable sucking and grasping reflexes. Many of the cases described by the authors may have fallen into this clinical group, but their paper makes no mention of the presence or absence of sucking and grasping reflexes.

As regards the use of nicotinic acid in the treatment of delirium tremens, a word of caution is necessary. We have recently completed a study at Bellevue, designed to discover the physiological and metabolic changes which accompany delirium tremens. Thirty per cent of our cases with delirium tremens had peripheral neuropathy, indicating a gross deficiency in vitamin B1. Many showed pellagrous lesions and all showed a marked deficiency in vitamin C. We concluded that nutritional factors were of great importance in the production of delirium tremens. The complexity of the problem and the difficulty in evaluating therapeutic procedures is emphasized by our findings in four cases of delirium tremens that were treated with glucose, saline and a diet that was *totally* inadequate in the entire vitamin B complex. Two of these cases recovered promptly and the other two took a marked turn for the worse, necessitating intravenous vitamin medication, before recovery took place. Prior to treatment, I could see no essential difference in the severity of these cases.

I have, however, seen many cases enter the hospital with delirium and then develop the typical nicotinic acid encephalopathy with marked clouding of consciousness, cogwheel rigidities and uncontrollable sucking and grasping reflexes. These cases invariably die unless they are given nicotinic acid.

In addition, great difficulties arise in evaluating the genesis of a psychotic episode in any particular individual. For example, case 18 is that of a 44-year-old alcoholic who entered the hospital for the surgical treatment of a peri-rectal abscess. The factors to be evaluated in the genesis of his psychotic episode are the following:

1. His pre-psychotic personality.
2. The patient was a chronic alcoholic. It is well known that alcoholism not only reduces the oxygen uptake of the brain, but that there are disturbances in carbohydrate utilization. That nicotinic acid deficiency can contribute to these metabolic difficulties is suggested by the work of the authors.
3. The operation, the anesthetic used, and the psychological and metabolic upset which attend such procedures.
4. His treatment with sodium amytal, sodium luminal and paraldehyde.
5. His treatment with nicotinic acid.

Were we dealing in this case with a specific nicotinic acid deficiency or did nicotinic acid augment brain oxidation in non-specific fashion so that normal functioning again became possible? Do the authors believe that this restoration to normal functioning could have been obtained by any other method? Furthermore, have the authors seen similar pictures which did not respond to nicotinic acid therapy?

It has been known for years that the adequate functioning of the brain is dependent upon a carbohydrate substrate and an adequate supply of oxygen. In addition, various enzyme and co-enzyme systems are necessary for the proper break down and utilization of this carbohydrate by the brain. Among the most important of these systems are vitamin B1 and nicotinic acid.

The authors are to be commended for bringing to our attention this noteworthy addition to therapeutics in psychiatry. While one may question the

specificity of nicotinic acid therapy in some of their cases, the hard and important fact that 28 psychotic patients were made well by the use of this substance is a discovery of first rate importance.

Dr. Hervey M. Cleckley.—The effect of nicotinic acid, mentioned by Dr. Aring, in dilating cerebral arterioles impresses me as a very interesting observation. It is, of course, possible, perhaps probable in some cases, that the beneficial effect we observed after the administration of nicotinic acid was the result of this dilatation rather than the correction of an actual deficiency state. The fact that many of our patients maintained a marked improvement, and some a recovery, suggests, however, that a true avitaminosis was at least sometimes present. The sudden emergence from confusion noted in case 23 suggests that the effect of nicotinic acid in this instance was probably a direct result of increased cerebral blood flow as described by Dr. Aring. I agree with Dr. Aring that one should be cautious about assuming that patients who improve after treatment with vitamins are necessarily cases of avitaminosis in the ordinary sense. It seems, however, an interesting fact that stuporous and delirious patients often respond favorably to the administration of nicotinic acid.

Cases of delirium tremens in my own experience have on the average taken longer to clear up than two and a half days. I hardly think this could be because most of them attained their status by drinking "Georgia corn." The three cases reported recovered so rapidly after the administration of the nicotinic acid that a causal effect seems likely. I do not mean to go so far as to say that all cases of delirium tremens or even most cases would respond similarly.

We have observed a few cases showing forced grasping and sucking who apparently were of the type described by Dr. Jolliffe and his co-workers and classified as encephalopathy with nicotinic acid deficiency. The majority of our cases did not seem typical of this syndrome. Many of our cases showed evidence of cerebral arteriosclerosis and I believe that the effects of nicotinic acid deficiency as well as the effects of cerebral arteriosclerosis contributed to their personality disorders.

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B Vitamins in Cancerous Tissues

II. Nicotinic Acid

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The importance of this member of the B vitamin family in human and animal nutrition has been demonstrated many times, often dramatically, in the last few years (4, 3, 14, 12). There is little doubt that noncancerous tissues require a supply of this vitamin for continuation of their essential functions, but practically nothing is known about the requirements of cancerous tissues.

Willheim and Ricobo (15) noted some improvement in the general condition when large doses of nicotinic acid were fed to human patients bearing tumors, and Masin (10) reported that nicotinic acid feeding was helpful in the inhibition of benzpyrene skin tumors in animals. In the case of liver tumors induced by feeding *p*-dimethylaminoazobenzene to rats on a rice-carrot basal diet, it was shown that nicotinic acid in combination with riboflavin has a protective action (6).

In attempting to judge the importance of nicotinic acid in cancer, it would be helpful to know the content of this vitamin in cancerous tissues and how the values change in the transformation from the noncancerous to the cancerous condition. Here, too, not much is known. von Euler and his coworkers (5) studied the ratio of reduced to oxidized coenzyme in different tissues and reported that this ratio was higher for Jensen rat sarcoma than for normal rat muscle. Bernheim and Felsovanyi (1) analyzed rat tissues for coenzymes I and II and found that the Walker carcinosarcoma 256 contained much smaller amounts of the coenzymes than did the noncancerous tissues. They mentioned further that they found only traces in three human carcinomas.

Kensler, Sugiura, and Rhoads (8) determined the effect on the coenzyme I content of rat livers of feeding *p*-dimethylaminoazobenzene, and noted that the concentration was decreased in the damaged livers and fell to still lower levels in the cancers which were produced. Kensler, Dexter, and Rhoads (7) were interested further in determining whether the azo dye or its metabolites had any direct action on enzyme systems involving diphosphopyridine nucleotide, and were able to establish *in vitro* that *p*-phenylenediamine and N,N-dimethyl-*p*-phenylenediamine, both probable metabolites of the azo dye, had a strong inhibiting action on fermentation systems in which coenzyme I was the limiting factor. They called attention to the possibility of correlating this inhibitory action of the metabolites with the carcinogenic potency of the parent azo dye.

In connection with the functions of nicotinic acid in cellular metabolism, it is pertinent that the pyridinoproteins were shown to act directly in many of the fermentative transformations of carbohydrate. Thus they might play an important part in metabolic processes whether or not the metabolites eventually underwent oxidation with oxygen. On the other hand, enzymes such as the flavoproteins and cytochrome *c* appeared to function mainly in the transport of hydrogen from the pyridinoproteins to oxygen, and so might be considered less essential for metabolic systems, such as in cancer, where carbohydrate is transformed largely into lactic acid rather than into carbon dioxide and water. This concept would be in agreement with the low cytochrome *c* (2, 6, 15) and riboflavin (11) contents in cancerous tissues and might lead one to expect comparatively high nicotinic acid values in cancer, although there is unquestionably a great deal yet to learn about the functions of the compounds in living tissues.

MATERIALS AND METHODS

The tissue extracts described in the first paper of this series (11) were analyzed for nicotinic acid by the microbiological method of Snell and Wright (13). The results for noncancerous tissues are given in Table I and for cancers in Table II.

RESULTS AND DISCUSSION

The constancy of the nicotinic acid contents of the different tumors is striking. Most of them contained between 13 and 29 γ of nicotinic acid per gm. of fresh tissue, the major exceptions being the two hepatomas produced by feeding rats *p*-dimethylaminoazobenzene on a basal Purina ration, where the values were 38 and 50. Considering the wide variation in nicotinic acid content of noncancerous tissues (Table I), the comparative constancy found for the tumors assumes a real significance.

The absolute level of the vitamin in tumors is low compared with noncancerous tissues. For example, the lowest value for a normal animal tissue was 44 γ per gm. (dba mouse brain), which is appreciably above the range for the cancers. This situation is different from that of riboflavin, which also was found to be low in cancerous tissues but not any lower than in a number of noncancerous tissues (11). The tentative conclusion may therefore be drawn that the transformation to the cancerous condition involves a decrease in the nicotinic acid content. This is most clearly seen in the case of the hepatoma induced by *p*-dimethylaminoazobenzene, where the adjacent noncancerous liver serves as a fairly satisfactory control tissue. It will be seen from Table III that the hepatomas contained about one-third to one fourth of the nicotinic acid found in the adjacent normal liver.

TABLE I: NICOTINIC ACID CONTENTS OF NONCANCEROUS TISSUES

Tissue	Sex	Number of samples	Solids content, per cent	Nicotinic acid content (γ per gm fresh tissue)
Liver—Wistar rat (rice-carrot diet)	♀	2	(30.5)	174
" Wistar rat (Purina diet)	♀, ♂	2	30.5	178
" C57 mouse	♀	3	29.6	104
" dba "	♀	3	28.1	107
" C3H "	♀	3	27.3	93
" Human	♀	1	27.1	51
Whole heart—Wistar rat	♀, ♂	2	20.6	123
" " C57 mouse	♀	3	22.2	126
" " dba "	♀	3	23.7	113
" " C3H "	♀	3	23.8	120
Myocardium—Human	♀	1	20.6	41
Whole brain—Wistar rat	♀, ♂	2	21.2	64
" " C57 mouse	♀	3	22.8	68
" " dba "	♀	3	21.0	44
" " C3H "	♀	3	22.2	50
Cerebrum—Human	♀	1	24.8	20
Lung—Wistar rat	♀, ♂	2	16.1	51
" Human	♀	1	21.4	18
Spleen—Wistar rat	♀, ♂	2	20.2	69
" Human	♀	1	22.7	30
Kidney—Wistar rat	♀, ♂	2	22.7	117
" Human	♀	1	20.3	33
Skeletal muscle—Wistar rat	♀, ♂	2	24.7	81
" " Human	♀	1	26.0	50

TABLE II: NICOTINIC ACID CONTENTS OF CANCEROUS TISSUES

Sample No.	Tissue	Sex	Solids content, per cent	Nicotinic acid content (γ per gm fresh tissue)
158, 159, 160	Rat carcinosarcoma (Walker 256)	♂	13.9	19 (17–20)
176, 180, 184	C57 mouse sarcoma (methylcholanthrene)	♀	17.5	29 (26–35)
207, 208, 209	dba mouse adenocarcinoma	♀	18.3	20 (17–26)
250, 251, 252, 274, 275	C3H " "	♀	16.3	28 (18–42)
105	Human mammary carcinoma	♀	35.7	25
106	" " "	♀	27.2	27
212	" " "	♀	19.1	15
213	" " "	♀	16.1	29
214	" " "	♀	31.4	21
215	" " "	♀	16.8	28
216	" " "	♀	35.3	13
217	" " "	♀	18.0	22
218	" spindle cell sarcoma	♂	16.4	29
219	" skin carcinoma	♀	17.8	18
220	" ovarian adenocarcinoma	♀	19.5	15
225	" " "	♀	14.8	27
221	" renal adenocarcinoma	♂	19.6	18
222	" sarcoma, axilla	♀	16.7	21
223	" melanoma, orbit	♀	14.3	23
224	" lymphosarcoma, groin	♂	16.7	36
284	" melanoma, lower leg	♂	18.7	11
286	" sarcoma, back	♂	20.4	28
288	" sarcoma, neck	♂	20.0	12
289	" adenoma malignum, sigmoid colon	♀	17.5	24
290	" adenocarcinoma, rectum	♂	20.0	30

This result is in agreement with the decrease in coenzyme I reported for the induction of this type of cancer (8).

tion is not clear. The comparative constancy of the vitamin level in tumors may be an indication of the essential nature of the vitamin for cancer metabolism.

TABLE III: NICOTINIC ACID CONTENTS OF CANCEROUS AND NONCANCEROUS RAT LIVER TISSUES

Diet	Days on diet	Sample No.	Tissue	Sex	Solids content, per cent	Nicotinic acid content (γ per gm. fresh tissue)
p-Dimethylaminoazobenzene, rice, carrots	199	169	Hepatoma	♀	17.6	[illegible]
" "	134	107, 111	Mixed cancerous and noncancerous tissue	♀	28.4	111, 137
" "	199	170	Noncancerous liver adjacent to hepatoma	♀	(30.5)	100
p-Dimethylaminoazobenzene, Purina	210 290	197, 280	Hepatomas	♀, ♂	(17.6)	58, 5[illegible]
" "	290	279	Mixed cancerous and noncancerous tissue	♀	(28.4)	83
" "	210 290	196, 278	Noncancerous liver adjacent to hepatoma	♀, ♂	(30.5)	127, 147

In view of the considerations presented in the introduction whereby one might be led to expect high nicotinic acid contents in tumors, it is interesting to speculate on the significance of the finding that this vitamin is actually decreased in cancer. Since the transformation to the cancerous state is accompanied by an increased ability of the cells to metabolize carbohydrate glycolytically (16), the most obvious conclusion is that nicotinic acid is not associated with the increased glycolysis. On the other hand, the constancy of the nicotinic acid content in various tumors is an indication that this vitamin is essential for at least some aspects of cancer cell metabolism. It may be that the cancer cell is able to utilize its nicotinic acid much more efficiently in glycolytic processes than are noncancerous tissues. If this should be the case, it would account for the apparent anomaly of low nicotinic acid content and high glycolysis. The low vitamin level might simply be a reflection of low storage capacity of the cancer cell. These questions await further investigation.

SUMMARY

The results of nicotinic acid assays on a variety of cancerous and noncancerous tissues are reported. Whereas values ranging from 18 to 178 γ per gm. of fresh tissue were found for noncancerous tissues, the range for the cancers was from 13 to 59 γ per gm., with most of the values falling between 18 and 29 γ per gm.

It is concluded that the transformation to the cancerous state involves a decrease in nicotinic acid content, although whether this signifies low utilization of this vitamin or low storage capacity and efficient utiliza-

REFERENCES

1. BERNHEIM, F., and FELSOVANYI, A. V. Coenzyme Concentration of Tissues. Science, **91**:76. 1940.
2. DEBOIS, K. P., and POTTER, V. R. Biocatalysts in Cancer Tissue. I. Cytochrome *c*. Cancer Research, **2**:190-203. 1942.
3. FEVERHEM, C. A. The Relation of Nicotinic Acid to Pellagra. Physiol. Rev., **20**:249-271. 1940.
4. FEVERHEM, C. A., MADDEN, R. J., STRONG, F. M., and WOOLLEY, D. W. Relation of Nicotinic Acid and Nicotinic Acid Amide to Canine Black Tongue. J. Am. Chem. Soc., **59**:1767-1768. 1937.
5. VON EULER, H. W., SCHLENK, F., HELWINKEL, H., and HOGBERG, B. Coenzymase und Nicotinsaure, und Gehalt im Tierkörper und in der Hefe. Ztschr. f. physiol. Chem., **256**:208-228. 1938.
6. JESOWICZ KOCHOLATY, R., and HOGNESS, T. R. The Spectroscopic Determination of Cytochrome C and Its Distribution in Some Mammalian Tissues. J. Biol. Chem., **129**:569-574. 1939.
7. KENSLER, C. J., DEXTER, S. O., and RHOADS, C. P. The Inhibition of a Diphosphopyridine Nucleotide System by Split Products of Dimethylaminoazobenzene. Cancer Research, **2**:1-10. 1942.
8. KENSLER, C. J., SEGURA, K., and RHOADS, C. P. Coenzyme I and Riboflavin Content of Livers of Rats Fed Butter Yellow. Science, **91**:623. 1940.
9. KENSLER, C. J., SEGURA, K., YOUNG, N. E., HALTER, C. R., and RHOADS, C. P. Partial Protection of Rats by Riboflavin with Casein against Liver Cancer Caused by Dimethylaminoazobenzene. Science, **93**:308-310. 1941.
10. MOSIN, J., POURRIAS, Y., and CAMPESTAN, J. P. Hypovitaminose du cancer au benzopyrene — action de fortes doses de vitamine B_1, d'amide nicotinique ou d'un système phosphopyridine. Compt. rend. Soc. de Biol., **132**:87-90. 1939.
11. POLYAK, M. V., TAYLOR, A., TAYLOR, J., and WHITTAKER, R. J. B Vitamins in Cancer Tissues. I. Riboflavin. Cancer Research, **2**:750-753. 1942.

