MONOGRAPH ON VITAMIN B_{12} #127 Vol I

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VITAMIN B_{12}

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TABLE OF CONTENTS

Summary

CHEMICAL INFORMATION

		Page
I.	Nomenclature	1
II.	Empirical Formula	7
III.	Structural Formula	8
IV.	Molecular Weight	18
V.	Specifications	18
VI.	Description	27
VII.	Analytical Methods	34
VIII.	Occurrence	48

BIOLOGICAL DATA

I.	Acute Toxicity	53
	Mice	53
	Guinea Pigs	53
	Humans	55
II.	Short-term Studies	59
	Mycota	59
	Rats	61
	Guinea Pigs	61
	Humans	61
III.	Long-term Studies	66
	Rats	66
	Humans	67
IV.	Special Studies	68
	Therapy	68
	Neuropathology	68
	Behavioral Studies	72
	Blood Studies	72

TABLE OF CONTENTS (Cont'd)

	Fertility Studies	73
	Cancer Studies	73
	Leukemias	79

BIOCHEMICAL ASPECTS

I.	Breakdown	86
II.	Absorption and Distribution	88
III.	Metabolism and Excretion	136
IV.	Netabolic Effects	145
V.	Drug Interactions	171
VI.	Consumer Exposure	183

SUMMARY

Chemical Information

According to the compendia, the important forms of supplementary B_{12} are cyanocobalamin and hydroxocobalamin, and the predominant forms in animal tissues are methylcobalamin and coenzyme B_{12}, or 5'-deoxyadenosylcobalamin. B_{12} is synthesized only by microorganisms and is prepared commercially by culturing them.

The molecule (0916) contains a corrin and nucleotide. The corrin resembles the porphyrins, with Co replacing Fe. The nucleotide contains the base 5,6-dimethylbenzimidazole, ribose, and an esterified phosphate. Analogs are formed at the propionamide side chain of the corrin, at the base, or at the ribose.

Three types of assay are generally used for estimating the amount of B_{12} compounds present in a person or a sample:

(1) Excretion of labeled Co, after a small oral dose of labeled Co and a large oral dose of unlabeled Co, called the Schilling Test (2425).

(2) Whole-body counting for a year or more after an oral or parenteral dose of labeled Co-B_{12} (0303).

(3) Bioassay based on growth of cultures of B_{12}-dependent microorganisms (2819).

Other methods are also described in the monograph.

Dietary B_{12} occurs in animal products such as meats, fish, and milk, but not in washed fruits, vegetables, or cereals (1015).

Acute Toxicity

Allergic sensitivity was produced in one (2787) but not another (3002) mouse experiment, and in guinea pigs (1656). All guinea pigs given 200 μg each were sensitized, some by 20 μg but none by 2 μg (1656).

A total of five human deaths were found attributed to B_{12} allergy (1820, 2187, 2352); a number of less severe cases of B_{12} allergy have been reviewed as "rare" (1015). Doctors have been cautioned to monitor the response when a patient receives B_{12} for the first time (0082).

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Short Term Studies

B_{12} has been reported to encourage the growth of cultured *Candida albicans* (1659). Excessive B_{12} accelerated weight-loss in undernourished rats (0948).

Human patients were given 0.5 mg/week for 10-14 weeks; after hydroxocobalamin their serum B_{12} remained high for 6-7 months, after cyanocobalamin only for 4-5 weeks (0982). Patients with Leber's hereditary optic atrophy, in which cyanide metabolism is deranged, responded well to hydroxocobalamin but not to cyanocobalamin (0866). However, other patients have developed acne as an occasional response to hydroxocobalamin (0744). The regular use of hydroxocobalamin or long lasting depot preparations has been deprecated owing to frequent pain at the injection sites (1015).

Long Term Studies

In a rat study covering five generations, additions of B_{12} up to 1 mg/kg of diet revealed no signs of toxicity (2287). A human female took B_{12} 50 μg t.i.d. orally for 10 years without apparent effect on her B_{12} body stores or blood picture (megaloblastic) (0366).

Special Studies

Monkeys are reported (2092) not to show clinical signs of neuropathy when B_{12}-deficient, even though lesions may be present. In 1973 Herbert and Tisman (1207) concluded that the human effects of B_{12} deficiency needed to be reclassified.

Many studies report roles of B_{12} in DNA replication and cell division, with reference to cancers. In mice, osteosarcomas took up more Co^{60}-B_{12} than normal tissues, and the label was concentrated in the most actively growing parts of the neoplasm. (0292). In other mice, B_{12} availability was found to be rate-limiting for thymidine synthesis and thus for DNA synthesis and cell division (2350). In rats, pharmacological amounts of B_{12} were taken up preferentially by tumor cells and enhanced the

tumor growth, but not all tumor types responded equally (2293). Such preferential uptake from serum with physiological content of B_{12} has been doubted (2631). In chicks, Rous sarcoma was found to be B_{12}-dependent (2067).

Diverse reports of human studies were found. Neuroblastoma was clinically unaffected by supplementary B_{12} (1571) and in one case the tumors contained less B_{12} than normal tissues (0561). HeLa cells responded only partially to pharmacologic amounts of B_{12} (1429). In 1973 Herbert (1206) concluded that the response of tumor tissues to B_{12} varied according to whether the type of tumor depended more on the de novo pathway of thymidine synthesis or the salvage pathway (from necrotic cell DNA).

Reports of B_{12} in leukemia are equally diverse. In rats with and without leukemia the serum B_{12} was proportional to the leucocyte population (0315). A similar finding in humans has been reported, and the authors concluded that the relationship between leucocyte count and serum B_{12} level was independent of the leukemic process (0451). In many reports (e.g., 1858) a high total B_{12}-binding capacity has been found in the serum of patients with myeloid leukemias but not in those with lymphoid leukemias. Other reports (e.g., 1812) associate high serum B_{12} in cancer patients with liver involvement or abnormal liver function.

Breakdown

The heat of ordinary food processing and cooking has little effect on B_{12} (1015), but many bacteria can degrade it (2458); they (2429) and tapeworms (1033) can deprive a host of B_{12}.

Absorption

Physiological amounts of B_{12} are absorbed by man only in the ileum; intrinsic factor is needed, and less than 2 μg of B_{12} are handled at a time (1015). Intrinsic factor, one of several secretions that bind B_{12}, comes from gastric parietal cells. Receptors in the ileal mucosa are specific for both parts of the complex (1706). Dogs may lack intrinsic factor (3063).

Pharmacological amounts of B_{12} are absorbed by diffusion at many sites including upper small bowel (0932), colon (0097), lungs (1902), and skin (1270). In man about 1.2% of any dose may be so absorbed (0244), but the process is reported as unreliable (1015).

Absorption may be diminished in iron deficiency (0277); it is increased in pregnancy (1187); the evidence is equivocal in regard to other factors.

Distribution

The process is somewhat analogous to that of iron. The two principal binders of B_{12} are transcobalamin I, comparable with α-globulin, and transcobalamin II, comparable with β-globulin (1015). The β-binder carries B_{12} rapidly from the ileum to the tissues, and the α-binder redistributes B_{12} that has been in the body for 24 hours or more (1108). Other binders have been identified but their roles, if any, remain uncertain (1108).

The B_{12} attached to α-binder is agreed to be methylcobalamin (1015, 1108). Usual body stores total 2-5 mg, 50-90% in the liver which contains about 1 mg/kg: turnover averages 0.1-2.0% of body stores/day, mainly via bile and without degradation, and enterohepatic recirculation handles 0.6-6.0 μg/day (1015). Thus even accelerated deficiency may take 3-6 years to show clinical signs (1015).

The B_{12} concentration has been measured in 17 tissues of human adults and fetuses and, despite wide variations, was greatest in liver and least in bone marrow (2246). In pregnant animals the placenta concentrates and stores B_{12} (e.g., 1025). Serum B_{12} levels in man tend to fall with increasing age (2037).

Of administered forms of B_{12}, hydroxocobalamin tends to be held in the serum more than cyanocobalamin (0983). In a recent study the authors concluded that human breast milk supplied the infant with B_{12} in a more readily utilized form than did formula milks (0584). A retarded-effect formulation of B_{12} was found to become attached to γ-globulin, and the authors queried whether this was an advantage "or the opposite" (2451).

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Metabolism

The ileal mucosa, probably in the epithelial cell mitochondria, converts cyanocobalamin to coenzyme B_{12}, but some cyanocobalamin enters the serum unchanged (2134). The ability to perform this conversion was missing in one male infant who died (1916). Other aspects are discussed in other Sections.

Excretion

Pharmacologic doses of labeled cyanocobalamin, hydroxocobalamin, or coenzyme B_{12} given to humans with or without megaloblastic anemia who were whole-body-counted for more than a year thereafter, indicated that loss rates became constant after 4-8 weeks and did not differ between the forms of B_{12} or the condition of the subjects (0302). In another study the constant daily fecal and urinary losses were each about 0.03% of the retained initial dose, and bioassay indicated that about 90% of the urinary label losses were in inactive metabolites (1106).

Urinary losses can be increased by pituitary insufficiency (0707). In the dog, the carrier transcobalamin II has been found too large a molecule to cross the renal glomerulus (0557).

Effects on Enzymes and Other Biochemical Parameters

B_{12} and folate are needed together for synthesis of thymidylate and thence DNA; megaloblastosis reflects deranged DNA synthesis, observed most readily in the constantly replicating cells of bone marrow, and B_{12} also participates in folate uptake by erythrocytes (1015).

B_{12} alone is rate-limiting for myelin synthesis; the author observed that the neuropathy of B_{12} deficiency was equal in rich and poor, but the hematopathy was more severe in the poor, indicating that hematopathy, but not neuropathy, was retarded by adequate dietary folate (1015).

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B_{12} also appeared to be involved in the reduction of SH groups so as, for example, to maintain the levels of reduced glutathione in erythrocytes and liver; but the precise chemistry remained uncertain (1015).

B_{12} coenzymes are required in reactions catalyzed by glutamate mutase, methylmalonyl-CoA mutase, glycal dehydrase, ribonucleotide reductase, and ethanolamine deaminase, and in the conversion of β-lysine to 3,5-diaminohexanoic acid; methyl-B_{12} is considered an intermediate in the synthesis of methionine, methane, and acetate (2955). Methylmalonyl-CoA isomerase is also reported as B_{12}-dependent (2322).

Some effects of B_{12} deficiency on metabolism are discussed in the monograph. Large dietary supplements of B_{12} did not affect protein metabolism (1913). Parenteral B_{12} was considered to increase glucose absorption by enhancing its phosphorylation (1094). A role of B_{12} in fat metabolism has long been debated (0730), but in 1974 remained undefined (1671).

Drug Interactions

Ethanol taken with an adequate diet is reported to cause malabsorption of B_{12} (1635). So do the biguanide drug Metformin (0235), and colchicine (2682).

Reports of B_{12} deficiency in patients treated with para-aminosalicylate (1164,2682) are disputed (2093), and similar reports in others given hydantoin (0063) and other psychiatric drugs (0453) lack confirmatory detail.

The compendium,Drug Interactions (2818) lists reports of interactions of B_{12} with procaine-HCl, streptomycin, thiotepa, strophantin, thioglycollic acid, thyreoidine, and thiamine-HCl; various interactions with steroids are reported.

Consumer Exposure

It has been stated that the only justified use of supplementary B_{12} is to remedy its own deficiency, which can be determined in advance of treatment; the author added that doses over 30 μg/day parenterally had "no proven

therapeutic advantage" (1015). Depot or long-lasting forms of B_{12} failed to justify their costs and might have undesirable side effects (1015).

The RDA (3106) for replacement of normal losses in adults is 5 μg/day, and to replenish depleted body stores is 15 μg/day. The RDA for infants is 1-2 μg/day on the ground that the average daily intake from human milk is 0.15-0.25 μg/day (3106). No RDA are reported for pregnant or lactating women, the authors stating that serum B_{12} declines throughout pregnancy and that true deficiencies develop (3106).

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CHEMICAL INFORMATION

I. Nomenclature

A. Common Names:

Herbert (1015) summarized the position adopted by IUPAC in 1973:

1. "Vitamin B_{12}" means only cyanocobalamin.
2. "Cyanocobalamin" is a permissive semi-systematic name for vitamin B_{12}.
3. In the literature, "B_{12}" can include all or any cobalamins active in man.
4. "Cobalamin" is an alternative name for B_{12}; both names also apply permissively to cyanocobalamin without the cyanide.
5. "Coenzyme B_{12}" means only 5'-deoxyadenosylcobalamin.
6. But "vitamin B_{12} coenzyme" means any form of B_{12} with coenzyme activity. See Figure 1 (1015) for some examples.

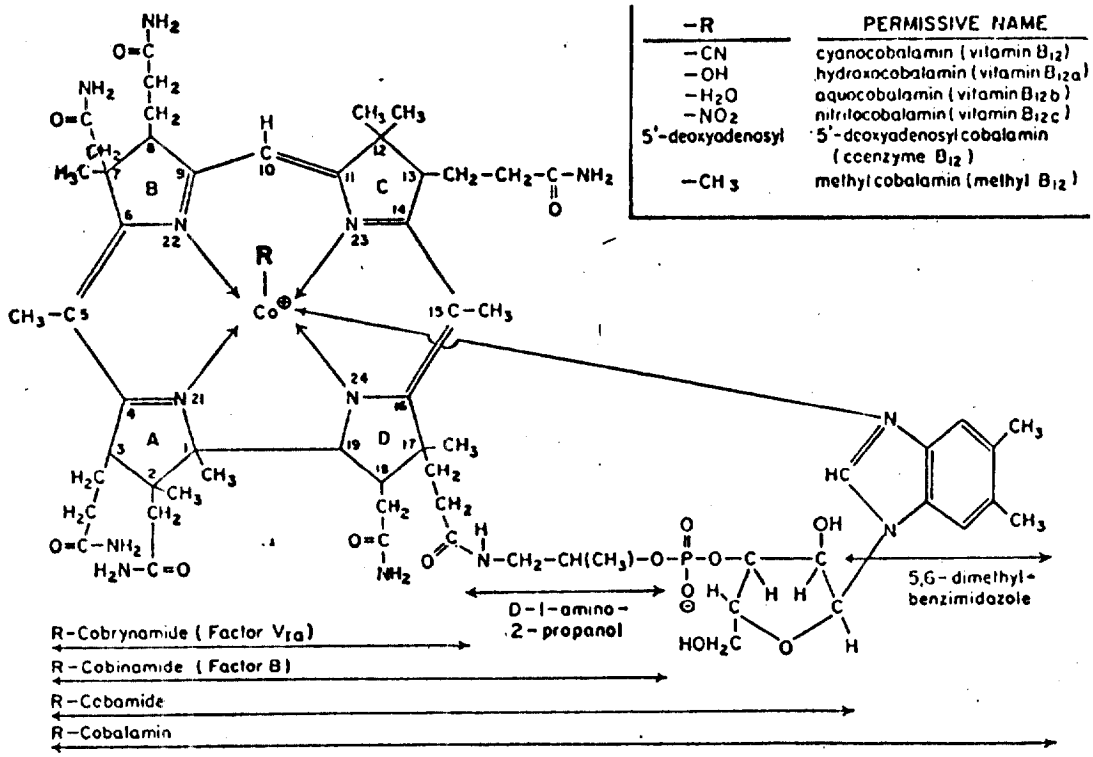

Figure 1. Structural Formula of Vitamin B_{12} (Cyanocobalamin). The Numbering System for the Corrin Nucleus is Made to Correspond to that of the Porphin Nucleus by Omitting the Number 20. (Modified from Brown and Reynolds: Biogenesis of Water-Soluble Vitamins. Annual Review of Biochemistry, 32, 419-462, 1963.) (1015)

Two other summaries of common nomenclature are shown in Tables 1 and 2.

Table 1 .

Common Names of Vitamin B_{12} (Merck, 2628)

Letter Designation	Major Common Name	Other Common Names
B_{12}	Cyanocobalamin	Cobinamide cyanide phosphate 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosyl-benzimidazole inner salt; LLD factor; Lactobacillus lactis Dornier factor; extrinsic factor; antipernicious anemia principle.
B_{12a}	Hydroxocobalamin	Hydroxocobemine; OHB_{12}.
B_{12a}-acetate	Acetatocobalamin	Idoxo-B_{12}.
B_{12b}	Aquocobalamin	Aquocobamide.
B_{12b}-hydroxide	See Hydroxocobalamin	
B_{12c}	Nitrosocobalamin	Nitrocobalamin; nitritocobalamin.
B_{12p}	Etiocobalamin	Cobinamide dicyanide; Factor B. Note: the term etiocobalamin is used by some authors to designate any cobalamin lacking the nucleotide group present in B_{12}.
B_{12r}	(no entry)	(no entry)
---	Sulfitocobalamin	Sulphitocobalamin.
B_{12s}	Hydridocobalamin	(no entry)
B_{12}-zinc tannate complex	Cyanocobalamin-zinc tannate complex	Zinc-vitamin B_{12}-tannate.
Coenzyme B_{12}	Dibenzcozamide	Dimebenzcozamide
B_{12} radioactive	Vitamin $B_{12}Co^{60}$	Radioactive cyanocobalamin; radiocyanocobalamin (Co^{60}); cyanocobalamin Co^{60}.

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Table 2.

Common Names of Vitamin B_{12} - According to the (British) Nutrition Society (0364)

Previous Name	Recommended Name
Vitamin B_{12} or Cobalamin	Cyanocobalamin
Vitamin B_{12a}, B_{12b}, or Hydroxocobarnide	Hydroxocobalamin
Vitamin B_{12c}	Nitritocobalamin

Vitamin B_{12}. The term vitamin B_{12} should be used as the generic descriptor for all corrinoids exhibiting qualitatively the biological activity of cyanocobalamin. The term corrinoids should be used as the generic descriptor for all compounds containing the corrin nucleus and thus chemically related to cyanocobalamin. The term corrinoid is not synonymous with the term vitamin B_{12}.

Amounts of vitamins and summation. All amounts of vitamins should be expressed in terms of their mass rather than in terms of i.u. (See Metric Units, Conversion Factors and Nomenclature in Nutritional and Food Sciences - London: The Royal Society 1972 (paras. 8 and 14 - 20.))

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B. Chemical Names

Table 3 .

Chemical Names of Vitamin B_{12} (Merck, 2628)

Letter Designation	Nomenclature
B_{12}	Cobalamin refers to all of the molecule except the cyano group. A new system for the analogs and degradation products is proposed. (See E. Lester Smith in the Monograph edited by H. C. Heinrich, Vitamin B_{12} and Intrinsic Factor, 1. Europaisches Symposion (Enke, 1957) pp 554 - 560: The fundamental ring system consisting of the four pyrrole nuclei joined in a macro ring with the three bridge carbon atoms and six conjugated double bonds, but without cobalt or side chains, would be called "corrin." The co-contg heptacarboxylic acid resulting from hydrolysis of all the amide groups present in vitamin B_{12}, without the CN and the nucleotide, is designated "corphyrinic acid." The corresponding hexacarboxylic acid which still retains the 2-hydroxypropionamide group on a side chain is called "corphinic acid" and the hexacarboxylic acid having the ribofuranosidophosphorylpropionamide side chain is called "cobamic acid." Thus "cobamide," the hexamide of cobamic acid, would be derived from vitamin B_{12} by removal of the cyano and the 5,6-dimethylbenzimidazole groups. By this system vitamin B_{12} may be called 5,6-dimethylbenzimidazolyl cyanocobamide.
B_{12b}	Cobinamide hydroxide (or chloride, hy hydrogen sulfate, hydrogen sulfite, etc.) hydrate phosphate 3'-ester with 5, 6-dimethyl-α-D-ribofuranosylbenzimidazole inner salt; α-(5,6-dimethylbenzimidazolyl)aquocobamide.
B_{12s}	Believed to be cobinamide hydride phosphate 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole inner salt; α-(5,6-dimethylbenzimidazolyl) hydroxocobamide.

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Table 3 . (Continued)

Chemical Names of Vitamin B_{12} (Merck, 2628)

Letter Designation	Nomenclature
B_{12a}	Cobinamide hydroxide phosphate 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosyl-benzimidazole inner salt; α-(5,6-dimethyl-benzimidazolyl)hydroxocobamide.
B_{12a} Acetate	Cobinamide acetate phosphate 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosyl-benzimidazole inner salt.
Sulfitocobalamin	Cobanamide sulfite phosphate 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosyl-benzimidazole.
Coenzyme B_{12}	5,6-Dimethylbenzimidazolylcobamide coenzyme.

C. Trade Names

Table 4 .

Trade Names of Vitamin B_{12} (Merck, 2628)

Letter Designation	Nomenclature
B_{12}	Anacobin; Antipernicin; Bedoce; Bedodeka; Bedoz; Behepan; Berubi; Berubigen; Betalin-12; Bevatine-12; Bevidox; Bexii; Bexil; Biocobalamine; Biocres; Bitevan; B-Teive; B-Twelve; Byladoce; Claretin-12; Cobalin; Cobamin; Cobamine; Cobione; Covit; Crystamin; Cycobemin; Cycolamin; Cykobeminet; Cytacon; Cytamen; Cytobion; Distivit (B_{12} peptide); Dobetin; Docemine; Docibin; Docigram; Docivit; Dodecabee; Dodex; Ducobee; Duodecibin; Embiol; Emociclina; Eritrone; Erycytol; Erythrotin; Euhaemon;

0016

Table 4 . (Continued)

Trade Names of Vitamin B_{12} (Merck, 2628)

Letter Designation	Nomenclature
B_{12} (Continued)	Fresmin; Hermo-B-Doze; Hemomin; Hepagon; Hepavis; Hepcovite; Hydroxamin; Macrabin; Megabiol (Indian); Megalovel; Milbedoce; Millevit; Nagravon; Normocytin; Peraemon; Pernaevit; Pernipur; Plecyamin; Poyamin; Redamina; Redisol; Rhodacryst; Rubesol; Rubivitan; Rubramin; Rubripca; Rubrocitol; Sytobex; Vibalt; Vibisone; Virubra; Vitarubin; Vita-Rubra; Vitral.
B_{12a}	Axion; Axlon; Ciplamin H; Cobalex; Depogamma; Docelan; Duradoce; Duralta-12; Hydrogrisevit; Hydrovit; Hyxobamine; Idrogriseovit; Neo-Cytamen; Neo-Macrabin; Neo-Rojamin; OH-Duphar; Oxobemin; alpha-Redisol; Redisol H; Sytobex-H; Vitadurin.
B_{12}-Zinc Tannate Complex	Ingredient of Depinar; Bevitam.
Coenzyme B_{12}	Heraclene; Indusil.
Vitamin B_{12}, Radioactive	Racobalamin.

D. Chemical Abstracts Services Unique Registry Numbers:

1. B_{12} 68199
2. B_{12a} 13422510
3. B_{12b} 68199
4. B_{12c} 13479613
5. B_{12} Factor IIIm 13980966
6. B_{12}-Co^{60} 13422532
7, B_{12}-Co^{57} 13548271
8. Coenzyme B_{12} glutathionic acid PM9001143

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II. Empirical Formula

$C_{63}H_{88}CoN_{14}O_{14}P$ (2819) for cyanocobalamin.

The empirical formulas for various forms of B_{12} are given in the Merck Index (2628) as follows:

Table 5 .

Empirical Formulas for B_{12}

Letter Designation	Symbol	
B_{12}	$C_{63}H_{88}CoN_{14}O_{14}P$	C 55.74%, H 6.68%, Co 4.34%, N 14.45%, O 16.50%, P 2.28%
B_{12a}	$C_{62}H_{89}CoN_{13}O_{15}P$	C 55.31%, H 6.66%, Co 4.38%, N 13.52%, O 17.83%, P 2.30%
B_{12a} Acetate	$C_{64}H_{91}CoN_{13}O_{16}P$	
B_{12s}	$C_{62}H_{89}CoN_{13}O_{14}P$	C 55.97%, H 6.74%, Co 4.43%, N 13.69%, O 16.84%, N 2.33%
B_{12p}	$C_{50}H_{72}CoN_{13}O_{8}$	C 57.62%, H 6.96%, Co 5.66%, N 17.47%, O 12.28%
Sulfitocobalamin	$C_{62}H_{88}CoN_{13}O_{17}PS$	C 52.76%, H 6.43%, Co 4.18%, N 12.90%, O 19.27%, P 2.19%, S 2.27%
Coenzyme B_{12}	$C_{72}H_{100}CoN_{18}O_{17}P$	

In 1948, Rickes et al. (2289) reported the isolation of red, needle-like crystals from a liver extract and proposed the same "Vitamin B_{12}." They reported two estimates of its potency:

1. A year earlier, Shorb had found that liver concentrates permitted growth of Lactobacillus lactis Dorner and had assigned a potency of 1000 LLD units/mg to an arbitrarily selected standard concentrate. Using the Shorb assay the authors estimated the potency of their crystals as 11 million LLD units/mg.

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2. The USP XIII (2819) had defined one USP unit as the amount of liver extract needed daily to produce clinical and hematological responses in pernicious anemia. From preliminary clinical tests the authors estimated the potency of their crystals as one USP injectable unit/μg.

In 1948, Smith and Parker (2568) reported the purification and crystallization of a substance that they said was probably the same as that recently described by Rickes et al. who had proposed the name "Vitamin B_{12}."

In 1948, Rickes et al. (2288) demonstrated that B_{12} contained cobalt, and referred to a parallel demonstration in press by Smith and Parker. The authors also reported that cobalt alone did not relieve pernicious anemia; and that B_{12} contained P and N but not S. Autoclaving at 121°C for 15 minutes did not affect B_{12}, but it was inactivated slowly by 0.015N NaOH or by 0.01N HCl.

III. Structural Formulas

In 1956, Hodgkin et al. (1240), using x-ray crystallography, obtained the electron density maps shown in Figure 2:

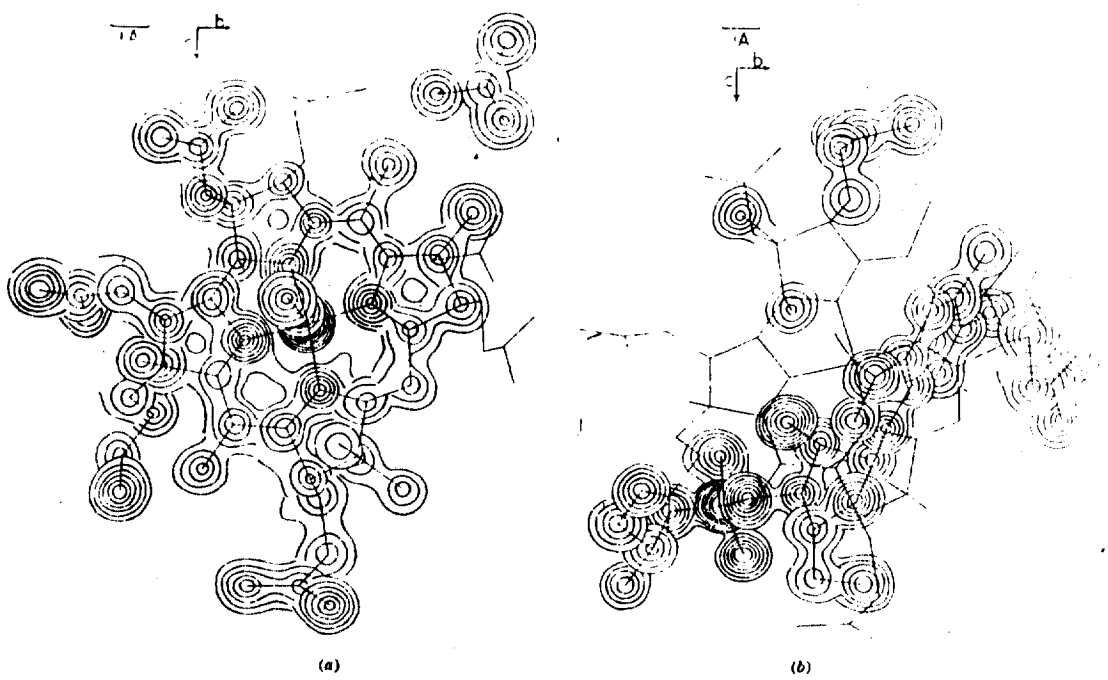

Figure 2. Electron Density Levels from the Three-Dimensional Electron Density Distribution for Wet B_{12} Crystals, Calculated with Terms Placed on 93 Atoms (1240)

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(In Figure 2, and in Figure 5, the contours are drawn in the sections of the calculated distribution parallel with the α plane, passing at or near the atomic positions. Owing to the complexity of the molecule, complete contours for every atom are not given and the figure is divided into two parts. (a) shows the cobalt-containing nucleus and cyanide group; (b) the benziminazole, sugar, phosphate and propanolamine groups, the side chains being divided between the two. The acetamide chain on ring B is inset. The contour interval is 1e/A.[3])

The authors then calculated the 3-D structure shown in Figure 3, from which they derived a formal structure for B_{12}, shown in Figure 6 (I), and for its hexacarboxylic acid (II); the double bonds formed a resonating system by intervention of the cobalt atom (III). The electron density distribution gave the inter-atomic distances shown in Figure 4, with peaks as shown in Figure 5.

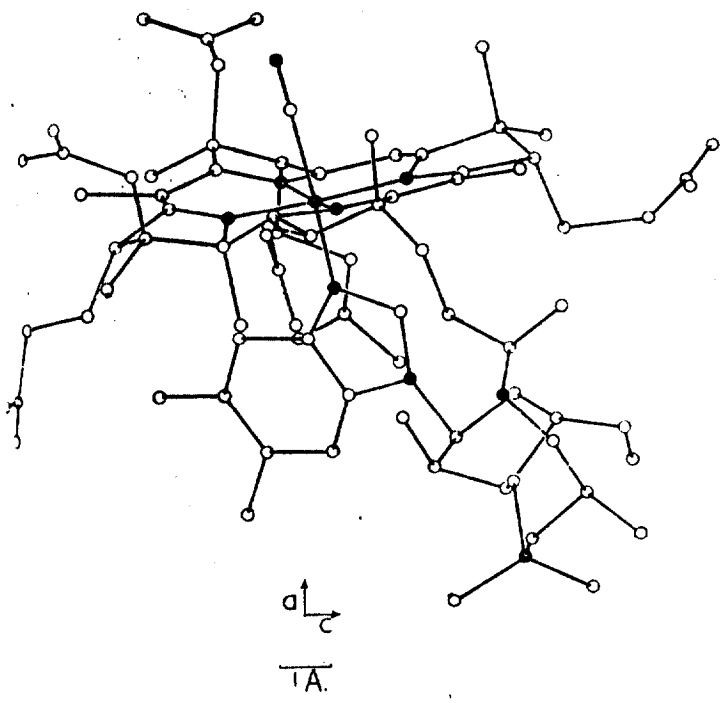


Figure 3. The atomic positions found in the molecule of vitamin B_{12}. These are shown as derived in the wet crystals, projected on the b plane. To distinguish different parts of the molecule, bonds within the cobalt containing nucleus, benziminazole and cyanide groups are shown in black, together with the cobalt and phosphorus atoms and the nitrogen atoms of the nucleus, benziminazole, propanolamine and cyanide groups. (1240)

0020

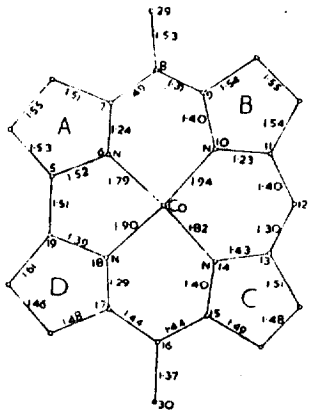


Figure 4. Interatomic Distances Found in the Inner Nucleus of the Hexacarboxylic Acid, Derived from Nine Refinements of the Calculated Electron Density Distribution (1240)

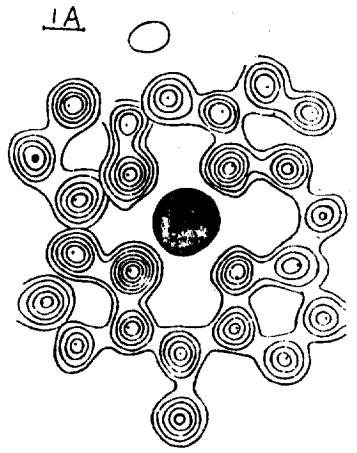
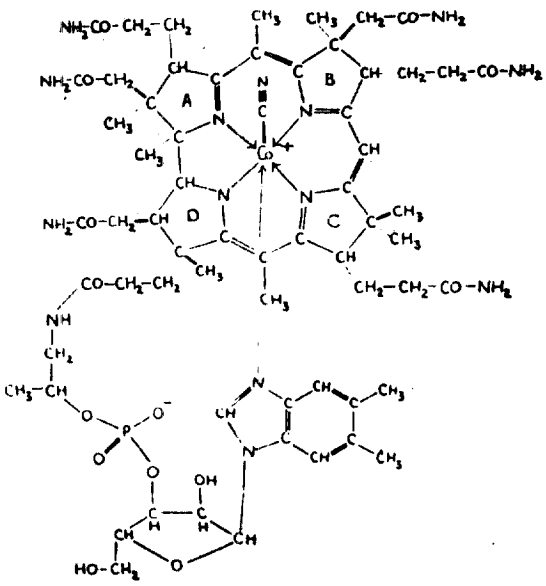


Figure 5. Electron Density Peaks Over the Nucleus in Air-Dried Vitamin B_{12}, Derived from the Three-Dimensional Electron Density Distribution Calculated with Terms Phased on 95 Atoms (Princeton Data) (1240)

0021



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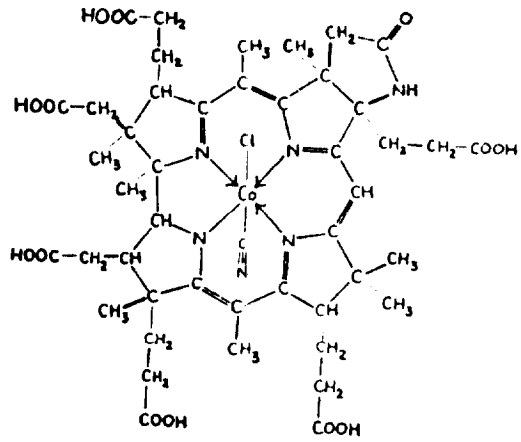
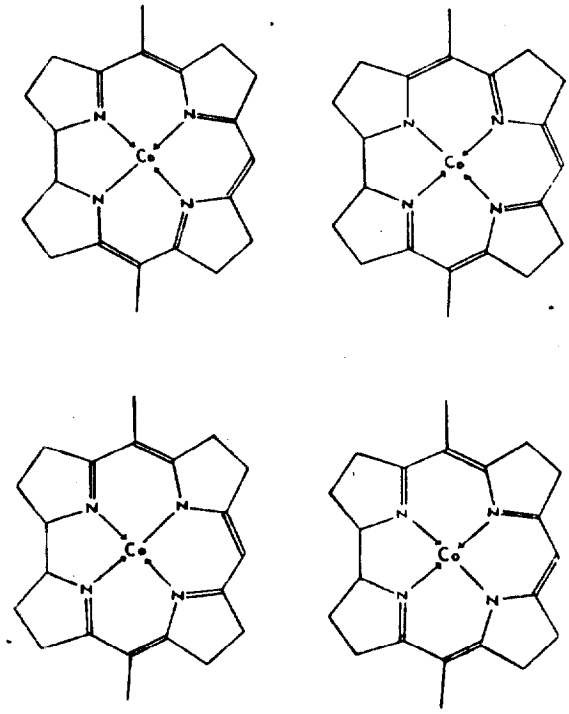


(II)



(III)

Figure 6. (1240)

0022

In 1961, Lenhert and Hodgkin (1600) elucidated the structure of the 5, 6-dimethylbenzimidazolylcobamide coenzyme recently isolated by Barker and his co-workers. Figure 7(a) shows the 3-D calculations from x-ray crystallography, and Figure 7(b) shows the proposed structure of the nucleoside.

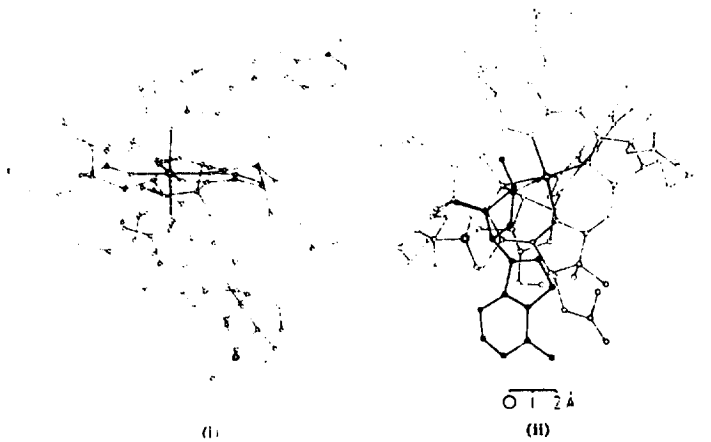


Figure 7(a). The Atomic Positions in One Molecule of the 5,6-Dimethylbenzimidazolylcobamide Coenzyme as Found in the Wet Crystals and Viewed Along (i) the b Axis, (ii) the a Axis. In (ii) the Atoms of the Nucleoside Unit are Marked by Filled Circles. (1600)

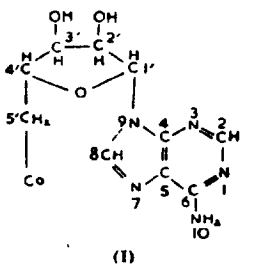


Figure 7(b) (1600)

In 1966, Wagner (2921) reviewed what was known about biosynthesis of corrinoid compounds, in particular the cobalamins (Figure 8). In his view B_{12} was synthesized "probably only" by micro-organisms, despite "apparent" evidence of synthesis by rabbits, mice, and mouse mammary tumors <u>in vitro</u>.

0023

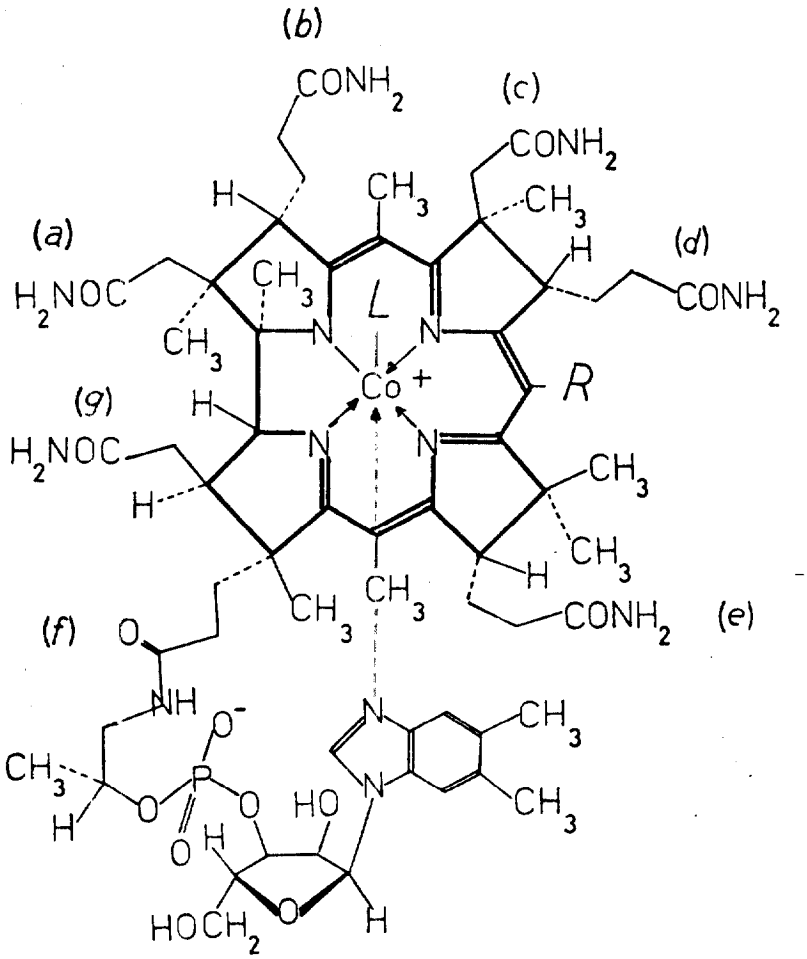
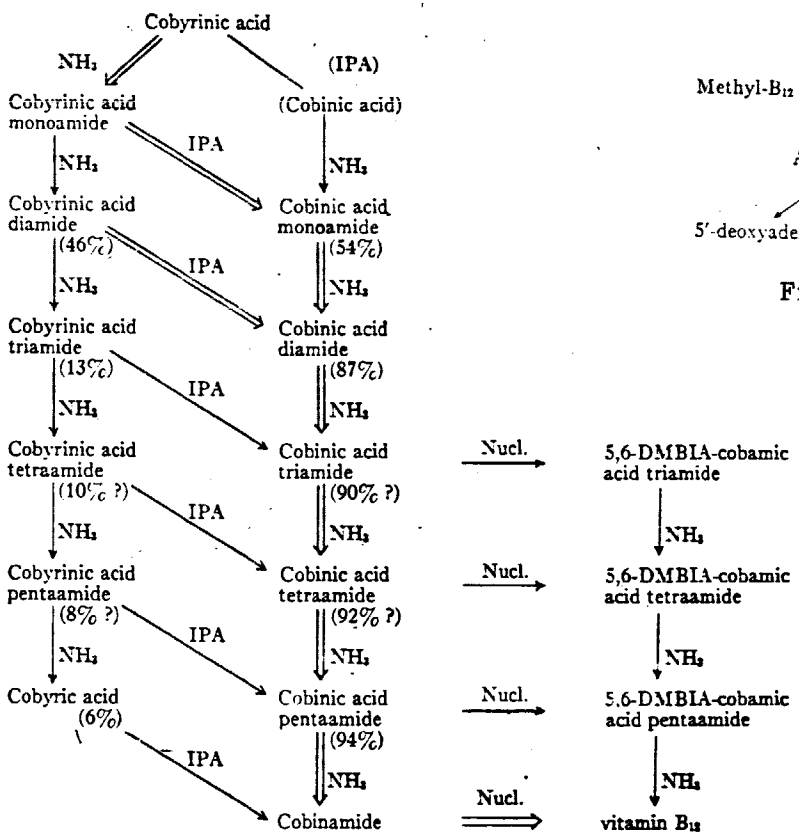


Figure 8. Structures of Cobalamins (2921)

The supposed pathway of biosynthesis of B_{12} is shown in Figure 9(a); of its 5'-deoxyadenosyl coenzyme in 9(b); and of some alkyl derivatives in 9(c).

Microbial degradation is described as partly by oxidation, partly by photolysis; but the chemistry is complicated, and the original paper should be consulted.

0024



⟹ = main pathway
→ = side pathway
} in the case of *Propionibacterium shermanii*
IPA = incorporation of the isopropanolamine group
NH_3 = amidation of one carboxylic acid group
Nucl. = incorporation of the nucleotide without considering the real pathway
? = estimate

Figure 9(a) (2921)

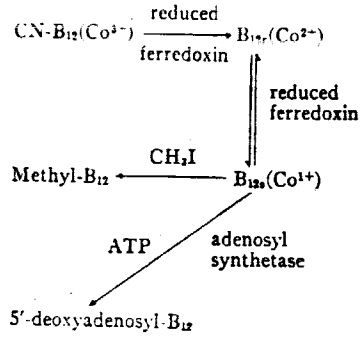


Figure 9(b) (2921)

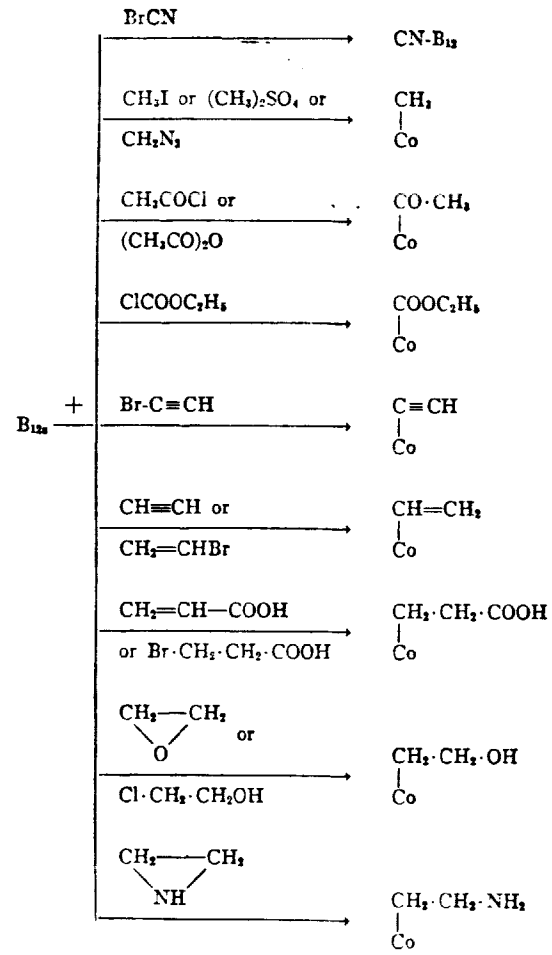


Figure 9(c) (2921)

0025

In 1970, Silber and Moldow (2521) summarized the 3-D structures of cyanocobalamin (B_{12}) and two derived coenzymes, 5'-deoxyadenosyl-B_{12} and methylcobalamin as in Figure 10.