12. Smith, D. T., Rullin, J. M., and Smith, S. G. Pellagra Successfully Treated with Nicotinic Acid: Case Report. J. A. M. A., **109**:2054-2055. 1937.

13. Snell, F. E., and Wright, L. D. A Microbiological Method for the Determination of Nicotinic Acid. J. Biol. Chem., **139**:675-686. 1941.

14. Spies, T. D., Bean, W. B., and Stone, R. E. The Treatment of Subclinical and Classic Pellagra, J. A. M. A., **111**:584-592. 1938.

15. Stotz, E. The Estimation and Distribution of Cytochrome Oxidase and Cytochrome C in Rat Tissues. J. Biol. Chem., **131**:555-565. 1939.

16. Warburg, O. Ueber den Stoffwechsel der Tumoren. Pp. 263. Berlin: Julius Springer. 1926.

17. Wilhelm, R., and Bocobo, E. Effects of High Doses of Nicotinic Acid on Human Epidermoid Carcinoma. Acta Med. Philippina. **2**:445-466. 1941; abstr., Cancer Research, **2**:69. 1942.

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STUDIES ON THE TOXICITY AND PHARMACOLOGY OF NICOTINIC ACID

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In 1913 Funk (1) working on the isolation of the anti-beriberi factor demonstrated that concentrates from rice polish and yeast contain nicotinic acid. Since the acid was not curative in experimental beriberi, Funk did no further work on the substance. The question of a possible biological action of nicotinic acid was raised again in 1935 when Warburg (2) reported the presence of nicotinic acid in his co-ferment and von Euler (3, 4) detected nicotinic acid as a component of cozymase. Later Knight (5) found nicotinic acid to have a growth-promoting action for certain micro-organisms and to be a component of the "staphylococcus growth factor." He also found nicotinic amide to be more potent than the acid itself in this respect. Recently Funk and Funk (6) and Frost and Elvehjem (7) have also shown the importance of these compounds for rats maintained on various diets deficient in some portion of the vitamin B_2 complex. It has been recently stated by Elvehjem and his coworkers (8) that nicotinic acid or its amide cures "blacktongue" in dogs. These observations were confirmed by Street and Cowgill (9) and others. Chick, Macrae, Martin and Martin (10) found nicotinic acid curative of a pellagra-like disease in pigs maintained on the Goldberger diet. Recently, Spies, Cooper and Blankenhorn (11), Fouts, Helmer, Lepkovsky and Jukes (12) and also Smith, Ruffin and Smith (13) have demonstrated the value of nicotinic acid, sodium nicotinate and nicotinic amide in the treatment of human pellagra. These observations and experiments have established the importance of nicotinic acid as a component of the vitamin B_2 complex. Since apart from the findings of

Hunt and Renshaw (14), that a dose of 20 mgm. of nicotinic acid hydrochloride per kilogram body weight is nontoxic in mice and does not influence the blood pressure of the cat, no information concerning the toxicity and pharmacology of nicotinic acid is to be found in the literature it has seemed advisable to undertake investigations of this nature.

Nicotinic acid, sodium nicotinate and nicotinic amide were used. Since nicotinic acid is only slightly soluble in water and is strongly acid in reaction in most of the experiments sodium nicotinate in aqueous solution corresponding to 10 per cent nicotinic acid was employed. Such a solution has a pH of 7.0 to 7.1. Sodium nicotinate is completely dissociated in solution and thus no difference in the action of this compound from that of the acid itself is to be expected. The readily soluble nicotinic amide was likewise used in 10 per cent aqueous solution. All experiments were carried out on normal animals maintained on a complete diet.

EXPERIMENTAL

Acute toxicity

Acute toxicity was determined in mice and rats orally and subcutaneously.

Up to 1 gram per kilogram of nicotinic amide or sodium nicotinate was tolerated by mice without any toxic symptoms. Death first occurred after the subcutaneous administration of 1.8 grams per kilogram of nicotinic amide or 3 grams per kilogram sodium nicotinate. Following lethal doses death occurred within 12 to 36 hours, though no specific symptoms of poisoning could be noticed. In the last stages the animals became unable to move and were atactic; the respiration became slow; cyanosis was observed. These symptoms were the same after the administration of either nicotinic amide or sodium nicotinate. Figure 1 shows the toxicity curves of these compounds in mice after subcutaneous and oral administration, 5 to 10 animals being used for each dose level. Nicotinic amide is approximately twice as toxic as sodium nicotinate. For both compounds the

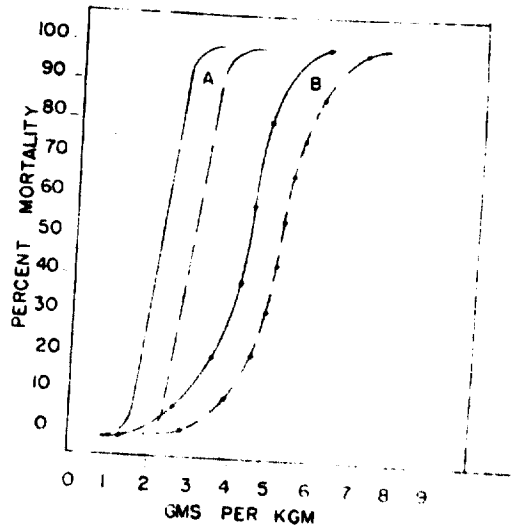

FIG. 1. TOXICITY OF NICOTINIC AMIDE AND SODIUM NICOTINATE IN MICE
A. Nicotinic amide after oral (———) and subcutaneous (- - - - -) administration. B. Sodium nicotinate after oral (—•—) and subcutaneous (—•— —•—) administration.

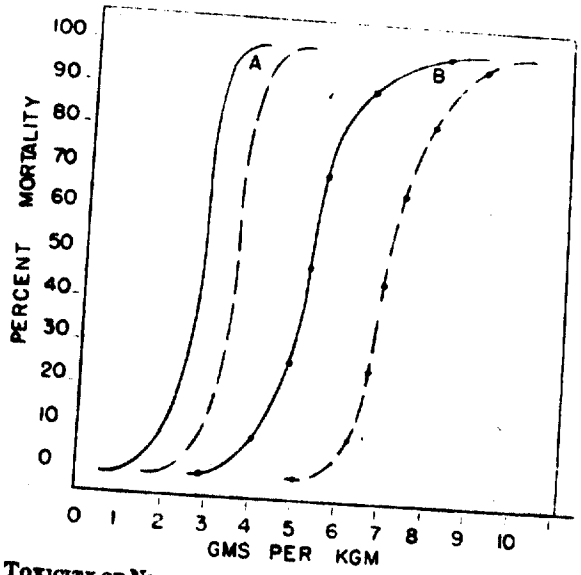

FIG. 2. TOXICITY OF NICOTINIC AMIDE AND SODIUM NICOTINATE IN RATS
A. Nicotinic amide after oral (———) and subcutaneous (— —) administration. B. Sodium nicotinate after oral (—•—) and subcutaneous (—•— —•—) administration.

difference in toxicity after subcutaneous and oral administration is very small.

Experiments with rats gave similar results. Even when injected intravenously 1 gram per kilogram of sodium nicotinate was tolerated without any reaction. Figure 2 shows that the toxicity of nicotinic amide and sodium nicotinate is approximately the same as that found in mice. The symptoms of poisoning in rats are likewise non-characteristic.

Dogs tolerated 2 grams per kilogram of sodium nicotinate without unfavorable reactions.

Chronic toxicity

In these experiments rats, chickens and dogs were used.

A group of 10 six weeks old rats was fed 1 gram per kilogram of sodium nicotinate daily over a period of 40 days. The animals showed no toxic symptoms and their weight increased as regularly as that of control animals. After 40 days the rats were killed for histological examination. Gross and microscopic examination of heart, lungs, liver, spleen, kidney, intestinal tract, bone marrow and genital organs showed no pathological changes.

A group of 5 chickens received 0.1 gram per kilogram of sodium nicotinate daily over a period of 21 days; the gain in weight was normal and no toxic reactions were observed.

Daily doses of 1 gram per kilogram of sodium nicotinate were fed to three young dogs for over 63 days with three littermates serving as controls. The growth was normal and no untoward results were observed. Two adult dogs tolerated 2 grams per kilogram daily over 35 days without untoward symptoms.

Fate of nicotinic acid in the organism

Since toxic symptoms were never observed in the experiments on chronic toxicity, even when the animals were fed with large doses for more than two months, it might be assumed that nicotinic acid is not stored to any great extent in the body but that it is either destroyed or excreted. A study was made of the excretion by feeding 1 gram per kilogram of sodium nicotinate

to a 5 kgm. dog and then analyzing the urine for nicotinic acid. The urine collected during the 24 hours after the administration of sodium nicotinate contained 1.32 grams of nicotinic acid as identified by chemical analysis and melting point determinations; or 30 per cent of the nicotinic acid ingested. The subsequent samples of urine contained no detectable amounts of nicotinic acid. No attention was paid to the possible excretion of trigonellin (Ackermann (15)).

Experiments on metabolism and circulation

The action of nicotinic acid on the metabolism of rats was investigated in 22 experiments by the method of Richards and Collison (16). The animals were fed or injected subcutaneously with sodium nicotinate in varying doses from 0.5 to 2.0 mgm. per kilogram. No change in the oxygen uptake could be found on observing the metabolism for five hours after the administration of the drug.

The blood pressure of rabbits and cats under urethane and chloralose anesthesia was not influenced by intravenous injection of sodium nicotinate or nicotinic amide even in doses up to 1 gram per kilogram. However, the injection of nicotinic acid (0.5 per cent solution pH 3.3) even in small amounts (5 to 10 mgm.) frequently raised the blood pressure by 10 to 20 mm. (fig. 3). The elevation of blood pressure lasted for a few minutes and was accompanied by an increase in the volume of the leg. Since a neutralized solution of nicotinic acid (pH 6.5) as well as an equal dose of sodium nicotinate (pH 7) did not influence the blood pressure and, on the other hand, hydrochloric acid (pH 3.3) gave similar results as the nicotinic acid (pH 3.3), it may be justifiable to ascribe this rise in blood pressure, which was first reported by McCrea (17) to the pH of the injected solutions and not to a specific action of nicotinic acid itself.

The respiration remained unaltered and the heart action as recorded by the electrocardiograph failed to show any pathological changes. Although the carotid blood pressure remained constant this did not exclude the possibility of a change in the blood distribution in different blood vessels. Therefore, the

action of nicotinic acid on the circulation of the rabbit's ear was investigated using the photoelectric method of Molitor and Kniazuk (18). Any possible influence of the amount of the injected fluid, of its temperature, and of its pH on the ear vessels was excluded. Following the injection of large doses of sodium nicotinate no immediate changes were observed either in the diameter of the vessels or in the temperature of the skin.

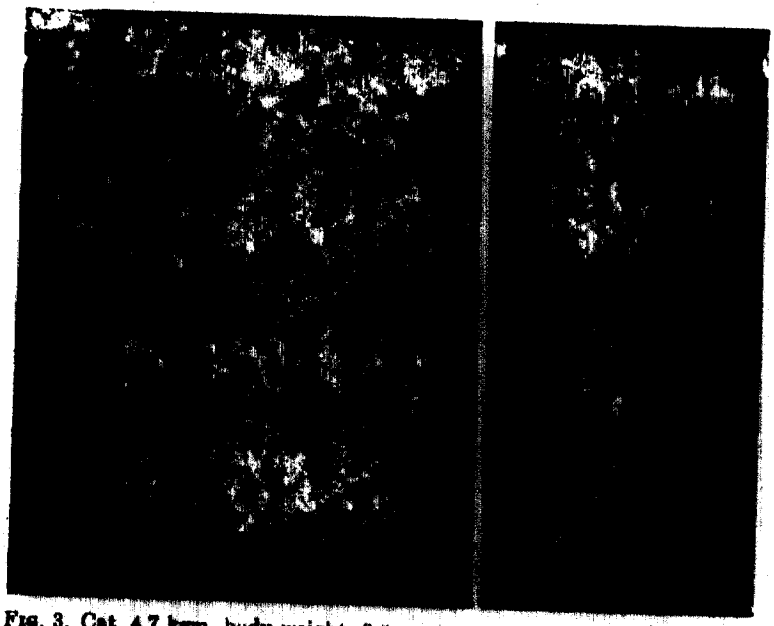

FIG. 3. Cat, 4.7 kgm. body weight; 0.6 gram per kilogram urethane and 0.06 gram per kilogram chloralose.

R: respiration; leg vol.: volume of the left hind-leg; BP: carotid blood pressure; time in 10 seconds. 1–2 cc. nicotinic acid (10 mgm.), pH 3.3 intravenously. 2–2 cc. hydrochloric acid, pH 3.3 intravenously. 3–2 cc. nicotinic acid buffered (10 mgm.), pH 6.5 intravenously. 4–2 cc. phosphate buffer, pH 6.3 intravenously.

DISCUSSION

The above experiments demonstrate that sodium nicotinate has only a very low toxicity ranging from 4 to 7 grams per kilogram in mice and rats. Nicotinic amide is approximately twice as toxic as sodium nicotinate.

The rather slow and non-characteristic symptoms following

lethal doses suggest that the lethal effect of high doses of nicotinic amide and sodium nicotinate is caused by the osmotic pressure of the 10 per cent solutions of the drugs rather than by a specific toxic action of the drugs themselves, since the injection of the same volumes of an equimolecular concentration of sodium chloride (4 per cent) may produce death with similar symptoms.

The experiments on chronic toxicity show that even large amounts, up to at least one-fifth of the lethal dose, are tolerated by rats and dogs over a long period of time without producing any toxic symptoms. In these experiments sodium nicotinate of a pH of 7 was used. Our results confirm the statement of Ackermann (15), who fed a "middle-sized" dog 9 grams of nicotinic acid as sodium nicotinate over a 5-day period without toxic effects. On the other hand, Elvehjem, Madden, Strong and Wooley (19) and Chen, Rose and Robbins (20) reported toxic symptoms in dogs after feeding 2 grams of nicotinic acid daily. In Elvehjem's investigation one dog (4.6 kgm.) showed spasmodic vomiting after 5 days; the two dogs (13.8 and 15 kgm.), observed by Chen et al., expelled bloody feces during the second week, and showed increased irritability, loss of appetite and the onset of convulsions. The type of toxic symptoms, vomiting, bloody feces, erosions and petechiae in the mucosa of the intestinal tract, hyperemia of the intestines and fatty metamorphosis of the liver may suggest that the acidity of the compound played a rôle in the development of the intestinal lesions and their sequelae, since our dogs when fed the neutralized compound in even larger doses (2 grams per kilogram) daily over a much longer period of time failed to develop any toxic symptoms.

The extremely low toxicity of nicotinic acid corresponds well with the low toxicity recorded of other vitamins, especially those of the B complex. Crystalline vitamin B_1 has been found by Molitor and Sampson (21) to be non-toxic to normal rats in subcutaneous doses up to 0.1 gram per kilogram and recently Kuhn (22) has emphasized the extremely low toxicity of riboflavin in rats. Although the minimal curative dose of nicotinic acid for blacktongue in dogs has not yet been determined, the

data presented by Elvehjem and coworkers and by Chick and others suggests that it is approximately 1 mgm. per kilogram daily, possibly less. From the above experiments there may be derived for nicotinic acid a very wide therapeutic range (1:1000) which is quite comparable to that of vitamin B_1 and riboflavin.

The above experiments concerning the pharmacological actions of nicotinic acid failed to demonstrate any influence on the metabolism, respiration and blood pressure. We duplicated the finding of McCrea (17), that small amounts of non-neutralized nicotinic acid cause a transient rise in blood pressure together with an increase in the leg volume, but this effect proved to be dependent upon the pH of the administered solution (fig. 3).

SUMMARY

1. Acute toxicity (L.D. 50) of nicotinic acid in mice and rats ranges from 4 to 5 grams per kilogram after subcutaneous and from 5 to 7 grams per kilogram after oral administration. Nicotinic amide is about twice as toxic.

2. Prolonged oral administration of large amounts (up to 2 grams per kilogram daily) of sodium nicotinate to rats, chickens and dogs over periods up to 2 months failed to produce toxic symptoms or pathological changes of the organs.

3. In the urine collected during 24 hours after oral administration of sodium nicotinate 30 per cent of the dose could be recovered as nicotinic acid.

4. The metabolism and the circulatory and respiratory system of normal animals was not influenced by sodium nicotinate or nicotinic amide.

Appreciation is expressed to Dr. J. C. Keresztesy and Mr. E. Rickes for the determination of nicotinic acid in the urine, to Dr. W. Antopol for the histological studies and Messrs. Fernandes and Kuna for valuable technical assistance.

REFERENCES

(1) Funk: J. Physiol., 46, [illegible], 1913.
(2) Warburg and Christian: Biochem. Ztschr., 275, 464, 1935.
(3) von Euler, Albers and Schlenk: Ztschr. f. physiol. Chem., 237, I, 1935.