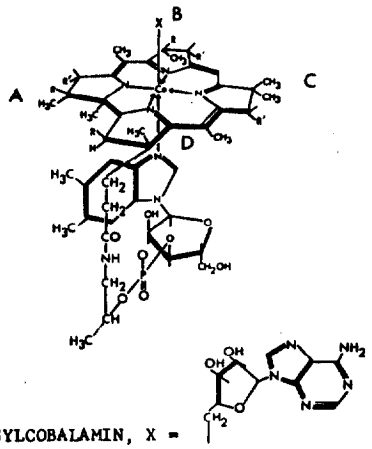


Figure 10. Structure of Vitamin B_{12} and B_{12} Coenzymes (2521)

The authors listed the reactions involving these compounds as in Tables 6, 7 and 8.

Table 6. (2521)

Reactions Requiring 5'-Deoxyadenosyl B_{12}

Reaction	Pathway	Organism
Glutamate mutase	Glutamic acid fermentation	Clostridium tetanomorphum
Methylmalonyl-CoA mutase	Propionate oxidation	Propionibacterium shermanii; animals, man
Dioldehydrase	Glycol metabolism	Aerobacter aerogenes
	Glycerol metabolism	Lactobacillus (unidentified)
Ribonucleotide reductase	Deoxyribonucleotide formation	Lactobacillus leichmanii
Ethanolamine deaminase	Ethanolamine fermentation	Choline-fermenting Clostridium
β-Lysine isomerase	Lysine fermentation	Clostridium sticklandii

0026

Table 7 (2521)

Reactions Requiring Methyl-B_{12}

Reaction	Pathway	Organism
N^5-methyl tetrahydrofolate: homocysteine methyl transferase	Methionine synthesis	Esch. coli, pig, man
Methane synthesis	Methanol fermentation	Methanosarcina barkeri
Acetate synthesis	Carbon dioxide metabolism	Clostridium thermoaceticum

Table 8. (2521)

Comparison of Ribonucleotide Reductases

Enzyme	L. leichmanii	Esch. coli	Mammalian
Nucleotide substrate	Triphosphate	Diphosphate	Diphosphate
Hydrogen donor	Thioredoxin-like protein	Thioredoxin	Thioredoxin
Cation requirement	None	Magnesium	Magnesium
Stimulation by metal	None	Iron	Iron
Allosteric regulation	Yes, dATP less important	Yes, dATP negative effector	Yes, dATP negative effector
Deoxyadenosyl B_{12} requirement	Yes	None	Probably none

The corrin nucleus is linked to D-1-amino-2-propanol, which is linked to ribose, which has an α-glycoside link to 5,6-dimethylbenzimidazole, of which an N has a coordinate link with the Co of the corrin nucleus. (1015)

A clear structural description is given by Gallagher et al. (0916): "The molecule is divisible into two portions, a corrin and a nucleotide. The corrin ring resembles the structure of the porphyrins. It contains a cobalt atom centrally and acetamide and propionamide side chains. The nucleotide consisting of the base 5,6-dimethylbenzimidazol, ribose, and phosphoric acid lies in a plane which is nearly at right angles to the corrin nucleus. The phosphate is esterified with 1-amino-2-propanol which is linked with the propionamide side chain of ring D of the corrin nucleus."

0027

Analogs were formed in the following ways;

1. By substituting the amide of the propionamide side chain ($-CH_2 \cdot CH_2 \cdot CO \cdot NH_2$) of the A, B, or C ring; thus the ethylamide, methylamide, monobasic acid, and anilide analogs.

2. Analogs differing from B_{12} at the nucleotide included 5-methylbenzimidazole cyanocobamide, and B_{12}-carbanilide (joined to a ribose hydroxyl). In pseudovitamin B_{12}, adenine replaced the 5,6-dimethylbenzimidazole.

3. The cyanide was replaced in hydroxocobalamin, sulfitocobalamin, methylcobalamin, ammonia cobalichrome, and 5'-deoxyadenosylcobalamin (coenzyme B_{12}) (0916).

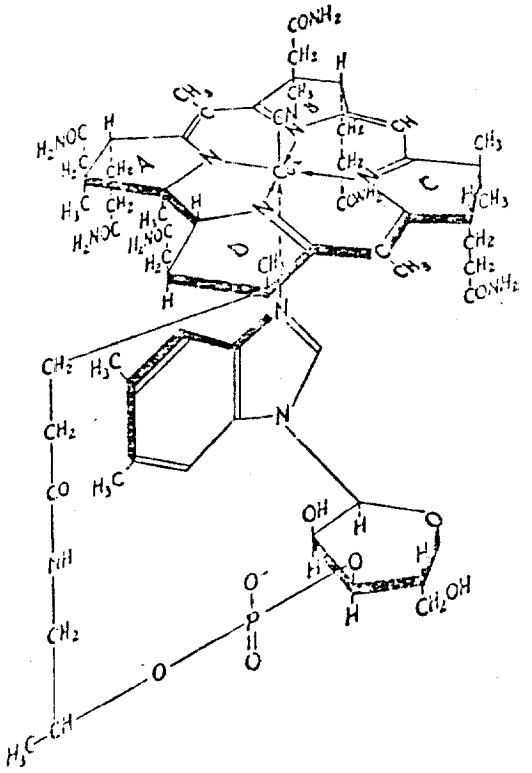


Figure 11. Spatial Formula of Vitamin B_{12}, α-(5,6-dimethylbenziminazolyl) cobamide cyanide (Lester Smith, 1965) (0916)

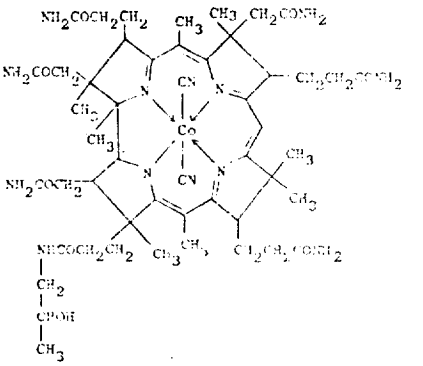


Figure 12. B_{12p} (Merck) (2628)

0028

IV. Molecular Weights

1.	B_{12}	mol wt 1355.42.
2.	B_{12a}	mol wt 1346.41.
3.	B_{12s}	mol wt 1330.40.
4.	B_{12p}	mol wt 1042.17.
5.	Sulfitocobalamin	mol wt 1409.47.
6.	Coenzyme B_{12}	mol wt 1579.57.

V. Specifications

Precise official specifications were found only in a therapeutic context, which seemed to imply parenteral use. The official abstracts are given first, below, and are followed by some information from a supplier, received from FDA.

For therapy, B_{12} is almost always given by injection (1015).

No mention of B_{12} was found in the Food Chemicals Codex (0547), or in Chemical Mutagens (1970) (0784).

No specifications for B_{12} were found in the Handbook of Food Additives (0895) which states on pages 105 and 106 that commercially available forms include both cyanocobalamin and cobalamin concentrate, and that usual standard dilutions possess 0.1% of the potency of the pure concentrate; also available are triturates and, more stable in humid conditions, gelatin-coated products and an ion-exchange-resin complex.

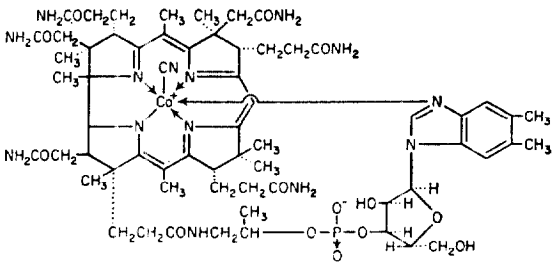
In Chemicals Used in Food Processing (0855) B_{12} is mentioned as "anti-pernicious anemia factor" but no level of use is entered.

In the USP XVIII (2819) cyanocobalamin is specified to contain not less than 96% and not more than 100.5% of $C_{63}H_{88}CoN_{14}O_{14}P$ on dry-weight basis.

Cyanocobalamin injections, in water or isotonic saline, must contain not less than 95% and not more than 115% of the amount on the label, but is exempt from tests if the label claims 100 µg or less per injection. Co^{57}-B_{12} capsules (for diagnostic use) must contain not less than 90% nor more than 110% of the labeled amount and of the labeled radioactivity, which must be not less than 0.5 µCi/µg $B_{12}\cdot Co^{57}$-B_{12} solution for oral use has similar specifications. The Co^{57} half-life is given as 270 days.

The relevant text in the USP is as follows:

0029



Cyanocobalamin

Vitamin B_{12}
$C_{63}H_{88}CoN_{14}O_{14}P$ 1355.40

Cyanocobalamin contains not less than 96.0 percent and not more than 100.5 percent of $C_{63}H_{88}CoN_{14}O_{14}P$, calculated on the dried basis.

Description: Dark red crystals or amorphous or crystalline red powder. In the anhydrous form, it is very hygroscopic and when exposed to air it may absorb about 12 percent of water.

Solubility: Sparingly soluble in water; soluble in alcohol; insoluble in acetone, in chloroform, and in ether.

Identification—

A: The ultraviolet absorption spectrum of the solution employed for measurement of absorbance in the *Assay* exhibits maxima within ±1 mμ at 278 mμ and 361 mμ and within ±2 mμ at 550 mμ. The ratio A_{361}/A_{278} is between 1.70 and 1.90, and the ratio A_{361}/A_{550} is between 3.15 and 3.40.

B: Fuse about 1 mg. with about 50 mg. of potassium pyrosulfate in a porcelain crucible. Cool, break up the mass with a glass rod, add 3 ml. of water, and dissolve by boiling. Add 1 drop of phenolphthalein T.S., and add sodium hydroxide solution (1 in 10), dropwise, until just pink. Add 500 mg. of sodium acetate, 0.5 ml. of diluted acetic acid, and 0.5 ml. of nitroso R salt solution (1 in 500): a red or orange-red color appears at once. Add 0.5 ml. of hydrochloric acid, and boil for 1 minute: the red color persists.

C: Dissolve about 5 mg. in 5 ml. of water in a 50-ml. distilling flask connected with a short, water-cooled, vertical condenser the tip of which dips into a test tube containing 1 ml. of 0.5 *N* sodium hydroxide. To the flask add 2.5 ml. of hypophosphorous acid, close, heat at simmering temperature for 10 minutes, then distil 1 ml. into the test tube. To the test tube add 4 drops of cold saturated ferrous ammonium sulfate solution, shake gently, then add about 30 mg. of sodium fluoride, and bring the contents to a boil. Immediately add, dropwise, dilute sulfuric acid (1 in 7) until a clear solution results, then add 3 to 5 drops more of the acid: a blue or blue-green color develops within a few minutes.

Loss on drying, page 935—Heat about 25 mg., accurately weighed, in a suitable vacuum drying apparatus at 105° and at a pressure of not more than 5 mm. of mercury for 2 hours, cool, and weigh: it loses not more than 12 percent of its weight.

Pseudo cyanocobalamin—Dissolve 1.0 mg. in 20 ml. of water contained in a small separator, add 5 ml. of a mixture of equal volumes of carbon tetrachloride and cresol, and shake well for about 1 minute. Allow to separate, draw off the lower layer into a second small separator, add 5 ml. of dilute sulfuric acid (1 in 7), shake well, and allow to separate completely (the complete separation of the layer may be facilitated by centrifuging): the separated upper layer is colorless or has no more color than a mixture of 0.15 ml. of 0.1 *N* potassium permanganate and 250 ml. of water.

Assay—Transfer about 3 mg. of Cyanocobalamin, accurately weighed, with the aid of water to a 100-ml. volumetric flask, dilute with water to volume, and mix. Dissolve an accurately weighed quantity of U. S. P. Cyanocobalamin Reference Standard in water, and dilute quantitatively and stepwise with water to obtain a Standard solution having a concentration of about 30 mcg. per ml. Concomitantly determine the absorbances of both solutions in 1-cm. cells at the wavelength of maximum absorbance at about 361 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg., of $C_{63}H_{88}CoN_{14}O_{14}P$ in the Cyanocobalamin taken by the formula $0.1C(A_U/A_S)$, in which C is the concentration, in mcg. per ml., of U. S. P. Cyanocobalamin Reference Standard in the Standard solution and A_U and A_S are the absorbances of the solution of Cyanocobalamin and the Standard solution, respectively.

Packaging and storage—Preserve in tight, light-resistant containers.

CATEGORY: Hematopoietic vitamin; also see *Decavitamin Capsules* and *Tablets*.

USUAL DOSE: Maintenance—Intramuscular, 100 mcg. once a month.
Therapeutic—Intramuscular, 100 mcg. once a week.

USUAL DOSE RANGE: 30 mcg. to 1 mg. per dose.

0030

Cyanocobalamin Injection

Cyanocobalamin Injection is a sterile solution of cyanocobalamin in water for injection, or in water for injection rendered isotonic by the addition of sodium chloride. It contains not less than 95.0 percent and not more than 115.0 percent of the labeled amount of $C_{63}H_{88}CoN_{14}O_{14}P$ (anhydrous cyanocobalamin). Cyanocobalamin Injection labeled to contain 100 mcg. or less of cyanocobalamin in each ml. is exempt from the requirements of the test for *Limit of cyanocobalamin solids.*

Identification—The absorption spectrum, in the range of 300 mμ to 550 mμ, of the solution employed for measurement of absorbance in the *Assay* exhibits maxima at the same wavelengths as that of a similar solution of U. S. P. Cyanocobalamin Reference Standard, concomitantly measured, and the ratio A_{361}/A_{550} is between 3.15 and 3.40.

pH, page 938: between 4.5 and 5.5.

Limit of cyanocobalamin solids—*If the Injection contains an ester of para-hydroxybenzoic acid* as an added substance, conduct the following preliminary steps: Place about 5 ml., or a volume equivalent to 5 mg. of cyanocobalamin, of Injection in a small, glass-stoppered centrifuge tube, and shake with 5 ml. of chloroform previously washed twice with equal volumes of water and filtered through paper. Centrifuge the mixture, discard the chloroform, and repeat the extraction with two 5-ml. portions of washed chloroform. Then proceed with the clear, aqueous liquid as directed in the following paragraphs.

Pipet 3 ml., or a volume equivalent to 3 mg. of cyanocobalamin, of Injection into a weighing bottle, 25 mm. in diameter and 40 mm. high, fitted with an outside cap and previously tared against a similar bottle and cap used as a counterpoise. Heat both the bottles and caps at 105° for 16 hours. Cool, with the caps in place, in a desiccator over phosphorus pentoxide, and weigh the difference between the bottle containing the residue and the counterpoise. Heat again at 105° for 2 hours, cool, and weigh. If the loss in weight is more than 0.1 mg., heat for another 2 hours, and again weigh.

Transfer the residue, with the aid of a small quantity of water, to a 50-ml. beaker, dilute with water to about 15 ml., and add 1 drop of nitric acid. Then add, dropwise and with constant stirring, 2 ml. of 0.1 *N* silver nitrate for each ml. of Injection taken, heat nearly to boiling for 1 or 2 minutes, and allow the mixture to stand for 1 hour. Decant the supernatant liquid through a sintered-glass crucible, previously dried for 1 hour at 110° and tared against a similar crucible treated in the same manner, wash the precipitate by decantation with dilute nitric acid (1 in 1000), and then transfer the precipitate to the crucible. Wash the precipitate with the nitric acid solution until a few ml. of washings fails to produce turbidity with 1 drop of diluted hydrochloric acid, and finally wash with a small quantity of water. Dry the precipitate at 110° until the loss of weight after successive 1-hour intervals of heating does not exceed 0.1 mg. The weight of silver chloride, multiplied by 0.4078, represents its equivalent of NaCl.

Subtract the weight of sodium chloride found from the weight of the residue obtained as directed above. The difference, corrected for the weight of any nonvolatile added substance declared on the label, does not exceed 1.20 mg. for each mg. of $C_{63}H_{88}CoN_{14}O_{14}P$ found by the *Assay.*

Other requirements—It meets the requirements under *Injections*, page 797.

Assay—Dilute, if necessary, an accurately measured volume of Cyanocobalamin Injection, equivalent to not less than 300 mcg. of cyanocobalamin, quantitatively and stepwise with water to a concentration of about 30 mcg. per ml. Dissolve an accurately weighed quantity of U. S. P. Cyanocobalamin Reference Standard in water, and dilute quantitatively and stepwise with water to obtain a Standard solution having a known concentration of about 30 mcg. per ml. Concomitantly determine the absorbances of both solutions in 1-cm. cells at the wavelength of maximum absorbance at about 361 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mcg., of $C_{63}H_{88}CoN_{14}O_{14}P$ in each ml. of the Injection taken by the formula $10(CV)(A_U/A_S)$, in which C is the concentration, in mcg. per ml., of U. S. P. Cyanocobalamin Reference Standard in the Standard solution, V is the volume, in ml., of Injection taken, and A_U and A_S are the absorbances of the solution from the Injection and the Standard solution, respectively.

Packaging and storage—Preserve in light-resistant, single-dose or multiple-dose containers, preferably of Type I glass.

Injections available—Injection usually available contains the following amounts of cyanocobalamin: 100 mcg. and 1 mg. in 1 ml.; 5 mg. in 5 ml.; 300, 500, and 600 mcg., 1 mg., and 10 mg. in 10 ml.; 3 and 30 mg. in 30 ml.

CATEGORY and DOSE: See *Cyanocobalamin.*

Cyanocobalamin Co 57 Capsules

Cyanocobalamin Co 57 Capsules contain cyanocobalamin in which a portion of the molecules contain radioactive cobalt (^{57}Co) in the molecular structure. Each Capsule contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{57}Co as cyanocobalamin expressed in microcuries at the time indicated in the labeling. The cyanocobalamin content is not less than 90.0 percent and not more than 110.0 percent of the labeled amount. The specific activity is not less than 0.5 microcurie per mcg. of cyanocobalamin.

Caution—In making dosage calculations, correct for radioactive decay. The radioactive half-life of ^{57}Co is 270 days.

Description: May contain a small amount of solid or solids, or may appear empty.

Radionuclide identification—A solution of 1 or more Capsules in water responds to the test for *Radionuclide identification* under *Cyanocobalamin Co 57 Solution*, page 156.

Content uniformity—Determine the radioactivity, in counts per minute, of each of 20 Capsules by measurement in a suitable counting assembly and under identical geometric conditions. Calculate the mean radioactivity value in counts per minute per Capsule. The requirements are met if not less than 19 of the Capsules are within the limits of 96.5 percent and 103.5 percent of the mean radioactivity value.

Cyanocobalamin content—Determine the content, in mcg. per Capsule, of cyanocobalamin as directed under *Vitamin B_{12} Activity Assay*, page 887.

Assay for radioactivity—Determine the radioactivity, in counts per minute, of a calibrated cobalt 57 standard by measurement in a suitable counting assembly, adjusting the concentration of the standard so as to obtain optimum counting accuracy with the particular assembly used. Dissolve 1 or more Cyanocobalamin Co 57 Capsules in water, and adjust the concentration as for the standard. Transfer an accurately measured aliquot to a container identical to that used for the standard, and determine the radioactivity at approximately the same time and under the identical geometrical conditions used for the standard. Correct both determinations for background, and calculate the radioactivity, in microcuries per Capsule, by the formula $SD(A/B)$, in which S is the microcurie strength of the standard, D is the dilution factor, and A and B are the radioactivities expressed in counts per minute of the sample and the standard, respectively.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Expiration date—The expiration date is not later than 6 months after date of standardization.

Labeling—Label Capsules to include the following: the name of the Capsules; the name, address, and batch or lot number of the manufacturer; the time and date of standardization; the amount of cyanocobalamin expressed in mcg. per Capsule; the amount of ^{57}Co as cyanocobalamin expressed in microcuries per Capsule at the time of standardization; and the statements, "Caution—Radioactive Material" and "Do not use after 6 months from date of standardization."

Capsules available—Capsules are usually available in such sizes as may be requested by the physician.

CATEGORY: Diagnostic aid (pernicious anemia).

USUAL DOSE: Oral, the equivalent of 0.5 to 1 microcurie.

Cyanocobalamin Co 57 Solution

Cyanocobalamin Co 57 Solution is a solution suitable for oral administration, containing cyanocobalamin in which a portion of the molecules contain radioactive cobalt (^{57}Co) in the molecular structure.

Cyanocobalamin Co 57 Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{57}Co as cyanocobalamin expressed in microcuries per ml. at the time indicated in the labeling. The cyanocobalamin content is not less than 90.0 percent and not more than 110.0 percent of the labeled amount. The specific activity is not less than 0.5 microcurie per mcg. of cyanocobalamin. Cyanocobalamin Co 57 Solution contains a suitable antimicrobial agent.

Caution—In making dosage calculations, correct for radioactive decay. The radioactive half-life of ^{57}Co is 270 days.

Description: Clear, colorless to pink solution.

Radionuclide identification—Its gamma-ray scintillation spectrum is identical to that of a specimen of cobalt 57 of known purity, which exhibits a major photoelectric peak having an energy of 0.122 MeV.

pH, page 938: between 4.0 and 5.5.

Radiochemical purity—[NOTE—Solutions of cyanocobalamin are light-sensitive. Prepare the strips in diffuse light, and perform the development and drying steps in the absence of light.] Place 0.01 ml. of a solution containing 1 mg. of cyanocobalamin per ml. about 45 mm. from one end of a 25- × 300-mm. strip of chromatographic paper (see *Chromatography*, page 792), and allow to dry. To the same area add a measured volume, representing an activity of not less than 20,000 counts per minute, of appropriately diluted Cyanocobalamin Co 57 Solution, and allow to dry. Develop the chromatogram over a period of about 24 hours by descending chromatography, using a freshly prepared, homogeneous solution prepared by mixing 1 liter of secondary butyl alcohol, 1 ml. of stronger ammonia water, 20 ml. of sodium cyanide solution (3.5 in 1000), and 300 ml. of water (if phases separate, add 10-ml. increments of secondary butyl alcohol, and shake until the mixture becomes homogeneous). Remove the paper strip from the apparatus when the cyanocobalamin spot has moved at least 75 mm. from the point of application. Dry the chromatogram in air, and determine the radioactivity distribution by scanning with a suitable collimated radiation detector, or divide the strip horizontally into sections not exceeding 65 mm. in width, and determine the radioactivity of the individual sections. The radioactivity of the cyanocobalamin band is not less than 95.0 percent of the total radioactivity.

Cyanocobalamin content—Determine the content, in mcg. per ml., of cyanocobalamin as directed under *Vitamin B_{12} Activity Assay*, page 887.

Assay for radioactivity—Determine the radioactivity, in counts per minute, of a calibrated cobalt 57 standard by measurement in a suitable counting assembly, adjusting the concentration of the standard so as to obtain optimum counting accuracy with the particular assembly used. Transfer an accurately measured aliquot of Cyanocobalamin Co 57 Solution, appropriately diluted, to a container identical to that used for the standard, and determine the radioactivity at approximately the same time and under the identical geometrical conditions used for the standard. Correct both determinations for background, and calculate the radioactivity, in microcuries per ml., by the formula $SD(A/B)$, in which S is the microcurie strength of the standard, D is the dilution factor, and A and B are the radioactivities expressed in counts per minute of the sample and the standard, respectively.

Packaging and storage—Preserve in single-dose or in multiple-dose containers.

Expiration date—The expiration date is not later than 6 months after date of standardization.

Labeling—Label it to include the following: the name of the Solution; the name, address, and batch or lot number of the manufacturer; the time and date of standardization; the amount of ^{57}Co as cyanocobalamin expressed as total microcuries and as microcuries per ml. at the time of standardization; the amount of cyanocobalamin expressed in mcg. per ml.; the name and quantity of the added preservative; and the statements, "Caution—Radioactive Material" and "Do not use after 6 months from date of standardization."

Solutions available—Solution is usually available in such sizes as may be requested by the physician.

CATEGORY and DOSE: See *Cyanocobalamin Co 57 Capsules*.

In the NF XIII (0061) cobalamin concentrate is specified as the dried, partly purified products of selected cultures of Streptomyces or other cobalamin-producing micro-organisms, containing not less than 500 µg of cobalamin per 1 g of concentrate, and may contain "harmless" diluents and stabilizers, but the actual cobalamin content must be stated on the label. Co^{60}-B_{12} capsules are limited to 90 - 110% of the claimed B_{12} content and radioactivity, and the radioactivity is not less than 0.5 µCi/µg B_{12} and, in no capsule may vary more than ±3% either side of the batch average. The Co^{60} half-life is given as 5.27 years. Co^{60}-B_{12} solution for oral use (diagnosis) is limited

to 90 - 110% of the claimed B_{12} content and radioactivity; the radioactivity is not less than 0.5 μCi/μg B_{12} nor more than 1.0 μCi/ml of solution, and must not be significantly contaminated with other radionuclides; the solution may contain a suitable bacteriostat. The relevant text in the NF is as follows:

Cobalamin Concentrate

Cobalamin Concentrate consists of the dried, partially purified product resulting from the growth of selected *Streptomyces* cultures or other cobalamin-producing microorganisms. It may contain harmless diluents and stabilizing agents. Cobalamin Concentrate contains, in each g., not less than 500 mcg. of cobalamin.

Description—Cobalamin Concentrate occurs as pink to brown granules or fine powder.

Identification—Ignite 1 g. of Cobalamin Concentrate at a temperature not exceeding 500°. If necessary, nitric acid may be added to destroy the organic matter, but sulfuric acid is not to be used. Dissolve the residue in 5 ml. of hydrochloric acid, transfer the solution to a 25-ml. graduate, add 1 ml. of stannous chloride solution (1 in 10), and dilute to 10 ml. Then add 2.5 ml. of potassium thiocyanate solution (1 in 2) and 12.5 ml. of acetone, and mix well: a bluish green color forms (cobalt).

Loss on drying, page 814—Dry Cobalamin Concentrate at 60° under a pressure of not more than 5 mm. of mercury for 2 hours: it loses not more than 5 percent of its weight.

pH, page 824—The pH of a solution of Cobalamin Concentrate (1 in 200) is between 4.0 and 8.0.

Assay—Proceed as directed under *Cobalamin Assay*, page 793.

Packaging and storage—Preserve Cobalamin Concentrate in tight containers, protected from light.

Labeling—The potency in terms of the number of mcg. of cobalamin in each g. of Cobalamin Concentrate must be stated on the label.

CATEGORY—Vitamin B_{12} supplement.

Cyanocobalamin Co 60 Capsules

Cyanocobalamin Co 60 Capsules contain cyanocobalamin in which a portion of the molecules contain radioactive cobalt (^{60}Co) in the molecular structure. Cyanocobalamin Co 60 Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{60}Co as cyanocobalamin expressed in microcuries at the time indicated in the labeling. The activity of each capsule in not less than 97.0 percent and not more than 103.0 percent of the mean radioactivity of the individual capsules of the lot. The cyanocobalamin content is not less than 90.0 percent and not more than 110.0 percent of the labeled amount. The specific activity is not less than 0.5 microcurie per mcg. of cyanocobalamin. Significant quantities of other radionuclides are absent.

Caution—In making dosage calculations, correct for radioactive decay. The radioactive half-life of ^{60}Co is 5.27 years.

Description—Cyanocobalamin Co 60 Capsules may contain a small, rectangular solid, or may appear empty.

Radionuclide identification—A solution of 1 or more Cyanocobalamin Co 60 Capsules in water responds to the test for *Radionuclide identification* under *Cyanocobalamin Co 60 Solution*, page 188.

Cyanocobalamin content—Determine the content, in mcg. per Capsule, of cyanocobalamin as directed under *Vitamin B_{12} Activity Assay*, page 792.

Content uniformity—Determine the radioactivity, in counts per minute, of each capsule by measurement in a suitable counting assembly and under identical geometrical conditions. Calculate the mean radioactivity of the individual capsules.

Assay for radioactivity—Determine the radioactivity, in counts per minute, of a calibrated cobalt 60 standard by measurement in a suitable counting assembly, adjusting the concentration of the standard so as to obtain optimum counting accuracy with the particular assembly used. Dissolve 1 or more Cyanocobalamin Co 60 Capsules in water, and adjust the concentration as for the standard. Transfer an accurately measured aliquot to a container identical to that used for the standard, and determine the radioactivity at approximately the same time and under the identical geometrical conditions used for the standard. Correct both determinations for background, and calculate the radioactivity, in microcuries per Capsule, by the formula $SD \times (A/B)$, in which S is the microcurie strength of the standard, D is the dilution factor, and A and B are the radioactivities expressed in counts per minute of the sample and the standard, respectively.

Packaging and storage—Preserve Cyanocobalamin Co 60 Capsules in well-closed containers.

Expiration date—The expiration date of Cyanocobalamin Co 60 Capsules is not later than 6 months after date of calibration.

Labeling—Label Cyanocobalamin Co 60 Capsules to include the following: the name of the Capsules; the name, address, and batch or lot number of the manufacturer; the time and date of calibration; the amount of cyanocobalamin expressed in mcg. per Capsule; the amount of ^{60}Co as cyanocobalamin expressed in microcuries per Capsule at the time and date of calibration; the warning, "Caution—Radioactive Material"; and the statement, "Do not use after 6 months from date of calibration."

Capsules available—Cyanocobalamin Co 60 Capsules are usually available in such sizes as may be requested by the physician.

CATEGORY—Diagnostic aid (pernicious anemia).

USUAL DOSE—**0.5** to **2 mcg.**, containing not more than 1 microcurie.

USUAL DOSE RANGE—The equivalent of 0.5 to 1 microcurie.

Cyanocobalamin Co 60 Solution

Cyanocobalamin Co 60 Solution is a solution suitable for oral administration, containing cyanocobalamin in which a portion of the molecules contain radioactive cobalt ^{60}Co in the molecular structure. Cyanocobalamin Co 60 Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{60}Co as cyanocobalamin expressed in microcuries at the time indicated in the labeling. The cyanocobalamin content is not less than 90.0 percent and not more than 110.0 percent of the labeled amount per ml. The amount of cobalt 60 as cyanocobalamin is not more than 1 microcurie per ml. The specific activity is not less than 0.5 microcurie per mcg. of cyanocobalamin. Significant quantities of other radionuclider are abcent. Cyanocobalamin Co 60 Solution contains a suitable bacteriostatic agent.

Caution—In making dosage calculations, correct for radioactive decay. The radioactive half-life of ^{60}Co is 5.27 years.

Description—Cyanocobalamin Co 60 Solution is a clear, colorless to pink solution.

Radionuclide identification—The gamma-ray scintillation spectrum of Cyanocobalamin Co 60 Solution is identical to that of a specimen of cobalt 60 of known purity, which exhibits photoelectric peaks having energies of 1.172 Mev. and 1.332 Mev.

pH, page 824—The pH of Cyanocobalamin Co 60 Solution is between 4.0 and 5.5.

Radiochemical purity—Place 0.01 ml. of a solution, containing 1 mg. of cyanocobalamin per ml., about 45 mm. from one end of a 25 × 300-mm. strip of chromatographic paper (see *Chromatography*, page 786), and allow to dry. To the same area add a measured volume, representing an activity of not less than 20,000 counts per minute, of appropriately diluted Cyanocobalamin Co 60 Solution, and allow to dry. Develop the chromatogram over a period of about 24 hours by descending chromatography, using a freshly

35

prepared homogeneous solution prepared by mixing 1 liter of secondary butyl alcohol, 1 ml. of stronger ammonia water, 20 ml. of sodium cyanide solution (3.5 in 1000), and 300 ml. of water (if phases separate, add 10-ml. increments of secondary butyl alcohol and shake until the mixture becomes homogeneous). Remove the paper strip from the apparatus when the cyanocobalamin spot has moved at least 75 mm. from the point of application. Dry the chromatogram in air, and determine the radioactivity distribution by scanning with a suitable collimated radiation detector, or section the strip into sections not exceeding 65 mm. in width and determine the radioactivity of the individual sections. The radioactivity of the cyanocobalamin band is not less than 95 percent of the total radioactivity. (*Caution:* Cyanocobalamin solutions are sensitive to light. Perform the preparation of strips in diffuse light and the development and drying of strips in the absence of light.)

Cyanocobalamin content—Determine the content, in mcg. per ml., of cyanocobalamin as directed under *Vitamin B_{12} Activity Assay*, page 892.

Assay for radioactivity—Determine the radioactivity, in counts per minute, of a calibrated cobalt 60 standard by measurement in a suitable counting assembly, adjusting the concentration of the standard so as to obtain optimum counting accuracy with the particular assembly used. Transfer an accurately measured aliquot of Cyanocobalamin Co 60 Solution, appropriately diluted, to a container identical to that used for the standard, and determine the radioactivity at approximately the same time and under the identical geometrical conditions used for the standard. Correct both determinations for background, and calculate the radioactivity, in microcuries per ml., by the formula $SD \times (A/B)$, in which S is the microcurie strength of the standard, D is the dilution factor, and A and B are the radioactivities expressed in counts per minute of the sample and the standard, respectively.

Packaging and storage—Preserve Cyanocobalamin Co 60 Solution in single-dose or in multiple-dose containers.

Expiration date—The expiration date of Cyanocobalamin Co 60 Solution is not later than 6 months after date of calibration.

Labeling—Label Cyanocobalamin Co 60 Solution to include the following: the name of the Solution; the name, address, and batch or lot number of the manufacturer; the time and date of calibration; the amount of ^{60}Co as cyanocobalamin expressed as total microcuries and as microcuries per ml. at the time and date of calibration; the amount of cyanocobalamin expressed in mcg. per ml.; the name and quantity of the added preservative; the warning, "Caution—Radioactive Material"; and the statement, "Do not use after 6 months from date of calibration."

CATEGORY and DOSE—See Cyanocobalamin Co 60 Capsules.

COBALAMIN ASSAY—RADIOTRACER METHOD

All radioactive determinations required by this method should be made with a suitable counting assembly over a period of time optimum for the particular counting assembly used. All procedures should be performed in replicate to obtain the greatest accuracy.

Cyanocobalamin Tracer Reagent—Dilute an accurately measured volume of a solution of radioactive cyanocobalamin* with sufficient water to yield a solution having a radioactivity between 500 and 5000 counts per minute per ml. Add 1 drop of cresol per liter of solution prepared, and store in a refrigerator.

Standardization—Prepare a solution in water of a weighed quantity of USP Cyanocobalamin Reference Standard to contain 20 mcg. to 50 mcg. in each ml. Perform the entire assay on a 10.0-ml. portion of this solution, proceeding as directed under *Assay Preparation*, beginning with "Add water to make a measured volume. . . ."

Cresol-Carbon Tetrachloride Solution—Mix equal volumes of carbon tetrachloride and freshly distilled cresol.

Phosphate-Cyanide Solution—Dissolve 100 mg. of potassium cyanide in 1000 ml. of a saturated solution of dibasic sodium phosphate, and mix well.

Butanol-Benzalkonium Chloride Solution—Dilute 3 volumes of 17 percent benzalkonium chloride solution with 1 volume of water, and mix with 36 volumes of 1-butanol.

Alumina-Resin Column—Place a pledget of glass wool in the bottom of a constricted glass tube such as a 50-ml. buret. With the tube held in an upright position, add a volume of a slurry of ion-exchange resin (see page 919), in water sufficient to give a column of settled resin 7 cm. in height. When the solid has settled somewhat, allow the water to drain so that there is only 1 cm. of liquid above the resin column, and tamp the resin lightly. Then add a volume of a slurry of anhydrous alumina (not acid washed) in water sufficient to increase the height of the settled column to 10 cm., and allow the water to drain to about 1 cm. from the top of the alumina. Add a pledget of glass wool, and wash the column, using a total of 50 ml. of water, and again draining to within 1 cm. of the top of the column. Prepare a fresh column for each determination.

Assay Preparation—Transfer to a beaker a weighed quantity or measured volume of the preparation to be assayed, equivalent in vitamin B_{12} activity to that of 200 to 500 mcg. of cyanocobalamin.

* A solution of cyanocobalamin made radioactive by the incorporation of ^{60}Co is available from Merck and Co., Inc., Rahway, NJ.

36

Add water to make a measured volume of not less than 25 ml., then add 5.0 ml. of *Cyanocobalamin Tracer Reagent*. Add, while working *under a hood*, 5 mg. of sodium nitrite and 2 mg. of potassium cyanide for each ml. of the resulting solution. Adjust the solution to approximately pH 4 with diluted hydrochloric acid, and heat on a steam bath for 15 minutes. Cool, and adjust the pH to between 7.6 and 8.0 with sodium hydroxide T.S. Centrifuge or filter to remove any undissolved solids.

Procedure—Transfer the *Assay Preparation* to a 250-ml. centrifuge bottle, add 10 ml. of *Cresol-Carbon Tetrachloride Solution*, suitably close the bottle with a glass, polyethylene or foil-wrapped rubber stopper, shake vigorously for 2 to 5 minutes, and centrifuge. Remove and save the lower, solvent layer. Repeat the extraction using a 5-ml. portion of *Cresol-Carbon Tetrachloride Solution*, and combine the lower, solvent-layer extracts in a centrifuge bottle or separator of 50 to 100-ml. capacity.

Wash the combined extracts with successive, 10-ml. portions of dilute sulfuric acid (1 in 7) until the last washing is practically colorless (two washings usually suffice). During each washing, shake for 2 to 5 minutes, allow the layers to separate, centrifuge if necessary, and discard the acid layer. Wash further with two successive, 10-ml. portions of *Phosphate-Cyanide Solution*. Finally, wash with 10 ml. of water. Discard all of the washings.

To the washed extract add 30 ml. of a mixture of 2 volumes of *Butanol-Benzalkonium Chloride Solution* and 1 volume of carbon tetrachloride. Extract with two successive, 5-ml. portions of water, each time shaking vigorously for 1 minute, centrifuging, and removing and saving the upper, aqueous layer.

Pass the combined aqueous extracts through the *Alumina-Resin Column* at a rate of about 1 ml. per minute, maintaining a 1-cm. layer of liquid on the head of the column by adding water as needed. Discard as much of the forerun as is colorless (usually about 5 ml.), and collect the colored eluate (usually about 10 ml.) in a 50-ml. centrifuge tube or separator containing 0.5 ml. of diluted acetic acid. Extract the eluate by shaking for 2 to 5 minutes with 5 ml. of *Cresol-Carbon Tetrachloride Solution*, and discard the upper, aqueous layer. To the extract add 5.0 ml. of water, 5 ml. of carbon tetrachloride and 10 ml. of 1-butanol. Shake, allow to separate until the upper layer is clear, and remove the upper, aqueous layer.

Determine the absorbance of the aqueous extract at 361 mμ and 550 mμ in a 1-cm. cell with a suitable spectrophotometer, using a tungsten light source. Make the 361 mμ reading using a filter capable of reducing stray light. Calculate the ratio A_{361}/A_{550}: the purity of the aqueous extract is acceptable if the ratio is not less than 3.10 and not more than 3.40. If a ratio outside this range is observed, purify the aqueous extract by repeating the extraction cycle, proceeding as directed in the foregoing paragraph, beginning with "Pass the combined aqueous extracts through the *Alumina Resin Column*. . .," using a fresh column.

If an acceptable absorbance ratio is observed in the aqueous extract, determine the radioactivity in counts per minute using a suitable counter over a period optimum for the particular counting assembly used. Average the results, and correct the average for the observed background radioactivity determined over two or more 30-minute periods.

Calculation—Calculate the efficiency, E, of the extraction process by the formula $E = (C_S - C_b)/(C_R - C_b)$, in which C_S and C_R are the average radioactivity counts per minute for the preparation under assay and the *Cyanocobalamin Tracer Reagent*, respectively, and C_b is the average count per minute of the background. The cobalamin content, expressed in mcg. of cyanocobalamin, of the portion taken for assay is given by the formula $(A_U/A_S) \times (C_S/C_U) \times R$, in which A_U and A_S are the absorbances determined at 361 mμ of the sample and standard solutions, respectively, C_S and C_U are the corrected average radioactivity values, expressed in counts per minute per ml., of the standard and sample solutions, respectively, and R is the quantity, in mcg., of cyanocobalamin in the portion of the standard solution taken.

In the USD XXV (2077), the purity of B_{12} is specified as not less than 95% of anhydrous cyanocobalamin dried to constant weight at 105°C, in vacuo.

In the Merck Index (2628) only the following information was found:

B_{12}	Medical Use: Prophylaxis and treatment of vitamin B_{12} deficiency; in pernicious and some macrocytic anemias,,certain dermatoses and neuritides. Dose: Usual, therapeutic, i.m. 10 - 100 mcg. Vet Use: Growth factor for hogs, dogs, chickens; for turkeys in the presence of antibiotics. Cobalt deficiency in sheep, macrocytic anemias, hepatic dysfunction resulting from infectious or nutritional origins. Has been suggested as useful in osteoarthritis and osteoporosis, as well as bovine ketosis. As a tonic. Dose: Horses and cattle: 1 - 2 mg; Dogs: 250 - 500 mg 1 or 2 times weekly
B_{12a}	Medical Use: See Vitamin B_{12}. Vet Use: Supportive treatment in conditions accompanied by defective erythropoiesis. Severe cobalt deficiency in ruminants.
B_{12}-Zinc Tannate Complex	Medical Use: Long-acting injectable vitamin B_{12} preparation. See Vitamin B_{12}.
Vitamin B_{12}, Radioactive	Medical Use: In study of absorption and deposition of vitamin B_{12}.

VI. Description

History:

According to Herbert, writing in 1973 (1015), in 1822 Combs reported a case of anemia attributable to some disorder of digestion and absorption. Addison's classic description of pernicious anemia followed in 1849 and 1855. In 1860, Flint associated it with gastric mucosal degeneration. In 1929, Castle demonstrated gastric intrinsic factor.

In 1926, Minot and Murphy (1870) reported their oral liver therapy; they received the 1934 Nobel Prize in Medicine. In 1937, Wills et al. found the "Wills factor" in crude but not purified liver extracts; in 1941, Mitchell et al. called it folic acid because they also found it in spinach, and in 1943, Stokstad purified pteroylglutamic acid. Only in 1948, were B_{12} and folic acid finally recognized as separate. Shorb, in 1948, showed that the LLD (Lactobacillus lactis Dorner) factor was present in liver at potencies parallel to anti-pernicious anemia factor. Rickes et al. proposed the name "vitamin B_{12}" when, in 1948, they and Smith and Parker crystallized the compound. In 1956, its structure was ascertained by Hodgkin et al. (1240); this contributed to her 1964 Nobel Prize in Chemistry.

In 1954, Bartilucci and Foss (0183) found that the optimum pH for stability of cyanocobalamin in solution was 4.5 - 5.0, and for a mixture of B_{12} and ascorbic acid was 6.0 - 7.0. Opposite effects on the stabilities of B_{12} and C were shown by EDTA-Na_4 and propyleneglycol. The mixture of B_{12} and C was most stable in equal parts of propyleneglycol and glycerin; 80 and 85% respectively survived six months at 40°C, and 100% of B_{12} and 90% of C survived six months at room temperature. The authors suggested that degradation products of C helped to decompose B_{12}.

In 1965, Hayward et al. (1153) reported equilibrium constants for several ligand replacement reactions of cobalamins and cobamides, interpreted in terms of the trans effect (thermodynamic) of the non-replaced ligand, changed in the order H_2O, NC^-, $HC{\equiv}C$, $H_2C{\equiv}CH^-$, CH_3^-, so that the trans Co-NC bond became less stable relative to the Co-benzimidazole bond, which became less stable relative to the Co-H_2O bond (Tables 9 and 10).

Cyanocobalamin crystals (dark red) absorb water; USP crystals contain 12% H_2O. They are soluble 1:80 in H_2O, solutions are neutral and stable; stability is greatest at pH 4.5 - 5.0. Cyanocobalamin is degradable by heavy metals, oxidants, and reducing agents, but not by brief autoclaving at 121°C (1015).

Table 9.