(4) VON EULER AND SCHLENK: Ztschr. f. physiol. Chem., **240**, 113, 1936.
(5) KNIGHT: Nature, **139**, 628, 1937.
(6) FUNK AND FUNK: J. Biol. Chem., **119**, 35, 1937.
(7) FROST AND ELVEHJEM: J. Biol. Chem., **121**, 225, 1937.
(8) ELVEHJEM, MADDEN, STRONG AND WOOLEY: J. Am. Chem. Soc., **59**, 1767, 1937.
(9) STREET AND COWGILL: Proc. Soc. Exp. Biol. & Med., **37**, 547, 1937.
(10) CHICK, MACRAE, MARTIN, AND MARTIN: Biochem. J., **32**, 10, 1938.
(11) SPIES, COOPER AND BLANKENHORN: Report to the Central Soc. for Chemical Research, November 5, 1937 at Chicago; J. A. M. A., **110**, 622, 1938.
(12) FOUTS, HELMER, LEPKOVSKY AND JUKES: Proc. Soc. Exper. Biol. & Med., **37**, 405, 1937.
(13) SMITH, RUFFIN AND SMITH: J. A. M. A., **109**, 2051, 1937.
(14) HUNT AND RENSHAW: J. Pharmacol. & Exper. Therap., **35**, 75, 1929.
(15) ACKERMANN: Ztschr. f. Biol., **59**, 17, 1912.
(16) RICHARDS AND COLLISON: J. Physiol., **66**, 299, 1928.
(17) MCCREA: J. Pharmacol. & Exper. Therap., **63**, 25, 1938.
(18) MOLITOR AND KNIAZUK: J. Pharmacol. & Exper. Therap., **57**, 6, 1936.
(19) ELVEHJEM, MADDEN, STRONG AND WOOLEY: J. Biol. Chem., **123**, 137, 1938.
(20) CHEN, ROSE AND ROBBINS: Proc. Soc. Exp. Biol. & Med., **38**, 241, 1938.
(21) MOLITOR AND SAMPSON: E. Merck's Jahresbericht, **50**, 51, 1936.
(22) KUHN: Klin. Wchnschr., **17**, 222, 1938.

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Original Articles

Niacin in the Long-Term Treatment of Schizophrenia

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A comprehensive study was done to determine the efficacy of niacin as a supplement in the treatment of schizophrenic patients over a two year period. Newly admitted schizophrenic men were assigned at random to either high-dosage niacin (3,000 mg/day) or low-dosage niacin (5 mg/day) as a control medication. The only significant untoward result was the occurrence of a pigmented hyperkeratosis in about one third of the patients receiving the high-dosage regimen.

Analyses of rating scale, social adjustment, and self-report data for patients in treatment at least 18 months failed to indicate any advantage for the high dosage of nicotinic acid group. Rate of attrition, duration of hospitalization, and need for tranquilizing medication failed also to reveal an advantage for this group.

Hoffer et al[1] first reported the use of niacin in the treatment of schizophrenic patients in 1957, but according to Hoffer,[2] their pilot trials began as early as 1952. The potential value of niacin as an aid in the treatment of schizophrenic patients has received some attention, but the various published accounts[3-5] of attempts to exhibit a therapeutic advantage for niacin relative to placebo are generally discouraging.

The present study was undertaken to examine the value of niacin as a supplement to treatment that the patient would ordinarily receive. Since a clinically desirable change might occur in any one of several forms, diverse criteria were included, and the study was planned to provide a sample large enough to establish the statistical significance of any clinically significant treatment-related changes. A 24-month-treatment regimen was undertaken to explore the cumulative effect of supplementary niacin.

The Sample

Patients appropriate for treatment with niacin have been variously described. It is the consensus of these descriptions, however, that patients whose status is no longer mobile and whose schizophrenia has attained a chronically fixed form are relatively resistant to the megavitamin therapy. The most appropriate patients are described as early schizophrenics—patients whose manifestations are labile. Patients whose illness is in its incipience or whose schizophrenia may be borderline are, of necessity, diagnosed with appreciable error despite the fact that at times a schizophrenic quality had been perceived and a schizophrenic development had been feared. As would be anticipated, therefore, the efforts of the project psychiatrists to select a sample appropriate for niacin therapy involved some patients for whom the designation "schizophrenic" eventually appeared to be debatable or possibly inappropriate.

Most of the sample was drawn from the Male Admission Ward of the New Jersey State Hospital at Marlboro. A few patients had been hospitalized but were seen on an outpatient basis at the time the treatment was assigned. Patients who were beyond 65 years of age, in questionable health, or suffering from diabetes, liver pathology, or a neurological disorder, were excluded, as were mental defectives, alcoholics, transients, or certain patients with character disorders. Insofar as possible, neurotic patients or patients with unambiguous affective disorders were excluded as well.

The research plan provided for 24 months of treatment with patients assigned to medication as they became available through hospital admissions. The present report is based on a total sample of 86 patients who were maintained with the project for a period of at least 18 months. Seventy-five of these patients continued in treatment for the scheduled 24-month period.

After several months of treatment, some of the patients in the experimental group developed a superficial hyperkeratosis (see Table 1). When the hyperkeratosis became definite, the patients were temporarily removed from treatment while dermatologic and precautionary measures were taken. Some of these patients could not be returned to treatment immediately, and in some cases more than a month elapsed before the full treatment program was resumed.

The effect of such temporary suspension or attenuation of treatment could not be anticipated and the presence of some patients for whom the diagnosis was questioned also created some uncertainty. Specifically, in the experimental group there were 14 patients (26%) for whom the diagnosis of schizophrenia was questionable, and in the control group there were eight patients (25%) whose diagnosis was questionable. Accordingly, a selected subsample was formed: a group of patients for whom treatment had not been interrupted and for whom the diagnosis had never been questioned. This selected group comprised 42 patients, 22 in the experimental group and 20 in the control group. All analyses conducted for the total sample were replicated for this small selected subsample.

The results of clinical investigations do not have a meaning independent of the sample on which they are based, and Table 2, as well as the Figure, offers some documentation of the nature of the present sample. Table 2 defines the sample as relatively young and relatively labile in the sense that most of the patients have had very little prior mental hospital treatment.

Since the development of symptoms brings the patient to treatment and their remission ordinarily precedes the conclusion of treatment, the symptomatic manifestations of the sample assume a central pertinence, and a comprehensive set of symptom rating scales is a useful point of reference in documenting the representative symptomatic composition of a sample. A comprehensive set of scales, such as the Wittenborn Psychiatric Rating Scale (WPRS), offers a descriptive spectrum not provided by simple diagnostic classifications and may be used also as criteria of change from pretreatment to posttreatment status.

The figure, based on *standard scores* for the WPRS factors, shows that the symptomatic qualities commonly ascribed to schizophrenic patients were well developed in the present sample at the time treatment was undertaken and that the characterizing symptoms were different from those found in a sample of newly admitted depressed patients. Certainly the symptoms were sufficiently well developed to reflect diminution in response to an effective therapeutic regimen.

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Table 1.—First Note of Pigmentation in Experimental Patients Completing at Least 18 Months of Treatment*

Month	Occurrence of Pigmentation
1	2 questionable
2	0
3	0
4	2 positive
5	4 positive; 1 questionable
6	2 positive
7	1 positive
8	1 positive
9	3 positive
10	0
11	2 positive; 1 questionable
12	1 positive; 1 questionable
13	2 positive
14	1 positive; 1 questionable
15	0
16	0
17	1 positive
18	0

* N = 86; 75 patients completed at least 24 months. Questionable pigmentation was noted in one control patient each in months 4, 14, and 20.

Table 2.—Comparison Between Experimental and Control Groups Who Completed 24 Months of Treatment

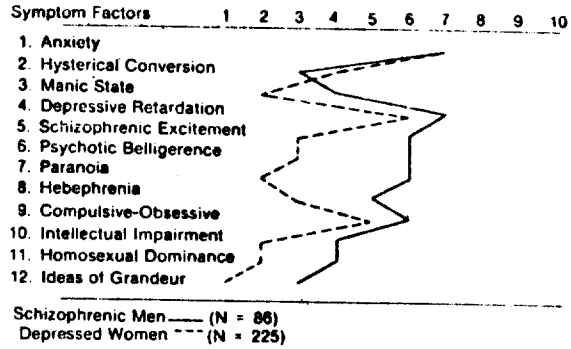
	Experimental (N=47)	Control (N=28)	Total (N=75)
Mean age when beginning niacin	28.7	29.1	28.8
Mean age at first hospitalization	23.9	26.1	24.7
Chronicity: median weeks in hospital in 5 years preceding niacin treatment	7½	7½	7½

The present report does *not* include patients who were treated for less than 18 months. Accordingly, the possibility that the present results may not be applicable to patients who remained in treatment for shorter periods must be examined in subsequent analyses.

General Procedure

The aim is to examine the efficacy of a regimen of 3,000 mg of niacin daily when administered under double-blind conditions as a supplement to whatever psychotropic medication or other treatment might be recommended by the physician. To encourage uniformity, thioridazine was recommended as the primary neuroleptic medication, but the treating physician was not held to this.

The efficacy of 3,000 mg of niacin was judged on a comparative basis by using a control sample of patients who received 6 mg of niacin per day, a quantity within normal daily requirements. Male Admission Ward patients identified as suitable by the project staff were assigned in an unbiased double-blind manner to either the high-niacin or the control group in a 60 to 40 ratio. Medication was packaged for the individual patient by the hospital pharmacist who followed a prepared assignment schedule and protected the doubleblind condition. All patients initially received 500 mg of niacin per day. Consequently, all who were susceptible to the flush that often accompanies large *initial* quantities of niacin could have this experience, and the double-blind conditions were thereby protected. The dosage was gradually increased for the patients receiving the megavitamin regimen and decreased for those receiving the control regimen. Each attained his assigned dosage level by the beginning of the second week.



Comparison of pretreatment WPRS symptom profiles (based on standard factor scores) for schizophrenic males and depressed females.

The general procedures provided three functions. The first and most essential was to maintain the patient in treatment to a maximum of 24 months. The labile condition of the patients, combined with current policies which tend to minimize inpatient care, meant that most patients left the hospital after relatively few weeks, and treatment was continued on an outpatient basis for the remainder of the scheduled period. The sustained interest and the cooperation of the patient, of his family if he were living at home, or of his associates if he were in a family care unit were necessary. A social worker called at the patient's home at approximately monthly intervals and talked to family informants and others about the patient's progress, about his use of medication, and about any particular problems or specific incidents that were relevant to the patient's circumstances or the family's reaction to the niacin program. In this way, the interest of the family was maintained, and an independent assessment of the patient's progress and cooperation with the treatment regimen was made.

The second function of the general procedures was to provide assessments of the patients prior to treatment and at intervals during the course of treatment. The assessments were designed to reflect three major areas in which mental disturbance may find expression: symptomatic developments observable by others, subjective discomfort as reported by the patient, and the quality of home and community adjustment as reported by the patient's family or other close associates. Major assessments were conducted every six months. In addition, each month the patient visited the outpatient clinic, where he was examined by the psychiatrist, interviewed by the nurse who collected the samples necessary for the laboratory tests, and tested and interviewed by the psychologist. On the basis of their respective observations, the WPRS short form was used by psychiatrist, nurse, and psychologist, independently. In addition, the nurse also used a special nurse's rating scale.

A third function was to protect the patient from any untoward effects. At the time the project was initiated, the literature provided very little information concerning the kinds of untoward reactions that might accrue from high-dosage medication of niacin over a long period of time. As a consequence, a comprehensive battery of laboratory tests was conducted at least every six weeks, usually on the occasion of the monthly visits to the outpatient clinic.

The present report is based on the WPRS (long form), the Rutgers Nurse's Rating Scale, Today's Mood Inventory, the Social Worker's Basic Data and Annual Follow-up Inventories, the Social Worker's Monthly Home Visit Inventory, and the Treatment Log. The WPRS long form was applied before treatment and at months 6, 12, 18, and 24. The Rutgers Nurse's Rating Scale and Today's Mood Inventory were completed before treatment and at

months 12 and 24. The Social Worker's Basic Data Inventory provided the baseline for the Social Worker's Follow-up Inventory, which was conducted at 12 and 24 months. The Social Worker's Home Visit Inventory was descriptive of the current behavior of the patient and was completed at monthly intervals. In addition to the usual hospital records, the standard Treatment Log was maintained on a monthly basis. Other factors, particularly attrition rate, duration of hospitalization, incidence of rehospitalization, use of tranquilizers, and changes in weight and vital signs, are of clinical interest and were examined as a part of the comparative scrutiny of the data.

Results

The results of the analyses that are currently available may be presented under three general headings: general changes of a clinical nature, symptom ratings and self-report inventories, and home and community adjustment.

General Changes of Clinical Interest.—The 75 patients who completed 24 months of treatment were a residuum of an original sample of 140 patients whose treatment was not arbitrarily concluded by the termination of the project. Of this original group, 60% continued in treatment through the first 12 months, and 54% continued in treatment throughout the 24-month period. The attrition appeared to be slightly greater in the control group than in the experimental group, but the small differences were not statistically significant. The analysis of the causes of attrition (Table 3) suggests that relatively more control patients than experimental patients were uncooperative; this difference does not meet the criterion for statistical significance.

A relatively larger portion of the experimental group was in the hospital at the close of each successive month. This difference between the treatment groups was apparent at the end of the first month when 27 (57%) of the 47 experimental patients were in the hospital, while 13 (46%) of the 28 control patients were in the hospital. At the end of the 12th month, 11 (24%) of the experimental group were in the hospital, while five (18%) of the control group were in the hospital. This difference continued throughout the course of treatment, but did not meet the criterion for statistical significance.

Because of the current policy of encouraging patients and their families to seek an outpatient adjustment, a substantial portion of patients leave the hospital only to return within a year or two. It was anticipated, therefore, that the incidence of rehospitalization would be sufficiently great in the control group to show an interesting contrast with the experimental group if, indeed, niacin were effective in improving the adjustment in the community and in reducing the incidence of recurrence.

When the number of patients who were rehospitalized during the course of treatment was examined, no difference between the treatment groups was found. Twenty [illegible] of the experimental group had been rehospitalized at least once; in the control group 12 (also 43%) had been rehospitalized at least once. The rehospitalizations occurred at any time between the second and the 24th month. The median month for rehospitalization was 12, and there were no significant differences between the treatment groups with respect to the time of rehospitalization.

Most of the patients required major tranquilizers throughout the period of treatment, but this factor failed to discriminate significantly between the treatment groups. Specifically, at the end of the first month, 87% of the experimental and 96% of the control group were receiving a major tranquilizer. At the end of the 12th month, the respective percentages were 77% and 89%, and at the end of the 24th month, 74% and 75%. Some of the patients received less than the standard dosage, but this factor also failed to be discriminating. It may be noted, however, that in both the experimental and the control groups there was a diminution in the percentage of patients requiring tranquilizer treatment at the end of the successive years.

Table 3.—Attrition From All Causes Except Arbitrary Termination at Close of Project

	Experimental	Control
No. uncooperative	20	21
No. moved	9	3
No. medical	7	5
(SGOT)	(1)	(1)
(Glucose)	(2)	(2)
(Pigmentation)	(3)	(0)
(Death)	(1)	(1)
(Neurological)	(1)	(1)
Totals	36	29

After the second month, both groups showed statistically significant increments in body weight. At the end of 24 months, the experimental subjects had gained 8 lb from a pretreatment average of 173 lb to an average of 181 lb. During the same period, the control group gained 11 lb with average weights increasing from 168 lb to 179 lb, but the difference between the two treatment groups with respect to the average increment in weight was not statistically significant.

Summaries of the monthly determinations of systolic and diastolic blood pressure were available also. There was virtually no change in systolic blood pressure, but there was some slight indication of reduction in diastolic blood pressure which reached a criterion for significance on a few occasions. The 24-month reduction in the experimental group was from a pretreatment 78 to 72, and in the control group from a pretreatment 79 to 71. The monthly differences between the two groups were not consistent.

Symptoms and Self-reports.—In the analysis of the data from the WPRS, the Rutgers Nurse's Rating Scale, and the Today's Mood Inventory for tension, a correction was always made for pretreatment differences. Specifically, any portion of a treatment score that could be predicted on the basis of the respective pretreatment score was calculated and removed. Thus, the significance of any differences that occurred during the course of treatment was based on residual scores corrected for individual differences in pretreatment scores. Parallel analyses were made for the total sample of 86 patients and for the selected subsample of 42 patients. These analyses were mutually confirmatory, and a presentation of both sets of analyses would be redundant. Since treatment was uninterrupted and the diagnosis of schizophrenia was not questioned in the selected subsample, the discussion of symptoms and

Table 4.—WPRS Raw Factor Score Means for Selected Subsample at Pretreatment, 6, 12, 18, and 24 Months

WPRS Symptom Factors	Pre (N=42)	6 (N=42)	12 (N=42)	18 (N=42)	24 (N=36)
1. Anxiety					
Experimental means	5.94	4.62	4.38	4.32	3.18
Control means	5.88	4.08	3.82	4.14	3.60
t*	.05	.73	.77	.20	−.68
2. Hysterical conversion					
Experimental means	1.77	.60	.54	1.17	.27
Control means	1.05	.99	.90	.69	.06
t*	1.34	−1.37	−.92	.36	.58
3. Manic state					
Experimental means	3.64	1.76	2.00	2.08	2.24
Control means	2.76	2.16	3.12	2.24	1.88
t*	1.41	−.98	−3.02	−.81	.47
4. Depressive retardation					
Experimental means	18.60	14.70	16.80	16.35	14.55
Control means	18.00	10.80	12.45	14.25	13.35
t*	.36	1.74	1.75	.81	.59
5. Schizophrenic excitement					
Experimental means	7.84	4.16	5.12	5.68	3.44
Control means	6.16	2.64	3.28	3.68	3.20
t*	1.62	1.55	1.56	.96	.06
6. Psychotic belligerence					
Experimental means	6.39	3.42	4.05	4.59	2.88
Control means	5.13	3.87	3.51	4.23	4.05
t*	.81	−.77	.73	.38	−1.87
7. Paranoia					
Experimental means	4.72	1.92	2.64	2.24	1.76
Control means	4.64	2.16	2.16	2.24	2.28
t*	.08	−.49	.79	.00	−.70
8. Hebephrenia					
Experimental means	5.85	3.33	3.51	4.41	2.70
Control means	4.95	2.16	2.79	3.51	2.34
t*	.91	1.56	.71	.75	.26
9. Compulsive-obsessive					
Experimental means	6.54	4.80	5.28	4.74	4.02
Control means	4.98	3.60	3.66	3.78	3.18
t*	1.61	.84	1.28	.57	.90
10. Intellectual impairment					
Experimental means	2.56	1.68	2.08	2.04	1.72
Control means	2.20	1.12	1.36	1.40	.96
t*	.60	1.13	1.40	.88	1.94
11. Homosexual dominance					
Experimental means	3.05	2.05	1.95	1.90	1.85
Control means	2.65	2.25	2.10	2.05	1.45
t*	.53	−.97	−.59	−.56	1.01
12. Ideas of grandeur					
Experimental means	2.24	1.00	1.08	.68	.96
Control means	1.92	.76	1.40	1.16	1.12
t*	.47	.54	−.88	1.52	−.46

* t is the statistic for significance of the difference between 6-, 12-, 18-, and 24-month treatment group means (Experimental − Control) computed after correction for pretreatment individual differences, ie, on the basis of residual scores.

self-reports will be limited to the findings for this subsample.

Observations and ratings required by the WPRS were made independently by the psychiatrist, the psychologist, and the nurse. For each of the 72 scales of the WPRS, the three sets of ratings were reconciled to generate a composite rating for each patient. Such composite ratings have a broader observational basis than ratings made by a single individual and are considered to be generally more reliable and valid than ratings from one rater.

The reconciled ratings for the set of 72 rating scales were scored in the usual manner to generate 12 symptom factor scores. The symptom factor scores on the WPRS may be stated in either a raw or a standardized score form. The raw score is simply the sum of the ratings for the scales comprising the factor. Although these raw scores are not suitable for interfactor comparisons, they are quite sensitive and even minor differences in raw scores for a given factor may be found to be statistically significant. The standardized scores are designed to facilitate a comparison between the factors or symptom complexes. For this purpose, the raw scores are referred to a standard scale of ten units. Since these ten units span the total range of psychopathological deviation, they are relatively coarse and cannot reveal minor differences. Thus, although the standard scores are useful to document a

Table 5.—Discriminating WPRS Items for Selected Subsample at Pretreatment, 6, 12, 18, and 24 Months

WPRS Item	Pre (N=42)	6 (N=42)	12 (N=42)	18 (N=42)	24 (N=36)
2 Failure and blocking					
Experimental means	1.64	1.50	1.45	1.27	1.22
Control means	1.50	1.40	1.20	1.25	1.33
t*	.66	.25	1.03	−.10	−.57
5 Flaccid face					
Experimental means	1.05	1.00	1.18	1.05	1.06
Control means	.90	.75	.55	.45	.61
t*	.54	.99	2.30	2.70	2.04
6 Nosy					
Experimental means	.95	.53	.59	.55	.44
Control means	.90	.75	1.05	.75	.39
t*	.26	−1.26	−2.62	−1.07	.25
14 Avoids people					
Experimental means	1.68	1.77	1.45	1.55	1.44
Control means	1.75	1.45	1.20	1.25	1.28
t*	−.29	1.71	1.19	−.34	1.02
15 Will not help others					
Experimental means	1.41	1.42	1.55	1.23	1.22
Control means	1.45	.94	1.00	1.35	1.11
t*	−.18	2.90	2.24	−.43	1.02
17 Participation apathetic					
Experimental means	1.68	1.47	1.55	1.50	1.06
Control means	1.60	1.13	1.10	1.10	1.17
t*	.34	1.65	1.96	1.97	−.57
20 Words not relevant					
Experimental means	.91	.36	.27	.59	.39
Control means	.65	.05	.00	.20	.22
t*	1.03	2.20	1.78	1.61	.95
32 Unaware of others' feelings					
Experimental means	1.23	1.00	1.09	.86	.94
Control means	1.05	.75	.75	1.00	.78
t*	1.01	1.19	1.57	−.95	.66
33 Restless and distractible					
Experimental means	1.68	1.42	1.36	1.45	1.11
Control means	1.55	.88	1.05	1.20	1.17
t*	.64	2.55	2.51	1.10	−.40
36 Tics or grimaces					
Experimental means	.68	.58	.73	.73	.44
Control means	.75	.44	.40	.50	.39
t*	−.31	1.16	2.22	1.44	.46
41 Little recent memory					
Experimental means	.86	.63	.73	.64	.56
Control means	.75	.38	.35	.50	.22
t*	.49	1.35	1.61	.46	1.76
66 Critical of others					
Experimental means	1.18	.89	1.00	.91	.83
Control means	1.00	1.00	.90	1.00	1.06
t*	85	−.63	.83	−.58	−2.12
68 Uncontrollable obsessions					
Experimental means	1.55	1.32	1.36	.95	.72
Control means	1.25	.80	.70	.80	50
t*	1.05	1.88	2.10	.45	77

* t is the statistic for significance of the difference between 6-, 12-, 18-, and 24-month treatment group means (Experimental − Control) adjusted after correction for pretreatment individual differences, ie, on the basis of residual scores.

pattern or a profile of differences within an individual or a group, they may not reveal the statistically significant, but modest changes that often accompany treatment. Table 1 is based on raw symptom factor scores, and Table 5 is based on individual symptom rating scales. In both tables, a substantial diminution in level of pathology within treatment groups may be noted over the course of treatment. For the present purposes, however, comparisons between treatment groups are the primary interest.

WPRS raw factor scores based on ratings made before treatment and at 6, 12, 18, and 24 months of treatment are summarized for the selected subsample in Table 4. In all comparisons, the control group means were subtracted from the experimental group means, and a t with a positive sign indicates that the experimental group was showing the greater abnormality while a t with a negative sign indicates that the greater abnormality was in the control group. There are 60 comparisons in Table 4. Forty-eight of

Table 6.—Rutgers Nurse's Rating Scale Items Which Distinguish Between the Treatment Groups at the .10 Level of Significance (Selected Subsample)

Item	Pre (N=42) t*	12-Month (N=42) t*	24-Month (N=36) t*
Good posture	.17	−3.27	1.44
Appropriate attire	−.71	−1.97	−.21
Concern for appearance	−.03	−1.85	.12
Smiles appropriately	−.25	−2.58	−.45
Initiates games	.67	−3.03	.52
Likes active games	.65	−1.76	.55
Likes group games	1.70	−1.76	.13
Approaches staff	.66	−1.70	−1.06
Interest in visitors	1.99	−2.66	−.33
Starts day unassisted	.98	−2.12	.07
Retires unassisted	2.03	.00	.00
Likes "prestige" jobs	−1.91	−.16	.29
Good appetite	−.23	−2.30	1.00

* t is the statistic for significance of the difference between treatment group means (Experimental − Control) computed after correction for pretreatment individual differences, ie, on the basis of residual scores.

Table 7.—Stereotyped Denial of "Tension" in Response to Today's Mood Inventory at Pretreatment, 12 Months, or 24 Months

	Experimental	Control	Sum
Total Sample			
No. for whom data were available	42	23	65
No. with stereotyped denial response			
Before treatment	9 (22%)	4 (17%)	13 (20%)
After 12 months	16 (36%)	7 (30%)	23 (35%)
After 24 months	18 (43%)	8 (35%)	26 (40%)
Selected Subsample			
No. for whom data were available	17	17	34
No. with stereotyped denial response			
Before treatment	4 (23%)	4 (23%)	8 (24%)
After 12 months	4 (23%)	5 (29%)	9 (26%)
After 24 months	6 (35%)	5 (29%)	11 (32%)

these refer to differences during the course of treatment, and 12 refer to pretreatment differences. Thirty-one of the 48 indicate a greater abnormality for the experimental group, while 16 indicate a greater abnormality for the control group. Only one of the comparisons meets the criterion for statistical significance, however. This is for the "manic state" factor score at 12 months and indicates that the control group was more manic than the experimental group at that assessment period. One significant t out of 48 could have occurred by chance, however, and does not alone provide an adequate basis for a conclusion.

The experimental and the control groups were compared in terms of each of the 72 scales comprising the WPRS, and this set of comparisons was conducted for both the selected subsample and the total sample at each of the assessment periods. In the course of these two sets of comparisons, 13 of the scales provided a significant discrimination on at least one occasion. Table 5, based upon

Table 8.—Mean Tension Scores for Patients Without Stereotyped Response to Today's Mood Inventory

	Experimental N	Experimental $\bar{X}$	Control N	Control $\bar{X}$
Total Sample				
Before treatment	(22)	66	(12)	69
After 12 months*	(21)	53	(12)	46
After 24 months*	(22)	51	(12)	43
Selected Subsample				
Before treatment	(10)	49	(9)	65
After 12 months*	(10)	39	(9)	46
After 24 months*	(10)	48	(9)	44

* Covariance analyses reveal no significant differences between the treatment groups.

the selected subsample, provides a complete set of average ratings for each of these 13 scales. Of the 65 comparisons summarized in Table 5, 52 are based on ratings made during the course of treatment. For 39 of these, the difference in direction is for greater abnormality in the experimental group, and 13 are in the direction to indicate greater abnormality in the control group. Twelve of the 52 comparisons based on ratings during treatment meet the criterion for statistical significance. Two of these significantly differentiating scales, "nosiness" (12th month) and "critical of others" (24th month), indicate the greater abnormality in the control group. The other ten significant differences show the greater abnormality in the experimental group.

One of the assessments in the present study was made on the basis of the Rutgers Nurse's Rating Scale, comprising 25 items which were not primarily symptomatic in their significance. These items described qualities of behavior of particular concern to nurses, and each was examined in the present set of comparisons. The items which discriminated between the two treatment groups at the .10 level in the selected sample, whether the discrimination occurred at 12 months or 24 months, are listed in Table 6. All the differences at the 12th month are in a direction to indicate less desirable responses in the experimental group. Six of these are significant at the .05 level. The differences at the 24th month are not marked or consistent.

Although the observable symptomatic aspects of mental illness are central to both our concept of mental illness and to practical implications, the discomfort which often accompanies psychic disorders cannot be disregarded. The Today's Mood Inventory, a self-report of tension, was included in the expectation that the responses it required would be within the competence of most patients and would elicit from them a report which could be used in the present comparison of the experimental and the control groups. Self-descriptive inventories are used at some risk with mental patients, particularly schizophrenics, because some patients may not provide a complete set of responses to the questions and because some patients tend to resort to a form of response which is monotonously stereotyped, if not meaningless. Such limitations introduce complications in the analysis of the data.

The Today's Mood Inventory comprises a set of 117 items descriptive of various aspects of tension. The pa-

tient was requested to mark each item as "true," "partly true," or "not true." A scrutiny of the patients' responses at pretreatment testing, at the end of one year, and at the end of two years revealed that some patients did, indeed, approach the inventory in a stereotyped manner. This stereotyped pattern may have a defensive denial, or it may have been merely a positional response. If a patient marked as many as 111 of the 117 statements as "not true," his response to the inventory was regarded as a stereotyped denial. The portion of patients in the experimental and control groups responding with a stereotyped denial of tension is indicated in Table 7 for the three assessment periods for which the inventory was used. It may be seen that the number of patients offering a stereotyped denial increased during the course of treatment, but the difference between the treatment groups was not statistically significant.

The responses of most patients were free from stereotypy, and for these individuals the inventory was scored to yield a measure of tension. The analyses of these scores are summarized in Table 8. An inspection of this table suggests that the greater reduction in tension during the course of treatment occurred in the control group. Nevertheless, both residual score analyses and analyses of covariance failed to reveal a significant difference between the treatment groups.

Home and Community Adjustment.—Although the quality of the patient's home and community adjustment is no less important than his symptomatic developments and his subjective state, formal assessments of home and community adjustment have traditionally received less attention than formal assessments by symptom ratings and self-reports. In the present inquiry the quality of the patient's adjustment outside the hospital and away from the clinic was examined on the basis of inventories used by the social worker to record the observations and information gathered on the occasion of home visits.

The effect of niacin may be examined from the standpoint of two questions for which home and community adjustment information are relevant. Specifically, the home and community adjustment information may be used to examine the possibility (1) that the continued high dosage of niacin results in some change in the patient's personality or (2) that high dosage of niacin is associated with changes in the quality of home and community adjustment per se.

There are many relevant facets of the personality and an almost endless variety of devices for assessing them. At the time of an episode of acute disturbance, however, expressions of personality, and probably other expressions as well, are either distorted or obscured. Thus, a pretreatment assessment based on behavior at the time treatment is undertaken may be appropriate for gauging changes that are a part of remission, but such an assessment does not provide an appropriate baseline for gauging changes in the personality. As a consequence, the question of personality change in the course of therapy must be examined on the basis of premorbid descriptions provided by family informants.

The basic data information gathered by the social worker at the beginning of treatment refers to the informant's observations and impressions of the patient's personality prior to the episode, and this information provided the baseline for observations and impressions at 12 and 24 months of treatment. The inventory forms used by the social worker on these various occasions included 46 common items of information perceptible to family informants and indicative of expressions of the personality. These 46 items were in standard format, and the relative incidence of "favorable" answers was examined for each item separately. There were 15 items for which the incidence of a "favorable" answer changed at least 12% and as much as 40% from the baseline to the end of treatment. Although significance is not claimed for all such changes, the nature of the items showing change and the direction of the changes are of interest.

Both the experimental and the control groups showed certain changes which might be viewed as a natural social consequence of recent hospitalization. Specifically, relative to their premorbid state, fewer were supporting themselves, fewer were seeing their relatives frequently, and fewer were maintaining their friendships. Other changes that would suggest a somewhat more expressive and less suppressive, cautiously defensive posture were also found in both groups. For example, more of the patients were disposed to argue when criticized, fewer were disposed to deny it when upset about something, and fewer were disposed to keep their feelings to themselves. In addition, fewer of the patients were wakeful.

Some changes were apparent in the experimental group only. Most of the items involved in these changes suggested that after niacin treatment the experimental patients showed some diminution in their sense of responsibility. For example, after treatment more of the experimental group of patients blamed others for their mistakes, and more of them displaced their anger. In addition, fewer denied their anger, and more of them procrastinated. The reports also indicated that fewer of the experimental patients took pride in their appearance, more were willing to throw things away, and fewer were devout. After treatment more of the experimental patients lacked confidence, and more of them complained of not feeling well.

The foregoing description of the trends in the social worker's data is based on the total sample of patients. When the data for the smaller selected subsample were examined, trends were diminished, but not reversed.

In addition to the comparative study of possible changes in personality, the quality of the home and community adjustment per se was examined from the standpoint of differences between the treatment groups. For this purpose an inventory was used to elicit information from family informants at the time of the social worker's monthly visit to the patient's home. This inventory, which comprised 42 items, was developed after the study was underway and the task of continuous outpatient monitoring and assessment could be clearly seen. The items were designed to represent the problems of maintaining male schizophrenics in an outpatient situation and in substantial degree were based on the kinds of complaints and difficulties that were associated with the patient's admission to the hospital.