Equilibrium Constant Measurements (1153)

	System	Method	Reagents	pK_a	Note	Ref.
$H_2O \rightarrow OH^-$	Aquocobalamin	1A	0·05M-Phosphate buffers	7·8 (6·9, 7·5, 7·65)	(a)	19–24
	Diaquocobinamide	2A	0·001M-H_2SO_4 + NaOH	6·0	(b)	
		2B		6·1		
	Cyanocobinamide	2	,,	11·0	(c)	
			Ionic strength → 0	(11·0)		13
	Methylcobinamide	1	Strong NaOH	≥14	(d)	
			?	(>12)		6
				log K		
$H_2O \rightarrow CN^-$	Diaquocobinamide	3C	0·001M-H_2SO_4	≥14	(e)	
	Aquocobalamin	3C	0·2N-Sodium acetate + 0·08N-HCl pH = 4·75	≥12	(e)	
	Cyanocobinamide		?	(8)		5
	Methylcobinamide	2	1N-NaOH + 1N-KCN	3·0 ± 0·2	(f)	
				pK_a		
Benz → H_2O	Aquocobalamin	1B	Conc. H_2SO_4 + H_2O	−2·4 ± 0·2	(g)	
	Cyanocobalamin	1B	,, ,,	+0·1	(h)	
	Ethynylcobalamin	2A	Dilute H_2SO_4	+0·7	(i)	
	Vinylcobalamin	2A	Dilute H_2SO_4	+2·1	(i)	
	Methylcobalamin	1A	0·2N-Acetate/0·08N-HCl buffers	+2·5	(i)	
			?	(+2·7)		22
	DBC	1A	0·2N-Acetate/0·08N-HCl buffers	+3·35	(i)	
			Various	(3·3–3·5, 3·52)		14, 22
				log K		
Benz → CN^-	Cyanocobalamin	?	?	(4)		5
	Ethynylcobalamin	2A	1N-NaOH + KCN	2·7	(j)	
	Vinylcobalamin	1A	,,	0·7	(j)	
	Methylcobalamin	1B	,,	0·1	(j)	

An estimated error of ±0·1 applies to all log (equilibrium constants) except where otherwise stated.

Notes on Table 1. (*a*) There is no spectrophotometric evidence for the formation of a phosphate complex under these conditions. The difference between our value and that of Hanania and Irvine (7·65),[21] the most reliable in the literature, is within experimental error.

(*b*) Diaquocobinamide was prepared by photolysing a 0·0001—0·001M-solution of Factor B in $HClO_4$ or H_2SO_4, pH 2—4, until no further change in spectrum was observed, the HCN being removed by a stream of air passing through the solution. The resulting solution showed the same spectrum above 300 mμ as vitamin B_{12a} in strong acid [see under (*h*)]:

	λ_γ	λ_β	λ_α	ε_{molar}
Diaquocobinamide	348	490	519	$2·8 \times 10^3$
B_{12a} in strong acid	348	491	518	$2·8 \times 10^3$

Table 10.

Summary of Equilibrium Constants* (1153)

	Cobalamins		Cobinamides	
	(*c*)	(*d*)	(*a*)	(*b*)
	Benz → H_2O	Benz → CN^-	$H_2O \rightarrow OH^-$	$H_2O \rightarrow CN^-$
trans-Ligand	log K (= pK_a) *	log K	pK_a *	log K
H_2O	−2·4	(→ B_{12})	6·0	≥14
$-CN$	+0·1	4	11·0	8
$-C{\equiv}CH$	+0·7	2·7	—	—
$-CH{=}CH_2$	+2·4	0·7	—	—
$-CH_3$	+2·5	0·1	>14 (No pK detected)	3·0
$-C_5'$-Deoxyadenosyl (DBC)	3·4	(→ dicyanide)	—	—

* See the Figure for the chemical formulation of the equilibria. The stability constant for reaction (*a*) is $pK_\gamma - pK_a$ and for reaction (*c*) is equal to pK_a, see p. 6488.

40

Various forms of B_{12} are described in the Merck Index (2628) as follows:

B_{12}

Hygroscopic, dark red crystals. When exposed to air may absorb about 12% water. The hydrated crystals are stable to air. Darkens at 210 - 220°. Not melted at 300°. $[\alpha]^{23}_{656}$ -59 ± 9° (dil aq soln). Absorption max (in water): 550 mμ ($A^{1\%}_{1cm}$ = 64), 361 mμ ($A^{1\%}_{1cm}$ = 204), 278 mμ ($A^{1\%}_{1cm}$ = 115). Odorless and tastless. One gram dissolves in about 80 ml water. Aq solns are neutral, maximum stability in the pH range 4.5 - 5. Solns in this pH range can be autoclaved for 20 min at 120°. Soluble in alc. Insoluble in acetone, chloroform, ether. Aq solns deteriorate in the presence of acacia, aldehydes, ascorbic acid, ferrous gluconate,ferrous sulfate, vanillin. Aq solns are stabilized by the addition of ammonium sulfate: Michel, Knight, U.S. pat 2,778,771 (1957 to American Cyanamid). Talc has a tenacious affinity for vitamin B_{12}, although this is not an incompatibility, it precludes the use of talc as a filter aid or lubricant for tablets, particularly in view of possible assay difficulties.

B_{12c}

Red cryst solid. Absorption max in water: 352, 527.5 mμ ($E^{1\%}_{1cm}$ 153.2, 59.5): 3540, 5300 Å ($E^{1\%}_{1cm}$ 185, 75). Absorption max in 0.01 N NaOH: 357, 535 mμ ($E^{1\%}_{1cm}$ 139, 62.5).

B_{12r}

A brown reduction product of vitamin B_{12}, Diehl, Murie, Iowa State Coll. J. Sci. 26, 555 (1952): also obtained by photolysis of coenzyme B_{12}, Brady, Barker, Biochem, Biophys, Research Communs. 4, 373 (1961); and by reduction of

B_{12r} (Continued)

vitamin B_{12a}, Hill et al., Chemistry & Industry (London) 1964, 197. Prepn of a stable soln by catalytic hydrogenation of vitamin B_{12} in methanol: Thesing, Koppe, Ger. pat. 1,178, 073 (1964 to E. Merck, AG), C.A. 61, 14479f (1964). Review: Bonnett, Chem. Rev. 63, 573 (1963). Obtained as a brown material in soln. Oxidized by air to a red material, vitamin B_{12a}. Absorption max: 473, 405, and 312 mμ ($E_{1cm}^{1\%}$ - 54, 43, and 153). Ref: Diehl, Murie, loc. cit.

B_{12s}

Prepd by reduction of vitamin B_{12a}, but not isolated: Hill et al., Chemistry & Industry, (London) 1964, 197. Postulated hydride form of vitamin B_{12s} questioned: Collat, Abbott, J. Am. Chem. Soc. 86, 2308 (1964). Review: Bonnett, Chem Rev. 63, 573 (1963). Obtained as gray-green product in soln.

B_{12a}

An analog of vitamin B_{12} where the CN group is replaced with OH. Prepn: Kaczka, Wolf, Folkers, U.S. pats. 2,738,301/2 (1956 to Merck and Co., Inc.). Apparently hydroxocobalamin exists in aq soln as an equilibrium mixture of the hydroxy isomer and the ionic aquo isomer (see Aquocobalamin); $[CoX]^+$ equals vitamin B_{12} without the cyanide group:

$$[HO\text{-}CoX] \underset{}{\overset{H_2O}{\rightleftharpoons}} [H_2O.CoX]^+OH^-$$

Dark red, orthorhombic needles or platelets from water + acetone. Darkens at 200°, but not melted at 300°. Principal absorption max in H_2O at 270 - 277, 351 - 354, and 520 - 530 mμ. Moderately sol in water and in the lower aliphatic alcohols. Practically

B_{12a} (Continued)	insol in acetone, ether, petr ether, halogenated hydrocarbons, benzene. Acids, replace the hydroxo group with the anion of the acid: Kaczka *et al.*, *Science* 112, 354 (1950).
B_{12a} Acetate	Prepn of stable solns: Marcus *et al.*, Fr. pat. 1,336,671 (1963 to Merck & Co., Inc.), C.A. 60, 380a (1964).
B_{12p}	Vitamin B_{12} factor obtained by removal of the nucleotide from cyanocobalamin by acid hydrolysis. Isoln from calf feces: Ford, Porter, *Biochem. J.* 51, V (1952). Prepn by acid hydrolysis: Gant *et al.*, *ibid.* 56, XXXIV (1954); Friedrich, Bernhauer, *Angew. Chem.* 65, 627 (1953). Prepn from factor V_{1a} and D(-)-1-amino-2-propanol: Bernhauer *et al.* *Helv. Chim. Acta* 43, 696 (1960: Bernhauer, U. S. pat. 3,072,674 (1963 to Hoffmann-La Roche).
B_{12}-Zinc Tannate Complex	Prepn: Thompson, U.S. pat. 2,920,015 (1960 to Armour & Co., Inc.). Practically insol in water. On reconstitution forms a colloidal suspension, incompatible with iron salts. After intramuscular injection of 500γ a high cyanocobalamin serum level persists for 28 days.
Sulfitocobalamin	An analog of vitamin B_{12} where the CN group is replaced with $-SO_3$. Prepn from cyanocobalamin or hydroxocobalamin with excess water-soluble bisulfite: Fricke, U.S. pat. 2,721,162 (1955 to Abbott Laboratories). Structure: Dolphin *et al.*, *Nature* 199, 170 (1963). Stable aq sol. Absorption max: 275, 365, 418, 516 mμ ($E_{1cm}^{1\%}$ 328, 130, 49, 61).

Coenzyme B_{12}	The metabolically active form of vitamin B_{12}. Its structure is similar to that of vitamin B_{12}. Major difference: The coenzyme has an adenine nucleoside instead of a cyano group attached to cobalt. Ref: H. A. Barker Chem. Eng. News, 38 (41), 44 (1960). Best isolated from a culture of Propionibacterium shermanii: Barker et al., J. Biol. Chem. 235, 181, 480 (1960); Biochem. Prepns. 10, 27 (1964). Structure: Lenhert, Hodgkin, Nature 192, 937 (1961). Deep red, six-sided, crystals. Absorption max (in H_2O): 260 mμ (A 34.7 X 10^6): 375 mμ (A 10.9 X 10^6): 522 mμ (A 8.0 X 10^6 cm^2/mole). Soluble in water (16.4 mmol at 24°), ethanol, phenol. Practically insol in acetone, ether, dichloroethylene, dioxane. Dry crystalline coenzyme B_{12} is stable for many months when stored at 0° or lower in the dark. Slowly dec by light at room temps. Aq solns are rapidly dec by visible or u.v. light or by alkaline cyanides. In the dark, solns are most stable at pH 6-7. Heating of acid or alkaline solns produces slow inactivation.
Vitamin B_{12} Radioactive	Prepd by fermentation in the presence of ^{60}Co: Chaiet, Rosenblum, Woodbury, Science 111, 601 (1950). Properties identical with normal vitamin B_{12}, except for the presence of radioactive cobalt, half-life 5.2 years, emitting beta and gamma rays. Distributed in dil aq soln, with or without preservatives. Specific activity is governed by that of the ^{60}Co available. Activities in excess of 1 mc/mg have been attained. Stable at room temp in the dark in concns of 1 μc/ml. There is also available

Vitamin B_{12} Radioactive (continued)	vitamin B_{12}-^{58}Co which is the same as vitamin B_{12}-^{60}Co except for incorporation of ^{58}Co which has a half-life of 72 days. Preferred for human use because of its shorter half-life.

VII. Analytical Methods

The Assay for B_{12} Activity specified in USP XVIII (2819) is the bioassay upon Lactobacillus leichmannii (see original paper for details). The procedure specified in NF XIII is similar (0061), but additionally NF XIII specifies a radio-tracer assay for cobalamins (see original paper).

Methods for identifying B_{12} and its compounds for research purposes are given in many of the research papers cited, and cover the usual spectrum of extraction, separation, and characterization techniques.

Clinical assessments of amounts of B_{12} present in tissues are commonly performed by one or more of the following types of techniques:

1. The Schilling Test (2425) measures urinary excretion of labeled cobalt after a small oral dose of labeled B_{12} followed by a large "flushing" dose of unlabeled B_{12}. It is used as a measure of B_{12} absorption.
2. Whole-body monitoring for assessing how much of a dose of labeled B_{12} is retained over periods up to a year and more, also detailed in research reports (e.g., 0303).
3. Microbiological assay for "activity" measured by growth of B_{12}-dependent organisms cultured in a medium containing a preparation of the sample to be assayed; the organisms usually are either Euglena gracilis or Lactobacillus lactis leichmannii. Other organisms, for example, Escherichia coli mutants, have been reported. This type of methodology is used especially for estimating serum B_{12} levels.

In 1950, Ross (2342) modified the Euglena gracilis assay for B_{12}, described by Hutner the year before for assaying liver extracts, for body fluids including serum and urine. The method remains one of the standard assay methods.

Table 11(a). Urinary Excretion of Radioactivity by Humans (2328)

Cobalamin Oral		Cobalamin Inj., 1 mg	Avg % of dose ± stand. dev.
Cyano	2 μg	Cyano; chloro	12*
Sulfato	"	Sulfato	3.5 ± 1.5
		Chloro	2.6 ± .8
		Cyano	3.7 ± 1.8
Nitro	"	Nitro	2.0 ± .8
		Chloro	3.1 ± .5
		Cyano	1.9 ± .2
Thiocyanato	"	"	2.0 ± .9
Nitro	.5	"	5.8 ± 3.6
Cyano	"	"	17.6 ± 9.0

* Avg of accumulated standard test data.

Table 11(b). Fecal Excretion of Radioactivity by Humans (2328)

Study	Cobalamin (.5 μg oral)	Avg % excr. ± stand. dev.	Avg % absorbed
1st (5 days)	Cyano	18.0 ± 7.1	82.0
	Nitro	41.8 ± 12.8	58.2
2nd (6 days)	Cyano	13.7 ± 1.4	86.3
	Nitro	16.5 ± 8.9	83.5

1 mg vit. B_{12} injected 2 hr after oral dose of tracer.

Table 11 (c). Serum Levels (μμg/ml) in Humans (2328)

Study	Cyano Initial	Cyano Difference (2 hr)	Chloro Initial	Chloro Difference (2 hr)
1st	280	682	222	4
3 mg cyano;	146	854	216	0
2 mg chloro	251	79	157	4
	1[illegible]	286	612	0
	2[illegible]	94	5[illegible]	305
2nd	99	204	169	76
3 mg cyano;	1[illegible]	158	140	41
5 [illegible] chloro	157	111	251	46
	227	94	100	0
	198	64	146	0

Table 11(d). Fecal Excretion of Radioactivity by Rats (2328)

Cobalamin (.050 μg oral)	Avg % excr. ± stand. dev.	Avg % absorbed
Cyano	65.4 ± 7.2	34.6
Chloro	90.6 ± 9.5	9.4
Nitro	85.2 ± 15.2	14.8

In 1956 Pollycove and Apt (2177) used fecal elimination, hepatic scan, and urinary excretion measurements to determine B_{12} absorption in six patients with pernicious anemia in remission and three normal controls. They found the urinary assay to be fastest, but preferred the scan because it avoided sampling errors and was convenient and accurate.

In 1959 Cooke et al. (0552) assayed bone marrow samples from ten volunteers and two hospital patients, to ascertain "normal values"; data are shown in Table 12, and the L. leichmannii assay was used for B_{12}.

Table 12. The Mean Cell Content of Vitamin B_{12} Activity, Folic Acid Activity and Ascorbic Acid in Twelve Control Subjects (0552)

(The range is given in brackets.)					
Concentration per unit volume of packed cells			Content per red blood cell		
B_{12} activity (pg/ml)	FFA (mg/100 ml)	Ascorbic acid (mg/100 ml)	B_{12} activity (pg)	FFA (mg)	Ascorbic acid (pg)
12,000	317	134	2.58	[illegible]	0.21
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
(900–19,800)	(15–726)	[illegible]	[illegible]	[illegible]	[illegible]

In 1969 Carmel and Coltman (0450) proposed the use of saliva as a source of reliable binders for separation of free and bound B_{12} during the radioassay for serum B_{12}.

In 1970 Sullivan (2682) reviewed tests for gastric intrinsic factor employing B_{12} as a testing agent; these will be found on page 13 of the original paper (2682).

He noted the variety of tests available for diagnosis of B_{12} deficiency, each giving a different kind of information. Deficiency of B_{12} could be discriminated from that of folate by the respective serum levels (50-100 pg/ml or less of B_{12}).

The Schilling test was affirmed as still "very important" in distinguishing pernicious anemia from small-bowel malabsorption of B_{12}, as shown in Figure 13. The related histamine test of intrinsic factor secretion is shown in Figure 14.

In 1970 Linnell et al. (1646) described a method of separating individual plasma cobalamins by two-dimensional thin-layer chromatography followed by

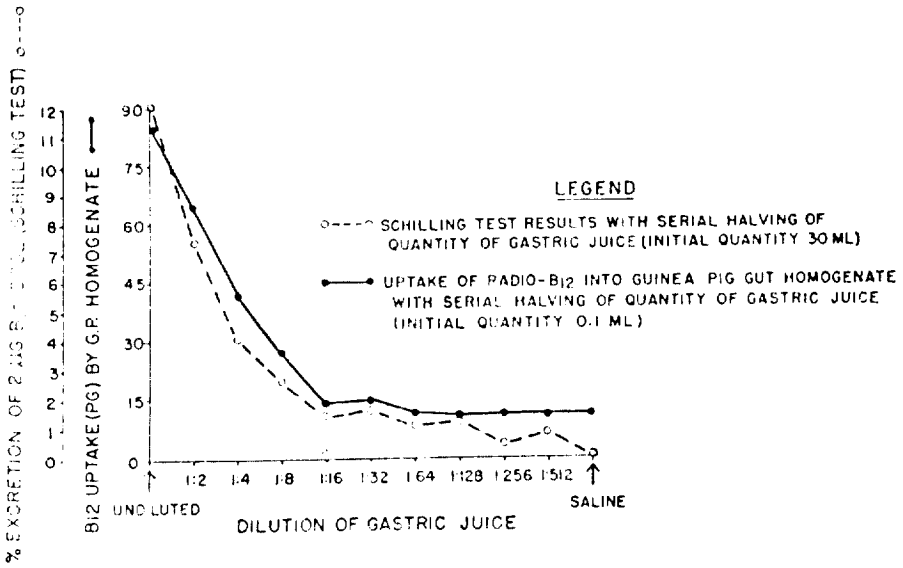


Figure 13. Correlation of in vitro Guinea-Pig Intestinal Mucosa Homogenate Assay with in vivo Assay (Schilling test) for IF in Serial Dilutions of Normal Gastric Juice (from Sullivan, L.W., Herbert, V., and Castle, W.B.: J. Clin. Invest. 42:1453, 1963) (2682)

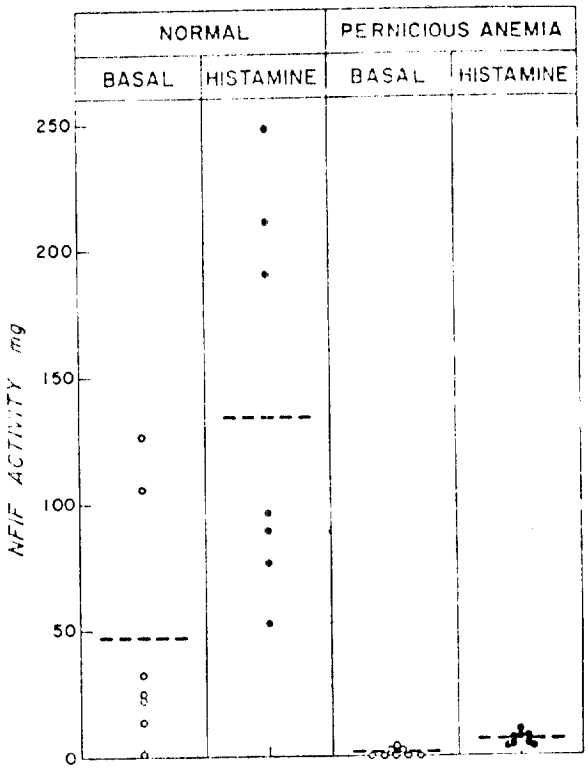


Figure 14. Comparison of IF Secretion, with and without Histamine Stimulation, in Normal Subjects and Patients (Sullivan, L.W., In Radioisotopes in Medicine: In Vitro Studies, p. 38. In Hayes, R.L., Gosivitz, F.A., and Murphy, B.E.P. (Eds.): Oak Ridge, Tenn., U.S. Atomic Energy Commission, Conference 671111, 1968) (2682)

bioautography, claimed of potential usefulness in patients with inborn errors of metabolism involving the B_{12} coenzymes.

In 1971 Linnell et al. (1645) reported the distribution of cobalamins in plasma from various groups of people, determined by chromatography-plus-bioautography as described earlier (1646). as in Tables 13-20.

In summary, methylcobalamin predominated, then deoxyadenosylcobalamin and hydroxocobalamin, and occasional traces of cyanocobalamin; large amounts of cyanocobalamin were found in pernicious anemia, lesser amounts after it had been administered, for some was converted to methylcobalamin. Injections of methylcobalamin increased its plasma level without affecting plasma deoxyadenosylcobalamin-plus-hydroxocobalamin. The authors suggested that a low methyl/hydroxo ratio might in some cases indicate incipient B_{12}-deficiency, but no constant patterns were seen in several conditions affecting B_{12} including folate deficiency, the leukemias, and postgastrectomy syndromes.

In 1971 White (2970) reported that gas-chromatographic determinations of urinary methylmalonic acid should be diagnostic for B_{12}-deficiency in man; values of 4-9 mg/day were cited as normal maxima, and to 0.5 g or more in severe deficiency.

In 1971 Cavallini and Scandurra (0475) described the conditions for spectrophotometric determination of deoxyadenosylcobalamin in the presence of other B_{12} compounds.

In 1971 Frenkel et al. (0881) described a radioisotopic assay for B_{12} in CSF, stating that the normal low concentration made bioassays and the radioassay for serum of little value. The authors claimed accurate repeatable determinations of B_{12} 1 pg/ml of CSF.

They reported a normal mean for human CSF of 17.8 (range 8-36) pg/ml, and no relationships between CSF B_{12}, CSF protein and serum B_{12}. However, CSF B_{12} values were low in patients with clinical B_{12} deficiency.

In 1971 Fill et al. (1232) described the identification of cobalamins and cobamide coenzymes by nmr and epr spectra (Figures 15-19).

Table 13. Plasma Cobalamins in Normal Subjects and Hospital Controls: Results Obtained by Photometric Scanning of Bioautograms (1645)

Subject	Smoking habits	Age	Sex	Total B_{12} (pg/ml)	Me B_{12} (pg/ml)	CN B_{12} (pg/ml)	Co-OH B_{12} (pg/ml)	Ratio Me/Co-OH B_{12}	CN B_{12} percentage of total
Normal subjects									
1	0	35	M	625	437	0	188	2·3	0
2	0	35	M	350	294	0	56	5·2	0
3	0	27	M	345	190	0	155	1·2	0
4	0	38	M	1085	597	0	488	1·2	0
5	40 Cigarettes per day	43	M	595	355	0	240	1·5	0
6	15 Cigarettes per day	52	F	490	314	3	173	1·8	0·6
7	30 Cigarettes per day	46	M	765	594	3	168	3·5	0·4
8	25-30 Cigarettes per day	55	M	385	292	0	93	3·1	0
9	25 Cigarettes per day	31	M	510	398	0	112	3·5	0
10	10 Cigarettes per day	46	F	570	467	0	103	4·5	0
11	20-25 Cigarettes per day	38	M	560	465	0	95	4·9	0
12	20-25 Cigarettes per day	48	M	400	270	0	130	2·1	0
13	3½ oz Tobacco per week	52	M	350	294	0	56	5·4	0
14	3 oz Tobacco per week	55	M	250	157	3	90	1·8	1·2
15	6 oz Tobacco per week	64	M	575	282	46	247	1·1	8
16	3½ oz Tobacco per week	63	M	335	171	3	161	1·1	0·9
17	10-15 Cigarettes per day	57	F	755	460	0	295	1·6	0
18	20 Cigarettes per day	43	M	555	480	0	75	6·4	0
19	25 Cigarettes per day	19	F	660	505	0	155	5·3	0
20	25 Cigarettes per day	22	M	275	170	0	105	1·6	0
21	3½ oz Tobacco per week	52	M	550	443	5	102	4·3	0·9
22	25-35 Cigarettes per day	62	M	575	418	3	154	2·7	0·5
23	20-25 Cigarettes per day	43	M	800	616	24	160	3·8	3·0
Hospital controls									
24	0	16	F	550	435	0	115	3·8	0
25	20 Cigarettes per day	31	F	405	247	0	158	1·6	0
26	10 Cigarettes per day	55	F	370	230	0	140	1·6	0
27	15-20 Cigarettes per day	55	M	425	342	0	83	3·0	0
28	15-20 Cigarettes per day	55	M	510	270	0	240	1·1	0
	Mean			522	364	3·2	155	2·9	0·5
	SEM			±33·8	±24·7	±1·8	±16·4	±0·3	±0·3
	Range			(250-1085)	(157-616)	(0-46)	(56-488)	(1·1-6·4)	(0-8)

Table 14. Plasma Cobalamins in Normal Subjects and Hospital Controls: Summary of Results Obtained by Scanning and by Visual Assessment of Bioautograms (1645)

Method of estimation of individual cobalamins	No. of subjects	Total B_{12} (pg/ml)	Me B_{12} (pg/ml)	CN B_{12} (pg/ml)	Co-OH B_{12} (pg/ml)	Ratio Me/Co-OH B_{12}	CN B_{12} as percentage of total
Scanning	28 (23 N, 5H*)	522 ± 34† (250-1085)	364 ± 25 (157-616)	3·2 ± 1·8 (0-46)	155 ± 16 (56-488)	2·9 ± 0·3 (1·1-6·4)	0-8
Visual same samples as above	28 (23 N, 5H)	522 ± 34 (250-1085)	343 ± 24 (150-600)	(0-45)	178 ± 14 (100-434)	2·1 ± 0·2 (1·0-3·0)	0-8
Visual	73 (39 N, 34H)	474 ± 25 (220-1085)	298 ± 17 (125-651)	(0-50)	174 ± 6 (66-434)	1·6 ± 0·1 (0·7-3·0)	0-8
Control range adopted‡		185-935	130-600	0-50	60-310	1-5·5	0-8

* N = normal, H = hospital control. † Mean ± S.E. Range in parenthesis.

‡ Values for individual cobalamins approximate to the 95% range of all estimations. The range for total B_{12} is derived from the present data and that of Matthews, Gunasegaram & Linnell (1967), and approximates to a 98% range from 173 subjects.

Table 15. Plasma Cobalamins in Untreated Pernicious Anemia: Uncomplicated and with Subacute Combined Degeneration of the Cord (1645)

Patient	Age	Sex	Total B_{12} (pg/ml)	Me B_{12} (pg/ml)	CN B_{12} (pg/ml)	Co-OH B_{12} (pg/ml)	Ratio Me/Co-OH B_{12}	CN B_{12} percentage of total	Haemoglobin (g/100 ml)	Serum folate (ng/ml)	Methylmalonate excretion test	
											Pre-valine	Post-valine
Uncomplicated pernicious anaemia												
1	60	M	50	0	6	44	0	12	12·0	13·0	+	+
2	61	M	50	5	0	45	0·2	0	11·2	28·0		
3	66	M	80	29	0	51	0·6	0	11·3	19·0	+	+
4	60	F	100	0	25	75*	0	25	10·0	9·6	+	+
5	77	F	10	0	3	7	0	30	6·0	11·8	+	+
6	71	F	75	0	0	75*	0	0	13·8	21·0		
7	77	F	68	0	0	68*	0	0	8·7	8·0		
8	85	F	64	16	0	48*	0·3	0	10·4	3·0		
9	67	F	86	17	17	52*	0·3	20	6·2	1·2		
10	75	F	50	13	0	37*	0·4	0	7·3	4·2		
11	65	F	30	0	0	30*	0	0	4·9	6·4		
12	65	M	65	26	0	39*	0·7	0	7·8	—		
13	71	F	35	14	0	21*	0·7	0	7·4	—		
14	63	F	75	trace	0	75*	0	0	7·7	4·7		
15	46	F	100	29	29	42*	0·7	29	11·5	8·4		
16	62	F	80	13	27	40*	0·3	34	5·0	2·9		
17	71	F	80	16	16	48*	0·3	20	7·7	>25		
18	34	M	60	0	24	36*	0	40	15·1	—		
19	43	M	35	0	14	21*	0	40	3·8	1·7		
20	74	F	77	trace	trace	75*	0	*ca* 5	11·6	32·0	−	−
21	63	F	130	33	0	97*	0·3	0	18·1	7·6	+	+
22	63	F	86	22	0	64*	0·3	0	7·5	24·0	+	+
23	68	F	49	0	20	29*	0	41	5·9	5·4	+	+
24	49	M	72	0	trace	70*	0	*ca* 5	7·8	28·0	+	+
25	53	F	100	trace	0	100*	0	0	6·1	7·6		
Cases with subacute combined degeneration of the cord												
26	66	M	30	8	2	20	0·4	7	10·0	—		
27	69	F	30	9	9	12*	0·8	30	12·5	—		
28	68	F	50	trace	12	38*	0	24	7·8	11·0		
29	72	M	55	trace	0	55*	0	0	14·9	20·0		
Mean ± SE			64·6 ± 3·8	9·0 ± 1·9	7·2 ± 1·8	48·8 ± 4·3	0·22 ± 0·05	12·5 ± 2·8				
Range			(10–130)	(0–33)	(0–29)	(7–100)	(0–0·8)	(0–41)				

Note: In calculation of statistics 'trace' has been assigned a value of 2.
* Derived from visual score.

Table 16 Plasma Cobalamins in Veganism (1645)

Subject	Diet	Age	Sex	Total B_{12} (pg/ml)	Me B_{12} (pg/ml)	CN B_{12} (pg/ml)	Co-OH B_{12} (pg/ml)	Ratio Me/Co-OH B_{12}	Haemoglobin (g/100 ml)	Serum folate (ng/ml)	Methylmalonate excretion test	
											Pre-valine	Post-valine
31	B_{12} unsupplemented	38	F	160	107	0	53*	2·0	11·5	8·0		
32	B_{12} unsupplemented	31	F	135	62	0	73	0·9	7·5	3·2	+	+
33	B_{12} unsupplemented	24	F	155	118	0	37	3·2	11·7	0·8	−	+
34	B_{12} unsupplemented	44	F	55	0	0	55	0	13·2	16·6	−	+
35	B_{12} unsupplemented	46	M	100	0	0	100	0	11·0	>25		
36	B_{12} supplemented	33	M	380	190	0	190*	1·0	14·0	>32		
37	B_{12} supplemented	31	F	300	150	trace	150*	1·0	13·6	>16		
38	B_{12} supplemented	64	M	455	273	0	182*	1·5	13·6	14·0		

* Derived from visual score.

Table 17. Plasma Cobalamins in Gastrointestinal Disease (1645)

Patient	Diagnosis	Age	Sex	Total B_{12} (pg/ml)	Me B_{12} (pg/ml)	CN B_{12} (pg/ml)	Co-OH B_{12} (pg/ml)	Ratio Me/Co-OH B_{12}	Haemoglobin (g/100 ml)	Serum folate (ng/ml)	Methylmalonate excretion test	
											Pre-valine	Post-valine
30	Partial gastrectomy: SACD	61	M	49	12	0	37*	0·3	7·2	19·2	+	+
39	Partial gastrectomy	67	M	112	44	0	68	0·7	10·1	2·4	–	+
40	Partial gastrectomy	54	M	135	81	3	53	1·5	13·5	8·2	–	–
41	Partial gastrectomy	29	M	135	56	0	81	0·7	9·3	7·0	–	–
42	Partial gastrectomy	50	M	155	83	0	72	1·2	11·5	11·0	–	–
43	Partial gastrectomy	56	M	205	84	0	121	0·7	13·3	8·4	–	–
44	Partial gastrectomy	68	F	425	170	trace	255	0·7	11·6	0·7		
45	Partial gastrectomy	63	M	255	102	0	153*	0·7	12·3	>32		
47	Partial gastrectomy	63	M	535	289	0	246	1·2	10·0	14·4		
48	Partial gastrectomy	66	F	265	159	0	106*	1·5	10·0	4·6		
49	Partial gastrectomy	59	F	625	375	0	250	1·5	11·6	17·4		
50	Partial gastrectomy	58	M	150	75	0	75	1·0	4·6	0·8	–	–
51	Atrophic gastritis	49	M	170	82	0	86	0·9	12·8	13·0	–	–
52	Atrophic gastritis	73	M	130	52	0	78	0·7	12·8	5·1	–	–
60	Atrophic gastritis	66	F	190	142	0	48*	3·0	10·4	8·0		
61	Atrophic gastritis	74	F	140	101	0	39	2·6	9·0	6·4		
53	Jejunal diverticulosis	38	M	275	170	22	83	2·0	12·0	30		
54	Jejunal diverticulosis	62	M	310	223	0	87	2·6	13·5	3·8		
55	Jejunal diverticulosis	72	F	265	116	0	149	0·8	14·4	13·1		
56	Jejunal diverticulosis	84	F	50	14	0	36	0·4	8·1	15·0	+	+
57	Jejunal diverticulosis: post-gastrectomy	74	M	185	74	0	112*	0·7	14·2	10·2		
58	Crohn's disease	42	M	150	40	0	110*	0·3	12·6	3·0		
59	Adult coeliac disease	53	M	420	252	0	168	1·5	9·9	0·6		

* Derived from visual score.

Table 18. Plasma Cobalamins in Leukaemias and Cases of Liver Disease (1645)

Patient	Diagnosis	Age	Sex	Total B_{12} (pg/ml)	Me B_{12} (pg/ml)	CN B_{12} (pg/ml)	Co-OH B_{12} (pg/ml)	Ratio Me/Co-OH B_{12}	Haemoglobin (g/100 ml)	Serum folate (ng/ml)
63	Chronic myeloid leukaemia	50	M	*ca* 2000	*ca* 1600	*ca* 140	*ca* 260	6·1	11·0	—
64	Chronic myeloid leukaemia	58	M	>3000	>1800	trace	>1200*	1·5	7·7	3·6
65	Myelomonocytic leukaemia	57	M	870	678	17	175	3·9	7·0	8·0
66	Myelomonocytic leukaemia	60	F	210	84	0	126*	0·7	5·9	2·1
67	Erythroleukaemia	48	F	185	66	39	80	0·8	6·1	4·4
68	Erythroleukaemia	47	M	385	192	0	193*	1·0	7·9	>32
69	Active chronic hepatitis	46	F	*ca* 2000	*ca* 960	0	*ca* 1040	0·9	11·4	7·5
70	Cirrhosis, idiopathic	74	M	1140	900	0	240	2·7	13·4	2·6
71	Cirrhosis, alcoholic	38	M	480	120	trace	360*	0·3	18·1	2·3
72	Cirrhosis, alcoholic	70	M	510	255	0	255	1·0	13·2	14·5
73	Cirrhosis, idiopathic	44	F	515	386	0	129*	3·0	13·1	2·4
74	Cirrhosis, alcoholic	58	M	1185	890	0	295	3·0	11·4	6·2
75	Cirrhosis, idiopathic	18	M	>2000	>1200	0	>800*	1·5	11·5	8·8
76	Active chronic hepatitis	26	F	995	458	0	537	0·9	13·3	—

* Derived from visual score.

Table 19. Plasma Cobalamins in Folate Deficiency (1645)

Patient	Diagnosis	Age	Sex	Total B_{12} (pg/ml)	Me B_{12} (pg/ml)	CN B_{12} (pg/ml)	Co-OH B_{12} (pg/ml)	Ratio Me/Co-OH B_{12}	Haemoglobin (g/100 ml)	Serum folate (ng/ml)
33	Vegan	24	F	155	118	0	37	3·2	10·8	0·8
78	Nutritional deficiency	56	F	285	196	0	89	2·2	8·3	0·9
79	Nutritional deficiency	65	F	205	110	0	95	1·2	6·9	2·4
80	Nutritional deficiency	77	F	130	65	0	65*	1·0	9·2	0·4
81	Nutritional deficiency	75	F	230	92	0	138	0·7	7·2	0·6
84	Nutritional deficiency	24	M	495	370	0	125	3·0	8·2	0·4
85	Nutritional deficiency	55	F	250	125	0	125*	1·0	6·9	0·6
46	Post-partum megaloblastic anaemia	26	F	500	360	0	140	2·6	12·8	0·8
44	Post-gastrectomy megaloblastic anaemia	68	F	425	170	trace	255*	0·7	16·0	0·7
50	Post-gastrectomy megaloblastic anaemia	58	M	150	105	0	45	2·3	6·5	0·8
59	Adult coeliac disease	53	M	420	252	0	168	1·5	9·9	0·6
82	Carcinoma of stomach	62	M	240	185	0	55	3·4	8·9	0·6
83	Anticonvulsant megaloblastic anaemia	27	M	165	92	0	73	1·3	7·8	1·5
71	Alcoholic hepatic cirrhosis	38	M	480	120	trace	360*	0·3	17·3	2·3

* Derived from visual score.

Table 20. Changes in Plasma Cobalamins after Cobalamin Administration by Oral and Parenteral Routes (1645)

Subject	Diagnosis	Age	Sex	Compound and dose	Route	Time	Total B_{12} (pg/ml)	Me B_{12} (pg/ml)	CN B_{12} (pg/ml)	Co-OH B_{12} (pg/ml)	Ratio Me/Co-OH B_{12}	CN B_{12} percentage of total
N 29	Normal	18	F	Cyanocobalamin 100 μg	i.m.	Pre-dose	510	306	0	204*	1·5	0
						6 h	1165	260	775	130	2·0	67
N 5	Normal	42	M	Cyanocobalamin 100 μg	i.m.	Pre-dose	595	355	0	240	1·5	0
						24 h	895	546	107	242	2·3	12
N 6	Normal	52	F	Cyanocobalamin 100 μg	oral	Pre-dose	490	314	3	173	1·8	<1
						5 h	475	270	43	162	1·7	9
						24 h	470	268	47	155	1·7	19
P 19	Pernicious anaemia	43	M	Cyanocobalamin 1000 μg	i.m.	Pre-dose	35	trace	14	21*	<0·1	40
						3 h	>2000	trace	>1800	>200*	<0·1	ca 90
P 86	Cirrhosis of liver	28	F	Cyanocobalamin 1000 μg	i.m.	7 days	>2000	>200	>1300	>500*	0·4	ca 65
P 87	Pernicious anaemia	67	F	Cyanocobalamin 4 μg	i.m.	6 days	92	18	56	18*	1·0	61
P 21	Pernicious anaemia	63	F	Cyanocobalamin 1 μg+IF	oral	Pre-dose	77	31	0	46*	0·7	0
						6 h	84	34	0	50*	0·7	0
P 34	Vegan	44	F	Cyanocobalamin 1 μg daily	oral	Pre-dose	55	0	0	55	0	0
						5 days	110	25	3	82	0·3	3
						8 days	115	40	7	68	0·6	6
P 32	Vegan	31	F	Cyanocobalamin 1 μg daily	oral	Pre-dose	135	62	0	73	0·9	0
						7 days	205	82	68	55	1·5	33
P 23	Pernicious anaemia	63	F	Methylcobalamin 1 μg daily	i.m.	Pre-dose	49	0	20	29	0	41
						10 days	175	117	0	58*	2·0	0
P 30	Post-gastrectomy with subacute combined degeneration of the cord	61	M	Methylcobalamin 1 μg daily	i.m	Pre-dose	49	12	0	37*	0·7	0
						14 days	295	250	0	35*	7·2	0
						21 days	320	274	0	46	6·4	0

* Derived from visual score.

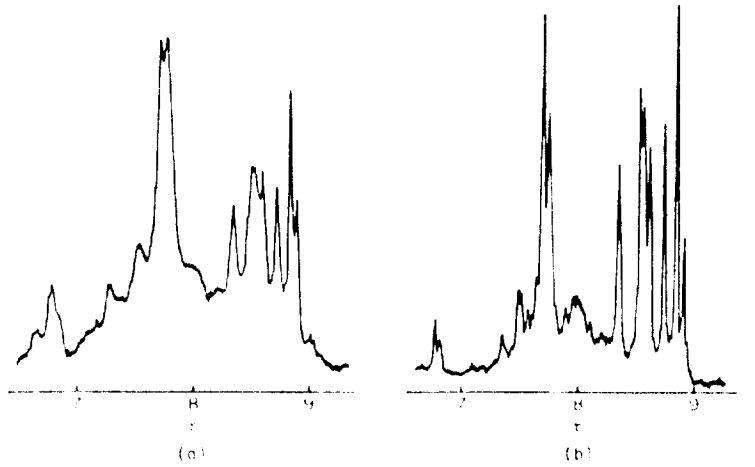


Figure 15. ^{1}H NMR Spectrum of Dicyanocobinamide in $(CD_3)_2SO$ Measured at 100 MHz and (a) at 31° and (b) 85° (1232)

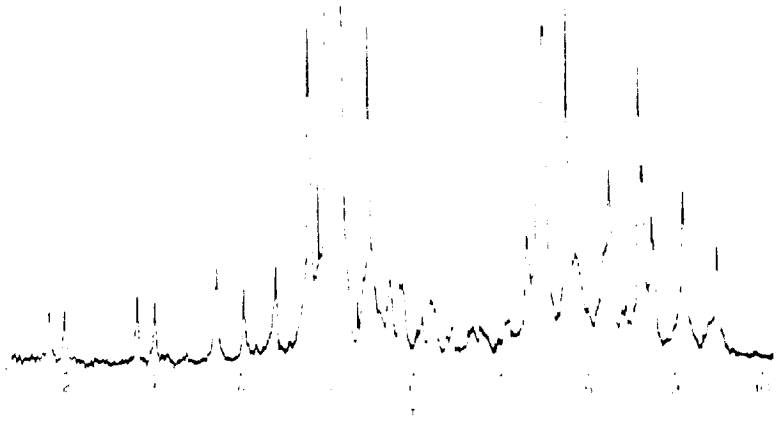


Figure 16. ^{1}H NMR Spectrum of DBC Coenzyme in D_2O at 220 MHz and 18°. (The Resonances Between 4.7 and 5.5τ are due mainly to residual HDO.) (1232)

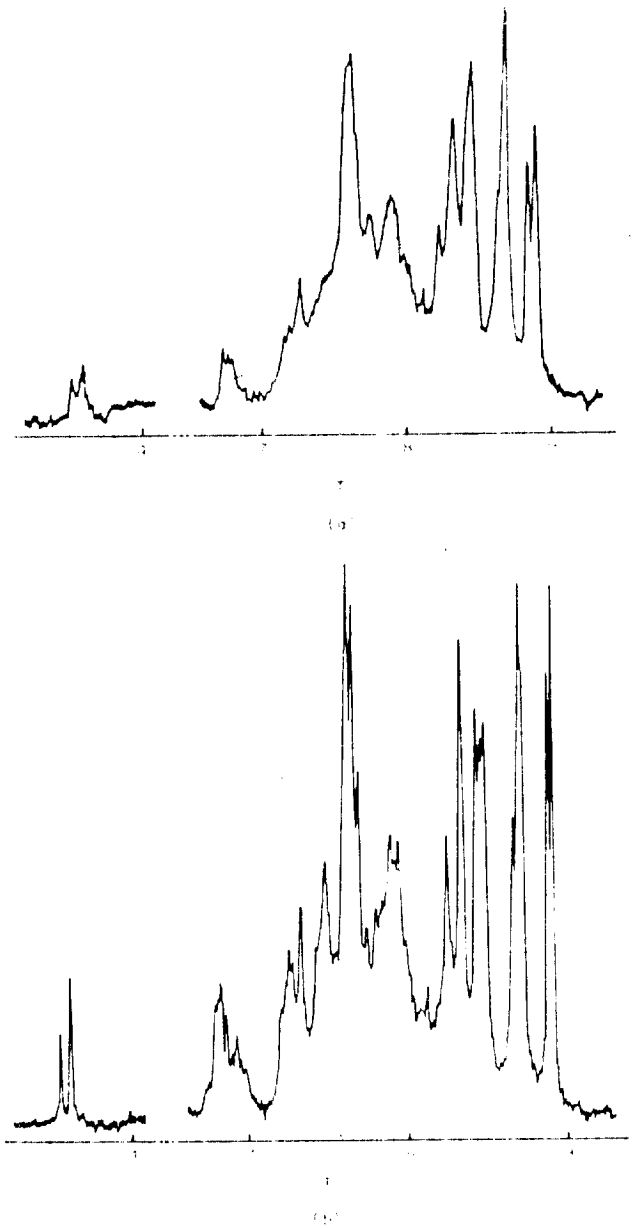


Figure 17. ^{1}H NMR Spectrum of Cyanoaquocobinamide in D_2O Measured at (a) 100 MHz and 31° and (b) 220 MHz and 18° (1232)

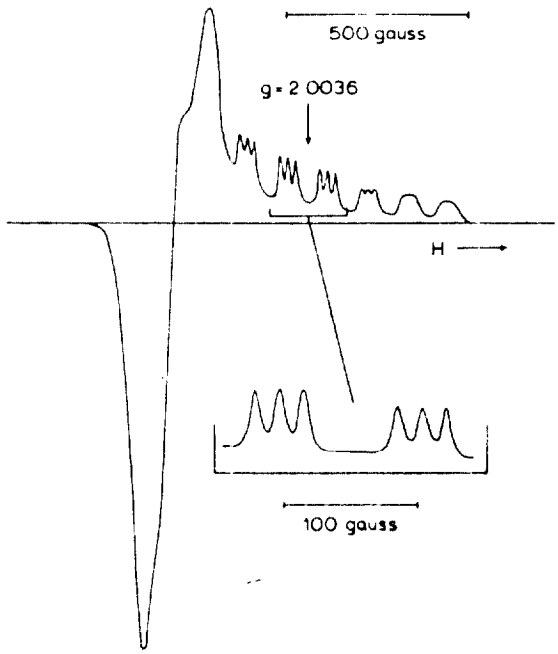


Figure 18. The EPR Spectrum of Base-on Cobalamin, B_{12r}, Prepared by Pt/H_2 Reduction in Propane-1,2-diol-water, 1:4, at pH 7 Measured at 100°K Using X-band Irradiation. (The enlargement shows the superhyperfine structure due to interaction with one ^{14}N nucleus of 5,6-dimethylbenzimidazole.) (1232)

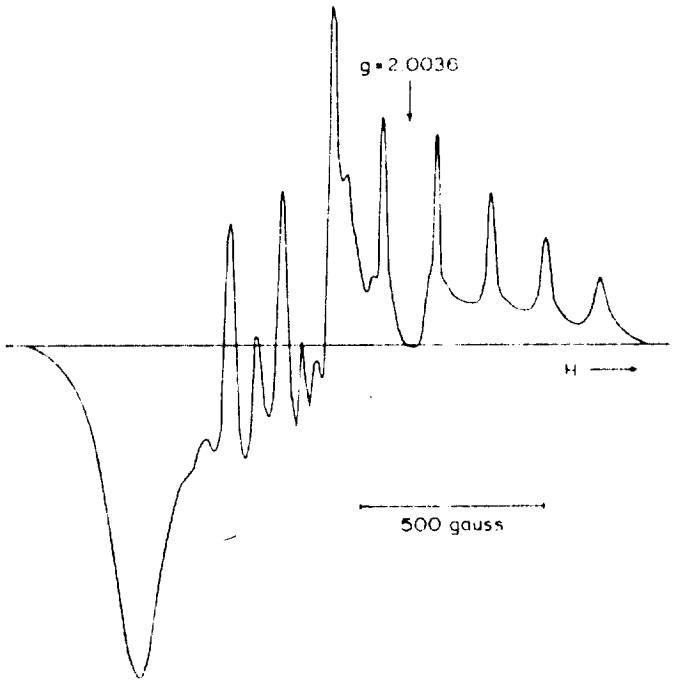


Figure 19. The EPR Spectrum of Base-off Cobalamin, B_{12r}, at pH 0 in Propane-1,2-diol-water, 1:4, Measured at 100°K using X-band Irradiation (1232)

In 1971 Boddy (0300) proposed five assumptions inherent in assessing metabolic "equilibrium" of B_{12}:

1. All body B_{12} was effectively in a single compartment.
2. After label, the specific radioactivities of significant tissues should all be the same.
3. Excretion rate should be describable by a single exponential term.
4. Whole-body excretion rates should correspond with tissue turnovers.
5. The daily loss should correspond with the daily intake.