To provide some basis for summarizing these 42 items gathered at each month, a factor analysis was made. Four factors were generated. The first factor, designated "a problem to the family," comprised such items as "a concern to the neighbors," "does not cooperate with household," "speech inappropriate," "is distressing or embarrassing to family." The second factor, designated "self-sufficient," represents such items as "participates in activities with others outside the home," "leaves the premises unescorted," "drives an automobile," "shops by himself." The third factor, "antisocial," includes "gets involved with police," "gets into bad company," "steals or pilfers." The fourth factor, "cooperates with treatment," includes "keeps appointments," "takes his tranquilizer," "has a positive attitude toward niacin."

Scores for these factors were computed for each monthly home visit and were analyzed for both the total sample and the selected subsample. There was a general trend toward improvement in both treatment groups, but very few of the many between-treatment-group differences met the .05 criterion for statistical significance. In most of the many comparisons, however, the direction of difference between the treatment groups would suggest that the home and community adjustment had become more favorable in the control group than in the experimental group.

Comment

The present account is limited to those criteria for which analyses were first completed. General improvement over the course of two years was indicated by both clinical developments and changes in the scheduled assessments. In view of the great amount of attention and helpful reassuring support that the patients and their families received from the project staff, general improvement is not surprising. Unfortunately, careful comparative analyses of the data revealed very little difference between the responses of the two treatment groups and no definite indication of a therapeutic advantage for the supplemental use of niacin over the course of two years. Despite the reassuring clinical observations of Hoffer and others, the present findings challenge claims of general efficacy for a two-year regimen of niacin supplementation in the treatment of schizophrenia.

Although the expected indications of disturbed carbohydrate metabolism and gastroenteritis did not appear in the course of the present study, a substantial portion of the sample developed a pigmented hyperkeratosis which in some cases bore a disturbing superficial resemblance to acanthosis nigricans.[9,10] Although this accompaniment of high-dosage niacin treatment had been described in the medical literature,[11,12] it had not been described for psychiatric patients. Reasons for the prevalence of pigmentation in the present sample are not known. The niacin was provided by Squibb, and the basic chemical was manufactured by Cobb-Warner. Special analyses of samples used by the patients were conducted by Squibb, and the methods of handling and preparing the material were reviewed. No foreign substances or unusual circumstances were found.

This pattern of pigmentation tended to be limited to parts of the body covered by clothing and was most conspicuous in moist areas. It is possible that it is unreported by most mental hospital patients and therefore overlooked. According to some outpatients, it is possible to remove the accumulated darkened skin by vigorous scrubbing. This pattern of pigmentation occurred in about one third of the patients in the experimental group and tended to develop after several months of continued high dosage. The nature of the concomitant psychotropic medication was examined, and it was found that pigmentation occurred in patients who were receiving phenothiazines as well as in those who were not.

The possibility that pigmentation might be associated with some generally adverse response to treatment was explored by conducting independent analyses comparing the therapeutic response of niacin-treated patients who were never pigmented with that of the control group. These analyses revealed no indication of therapeutic efficacy in patients who were receiving niacin and were free from pigmentation.

The present assessment of niacin as a supplement in the treatment of schizophrenia was conducted with patients considered to be representative of those for whom niacin treatment could be recommended. The numerous criteria used were selected because of their practical clinical significance and obvious face validity. The size and composition of the sample, combined with the diversity of the criteria, confer great pertinence on the present findings and are discouraging to the expectation that a general two-year regimen of niacin supplementation will be an important aid in the treatment of the great mass of schizophrenic patients who currently come to public hospitals.

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Nonproprietary and Trade Names of Drug

Thioridazine–*Mellaril*.

References

1. Hoffer A, et al: Treatment of schizophrenia with nicotine acid and nicotinamide. *J Clin Exp Psychopathol* 18:131-158, 1957.
2. Hoffer A: *Manual for Treating Schizophrenia and Other Conditions Using Megavitamin Therapy*. Saskatoon, Canada, Modern Press, 1968.
3. Ananth JV, et al: Nicotinic acid in the prevention and treatment of methionine-induced exacerbation of psychopathology in schizophrenics. *Can Psychiatry Assoc J* 15:15-20, 1970.
4. Ashby WR, Collins GH, Bassett M: The effects of nictotinamide and placebo on the chronic schizophrenic. *J Ment Sci* 106:1545, 1960.
5. Ban TA: *Nicotinic Acid in the Treatment of Schizophrenias*. Toronto, The Canadian Mental Health Association, 1971.
6. Ban TA, Lehmann HE: *Nicotinic Acid in the Treatment of Schizophrenias*. Toronto, The Canadian Mental Health Association, 1970.
7. O'Reilly PO: Nicotinic acid therapy and the chronic schizophrenic. *Dis Nerv Syst* 16:3, 1955.
8. Ramsay RA, et al: Nicotinic acid as adjuvant therapy in newly admitted schizophrenic patients. *Can Med Assoc J* 102:929-942, 1970.
9. Brown J, Winkelmann RK: Acanthosis nigricans: A study of 90 cases. *Medicine* 47:33-51, 1968.
10. Tromovitch TA, Jacobs PH, Kern S: Acanthosis nigricans-like lesions from nicotinic acid. *Arch Dermatol* 89:222-223, 1964.
11. Christensen NA, et al: Nicotinic acid treatment of hypercholesteremia. *JAMA* 177:76-80, 1961.
12. Parsons WB Jr, Flinn JH: Reduction of serum cholesterol levels and beta-lipoprotein cholesterol levels by nicotinic acid. *Arch Intern Med* 103:783-790, 1959.

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NICOTINIC ACID AND NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD) THERAPY IN SCHIZOPHRENIA: A REVIEW

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ABSTRACT

A brief review of the available literature on studies of nicotinic acid, nicotinamide, and NAD therapy in schizophrenia shows few studies other than those performed by Abram Hoffer and his associates. Besides Hoffer, all other investigators except Denson have found little or no therapeutic value for nicotinic acid or NAD in the treatment of schizophrenia. However, all published attempts to duplicate Hoffer's results have dealt with cases of chronic schizophrenia, whereas Hoffer's studies report the effect of the vitamin on early schizophrenia. We conclude that further controlled studies should be made using nicotinic acid or NAD in the treatment of early schizophrenia, since there is virtually no negative evidence to refute the use of nicotinic acid as a positive adjunct in the treatment of acute schizophrenia. According to the available literature, the use of nicotinic acid in the treatment of chronic schizophrenia, would not seem to be of significant value and—save for Hoffer's study—NAD has also been reported to have little therapeutic value.

In 1952, Abram Hoffer (*1*) began his first clinical evaluations of the usefulness of nicotinic acid in the treatment of schizophrenia. He has subsequently conducted several other studies on the effectiveness of this vitamin and its amide, nicotinamide, in improving the clinical condition of the schizophrenic patient; in fact, Hoffer's studies far outnumber all other papers combined on the subject, and controlled studies on the subject, other than Hoffer's, are few in number, although several investigators have attempted to either support or disprove his findings. However, nowhere in the literature has there been a review of these studies in an attempt to evaluate individual as well as collective validity and results. In this paper, we will review the published studies and correlate the findings of each into an overall statement on the effectiveness of niacin therapy in the treatment of schizophrenia.

The basis for using nicotinic acid therapy in schizophrenia is almost entirely empirical. No one knows why nicotinic acid or its amide controls the disease, if indeed it does control it. The potential of nicotinic acid in psychiatry was first suggested by the observation of psychosis in certain patients suffering from pellagra. Abram Hoffer (*1*) was the first to investigate on a large scale the effect of this vitamin on psychotic individuals who had no apparent vitamin deficiency. Hoffer and Humphry Osmond (*1*) have, in the ensuing years, formulated the adrenochrome hypothesis, which predicts the presence in schizophrenic patients of chemical substances that inhibit the conversion of adrenochrome, a psychotomimetic, and a postulated metabolite of epinephrine, to nonpsychotomimetic substances (leuco-adrenochrome). Thus, the amount of adrenochrome available for conversion into adrenolutin, which is psychotomimetic, is increased in schizophrenia. Nicotinic acid, a methyl acceptor, if used in large quantities would compete with norepinephrine for methyl

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groups and thus decrease the production of the psychotomimetic substance, adrenolutin. Although this theory is intriguing, solid evidence in its support has not yet been published. Still, it has not been disproved and has been used as the rationale for niacin therapy.

Ananth, *et al.* (*2*), in 1970 were able to exacerbate schizophrenic psychopathology by administering methionine, a methyl donor, and tranylcypromine, a monoamine oxidase inhibitor. This report might lend some support to a biochemical basis for schizophrenia. Nicotinic acid in doses of 3 gm/day, however, failed to prevent by prior administration or to relieve by subsequent administration the methionine-tranylcypromine- induced exacerbation in schizophrenic psychopathology. This failure was interpreted to be due to inadequate dosage of nicotinic acid given. A possibility of a toxic psychosis due to the metabolite, methionine sulfoximine, was raised.

Linus Pauling (*3*), the Nobel Prize-winning chemist, has suggested that in schizophrenia (and other mental disorders as well) there is a less than optimum concentration (a deficiency) of certain substances normally present in the brain as a result of a physiological abnormality induced by a "gene for schizophrenia." This may decrease the permeability of the blood-brain barrier for certain substances or increase the rate of cerebral metabolism of certain substances, and thus cause a selective central nervous system deficiency. He concludes that orthomolecular therapy (increasing to the optimum the concentrations of these important substances in the brain) may be the treatment of choice in certain mental illnesses.

NICOTINIC ACID STUDIES

The first published paper on the use of nicotinic acid in schizophrenia was by O'Reilly (*1*) in 1955. He administered 3 gm per day of nicotinic acid to 11 chronic schizophrenics over a period of 8 weeks. He also observed a control group of 43 chronic patients but administered no placebo and used no other blind techniques. Three of the treated patients showed some behavioral improvement; however, other schizophrenic features (delusions, hallucinations, etc.) remained unchanged. There is no mention in this study of the concomitant use of neuroleptic agents.

Hoffer's (*5*) research contribution, first published in 1957, began in 1952 with a small, double-blind study involving 30 schizophrenic patients, 21 of whom received 3 gm of nicotinic acid for a period of 30 days. The control group of 9 patients received placebo capsules. Both groups received concomitant psychotherapy, sedatives, insulin shock, and electroshock therapy (EST). A two-year follow-up revealed an improvement in 13 of 21 treated patients (61%) and in 3 of 9 control patients (33%).

Hoffer (*5*) also started a larger double-blind study in 1952 involving 171 patients divided into two randomly selected groups, one group using nicotinic acid or nicotinamide along with psychotherapy, sedatives, insulin shock, and EST, the other group receiving identical treatment without nicotinic acid. A placebo was given to some members of the control group. The treatment group received the nicotinic acid both on an inpatient and outpatient basis, and a five-year follow-up was carried out on both groups. Results of the study showed the treatment group to have significantly fewer readmissions to the hospital than the control group (21 of 74 or 28% in the treatment group, 56 of 97 or 58% in the control group). Also, when nicotinic acid was discontinued in the treatment group, the readmission rate began to approach that of the control group.

In 1953, another double-blind study was begun by Hoffer (*1*). This study involved 82 patients divided at random into two groups. Group A, 39 patients, received EST, barbiturates, psychotherapy, and nicotinic acid or nicotinamide, 3 gm/day for 33 days. Group B, 43 patients, received similar therapy with a placebo replacing the nicotinic acid. Hoffer found significantly greater improvement in the nicotinic acid group. A follow-up survey was conducted on some of these patients in 1959 (*1*), using readmission to the hospital and length of hospital stay as comparison criteria; this follow-up indicated that 20 placebo patients required 16 readmissions for a total of 9.1 years and an average stay of 207 days. However, 25 nicotinic acid patients required 9 readmissions for a total of 2.5 years and an average stay of 106 days.

Denson (*6*), in 1962, published a study in which he administered nicotinamide on a schedule of 3 gm/day for 5 weeks to a randomly selected group of 17 newly admitted male schizophrenic patients (Group A). He also administered an equal amount of placebo to a randomly selected group of 19 newly admitted male schizophrenic patients (Group B). Patients were handled by their own physicians as if they were not on a study. The staff did not know which pills contained nicotinamide and which pills were placebo. The patients were evaluated on the

basis of duration of stay in the hospital. The results showed that Group A patients spent a total of 1810 days in the hospital (average, 106.5 days each) during the first year following entry. Group B patients spent a total of 3373 days in the hospital (average, 177.5 days each) during the first year. However, it is interesting to note that although the patients in this study were picked randomly, only 2 of 17 patients in Group A had had 3 or more previous admissions, whereas 7 of 19 patients in Group B had had 3 or more previous admissions. The chronicity of the Group B patients would seem to favor Group A patients leaving the hospital sooner.

Another study by Hoffer (*7*) was conducted using patients of psychiatric staff members not directly involved with his research group, at the University Hospital, Saskatoon, Saskatchewan, between 1956 and 1962. Patients were divided into three groups, depending on the frequency of nicotinic acid use by the treatment staff. The 76 schizophrenic patients who received nicotinic acid along with other conventional therapy required a total of 2453 hospital treatment days over a seven-year period for an average of 5 days/patient/year. The 226 patients treated with standard tranquilizers, EST, and psychotherapy, but no nicotinic acid, required 25,341 total hospital treatment days over seven years for an average of 16 days/patient/year.

Hoffer (*7*) in 1964 reported a ten-year follow-up of 43 clinically diagnosed schizophrenics, 16 of whom were placed on at least 3 gm of nicotinic acid or nicotinamide for at least 33 days. Concomitant therapy, such as EST, psychotherapy, and barbiturates was allowed. A comparison group of 27 patients received only EST, barbiturates, and psychotherapy. No placebo was given. There were no phenothiazines available at the time the study was started. Comparison of the two groups was based on readmission to the hospital. The results showed that 12 of 16 treatment group patients (75%) did not require readmission for ten years. Ten of 27 comparison group patients (36%) did not require readmission for ten years. Also, total time in hospital on readmission was much less for nicotinic acid patients.

Ramsay, *et al.* (*8*) in 1970 divided 30 newly admitted schizophrenic patients into three equal of 10 patients each. All patients received standard phenothiazine treatment. One group received placebo, another received nicotinic acid 3 gm/day and the last group received nicotinamide 3 gm/day. Duration of treatment was six months. The addition of nicotinic acid or nicotinamide to the regular phenothiazine treatment regimen did not have any measurable therapeutic effect in this sample of patients.

In summary, nine studies of nicotinic acid therapy in schizophrenia (Table I) have been published, six of which [the six studies by Hoffer, *et al.* (*5*)] showed nicotinic acid to be beneficial, two [the O'Reilly (*4*) and Ramsay, *et al.* (*8*) studies] which showed nicotinic acid not to be beneficial, and one (the Denson (*6*) study) which was equivocal. Of these nine studies, with a total of 830 schizophrenic patients, an improvement was shown in 225 of 306 patients (73.5%) treated with nicotinic acid. However, in a control group total of 469 patients, 193 (41.2%) showed improvement. The chronicity of these patients ranged from 0 to 22 years. Nicotinic acid or nicotinamide was administered in these studies in amounts from 1 to 3 gm and over periods of time ranging from 30 days to 6 years. Follow-up varied from none to 10 years, and study controls ranged from none to placebo double-blind. It must also be noted that several patients in Hoffer's studies have been used in more than one study.

Recently, there have been attempts at the use of nicotinamide in the treatment of severely disturbed children. Roukema and Emery (*9*) reported giving 1 gm of nicotinamide per 50 lb of body weight to 9 severely emotionally disturbed children (8 childhood autism, 8 childhood schizophrenia, 2 severe anxiety, and 1 chronic brain syndrome with grand mal epilepsy). The patients were treated with nicotinamide for 12 months (two children with a diagnosis of autism and two children with a diagnosis of schizophrenia terminated after seven months). There was no control group. Although in the early treatment phase some parents observed what they felt to be improvement in behavior, improvement was transient, and after one year of treatment, the staff and consultants working with these children felt there was no significant improvement in their motor or mental behavior.

Greenbaum (*10*) reported in 1970 on a study in which 57 schizophrenic children (ages 4 to 12) were divided into 3 groups: One group (17 patients) received niacinamide, the second group (16 patients) received niacinamide plus a tranquilizer, and the third group (24 patients) received placebo. The children were treated for six months, and, at the end of the study period, no significant differences were noted between the three groups.