After citing evidence to justify these assumptions, the author proposed that measurement of B_{12} content of random urine sample could be interpreted as:

$$\text{Total body } B_{12} \ (\mu g) = 0.95 \times \text{administered dose } (\mu Ci) \times \frac{B_{12} \text{ content/ml urine } (\mu g/ml)}{\text{Activity/ml urine } (\mu Ci/ml)}$$

For this, a random urine sample should be taken 1-2 weeks after the label, and could be dealt with simply, and on an outpatient basis; the author suggested that, though oversimplified, it should be an adequate approximation for most clinical purposes, and should eliminate the need for serum investigations.

In 1972 Boddy et al. (0303) described clinical experience with a double-isotope method of assessing B_{12} absorption. Free Co^{58}-B_{12} and intrinsic factor-bound Co^{57}-B_{12} were measured simultaneously by a whole-body monitor, and errors were claimed to be within acceptable limits.

In 1972 Raven et al. (2250) compared three methods of determining serum B_{12}: bioassay by E.gracilis or by L.leichmannii, and the Lau radioisotopic assay as modified by the authors, using respectively 478, 396, and 481 samples. Normal sera contained B_{12} 460 (170-1144) pg/ml by E.gracilis, 471 (155-1075) pg/ml by L.leichmannii, or 497 (235-2470) pg/ml by label. The E.gracilis bioassay was held to distinguish best between normals and pernicious anemics; otherwise, the comparisons varied widely from sample to sample.

In 1972 Jacob and O'Brien (1325) described an assay for intrinsic factor -B_{12} complex in man that used the reaction with intrinsic factor antibody.

In 1972 Gizis and Meyer (0968) used DEAE-cellulose column chromatography to separate transcobalamins I and II and a third binder of high-mw from human serum.

VIII. Occurrence

In In 1955 Evans et al. (0800) determined the B_{12} contents of fresh and stored eggs as follows:

Fresh eggs	387 ng/egg	6.54 ng/g	
Fresh yolk	362	18.53	
Fresh white	25	0.63	
Stored eggs*	260	5.03	*12 months at $0^{o}C$
Stored yolk	237	11.35	
Stored white	23	0.77	

Thus, eggs stored a year at $0^{o}C$ lost about one-third of their B_{12}, almost all of it from the yolk, not from the white.

In 1963 Banerjee and Chatterjea (0163) assayed various Indian foods for B_{12} activity, with the results shown in Table 21.

Table 21. Vitamin B_{12} Activity (Euglena gracilis assay) of articles of Indian Diets, and Effect of Boiling and Cooking (0163)

Item	Local name	Vitamin B_{12} activity ($\mu\mu$g/100 g fresh weight) Raw	Boiled	Cooked	Loss after cooking as a percentage of activity of boiled material
Fish (muscle):					
Catla catla	Catla	0·7	1·6	0·48	70·0
		2·08	4·5	0·61	86·4
Lates calcarifer	Vetki	3·4	1·0	0·5	50·0
Labeo rohita	Rui	1·6	--	--	--
		6·7	1·3	0·08	93·8
Mystus vittatus	Tangra	1·18	3·08	1·0	67·5
		7·5	4·85	3·7	23·7
Heteropneustis fossilis	Singee	4·04	1·36	0·8	41·1
Clarias batrachus	Magur	3·7	2·9	0·3	89·6
Anabas testudineus	Koi	1·9	1·1	0·05	40·9
Mugil parsia	Parsey	3·6	1·7	1·1	35·2
		5·6	2·7	2·0	25·9
Glossogobius giuris	Bele	2·2	--	2·2	--
Ophiocephalus striatus	Shole	1·0	--	0·3	--
Alpocryptus lanceolatus	Guley	2·6	--	0·24	--
Wallagio attu	Boal	4·6	1·36	1·32	--
Hilsa ilisha	Ilish	4·0	4·5	0·16	96·4
Polynemus paradiseus	Tapsey	8·0	1·0	0·47	53·0
Prawn	Bagda, chingree	1·01	·	0·45	
Meat:					
goat muscle	Mangsha	1·0	0·26	0·08	69·6
		1·26	--	--	--
goat liver	Mete	40·0	104	26·0	75·0
		100	--	-	
egg, duck	Dim (patihans)	--	6·0	--	--
Milk, cow	--	--	4·8*	--	--

* $\mu\mu$g/L

In 1963 Brady and Newton (0342) assayed the livers of germfree white Swiss mice and genetically similar controls, fed a sterilized semi-synthetic diet, for coenzyme-B_{12} activity. They found this at 190 nmoles/kg in control and 239 nmoles /kg in the germfree mice, compared with 220 nmoles/kg for human liver and 180 nmoles/kg for lamb liver. They had too little tissue to identify chemically the base of the mouse liver coenzyme, and concluded that the presence of methylmalonyl-CoA isomerase in the germfree animals would account for the presence of the coenzyme B_{12}.

In 1964 Evans and Kliewer (0798) surveyed the occurrence of B_{12} compounds in plants and micro-organisms. They concluded that the main, perhaps only source comprised organisms that fixed atmospheric nitrogen, including blue-green algae and nodule symbionts of leguminous and nonleguminous plants (for example, Table 22. There was no compelling evidence that higher plants either synthesized B_{12} or required it. The only demonstrated B_{12} coenzyme of micro-organisms was 5,6-dimethylbenzimidazolylcobamide.

Sources

In 1973 Herbert (1015) stated that B_{12} arises only in micro-organisms; plants carry it by contamination, e.g., legumes because of their root nodules. Fruits, vegetables, and cereals contain no B_{12} when washed. Usual dietary sources include meat and fish products,and (less) milk and its products. Rich sources (over 10 μg/100 g wet weight) are listed as the liver, kidney, and heart of mammals, and marine bivalves. Crabs, rockfish, salmon, sardines, egg-yolk, and non-fat dry milk are given as containing 3-10 μg/100 g. Muscle-meat, lobster, scallops, flatfish, tuna, and fermenting cheeses are given as containing 1-3 μg/100 g. Sources with less than 1 μg/100 g are listed as fluid milk, cream, Cheddar and cottage cheeses.

The natural form in liver is stated to be coenzyme B_{12} but its 5'-deoxyadenosyl anionic group linkage is unstable; during the original isolation of B_{12}, this group was replaced by cyanide leaching from charcoal in the apparatus, and the coordinate link of cyanide to Co was stable. Methyl-B_{12} is also found in mammalian tissues; it and coenzyme B_{12} are photolabile and tend to form aquocobalamin when KCN is not present (1015).

Table 22. Cobamide Coenzyme Content of Nitrogen-Fixing Symbionts and Microorganisms* (0798)

Species	Part analyzed	No. of samples	Cobamide coenzyme (mμmoles/gm fresh tissue)†
Medicago sativa	nodules	3	45-64
Glycine max	nodules	8	30-40
Glycine max (nodulated)	roots	2	0
Glycine max (nodulated)	stems	2	0
Glycine max (nodulated)	leaves	2	0
Pisum sativum	nodules	4	36-47
Pisum sativum (nodulated)	roots	2	0
Pisum sativum (nodulated)	stems	2	0
Pisum sativum (nodulated)	leaves	2	0
Trifolium pratense	nodules	2	40
Phaseolus vulgaris	nodules	2	18
Alnus oregona	nodules	5	24-62
Ceanothus velutinus	nodules	2	5-18
Rhizobium meliloti	cells	4	26-30
Rhizobium phaseoli	cells	2	23-25
Rhizobium japonicum	cells	2	15-21
Rhizobium trifolii	cells	2	7-8
Rhizobium leguminosarum	cells	2	7-9
Azotobacter vinelandii	cells	2	3-11
Clostridium pasteurianum	cells	1	4
Unidentified bacteria from nodules of *Ceanothus velutinus*‡	cells	1	2-3
Unidentified actinomycete from nodules of *Ceanothus velutinus*‡	cells	1	1-3

* A portion of the results in this table were reported in a previous publication and are included in this paper by permission of *Nature*.

† Unless otherwise indicated, assays for cobamide coenzyme were conducted by the glutamate isomerase assay method of Barker *et al.*,[51] and results are expressed as amounts of 5,6-dimethylbenzimidazolylcobamide coenzyme.

‡ The organisms were isolated from nodules of *Ceanothus velutinus* by Arthur Wollum, Oregon State University, Corvallis, Oregon.

In 1974 Scott (2457) discussed the mechanism of B_{12} biosynthesis by bacteria, which he had found to involve the pathway succinate-glycine to δ-aminolevulinic acid to cobyrinic acid; the question was at what step the synthesis of the B_{12} corrinoid diverged from the pathway of heme synthesis [which is rate-limited in mammals by the relative activities of δ-aminolevulinate synthetase and dehydrase, beyond the scope of this monograph and relevant only in that the neuropathies of deranged porphyrin synthesis and metabolism are well known]. Scott proposed that the corrin ring of B_{12} was elaborated in Propionibacterium shermanii from uroporphyrinogen III, accepting Co^{++} instead of Fe^{++} (Figures 20 and 21).

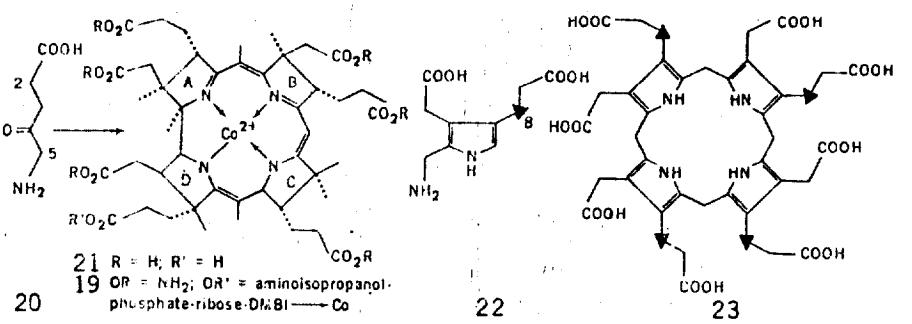


Figure 20. Biosynthesis of B_{12} (2457)

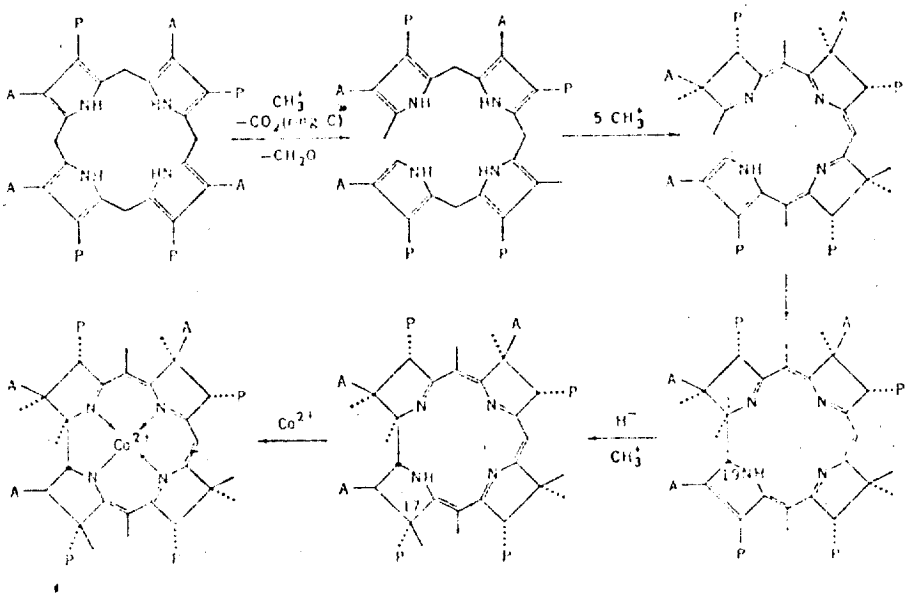


Figure 21. Proposed Mechanism for the Biosynthesis of Cobyrinic Acid from Uroporphyrinogen III (2457)

The Merck Index (2628) lists the occurrence of three forms of B_{12} as follows:

B_{12}	A cobalt-containing coordination compd, first obtained from liver, now usually produced by the growth of suitable micro-organisms. Isoln from liver: Rickes, Brink, Koniuszy, Wood, Folkers, Science 107, 396 (1948); from cultures of Streptomyces griseus: Rickes et al., ibid. 108, 634 (1948); Rickes, Wood, U.S. pats. 2,703,302 and 2,703,303 (1955 to Merck & Co., Inc.); Speedie, Hull, U.S. pat. 2,951,017 (1960 to Distillers Co., Ltd.); McDaniel, U.S. pat. 3,000,793 (1961 to Merck & Co., Inc.). Long, U.S. pat. 3,018,225 (1962 to Merck & Co., Inc.). Also recovered from sewage sludge, see Milorganite: Van Melle, U.S. pat. 3,057,851 (1962 to Armour-Pharm.); Bernhauer et.al., U.S. pat. 3,120,509 (1964 to Hoffmann-La Roche).
$B_{12}c$	Isolated from Streptomyces griseus fermentation liquors and prepd by treating vitamin $B_{12}b$ with nitrous acid: Smith et al., Brit. pat. 688,132 (1953 to Glaxo Laboratories Ltd.); Smith et al., Biochem. J. 52, 389 (1952). Prepd from hydroxocobalamin, sodium nitrite and acetic acid: Kaczka et al., J.Am. Chem. Soc. 73, 3569 (1951).
$B_{12}s$	Occurrence in marine algae: Ericson, Lewis, Arkiv. Kemi 6, 427 (1953), C.A. 48, 7684f (1954).

I. Acute Toxicity

A. Mice

In 1950 Traina (2787) noted a lack of reports on B_{12} toxicity, attributed this to small dosages, and studied the effects of large doses given to albino mice.

Three groups of ten mice (average 11 g) were given B_{12} (form not stated) i.p. in doses of 7.5, 15, or 30 μg/mouse, and a fourth group was given 30 μg/mouse s.c. The results (Table 23) showed that "about" 0.75 mg/kg i.p. was nontoxic, 1.5 mg/kg i.p. was "decidedly toxic", and 3 mg/kg i.p. or s.c. was 100% lethal. Necropsy revealed pulmonary edema and slight visceral edema. No pathological changes were seen at histology of liver, kidney, adrenals, intestines, thymus, testicles, and spleen.

The possibility of allergy was studied in 12 guinea-pigs (average 400 g) each given B_{12} 5 μg/day s.c. for 21 days. After 37 days intermission each received 15 μg i.p. in one dose. No sensitivity was observed.

The author commented that a patient allergic to liver extract had reportedly not shown sensitivity to parenteral B_{12}, and that B_{12} was reputed to have antianaphylactic and antihistaminic properties.

In 1950 Winter and Mushett (3002) disagreed with Traina's findings (2687). They reported no deaths from crystalline B_{12} given i.p. to mice in doses up to 1600 mg/kg (Table 24, no further details given), and to rats and guinea-pigs in doses up to 100 mg/kg. The authors claimed that there were no toxic manifestations, no deaths, and no gross pathological changes at autopsy, from doses 500 times higher than Traina's. They attributed his findings to contamination of the dose.

B. Guinea Pigs

In 1964 Lipton and Steigman (1656) investigated sensitivity of guinea-pigs to pure B_{12} crystals, for two reasons: crude B_{12} preparations contained many possible antigens, and isolated reports of human sensitivity to pure B_{12} were complicated by factors in the case histories. The authors also cited Traina's failure to produce anaphylaxis in guinea-pigs with small doses of B_{12}, and his conclusion that B_{12} was anti-anaphylactic (2787).

Male and female Hartley guinea-pigs, 500-650 g, were fed stock diet with alfalfa hay; they were treated to induce sensitivity, and later were tested

Table 23. Data Concerning Experimental Administration of Vitamin B_{12} (2787)

Group	Animals Treated	Route of Injection	Amount of Vitamin B_{12} Micrograms	Signs of Toxicity	Mortality Rate
1	10	Intraperitoneal	7.5	None	None
2	10	Intraperitoneal	15	Excitatory state with convulsions	2/10
3	10	Intraperitoneal	30	Excitatory state with convulsions ending in cardiac and respiratory failure	10/10
4	10	Subcutaneous	30	Excitatory state with convulsions ending in cardiac and respiratory failure	10/10

Table 24. Absence of Toxic Effects in Albino Mice from Single Injections of Large Doses of Crystalline Vitamin B_{12} (2787)

Sex	Dose, Mg/Kg.	Mortality Ratio, Dead/Total	Av. Body Weight, Gm. Initial	Av. Body Weight, Gm. 1 Week
M	100 i. p.	0/10	20.3	25.1
M	200 i. p.	0/10	20.5	21.8
M	400 i. p.	0/10	20.5	25.0
M	1600 i. p.	0/4	...	...
F	800 i. v.	0/3	...	...
F	1600 i. v.	0/3	...	...
M	Uninjected controls	0/15	21.0	21.8

for results. Two such experiments were reported:

(1) Cyanocobalamin prepared from streptomyces ferment was emulsified with Freund's adjuvants and was given intracutaneously (i.c.) at seven sites, to a total per animal of 2 mg B_{12} and 0.8 mg killed tubercle bacilli in 0.4 ml emulsion. Eight animals were so treated, eight controls received only the adjuvants, and another eight were not injected.

After 28 days each animal was challenged with i.c. injections of 0.1 ml distilled H_2O containing purified B_{12} 2, 20, and 200 μg. Injection sites were observed after 5, 24, 48, and 72 hours.

No reactions were seen at 5 hours; peak reactions were seen at 24-48 hours and most remained visible at 72 hours, indicating a tuberculin or delayed type of sensitivity. No reactions were seen in any controls, nor

at any site challenged with 2 μg B_{12}. Two of the eight sites challenged with 20 μg B_{12} reacted, and so did all eight challenged with 200 μg (Table 25).

(2) One group of eight animals was sensitized as above, and another received only the adjuvants. At 13 days all animals were challenged on the right side with 100 μg of the B_{12}, with further challenges at the same side at 20 days (100 μg) and 27 days (10 μg). The controls did not react, then or later. Weak reactions were seen in the experiment group at 13 days, stronger at 20 and well-defined at 27 days, except in one animal that did not react. Four of the animals reacted to 10 μg.

The three strongest reactors and three controls were then challenged with liver-derived B_{12} crystals, 40 μg in 0.2 ml, given similarly in the left side on day 35. The remainder were given 20 μg in 0.1 ml similarly on day 40, and the authors explained that B_{12} crystals were difficult to prepare from liver. All except the controls reacted to this challenge, the first three strongly (Table 25).

The authors added without detail that they had failed to develop neutralizing antibodies, using serum from a sensitized animal. They concluded that they had sensitized guinea-pigs to B_{12} itself, and that sensitization was therefore possible under these artificial conditions.

C. Humans

In 1950 Young et al. (3080) reported a case of sensitization to liver extract in a male with five years history of pernicious anemia. He was found to be equally sensitive to B_{12} concentrate made from streptomyces broth. Intradermal tests indicated that the sensitivity was acquired. At the time of the report there was "yet" no sensitivity to crystalline B_{12}.

In 1961 Roy (2352) briefly reported a death after B_{12} injection. A 48-year-old Hindu male was receiving insulin for diabetes, and became sensitive to thiamine injections. On the day this was changed to B_{12} his morning urine contained 3.5% sugar. Immediately after receiving B_{12} i.m. 500 μg in the deltoid muscle (from a freshly bought vial of 5 ml, 1 mg/ml), the patient went into what apparently was anaphylactic shock, and despite injections of adrenaline, antihistamines, and percorten, he died within 15 minutes. The author commented only that such an event must be very rare.

Table 25. Skin Reactions in Guinea Pigs Sensitized with Crystalline Vitamin B_{12} (Streptomyces) in Complete Freund Adjuvants and Skin Tested with Crystalline Vitamin B_{12} Derived from Streptomyces and from Liver* (1656)

Test Dose Source Amount	Test Day	Time of Reading of Reaction (Hours After Injection of Test Dose) 24	48	72
Strep. 100	27	WDP-Ind. 14	WDP-Ind. 14	WDP-Ind. 14
Strep. 10	27	P-Ind. 9	WDP-Ind. 12	WDP-Ind. 12
Liver 40	35	WDdP-Ind. 16	WDdP-Ind. 16	WDdP-Ind. 14
Strep. 100	27	P-Ind. 14x10	WDP-Ind. 11	WDP-Ind. 15
Strep. 10	27	P-Ind. 6	Neg.	Neg.
Liver 40	35	WDP-Ind. 11	WDP-Ind. 12	WDP-Ind. 12
Strep. 100	27	WDP-Ind. 12	WDP-Ind. 12	WDP-Ind. 12
Strep. 10	27	WDP-Ind. 12	WDP-Ind. 12	WDP-Ind. 12
Liver 40	35	WDP-Ind. 15	WDP-Ind. 11	WDP-Ind. 9
Strep. 100	27	P-Ind. 10	P-SS 10	P-SS 10
Strep. 10	27	Neg.	Neg.	Neg.
Liver 20	40	WDP-Ind. 13	WDP-Ind. 10	P-Ind. 10
Strep. 100	27	P-S 12x8	P-S 9	Neg.
Strep. 10	27	P-Ind. 13x10	P-Ind. 10	Neg.
Liver 20	40	P-Ind. 11	P-Ind. 8	P-Ind. 9
Strep. 100	27	Neg.	Neg.	Neg.
Strep. 10	27	Neg.	Neg.	Neg.
Liver 20	40	WDP-Ind. 12	P-Ind. 8	P-Ind. 8
Strep. 100	27	WDP-Ind. 14	WDdP-Ind. 12	WDP-Ind. 12
Strep. 10	27	P-Nod. 5	P-Nod. 4	Neg.
Liver 20	40	P-Ind. 11	WDP-Ind. 9	P-Nod. 6
Strep. 100	27	P-Ind. 11x8	P-Ind. 6	Neg.
Strep. 10	27	Neg.	Neg.	Neg.
Liver 20	40	WDP-Ind. 14x11	IDP-Ind. 9	P-Nod. 6

Legend: WD-Well defined; ID-ill defined; Nod.-nodule; Ind.-induration (thickness 1 to 3 mm.); P-pink; R-red; dP-dark pink; SS-soft swelling.

*S controls injected with complete Freund adjuvants less Vitamin B_{12} were negative. Strep. - Vitamin B_{12} derived from Streptomyces Liver - Vitamin B_{12} derived from liver.

See Table 1.

In 1963 Portigliatti (2187) described a rapidly fatal anaphylactic reaction to B_{12} in a 34-year-old pregnant woman. The symptoms developed apparently without warning after the third injection of 100 μg prescribed for anemia; they included collapse, cyanosis, dyspnea, hypotension, retrosternal pains, and urticaria. The patient did not respond to therapy, and died within half an hour of admission to hospital. Analysis of unused doses from the "same box", pathological and laboratory investigations following the autopsy, were all reported negative. The author concluded that the case was idiosyncratic and recommended precautionary skin tests before B_{12} therapy.

In 1966 Menon (1820) reported what he claimed to be the first three cases of adverse reactions to cyanocobalamin. All were fatal.

The first case was a 58-year-old man with a past history of rheumatic fever and a recent history of 16 years of increasing lassitude. Marrow biopsy revealed megaloblastic changes, and he was given cyanocobalamin 1 mg i.m. Half a day later he collapsed and died; autopsy revealed acute pulmonary edema and mild mitral stenosis.

The second case was a 75-year-old multipara with a six-weeks history of increasing weakness and anorexia; examinations disclosed skin symptoms, a systolic murmur, and megaloblastic marrow. After cyanocobalamin 1 mg she went into coma overnight and died the following evening. At autopsy she had acute pulmonary edema, atherosclerotic aortic stenosis, and left ventricular hypertrophy.

The third case was a male aged 72 with a four-months history of anemia and progressive dementia; his peripheral blood contained late megaloblasts. After three daily (evening) injections of B_{12}, he was found dead on the morning of the fourth day. Autopsy revealed severe extensive pulmonary edema, and moderately severe atheromata of the aorta and coronary arteries.

In addition, all three deaths occurred in the hospital, and all three patients had ante-mortem hemoglobins of 31-36%.

The author dismissed coincidence as an explanation of all three findings. Citing reports that B_{12} therapy of pernicious anemia resulted in rapid increases of blood volume and uric acid content, he concluded that B_{12} therapy should be started with caution in the presence of cardiovascular disease.

Hovding (1266) described in 1968 a severe anaphylactic reaction to hydroxocobalamin i.m. in a man aged 67 without previous history of allergy or reactions to drugs. His pernicious anemia had been treated for 17 years with various forms of parenteral B_{12}. Shock developed two minutes after his last injection, and responded slowly to adrenalin 0.75 ml s.c. Intradermal tests were positive (see Table 26). Subsequently he did not react adversely to oral B_{12}.

The author commented that in this case, unlike others cited, it was difficult to attribute the allergy to contaminants; nevertheless, it was also difficult to postulate that B_{12} was a complete antigen.

Table 26. Results of Intradermal Tests (by Injection) (1266)

Test Substance	Test Concentration	Test Dose	Reaction
Cyanocobalamin with 1.5% benzyl alcohol, commercial brand	100 μg/ml.	0.05 ml.	Weal with pseudopodia
Hydroxocobalamin, commercial brand	100 μg/ml.	0.05 ml.	" "
Hydroxocobalamin very highly purified	100 μg/ml.	0.05 ml.	" "
Cyanocobalamin prepared from very highly purified hydroxocobalamin	100 μg/ml.	0.05 ml.	" "
Coenzyme B[illegible]	100 μg/ml.	0.05 ml.	" "
Methylcobalamin	100 μg/ml.	0.05 ml.	" "
Benzylalcohol	1.5%	0.05 ml.	No reaction
Control blank	10%	0.05 ml.	No reaction

In 1968 an editorial in the British Medical Journal (0082) commented that "occasional cases of allergic sensitivity..., anaphylactoid reactions, and a single fatality in a 48-year-old Indian has been reported." Additionally, "antibodies develop to hog intrinsic factor, and vitamin B_{12} so linked is no longer absorbed." Whenever B_{12} was given for the first time, the response should be carefully monitored (0082).

In 1971 James and Warin (1340) described a case of sensitivity to cyanocobalamin and hydroxocobalamin in a woman aged 58, who for eight years had received parenteral cyanocobalamin after diagnosis of pernicious anemia. After complaining of urticaria, bronchospasm, dyspnea, and aphonia, she was admitted to hospital, and intradermal tests with both cobalamins, 100 μg/ml, proved negative or doubtful. However, the second of two monthly injections i.m. of 1 mg cyanocobalamin cytamen reproduced her symptoms, as did a change to oral B_{12} 100 μg twice daily. Therapy was stopped, and signs of pernicious anemia returned. Different forms of parenteral B_{12} were tried, and the urticaria

returned and persisted. On readmission to the hospital she had a normal blood count but a positive Schilling test; then, her urticaria responded immediately to intrinsic factor 40 mg thrice daily.

The authors commented that this patient was indeed sensitive to cyano- and hydroxo-cobalamin, both oral and parenteral, and showed both anaphylaxis and urticaria. They could not explain the negative intradermal tests. The pernicious anemia was controlled by intrinsic factor alone. They cited four severe and four mild cases of similar allergy reported in the literature.

In 1971 Nava (1965) reported three cases of acute allergic reaction to B_{12} (Table 27), which he attributed speculatively to abnormal binding of the vitamin.

In 1972 Ivanchenko (1317) reported allergic reactions including anaphylaxis in "a few" patients with atherosclerosis, following repeated administration of B_{12}, and confirmed by intradermal tests. The author commented that prolonged high doses of B_{12} also favored cell replication and should be "restricted" in oncologic practice.

In 1973 Herbert (1015) reviewing the toxicity of B_{12} and folic acid concluded: "It is hard to accept that either vitamin B_{12} or folic acid, being necessary for life, could, in quantities close to minimal daily requirements, be toxic in man. In fact, these substances are non-toxic in man not only in small doses but also in doses which exceed the minimum daily adult human requirement by ten thousand-fold for vitamin B_{12} and one thousand-fold for folic acid." Nevertheless he noted the reports of "rare" allergic reaction.

II. Short Term Studies

A. Mycota

In 1963 Littman and Miwatani (1659) studied the growth of *Candida albicans* in biotin-based mineral synthetic medium to which were added various water soluble vitamins, their analogs, and cell-division inhibitors. Growth of *C. albicans* was markedly stimulated by B_{12}, which non-competitively reversed growth inhibition by 5-fluorouracil. The authors concluded that *C. albicans* was partly dependent on B_{12}, which appeared to have a role in the nucleic acid biosynthesis of this organism (this report is placed here because infection by *C. albicans* is widespread, especially in the human female).

Table 27. Reactions to Intradermic Tests (Test Reading after 20, 24, and 48 hours) (1965)

Substance:	Case 1.	Case 2.	Case 3.
Streptomycin sulfate	++	-	-
dihydrostreptomycin sulfate	++	-	-
commercial hepatic extract	+	++	+
bovine hepatic extract	+	+	+
sieroalbumin of the hog	-	-	-
bovine sieroalbumin	-	-	-
thiamine	-	-	-
riboflavin	-	-	-
pyridoxine	-	-	-
nicotinamide	-	-	-
commercial cobalamin	++	++++	+++
hyper-purified cobalamin	++	++++	+++
commercial hydroxycobalamin	++	+++	+++
coenzyme B_{12}	++	+++	+++
cobalt chloride	-	-	-
benzilic alcohol	-	-	-
cytidine	-	-	
uridine	-	-	-

As usual, the interpretation of the intradermic reactions is as follows: focus*)with an average diameter of 5 mm = +; 10 mm = ++; 15 mm = +++; over 15 mm = +++.

*) "ponfo"

B. Rats

In 1955 Giacalone (0948) reported that "excess" B_{12} given to undernourished rats accelerated weight loss to the point of death but did not otherwise alter the observed effects of the undernourishment.

C. Guinea Pigs

One Italian report (1603) could not be obtained in the original.

D. Humans

In 1963 Glass et al. (0982) measured the "long term" effects of massive parenteral doses of hydroxocobalamin and cyanocobalamin on blood levels of B_{12} in 50 geriatric patients aged 48-92, average 71, 24 men and 26 women with starting blood B_{12} below 250 pg/ml. Six had pernicious anemia in partial remission; other blood data were considered normal.

All of these patients received B_{12} 500 µg/week i.m. in one dose. Half of them received cyanocobalamin, half hydroxocobalamin. Twenty-three were treated for 10 weeks and the rest for 14. Blood B_{12} was determined twice before treatment, biweekly during treatment, and bimonthly and then monthly after treatment, with careful attention to methods and timing of determinations. All patients were studied for eight months after treatment; however, several in each group failed to complete this period for reasons unconnected with B_{12}.

The results are summarized in Figure 22 and Table 28. Blood B_{12} levels after hydroxocobalamin were higher, and the elevations lasted longer, than those after cyanocobalamin. The differences were "statistically significant at any point of the study" and the authors attributed them to more efficient retention of hydroxocobalamin. "After discontinuation of the cyanocobalamin treatment, B_{12} blood levels reverted to normal within four to five weeks, but after hydroxocobalamin they did not return to the upper limit of the norm for six to seven months. At the end of the year, they were still about three times higher than before the treatment."

Toxicity was not mentioned in this report.

In 1968 Temperley et al. (2745) reported an association of premature delivery with low maternal serum B_{12}. This was from a survey of women attending the antenatal clinic at the Rotunda Hospital, Dublin, Eire; the trends are shown in Tables 29 and 30, and the paper itself should be consulted for details. The

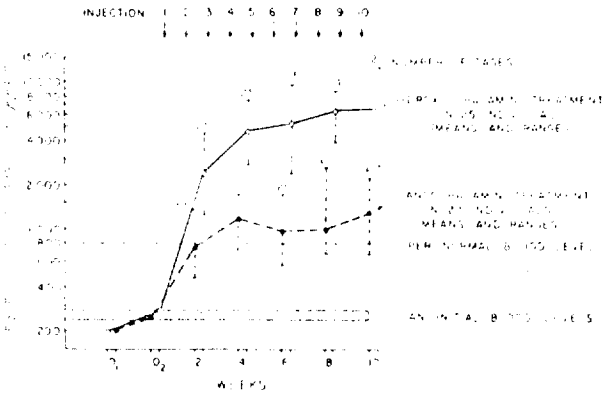


Figure 22(a). Vitamin B_{12} Blood Serum Levels During Ten Weekly Intramuscular Injections of 500 µg Serum Hydroxocobalamin or Cyanocobalamin in 47 Individuals with Initial B_{12} Blood Levels Below 250 µµg/ml (0982)

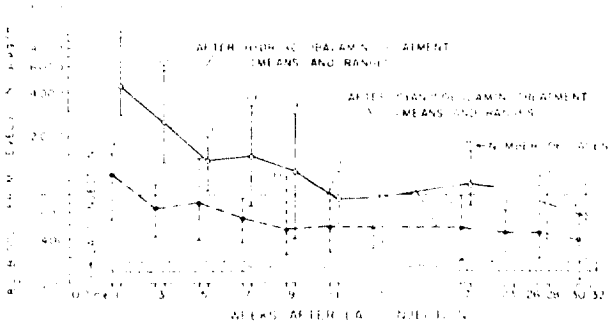


Figure 22(b). Vitamin B_{12} Blood Serum Levels After Ten Weekly Intramuscular Injections of 500 µg Hydroxocobalamin or Cyanocobalamin in 23 Individuals, Determined for Duration of 8 Months (0982)

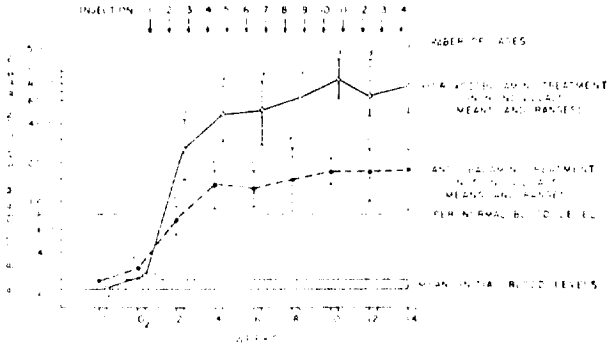


Figure 22(c). Vitamin B_{12} Blood Serum Levels During 14 Weekly Intramuscular Injections of 500 μg Hydroxocobalamin or Cyanocobalamin in 14 Individuals with Initial B_{12} Blood Levels Below 250 μμg/ml (0982)

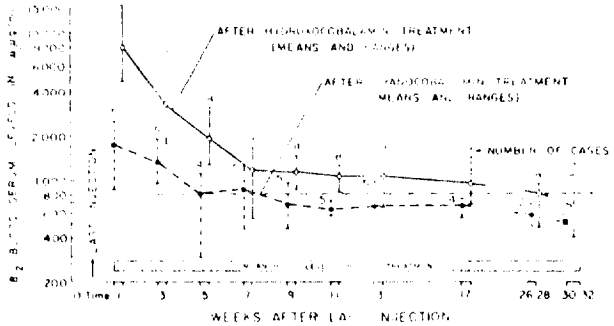


Figure 22(d). Vitamin B_{12} Blood Serum Levels After 14 Weekly Intramuscular Injections of 500 μg Hydroxocobalamin or Cyanocobalamin in 16 Individuals, Determined for Duration of 8 Months (0982)

Table 28. Statistical Evaluation of Vitamin B_{12} Blood Serum Levels During and After 10 to 14 Weekly Intramuscular Injections of 500 µg Hydroxocobalamin or Cyanocobalamin (0982)

	Weeks of Treatment	Blood Serum B_{12} Levels in µg/ml (Means with Standard Deviations)		Statistical Evaluation of Differences in the Means		
		Hydroxocobalamin Treatment	Cyanocobalamin Treatment	'n'	't'	'p'
Group treated with 10 weekly intramuscular injections of hydroxo- or cyanocobalamin	0_1	190±45	167±53	27	1.3	>.2
	0_2	283±236	226±86	28	0.8	>.4
	2	2,208±914	769±219	28	5.4	<.001
	4	3,995±939	1,135±280	28	10.2	<.001
	6	4,919±1,912	887±242	27	7.3	<.001
	8	4,974±1,573	1,055±329	14	2.5	<.05
	10	4,385±1,868	1,076±281	20	5.6	.001
Group treated with 14 weekly intramuscular injections of hydroxo- or cyanocobalamin	0_1	213±133	210±64	15	0.7	.5
	0_2	276±193	306±112	15	0.4	>.7
	2	2,677±1,100	721±160	15	5.7	<.001
	4	4,655±1,613	1,358±348	15	6.3	<.001
	6	5,272±1,613	1,246±336	15	7.8	<.001
	8	6,368±1,502	1,478±690	15	8.6	<.001
	10	8,826±2,304	1,702±323	14	8.8	<.001
	12	6,450±2,383	1,705±773	13	5.3	<.001
	14	7,594±2,931	1,745±749	15	5.9	<.001
	Weeks After Treatment					
Group treated with 10 weekly intramuscular injections of hydroxo- or cyanocobalamin	1	3,977±1,114	944±292	18	8.3	<.001
	3	2,160±775	631±192	20	6.0	<.001
	5	1,404±366	691±312	19	7.1	<.001
	7	1,439±678	552±137	18	3.8	<.01
	9	1,145±712	472±221	18	2.6	<.02
	11	839±229	479±142	18	3.9	<.001
	13	761±296	472±108	16	2.4	<.05
	17	982±376	421±55	17	3.9	<.001
Group treated with 14 weekly intramuscular injections of hydroxo- or cyanocobalamin	1	6,947±2,083	1,749±748	12	6.3	<.001
	3	2,687±942	1,299±418	10	3.1	<.01
	5	1,982±664	795±319	10	3.5	<.01
	7	1,186±371	869±286	12	1.6	>.1
	9	1,115±221	680±206	11	3.3	<.01
	11	1,037±141	626±72	11	6.4	<.001
	13	1,065±265	661±208	12	2.9	<.02
	17	959±230	673±93	11	3.0	<.02

Table 29. Serum Vitamin B_{12} Levels at Various Stages of Pregnancy (2745)

Stage of Pregnancy (Weeks)	No. of Cases	Serum Vitamin B12 (pg./ml.)		
		Range	Mean	S.E. of Mean
First visit	[illegible]	[illegible]	[illegible]	[illegible]
32	152	40-450	164	6·1
36	134	50-475	162	7·0
40	133	20-510	155	7·3
Non-pregnant	36	205-1,025	454	31·5

Table 30. Comparison of Cord and Maternal Serum Vitamin B_{12} Levels in 53 Instances (2745)

Cord Serum Vitamin B12 (pg./ml.)	Mean Maternal Levels (pg./ml.)				Mean Cord Levels (pg./ml.)
	First Visit	32 Weeks	36 Weeks	40 Weeks	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

authors inferred that a major drop in serum B_{12} occurred in the first four or five months of pregnancy, after which levels tend to rise somewhat. Levels were especially low with twins. Cord blood levels paralleled maternal blood levels but were in general slightly higher. The authors commented that they had too few cases to associate low B_{12} with teratogenicity.

In 1968 Foulds et al. (0867) unsuccessfully gave cyanocobalamin to two patients with Leber's hereditary optic atrophy, but had positive results with hydroxocobalamin (1 mg weekly, 1 mg twice-weekly). They argued that deranged cyanide metabolism was a facet of the condition, as in tobacco amblyopia where hydroxocobalamin had also been found superior to B_{12}, and implied that the cyano group of B_{12} might be harmful to such patients.

In 1969 Dugois et al. (0744) described exogenous B_{12}-dependent acne in four patients aged 26, 32, 50, and 60 years. Other chemotherapy was given, but withdrawal of B_{12} resolved the acne. The authors attributed the disorder to the hydroxo- form of B_{12}.

Two other similar reports were found (one from France, the other from Germany).

An Italian report claiming ototoxicity with B_{12} (0600) could not be obtained in the original.

Reviewing B_{12} toxicity data in 1973, Herbert (1015) concluded that B_{12} components could not be toxic in doses close to the minimum effective doses, which were "in fact" nontoxic in doses exceeding the daily adult human requirement by ten thousand-fold. Because B_{12} was water soluble, amounts exceeding the binding capacity of the polypeptide binders were excreted rapidly in the urine. The author judged allergy to be rare, and use of hydroxocobalamin and depot preparations to be in general unjustified; he drew attention to frequent pain at the injection site.

III. Long Term Studies

Only two studies were located.

A. Rats

In 1958 Richardson and Broch (2287) reported two studies on reproduction of rats fed (a) highly purified soybean proteins, and (b) large doses of B_{12}. They stated that most pregnant women received large doses of B_{12} and it was desirable to know if this had "a detrimental effect on the survival and well-being of the offspring."

Female rats fed soybean oil meal without added B_{12} from weaning were given an experimental diet when they weighted 150-160 g. After 4 weeks a male was introduced, and females in succeeding generations were fed the experimental diet through their life spans. The B_{12} levels and the results are summarized in Table 31. In a second study, two highly purified soybean protein fractions were fed as sole sources of protein through $P-F_3$ and $P-F_4$ generations respectively, without observed detriment.

The authors concluded that the weaning rate was unaffected by B_{12} added at 10, 25, 500, or 1000 μg/kg of diet. There was no evidence that large doses in

Table 31. Vitamin B_{12} and Reproduction in Rats (2287)

VITAMIN B_{12}	NO. OF FEMALES	YOUNG			LITTERS		AVERAGE NUMBER OF YOUNG PER LITTER		
		Obs.	Weaned	Av. wt.	Born	Weaned	Born	Obs.[2]	Weaned
		no.	%	gm	no.	%			
Soybean protein (diet 1)									
Series A									
None	10	258	43	31.7	41	49	8.1	6.9	5.5
10	9	259	95	37.6	37	95	8.2	7.0	7.0
25	10	243	92	39.3	34	94	8.8	7.1	7.0
100[1]	10	256	92	35.1	39	92	8.0	6.6	6.5
Series B									
None	10	272	69	28.8	51	67	6.9	5.6	5.5
25	10	274	87	35.6	40	92	7.8	6.9	6.5
500	10	230	96	35.5	30	100	9.1	7.6	7.3
1000	8	86	99	35.0	12	100	8.1	7.2	7.1
Series C									
Vitamin free casein (diet 1)									
None	21	449	61	29.2	71	68	6.9	6.2	5.9
25	10	302	95	39.0	40	100	9.0	7.6	7.2
500	10	291	93	37.9	40	100	8.8	7.3	6.8
Series D									
Soybean oil meal (diet 2)									
None	30	706	38	25.0	114	51	6.9	6.2	4.6
10	38	492	96	36.1	70	96	8.9	7.1	7.0
100	19	164	99	35.9	21	100	10.0	7.8	7.7
500	10	161	93	34.9	21	95	9.5	7.6	7.4
Series E									
Natural foodstuffs (diet 3)									
None	10	285	95	33.2	38	100	8.7	7.5	7.1
25	10	315	91	34.2	40	98	9.9	7.9	7.3

[1] Injected per rat per week.

[2] Average number observed after the litters containing more than 8 young had been reduced to 8.

the diet of the mother were toxic to the offspring, and weaning weights and rates were slightly greater with B_{12} than without it (2287).

B. Humans

In 1967 Brody (0366) reported one case of a 68-year-old white female who had taken B_{12} 50 μg t.i.d. orally for ten years without, in the author's opinion, replenishing her body stores of B_{12}. At the start she had a hemoglobin of 10.7 g% and megaloblastic marrow; at the end the hemoglobin was 13.6 g%. The serum B_{12} was 32 pg/ml at start, rose to 212 pg/ml in the first year, and averaged 203 pg/ml for nine more years. At the end, a liver sample removed surgically contained B_{12} 0.29 μg/g, considered low.

IV. Special Studies

Additional studies will be found at the start of the section on Biochemical Aspects IV, Effects on Enzymes and Other Biochemical Parameters.

A. Therapy

1. Hemorrhagic Shock

In 1951 Howard and DeBakey (1268) studied the production and treatment of experimental hemorrhagic shock in a total of 85 dogs. Cortisone and B_{12} were among the treatments tried. The authors concluded that neither treatment was effective.

2. Wound healing

In 1953 Findlay (0835) found that the tensile strength of scar tissue on experimental wounds in rats was increased by B_{12}, and healing was accelerated, when the rats were fed 19% or 25% protein diets but not when they were fed 0.9% protein diets.

3. Growth

In 1966 Flinn and Oxnard (0844) gave locally bred, normal rhesus monkeys B_{12} 0.5 mg i.m. monthly from weaning to before the prepubertal growth spurt, verified their high levels of circulatory B_{12}, and compared their growth records with those of similar untreated monkeys. Within the conditions of their study (a caution emphasized by the authors) the treated animals grew significantly better than the untreated.

B. Neuropathology

1. Monkeys

In 1970 Oxnard et. al. (2092) studied a total of 83 monkeys, mostly rhesus, in a zoo colony. These had been fed vegetarian diets for various periods since being captured, and a number were paralyzed or part-paralyzed. Signs typical of cerebral and column degeneration in man were absent, but lesions were found at autopsy, and were correlated with degrees of B_{12} deficiency and abnormal hematology. The authors concluded that diets fed to captive monkeys should contain adequate B_{12} and that newly captured monkeys should be checked for B_{12} status before being used for research.

In 1974 Kark et al. (1396) studied serum and rbc B_{12} for 20-31 months in 12 monkeys supplied controlled amounts of B_{12}, other dietary deficiencies being monitored and corrected by assays for folate, B_6, Fe, C, E, and minerals.

Serum and rbc B_{12} fell constantly, and urinary methylmalonate increased when assayed at 16 months; at 21 months liver B_{12} was 5% of control values (Tables 32 and 33). Growth, behavior, and health appeared normal, and 8-15 months after B_{12} deficiency was documented there were no signs of megaloblastosis or subacute combined degeneration.

Table 32. Blood vitamin B_{12}, pg/ml (1396)

	I-A; 5 monkeys (Diet alone)		I-B; [illegible] monkeys (Diet + B_{12})		II-A; 1 monkey (Diet alone)		II-B; 3 monkeys (Diet + folate)	
Months on diet	Mean S B_{12}[a]	Mean RC B_{12}[b]	Mean S B_{12}	Mean RC B_{12}	Mean S B_{12}	Mean RC B_{12}	Mean S B_{12}	Mean RC B_{12}
1	224	704	162	226	125	190	160	228
7	76	262	230	776	40	74	45	119
13	39	89	313	468	10	78	20	111
19	18	44	220	301	10	89	10	115
25	5.5	76	130	368				
31	11	54	371	401				

[a] S = serum. [b] RC = red cell.

Table 33 . Liver B_{12} in nanograms/gram wet tissue (1396)

Months on diet	Monkey	B_{12}	A as percent of B
21	1-A #1[a]	156.3	4.9%
	1-B #3[b]	3,175.0	
26	1-A #7[a]	73.3	4.8%
	1-B #2[b]	1,570.0	

[a]Group 1 monkeys on vitamin B_{12}-deficient diet.

[b]Group 1 monkeys on vitamin B_{12}-supplementation.

2. Humans

In 1973 Herbert and Tisman (1207) reviewed knowledge of B_{12} deficiency effects in man, emphasizing the interrelationships with folic acid deficiency and that CSF selectively accumulated folate and excluded B_{12}. Biochemical roles were summarized (Table 34), and four clinical conditions were described (summarized in Table 35). The authors stated their opinion that current terminology was inappropriate, e.g., that "subacute combined degeneration" started insidiously, not subacutely, and that combined lesions were often absent (peripheral lesions seen earlier and more often than central lesions). The authors appended a long list of mental and motor signs and symptoms.

Table 34. Biochemical Roles in Man of Coenzymes of Folic Acid and Vitamin B_{12} (1207)

A. Folate coenzymes in one-carbon transfers
   1. Metabolism of purines, pyrimidines, and their derivatives
      a. Purine nucleotides
      b. Pyrimidine nucleotides
         (1) Thymine deoxyribonucleotide
         (2) Deoxycytidylate hydroxymethyltransferase
   2. Metabolism of amino acids
      a. Serine and glycine
      b. Phenylalanine and tyrosine
      c. Histidine
   3. Initiation of peptide chain biosynthesis
   4. Lipid metabolism
   5. Biosynthesis of methyl groups
      a. Choline
      b. Methionine
         (1) B_{12}-independent synthesis
         (2) B_{12}-dependent synthesis
B. Vitamin B_{12} coenzymes
   1. B_{12} in folate metabolism
      a. Methionine biosynthesis from homocysteine
      b. B_{12}-dependent cell uptake of folates
      c. Other?
   2. Methyl B_{12} in methyl group transfers
      a. Methionine synthesis (methyltetrahydrofolate-homocysteine methyltransferase mediated)
      b. Other methyl group transfers?
   3. 5′-Deoxyadenosyl B_{12} in isomerase reactions
      a. Propionate oxidation (methylmalonyl CoA mutase mediated)
      b. Other isomerase reactions?
   4. Other roles of B_{12}
      a. Nucleic acid synthesis
      b. Lipid metabolism
      c. Protein and amino acid metabolism
      d. As a reducing agent
      e. Other?

Table 35. Clinical Conditions Resulting from B_{12} Deficiency

(Summarized from 1207)

Onset	Result	Metabolic Defect	Response to	Megalo-blastic anemia Yes/No	State of knowledge firm/ suspected
Congenital	Fatal	Low activities of: CH_3-4H-folate transferase Methylmalonyl reductase	- Hydroxo-B_{12}	No	Suspected
Congenital (autosomal recessive)	Methylmalonic aciduria (B_{12}-dependent)	5'-deoxyadenosyl-B_{12} (abnormal deoxyadenosyl transferase enzyme)	B_{12} 0.2 mg/day	No	Suspected
Congenital (autosomal recessive)	Methylmalonic aciduria (B_{12}-deficient)	Methylmalonyl-CoA aponenzyme	No response to B_{12}	No	Suspected
Congenital or later	Neuropathy: all axons can be demyelinated in brain, spinal cord.	None genetic - material or personal diet deficient of B_{12} - biochemistry of effects unknown.	B_{12}, incomplete if diabetes is a complication	Yes	Suspected or conjectured

C. Behavioral Studies

1. Rats

In 1971 Corson et al. (0569) studied behavioral effects of B_{12} 0.4 μg/day injected into adult Sprague-Dawley rats fed a diet supplying about 0.3 μg/day, the rat minimum requirement being less than 0.1 μg/day. Pattern discrimination was improved, as in a previous cited study in adult Long-Evans rats. However, juvenile Long-Evans rats showed no significant improvement. The authors commented that high levels of B_{12} supplementation seemed to be related to some aspects of cognitive performance, but definitive studies were hard to design.

2. Humans

In 1970 Kral et al. (1504) studied two aspects of memory function (memory quotient and retention span) in 63 aged subjects with senile or arteriosclerotic brain impairments. Although B_{12} and folate deficiencies were found "in a high percentage of all subgroups" levels were not correlated with degrees of impairment, and administration to 18 subjects of B_{12} 7 mg within 3.5 months did not improve memory function compared with that in a matched control group.

D. Blood Studies

1. Rats

In 1951 Levey and Orten (1614) concluded that cobalt-induced polycythemia did not arise by intermediary formation of B_{12}. Young male rats were injected with $CoSO_4.5H_2O$ 0.5 mg/day s.c., or B_{12} 3 μg/day s.c., or were untreated controls. Hemoglobin determinations over a 2-month period showed no significant increases in the B_{12} group compared with the controls, while the cobaltous sulfate produced polycythemia without increasing liver B_{12}, although fecal B_{12} increased somewhat.

2. Humans

In 1972 Beard et al. (0200) reported a case of inborn agranulocytosis in a 6-day-old baby who died in the 12th week of life. Neutrophil granulocyte formation in marrow was arrested at the promyelocyte stage, and there was a "marked reduction" of B_{12} binders. The authors inferred that transcobalamin I and/or fetal binders were derived from neutrophil granulocytes.

E. Cell division

In 1968 Das (0616) showed in lichen extracts that under some conditions B_{12} could become rate-limiting for DNA replication during cell division owing to its role as a cofactor. This role was inferred from the finding that B_{12} could replace "major nucleosides."

F. Fertility Studies

1. Rats

In 1961 Chow et al. (0517) studied the interactions of B_{12} and thyroid on the fertility of female rats. They found that B_{12}-depleted rats (by several methods) lost their fertility and recovered it after B_{12} injections. Thyroidectomy also cost rats their fertility, which was partly replaced by B_{12} or thyroid in the diet and "greatly improved" when both were given. The authors inferred that conceivably there were interactions between B_{12} and thyroid on fertility of female rats.

2. Hogs

In 1961 Frederick and Brisson (0880) maintained six sows on B_{12}-deficient diet. Two so fed for 2 years before their first litters aborted. Four others farrowed 8 litters with 68 live piglets of which 27 died within three days. All piglets that were fed B_{12}-deficient synthetic milk diet died within 14 days. Serum B_{12} and weight gain were related to B_{12} intakes, but piglets fed B_{12} did not improve their feed conversion. The authors concluded that B_{12} influenced reproduction and neonatal survival in pigs.

G. Cancer Studies

In addition to the English-language papers abstracted, a much larger number of reports were found, mainly Russian. None of these are given here, because they were considered to give little information that was not repeated in the English-language reports.

1. Mice

In 1951 Shapiro and Gellhorn (2476) found that B_{12} did not inhibit the 755 transplantable breast cancer of C57 black mice but appeared to enhance inhibition by 8-azaguanine (Table 35). In no case was tumor eradicated, and the mechanisms were not known.

In 1955 Woolley (3040) fed a B_{12}-deficient diet to mice and determined their body content of B_{12}. Mice without tumors contained an average 9 ng/g live weight, but mice with spontaneous mammary tumors contained an average 17 ng/g. The author considered that these tumors synthesized the vitamin. A strain of transplanted mammary tumors gave similar findings, but a second strain was observed to destroy the vitamin. Destruction was also observed in some mice with spontaneous tumors. In vitro studies showed that the destruction was not by way of protein-binding.

Table 35. Effect of Vitamin B_{12} and 8-Azaguanine on the 755 Tumor in C57 Mice (2476)

Exp. No.	Group	No. Animals Dead/Alive	No. Tumors	Duration Tumor Growth (Days)	Day Therapy Begun After Transplantation B_{12}	Day Therapy Begun After Transplantation 8-AG	Daily Dosage μgm/kg B_{12}	Daily Dosage mg/kg 8-AG	Mean Tumor Weight ± Standard Deviation of Mean (mg.)	Av. Body Weight (gm.) Beginning	Av. Body Weight (gm.) End
67 ♂	Controls	0/20	19	16					587 ± 61	22.4	22.3
	B_{12}	0/10	10	16	5		*		618 ± 116	23.3	22.3
	8-Azaguanine	0/18	18	16		5		50	82 ± 11	22.2	22.5
	B_{12}+8-AG	1/10	9	16	5	5	*	50	37 ± 7	23.3	22.6
86 ♂	8-Azaguanine	6/30	24	28		15		50	1055 ± 99	21.6	20.6
	B_{12}+8-AG	0/30	28	28	14	15	200	50	1205 ± 75	21.9	19.9
74 ♂	Controls	1/10	9	18					888 ± 51	22.3	23.3
	B_{12}	0/10	10	18	8		1,250		630 ± 95	21.2	22.1
	8-Azaguanine	0/10	10	18		8		50	51 ± 7	21.4	21.4
	B_{12}+8-AG	0/10	10	18	8	8	1,250	50	86 ± 9	20.7	20.1
87 ♂	8-Azaguanine	5/30	25	28		15		50	1404 ± 98	21.4	20.4
	B_{12}+8-AG	8/30	22	28	14	15	2,000	50	1149 ± 93	21.5	20.0
91 ♀	Controls	1/10	9	19					788 ± 111	17.7	18.4
	8-Azaguanine	0/10	10	19		7		50	278 ± 58	17.9	17.6
	B_{12}+8-AG	0/10	10	19	4	7	1,250*	50	85 ± 14	18.5	19.2
95 ♀	Controls	0/10	10	20					1125 ± 147	22.9	23.8
	8-Azaguanine	0/10	10	20		8		50	200 ± 28	20.6	19.9
	B_{12}+8-AG	0/10	10	20	5	9	† ‡	50	93 ± 15	20.3	20.4
108A ♂	8-Azaguanine	0/10	10	22		8		50	386 ± 47	19.2	19.3
	B_{12}+8-AG	0/10	10	22	6	8	1,000*	50	249 ± 42	14.1	19.9
108B ♂	8-Azaguanine	0/10	10	22		8		50	386 ± 47	19.2	19.3
	B_{12}+8-AG	0/10	10	22	6	8	500*	50	285 ± 30	19.7	19.9
118 ♀	8-Azaguanine	0/10	8	33		7		50	785 ± 113	17.1	18.9
	B_{12}+8-AG	1/15	14	33	7	7	1,000*	50	983 ± 112	17.9	19.5

* 25 (×5), then 250 (×5).
† = B_{12} dose given ½ hour before 8-azaguanine dose.
‡ 1000 (×6), then 300 (×7).

The author surmised, with cautions, that the B_{12} destroying system might be the synthesizing system acting in reverse. He inferred, from his methodology, that the B_{12} synthesis was not due to bacterial infection or necrosis of tissue.

In 1963 Woolley and Stewart (3047) observed a selective partial inhibition of mouse mammary tumors by a mixture of two antimetabolites, 1,2-dimethyl-4-(p-carboxyphenylazo)-5-hydroxybenzene (CPA) and 1,2-dichloro-4-benzenesulfonamido-5-nitrobenzene (DCBN), and by a related compound, 1,2-dimethyl-4,5-bis(benzenesulfonamido)benzene (DMDB), all when fed in the diet. All three were analogs of a microbial B_{12} precursor, 1,2-dimethyl-4,5-diaminobenzene, and the analogs inhibited microbial B_{12} synthesis. Permanent regressions of spontaneous mammary tumors were seen in about one-third of SPFS mice but not in C3H mice. Tumors found sensitive to CPA, DCBN, and DMDB were those that synthesized B_{12}, and no harmful effects were detected in the treated mice. The authors cautioned that there was no direct proof of a relationship between the tumor regressions and the effects of these compounds on B_{12} synthesis.

In 1969 Blomquist et al. (0292) induced soft fibroblastic osteosarcomas in mice using Sr^{90} and found that the tumors took up more Co^{60}-B_{12} than did any normal tissues, label being localized to the most actively growing portions. The authors concluded that B_{12} was required for rapid cell multiplication, and that labeled B_{12} might prove useful for clinical diagnosis of cancers.

In 1970 Price et al. (2196) studied the need for B_{12} for proliferation of neoplastic mouse cells C3H, strain NCTC 3681, in culture.

1. Given folate and B_{12} in a protein-free medium, no addition of purines, pyrimidines, or their nucleosides was needed.

2. If folate alone was reduced by 90%, thymidine or deoxycytidine had to be added.

3. If then B_{12} was also removed, one of adenine, deoxyadenosine, or deoxyguanosine had to be added.

4. If B_{12} alone was removed, thymidine and deoxyadenosine were needed but thymidine could be replaced by cytidine, uridine, or their deoxyderivatives, or alternatively, deoxyadenosine could be replaced by adenosine, adenine or guanine, and if cytidine or uridine were present, the deoxyadenosine could be replaced by adenine.

In 1970 Rotherham et al. (2349) reported that in strain NCTC 5905 of C3H neoplastic mouse cells the incorporation of C^{14}-nucleosides into DNA-thymidine was halved in the absence of B_{12} and was almost halted when the culture was given B_{12} but was deprived of folate. The authors concluded that the stimulating effect of B_{12} on DNA synthesis could be attributed partly to enhanced conversion of deoxycytidine and deoxyuridine to DNA-thymidine procursors.

In 1971 Rotherham et al. (2350) reported that strain NCTC 5905 of C3H neoplastic mouse cells in culture synthesized little DNA in the absence of B_{12} but was increased if thymidine were substituted for deoxyuridine. When adenine was omitted instead of B_{12}, or when folate was reduced, the same applied. Absence of B_{12} also lowered transfer of label to thymidine from C^{14}-formate and deoxyuridine-2-C^{14}. Continuous cell replication was insured by B_{12}, or hydroxocobalamin, or methylcobalamin, but the last did not contribute methyl groups for DNA-purine or -thymidine synthesis. The authors surmised that the root function of B_{12} was to raise the limiting levels of folate coenzymes required for metabolism of 1-carbon fragments.

2. Rats

In 1950 Day et al. (0635) found that B_{12} "markedly" enhanced hepatoma formation in rats fed a methionine-deficient diet plus p-dimethylaminoazobenzene (Table 36). However, when the carcinogen was omitted (control group) no tumors were formed.

Table 36. Influence of Vitamin B_{12} and Methionine on Incidence of Hepatomas in p-Dimethylaminoazobenzine-Fed Rats (0635)

Supplement to diet	Avg daily food intake, g	Avg daily wt gain, g	Incidence of hepatomas, %	Liver wt*— % of body wt
None	6.4	0.1	17	9.3
Vitamin B_{12}	7.0	0.2	78	15.7
Methionine	8.1	1.2	11	7.0
Methionine + vit. B_{12}	10.5	1.2	33	11.0

* Liver weights include tumors, where present.

In 1958 Stein et al. (2631) studied the uptake of pharmacological doses of labeled B_{12} by rats with experimental hepatomas. They concluded that this did not reflect uptake of normal serum B_{12} by these tissues. They suggested that the tumors would take up very little B_{12} from serum carrying normal amounts of it.

In 1963 Rigby and Bodian (2293) studied the effects of massive injections of B_{12} on serially transplanted tumors in August rats and CAF1/JAX mice. In rats 15 series of PWA2 fibrosarcoma were completed in 2 years; in mice 100 series of C1300 neuroblastoma were completed in 3 years, 32 series in 1 year. Rats received 30 μg B_{12}/day for 5-7 weeks; mice received 40 μg each in 8 daily doses.

In the rats B_{12} increased tumor growth 200% over controls and tumor B_{12} content 55%. In mice B_{12} decreased tumor growth 23% but increased tumor B_{12} content 90%. Affinity for B_{12} in mouse tumors was 17.6-fold that in rat tumors.

These differences, according to the authors, reflected different actions of B_{12} on the two tumor types, the inhibitory action being contrary to most published reports.

In 1965 Buinauskas et al. (0383) studied the "take level" of Walker 256 tumor cells in rats. In their system they concluded that B_{12} had a role in the enhancement of takes; antihistamines markedly enhanced takes, and reserpine decreased takes. The "slight" enhancement by B_{12} was unexplained.

3. Chicks

In 1949 Oleson and Little (2067) reported that Rous sarcomata implanted in young chicks depended for growth on B_{12}, comparably but separately from similar dependence on folic acid. (The authors did not claim that this effect was specifically oncogenic).

4. Humans

In 1962 Nelson and Doctor (1969) determined B_{12} levels in liver biopsies and sera from 62 cancer patients with liver involvement, 49 cancer patients without liver involvement, six leukemics, 21 with lymphoma, and 38 controls. Liver tissue B_{12} was depressed in association with tumors particularly in liver, and serum values did not correlate with liver values, which were elevated in all cancer patients regardless of liver involvement. The authors commented that the mechanisms behind these findings were unknown.

In 1965 Sawitsky and Desposito (2410) questioned 20 investigators who had used B_{12} alone or with other chemotherapy or X-ray in treating neuroblastoma in children. They concluded that B_{12} had no effect.

In 1967 Finkler and Hall (0836) found that B_{12} uptake by normal and malignant human cells was promoted in vitro by transcobalamin II but not by transcobalamin I. However, after uptake, a B_{12}-transcobalamin II complex was altered by tumor cells to a macromolecule that behaved chromatographically like transcobalamin I.

In 1970 Langman (1571) reported a retrospective survey of 108 children with neuroblastoma, of whom 61 received B_{12} as part of their treatments and 47 did not. They could find no significant difference of survival rates, and in discussion ruled out inadequate dosage as a likely factor.

In 1971 Kerwar et al. (1429) studied the metabolism of B_{12} in HeLa cells. They showed that hydroxy-B_{12} was readily converted to coenzyme B_{12} in the presence of ATP and a reducing system. When the medium contained enough B_{12}, oxidation of propionate to CO_2 was uninfluenced by additions of B_{12}, suggesting that its conversion to the coenzyme was rapid enough so that the methylmalonyl-CoA isomerase reaction was not rate-limiting. The HeLa cells were found to depend on exogenous B_{12} for optimal levels of N-methyltetrahydrofolate-homocysteine transmethylase, but not for a sufficiency of 5'-deoxyadenosylcobamide for oxidation of propionate.

In 1971 Herbert (1206) reviewed the techniques of short-term in vitro tissue cultures of marrow and tumors, developed mainly in his laboratory, for diagnosis of conditions involving DNA synthesis and B_{12} and/or folate metabolism.

1. Synthesis of DNA from uridine required the presence of 5,10-methylenetetrahydrofolic acid, derived from folate by reactions involving B_{12}. This was described as de novo DNA synthesis, contrasted with salvage of thymidine from destroyed DNA.

2. Different tumors utilized these two pathways in different proportions which could be determined by use of H^3-thymidine on biopsy samples in vitro. Thus, for example, the de novo pathway predominated in adenocarcinoma of the lung, and methotrexate was indicated as therapy, while in squamous carcinoma of the lung the salvage pathway predominated and methotrexate would not be indicated.

3. A B_{12}-deficient person would be functionally deficient of folate even if he were consuming and absorbing enough of it.

In 1972 Cooperman (0561) gave an 8-month, 16.5 lbs, male human infant with disseminated neuroblastoma three doses of labeled B_{12} at intervals, and the infant died 9 days after the last dose. Organs obtainable at autopsy were analyzed for label and for B_{12} content (LLD bioassay), as in Tables 37 and 38. The authors commented that tumor tissue had a far lower content of label and of B_{12} than normal tissues, that the label was an adequate indicator of distribution, and that the organ distribution in this infant was similar to that found in guinea pigs but dissimilar to that found in some other species. The authors found that this case did not support animal data in which tumors had been inhibited by B_{12}, nor did it shed light on the role of B_{12} in cell division in tumors compared with normal tissues.

H. Leukemias

1. Rats

In 1967 Bonelli and Rinaldini (0315) bioassayed the B_{12} levels of whole blood, rbc, plasma, and leucocytes of normal and leukemic A x C inbred rats, using the E. gracilis method. They found no marked differences in fractional concentrations of B_{12}, but leukemic whole blood contained more B_{12} in approximate proportion to the greater leucocyte population. The authors concluded that in discussion that the leucocyte population differences were "more than sufficient" to account for the B_{12} differences in whole blood, and that there was no need to invoke metabolic explanations.

In 1970 Rao and Bose (2241) reported that B_{12} deficiency decreased and altered the process of collagen synthesis in weanling rats, both in the skin and in granulomata induced by cotton implants. They compared this with the effect of C deficiency.

2. Humans

In 1957 Rachmilewitz et al. (2225) found high serum B_{12} in chronic myeloid leukemia and in acute leukemia with myeloid differentiation; the B_{12} diminished after X-rays and repeated transfusions. The B_{12} was in bound form, and binding capacity was high. Serum B_{12} was normal in other leukemias studied, multiple myeloma, and polycythemia.

Table 37. Percentage of the Total Radioactivity and the Total Vitamin B_{12} Recovered in Each of 8 Visceral Organs of an Infant with Neuroblastoma (0561)

Organ	% Total radioactivity	% Total vitamin B_{12}
[illegible]	80.8	82.6
[illegible]	6.0	5.7
[illegible]	4.8	2.6
[illegible] gastrointestinal tract	3.4	3.2
[illegible]	2.4	2.2
[illegible]	1.2	0.83
[illegible]	0.75	0.94
[illegible]	0.54	0.72
[illegible]	98.8	98.8

Table 38. Concentration of Vitamin B_{12} and Radioactivity in Normal and Malignant Tissues of an Infant with Neuroblastoma (0561)

Tissues	Concentration (μg/g, wet weight)	Radioactivity (μCi/g, wet weight)
Normal tissues		
Liver	0.162	332
Adrenals	0.081	182
Pancreas	0.055	90.7
Kidneys	0.048	99.9
Heart	0.030	64.7
Peripheral nerve	0.024	31.4
Spleen	0.017	47.3
Stomach	0.015	28.9
Colon	0.012	33.1
Testes	0.012	23.8
Duodenum	0.011	[illegible]
Diaphragm	0.010	12.1
Bladder	0.009	19.8
Jejunum and upper ileum	0.009	23.5
Lung	0.008	27.8
Bile	0.005	10.4
Malignant tissues		
Liver tumor	0.031	53.3
Paravertebral tumor	0.012	22.7
Adrenal tumor	0.010	22.3
Superior mediastinal tumor	0.006	11.7
Inferior mediastinal tumor	0.006	11.4

In 1958 Mendelsohn and Watkin (1812) demonstrated a procedure for the L. leichmannii bioassay of serum from normal subjects and from cancer and other patients. High serum B_{12} was found in most with chronic myelocytic leukemia, and in one of three with lymphocytic leukemia, but normal serum B_{12} was found in most with nonleukemic cancers; high B_{12} was associated with liver metastases and abnormal liver function data.

In 1958 Miller and Sullivan (1858) determined the serum B_{12}, the unsaturated B_{12} binding capacity (UBBC), and by addition of these two, the total B_{12} binding capacity (TBBC), in normal subjects and patients with chronic myelogenous leukemia:

	Serum B_{12}	Averages UBBC	TBBC
Normals	0.64 ng/ml	1.51 ng/ml	2.23 ng/ml
Chronic myelogenous leukemia	8.09	8.87	16.86

Two patients with chronic monocytic leukemia and one with leukocytosis had increases in serum B_{12} and UBBC. Six of eight with leukocytosis and one of three with acute leukemia had normal serum B_{12} but increased UBBC. Others with chronic lymphocytic leukemia had normal values. The patients with chronic myelogenous leukemia who were given extra B_{12}, distributed it abnormally between the various serum protein fractions (for details see original paper).

In 1959 Beard (0201) reported a several-fold elevation in B_{12}-binding capacity in human non-lymphatic leukemias compared with normal subjects (and patients with lymphatic leukemia). He also reported a qualitatively abnormal α-globulin generated by the liver and associated with these elevations. On the basis that bound B_{12} was the biologically active form of B_{12}, and that B_{12} was essential for replication of the cell nucleus the author proposed an hypothesis that B_{12} had a role in the non-lymphatic leukemogenic process.

In 1960 Ritz and Meyer (2297) found that Co^{58}-B_{12} i.v. was cleared more slowly from the plasma of 8 myeloid leukemics than from normal subjects, but was normal if an unlabeled loading dose were also given. Increased excretion was eliminated as a possible cause.

In 1961 Meyer et al. (1844) found similar increases in chronic myelocytic leukemia, in 50% of patients with polycythemia vera, in those with myeloid metaplasia, and in some with acute myeloblastic or lymphoblastic leukemia. TBBC was correlated in most cases with number of circulating myelocytes; the increase in chronic myelocytic leukemia suggested enhanced catabolism of myelocytes regardless of leucocytosis, and the data also suggested that the specific protein was derived from younger rather than mature leucocytes. In polycythemia normal TBBC was associated with reduced leucocytes (below $10,000/mm^3$), and in myeloid metaplasia high TBBC was associated with previous history of polycythemia or chronic myelocytic leukemia. TBBC was unrelated to rbc or platelet levels, but high values were seen in some cases of hepatitis.

In 1962 Kidd and Thomas (1449) used 34 leukemic patients and 8 controls to study B_{12} levels in peripheral leucocytes. Values were low in chronic granulocytic leukemia, normal in lymphatic leukemia, and high in acute leukemia and reticulum cell leukemia. High levels were associated with high proportions of blast cells in the cell populations. Free B_{12} was "usually less than" 10% of the total cell B_{12}, was elevated in chronic lymphocytic leukemia when the disease was "out of control," and was measurable in acute and reticulum cell leukemias and occasionally in chronic leukemias and controls. Cell B_{12} levels were unrelated to serum B_{12} levels and to peripheral leucocyte counts.

In 1965 Kidd (1439) assayed by E.gracilis 116 samples of leucocytes from 25 patients with acute leukemias. B_{12} in $pg/10^8$ cells: monocytic 200, lymphoblastic 464, myeloblastic 1058. Only in myeloblastic leukemia and reticulum cell leukemia was mean cell B_{12} high enough to be diagnostic, and the latter could be diagnosed morphologically. Blast cells contained more B_{12} than mature cells, and this was seen even in lymphoblastic leukemia, where the percentage of blast cells correlated statistically with the mean cell B_{12} level.

In 1966 Hall and Finkler (1112) found that the binding capacity of transcobalamin II was "very much diminished or absent" in patients with chronic myelogenous leukemia, and that of transcobalamin I was "very much increased." Both tendencies were smaller in acute myelogenous leukemia and during remissions of the chronic condition. In pernicious anemia B_{12} binding to transcobalamin II was diminished or absent, but to transcobalamin I was unaltered.

In 1966 Skaff et al. (2534) reported that in chronic myelogenous leukemia Co^{57}-B_{12} was cleared from plasma abnormally slowly (Table 39) and they suggested that the clearance test might be diagnostic for this form of leukemia.

In 1967 Mikkonen et al. (1850) reported that high ratios of Co^{57}-B_{12} were bound to transcobalamins I and II in chronic myelogenous leukemia, acute leukemia (some cases), and myeloid metaplasia, but not in lymphocytic leukemias, polycythemias, or malignant lymphoma.

In 1968 Stenman et al. (2635) studied B_{12} binders in normal and leukemic human leucocytes. Leucocyte B_{12} binder and transcobalamin I appeared identical by chromatography and by immunodiffusion, and it was produced by leucocytes in vitro. The authors suggested that in chronic myelogenous leukemia, transcobalamin I was largely derived from leucocytes.

In 1971 Corcino et al. (0564) reported an eight-year period of observation on a rare case of coexisting chronic myeloid leukemia and pernicious anemia. The B_{12} deficiency coexisted with high or normal serum B_{12} and with serum γ-binder that the authors considered to have defective delivery capability to the tissues. Thus the patient's leucocytosis was not stimulated until he was given B_{12} i.v. Then the leucocyte count rose spectacularly by carefully witholding B_{12} and watching for neuropathy the peripheral leucocyte count was maintained at ca. 50,000/ μl. The authors commented on the association of available B_{12} and leucocytosis, in this case also associated with elevation of unsaturated B_{12} binding capacity. However, they did not comment on the process of leukemogenesis.

In 1971 Carmel and Coltman (0451) studied five patients with non-leukemic leucocytosis. They found a constant, direct, and time-dependent relationship between the degree of leucocytosis and the serum B_{12} level,

Table 39. (2534)

No	Patient	Diagnosis	Total B_{12} level (μμg/ml) (Normal 350–600 μμg/ml)	B_{12} clearance
		Myelogenous leukemia		
1	M. J.	CML	1005	-
2	D. E.	CML	2380	-
3	D. S.	CML	4000	-
4	S. M.	CML	6120	-
5	K. B.	CML	524	-
6	A. S.	CML	3000	Prolonged
7	W. B.	CML	189	Prolonged
8	K. H.	CML	131	Prolonged
9	R. S.	AML	-	Prolonged
10	G. G.	AML	1155	Prolonged
11	D. B.	AML		Prolonged
12	A. P.	AML	320	-
13	M. W.	AML	630	-
14	R. L.	AML	280	-
		Other leukemias		
15	M. K.	ALL	-	Normal
16	M. H.	ALL	-	Normal
17	L. L.	ALL	-	Normal
18	L. R.	ALL	125	Normal
19	J. L. N.	ALL	-	Normal
20	M. L.	ALL	-	Normal
21	M. M.	Lymphosarcoma with leukemic transf.	240	Normal
22	C. P.	Erythroleukemia	600	Normal
23	S. B.	Myelomonocytic leukemia	950	Normal
24	M. W.	Leukemic reticuloendotheliosis	-	Normal
		Other diagnoses		
25	L. J.	Chediak-Higashi with lymphosarcoma	-	Normal
26	K. B.	Post-rubella syndrome	250	Normal
27	E. B.	Wiskott-Aldrich syndrome	755	Normal
28	M. B.	Hemolytic anemia	>2000	Normal
29	W. V.	Neuroblastoma	-	Normal
30	J. L.	Teratocarcinoma	-	Normal
31	W. H.	Regional enteritis	-	Normal
32	B. S.	Pancreatic insufficiency	-	Normal
[illegible]	W. N.	Agranulocytosis, fever, hepatomegaly	-	Normal
34	T. B.	Febrile disease	-	Normal
35	S. K.	Bronchiectasis and hepatosplenomegaly	-	Normal
36	T. S.	Spinocerebellar atrophy	-	Normal
37	D. O.	Progressive neurologic deterioration	-	Normal
38	D. G.	Extrahepatic biliary atresia with cirrhosis	-	Normal
39	K. B.	Normal	259	Normal

similar to relationships reported by others (cited) in chronic myelogenous leukemia. B_{12} electrophoretic and reticulocyte uptake data also paralleled those reported in leukemia. However, these patients did not have leukemia; for example, one patient was recovering from iatrogenic agranulocytosis.

The authors commented that the reasons for their findings were unknown. They concluded that relationships between leucocyte count and serum B_{12} level did not reflect a leukemic process and were not diagnostic for leukemia.

In 1972 Fischer (0838) found serum B_{12} levels to be above 2000 pg/ml in 91% of 47 patients with chronic myeloid leukemia. Only one binder with α-globulin-like electrophoretic mobility was detected. The author inferred that increases of leukemic leucocytes would liberate increased amounts of binder into the serum, rather than liberating an abnormal binder with high B_{12} affinity. He found no correlation between leucocyte population and serum B_{12} level.

BIOCHEMICAL ASPECTS

I. Breakdown

In 1973 Herbert (1015) stated that B_{12} was almost indestructible unless heated in alkali at over 100°C; "the molecule splits at 250°C." Thus, he stated that hamburgers lose B_{12} only from their surface while being cooked, not from the interior. This B_{12} would be present not as cyanocobalamin but probably as natural B_{12} coenzymes.

Liver is said to lose 8% by boiling at 100°C for 5 minutes; muscle to lose 30% by boiling at 170°C for 45 minutes. Pasteurization for 2-3 seconds destroys 7% of the B_{12} in liquid milk, 30% when boiled for 2-5 minutes, 77% when sterilized in bottle at 119°C for 13 minutes, but only 10% when steam-sterilized at 143°C for 3-4 minutes (1015).

In 1957 Chapman et al. (0486) treated one batch of raw whole milk by pasteurizing, sterilizing, UHT-treatment, UHT-treatment plus sterilizing, evaporation, sweetened-condensation, roller-drying, or spray-drying. Under conditions in which little or no loss (from any of the above) occurred of riboflavin, pantothenate, nicotinic acid, B_6, or biotin, and 10-50% loss of thiamine, sterilization caused nearly complete loss of B_{12}.

In 1962 Grasbeck et al. (1033) surveyed 1,345 subjects in a "tapeworm district" of east Finland. Confirmed carriers amounted to 27.5%, and their mean serum B_{12} was significantly lower than noncarriers. In carriers the threshold for hemopoietic deficiency was 60-90 pg/ml B_{12}, but deficiency was seen only in mean corpuscular volume and hemoglobin, not in hemoglobin concentration nor packed rbc volume. The main conclusion was that in Finland, Diphyllobothrium latum deprived its host of B_{12}.

In 1964 Burgus et al. (0396) incubated Pseudomonas rubescens in broth containing Co^{57}- or P^{32}-B_{12} and, on extraction and electrophoresis of the corrinoids, found two major, yellow, radioactive fractions, both of which yielded four fractions on chromatography. Each of these peaked as if characteristic of 5,6-dimethylbenzimidazole, and lacked a peak typical of B_{12} and its analogs. The pigments were stable to cyanide, and were photolysed more slowly than B_{12} coenzymes and analogs. The authors inferred that the bacteria had altered the corrin nucleus of the B_{12}.

97

In 1964 Scott et al. (2458) examined more than 200 isolates from micro-organisms that attacked B_{12}; all produced reversible fading of the red color of pure B_{12}, restored by aeration. Many partially degraded B_{12} to new pigments, a very few to permanently colorless products; radiotracers and electrophoresis showed these to be metabolites. All of the degradative micro-organisms were bacteria and the most active was found to be Pseudomonas rubescens.

In 1965 Bonnet et al. (0316) investigated the conditions for hydrolysis of the amides in, or related to, B_{12}. He synthesized, and caused hydrolysis of, a number of compounds including:

(1-methylcyclopentyl) acetamide

β-(1-methylcyclopentyl) propionamide

β-(trans-2,2,3-trimethylcyclopentyl) propionamide

Rates of hydrolysis were recorded in aqueous HCl-dioxane at 50°C. When aquocobalamin was hydrolyzed under the same conditions, the kinetics indicated that the hydrolysis of the vitamins B_{12} was largely influenced by steric factors. For example, all the simple amides gave straight-line plots for t against log $\frac{a}{(a-x)}$, showing that hydrolyses were first-order with regard to the amide, and worst-plot deviations were no greater than 4%. Values for a group of amides described in the original paper are shown in Table 40.

Table 40. Rates of Acid Hydrolysis of Amides in Aqueous Dioxane at 50° (1.5 N HCl) (0316)

Amide	First-order rate constant $k \times 10^4$ min.$^{-1}$ First series	Second series	Average
II	13.4	13.3	13.3
IV	36.5	37.4	37.0
III	1.22	1.19	1.2
V	36.5	34.9	35.7
XIII	11.2	11.2	11.2
XVI	30.7	29.9	30.3
XVII[a]	6.65	6.77	6.7
XVIII[b]	0.94	0.96	0.95

[a] $(CH_3)_2CHCH_2CONH_2$. [b] $(CH_3)_3CCH_2CONH_2$.

In 1971 Agnes et al. (0030) reported that transfer of the methyl from methyl-B_{12} to thiolates and other anions in a purified system was oxygen-dependent. The authors argued that the transfer mechanism could, given certain conditions, be relevant to the glycol rearrangement catalyzed by B_{12} enzymes.

In 1972 Sasaki (2394) studied the B_{12}-binding property of Lactobacillus leichmannii ATCC 7830, finding it could bind 0.52 μg/mg of cells. Of this, 75% was bound to the cell wall, 25% to ribosomes. Of B_{12} bound to the cell wall, 60% was impervious to ribonuclease, lipase, and trypsin treatments, but the binding capacity of the wall was destroyed by pretreatment with pepsin, trypsin, or "Pronase". The author concluded that B_{12} was bound to a polypeptide that was then protected against these enzymes. Such a polypeptide was isolated, purified, and its mw was estimated as 21,500.

In 1972 Kamikubo et al. (1388) found, spectrophotometrically and microbiologically, that in the presence of heat, KCN converted every B_{12} analog to cyanocobalamin, regardless of the sterilization conditions and identity of the test organism. They suggested that heat affected the upper ligands of the coenzyme-B_{12} forms, permitting them to pass through membranes more easily.

In 1972 Schjonsby (2429) concluded from rat experiments that bacteria took up B_{12} even in the small intestine, and could thus inhibit uptake of B_{12} by the animal.

II. Absorption and Distribution

With B_{12}, absorption and distribution are sharply distinct processes. The protein or proteins (not yet fully characterized) that bind B_{12} before it passes through the gut mucosa into the system are different from those to which B_{12} is attached on emergence from the mucosal cells. The former are called the "intrinsic factor" of Castle, and the latter are grouped under the name "transcobalamins". The intrinsic factor has the specific property of releasing its bound B_{12} to certain mucosal cells of the ileum; other proteins found in human and animal secretions which bind B_{12} but do not release it in that way are grouped as "non-intrinsic factors" or "R-binders". This section of the monograph will thus deal with three classes of proteins to which B_{12} is found attached -- intrinsic factor, R-binders, and transcobalamins. Absorption and distribution will be considered in separate subsections.

A comparison is added to help readers who are familiar with mechanisms of intestinal absorption but not with B_{12}. There are parallels between cobalt and iron; although heme is made by plants and animals as well as by micro-organisms, its structure is like that of the B_{12} corrin (page). Iron is ingested bound to various proteins (globins and enzymes), and emerges from the mucosa bound to

different proteins (mainly transferrins). It is taken up by tissues that make heme, or by storage proteins (ferritins). Both iron and cobalt are active in hemopoiesis, are retained and recycled somewhat similarly by the body, and heme anomalies and B_{12} deficiency can both be neurotoxic. There are also many differences, but these parallels may help the new reader to understand the absorption and disposal of B_{12}.

A. Absorption

In a recent review (1973) Herbert (1015) categorized the two mechanisms of B_{12} absorption by man as:

1. Physiologic - being intrinsic factor-dependent, restricted to the ileum, and having capacity for no more than 1-1.5 μg of B_{12} at any one time; and
2. Pharmacologic - being dose-dependent, not restricted to the ileum, acting by diffusion, and with capacity limited only by the size of the dose.

Under deficiency conditions the author commented that massive-dose oral therapy, relying on pharmacologic absorption, tended to be relatively unreliable.

Intestinal B_{12} Binders

In 1956 Bauriedel *et al*. (0192) used short-term dialyses to study binding of cobalamin to various protein fractions. They found that aquocobalamin (B_{12b}) was bound more readily than cyanocobalamin, and that binding could be increased by denaturation and inhibited by acid pH. A gastric mucosal extract bound both cobalamins equally, apparently at the same sites, and cyanide inhibited this at high but not at neutral pH. The cyano group of cyanocobalamin remained bound and photolabile.

In 1964 Hoedemaeker *et al*. (1243) studied the elaboration of Castle's intrinsic factor by human stomach specimens *in vitro*, using a combination of autoradiographic and immunologic methods developed in previous studies on rats. They found parietal-cell affinity for B_{12}, and uptake of B_{12} was inhibited by exposure to anti-intrinsic factor γ-globulin.

The authors interpreted this to mean that in man intrinsic factor was elaborated by the HCl-producing parietal cells. They commented that in rats the factor was elaborated by pepsinogen-producing cells.

In 1967 McColl et al. (1788) instilled hog intrinsic factor and labeled B_{12} into isolated loops of proximal jejunum and distal ileum of fourteen patients at laparotomy. They found no evidence that intrinsic factor influenced uptake of B_{12}, and concluded that it might play no part in absorption of normal amounts in normal man. However, they admitted there might be flaws in their experiment. Nevertheless, they did not comment on the fact (stated under Methods) that 15 minutes or less were allowed for absorption -- a constraint imposed by the consent form that the patients signed.

In 1968 Berlin et al. (0244) confirmed, in 64 patients, that there was a mechanism for absorption of B_{12} independent of intrinsic factor, and that about 1.2% of a "very wide" range of doses was thereby absorbed in man, regardless of pernicious anemia, normality of absorption, or resistance to the intrinsic factor. In addition, the authors stated that clinical experience in Sweden had shown that daily oral doses of 0.5-1.0 mg B_{12} were effective to normalize and maintain body B_{12} stores except in some particular disease conditions, such as iron deficiency, malignancy, and certain chronic infections.