TABLE 1

Investigator and type of study	NIC/N*	Previous hospitalization	Daily dose (gm)/day	Period of drug admin. and follow up (FU)	Results: Nic Imp/Unimp	Results: Cont Imp/Unimp
O'Reilly (1955) Pilot Study	11/54	3–22 hr	3	8 weeks No FU	3/8	No Data
Hoffer, *et al.* (1957) Double Blind Placebo Control	21/30	Unknown	3	30 days 2 yr FU	13/8	3/6
Hoffer, *et al.* (1957) Single Blind Placebo Control	73/171	Unknown	3	30 days–2 yr 5 yr FU	59/14	24/62
Hoffer (1962)-I Double Blind Placebo Control	39/82	Unknown	3	33 days No FU	31/8	18/25
Hoffer (1962)-II Double Blind Placebo Control	33/82	At least 14–179 days	1	1–6 yr 1–6 yr FU	16/17	14/35
Denson (1962) Double Blind Placebo Control	17/36	0–5 Prev. admissions	3	5 weeks 12–20 months FU	16/1	11/8
Hoffer & Osmond (1964)-I Pilot Study	76/302	Unknown	3	Unknown 7 yr FU	55/21	104/122
Hoffer & Osmond (1964)-II Single Blind Placebo Control	16/43	0–5000 days	3	At least 33 days 10 yr FU	12/4	10/17
Ramsay, *et al.* (1970) Double Blind Placebo Control	20/30	70% prev. hosp. 30% no prev. hosp.	3	6 months No FU	20/0	9/1
Total	306/830	0–22 yr	1–3	30 days–6 yr 0–10 yr FU	225/81	193/276

*NIC/N = Number of patients taking nicotinic acid or nicotinamide/total number of patients in study.

NICOTINAMIDE ADENINE DINUCLEOTIDE STUDIES

Nicotinic acid, in the form of its amide, nicotinamide, is a precursor in the synthesis of nicotinamide adenine dinucleotide (NAD), formerly termed diphosphopyridine nucleotide (DPN). In recent years, nicotinamide adenine dinucleotide, NAD, has been investigated as a therapeutic adjunct in the treatment of schizophrenia. This nicotinamide-containing nucleotide functions as a coenzyme in electron and hydrogen transfer in reversible oxidation-reduction reactions, and its therapeutic use stems from a new postulation: an NAD deficiency in schizophrenia.

In 1966, at the Carl Neuberg Society for International Scientific Relations, Hoffer (*11*) reported that he had administered diphosphopyridine nucleotide (DPN or NAD) to 17 schizophrenic patients and had found that 13 of the 17 patients improved; and, although Hoffer (*12*) had stated in 1963 that he had encountered limited, if any, success with the use of nicotinic acid in chronic schizophrenic patients, he stated, at this time, that among the 13 patients who improved with NAD, all were chronic schizophrenics.

Prompted by this statement of NAD efficacy, the American College of Neuropsychopharmacology, through the work of Kline (*13, 14*) and his associates, investigated the effect of NAD on 20 chronic male schizophrenics at Rockland State Hospital, Orangeburg, N.Y. The patients were matched as closely as possible on the basis of age, length of illness, and severity and nature of symptoms. Fourteen of the 20 patients had not received a psychopharmaceutical agent for at least 2 months. Rating and evaluation were done before and after the administration of the nicotinamide adenine dinucleotide (NAD) by eminent psychopharmacologists, J. Cole, H. Lehmann, and J. Wittenborn. The treatment group received 1 gm/day of NAD for days 1–10, and 2 gm/day for days 11–20. The control group received an equal number of lactose placebo tablets. The results showed no systematic improvement in either group. Kline attempted to enumerate possible explanations for the discrepancy between this study and that of Hoffer. These explanations included: (1) Hoffer's patients were not as deteriorated as the patients in this study. Kline stated, however, that he had had some experience with NAD in acute schizophrenia, but with no success. (2) Kline's NAD was not active.

TABLE II

Investigator and type of study	NAD/N*	Previous hospitalization	Amt/day	Period of drug admin. and follow up (FU)	Results NAD Imp/Unimp	Results Cont Imp/Unimp
Hoffer (1966) Pilot Study	17/17	Chronic	1–2 Grams	At least 10 days No FU	13/4	None
Gallant, *et al.* (1966) Pilot Study	10/10	16-yr average	0.8 Gram Day 1–2 1.8 Gram Day 3–4 3.0 Gram Day 5–15 4.0 Gram Day 16–43 2.2 Gram Day 44–49	49 days No FU	0/10	None
Kline, *et al.* (1967) Double Blind Placebo Control	10/20	4–31 yr	1 Gram Day 1–10 2 Gram Day 11–20	20 days No FU	0/10	0/10
Meltzer, *et al.* (1969) Pilot Study	10/10	Greater than 5 yr	2 Grams	21 days 21 days FU	0/10	None
Total	47/57	?–31 yr	0.8–4.0 Grams	10–49 days 0–21 days FU	13/34	0/10

* NAD/N = Number of patients taking NAD/total number of patients in study.

Kline explains, though, that precautions were taken to preserve the NAD, and an assay upon completion of the study showed 70% of the NAD to be active. (3) The capsular material used in this study was different than Hoffer's material.

However, Gallant, *et al.* (*15*), began a study in 1966 in which they used both a specially prepared capsule coated with oharmaceutical shellac and the regular enteric coated Enzomedic Laboratory material, which is what Hoffer used. His study included ten chronic schizophrenic patients who were given DPN on a schedule of increasing dosages up to 4 gm/day for 27 days with a total DPN treatment period of 49 days. He found that no patient showed observable improvement.

Kline's and Gallant's failures to replicate Hoffer's results seemed to slow other attempts by different investigators to assess the therapeutic possibilities of either nicotinic acid or NAD. Meanwhile, Hoffer continued to write of his successful therapeutic approach, now termed the "megavitamin" treatment, in which he used both nicotinic acid and ascorbic acid in large quantities. In 1966, he wrote of the results of thirteen years of experience with nicotinic acid (*16*). A total of 128 patients treated by four psychiatrists were included in his nicotinic acid group. This group showed significantly fewer hospital readmissions, shorter hospital stays, and no suicides as compared to the control group of 346 patients which, in addition to their higher readmission rate and longer hospital stays, had six suicides.

In 1968, Hoffer (*17*) also responded to the study of Kline, *et al.*, by attempting to substantiate poor research technique on their part. His criticisms included poor patient selection and evidences for ineffective metabolic utilization of NAD by the patients.

In May 1969, Meltzer, Shader, and Grinspoon (*18*) published a study in which they administered NAD, 2 gm/day for 21 days, to 10 chronic schizophrenic patients, five of whom were also receiving thioridazine. They found no gross clinical improvement in any of the patients, and, in fact, in those patients not receiving thioridazine, there was a tendency toward increased irritability, aggressiveness, and hostility.

In summary (Table II), four studies (one showing NAD use to be beneficial and three not showing it to be beneficial) with a total of 57 chronic schizophrenic patients, showed an improvement in 13 of 47 patients (27.7%) treated with NAD (all improvements were limited to one study). Only one study used a control group (double-blind placebo) and, of 10 control group patients, none showed improvement. All patients were chronic with previous hospitalization as high as 31 years. The patients were treated with from 0.8 to 4.0 gm NAD administered over a period of time ranging from 10 to 49 days. A follow-up was conducted in only one study (*14*), and that follow-up period was only 21 days (Table II).

DISCUSSION

Before attempting to draw some conclusions from the studies cited, it is appropriate to consider some of the difficulties encountered in attempting comparisons between the work of different investigators into a subject such as schizophrenia and its treatment.

First, the criteria for diagnosis of schizophrenia vary with individuals. Different men interpret schizophrenia in different ways: What is schizophrenia for one individual may not be schizophrenia for another. This becomes a problem in assessing the value of a treatment when the possibility exists of different treatment groups not possessing the same psychopathology.

Secondly, evaluation of improvement or deterioration of patients is dependent on two variables that have not been equal from study to study, (1) the method of evaluation, and (2) the personnel doing the evaluating. Different investigators use different tests to determine changes in a patient's status. Improvement on one test may not show as improvement on another test. Besides the possibility of emphasis inadvertently being placed on one segment of the evaluating population, the evaluators themselves view patient change in different ways at different times. Even Hoffer's evaluating criteria, hospital readmission, although superficially appearing unbiased, does not take into account the bias of the admitting physician who may, indeed, be swayed by his belief that patients on one treatment form or another, deserve a longer trial out of hospital in hopes of future correction.

Other shortcomings of this comparative study are also painfully evident. First, Hoffer's studies have been, for the most part, long-term follow-up studies. No one else has conducted studies of comparable length. Also, Hoffer's studies have always included concomitant therapy (EST, psychotherapy, barbiturates, tranquilizers) which makes his method even more difficult, if not impossible, to replicate. Again, the fact that nicotinic acid produces a vasodilatation of the skin in the great majority of patients, and the fact that this flushing may indeed give away the drug, is not dealt with in any study of nicotinic acid. No attempts are made to explain how this drug effect is masked such that the investigators would not be influenced by it.

Unfortunately, then, we are faced with an attempt to compare and integrate studies which are not validly comparable as written. We will, however, correlate the studies as published, deriving information from the data which, as has been noted, we are not completely at liberty, academically, to report as valid.

If we assume that the diagnosis of schizophrenia was a generally accepted diagnosis for all patients in all the studies, and we also assume that the patient evaluations were valid and comparable for all patients in all the studies, then we can make the following comprehensive statements:

1. Nicotinic acid therapy as an adjunct added to the treatment of schizophrenia seems to have a beneficial effect, if the chronicity of the disease is not substantial. This statement is derived more from the fact that there is a lack of data contradicting it than from evidence which supports the statement. Abram Hoffer's repeated success with nicotinic acid therapy is encouraging, but aside from his work and that of his immediate associates, the use of the nicotinic acid approach in the treatment of early schizophrenia has not been subjected to a rigorous research program.

2. Neither nicotinic acid nor nicotinamide adenine dinucleotide alone in the treatment of chronic schizophrenia seems to be of benefit. The studies conducted to this date have not been encouraging. The usefulness of the vitamin in the treatment of schizophrenia would, at first glance, seem to be inversely proportional to the length of illness. This is, however, assuming that nicotinic acid is, indeed, a useful tool, and this assumption cannot be confidently made without more sound studies.

A statement on the effect of nicotinic acid would not be complete, however, without a word about side effects. Mosher (*19*) has recently reviewed the literature on this subject. His review indicates that, although the drug seems to be relatively harmless, there is some evidence of animal toxicity and a small incidence of peptic ulcer, hepatic impairment (probably causing secondary metabolic effects), hyperglycemia, and hyperuricemia. There have also been reports of exacerbation of psychosis with the use of the drug (*20*).

The megavitamin approach to the treatment of schizophrenia is further complicated by the claim of its proponents that higher doses than 3 gm per day of nicotinic acid are necessary. Although these claims for high doses of nicotinic acid have not appeared in the scientific literature, any study that utilizes only 3 gm is considered inadequate. The scene is further complicated by the simultaneous administration of ascorbic acid as well as other vitamins in high doses. The superimposition of a hypoglycemic diet and the correction of the endocrine imbalance in schizophrenia through replacement therapy of thyroxin and cortisone renders the whole approach redolent of a quasi-scientific cult. The simultaneous administration of several remedies renders the establishment of a rigidly controlled scientific study infinitesimally

difficult, if not impossible. For these reasons, most psychiatrists have totally ignored this modality of treatment, leaving a minority of our colleagues zealously advocating the megavitamin approach. The megavitamin therapy of schizophrenia has acquired some application within the drug-using hippy subculture. It is claimed that nicotinic acid is effective in counteracting the "bum trip" of LSD.

Agnew and Hoffer (*21*) reported that nicotinic acid when administered intravenously at the height of the LSD experience had a markedly normalizing effect. Peters (*22*) reported success using the drug orally to counteract the toxic reactions of LSD. Also, to treat or prevent recurring symptoms of the LSD experience, such as hallucinations, he has used oral nicotinic acid or nicotinamide with success.

REFERENCES

1. Hoffer, A.: Niacin Therapy in Psychiatry. Springfield, Ill.: Charles C Thomas, 1962.
2. Ananth, J. V., Ban, T. A., Lehmann, H. E., and Bennett, J.: "Nicotinic Acid in the Prevention and Treatment of Methionine-Induced Exacerbation of Psychopathology in Schizophrenics," *Canad. Psychiat. Ass. J.*, 15: 15–20, 1970.
3. Pauling, L.: "Orthomolecular Psychiatry," *Science*, 160: 265–271, 1968.
4. O'Reilly, P. O.: "Nicotinic Acid Therapy and the Chronic Schizophrenic," *Dis. Nerv. Syst.* 16: 67–72, 1955.
5. Hoffer, A., Osmond, H., Callbeck, M., and Kahan, I.: "Treatment of Schizophrenia with Nicotinic Acid and Nicotinamide," *J. Clin. Exp. Psychopath.* 18: 131–158, 1957.
6. Denson, R.: "Nicotinamide in the Treatment of Schizophrenia," *Dis. Nerv. Syst.*, 23: 167–172, 1962.
7. Hoffer, A., and Osmond, H.: "Treatment of Schizophrenia with Nicotinic Acid; A Ten-Year Follow-up," *Acta. Psychiat. Scand.*, 40: 171–189, 1964.
8. Ramsay, R. A., Ban, T. A., Lehmann, H. E., Saxena, B. M., and Bennett, J.: "Nicotinic Acid as Adjuvant Therapy in Newly Admitted Schizophrenic Patients," *Canad. Med. Ass. J.*, 102: 939–942, 1970.
9. Roukema, R. W., and Emery, L.: "Megavitamin Therapy with Severely Disturbed Children," *Amer. J. Psychiat.*, 127: 249, 1970.
10. Greenbaum, G. H., "An Evaluation of Niacinamide in the Treatment of Childhood Schizophrenia," *Amer. J. Psychiat.*, 127: 89–92, 1970.
11. Hoffer, A.: Enzymology of Hallucinogens, in Martin, G. S. and Kisch, B. ed., Enzymes in Mental Health, Transactions of the Third Symposium of the Carl Neuberg Society for International Scientific Relations on Progress in Biochemistry and Therapeutics, Philadelphia, Pa.: J. B. Lippincott, pp. 43–55, 1966.
12. Hoffer, A.: "Nicotinic Acid: An Adjunct in the Treatment of Schizophrenia," *Amer. J. Psychiat.*, 120: 171–173, 1963.
13. Kline, N. S., Barclay, G. L., Cole, J. O., Esser, A. H., Lehmann, H., and Wittenborn, J. R.: Controlled Evaluation of NAD in the Treatment of Chronic Schizophrenic Patients, *Brit. J. Psychiat.*, 113: 731–742, 1967.
14. Kline, N. S., Barclay, G. L., Cole, J. O., Esser, A. H., Lehmann, H., and Wittenborn, J. R.: "Diphosphopyridinenucleotide (DPN) in the Treatment of Schizophrenia," *J.A.M.A.*, 200: 881–882, 1967.
15. Gallant, D. M., Bishop, M. P., and Steele, C. A.: DPN (NAD Oxidized Form): A Preliminary Evaluation in Chronic Schizophrenic Patients, *Curr. Ther. Res.*, 8: 542, 1966.
16. Hoffer, A.: "The Effect of Nicotinic Acid on the Frequency and Duration of Rehospitalization of Schizophrenic Patients, A Controlled Comparison Study," *Int. J. Neuropsychiat.*, 2: 234–240, 1966.
17. Hoffer, A., and Osmond, H.: Nicotinamide Adenine Dinucleotide in the Treatment of Chronic Schizophrenic Patients, *Brit. J. Psychiat.*, 114: 915–917, 1968.
18. Meltzer, H., Shader, R., and Grinspoon, L.: The Behavioral Effects of Nicotinamide Adenine Dinucleotide in Chronic Schizophrenia, *Psychopharmacologia*, 15: 144–152, 1969.
19. Mosher, L. R.: "Nicotinic Acid Side Effects and Toxicity:" A Review, *Amer. J. Psychiat.*, 126: 124–130, 1970.
20. Henninger, G., and Bowers, M.: "Adverse Effects of Niacin in Ergent Psychosis," *J.A.M.A.*, 204: 1010–1011, 1968.
21. Agnew, A., and Hoffer, A.: "Nicotinic Acid Modified Lysergic Acid Diethylamide Psychosis," *J. Ment. Sci.*, 101: 12–27, 1955.
22. Peters, G., "A Study of Psychedelic Drug Users, Schizophrenia" 2: 103–108, 1970.
23. Hoffer, A.: "Biochemistry of Nicotinic Acid and Nicotinamide" *Psychosomatics*, 8: 95–100, 1967.
24. Hoffer, A., and Osmond, H.: "Some Schizophrenic Recoveries" *Dis. Nerv. Syst.*, 24: 204–210, 1962.
25. Martz, D. M.: "Acute Brain Syndrome Secondary to Niacin Deficiency," *Amer. J. Psychiat.*, 122: 215–216, 1965.
26. Osmond, H., and Hoffer, A.: "Massive Niacin Treatment in Schizophrenia: Review of a Nine-Year Study," *Lancet*, 2: 316–319, 1962.
27. Osmond, H., and Hoffer, A.: "A Comprehensive Theory of Schizophrenia," *Int. J. Neuropsychiat.* 2: 302–309, 1966.

Science 128(3334): 1277-1278. 1958.

Woolley-'58
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Tranquilizing and Antiserotonin Activity of Nicotinamide

Abstract. Nicotinamide in large amounts antagonized the action of serotonin on smooth muscles in vitro and in vivo. It also tranquilized animals. The antagonism differed in some respects from that of an antimetabolite of serotonin.

Two recent events have suggested that nicotinamide might act as an antagonist to the hormone serotonin. These are (i) the suggestion by Woolley and Shaw (*1*) that the cerebral serotonin content plays a role in mental disorders such as schizophrenia, and (ii) the claim of Hoffer *et al.* (*2*) that massive doses of nicotinamide or nicotinic acid control most cases of schizophrenia.

Woolley and Shaw pointed out that a variety of chemical compounds which they had shown to be antimetabolites of serotonin were able to call forth in normal men and animals some of the signs characteristic of mental disturbances and suggested that this was to be interpreted to mean that the naturally occurring mental disorders of similar type probably arose from an abnormality in serotonin in the brain. Some evidence was found to indicate that the difficulty was a deficiency of cerebral serotonin, but other findings suggested that instead an excess of this hormone might be involved (*3, 4*). It has not yet been possible to decide between these two alternatives. When Hoffer *et al.* announced that large amounts of nicotinamide controlled the disease, the idea occurred to us that if nicotinamide could be shown to act as an antagonist to serotonin this fact would argue in favor of the "too much" alternative.

In isolated smooth muscles and also in whole animals nicotinamide has now been found to act as an antagonist to serotonin. The isolated uterus from estrogenized rats is known to be a suitable test object with which to demonstrate antiserotonin activity (*5*). The muscle was standardized with serotonin, as previously described (*6*). Nicotinamide was applied and the response to serotonin was again measured. Usually nicotinamide caused half maximal inhibition of the contraction when it was present in a final concentration of 0.002*M*, and complete inhibition at 0.01*M* (eight experiments). An occasional tissue required more, but the most needed was 0.01*M* for half, and 0.02*M* for complete, inhibition.

These were the amounts needed to counteract an amount of serotonin just sufficient to elicit a maximal contraction in the untreated muscle. When the dose of serotonin was increased, the amount of nicotinamide required to counteract it was also increased, but not proportionately—that is, the antagonism was not strictly competitive. Once a uterus which had been very sensitive to serotonin (for example, maximal contraction to 0.003 μg/ml) had been treated with an inhibitory amount of nicotinamide, washing would not restore the sensitivity. Such a tissue would, however, respond to larger amounts of the hormone (0.02 μg/ml). The effect of the inhibitor then could be washed away readily, so that the washed tissue would again respond to 0.02 μg. There was thus only loss of the original sensitivity to the hormone, but the newly established level of response could be regained after removal of the nicotinamide.

The specificity of nicotinamide as an antagonist to serotonin was examined by determination of whether it also would counteract the action of acetylcholine on the same muscle. An amount of nicotinamide which would inhibit the serotonin response almost totally reduced only slightly the acetylcholine response (see Table 1). However, larger amounts of nicotinamide did prevent acetylcholine-induced contractions. Washing of the tissue restored the ability to contract to acetylcholine or to serotonin, so that no irreversible damage had been done to the muscle. Nicotinamide was thus not a specific antagonist to serotonin, but in the uterus the antiserotonin action was more prominent than the acetylcholine antagonism.

Table 1. Contractions of an isolated rat uterus caused by serotonin or acetylcholine in the presence and absence of nicotinamide.

Serotonin (μg/ml)	Acetylcholine (μg/ml)	Nicotinamide (*M*)	Contractions (cm)
0.01	0	0	5.5
0	0.04	0	4.0
0.01	0	0.003	0.5
0	0.04	0.003	3.0

Sodium nicotinate did not show any antagonism to serotonin in this tissue, even at 0.1*M* concentration. All solutions were of course adjusted to physiological *p*H in order to avoid the inhibition caused by acidity.

The antiserotonin activity of nicotinamide in living animals was shown in mice treated with 5-hydroxytryptophan according to a method recently described for the evaluation of antimetabolites of serotonin (*7*). This is a severe test of a compound, but 43 mg of nicotinamide gave 50 percent protection against 1 mg of hydroxytryptophan. When the test was made slightly less severe by reduction of the hydroxytryptophan to 0.4 mg per mouse, a complete protection of all mice was observed with 25 mg of nicotinamide.

One prominent feature seen in mice given these massive amounts of nicotinamide was marked lethargy or tranquilization. This was more severe than that seen in mice given reserpine. If lethargy is a feature of antiserotonins which reach the brain (*4*) (reserpine, chlorpromazine, certain synthetic antimetabolites of serotonin) then this effect of nicotinamide is noteworthy in understanding the relationship of serotonin to the mind.

One wonders about the mechanism of the antiserotonin action. Nicotinamide is

Table 2. Antagonism of uterine contraction by various antiserotonins.

Serotonin (μg/ml)	$CaCl_2$ (μg/ml)	Nicotinamide (*M*)	BAS* (μg/ml)	Contractions (cm)
0.01	0	0	0	4.1
0	200	0	0	4.3
0.01	0	0.02	0	0
0	200	0.02	0	0.5
0.01	0	0	1	1.0
0	200	0	1	4.5

* 1-benzyl-2,5-dimethyl serotonin hydrochloride.

not a structural analog of serotonin. This, and the lack of competitive antagonism, would argue against its being an antimetabolite of the hormone. Present data indicate that the action is indirect. Thus, nicotinamide was found to inhibit the muscle-contracting action of Ca^{++}, whereas a specific antimetabolite of serotonin, BAS (*8*), did not (see Table 2). If the action of serotonin on muscle and nerve cells is to transport Ca^{++} into them (*6, 9*), then a specific antiserotonin should not interfere with the serotonin-like action of Ca^{++}. Conversely, an agent which did not antagonize directly the basic action of serotonin, but which interfered with some other steps of the contractile process of muscle (for example, the energy-yielding ones), should also interfere with the action of Ca^{++}. This is what nicotinamide was found to do. Such indirect inhibitions might be of DPNase or the transmethylation processes which are known to be sensitive to nicotinamide. Elucidation of the precise mechanism must await further study.

The main purposes of this note (*10*) are to point out that nicotinamide affects the behavior of normal animals and that its effects are not incompatible with its ability to act as an antagonist to serotonin and to acetylcholine.

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References and Notes

1. D. W. Woolley and E. Shaw, *Proc. Natl. Acad. Sci. U.S.* **40**, 228 (1954).
2. A. Hoffer, H. Osmond, M. J. Callbeck, I. Kahan, *J. Clin. Exptl. Psychopathol.* **18**, 131 (1957).
3. D. W. Woolley and E. Shaw, *Brit. Med. J.* **2**, 122 (1954); E. Shaw and D. W. Woolley, *Science* **124**, 121 (1956).
4. D. W. Woolley, *Proc. Assoc. Research Nervous Mental Disease* **36**, 381 (1958).
5. V. Erspamer, *Arch. intern. pharmacodynamie* **103**, 293 (1953); J. H. Gaddum and K. A. Hameed, *Brit. J. Pharmacol.* **9**, 240 (1954); E. Shaw and D. W. Woolley, *J. Pharmacol. Exptl. Therap.* **111**, 43 (1953).
6. D. W. Woolley, *Proc. Natl. Acad. Sci. U.S.* **44**, 197 (1958).
7. D. W. Woolley, *Proc. Soc. Exptl. Biol. Med.* **98**, 367 (1958).
8. D. W. Woolley and E. Shaw, *J. Pharmacol. Exptl. Therap.* **121**, 13 (1957).
9. D. W. Woolley, unpublished results.
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Molnar-'64
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The Effect of Nicotinic Acid in Diabetes Mellitus

By George D. Molnar, Kenneth G. Berge, John W. Rosevear, Warren F. McGuckin and Richard W. P. Achorl

The metabolic effects of nicotinic acid therapy were studied in 6 diabetic subjects. In addition to the expected lowering of concentrations of blood lipids when these were high initially, temporary aggravation of the diabetic process occurred in all patients. This was manifested by increased glycemia, glycosuria, elevated concentrations of serum ketone bodies and free fatty acids, and heightened requirements for insulin or oral hypoglycemic drugs. There was a suggestion of increased mobilization and catabolism of fat during nicotinic acid therapy. The effects of nicotinic acid were promptly reversible when administration of the agent was stopped.

NICOTINIC ACID in the large oral dosage that is used for its cholesterol-lowering effect has been reported to impair carbohydrate tolerance in hypercholesteremic and hyperlipemic nondiabetic subjects[1-3] and to aggravate known diabetes mellitus in hyperlipemic subjects.[4] In some subjects, however, the control of known diabetes mellitus was reportedly unaffected by such therapy.[1,5-7]

The present study was designed to assess the effect of nicotinic acid* on 6 diabetic volunteers, 3 of whom were normolipemic. The uniformly diabetogenic action of nicotinic acid in all 6 patients prompted us to report our observations.

Methods

Three patients (nos. 1, 2 and 3) were studied in a metabolic ward, where their nutrients were weighed but not analyzed. The diet for each patient consisted of several menus which were rotated. Constituents of the diets were computed by means of standard tables.[8] All urine was collected and analyzed daily for glucose, ketones and nitrogenous constituents. Stools were collected in weekly periods. The start of each stool collection was signaled with a carmine marker. Stools were analyzed for nitrogen and total fat content. The patients were weighed daily before breakfast. Blood samples, which were collected at least twice weekly, were taken at 8 a.m. before breakfast and, often, at 3 p.m. on the afternoon of the same day. Analysis of blood, urine and stool constituents was carried out according to standard procedures in use in Mayo Clinic laboratories. Urinary glucose,[9] serum ketone bodies,[10] and free fatty acids[11] were determined by the methods indicated by the references.

The 3 subjects (nos. 4, 5 and 6) who were not studied in a metabolic ward had their studies initiated under close outpatient supervision. These patients, as well as the first

From Mayo Clinic and Mayo Foundation, Rochester, Minnesota
†*Deceased.*
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*Nicotinic acid tablets and capsules (500 mg.) were generously supplied by Eli Lilly and Co., Indianapolis, Indiana.

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Table 1.—*Therapeutic Program*

Patients			Diabetes			Nicotinic Acid Therapy				
				Start of Therapy						
No.	Sex	Age, yr.	Onset	Insulin	Oral*	Interval of Therapy	Dose, Gm./day	Side Effects†	Additional Findings	Additional Therapy‡
1	F	48	1957	1957	—	9-7-61 to 2-10-62	3	Anorexia, nausea	Hyptertension, cholelithiasis, eruptive xanthomas	Digitalis, thiazide diuretic
2	F	67	1947	1956	—	4-19-62 to 9-20-62	2	Mild anorexia	Cholelithiasis	Thiazide diuretic
3	M	55	1943	—	Feb. 1962 C	6-24-62 to 1-17-63	2	None	None	None
4	M	31	1945	1945	—	3-2-62 to 9-14-62	1 to 3	Periodic nausea	None	None
5	F	70	1944	1956	1959, T 1962, C	4-25-62 to 5-8-62	1.5	Anorexia, nausea, emesis	Hypertension since 1944, eruptive xanthomas	Digitalis, thiazide diuretic
6	F	65	1954	1954	—	8-27-62 to 3-11-63	2	None	Cerebrovascular insufficiency	None

*Type of oral therapy indicated by: C, chlorpropamide; T, tolbutamide.

†Of sufficient magnitude to interfere with comfort or to require reduction of dose.

‡When additional therapy was given, the nature and dosage was constant in the study periods before, during and after treatment with nicotinic acid.

3 when they were subsequently followed up as outpatients, underwent essentially the same type of investigation as is described for the metabolic-ward type of observation. However, during the studies outside the metabolic ward, no attempt was made to monitor nitrogen balance or to quantitate urinary excretion of sugar and ketone bodies.

Results

Clinical Data: Table 1 shows the therapeutic program for the patients whose biochemical responses to nicotinic acid are detailed in figures 1 to 4 and summarized in table 2. In contrast to other patients with diabetes mellitus whose experiences with nicotinic acid have been reported,[1,2,4-7,12] 3 of our patients (nos. 1, 4 and 6) were insulin-dependent subjects with labile diabetes; patient 4 had had diabetes since childhood. Patients 2, 3 and 6, despite close observation before the nicotinic acid therapy was initiated, were never shown to have hyperlipemia or hypercholesteremia.

Patients' Requirements for Hypoglycemic Agents: As indicated in figure 1 and table 2, daily insulin dosage had to be increased for patients 1, 2, 4 and 6 to maintain at least as good diabetic regulation as these patients had before nicotinic acid therapy was instituted. A larger dosage of an oral hypoglycemic drug in patients so treated (nos. 3 and 5) was necessary during nicotinic acid therapy as compared with periods when no nicotinic acid was given. Conversely, after nicotinic acid therapy had been stopped less insulin or less of the oral agent was needed than was the case during nicotinic acid therapy.

It is evident in figures 3 and 4, however, that in subject 3 the omission of tolbutamide therapy for 7 days during nicotinic acid therapy led to only a gradual increase in glycosuria and hyperglycemia. Similarly, diabetic control began to revert toward the previous, more satisfactory, level only after 7 days of further tolbutamide therapy while nicotinic acid was still being administered.

Biochemical Findings: Nitrogen balance, when determined (fig. 1 and 3), was not appreciably affected by nicotinic acid therapy. Levels of serum free fatty acids and total ketone bodies were generally higher during nicotinic acid therapy in all patients. Postprandial concentrations of free fatty acids and ketones were usually lower than the respective fasting levels. However, these postprandial levels were higher during nicotinic acid therapy as compared with postprandial levels without such treatment (fig. 4). The concentrations of free serum ketone bodies (acetone and acetoacetic acid) were also determined, although the values are not shown: they were usually one third of the so-called total ketone bodies, which included beta-hydroxybutyric acid as well. There was, however, no consistent difference in urinary excretion of ketone bodies, as is evident in figures 1 and 3. Total excretion of fat in the stools was similarly unchanged during nicotinic acid therapy (table 3). Major changes in the concentration of plasma cholesterol, fatty acid and phospholipid occurred only when concentrations of these constituents were elevated initially (table 2). Such changes, when they occurred, were evident within a week of the start or cessation of administration of nicotinic acid.