In 1969 Mackenzie and Donaldson (1706) reviewed knowledge of B_{12} uptake by intestinal cell surfaces during absorption. A very small proportion of B_{12} present at any mucous surface was absorbed by diffusion, an inefficient process that could be seen only after high doses of B_{12}. Physiologic intakes, not over 2 μg, were absorbed by an efficient process restricted to the ileal mucosa, and requiring intrinsic factor, which inhibited this process in the proximal small intestine.

Intrinsic factor, secreted in man by the gastric parietal cells, was a glycoprotein of about 50,000 mw, that bound B_{12} tightly. The complex was absorbed preferentially over free B_{12} by the specific process. B_{12} was liberated by cooking or, in the stomach, by pepsin, and the complex resisted digestion and arrived in the ileum by peristalsis.

Receptor cells of the ileal mucosa possessed sites specific to both parts of the complex. Complexes of B_{12} with other binders (from serum, saliva, tears, or colostrum) were not absorbed; B_{12} analogs complexed with intrinsic factor were, at best, absorbed poorly.

The receptor sites were on the brush-border membranes, probably involving the mucopolysaccarides, and, from affinity studies, were highly specific. From

preliminary data, they might be the same sites that attracted ferritin-conjugated antibodies. Both glycoproteins and mucopolysaccharides were strongly antigenic. However, the receptors had not yet been identified. The authors considered that attachment of the complex to a receptor did not require energy, but subsequent absorption did. They argued against pinocytosis as a mechanism of absorption in mammals, preferring a theory of carrier-mediation proposed by Grasbeck. Their reasons included the slow absorption of B_{12} (4-8 hours), the fact that B_{12} reappeared attached to other binders, and the lack of evidence for absorption of intrinsic factor.

In 1969 Carmel et al. (0452) found two sorts of B_{12} uptake by homogenates of human intestinal mucosa. One, uniform through jejunum and ileum, was unrelated to intrinsic factor, pH, or cations. The other was confined to the ileum, depended on intrinsic factor and Ca^{++} or Mg^{++}, and had a pH optimum of ≥ 6.6. Some but not all ileal homogenates from patients with regional ileitis took up little B_{12}.

In 1971 Shum et al. (2515) confirmed this pH optimum, adding that about 10% of B_{12}-binding was independent of intrinsic factor and pH, that the pH range for the dependent binder was 2-12.2, and that binding inhibited by adverse pH was restored by neutralization.

In 1971 Grasbeck et al. (1037) isolated human saliva B_{12} binder as a complex with B_{12}, and after various procedures concluded it was a glycoprotein that had progressively lost sialic acid during purification. Like other R-binders, the authors concluded it was heterogenous for isoelectric point.

In 1971 Grasbeck and Aro (1035) described the isolation of an R-type B_{12}-binding protein from hog intrinsic factor, using antiserum from rabbits immunized with a hog leucocyte fraction. R-type binder is defined as one that lacks intrinsic factor activity, and the material from which it was separated was shown to contain the activity, by administration to a patient with pernicious anemia.

In 1972 Rothenberg et al. (2348) exposed guinea-pig ileal loops to Co^{57}-B_{12} bound to human intrinsic factor, and for two hours studied mucosal subcellular distribution of the label. Most label appeared in cell debris and mitochondria, least in microsomes and cytosol. Most of the former remained bound to intrinsic factor (by immuno-precipitation), but a small fraction was altered so as to suggest either migration of label to a different protein or alteration of the intrinsic factor binder.

In 1973 Allen and Mehlman (0055) separated hog intrinsic factor from hog nonintrinsic factor by column chromatography (confirmed by bioassay in a pernicious anemia patient) and found that the intrinsic factor bound B_{12} 30.3 μg/mg of protein; its mw was 52,300-58,600 after removal of 17.5% carbohydrate, and in the presence of B_{12} it aggregated into dimers and higher oligomers. By contrast, the nonintrinsic factor bound 25.1 μg B_{12}/mg of protein; its mw was 61,000-66,000 after removal of 35.5% of carbohydrate, and it remained a monomer in the presence of B_{12}. The authors concluded that intrinsic and nonintrinsic factors were different proteins, not states or variants of one protein.

Sites of Absorption

(a) Small Bowel

In 1959 Booth and Mollin (0319) reported three studies on 16 patients using Co^{56} or Co^{58} to estimate B_{12} absorption.

1. Four surgical patients received labeled B_{12} orally, three hours before laparotomy (considered the lag time for absorption in man). The small bowel was scanned at available positions from the duodenal flexure to the cecum. Feces were counted, and plasma was counted at intervals for 24 hours.

From the plasma and feces, gastric operations did not interfere with B_{12} absorption. The small bowel scan showed that all label reached the distal half before any appeared in the plasma, whether or not intrinsic factor had been given.

2. Twelve patients with previously resected or short-circuited small bowels received oral B_{12} 1 μg. Their feces showed subnormal B_{12} absorption in some cases. If this was not improved by addition of intrinsic factor to a second dose of B_{12}, chlortetracycline 250 mg was given 6-hourly for four days to sterilize the bowel for a third test.

In those who had lost six feet or more of active ileum, absorption did not improve at the third test. In those who had lost no more than one foot of ileum, absorption was or became normal.

3. Eleven patients with losses of distal small bowel had clinical B_{12} deficiency. Four responded to B_{12} 200 μg/month by injection, two others to this plus oral folic acid 10 mg b.d.

The authors concluded that man absorbed B_{12} only from the ileum, but would not speculate as to how or why.

In 1965 Rønnov-Jessen and Hansen (2315) fed Co^{58}-B_{12} with polyethylene-glycol marker to ten normal subjects, and collected small intestine contents by tube from each third of the small intestine. Between the upper and middle third about 6% of the B_{12} disappeared; between the middle and lower third about 25% disappeared. In certain cases (3 of 9 experiments) absorption was considered to have begun "far up in the jejunum", contrary to the generally accepted view, and without explanation (2315).

In 1967 Gazet and McColl (0932) studied the absorption of B_{12} by isolated loops of proximal jejunum and distal ileum in 9 cats, 36 dogs, 10 monkeys, and 20 human patients undergoing laparotomy. The experiments were designed to rule out bowel anomalies, bowel contents, transit time, and intrinsic factor. According to the authors the results (Tables 41-46) did not support the contention that B_{12} was absorbed by an exclusive mechanism limited to the ileum, and they drew attention to the constancy of absorption in the absence of intrinsic factor.

Table 41. Absorption of Vitamin B_{12} in Man (0932)

Patient No.	Per Cent Absorption		Vitamin B_{12} Injected into Each Segment		Serum Vitamin B_{12}
	Jejunum	Ileum	Volume (ml.)	Concentration (μg. per ml.)	(μg. per ml.)
1	20.0	16.6	50	0.0002	[illegible]
2	16.7	11.2	50	0.0002	[illegible]
3	12.6	8.4	25	0.0002	[illegible]
4	28.0	11.1	25	0.0002	[illegible]
5	20.2	7.2	25	0.0002	[illegible]
6	16.0	13.0	25	0.001	[illegible]
7	19.6	7.3	25	0.001	[illegible]
8	17.8	16.7	25	0.001	[illegible]
9	8.6	9.4	50	0.001	[illegible]
10	13.5	16.5	50	0.001	[illegible]
11	17.1	6.6	50	0.001	[illegible]
12	15.0	25.0	50	0.001	[illegible]
13	11.7	2.9	50	0.002	[illegible]
14	33.3	28.8	50	0.002	[illegible]
15	31.8	14.1	50	[illegible]	[illegible]
16	20.7	18.1	50	[illegible]	[illegible]
17	13.5	6.4	50	[illegible]	—
18	26.8	9.4	50	[illegible]	[illegible]
19	30.5	32.9	25	[illegible]	—
20	25.9	17.4	25	0.004	[illegible]

In 1967 Donaldson et al. (0711) found in vitro that Co^{57}-B_{12} was taken up by brush-borders and their membranes from distal but not proximal hamster intestine. Uptake was enhanced by intrinsic factor preparations from hamster, rat, or rabbit but not from man, dog, or hog. Uptake was reduced in the absence of divalent cations, but unaffected by temperature changes (37-7°C), or absence of

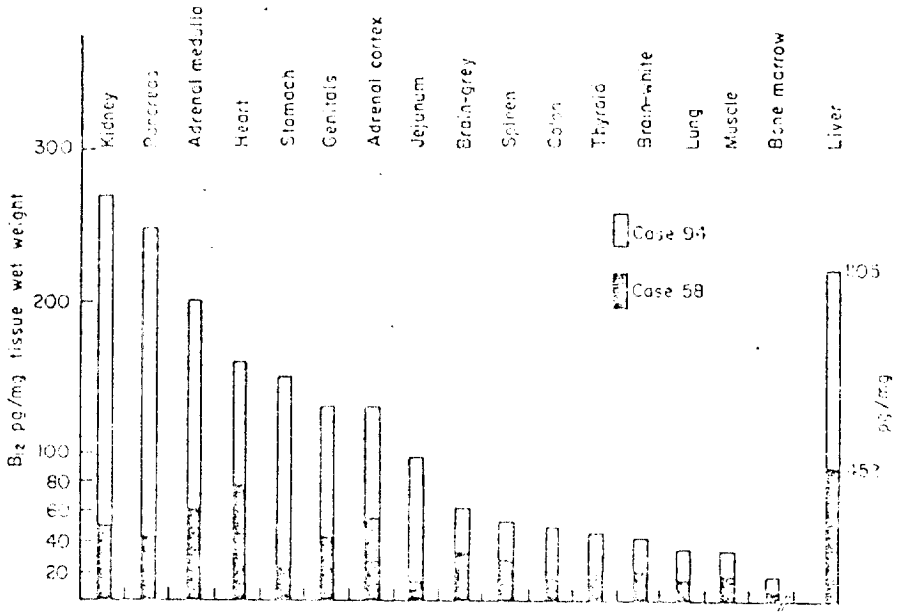


Figure 28. Comparison of Median Values for All Tissues Assayed from Two Individuals (2246)

In 1972 Rappazzo and Hall (2245) studied the distribution of B_{12} by transcobalamin II (other factors not entirely excluded) in isolated perfused dog liver and kidney, and observed:

1. Good uptake of the complex by both liver and kidney.
2. In liver, the complex was taken up better than was free B_{12}.
3. In kidney, free B_{12} was taken up better than was the complex; apparently, uptake was complete.
4. Even so, more complex/g of tissue was taken up by kidney than by liver.
5. Kidney released or produced transcobalamin II; liver released or produced a larger-molecule binder, and some transcobalamin II.
6. Passing free B_{12} through kidney enhanced its uptake by liver; passing free B_{12} through liver depressed its uptake by kidney.

The authors concluded that the distribution of B_{12} could be modified by tissue responses to its presence, including synthesis of transcobalamin II.

Table 42. Absorption of Vitamin B_{12} in Monkeys (0932)

Animal No.	Per Cent Absorption		Serum Vitamin B_{12} (μg. per ml.)
	Jejunum	Ileum	
1	24 (27)	33 (25)	0.001200
2	19 (18)	19 (26)	0.000580
3	14 (38)	18 (21)	—
4	25 (18)	13 (20)	0.001[illegible]0
5	39	31	0.000320
6	12	11	0.001000
7	14	55	—
8	14	2	—
9	35	39	—
10	14	17	0.001350

Each value is the mean of the percentage absorption of three segments. The figures in brackets are the values obtained when the tests were repeated in the same animals 3 months later. The concentration of vitamin B_{12} injected into the segments was 0.011 μg. per ml. There was no significant difference (0.4 < P < 0.5) between the absorption in the jejunum ($\bar{x}$ = 20.1, S.E. = 3.2) and the ileum ($\bar{x}$ = 23.8, S.E. = 4.9).

Table 43. Absorption of Vitamin B_{12} in Dogs (0932)

Animal No.	Per Cent Absorption		Serum Vitamin B_{12} (μg. per ml.)
	Jejunum	Ileum	
1	19	14	0.0[illegible]050
2	23	50	0.0[illegible]580
3	5	15	0.000130
4	12	14	0.000130
5	13	9	0.000[illegible]80
6	12	6	0.000200
7	7	9	0.000320
8	19	24	0.0[illegible]18
9	8	13	0.000010
10	10	15	0.000[illegible]25
11	33	13	0.0[illegible]
12	9	14	0.0[illegible]
13	11	4	0.000340
14	14	7	0.[illegible]
15	21	5	0.000120
16	11	15	0.000400
17	18	4	—
18	12	23	0.000200
19	12	6	0.000[illegible]5
20	2	6	0.000350
21	4	20	0.000130
22	25	25	—
23	7	11	—
24	7	19	—
25	8	12	—
26	3	6	—
27	8	13	—
28	19	24	—

Each of the values in the first 7 dogs is the mean of the percentage absorption of three segments. The concentration of vitamin B_{12} injected into the segments was 0.011 μg. per ml. There was no significant difference (0.4 < P < 0.5) between the absorption in the jejunum ($\bar{x}$ = 11.6, S.E. = 1.5) and the ileum ($\bar{x}$ = 14.1, S.E. = 1.8).

Table 44. Absorption of Differing Concentrations of Vitamin B_{12} in 8 Dogs (0932)

Concentration of Vitamin B_{12} injected into Each Segment (µg. per ml.)	Per Cent Absorption	
	Jejunum	Ileum
0.011000	6.8	12.7
0.005500	9.6	6.5
0.002800	8.1	4.2
0.001400	0.5	4.5
0.000700	7.5	9.2
0.000350	7.8	12.7
0.000180	7.9	14.2
0.000090	14.6	24.6

Each value is the mean of the percentage absorption of four segments.

Table 45. Absorption of Vitamin B_{12} in Cats (0932)

Animal No.	Per Cent Absorption		Serum Vitamin B_{12} (µg. per ml.)
	Jejunum	Ileum	
1	14	11	0.000390
2	15	11	0.000330
3	13	16	0.000300
4	13	14	0.000200
5	15	7	0.000500
6	7	13	0.000190
7	6	14	0.000180
8	13	13	0.000325
9	14	9	0.000040

Each value is the mean of the percentage absorption of three segments. The concentration of vitamin B_{12} injected into the segments was 0.011 µg. per ml. There was no significant difference ($0.8 < P < 0.9$) between the absorption in the jejunum ($\bar{x} = 12.2$, S.E. ± 3.5) and the ileum ($\bar{x} = 12.[illegible]$, S.E. ± 0.9).

Table 46. Liver Uptake of Vitamin B_{12} in Man (0932)

Patinet No.	Per Cent Uptake by Liver from Jejunum	Per Cent Absorption from Jejunum	Per Cent Uptake by Liver from Ileum	Per Cent Absorption from Ileum
1	2.0	20.0	1.26	16.6
2	1.4	16.7	0.5	11.2
12	2.4	15.0	1.6	25.0

106

glucose or O_2. Uptake was proportional, on further fractionation, to B_{12} binding capacity. Purification of intrinsic factor improved the data, appearing to remove a lytic factor for the membrane preparations.

In 1968 Cooper (0553) studied the association of B_{12} and intrinsic factor with extracts of normal ilea removed at surgery from two elderly women with cancer of the colon after test doses of Co^{57}-B_{12}. Labeled material recovered *in vitro* was found identical with a complex of human intrinsic factor and B_{12}, as to biological properties, but its immunological properties were thought to have been modified. The complex was considered to have been associated intimately with the ileal wall during absorption of B_{12}.

In 1970 Peters and Hoffbrand (2130) studying the transfer of B_{12} across the ileal mucosal cell during absorption by guinea pigs, concluded that B_{12} was separated from intrinsic factor at the brush border, that only B_{12} entered the cell, and that most such B_{12} was stored in the mitochondria. There, about 20% was converted to coenzyme B_{12}. During its delay in the cell labeled B_{12} was apparently bound to a relatively low-mw protein. The authors noted that such a binder had been demonstrated in human plasma, but cautioned that the mechanisms were still "complex and poorly understood."

In 1971 Miettinen reported in a total of 13 patients that terminal resection of the ileum decreased absorption of B_{12} and also diminished the reabsorption of cholesterol and other bile lipids and salts more than their increased production, which was also shown (1849).

In 1972 Gronqvist (1055) interchanged the proximal and distal small intestines of some rats. They subsequently showed no differences from controls in BW changes, hemoglobins, hematocrits, or B_{12} absorptions. The authors concluded that in the rat B_{12} absorption was governed by duration of contact with the mucosa rather than by specific ileal receptors.

(b) Colon

Henderickx *et al.* in 1964 (1191) cannulated the proximal colons of three Duroc barrows (17-26 lbs), and found that 42-58% of instilled Co^{60}-B_{12} was absorbed.

In 1968 Armstrong (0097), following a report that isolated, sterilized dog colon had absorbed B_{12}, gave three human subjects a nonresidue diet for 84 hours, plus oral kanamycin and other preparations, and then catheterized Co^{57}-

cyanocobalamin 0.8 μg/subject into the sigmoid colon. Hog intrinsic factor was added to two of the doses. Six hours later each subject received hydroxocobalamin (unlabeled) 1 mg i.m., and plasma, urine, and feces were studied, some plasma being drawn before the flushing dose. Under these conditions there was evidence that no B_{12} was absorbed from physiological amounts in the sigmoid colon, with or without intrinsic factor.

(c) Lungs

In 1953 Monto et al. (1902) treated three pernicious anemia patients with B_{12} inhalations, two with aerosols of B_{12} 15 μg/1 ml saline/day, and one with B_{12}-lactose dust, quantity/day not stated. The authors claimed excellent responses including evidence of urinary excretion, using dosages lower than then customary. However, further reports on this route of B_{12} therapy have not been found.

(d) Skin

In 1967 Howe et al. (1270) studied the percutaneous absorption of B_{12} by weanling rats and guinea-pigs.

1. Growth shortfall in B_{12}-deprived animals was restored by dorsal application of cyanocobalamin 5 μg; 0.1 μg was equally effective.
2. Application of Co^{57}-cyanocobalamin in ethanol was absorbed better than in water or dimethyl sulfoxide solution.
3. Percent absorption was constant over a wide range of dosages, and was similar in rats and in guinea-pigs.
4. The skin acted as a reservoir, releasing B_{12} slowly to other tissues

The authors suggested that B_{12} therapy might be more effective if applied to the skin than when injected.

Absorption in Particular Species

(a) Dogs

In 1968 Weisberg et al. (2950) studied the absorption of labeled B_{12} in the dog by light and electronmicroscopic autoradiography. For two hours after instillation into the distal ileum, label was seen in surface mucus and in mucus granules of goblet cells in both crypts and villi. At three hours the label was mostly in mucosal absorbing cells, in the microvilli, terminal web, rough endoplasmic reticulum, Golgi apparatus, lateral membranes and intercellular spaces, and lamina propria and its capillaries. The authors inferred that in the dog, B_{12} binders from goblet cells were involved in absorption, some probably being

synthesized on the endoplasmic reticulum and being complexed with B_{12} during its passage through the cell to the bloodstream.

In 1969 Yamaguchi et al. (3063) concluded, from double-label studies in guinea-pig and dog mucosal homogenates and in dog ileal sacs in vivo, that B_{12} absorption by dogs was not mediated by intrinsic factor. Their data failed to show the presence of an intrinsic factor mechanism but, according to the authors, did not unequivocally prove the absence of one.

(b) Sheep

In 1970 Smith and Marston (0575) fed sheep a Co-deficient diet with or without added Co (1 mg/day) and measured B_{12}-to-lignin ratios in the rumen as an index of B_{12} production by rumen bacteria. They found that labeled Co adhered to rumen particles and was mostly excreted in feces. Most rumen B_{12} was in bacteria and was released at pH 2; added B_{12} was partly degraded in the rumen. The B_{12}/lignin ratio declined from 1-3 days after withdrawing supplements. Without supplement the rumen produced 50-110 μg/day from Co, and with supplements 400-700 μg/day, in both cases limited by food intake. Efficiency of B_{12} production was estimated as 13% without supplemental Co, and as 3% with added Co. Only some 5% was absorbed, and the MDR was assessed as about 11 μg/day. 5'-Deoxyadenosylcobalamin was retained better than cyanocobalamin, and more of both appeared in feces than in urine. Retention was mainly by liver, kidneys, and gut walls; in liver mainly by mitochondria. B_{12} was secreted into the duodenum and reabsorbed in the ileum.

(c) Chimpanzee

In 1967 Frenz et al. (0883) compared B_{12}-binders of human gastric juice with those of chimpanzee stomach mucosa, using Sephadex G-100 column chromatography. Two binders from each were judged respectively to be identical, with mw about 50,000 and 90,000, and according to reactions with antibodies from pernicious anemia serum that neutralized human intrinsic factor.

Factors Reportedly Influencing Absorption

In 1958 Draper and Lowe (0725) reported that adult rats absorbed more B_{12} than immature or aged rats (see Figure 23), while digestibility of stock diet proteins remained approximately constant.

In 1965 Davis et al. (0623) reported the responses of 40 elderly subjects to oral B_{12} 20 μg/day for 12 weeks, as in Figure 24. They concluded that absorption was not diminished by age.

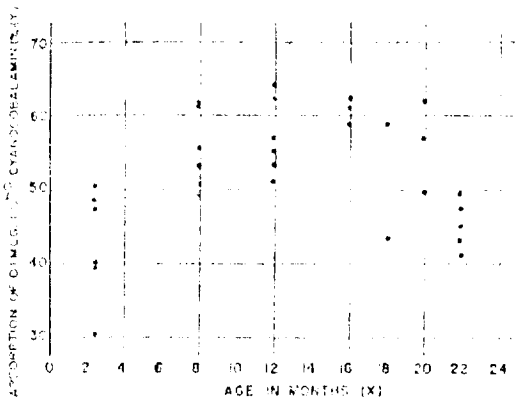


Figure 23. Intestinal Absorption of Co^{60}-cyanocobalamin by Rats of Various Ages (0725)

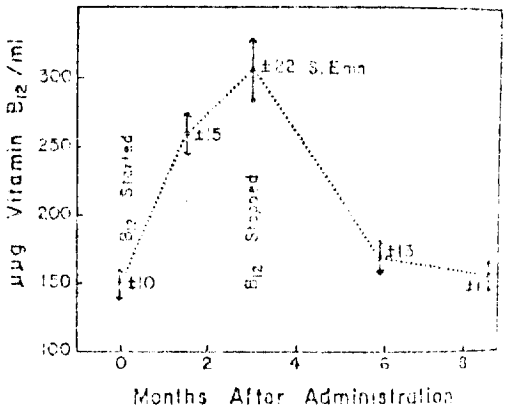


Figure 24. Mean serum Vitamin B_{12} levels of 40 Domicile members, average age 87, after oral administration of 20 µg Vitamin B_{12}. Vertical lines represent standard error for each mean value. Each point represents the average of microbiological assays of 40 serum Vitamin B_{12} determinations of Domicile members who received 20 µg of the four Vitamin B_{12} preparations described earlier, during 12-week test period (0623).

In 1967 Batata et al. (0189) surveyed 168 miscellaneous geriatric patients aged 60 to over 90. L.leichmannii bioassay of serum B_{12} was among the tests, and a tendency to diminished values was reported (Figure 25).

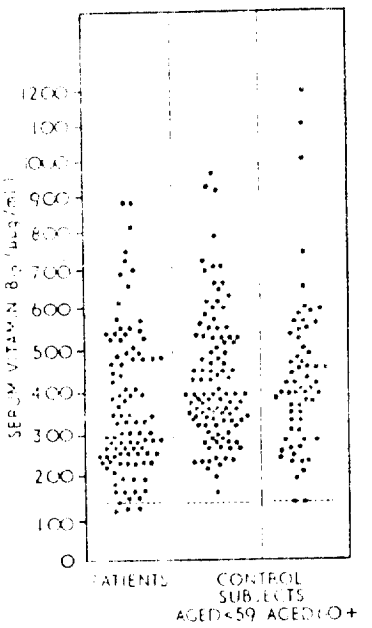


Figure 25. Serum Vitamin B_{12} Concentrations in Patients Aged 60 and Over and in Control Subjects (0189)

In 1968 Williams and Spray (2983) gave Co^{58}-cyanocobalamin by tube to Wistar rats aged 6 hours to 24 days and estimated retention by whole-body-counting seven days later. Up to 4 days of age at dosage, 90% was retained; at 8 days 83%, at 16 days 66%, and at 24 days 47%. These percentages were unaffected by fasting up to 24 hours, by raising the dose from 0.05 to 0.25 ng/g BW, or by mixing the dose with rat's milk. The authors suggested that neonatal rats absorbed B_{12} by a different mechanism from adult rats.

In 1972 Yamade et al. (3060) observed that neonatal rats' gut mucosal homogenate adsorbed extremely high amounts of B_{12} without gastric mucosal extract. The GME-independent B_{12} adsorption fell gradually to adult levels at 20 days of age. The gastric mucosal extract stimulation of B_{12} adsorption reached

adult levels at 20 days, but intrinsic factor and pepsinogen did not reach this till 30 days. Intrinsic-factor-dependent B_{12} absorption also became prominent at about 30 days of age.

In 1972 Gallagher et al. (0916) used thirteen B_{12} analogs (see page) to study the B_{12} transport system of neonatal rat intestine. Eight interfered with transport. Binding of cyanocobalamide to the transport protein was found to involve two of the propionamide side chains of the corrin nucleus and an unidentified portion of the 5,6-dimethylbenzimidazole base. According to the authors, this was closely similar to B_{12}-binding in human gastric juice.

(b) Inborn Errors of Metabolism

In 1963 Imerslund and Bjørnstad (1302) described 10 patients with B_{12} malabsorption with signs of pernicious anemia but with normal intrinsic factor. They regarded these as reflecting a specific, unidentified, biochemical defect.

In 1972 Walters and Koch (2931) reported pernicious anemia with generalized malabsorption in a 16-month-old boy, which responded to parenteral B_{12}. However, abnormal Schilling tests were not corrected by exogenous intrinsic factor, and the patient was found to elaborate intrinsic factor. The condition was diagnosed as Imerslund-Grasbeck syndrome, i.e., a specific defect in ileal mucosal handling of the intrinsic factor-B_{12} complex.

(c) Pancreatic Sufficiency

In 1972 Toskes and Deren (2779) found that absorption of Co^{57}-B_{12} 5 ng was halved in rats by subtotal pancreatectomy (80-90%). Hog pancreatic extract 0.17 g/kg improved B_{12} absorption in these rats but not in controls. Chloramphenicol produced no further improvement. Intrinsic factor from control rats was no more effective than from part-pancreatectomized rats. The authors concluded that in the part-pancreatectomized rats, B_{12} was complexed to intrinsic factor in a form less available for absorption.

(d) Sorbitol

In 1960 Okuda et al. (2056) added D-sorbitol to diets lacking B_6 or B_{12} for rats. When B_6 was deficient, sorbitol increased liver and urinary concentrations of B_6 in adults and increased the growth rate of weanlings. When B_{12} was deficient, sorbitol did not increase the growth rate of weanlings, and when fed for 8-12 weeks as 10-12% of the diet, it reduced the absorption of labeled B_{12} supplements given orally.

(e) Iron

In 1962 Biggs et al. (0277) gave B_{12} by tube to iron-deficient and control rats, and reported 50% more label in the iron-deficient rats' feces. Gastric juice from control rats diminished B_{12} excretion by gastrectomized rats, but juice from iron-deficient rats did not. Intrinsic factor secretion was impaired after 4 weeks on iron-deficient diet, and recovered after 10 or more weeks of iron supplementation. Neither antibiotics nor removal of the cecum affected these results, and apparently no other small-intestine function was disturbed.

The authors cited data suggesting that in man B_{12} absorption was also diminished by low iron status.

(f) Cholic Acid

In 1973 Coronato and Glass (0567) studied the uptake of labeled B_{12} by guinea-pig intestinal mucosal homogenates and by two normal adult human volunteers. Deconjugated cholic acid halved the uptake of B_{12} by the homogenates, and decreased its absorption by the volunteers. Deoxycholic, glycocholic, and glycodeoxycholic acids had no significant effects on B_{12} uptake by the homogenates. The authors inferred that cholic acid was directly toxic to ileal mucosa.

(g) Glutamic Acid

In 1966 Spray and Warner (2614) investigated a report that oral B_{12} in pernicious anemia was more efficient when given with five-fold (w/w) L-glutamic acid. In two patients they found that B_{12} absorption was not affected, when Co^{58}-B_{12} 0.5 μg was given with 5 μg or 50 mg L-glutamate.

(h) Form of B_{12}

In 1973 Okuda et al. (2058) studied the absorption of $C^{14}H_3$- and Co^{57}-methylcobalamin at various levels by rats. At physiologic levels this was similar to cyanocobalamin, but the liver accumulated more label, indicating gradual conversion of the methylcobalamin to hydroxocobalamin and cobamide coenzyme. Pre-photolysis, however, led to quick and massive expiration of $C^{14}O_2$. Other studies also indicated, to the authors, that methyl cleavage in vivo was different in mechanism from that observed in vitro or after photolysis. They suggested that normally, free methylcobalamin was labile and readily lost its CH_3, and that binding to intrinsic factor might protect it.

(i) Immunology and Rheumatoid Arthritis

In 1967 Fisher et al. (0839) studied 21 patients with pernicious anemia, 35 with chronic atrophic gastritis, 24 post-gastrectomy, and 48 with other

diseases and normal gastric biopsy. Clinical data and gastric microscopy were evaluated in Australia; immunological studies were performed in California, after which the data were combined.

Intrinsic factor antibodies always entailed poor B_{12} absorption; parietal cell antibodies were found in most who showed grossly or moderately poor B_{12} absorption, and were rare in normal absorbers. Gastric antibodies were found in no post-gastrectomy patients, with or without poor absorption, and were never present when microscopy was normal.

In 1968 Couchman et al. (0574) studied B_{12} absorption (Schilling) and gastric antibodies on 52 consecutive patients (42 F, 10 M) with rheumatoid arthritis, and in matched controls. Seven of 10 patients increased their absorptions after intrinsic factor. Five of ten over 65 years old had low absorption with parietal cell antibody.

In 1970 Fitcher et al. (2156) found B_{12} malabsorption in three of 100 consecutive patients with definite rheumatoid arthritis.

(j) Pregnancy

In 1957 Hellegers et al. (1187) concluded from human and rat studies that "as yet, pregnancy is the only known method of increasing vitamin B_{12} absorption in the adult." Nevertheless serum, liver, and kidney B_{12} decreased, presumably being transferred to the fetus. The authors claimed that a good test of absorption was an oral tolerance test, using B_{12} 1 mg unlabeled (important in pregnancy). They also reported a fetal and neonatal relationship between thyroid function and B_{12} absorption that was "imperfectly understood."

(k) Hormone Therapy

In 1961 Canelas et al. (0436) treated nine cases of subacute combined degeneration of the spinal cord with ACTH i.v. for 19-43 days, and in 7 cases observed increased absorption of B_{12}. They suggested that ACTH might influence B_{12} absorption directly, not through stimulation of intrinsic factor or mobilization of B_{12} body stores.

(i) Bacterial Competition

In 1971 Gianella et al. (0950) studied B_{12} uptake by microorganisms representing those common in the intestines and found binding constants comparable with that of intrinsic factor. They inferred competition with intrinsic factor which, in "bacterial overgrowth syndromes", might account for poor uptakes of B_{12} by patients.

B. Distribution

(a) Systemic B_{12} Binders

In 1973 Herbert (1015) in a review summarized the systemic binders of B_{12} as follows:

1. Transcobalamin II, comparable with β-globulin, is judged primarily a transport and delivery protein.
2. Transcobalamin I, comparable with γ-globulin, is considered primarily a storage protein with perhaps minor delivery functions. It is made by granulocytes, which may also make some of the transcobalamin II.
3. The third serum binder is judged to be present in smaller amounts, and its function is not commented on.

The usual serum binding capacity is stated as about 1.8 ng, of which 20-30% is saturated, all of this being transcobalamin I. Of the unsaturated capacity 80% is stated to be transcobalamin II, and 20% transcobalamin I. The third binder is not considered by the author.

Body stores are described as: 1-10 mg, 50-90% in the liver (average 1 μg/g), usual stores totaling 2-5 mg. Coenzyme B_{12} is the normal form stored, and methyl-B_{12} the form transported in serum. Turnover is stated to be 0.1-0.2% of stores/day, regardless of level, without catabolism, and mainly via bile. Enterohepatic recirculation may handle 0.6-6.0 μg/day, explaining why clinical deficiency develops slowly -- even accelerated onset is given as 3-6 years after a reason develops.

In 1969 Hall (1107) reviewed the transport of B_{12} in humans, reporting new data showing that transcobalamin II was not made in the ileum. Although it was made in the livers of mice, this did not necessarily apply to man, whose site of synthesis for transcobalamin II was unknown. He found that less than 2% of available transcobalamin II was used at any one time, and that there was no reuse after B_{12} had been transported. The plasma content was about 25 μg/liter, compared with 60 μg/liter of transcobalamin I. The latter removed B_{12} from cells to which it had been distributed and held it within the plasma for months, but the next step was unknown. This B_{12} was in the form of methylcobalamin, and there was evidence that it was reused. An additional binder for B_{12} was found in fetal blood, but its function was unknown and it disappeared within a few weeks.

The author concluded that no harmful effects could be attributed to abnormalities of B_{12} transport that were seen in leukemias, polycythemia vera, or pernicious anemia, and of which the etiologies were still obscure.

In 1970 Gilbert et al. (0952) determined the unsaturated B_{12} binding capacity in normal subjects and in various conditions (Table 41). They found no correlations with blood count, spleen size, or uric acid. The observation that binders rose without increases of serum B_{12} in polycythemia vera suggested (with other data) that some γ-proteins binding B_{12} were abnormal in this condition, failing to bind endogenous B_{12}.

Table 41. Serum B_{12} and Unsaturated B_{12}-Binding Capacity (UBBC) in Normal Subjects and Patients with Spurious Polycythemia, Erythrocytosis, and Various Stages of Myeloproliferative Disease (0952)

Diagnosis	Number of Patients	Mean Age (Range)	Serum B_{12} (Mean ± SD)	Serum UBBC (Mean ± SD)
		yr	pg/ml	
Normal	28	51 (27-70)	445 ± 245	1,605 ± [illegible]
Spurious polycythemia	32	58 (41-81)	391 ± 217	1,662 ± 438
Secondary erythrocytosis	8	59 (35-73)	545 ± 171	2,040 ± 465
Unclassified erythrocytosis	7	47 (22-74)	435 ± 171	1,583 ± 384
Polycythemia vera				
I active, untreated	22	61 (46-78)	984 ± 1,072	3,215 ± 1,462
II active, phlebotomized	16	61 (32-78)	1,089 ± 865	3,012 ± 1,219
III active, on myelosuppressive therapy, no erythroid response	7	61 (50-71)	517 ± 335	2,863 ± [illegible]
IV controlled	27	57 (27-73)	494 ± 325	1,803 ± [illegible]
Spent polycythemia vera	10	63 (48-73)	977 ± 380	3,164 ± 1,038
Myeloid metaplasia, myelofibrosis	9	66 (44-80)	1,082 ± 623	3,112 ± 1,343

In 1971 Meyer and Gizis ([illegible]) studied the dynamics of Co^{57}-B_{12} binding to transcobalamins I and II in normal subjects and patients with pernicious anemia or chronic myelocytic leukemia. Clearance of both of the endogenously labeled transcobalamins from the blood was slower in the leukemics than in the normals or pernicious anemics. According to the authors, if transcobalamin I took up B_{12} that had been bound to transcobalamin II, this happened more slowly than the disappearance of transcobalamin I-bound B_{12}.

In 1971 Hippe et al. (1237) studied the attachments of coenzyme B_{12} to its binders in vitro. They concluded that the molecule was bound to albumin covalently at the PO_4 group, shown as position IV in Figure 26. Binding to poly-L-glutamic acid or succinylated γ-G globulin was also covalent, to the deoxyadenosine moiety as at position I in Figure 26. Other binding sites (positions II and III) were inferred when human transcobalamins I and II, sputum binder, and intrinsic factor were used, and the authors concluded that a major area of contact was in the region of the B ring probably with overlap to the adjacent dimethylbenzimidazole moiety. They also concluded, from other measurements that these four binders had but one binding site apiece.

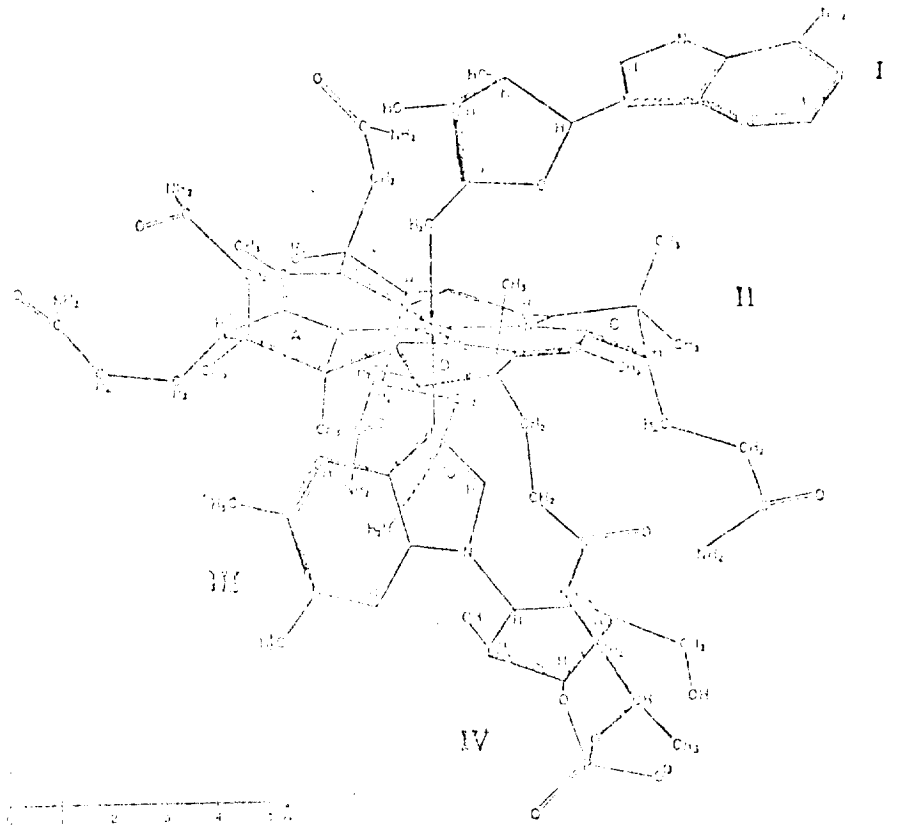


Figure 26. Atomic Positions in 5'-deoxyadenosylcobalamin. Adapted from Hodgkin (1964) (1237)

In 1971 Hall (1108) reviewed knowledge of the B_{12}-binding proteins of man. Those characterized were glycoproteins. There were five functional categories:

(1) Transport, naturally occurring.

(2) Unknown, naturally occurring.

(3) Binders used in diagnosis.

(4) Those useful for isotope-dilution assay of B_{12}.

(5) Artifacts.

(1) (a) Intrinsic factor was required to carry dietary B_{12} from the stomach to the ileum.

(b) Transcobalamin II (beta B_{12} binder) of plasma was considered to transport B_{12} rapidly from the ileal mesentery to and into the tissues. No other role was defined, though it occurred in CSF and seminal plasma as well as in blood plasma.

(c) Transcobalamin I (alpha B_{12} binder) carried B_{12} that had been absorbed more than 24 hours ago, recirculating B_{12} that had already been taken up by cells, for some months. It was not efficient in primary distribution of B_{12}. This description was considered incomplete.

(2) The unknown-function binders were found in, e.g., saliva, tears, milk, fetal plasma, bile, gastric juice, CSF, seminal plasma, rbc, and wbc. Some probably had no function.

All of these plus transcobalamin I had been grouped as "R" binders. Their mw was about 120,000, except saliva R (60,000), and isoelectric point studies suggested that all had a common derivation and differed mainly by content of sialic acid.

(3) Diagnostic value was attached to intrinsic factor varieties, transcobalamin I level, and total serum binding capacity.

(4) Binders for isotope dilution studies should be selected as required for specific relevant properties.

(5) Artifacts and nonspecific binders resulted from <u>in vitro</u> methods of preparing samples for analysis, according to the author. They varied according to conditions; many proteins could bind B_{12}. Even transcobalamin II was altered during purification, as to molecular size and isoelectric point.

The author commented further that separation of binders was not always feasible; thus claims for discoveries should be crosschecked rigorously. Also, the nomenclature of binder taxonomy was still unsettled.

In 1972 Allen and Majerus (0054) used affinity chromatography to isolate transcobalamin II from a preparation of 1,400 liters of human plasma. After two million-fold purification (yield 12.8%), it bound 28.6 μg of B_{12}/mg of protein, contained one B_{12}-binding site per 59,500 g of protein according to amino acid analysis, had mw of 53,900 or 60,000, and probably consisted of two subunits of mw 38,000 and 25,000. When B_{12} was bound, peak absorption shifted from 361 to 364 nm, and chemical analyses suggested that the transcobalamin was not a glycoprotein.

In 1972 Bloomfield and Scott (0293) identified transcobalamin III in normal human serum, demonstrating that it was separate from transcobalamins I and II in 50 different normal samples. Data from 19 subjects are shown in Table 42. The authors described this binder as semi-purified, and as under investigation for similarity to fetal B_{12} binder or the binder reported by others in polycythemia vera.

In 1972 Chanarin et al. (0481) investigated the physiological role of transcobalamin III, regardless of whether it might be a polymer of transcobalamin II or an antigenically different protein. After giving Co^{57}-B_{12} orally to two volunteers aged over 60, their three serum binders were isolated, and the distribution of label was measured (Table 43). The authors commented that all three binders appeared to have taken up label at the same time; they concluded that unsaturated B_{12}-binding capacity was the governing factor, not new protein synthesis, and that the third binder participated in uptake under physiological conditions.

In 1972 Carmel (0448) submitted R binders from tears and saliva to gel filtration, sucrose gradient centrifugation, and electrophoresis, reporting that saliva R binder was identical in size with other R binders, serum third binder, and transcobalamin I; however, it differed from transcobalamin I in electrophoetic mobility. Tear R binder also differed in mobility, and the author concluded that all of the R binders were identical, and that heterogeneity of their isoelectric points was probably acquired.

Table 42. Distribution of Human UBBC Between the Different Transcobalamins in (a) Normal and (b) Fasted Sera on DEAE-cellulose Fractionation After Treatment with Uncoated Charcoal (0293)

Subject		Total UBBC (pg/ml)	TCIII		TCI		TCIII and TCI		TCII*	
			pg/ml	%	pg/ml	%	pg/ml	%	pg/ml	%
P.E.	a	922.3	204.5	22.1	64.3	6.9	268.3	29.0	654.0	71.0
	b	1328.9	221.9	16.7	238.0	17.9	459.9	34.6	869.0	65.4
J.S.	a	994.7	122.1	12.3	71.2	7.1	193.3	19.4	801.4	80.6
	b	1527.1	166.3	10.9	198.0	13.0	364.3	23.9	1162.8	76.1
A.C.	a	1090.8	114.7	10.5	70.4	6.5	185.1	17.0	905.7	83.0
	b	1674.0	346.6	20.7	276.3	16.5	622.9	37.2	1051.1	62.8
L.H.	a	1206.9	131.3	10.9	55.3	4.6	186.6	15.5	1020.3	84.5
	b	1197.7	230.0	19.2	104.7	8.7	334.7	27.9	863.0	72.1
T.B.	a	1002.2	177.3	17.7	75.1	7.5	252.4	25.2	749.8	74.8
	b	1749.6	196.6	11.2	178.4	10.2	375.0	21.4	1374.6	78.6
N.F.	a	959.6	199.3	20.8	88.9	9.3	288.2	30.1	671.4	69.9
	b	1871.1	210.2	11.2	496.1	26.5	706.3	37.1	1164.8	62.3
C.B.	a	984.9	134.9	13.7	95.7	9.7	230.6	23.4	754.3	76.6
	b	1708.6	232.4	13.6	411.6	24.1	644.0	37.7	1064.6	62.3
B.P.	a	1132.0	249.4	22.0	35.6	3.0	285.0	25.0	847.0	75.0
	b	2107.1	438.8	20.8	269.9	12.8	708.7	33.6	1398.4	66.4
A.J.	a	1309.5	133.3	10.2	54.3	4.1	187.6	14.3	1121.9	85.7
	b	1423.4	183.8	12.9	280.5	19.7	464.3	32.6	959.1	67.4
C.L.	a	1064.9	116.7	11.0	171.9	16.1	288.6	27.1	776.3	72.9
	b	1989.9	176.0	8.8	290.5	14.6	466.5	23.4	1523.4	76.6
B.G.	a	938.5	182.5	19.4	60.3	6.4	242.8	25.8	695.7	74.2
	b	1327.3	182.9	13.8	257.0	19.4	439.9	33.2	887.4	66.8
T.McC.	a	897.1	161.2	18.0	31.3	3.5	192.6	21.5	705.1	78.5
	b	1187.5	184.7	15.6	225.1	18.9	409.8	34.5	777.7	65.5
A.O'C.	a	1332.2	127.8	9.6	54.6	4.1	182.4	13.7	1149.8	86.3
	b	2124.9	199.2	9.4	211.7	9.9	410.9	19.3	1714.0	80.7
E.O'C.	a	1320.6	143.7	10.9	63.2	4.8	206.9	15.7	1113.7	84.3
	b	1431.0	242.0	16.9	247.3	17.3	489.3	34.2	941.7	65.8
M.D.	a	1343.3	265.0	19.7	74.6	5.6	339.6	25.3	1003.7	74.7
	b	1532.2	162.8	10.6	386.6	25.2	549.4	35.8	982.8	64.2
G.W.	a	1037.3	133.2	12.8	69.4	6.7	202.6	19.5	834.7	80.5
	b	1079.5	177.2	16.4	308.2	28.6	485.4	45.0	594.1	55.0
H.M.	a	961.2	180.0	18.7	72.2	7.5	252.2	26.2	709.0	73.8
	b	1258.2	213.9	17.0	225.2	17.9	439.1	34.9	819.1	65.1
M.K.	a	1242.4	193.9	15.6	80.6	6.5	274.5	22.1	967.9	77.9
	b	1416.4	247.4	17.0	196.4	14.0	443.8	31.0	972.6	69.0
D.G.	a	939.6	130.8	13.9	27.8	3.0	158.6	16.9	781.0	83.1
	b	1239.3	139.9	11.3	298.3	24.1	438.2	35.4	801.1	64.6
Mean values	a	1088.4	163.2	15.3	69.3	6.4	232.5	21.7	855.9	78.3
	b	1535.5	218.6	14.4	268.4	17.9	487.0	32.3	1048.5	67.7

* By subtraction of TCI and TCIII from total UBBC.