Liver Function: Only 1 patient (case 1) had appreciable impairment of

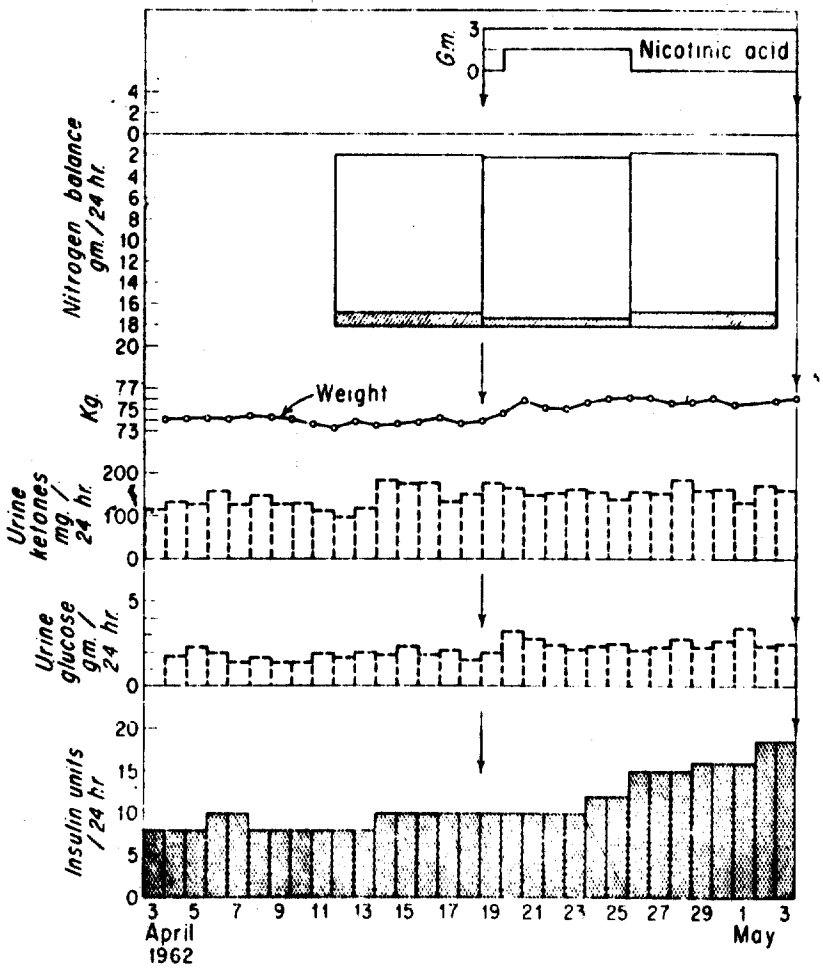

Fig. 1.—Continuous record of insulin therapy, urinary glucose and ketone body excretion, body weight, nitrogen balance and nicotinic acid therapy in patient 2. For insulin therapy, the hatched columns indicate the daily dose of Lente insulin. Dotted vertical columns indicate amounts of glucose or ketone excreted in urine daily. Nitrogen balance is charted conventionally, a negative balance being indicated by extension of the column above the zero line and a positive balance by a clear zone below the zero line; cross-hatched zone represents fecal excretion of nitrogen.

hepatic function: 18 per cent retention of sulfobromophthalein and elevation of the serum glutamic-oxalacetic transaminase level to 2.98 μmoles/hr./ml. and the alkaline phosphatase to 26.0 King-Armstrong units were the changes observed. This patient had cholelithiasis, as did patient 2, in whom no measurable hepatic dysfunction was demonstrable after a total of 6 months of therapy with nicotinic acid. The abnormal results noted in case 1 all returned to normal during the metabolic-ward study 2 weeks after discontinuation of

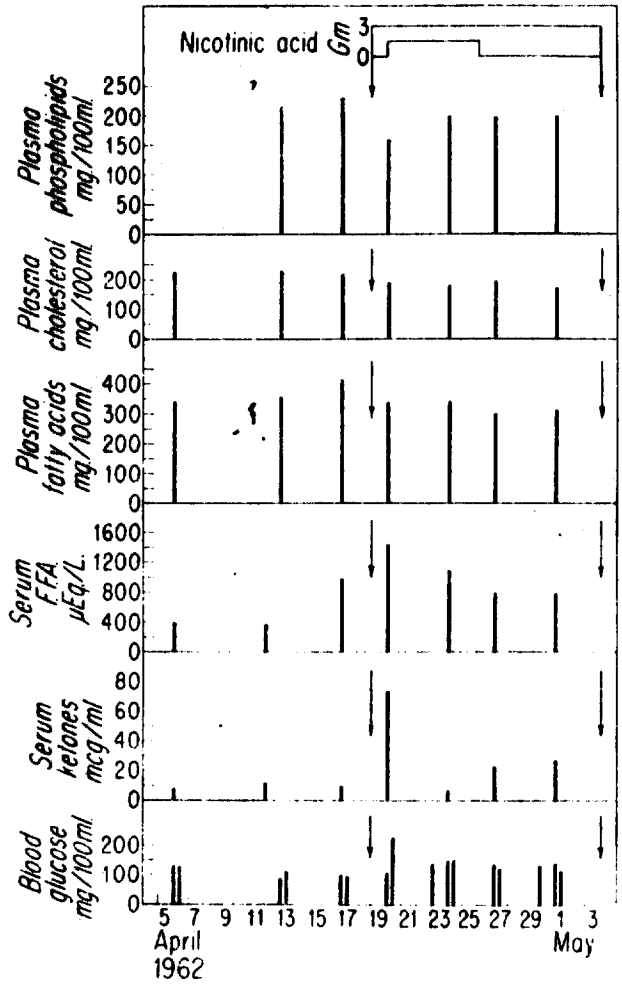

Fig. 2.—Companion figure to figure 1. Observations on blood constituents in patient 2 during metabolic-ward study. Vertical bars indicate concentration of blood constituents diagrammed. Single values represent determinations made on fasting morning specimens. When 2 bars appear in a single day, the second one represents a postprandial value (3 p.m.). F.F.A. = free fatty acids.

nicotinic acid therapy; however, the abnormalities recurred after the same period of time when therapy was reinstituted. The other patients had no appreciable impairment of hepatic function, although the trial of therapy in patient 5 was of too brief duration to permit any conclusion to be drawn.

Clinical Observations: Once the patients were given adequate antidiabetic therapy, none had any difficulty in maintaining body weight. Side reactions from the large doses of nicotinic acid, such as flushing, mild anorexia and nausea, were common initially (table 1) but cleared or diminished in intensity when capsules were substituted for tablets of nicotinic acid and when nico-

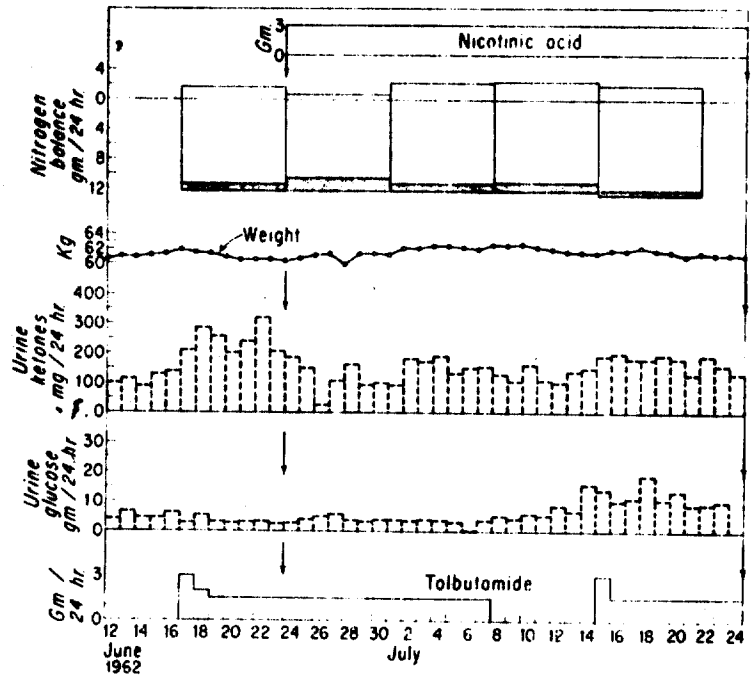

Fig. 3.—Continuous record of tolbutamide therapy, amounts of glucose and ketone bodies excreted in the urine, body weight, and nitrogen balance in patient 3. Charting is essentially identical to that in figure 1.

tinic acid was taken during or after meals instead of when the stomach was empty. The exception to this was patient 5, who, for reasons perhaps not entirely attributable to the nicotinic acid (she also received digitalis and large doses of oral hypoglycemic agents), had such severe anorexia, nausea and emesis that the trial with the drug had to be discontinued.

Comment

The data demonstrate that nicotinic acid administered under the conditions described has a diabetogenic effect, namely, impaired utilization of carbohydrate as indicated by increased glycemia and glycosuria. Glycemia and glycosuria could be kept near pretreatment levels by increasing the dosage of insulin or oral hypoglycemic drug. Even when such an increase in dosage was made, however, blood levels of ketone bodies and free fatty acids remained elevated. All of these biochemical observations may be interpreted as reflecting changes related to the diabetic process.[13]

The increase in serum concentration of ketone bodies and free fatty acids during nicotinic acid therapy, at the same time that nitrogen balance, stool fat, and urinary excretion of ketone bodies remained unchanged, suggests an increase in the mobilization and catabolism of fat. Although other explana-

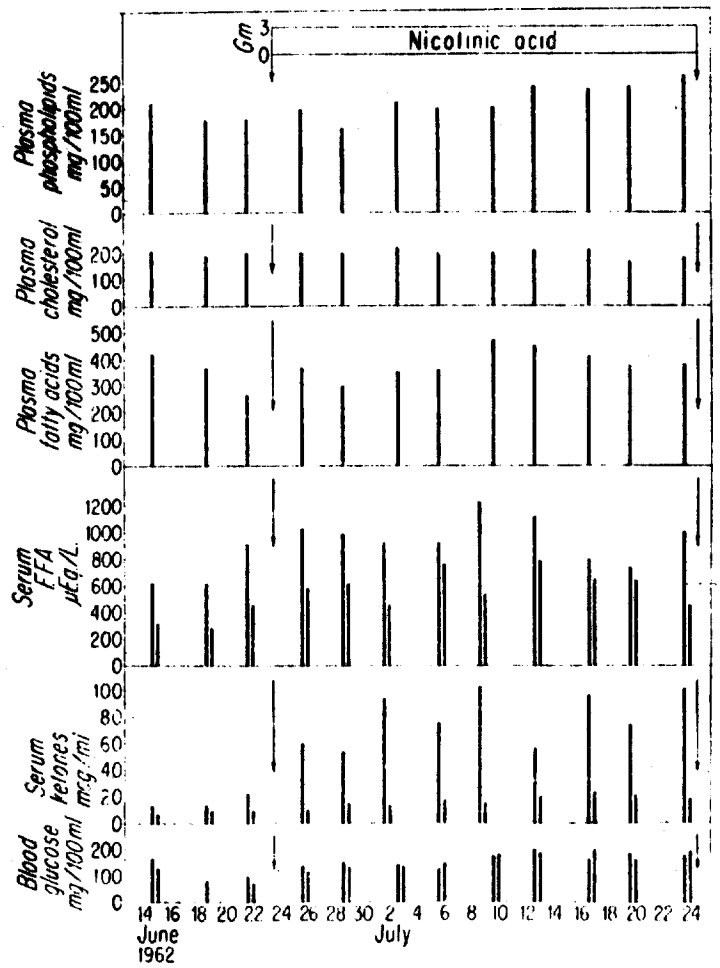

Fig. 4.—Blood chemical values in patient 3 during the period of study illustrated in figure 3. Charting is identical to that in figure 2.

tions are possible, increased catabolism of fat is also a mechanism by which nicotinic acid could cause a decrease in the concentration of blood lipids (patients 1, 4 and 5).

Other investigators[1,5,6] have reported that the requirement for insulin was unaffected in diabetic subjects who received nicotinic acid therapy. However, few data are given by these authors as to the detail with which diabetic regulation was monitored. It is possible, in stable, ketoacidosis-resistant diabetes of adult onset, to permit increased glycemia and glycosuria without appreciable clinically observable consequences. Moreover, such patients are classically not insulin-sensitive; and despite impaired diabetic control, the dosage of insulin may be kept constant without serious change in the more evident diabetic parameters such as maintenance of body weight, sense of

Table 2.—*Biochemical Data before, during and after Nicotinic Acid Therapy**

Parameter	Patients 1 Before	1 During	1 After	2 Before	2 During	2 After	3 Before	3 During	3 After
Daily insulin dose, units or daily oral therapy, Gm.†	57.9 (169)	73.2 (111)	59.6 (183)	8.2 (110)	21.4 (155)	9.0 (86)	None	T, 3.0 C, 0.35	None
Glucose, mg./100 ml. blood (normal: 65–90)	191 (7)	194 (12)	210 (10)	125 (8)	142 (10)	123 (2)	115 (9)	154 (13)	82 (4)
Free fatty acids, μEq./L. serum (normal: 239–843)	—	1,172 (6)	558 (8)	588 (3)	1,045 (5)	778 (1)	714 (3)	909 (12)	534 (3)
Ketone bodies, μg./ml. serum (normal: 2.3–9.7)	—	17.0 (6)	4.6 (7)	10.1 (3)	29.6 (5)	11.7 (1)	15.6 (3)	67.6 (12)	18.8 (4)
Cholesterol, mg./100 ml. plasma (normal: 150–250)	1,358 (2)	218 (8)	366 (7)	208 (4)	196 (8)	230 (2)	202 (6)	213 (11)	265 (4)
Total fatty acids, mg./100 ml. plasma (normal: 250–400)	9,054 (2)	683 (7)	1,194 (5)	371 (4)	338 (8)	399 (1)	363 (4)	398 (12)	395 (4)
Phospholipids, mg./100 ml. plasma (normal: 150–250)	1,188 (1)	287 (5)	423 (4)	211 (3)	205 (7)	230 (1)	195 (4)	220 (12)	250 (4)

Parameter	Patients 4 Before	4 During	4 After	5 Before	5 During	5 After	6 Before	6 During	6 After
Daily insulin dose, units or daily oral therapy, Gm.†	64.5 (197)	89.3 (197)	60.0 (107)	T, 1.5	T, 3.0 C, 0.5 P, 0.1	C, 0.1	39.5 (148)	62.3 (185)	37.2 (98)
Glucose, mg./100 ml. blood (normal: 65–90)	207 (11)	258 (5)	—	178 (4)	185 (6)	118 (5)	155 (3)	161 (5)	155 (4)
Free fatty acids, μEq./L. serum (normal: 239–843)	748 (3)	1,346 (2)	—	—	—	—	875 (1)	1,101 (3)	938 (3)
Ketone bodies, μg./ml. serum (normal: 2.3–9.7)	15.5 (3)	44.6 (2)	—	—	—	—	13.8 (1)	47.2 (3)	10.3 (3)
Cholesterol, mg./100 ml. plasma (normal: 150–250)	285 (6)	230 (7)	—	360 (3)	272 (1)	354 (2)	189 (1)	186 (3)	195 (3)
Total fatty acids, mg./100 ml. plasma (normal: 250–400)	554 (4)	423 (7)	—	1,288 (1)	688 (1)	—	363 (1)	343 (3)	380 (3)
Phospholipids, mg./100 ml. plasma (normal: 150–250)	260 (1)	211 (7)	—	—	—	—	188 (1)	221 (3)	247 (3)

*Data shown as means with number of determinations indicated in parentheses. Data in each time interval were collected, when possible, for a period equal to the duration of therapy or for 6 months, whichever was longer. All samples of blood were taken before breakfast.

†Type of oral therapy indicated by: C, chlorpropamide; P, phenformin; T, tolbutamide.

well being, or even qualitative tests for glycosuria (especially in patients with a high renal threshold).

The diabetogenic effect of nicotinic acid that we observed in patients who were already known to have diabetes was promptly reversible when use of this agent was discontinued. After periods of therapy as long as 6 months,

Table 3.—*Analysis of Stool Fat*

Patient	Periods of Therapy with Nicotinic Acid	Stool		
		Solids, Gm./period	Fat	
			Gm./period	%
2	(4/12–18/62—pretreatment)	136	13.6	10
	4/19–25	91	10	11
	4/26–5/3	162	17	10
3	(6/17–23/62—pretreatment)	135	25	19
	6/24–30	144	18	13
	7/1–7	134	16	12
	7/8–14	135	18	13
	7/15–21	82	10	12
	1/11–16/63	123	14	11
	(1/17–24/63—post-treatment)	76	10	13

no lasting deleterious effects could be observed in these patients. In view of the results of this study, we do not consider diabetes mellitus a contraindication to the investigative use of nicotinic acid. We do recommend, however, that such treatment in diabetic patients be closely supervised so that the necessary measures for maintenance of proper metabolic regulation are not overlooked.

REFERENCES

1. Gurian, H., and Adlersberg, D.: The effect of large doses of nicotinic acid on circulating lipids and carbohydrate tolerance. Am. J. M. Sc. 237:12, 1959.
2. Berge, K. G.: Side effects of nicotinic acid in treatment of hypercholesteremia. Geriatrics 16:416, 1961.
3. Pollack, H.: Nicotinic acid and diabetes. Diabetes 11:144, 1962.
4. Belle, M., and Halpern, M. M.: Oral nicotinic acid for hyperlipemia with emphasis on side effects. Am. J. Cardiol. 2:449, 1958.
5. Parsons, W. B., Jr., and Flinn, J. H.: Reduction of serum cholesterol levels and beta-lipoprotein cholesterol levels by nicotinic acid. Arch. Int. Med. 103:783, 1959.
6. —: Studies of nicotinic acid use in hypercholesteremia: Changes in hepatic function, carbohydrate tolerance, and uric acid metabolism. Arch. Int. Med. 107:653, 1961.
7. —: Use of nicotinic acid to reduce serum lipid levels. J. Am. Geriatrics Soc. 10:850, 1962.
8. Committee on Dietetics: Mayo Clinic Diet Manual. Philadelphia, W. B. Saunders Company, 1961.
9. Molnar, G. D., McGuckin, W. F., Striebel, J. L., and Gastineau, C. F.: Effects of therapeutic measures in a hyperlabile diabetic. Proc. Staff Meet., Mayo Clin. 36:45, 1961.
10. Bloom, W. L.: The determination of ketone bodies in biologic fluids. J. Lab. & Clin. Med. 51:824, 1958.
11. Bierman, E. L., Dole, V. P., and Roberts, T. N.: An abnormality of nonesterified fatty acid metabolism in diabetes mellitus. Diabetes 6:475, 1957.
12. Parsons, W. B., Jr.: Reduction in serum cholesterol levels and other metabolic effects of large doses of nicotinic acid. Circulation 20:747, 1959.
13. Siperstein, M. D.: Inter-relationships of glucose and lipid metabolism. Am. J. Med. 26:685, 1959.

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