Table 43. Relative Distribution of Vitamin B_{12} Absorbed from the Gut Among Serum Vitamin B_{12} Binding Proteins[1] (0481)

Time after Oral Dose of ^{57}Co-B_{12} (Hours)	Percentage of Oral Dose per Litre of Plasma			
	Whole Plasma	Transcobalamin		Binder II
		I	II	
1	0	0	0	0
2	0	0	0	0
3	0.41	0.23	0.13	0.13
4	[illegible]	[illegible]	0.74	0.17
5	[illegible]	[illegible]	[illegible]	[illegible]
6	[illegible]	[illegible]	0.23	0.13
24	[illegible]	[illegible]	0.21	0.16

(b) Systemic Transport of B_{12}

In 1967 Meyer et al. (1838) studied 14 patients with pernicious anemia and one with post-gastrectomy megaloblastic anemia; plasma B_{12} label was determined after single doses of Co^{57}-B_{12} i.v. In 7 patients clearance of label from plasma was judged significantly "slow"; in the others it was "normal". When these sera were extracted and used for binding doses of labeled B_{12} --

1. Doses bound to "slow" serum and given to "normal"-clearing persons cleared normally.
2. Doses bound to "normal" serum and given to "slow"-clearing persons also cleared normally.
3. Mixtures of the above doses given to "slow"-clearing persons also cleared normally.

The authors suggested that "normal"-clearing serum contained some factor that enhanced the clearance of B_{12} label from "slow"-clearing serum.

In 1968 Hom and Ahluwalia (1260) studied B_{12} binding in serum from 39 female and 11 male hospital workers aged 18-42, with normal Hb and ESR determinations, after storage at -20°C. They found that the binding capacities of transcobalamins I and II were correlated with each other when compared with the unsaturated binding capacities of the sera regardless of how much B_{12} was added. These were the only binders of added B_{12} between 75 and 20,760 pg/ml of serum. Some B_{12} was bound to transcobalamin 0 between 0 and 75 pg/ml. The ratios of binding to transcobalamins I/II were individual and constant through the range of amounts of added B_{12}.

The authors commented that their results in normals differed from those in chronic myelogenous leukemia patients (who bound more B_{12} to transcobalamin I)

and in pernicious anemia patients with antibodies to transcobalamin II. They also discussed their methodology (see original paper for details).

In 1968 Olesen et al. (2066) went on to demonstrate the presence of an antibody of the γG-globulin type reacting with transcobalamin II, present in 8 of 19 patients, with affinity "very sensitive" to changes of pH, ionic strength, and temperature.

In 1971 Fletsch and Coffey (2168) studied B_{12}-binding in rat liver. Five minutes after injection, B_{12} in plasma membrane fractions apparently was bound to transcobalamin II; at 30 minutes, 70% of the lysosomal B_{12} was so bound; at 24 hours 90% of the cytosol B_{12}, and at 72 hours 40% of the mitochondrial B_{12} were so bound. The remainders were found to be free B_{12}. The authors concluded that much of the injected B_{12} was taken up by rat liver as the transcobalamin II complex, which was then further metabolized.

In 1972 Fletsch and Coffey (2167) reported that Co^{57}-B_{12} given to rats by intracardiac injection was 98% transported to tissues bound to transcobalamin II. Five minutes after injection, 46% of the label in liver was found in microsomes, primarily in plasma membrance fragments rather than endoplasmic reticulum. At 72 hours 9% of the liver label was in microsomes, 33% in heavy mitochondria, and 32% in cytosol. Lysosomes contained little label 5 minutes and 72 hours after injection, but 15% of the liver total at 30 minutes. At 20 minutes and 72 hours all the label was attached to B_{12} or a derivative, and 80% of the label in the lysosomes was on B_{12} itself.

(c) Organ Distribution of B_{12}

In 1950 Lewis et al. (1623) measured the B_{12} contents of kidney, liver, heart, small intestine, and femoral muscle of rats fed a corn-soybean diet. Most B_{12} was found in kidneys, and "no appreciable amount" was found in liver, heart, intestine, or muscle after 6 weeks on diet, but some was found in all of these when B_{12} was added to the diet.

In 1956 Miller et al. (1860) determined the tissue distribution and excretion of labeled B_{12} given to four species of rodents, as in Table 44. The authors commented that rats concentrated most label in the kidneys, the others in the liver, and that rats and mice excreted more label in the feces, guinea-pigs and hamsters in the urine.

Table 44. Tissue Distribution and Excretion of Co^{60}-B_{12} in Mice, Rats, Hamsters and Guinea Pigs (1860)

	Mice		Rats		Hamsters		Guinea pigs	
	% of dose*		% of dose		% of dose		% of dose	
Organ	% of inj. dose*	g wet wt	% of inj. dose	g wet wt	% of inj. dose	g wet wt	% of inj. dose	g wet wt
Kidney	6.2 ± .4	13.0 ± 1.3	16.2 ± 2.9	9.7 ± 1.0	7.2 ± .6	6.3 ± .1	2.4 ± .1	.3 ± 0
Liver	23.7 ± 2.5	11.2 ± 1.1	7.4 ± .1	.8 ± 0	18.0 ± 2.9	6.1 ± .1	29.7 ± 4.1	1.3 ± 0
Testes	1.5 ± .1	7.0 ± 1.1	1.0 ± 0	.6 ± 0	not done		.3 ± 0	.1 ± 0
Spleen	1.1 ± .2	1.7 ± .5	.8 ± 0	.6 ± 0	.3 ± 0	.8 ± 0	.2 ± 0	.3 ± 0
Heart	.1 ± .1	1.5 ± .1	.7 ± 0	.9 ± 0	.4 ± 0	.6 ± 0	.2 ± 0	.1 ± 0
Muscle	15.9 ± .9	1.1 ± 0	13.6 ± 1.1	.2 ± 0	7.7 ± 1.5	.3 ± 0	not done	-
Carcass	26.0 ± 2.9		31.5 ± 1.0	-	43.0 ± 3.8*	-	" "	--
Urine	5.9 ± 1.8	--	7.1 ± 1.1	--	14.1 ± 1.0	--	12.5 ± .9	--
Stool	15.5 ± 1.8		18.5 ± 6.2	--	3.5 ± .9		5.5 ± .1	--
Recovery	96.1		100.7		95.1		5[illegible]	

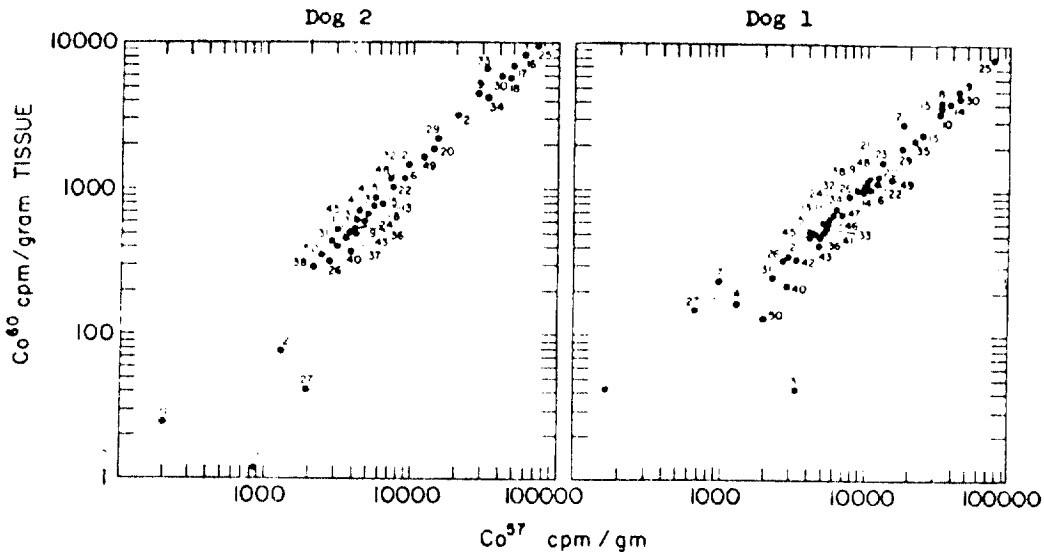
*Mean and stand. error of mean.

In 1958 Schloesser et al. (2433) found, in seven human males, one healthy and six with pernicious anemia, that the biologic half-life of label from Co^{60}-B_{12} in the liver was 11-14 months, or approximately one year.

In 1963 Rosenblum et al. (2327) gave dogs simultaneously oral Co^{57}-B_{12} and i.v. Co^{60}-B_{12}, and studied the distribution of storage forms of labeled B_{12} by the reverse isotope dilution method. Thirty-one days after the test loads were complete, the ratio of Co^{57}/Co^{60} was constant in all tissues (Figure 27). The authors concluded there was a single common pool for B_{12} and related compounds, and that B_{12} was always converted to non-cyano forms. The authors commented that the excretion pattern was complex, and related probably to the conversions of B_{12} in the tissues.

In 1963 Joske (1367) analyzed human liver needle-biopsy samples for B_{12}, which they found to be unrelated to serum B_{12}, bilirubin, alkaline phosphatase, glutamic-oxaloacetic transaminase, or albumin. The authors associated values with liver pathologies, noting that transport defects would be reflected by large sampling errors in needle-biopsies. Normal values in this series averaged 0.91 μg/g of liver (0.39-1.33). Other values are shown in Table 45.

In 1964 Nyberg et al. (2013) compared serum B_{12} levels among 20 patients with chronic renal failure, 14 with acute tubular necrosis, and 636 controls. The acute group, but not the chronic group, was significantly above the control group. Values were not altered significantly by hemodialysis. The authors attributed the high values of the acute group to release of B_{12} from injured tissue and perhaps also to damaged tissue acceptors of B_{12}.



1. Aorta
2. Heart
3. Skin
4. Skeletal muscle
5. Diaphragm muscle
6. Thyroid
7. Parathyroid
8. Lung
9. Thymus
10. Cartilage (sternum)
11. Bone
12. Bone marrow
13. Urinary bladder
14. Gall bladder
15. Spleen
16. Kidney
17. Adrenals
18. Pancreas
19. Liver
20. Submaxillary gland
21. Axillary lymph node
22. Mesenteric lymph node
23. Cerebrum
24. Thoracic duct
25. Pituitary
26. Femoral nerve
27. Cornea
29. Testis
30. Prostate
31. Esophagus
32. Stomach-cardia-wall
33. Stomach-fundus-mucosa
34. Stomach-fundus-wall
35. Stomach-pylorus-wall
36. Duodenum-mucosa
37. Duodenum-wall
38. Jejunum-mucosa
40. Ileum-mucosa
41. Ileum-wall
42. Cecum-mucosa
43. Cecum-wall
45. Colon-wall
46. Rectum-wall
47. Tonsil
48. Popliteal lymph node
49. Parotid
50. Omentum fat

Figure 27. Radioactivities in Tissues of 2 Experimental Animals Receiving Oral Vitamin B_{12}-Co^{57} and Intravenous Vitamin B_{12}-Co^{60}. Numbers Indicate the Tissues (2327)

Table 45. Serum and Liver B_{12} Contents in Relation to Histological Diagnosis (1367)

Diagnostic Group	No. of Cases	Serum B12 (μμg./ml.)		Liver B12 (μg./g.)	
		Mean	Range	Mean	Range
Normal histology	7	430	160-1,060	0.91	0.39-1.33
Fatty change	12	475	220-770	0.47	0.19-0.93
Parenchymal cell damage	9	630	260-1,840	0.65	0.25-0.93
Metastatic neoplasm	7	5,980	450-20,400	0.51	0.25-0.75
Portal cirrhosis	7	900	330-1,990	0.43	0.19-0.69
Cholestatic jaundice	7	600	290-980	0.55	0.26-1.17
Viral hepatitis	3	1,240	700-1,920	0.57	0.29-1.11
Hemochromatosis	5	870	370-1,410	0.49	0.18-0.73
External biliary obstruction	3	1,100	510-1,940	0.27	0.16-0.45

In 1966 Kristensen and Hansen (1517) gave the treatment in Table 46 i.m. to rabbits. They found prolonged liberation of B_{12} from the injection depot into muscle, rise of liver and kidney B_{12} interpreted as a rise of body stores, and "minimum" urinary B_{12}.

Table 46. Dosage Schedule of Various Vitamin B_{12} Preparations (1517)

Prepn.	Form of Vitamin B_{12}	Vehicle	Vit B_{12} Concn., meg/ml	B_{12} ^{60}Co Concn., μc/ml	Quantity Injected, ml
A	Cyanocobalamin	Aqueous 0.9% NaCl soln.	500	0.18	0.30
E[a]	B_{12}-zinc-tannate	Aqueous suspension	500	0.18	0.30
C	B_{12}-zinc-tannate	Suspended in 2% aluminum monostearate oil gel	500	0.5	0.25
D[b]	B_{12}-tannate	Suspended in 2% aluminum monostearate oil gel	500	0.5	0.25
E	B_{12}-tannate	Suspended in sesame oil	500	0.5	0.25
F[b]	B_{12}-tannate	Suspended in 2% aluminum monostearate oil gel	1000	1.0	0.50
G[b]	B_{12}-tannate	Suspended in 2% aluminum monostearate oil gel	1000	1.0	0.50

[a] Trademarked preparation is Depinar. [b] Trademarked preparation is Betolvex.

In 1967 Rosenthal et al. (2339) gave Co^{57}-B_{12} to four normal subjects i.v. (a) bound to pernicious anemia gastric juice, to all, (b) bound to autologous plasma, to two, and (c) unbound, as pretreatment to all. The gastric juice-bound B_{12} remained longer in the blood, less was taken up by the arm, and more by the liver, than of either plasma-bound or unbound B_{12}. The authors inferred that this was due to some property of the gastric juice B_{12}-binders unrelated to intrinsic factor activity.

In 1967 Rosenthal et al. (2338) also measured in vivo uptake of labeled B_{12}, unbound (control) or bound by extracts containing binders, by the livers of 48 rats perfused in situ without recirculation.

1. Normal human gastric juice did not increase B_{12} uptake.
2. Pernicious anemia gastric juice did increase B_{12} uptake, and so did human saliva, and hog intrinsic factor (even if boiled).
3. Another experiment suggested that the parenchymal, not the reticulo-endothelial cells of the liver were involved.

In 1970 Newmark et al. (1985) found in rat kidney that a constant 50% of injected B_{12} was primarily associated with lysosomes between 6 and 29 days after administration.

In 1970 Adams et al. (0025) calculated the total body B_{12} for 18 patients by giving Co^{57}-B_{12} and measuring label in serum and in liver biopsies obtained at laparotomy. Microbial assays were also performed. Values found were 2528 (range 960-5984) μg, with significant correlations between serum and total, serum and liver, and liver and total values.

In 1970 Rappazzo et al. (2246) measured the distribution of B_{12} in 17 tissues from 28 human adults (sudden deaths) and 17 fetuses (therapeutic abortions), by E.gracilis assay. Data are shown in Tables 47 and 48, and in Figure 28.

In 1971 Wisniewski and Glass (3004) reported that insulin increased the one-hour uptake of B_{12} by perfused rat liver, and that the 90-minute uptake by liver slices in vitro was also increased significantly. The authors cited studies showing that hypoglycemic doses of insulin raised serum B_{12} levels in man, and that glucose loading lowered serum B_{12}, effects possibly mediated by shifts of growth hormone secretion. The authors concluded that these effects occurred under physiological conditions.

Table 47. Adult and Foetal Levels of Vitamin B_{12} Recorded as pg/mg Wet Wt of Tissue (2246)

Source	Adult		Foetal	
	Median	Range	Median	Range
Liver	698	1137–345	220	369–100
Kidney	161	367– 43	109	141– 65
Adrenal medulla	120	252– 55	128	183– 68
Adrenal cortex	115	195– 43	128	183– 68
Pancreas	98	250– 13	58	67– 42
Heart muscle	92	179– 56	42	55– 27
Jejunum	51	97– 13	58	94– 29
Stomach	47	154– 20	55	67– 27
Colon	39	160– 15	64	101– 37
Gonads	40	134– 20	37	72– 25
Thyroid	39	116– 21	57	101– 20
Brain—grey	39	74– 15	18	36– 11
Brain—white	28	50– 16	18	36– 11
Spleen	38	67– 21	57	88– 34
Skeletal muscle	25	51– 17	33	57– 18
Lung	19	43– 11	80	136– 47
Bone marrow	16	33– 7	29	52– 13

Table 48. Vitamin B_{12} Levels in Adult Tissues as Compared with Foetal Tissues (2246)

Tissue	Adult			Foetal			Significance of difference between adult and foetal tissue vitamin B_{12} levels
	N	Mean	SD	N	Mean	SD	
Liver	28	746.07	232.74	17	229.94	71.89	$P < 0.01$
Kidney	28	174.54	65.87	17	105.59	24.26	$P < 0.01$
Adrenal*	27	120.56	42.61	15	133.47	30.38	NS
Pancreas	27	103.41	64.21	5	55.00	10.63	NS
Heart muscle	28	99.93	36.17	13	42.08	9.24	$P < 0.01$
Jejunum	28	51.57	21.23	17	60.76	18.50	NS
Stomach	28	58.11	35.23	13	48.46	14.31	NS
Colon	26	38.54	18.79	17	63.82	16.16	$P < 0.01$
Gonads	27	45.81	26.76	3	44.67	24.42	NS
Thyroid	28	40.18	20.27	12	62.08	22.43	NS
Brain—grey	28	44.11	16.36	12	19.25	6.31	$P < 0.001$
Brain—white	27	29.56	9.12	12	19.25	6.31	$P < 0.01$
Spleen	27	40.22	11.44	12	56.00	14.22	$P < 0.01$
Skeletal muscle	28	26.93	7.92	16	31.56	10.49	NS
Lung	28	22.18	9.45	14	84.43	21.40	$P < 0.01$
Bone marrow	28	16.79	6.29	17	21.88	8.94	$P < 0.05$

Mean values = pg/mg tissue; Significance of difference by matched *t*-test.

* Foetal adrenal compared with adult adrenal cortex. Foetal adrenal and brain not separated into its components.

In 1972 Newmark (1987) studied *in vivo* uptake of B_{12} by rat kidney in terms of protein-bound Co^{57}-B_{12} 0.25-4.0 hours after Co^{57}-cyanocobalamin i.m. A steady overall increase was observed, and the main conclusion was that the transcobalamin II complex was assimilated by pinocytosis at the post-glomerular tubules. Release of B_{12} from transcobalamin II occurred in the lysosomes.

In 1973 Wickramsinghe and Moffatt (2972) reported that uptake of serum bound Co^{57}-B_{12}, by freshly aspirated human marrow cells depended on calcium, cell respiration, oxidative phosphorylation, and free SH groups, and was 2.7 times greater for B_{12}-deficient marrow than normal marrow. Free Co^{57}-B_{12} (absence of serum) uptake depended on respiration, but not on calcium nor free SH groups. The authors contrasted this uptake with that reported for reticulocytes and rbc (surface adsorption, no energy requirement).

(d) Nervous System

In 1959 Meyer *et al.* (1846) found, in man, that normal CSF bound Co^{57}-B_{12} in amounts that increased with the amount provided. Normal CSF had more binding capacity per g of protein than had normal serum.

In 1962 Newman *et al.* (1983) measured the B_{12} activity in cell fractions from brains of 21 rats between 6 hours and 22 days after Co^{58}-B_{12} i.m. At 6 and 12 hours most label was in the nuclei, but shifted to mitochondria, for three days at the expense of nuclear label and then from both nuclei and microsomes. The cytosol proportion remained constant. The injected B_{12} took 8 days to equilibrate with the B_{12} already present. The B_{12} concentration in brain was one-third of that in liver. Data indicated that injected B_{12} was distributed similarly to oral B_{12}, and rapidly.

In 1963 Kidd *et al.* (1441) assayed serum and cerebrospinal fluid (CSF) B_{12} in 43 neurological patients. In CSF, the level was 21 (0-50) pg/ml, and in 42 patients free and total B_{12} were the same. In 40% CSF total B_{12} was the same as serum free B_{12}; in 37% the CSF level was lower, and in 23% it was higher than serum free B_{12}. In demyelinating diseases of these patients there was a suggestion that B_{12} was bound in the CSF, but data were equivocal. The authors noted, in evaluating their data, that the arithmetical significance was greater than the biological significance, and they claimed no diagnostic correlations.

(e) Artery Walls

In 1969 Hosoda and Kirk (1264) measured the B_{12} content of artery walls in subjects aged 0-82, as shown in Tables 49 and 50. They commented that no age trends appeared between 20 and 82 years, similarly to human liver, and unlike human serum levels.

Table 49. Vitamin B_{12} Content of Human Vascular Tissue in Various Age Groups (1264)

Age Group (Years)	N	Mu. Nanograms of Vitamin B_{12} Gm. Wet Tissue	S.E.	Mu. Nanograms of Vitamin B_{12} Gm. Tissue Nitrogen	S.E.
		Normal Aortic Tissues*			
0-1	5	2.30	0.52	61.0	15.5
1-9	4	4.10		99.8	
10-19	5	4.22	0.39	91.0	11.6
20-29	11	6.55	1.01	157.1	22.0
30-39	14	6.18	0.93	153.9	21.9
40-49	8	5.84	1.37	160.8	38.6
50-59	16	5.85	0.63	151.7	16.0
60-69	16	7.00	0.84	192.2	21.5
70-82	4	7.42		207.0	
0-82	83	5.90	0.36	145.0	9.2
20-82	69	6.39	0.41	157.5	10.4
		Lipid-Arteriosclerotic Aortic Tissues*			
20-29	5	7.58	0.87	183.6	25.2
30-39	4	7.67		201.2	
40-49	4	5.92		160.0	
50-59	9	7.90	0.73	238.2	24.3
60-69	5	6.60	1.34	206.0	42.4
70-82	1	8.60		271.0	
20-82	28	7.33	0.51	207.9	15.2
		Fibrous-Arteriosclerotic Aortic Tissues*			
40-69	9	4.90	0.90	136.2	24.4
		Pulmonary Artery			
20-29	6	16.29	2.97	463.2	96.0
30-39	6	14.50	2.47	418.7	82.0
40-49	4	8.10		246.1	
50-59	10	10.27	0.76	323.3	43.7
60-69	5	14.92	4.10	511.8	158.4
70-82	2	11.50		397.5	
20-82	33	12.63	1.23	389.7	40.3
		Normal Coronary Artery Tissue			
20-29	5	13.02	1.96	403.6	47.8
30-39	2	13.35		376.0	
40-49	1	18.50		600.0	
50-59	5	16.32	2.09	527.8	73.6
60-69	1	14.31		482.2	
70-82	1	16.40		587.9	
20-82	15	14.84	1.05	471.9	34.7
		Lipid-Arteriosclerotic Coronary Artery Tissue			
40-82	9	9.08	1.19	299.9	4.11
		Vena Cava Inferior			
20-29	3	35.70		975.0	
30-39	7	15.87	2.45	486.0	78.6
40-49	6	18.17	3.91	532.0	117.9
50-59	7	23.59	4.19	669.8	115.8
60-69	4	25.08		774.5	
70-82	2	16.45		495.5	
20-82	29	21.60	2.44	613.9	62.0

*Thoracic descending aorta

Table 50. Mean Vitamin B_{12} Concentrations of Pulmonary Artery, Normal Coronary Artery, and Vena Cava Inferior Samples Expressed in % of Contents of Normal Aortic Tissue from the Same Subjects (1264)

	N	Wet Tissue	Tissue Nitrogen
Pulmonary artery	32	172.5% $p<0.001$	209.4% $p<0.001$
Coronary artery, normal	14	191.0% $p<0.001$	234.3% $p<0.001$
Vena cava inferior	27	328.5% $p<0.001$	368.9% $p<0.001$

(f) Eye

In 1968 Phillips et al. (2147) determined the levels of B_{12} in the aqueous humor of 16 subjects (Table 51); no correlations with serum B_{12} were seen, but the authors remarked that the E.gracilis bioassay was somewhat insensitive. Responses to B_{12} intake were not reported.

Table 51. Aqueous B_{12} Determined by Euglena Assay (2147)

Number	Age	Sex	Concomitant Diseases	Serum B_{12} (pg/ml)	Aq. Hum. B_{12} (pg/ml)
1	87	F		490	58
2	65	F		224	32
3	58	M	40-day	434	24
4	83	M		260	14
5	75	F		329	42
6	74	F		194	35
7	87	F		343	12
8	67	F	10-day	[illegible]	14
9	75	F		125	60
10	45	M	Heavy pipe	215	15
11	71	F		135	39
12	53	F	10-day	161	25
13	57	M	Heavy pipe	158	15
14	67	M		252	14
15	74	F		454	18
16	72	F		564	28

Ranges, 12-60 pg/ml. Crude mean 29.9 pg/ml.

(g) Blood Platelets

In 1968 Weiss et al. (2951) reported that human platelets contained sixfold the concentration of B_{12} of rbc, and one-sixth that of leucocytes. Platelets at 300,000/µl of whole blood (normal) would contribute 6-21 pg of B_{12}/ml of blood, and their contribution of folate was 0.4-1.7 µg/ml.

(h) Red Blood Cells

In 1964 Biggs et al. (0275) assayed B_{12} activity in packed human rbc. The range in 50 control subjects was 110-500 pg/ml, and the mean, 213 pg/ml, was 35% of the plasma mean. In untreated pernicious anemia the rbc B_{12} was 63

pg/ml (25-110) and was 103% of the plasma mean. Intermediate values were reported for "latent" pernicious anemia and for hypochromic anemia. Subnormal values were reported for seven of ten gastrectomy patients, and for treated polycythemia vera, but levels were normal in chronic myeloid and lymphatic leukemias.

In 1966 Rachmilewitz et al. (2224) bioassayed the B_{12} contents of blood, bone marrow, and liver of rats. Content per 10^6 nucleated cells was highest in liver, lowest in rbc, and similar in bone and leucocytes.

In 1970 Harrison (1139) reported rbc B_{12} levels in normal subjects and patients with pernicious anemia. He found a normal mean of 155±35 pg/ml packed rbc, range 85-225 pg/ml. Levels were higher in neonates, and lower in males aged 10-19 and in all subjects over 70. Blood group (Rh, ABO) made no difference. Treatment of pernicious anemia elevated rbc B_{12} from a mean of 91 pg/ml to a mean peak of 482 pg/ml which thereafter fell gradually toward the norm.

In 1970 Omer et al. (2070) reported rbc B_{12} levels in control subjects and patients with B_{12} deficiency, folate deficiency, primary and secondary polycythemia (Tables 52-55, and Figures 29-30). They also described the application of E.gracilis assay to rbc.

Table 52. Recovery of Vitamin B_{12} from Erythrocytes (three normal subjects) (2070)

Subject Number	Vitamin B_{12} Recovery (pg./ml.)		
	Basal Level	100 pg./ml. Added	200 pg./ml. Added
1	120	261	411
2	140	233	344
3	135	255	368

In 1972 Harrison (1141) found depressed rbc B_{12} levels in 13 pregnant women despite normal serum values and no anemia (Table 56).

(i) Transfer of B_{12} Across the Placenta

In 1959 Luhby et al. (1691) studied the placental transfer of Co^{60}-B_{12} in the dog, and found that the level in the litter added up to 20% of the residue in the bitch at the time of delivery. Organ distribution and biological half-life

Table 53. Folate Deficient Patients (Hematological Investigations and Diagnoses (2070)

No.	Vitamin B_{12} R.B.C. (pg./ml.)	Vitamin B_{12} Plasma (pg./ml.)	Cyanocobalamin Absorption Schilling Test	Cyanocobalamin Absorption Whole Body Count	Folate Plasma (mg./ml.)	Marrow	Diagnosis
1	24	208	16 per cent	–	0.8	Megaloblastic	Primary Malabsorption
2	21	132	5.7 per cent	–	2.0	Megaloblastic	Primary Malabsorption
			(+IF°—6 per cent)	–			
3	93	216	–	–	2.0	Megaloblastic	Epileptic on Phenytoin Treatment
4	87	132	–	59 per cent	2.2	Megaloblastic	Alcoholic
5	87	168	–	31 per cent:59 per cent	1.6	Megaloblastic	Idiopathic Folate Deficiency
6	120	121	–	–	1.0	–	Crohn's Disease
7	132	292	11.1 per cent	–	1.5	Megaloblastic	Partial Gastrectomy
8	195	621	–		1.6	–	Rheumatoid Arthritis

° I.F. = Intrinsic Factor.

Table 54. Primary Polycythemia Patients (Hematological Investigations) (2070)

No.	Sex	Hb (G per cent)	Peripheral Blood R.B.C. (M/cu. mm.)	Peripheral Blood W.B.C. (cu. mm.)	Platelets (1000s/cu. mm.)	Blood Volume R.B.C. (ml./Kg.)	Blood Volume Plasma (ml./Kg.)	Vitamin B_{12} R.B.C. (pg./ml.)	Vitamin B_{12} Plasma (pg./ml.)	Folate Plasma (mg./ml.)
1	F	19.0	6.5	9000	736	–	–	186	685	5.0
2	F	20.4	7.7	10400	580	65.0	26.4	111	1120	4.8
3	F	18.6	5.7	9800	360	51.8	31.0	120	816	5.5
4	F	17.4	6.5	5700	635	34.7	38.6	171	472	8.0
5	M	17.9	6.0	11300	442	43.5	22.0	198	1088	11.0
6	F	17.2	8.1	13700	320	55.0	37.0	114	544	5.0
7	F	16.2	6.0	18000	550	45.4	31.0	150	808	4.2
8	M	20.0	7.5	8600	250	40.4	25.0	165	1354	3.8
9	M	17.0	6.2	13400	650	42.0	44.4	152	388	4.0
10	M	19.0	8.1	19100	330	63.0	42.0	51	62.0	7.6
11	F	20.4	9.1	19700	205	65.8	31.7	54	950	4.4
12	M	18.0	7.2	21200	305	60.0	38.0	[illegible]	852	[illegible]
13	F	14.8	5.0	46000	670	35.7	44.0	56	452	2.0
14	F	18.1	7.4	12600	200	45.0	37.0	65	720	4.2

Table 55. Secondary Polycythemia Patients (Hematological Investigations and Diagnoses) (2070)

No.	Sex	P.C.V. per cent	Blood Volume R.B.C. (ml./kg.)	Blood Volume Plasma (ml./kg.)	Vitamin B_{12} R.B.C. (pg./ml.)	Vitamin B_{12} Plasma (pg./ml.)	Folate Plasma (ng./ml.)	Diagnosis
1	M	57	40.0	37.5	128	880	2.8	Bronchial Carcinoma
2	F	62	47.4	33.0	126	948	6.0	Calcified Cerebral Lesion
3	M	65	68.0	31.0	133	524	4.4	Chronic Bronchitis Cor Pulmonale
4	M	58	61.0	39.0	75	852	2.8	"
5	F	55	–	–	222	524	[illegible]	Tetralogy of Fallot
6	F	57	–	–	201	784	[illegible]	"
7	F	70	–	–	360	764	6.2	"
8	M	75	–	–	93	260	4.0	"

Table 56. Plasma and Erythocyte Vitamin B_{12} and Serum Folate Levels in Normal Pregnant Women (1141)

Case no.	Age (years)	Parity	Duration of gestation (weeks)	Vitamin B_{12} (pg./ml.) Plasma	Vitamin B_{12} (pg./ml.) Erythrocyte	Serum folate (ng./ml.)	Haemoglobin (g./100 ml.)
1	19	0	26	370	180	12·6	13·8
2	22	1	30	260	124	9·6	13·6
3	20	0	27	242	140	13·5	13·8
4	31	4	32	195	104	8·5	13·2
5	19	1	34	376	120	9·1	12·6
6	17	0	30	244	148	12·3	13·5
7	23	0	28	320	150	15·5	13·1
8	21	2	28	200	132	8·3	14·0
9	24	1	24	300	132	10·6	13·5
10	25	0	23	440	140	8·3	13·1
11	22	0	32	184	120	12·7	12·2
12	20	0	30	280	110	13·2	13·6
13	20	1	32	250	132	10·6	13·9

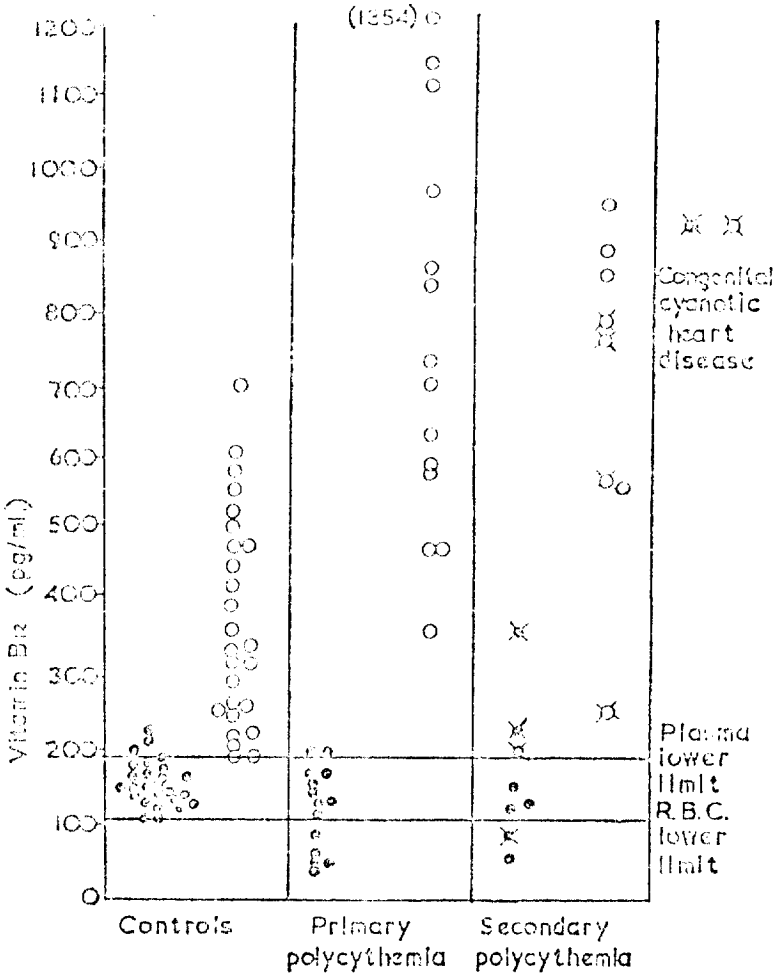


Figure 29. Erythrocyte (Filled Circles) and (Plasma Open Circles) Vitamin B_{12} Levels in Controls and Polycythemia (2070)

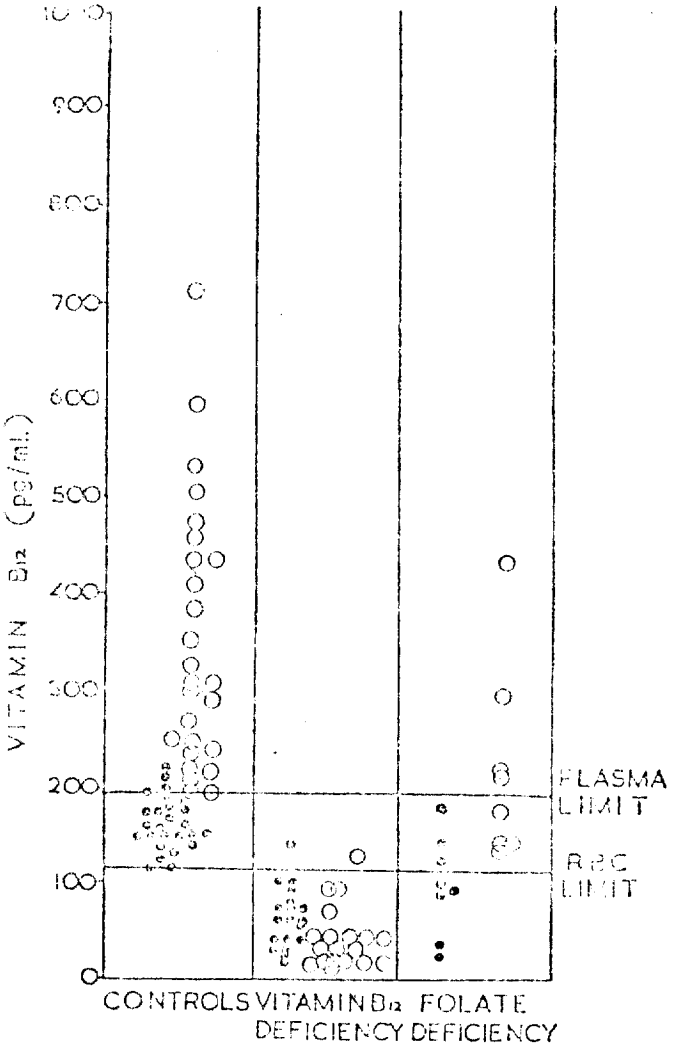


Figure 30. Erythrocyte (Filled Circles) and Plasma (Open Circles) Vitamin B_{12} Levels in Controls, and in Vitamin B_{12} and Folate Deficiency (2070)

(two months) were similar in bitch and litter, after delivery. However, organ concentrations of Co^{60}-B_{12} were much less in the litter than in the bitch, while plasma concentration was much greater in the litter. The authors commented that the reason was unknown but might be "due to a characteristic of placental B_{12} transfer system." They also argued that the dog's disposal of B_{12} was similar to that in man, except for the "surprisingly short" biological half-life.

In 1965 Ullberg (2830) investigated the distribution of labeled B_{12} given i.v. to pregnant mice. Autoradiography showed "a great portion" rapidly in the placenta, with slow transfer to the fetuses after about an hour. After 24 hours nearly all the label was in the fetuses, the fetus/mother ratio being dose-dependent. The ratio with the smallest dose (but only one level was reported, 0.056 μg/mouse) was 130/1. B_{12} also concentrated in a fast-growing transplanted tumor, but not in slower-growing tumors. Distribution within fetuses was similar to that within adults -- all endocrines except the adrenal medulla; part of the brain-stem. Concentration in marrow was low, the authors concluding that B_{12} influenced marrow through folate. Distribution in adults remained constant (except for brain) for a month, and the B_{12} molecules were largely intact after 2 weeks.

In 1967 Ullberg et al. (2831) showed that labeled B_{12} given to pregnant mice accumulated "strongly and rapidly" in the placenta, followed by slow transfer to the fetuses. Fetal accumulation was dose-dependent, and at the smallest dose was 130 times the maternal accumulation. In fetuses and mother the distribution was to all tissues, especially endocrines, renal cortex, and gastric mucosa.

In 1971 Graber et al. (1025) studied placental transfer of B_{12} in pregnant rats. The amount transferred/day was proportional to fetal weight, not to placental weight. At all times the placental concentration of B_{12} was greater than in maternal plasma or fetal tissue. Uptake of label by placenta was rapid at first, but no label appeared in fetuses until 2 hours after injections.

(j) Serum Levels of B_{12}

In 1955 Patrick (2115) surveyed the B_{12} levels of two matched groups of 19 Jamaican children of mixed African descent, aged 8-15 years, with low animal protein intakes. One group had B_{12} added to their diet, totaling about 14 mg over 9 months; the other group did not, and their serum B_{12} averaged 0.21 (0.08-0.43) ng/ml versus 0.33 (0.07-9.0) ng/ml in the supplemented group. The

authors commented that the control values were similar to those of healthy American adults, and on the small effect of massive supplementation, possibly owing to enhanced fecal excretion.

In 1960 Brandt and Metz (0347) found serum B_{12} levels in South Africa for Whites of 648 (220-1076) pg/ml, and for Blacks of 682 (214-1150) pg/ml, regarded as similar.

In 1961 Cape and Shinton (0439) measured serum B_{12} in 98 elderly subjects who were grouped as normal, geriatric, or demented. Comparison with an earlier study revealed a sharp fall at the seventh decade, but neither the geriatric nor the demented group differed significantly from the normals.

In 1963 Shimazono et al. (2502) reported a one year experiment in which 510 normal Japanese children aged 3-14 were given either B_{12} 25 μg/day orally or a placebo. The average whole-blood B_{12} in untreated children aged 9-14 was 0.361 ng/ml. Serum B_{12} values increased with treatment, but no growth-promoting effect of B_{12} was found. The authors commented that a growth-promoting effect in B_{12}-deficiency was neither studied nor excluded by these data.

In 1964 Oxnard (2090) showed that serum B_{12} of rhesus monkeys diminished with time spent in captivity (Figure 31), and that the same was true of other primate species, with much variation between species (Table 57).

In 1965 Kilpatrick and Withey (1451) estimated the serum B_{12} of random samples of two selected populations (urban and rural) in the United Kingdom. In 890 subjects the range was wide, but there was a fall with increasing age (-1.254 pg/ml/year, standardized at age 50). Adjusted means ± SE were:

Urban men	355.2±5.45 pg/ml
Urban women	262.0±10.06 pg/ml
Rural men	260.0±9.52 pg/ml
Rural women	272.0±8.45 pg/ml

In 1971 Waters et al. (2937) reported a ten-year longitudinal study of serum B_{12} levels in community samples totaling 673 subjects, of whom 134 died during the study. Death rates did not correlate with the original serum B_{12} levels. Levels in 1958 and 1968 in subgroups from 480 subjects showed r values between 0.46 and 0.71. Mean levels were lowest in the oldest age-cohort. Several subjects with levels consistently low during the whole 10 years maintained satisfactory hemoglobin levels. Data are shown in Tables 58-62 and Figure 32.

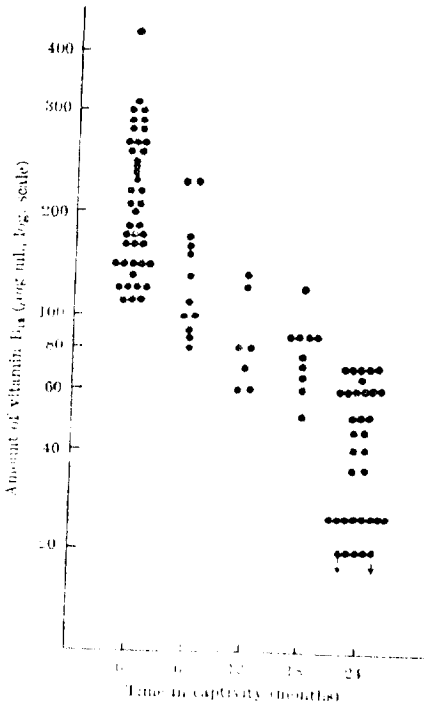


Figure 31. Relationship Between Amount of Vitamin B_{12} in Serum and Time Spent in Captivity (2090)

Table 57. Vitamin B_{12} Levels in Some Other Primates (μμg/ml of serum) (2090)

Recently captive		Captive for long periods	
Species	Vitamin B_{12}-level	Species	Vitamin B_{12}-level
Erythrocebus patas	450	*E. patas*	100
E. patas	470	*Aotes trivirgatus*	100
E. patas	310	*Papio anubis*	60
E. patas	820		
Cercopithecus talapoin	860	*C. talapoin*	240
C. talapoin	800	*C. talapoin*	280
C. talapoin	700	*C. talapoin*	340
C. talapoin	1,100	*C. talapoin*	870
Perodicticus potto	4,000+		
Galago crassicaudatus	4,000+		
G. crassicaudatus	4,000+		
G. crassicaudatus	2,000+		

Table 58. Deaths Between 1958 and 1968 and Serum Vitamin B_{12} Concentration (pg/ml) in 1958 (2937)

		Serum vitamin B_{12} concentration in 1958					*Total*
		0–	150–	250–	450–	*No serum*	
Miners and ex-miners	No.	39	115	86	19	19	278
	Dead	11	30	10	5	6	62
	(%)	(28)	(26)	(12)	(26)	(32)	(22)
Non-miners	No.	30	111	93	17	14	265
	Dead	4	23	15	2	1	45
	(%)	(13)	(21)	(16)	(12)	(7)	(17)
Total	No.	69	226	179	36	33	543
	Dead	15	53	25	7	7	107
	(%)	(22)	(23)	(14)	(19)	(21)	(20)
Women	No.	30	74	51	9	16	180
	Dead	8	13	12	1	6	40
	(%)	(27)	(18)	(24)	(11)	(38)	(22)

Table 59 Serum Vitamin B_{12} Concentrations (in pg/ml) in 1958 and in 408 Subjects Seen in Both 1958 and 1968 (standard deviations given in parentheses) (2937)

Age group (in 1958)	*Group*	*All subjects*		*Results for both 1958 and 1968*			
		No.	*Mean 1958*	*No.*	*Mean 1958*	*Mean 1968*	*Correlation coefficient 'r'*
35–44	Miners	87	264	78	253 (138)	209 (110)	0.69
	Non-miners	82	280	79	279 (126)	354 (133)	0.69
45–54	Miners	88	265	58	256 (114)	307 (109)	0.58
	Non-miners	84	237	63	229 (83)	295 (87)	0.70
55–64	Miners	83	229	50	223 (115)	250 (105)	0.71
	Non-miners	85	264	49	253 (153)	281 (127)	0.49
55–64	Women	164	249	104	224 (124)	268 (118)	0.46

Table 60. Comparison of Serum Vitamin B_{12} Concentrations (in pg/ml) in 104 Women (aged 55-64 yr in 1958) Who Had Estimations in Both 1958 and 1968 (2937)

Concentration in 1968	Concentration in 1958					Total (1968)
	0-	100-	200-	300-	400-	
0-	2	2	0	0	0	4
100-	3	10	10	0	1	24
200-	0	17	21	4	0	42
300-	0	1	12	7	4	24
400-	0	1	2	2	5	10
Total (1958)	5	31	45	13	10	104

Correlation coefficient r is 0.46.

Table 61 Subjects with Low Serum Vitamin B_{12} Concentration (less than 100 pg/ml) on at Least Four Occasions and Circulating Haemoglobin Level (g/100 ml) in 1968 (2937)

Sex	Age (yr) 1958	Serum vitamin B_{12} concentration					Haemoglobin 1968
		1958	1961	1965	1967	1968	
M	61	29	83	37	52	48	13.5
M	49	39	97	92	91	151	16.1
M	57	51	49	126	80	47	14.8
M	6[illegible]	64	118	93	82	82	16.7
M	3[illegible]	70	49	35	46	61	14.4
F	6[illegible]	71	92	93	76	98	14.8
M	60	92	113	52	66	59	15.7
M	42	97	122	97	98	95	15.5

M = male, F = female.

Table 62. Number of Serum Vitamin B_{12} Concentrations Estimated and the Number with Levels of 100 pg/ml or Less (percentages in parentheses) (2937)

Age group (in 1958)	Group	1958		1968	
		No. of estimations	No. with 100 pg/ml or less	No. of estimations	No. with 100 pg/ml or less
35–44	Miners	87	2 (2.3)	80	2 (2.5)
	Non-miners	82	2 (2.4)	80	2 (2.5)
45–54	Miners	88	2 (2.3)	65	1 (1.5)
	Non-miners	84	3 (3.6)	66	1 (1.5)
55–64	Miners	83	7 (8.4)	55	5 (9.2)
	Non-miners	85	7 (8.2)	55	3 (5.5)
55–64	Women	164	11 (6.7)	113	5 (4.4)

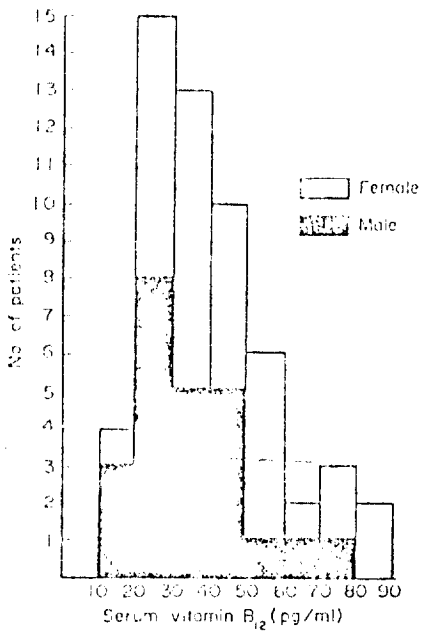


Figure 32. The Presenting Serum Vitamin B_{12} Levels in 55 Patients Diagnosed as Pernicious Anemia Over a 4-Year Period (2937)

In 1972 Adams et al. (0025) found, in 22 patients with pernicious anemia, using Co^{57}- and Co^{58}-B_{12} and labeled coenzyme-B_{12} (photolysis avoided) with whole-body monitoring, that the serum/body B_{12} ratio was less in the patients than in controls, and the serum level was also less. Post-treatment data suggested that megaloblastosis started when the serum B_{12} was 70-154 pg/ml, or usually when the body B_{12} was 100-660 μg, but the serum level was more decisive. Abnormal peripheral blood films were probable for megaloblastosis, but normal films no guide; thus marrow abnormalities probably developed first.

The authors concluded that two mechanisms regulated serum/body B_{12} balance, both folate-requiring: one mechanism should release B_{12} from stores to plasma, and the other should clear B_{12} from plasma.

(k) Various Formulations of B_{12}

In 1960 Sobell et al. (2580) gave B_{12} to four dogs i.m. in water, and to another four in a "depot" lipid formulation. Serum B_{12} levels remained high for three times longer after the lipid injection than after the water, and the levels themselves were two-to-three times higher. When two beagles and two rhesus monkeys were given the depot preparation at 15 μg/kg for 170 days (two injections/week, 46 in all), no changes were observed at the injection sites, or in the blood counts, hemoglobins, and hematocrits.

In 1966 Glass et al. (0983), searching for a cobalamin equivalent to B_{12} at hemopoiesis but more stable in the body, gave hydroxocobalamin 1 mg i.m. alternate days for 10 days (six injections) to 15 patients with initial serum B_{12} 185 pg/ml (range 81-242), and they observed serum B_{12} levels for 6-15 months. At six months all levels were over three times the initial values. In 12 patients observed at 10 months, levels were still double the initial values ($P = 0.001$). In seven of 11 observed at 15 months, levels were still above the initial values. The authors concluded: "No comparable results were ever reported with cyanocobalamin therapy."

In 1968 Schwartz and Bastrup-Madsen (2451) studied patients treated with a new, retarded-effect B_{12} preparation containing 1 mg cyanocobalamin tannate in aluminum-monostearate-sesame oil gel. The Tables 63-64 and Figure 33 show that serum B_{12} values became and remained very high, because of the capacity to bind to a γ-globulin, considered by the authors to be an antibody. They commented

that they found the data hard to evaluate; although pernicious anemia patients treated with the new compound became well and in full hematological remission over long periods, they could not "say whether the presence of the very large amounts of Vitamin B_{12} bound to a γ-globulin should be considered an advantage to the patient -- or the opposite."

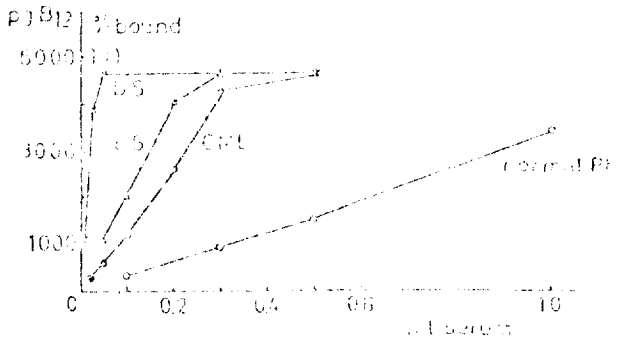


Figure 33. Vitamin B_{12} Binding Capacity in Two Patients with P.A. with Very High Serum B_{12} Values (D.S. and E.S.), One Patient with CML and a Normal Person. The Figure Shows the B_{12}-binding Capacity of Increasing Amounts of Serum Following Exposure to 5000 pg B_{12} (2451).

In 1969 Linnell et al. (1647) studied the cobalamins contributing to total plasma B_{12} in 35 control subjects and 14 patients with untreated pernicious anemia. Tables 65 and 66 show that cyanocobalamin was seldom present except after its administration, and that in normal subjects hydroxo- and methyl-B_{12} were evenly balanced. The shift toward methyl-B_{12} in B_{12} deficiency was stated by the authors to be at variance with findings by other workers.

Further studies by this group in 1971 (0584) led the authors to suggest that methylcobalamin in plasma might be more labile than B_{12}-coenzyme. The coenzyme/methyl-B_{12} ratio in breast milk was higher than in the corresponding plasma, and the coenzyme was preponderant in fresh cows' milk; dried milk contained only hydroxo- and a little cyano-B_{12}. The authors commented that breast milk supplied an infant with B_{12} in a more readily utilizable form than did formula milks.

Table 63. Serum Vitamin B_{12} Values in a P.A. Patient During Oral Treatment and Following Treatment with Betolvex (1 mg Cyanocobalamin in Aluminum-Monostearate Sesame Oil Gel Every Second Month) (2451)

Two values are given for each year

Year	Serum B_{12} pg/ml	Treatment
1959	246 298	
1960	141 427	Oral (IF + B_{12} preparation)
1961	160 314	
1962	450 4,450	
1963	8,500 85,000	
1964	92,000 114,000	Betolvex®
1965	34,000 100,000	
1966	24,800 30,000	
1967	23,600	

Table 64. Serum Vitamin B_{12} Values and Vitamin B_{12}-binding Capacity (unbound binding capacity) in 41 Normal Persons, 4 Patients with Chronic Myeloid Leukaemia and 4 P.A. Patients with High B_{12} Values Following Treatment with Betolvex (2451)

	Serum vitamin B_{12} values (pg B_{12}/ml serum)	Vitamin B_{12} binding capacity (pg B_{12}/ml serum)
41 normal persons (donors)	200–800	900–2,400
Chronic myeloid leukaemia	6,960 5,460 6,800 6,100	4,300 3,620 6,550 7,650
P.A. patients treated with Betolvex	90,000 38,000 11,100 64,000	105,000 21,200 5,900 33,600

Table 65. Results in Normal Subjects and Hospital Controls (1647)

	Age	Sex	Total Plasma B_{12} (μμg/ml)	Smoking Habits (cigarettes/day)	Plasma Cobalamins		
					$OH\text{-}B_{12}$	$CN\text{-}B_{12}$	$Me\text{-}B_{12}$
Normal Subjects							
1	34	M	470	Nil	+++	0	+++
2	32	M	505	Nil	+++	0	+++
3	22	F	380	Nil	+++	0	+++
4	35	M	625	Nil	+++	0	++
5	21	F	250	Nil	+++	±	+++
6	21	M	270	Nil	++	+	+++
7	25	F	450	Nil	++	0	+++
8	24	F	375	Nil	++	0	+++
9	27	M	345	Nil	++	0	+++
10	30	M	415	Nil	+	0	+++
11	30	F	375	Nil	++	+	+++
12	23	F	—	Nil	++	0	+++
13	26	F	490	Nil	+++	0	++
14	30	M	510	Nil	+++	0	+++
15	40	M	550	40/day	+++	0	+++
16	26	F	415	10/day	+++	+	++
17	47	M	300	10/day	+++	+	++
18	32	M	—	15/day	±±	0	+++
19	52	M	380	20/day	+++	+	++
20	26	F	265	10/day	+++	0	+++
Hospital Controls							
1	48	F	—	Nil	+++	0	+++
2	55	F	415	Nil	+++	0	+++
3	62	M	365	Nil	++	0	+++
4	78	M	—	Nil	+++	+	++
5	60	F	540	Nil	+++	+	+++
6	43	M	265	Nil	+++	0	+++
7	40	F	320	Nil	+++	0	+++
8	63	M	575	10/day	+++	±	++
9	65	F	525	5/day	+++	0	+++
10	42	M	430	5/day	++	0	++
11	58	F	630	10/day	+++	+	++
12	44	M	455	15/day	+++	±	+++
13	65	M	615	5/day	+++	±	+++
14	67	M	530	50/day	+++	0	+++
15	59	M	285	5/day	+	0	+++

Table 66. Results in Patients with Pernicious Anemia and in Vegans (1647)

	Diagnosis	Age	Sex	Total Plasma B_{12} (μμg/ml)	Hb (g/100 ml)	Serum Folate (mμg/ml)	Smoking Habits (cigarettes/day)	Plasma Cobalamins		
								$OH\text{-}B_{12}$	$CN\text{-}B_{12}$	$Me\text{-}B_{12}$
Patients										
1	Untreated pernicious anaemia	71	F	75	13·8	21	Nil	+++	0	0
2	Untreated pernicious anaemia	77	F	68	8·7	8·0	—	+++	0	0
3	Untreated pernicious anaemia	85	F	65	10·4	3·0	Nil	+++	0	+
4	Untreated pernicious anaemia	67	F	150	6·2	1·2	Nil	+++	+	+
5	Untreated pernicious anaemia	75	F	50	7·3	4·2	10/day	+++	0	+
6	Untreated pernicious anaemia	65	F	30	4·9	6·4	Nil	+++	0	0
7	Subacute combined degeneration of the cord	69	F	30	12·5	—	Nil	+++	++	++
8	Untreated pernicious anaemia	80	F	65	7·8	—	—	+++	0	++
9	Untreated pernicious anaemia	71	F	35	7·4	—	Nil	+++	0	++
10	Untreated pernicious anaemia	63	F	75	7·7	4·7	—	+++	0	±
11	Subacute combined degeneration of the cord	68	F	50	7·8	11·0	Nil	+++	+	±
12	Untreated pernicious anaemia	46	F	100	11·5	8·4	8/day	+++	++	++
13	Untreated pernicious anaemia	62	F	80	5·0	2·9	Nil	+++	+	+
14	Untreated pernicious anaemia	71	F	80	7·7	>25	Nil	+++	+	+
Pernicious Anaemia Cases										
15	One hr after 1 mg $CN\text{-}B_{12}$	—	F	>1,000	8·0	2·0	—	++	+++	+
16	Six days after 4 mg $CN\text{-}B_{12}$	67	F	>1,000	11·4	6·8	—	+	+++	+
Vegans										
17	B_{12}-supplemented diet	33	M	380	14·0	>32	Nil	++++	0	++++
18	B_{12}-supplemented diet	31	F	300	13·6	>16	Nil	++	±	++++
19	B_{12}-supplemented diet	64	M	455	13·6	14	Nil	++	0	++++
20	Diet not B_{12}-supplemented	46	M	100	11·0	>2·5	Nil	+++	0	0

146

III. Metabolism and Excretion

Metabolism and excretion are discussed separately. Much of the metabolism has been discussed already in the sections on Absorption and Distribution. Some cases of practical B_{12} deficiency due to specific failures or defects in metabolic pathways will be discussed. Other cases will be discussed in the sections on Metabolic Effects and on Drug Interactions.

A. Metabolism

In 1949 Brink and Folkers (0361) characterized by analysis and synthesis a new basic degradation product of B_{12}, 5,6-dimethylbenzimidazole, noting that its 1,2-diamino-4,5-dimethylbenzene moiety also appeared in riboflavin. However, 5,6-dimethylbenzimidazole itself was not recovered when riboflavin was hydrolyzed under the same conditions.

In 1955 Kuehl et al. (1529) characterized DL-3,3-dimethyl-2,5-dioxo-4-hydroxypyrrolidine-4-propionic acid lactone, and DL-3,3-dimethyl-2,5-dioxypyrrolidine-4-propionic acid as degradation products of B_{12}, with structures as in Figures 34 and 35.

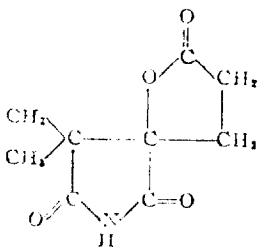


Figure 34. DL-3,3-dimethyl-2,5-dioxo-4-hydroxypyrrolidine-4-propionic acid lactone (1529)

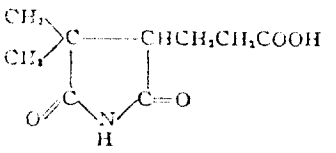


Figure 35. DL-3,3-dimethyl-2,5-dioxypyrrolidine-4-propionic acid (1529)

In 1958 Barker *et al.* (0175) isolated from *Clostridium tetanomorphum* a B_{12} derivative that acted as a coenzyme for conversion of glutamate to β-methylaspartate. By 1960 the same team (0176) had described the purification of three B_{12}-derived coenzymes from different micro-organisms: adenylcobamide, benzimidazoleylcobamide, and 5,6-dimethylbenzimidazolylcobamide. All of these were coenzymes for conversion of glutamate to β-methylaspartate, and in each case one mole of adenine had been added *in vivo* to the original cobamide vitamin.

By 1965, when Weissbach and Dickerman (2953) reviewed progress in B_{12} coenzyme biochemistry, x-ray crystallography by Hodgkin's team had revealed the structure of deoxyadenosyl-B_{12}, which had also been synthesized.

By 1966, according to Huennekens (1279), a second B_{12} coenzyme, methyl-B_{12}, had also been characterized and synthesized.

In 1968 Weissbach and Taylor (2955) reviewed the metabolism of B_{12} to its coenzyme 5'-deoxyadenosyl-B_{12}. Light-sensitive synthesis of the carbon-to-cobalt bond *in vitro* was as shown in Figure 36; enzymatic synthesis of the carbon-to-cobalt bond is summarized in Figure 37.

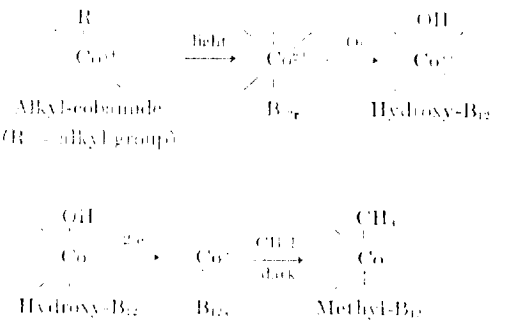


Figure 36. Light-sensitive Synthesis of the Carbon-to-Cobalt Bond *in vitro* (2955)

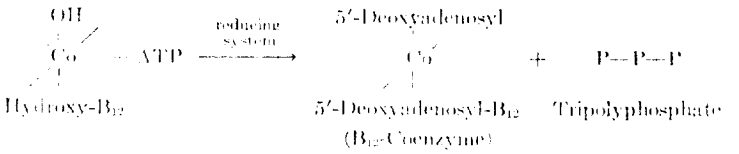


Figure 37. Enzymatic Synthesis of the Carbon-to-Cobalt Bond (2955)

The complete structure of the coenzyme as elucidated in 1961 by Lenhert and Hodgkin is shown in Figure 38.

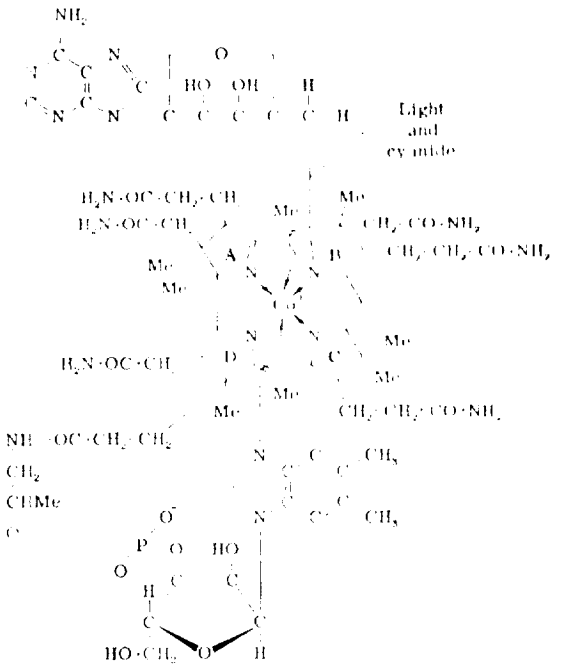


Figure 38. Structure of B_{12}-coenzyme (5'-deoxyadenosyl-B_{12}) (2955)

In 1969 Mudd et al. (1916) reported the death of a male infant with multiple biochemical anomalies including failure to convert B_{12} to coenzyme-B_{12} (high urinary methylmalonate, normal serum B_{12}, no demonstrable coenzyme).

In 1969 Akhtar (0037) proposed a mechanism, in theory, to account for the biochemical roles of the B_{12} coenzymes 5'-deoxyadenosyl-B_{12} and methyl-B_{12}. He suggested that the cobalt-carbon bond might dissociate into two reactive species, a highly reduced cobalt and a carbonium ion. He applied his theory illustratively to the conversion of 1,2-propanediol to propionaldehyde, the ribonucleotide reductase reaction, and methionine biosynthesis.

In 1971 Peters et al. (2134) studied the metabolism of B_{12} during its absorption by the guinea-pig. Hartley guinea-pigs, 350-450 g, were fasted and fed 10 ng of Co^{57}-B_{12}, 80-120 μCi/μg, and were dissected after half to 24 hour intervals;

all work was in the dark. Chromatographic and densitometric procedures were used. In ileal mucosa, ileal mitochondria, liver, and portal plasma, 5'-deoxyadenosylcobalamin was found in largest amounts, an unidentified cobalamin next, methylcobalamin in small amounts in ileal mucosa, liver, and portal plasma, and cyanocobalamin only in liver. The ileum converted part of the cyanocobalamin to 5'-deoxyadenosylcobalamin, probably in the epithelial mitochondria, but enough cyanocobalamin entered the portal plasma without conversion to indicate that metabolism was not the only reason for attraction of B_{12} to the mitochondria during absorption.

B. Excretion

Reports of excretion of B_{12} mainly concern:

1. Physiological excretion in the bile.
2. Pharmacological excretion in the urine.

Urinary excretion following a large excessive oral dose is measured to estimate a person's ability to absorb and excrete, with the object of estimating absorption. See Assay section.

Excretion data are also used in balance experiments to measure retention, discussed in the present section.

Bile excretion data and fecal data are reported as measures of enterohepatic recirculation, that is, conservation of B_{12}. Fecal losses of B_{12} are therefore discussed as losses taken into account in estimating RDA (see Consumer Exposure section).

This position was arrived at gradually during many years of research.

In 1950 Chow et al. (0518) gave B_{12} to rats orally, and found none in the urine until the dose was at least 270 μg/300 g rat, and then only minor amounts. But crystalline B_{12} s.c. was virtually all found in the urine. The authors commented that since absorption and utilization of B_{12} had been demonstrated, it was not contradicted by failure of oral B_{12} to appear in the urine.

In 1951 Chow (0504) found in man that oral B_{12} over several months, or as a single dose of 5 g, failed to produce urinary B_{12}. Most of the oral B_{12} appeared in the feces, indicating poor absorption. B_{12} i.v. was recoverable from the urine, or, in other experiments, from the plasma, where it did not penetrate the rbc within 15 minutes. In clinical experiments B_{12} injected into infants fed a

soy protein diet did not increase their retention of nitrogen, but both healthy and chronically ill children gained more weight than controls when their diets were B_{12}-supplemented. The authors cautioned that the last-mentioned study was not definitive.

In 1952 Lang et al. (1565) gave pure B_{12} i.m. to healthy male subjects in doses of 20, 30, 50 or 75 μg, and assayed their urines. They concluded that more than 50 μg/day were retained, depending on the dose.

In 1958 Grasbeck et al. (1039) administered single doses of Co^{56}-B_{12} to human subjects and observed the excretion patterns in Figure 38. The difference between fecal and biliary excretions was interpreted as showing reabsorption. The authors concluded that if uniform mixing of label with body B_{12} stores were assumed, losses and requirements might be larger than hitherto suspected.

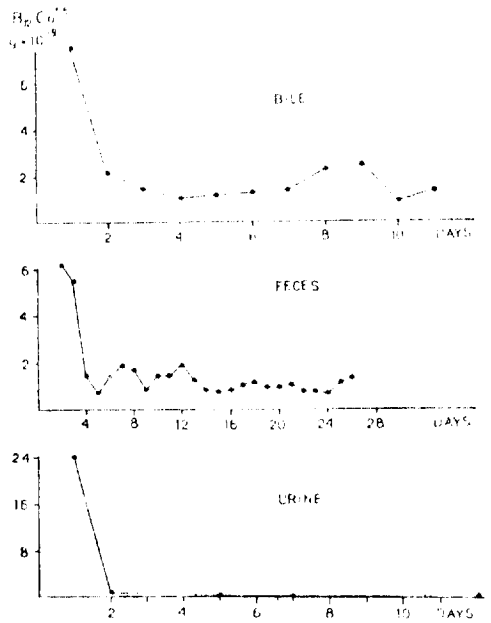


Figure 38. Difference between early (1-4th day) and late (4th-30th day) period after parenteral administration of Vitamin B_{12}-Co^{56} as regards the pattern of radiovitamin excretion in 3 cases. Regarding excretion in the bile and urine, those cases were chosen in which the largest number of samples were obtained. As regards fecal excretion, the case was chosen at random. There was considerable day-to-day variation, probably explained by differences in frequency of defecation and quantity of stools passed on different days. The curve represents successive mean values. (1039)

In 1959 Gaffney et al. (0905) amplified the Schilling test, measuring urinary label 12, 24, and 48 hours after 2, 8, 50, or 250 μg of Co^{60}-B_{12} given by mouth to a total of 148 healthy men aged 20-92, and flushed two hours later with 1000 μg stable B_{12} i.m. As doses increased, total excretion rose faster than specific radioactivity. Age differences were not expected at these high dose levels, and none were seen.

In 1961 Feeley and Moyer (0817) studied the B_{12} intake of 23 healthy girls aged 7-9, each given one of six controlled diets. Diets supplying 48-88 g/day total (65% animal) protein supplied 3.9-4.5 μg/day of B_{12}; those with 18-22 g/day total (40% animal) protein supplied 0.7-1.1 μg/day of B_{12}. Girls on the latter diet excreted 9% of their B_{12} intakes at the start, and 3-4% later. Diets of ordinary foods that supplied the RDA for children aged 7-9, supplied "about" 4 μg/day of B_{12}.

In 1961 Stokes (2653) used Co^{56}-B_{12} to study the possibility of enterohepatic circulation of B_{12} in the rat, by chromatography of cannulated bile. They reported that three-fourths of the label in bile was attached to B_{12} and one-fourth to B_{12} analogs, at least two in number. They inferred that fecal B_{12} determinations represented analogs, and that reabsorption of such analogs would be incomplete, because absorption had been shown to be specific to the benzimidazole group of cyanocobalamin.

In 1962 Matthews and Beckett (1781) found abnormally high serum B_{12} levels in 14 or 32 patients with renal failure. Excretions of labeled B_{12} did not correlate with serum levels in individuals, and the authors queried the relevance of tests employing unphysiological doses. Nevertheless they concluded that renal failure was among the possible causes of high serum B_{12}.

In 1963 Hift and Adams (1221) measured urinary excretion of B_{12} in 16 African and Indian patients with folate-deficiency megaloblastic anemia, at Durban, South Africa. Mean excretion was 6.5% of the dose compared with 20.3% in controls.

In 1964 Hall (1106) studied the excretion of B_{12} by eight subjects described as controls. They were cardiovascular patients aged 65-90, with normal plasma B_{12} determinations. They received an average 1.0 μg Co^{57}-B_{12}, three by mouth, four i.v., one i.m. Radioactivity was measured in blood, urine, and feces, and total B_{12} was bioassayed microbiologically, for 70 to over 500 days after the single dose.

1. Radioactivity disappeared from plasma rapidly for 70 days, and then linearly with half-time average 690 days.
2. Urine radioactivity in all cases decreased to a uniform rate after a few days, and then was 0.28% of the retained dose/day.
3. Fecal radioactivity after an i.v. dose took a month to become uniform, a week after the other routes, and then was 0.031% of the retained dose/day.
4. The calculated total daily excretion of B_{12} was 1.3 (0.66-2.1) ug/day, and microbioassay suggested that only 10% of urinary B_{12} was "in an active form".

In 1968 Schiffer et al. (2422) measured the rates of disappearance of Co^{60}-labeled cyano- and hydroxo-cobalamins with and without unlabeled B_{12}, in patients monitored by whole-body counting. Biologic half-lives of the two analogs were similar. Large, but not small, doses of unlabeled B_{12} decreased the biologic half-life of the label, and large doses of each labeled analog decreased the biologic half-life of the other.

In 1968 Boddy and Adams (0301) defended the assumption that B_{12} label was rapidly equilibrated with unlabeled B_{12} in the body distribution. They stated that whole-body monitoring, and clinical data, agreed with excretion rates calculated on the assumption that B_{12} was equilibrated; contrary findings were attributed to pooling of data from different individuals, and such data were stated to underestimate true excretion rates.

In 1968 the same authors (0302) studied the excretion of cobalamins and coenzyme B_{12} by one normal volunteer and 13 patients with megaloblastic marrows, all given 5 mg i.v. or 10 mg i.m. of labeled cyano- or hydroxocobalamin, or coenzyme-B_{12}. Whole-body monitoring was continued up to 488 days. After 4-8 weeks the excretion rates became constant, and no significant differences were reported between patients or between forms of B_{12}.

Toxicity was not a topic of this report.

In 1969 Loehry and Creamer (1669) gave adult male rats Co^{58}-B_{12} i.v. or i.p. and measured the excretion of label into the lumen of the small intestine. They found an immediate peak, thought to reflect exudation of plasma into the lumen, and a 36-48 hour phase reflecting desquamation due to cell turnover (they

cited similar findings with Fe^{59}). The authors suggested that this, combined with failure of reabsorption, might be partly responsible for B_{12} deficiency in malabsorption syndromes.

In 1970 Donaldson and Lascelles (0707) found significantly raised urinary excretion of B_{12} label (Schilling test) in five patients with pituitary insufficiency. They also found, differently from some others, no significant differences in the urine or serum values of ten folate-deficient patients on anticonvulsant therapy, as well as finding expected pernicious anemia values. The data are shown in Tables 67 - 71.

Group	*Number of Patients*	*Urine Values*	*Number of Patients*	*Serum Values*
Ten normal controls and part 2 Schilling tests on patients with pernicious anaemia	11	$0{\cdot}50 > P > 0{\cdot}40$	12	$0{\cdot}95 > P > 0{\cdot}90$
Ten normal controls and part 1 Schilling tests on patients with hypopituitarism	5	$0{\cdot}01 > P > 0{\cdot}001$	5	$0{\cdot}20 > P > 0{\cdot}10$
Ten normal controls and part 1 Schilling tests on epileptic patients with folate deficiency on anticonvulsant drugs	12	$0{\cdot}70 > P > 0{\cdot}60$	11	$0{\cdot}60 > P > 0{\cdot}50$
Ten normal controls and part 1 Schilling tests on gastrectomy patients	7	$0{\cdot}01 > P > 0{\cdot}001$	7	$0{\cdot}20 > P > 0{\cdot}10$

Table 67. Significance Between Results in Different Groups (0707)

Patient	*Sex*	*Haemoglobin Level (g/100 ml)*	*Serum Vitamin B_{12} Level (μμg/ml)*	*Schilling Test*			
				Part 1		*Part 2*	
				24-Hour Urine Excretion (% of dose administered)	*Eight-hour Serum Level (% of dose/l)*	*24-Hour Urine Excretion (% of dose)*	*Eight-hour Serum Level (% of dose/l)*
M.C.	F	12·2	65	2·4	—	25·0	1·65
D.T.	F	5·8	95	0·8	0·00	—	0·20
B.F.	M	14·1	130	1·3	0·11	12·2	1·08
A.F.	M	10·5	67	2·1	0·00	17·5	0·74
B.M.	F	10·0	80	1·1	0·00	12·6	1·22
G.G.	F	11·9	81	1·7	0·20	11·6	1·58
T.L.	M	12·2	—	2·4	0·18	21·3	0·84
J.S.	F	13·0	150	2·7	0·26	11·3	0·99
E.T.	F	12·6	30	0·6	0·01	20·8	0·95
E.N.	F	7·9	56	0·5	0·04	11·7	0·88
M.E.	F	11·4	130	2·2	0·18	21·6	1·11
W.C.	F	12·8	—	0·4	0·00	14·0	1·22
Mean				1·5	0·09	16·4	1·07
SD				0·8	0·09	5·2	0·39
Normal mean				18·1	1·05	—	—
SD				3·8	0·25		

Table 68. Results of Schilling Tests on Patients with Pernicious Anemia (0707)

Table 69. Results of Part I Schilling Tests on Patients with Hypopituitarism (0707)

Patient	*Sex*	*24-Hour Urine Excretion (% of dose administered)*	*Eight-hour Serum Level (% of dose administered/l)*
W.M.	M	31·5	1·03
J.C.	M	21·2	2·67
V.T.	F	23·9	1·70
S.S.	M	29·6	1·07
P.C.	M	20·5	0·81
Mean		25·3	1·46
SD		5·0	0·76

Table 70. Results of Part I Schilling Tests on Folate-Deficient Epileptic Patients on Anticonvulsant Drugs (0707)

Patient	*Sex*	*Hb Level (g/100 ml)*	*Serum Folate Level (mug/ml)*	*24-Hour Urine Excretion (% of dose)*	*Eight-hour Serum Level (% of dose/l)*
D.T.	M	14·9	1·8	32·2	0·84
A.R.	M	13·2	2·9	19·6	0·93
S.P.	F	13·2	1·4	27·2	1·80
P.K.	M	14·4	3·0	5·3	0·47
F.R.	F	13·2	1·8	12·0	0·53
J.S.	F	5·8	3·0	10·0	0·60
J.W.	M	13·0	1·9	33·0	1·28
J.M.	M	14·1	2·0	12·9	1·43
J.U.	F	12·6	3·6	28·9	—
M.B.	F	7·4	1·8	14·6	2·91
Mean				19·0	1·18
SD				9·7	0·72

Table 71. Results of Schilling Tests on Patients Following Partial Gastrectomy (0707)

Patient	*Age (yr)*	*Sex*	*Hb Level (g/100 ml)*	*Serum Vitamin B_{12} (μμg/ml)*	*Time since Gastrectomy (yr)*	*Diagnosis*	*Schilling Test*			
							Part 1		*Part 2*	
							24-Hour Urine Excretion (% of dose)	*Eight-hour Serum Level (% of dose/l)*	*24-Hour Urine Excretion (% of dose)*	*Eight-hour Serum Level (% of dose/l)*
V.R.	60	M	12·6	160	6	DU	6·0	0·68	9·6	1·06
R.S.	54	M	12·6	190	14	PU	7·5	0·66	16·2	1·00
W.C.	67	M	14·5	517	2	DU	16·1	0·83	10·5	0·66
									10·0	0·58
A.W.	62	M	13·0	—	14	DU	17·0	1·00	10·4	0·58
J.McS.	58	M	12·3	650	10	DU	14·2	1·39	10·5	1·22
A.B.	69	F	12·1	544	1	PU	3·6	0·50	9·2	0·85
R.D.	46	M	11·8	330	1	DU	11·2	0·70	—	—
Mean							10·8	0·83	11·1	0·89
SD							5·2	0·30	2·6	0·24

DU = duodenal ulcer
PU = peptic ulcer

In 1973 Cooper and Dirks (0557) investigated the passage of B_{12} and dog or human transcobalamin II across the renal glomerulus of the dog. The human glomerular pore size had been calculated as 24 Å, and the Stokes radius of the transcobalamin II-B_{12} complex as 25.5±0.6 Å. When labeled B_{12} alone was injected i.v., fluid from the proximal convoluted tubule contained no measurable label. When a large dose of unlabeled B_{12} was injected first, label appeared in the fluid. The authors concluded that transcobalamin II did not cross the dog glomerulus, and that it circulated as a complex with a Stokes radius larger than that of the transcobalamin II monomer.

IV. Metabolic Effects

In 1973 Herbert (1015) reviewed current knowledge of the metabolic functions of B_{12}, adding fresh observations, as follows:

1. B_{12} and folate were needed together for synthesis of thymidylate and thereby DNA. A B_{12}-containing enzyme accepted a $-CH_3$ from methylfolate and released it to homocysteine (methylhomocysteine is methionine), as a step in regeneration of tetrahydrofolic acid, the precursor of 5,10-methylenetetrahydrofolic acid that was involved in thymidylate synthesis. Then megaloblastosis was a general nonspecific effect of deranged DNA synthesis resulting in arrest of the S (synthesis) phase of cell replication, and was seen most readily in the continually replicating cells of the bone marrow. Thus B_{12} and folate both were needed for any growth involving cell replication. B_{12} also assisted in the uptake of folate by rbc.
2. B_{12} alone was required for myelin synthesis, but the chemistry was still unknown; the author argued that it should concern either the lipid or the protein moiety of lipoproteins contributing to myelin. He reported his observation that B_{12}-deficient rich people had relatively severe neuropathy and mild hematopathy, while the severities were more equal in the poor; he attributed this difference to better diets with adequate folate that selectively retarded hematopathy. He stated that nerve axons were remyelinated from the cell body after B_{12} was given, at 0.1 mm/day.

   The roles of B_{12} in carbohydrate and fat metabolism followed partly from the action of coenzyme B_{12} in converting methylmalonate to succinate;

the author stated that there was not yet evidence to relate this action to the normal upkeep of myelin. Methionine was also involved in fat metabolism by enhancing the availability of the lipotropes choline and betaine, and, as an amino acid, contributed to protein synthesis.

3. A third action of B_{12}, less well defined, was concerned with reduction of SH groups that activated enzyme systems such as those which maintained the level of reduced glutathione in rbc and liver; B_{12} derivatives *in vitro* also catalyzed the nonenzymatic oxidation of SH derivatives.

Clinical Studies - Prior to 1973

(a) General

In 1951 Smith (2561) emphasized that little was known in detail about B_{12}. He suspected the following areas of activity that were to be supported in detail by later studies:

1. Transmethylation reactions, especially in methionine synthesis.
2. Reduction of sulfhydryl compounds.
3. Lipotropic reactions.
4. Protein metabolism.
5. Nucleic acid synthesis.

The nutritional effects of B_{12} had, according to the author, been confused by over-emphasis of its hemopoietic and neglect of its growth-promoting activities (later, opposite complaints were to be made 1279). He cited studies in chicks, which drew attention to the role of intestinal flora in B_{12} availability, and the author concluded that all B_{12} found in nature was of microbial origin. Deficiency in chicks and mice was produced easily enough for these animals to be used for bioassay purposes. Pigs, dogs, foxes, and mink had all been found to require B_{12}, but hamsters did not.

By 1965, when Weissbach and Dickerman (2953, see also page 137) reviewed knowledge of B_{12}-dependent metabolism, four such reactions were known, and three more were suspected:

1. Isomerization of glutamate to β-methylaspartate, in bacteria, known.
2. Isomerization of methylmalonyl CoA to succinyl CoA, in bacteria and animals, known.

3. The glycol dehydrase step in conversion of ethylene-glycol to acetaldehyde (or propylene-glycol to propionaldehyde), in bacteria, known.
4. In methionine synthesis, S-adenosylmethionine, a reducing system, and a cobamide-containing protein, were all required for transfer of methyl from N^5-methyl-folate-H_4 to homocysteine, in bacteria and animals, known.
5. Fermentation of lysine to acetate and butyrate, requirement for a B_{12} coenzyme suspected, in bacteria.
6. Reduction of ribonucleotides to deoxyribonucleotides in DNA formation, need for an unknown form of B_{12} suspected, in bacteria and possibly animals. In vitro, deoxyadenosyl-B_{12} was needed for reduction of cytidine-PO_4 to deoxycytidine-PO_4.
7. Stabilization of the enzyme for CO_2-pyruvate exchange under aerobic conditions, i.e., sulfhydryl reactions, by an unknown form of B_{12}, in bacteria and animals, suspected.

In 1966 Huennekens (1279) pointed out that the mechanisms of B_{12} coenzyme-dependent reactions remained speculative. Communication was required between clinicians, who had shown that the "paramount" importance of B_{12} was in production of blood cells, and biochemists, who tended to study the dependent reactions in other animal tissues and bacteria. The author stated that the reactions so far established did not account for the clinical effects of B_{12} deficiency on blood cells or nerve cells.

In 1968 Weissbach and Taylor (2955) summarized the reactions requiring 5'-deoxyadenosyl cobamide coenzymes as shown in Figure 39. In the third example in Figure 39, the conversion of propane-1,2-diol to propionaldehyde had been postulated as shown in Figure 40.

The authors described three methyltransferase reactions not requiring the coenzyme but instead, methyl-B_{12} was thought to serve as a protein-bound intermediate, shown in Figure 41.

In animal metabolism the authors (2955) proposed that B_{12} was required mainly for DNA synthesis during hemopoiesis, interacting with the role of H_4-folates as shown in Figure 42.

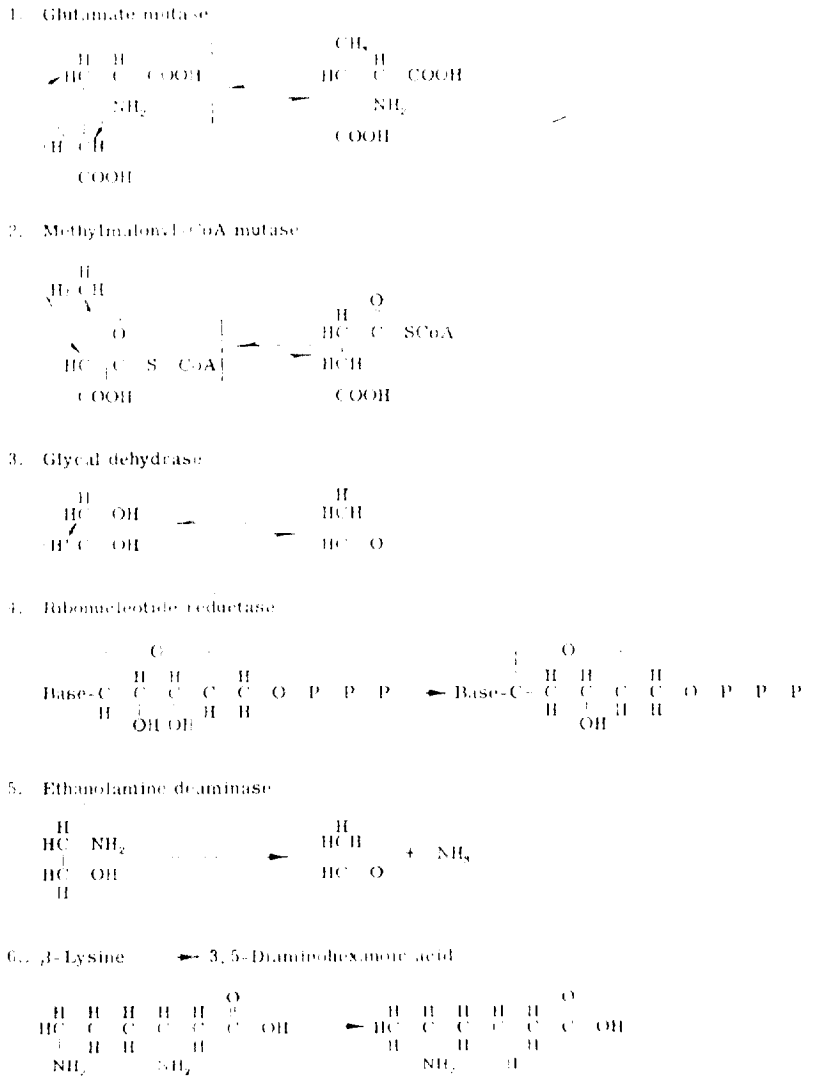


Figure 39. B_{12}-Coenzyme-dependent Reactions (2955)

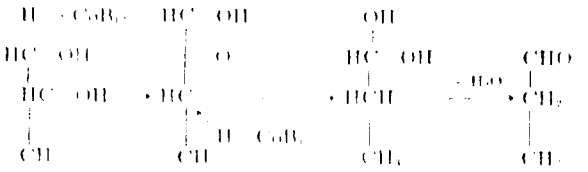


Figure 40. Conversion of Propane-1,2-diol to Propionaldehyde (2955)

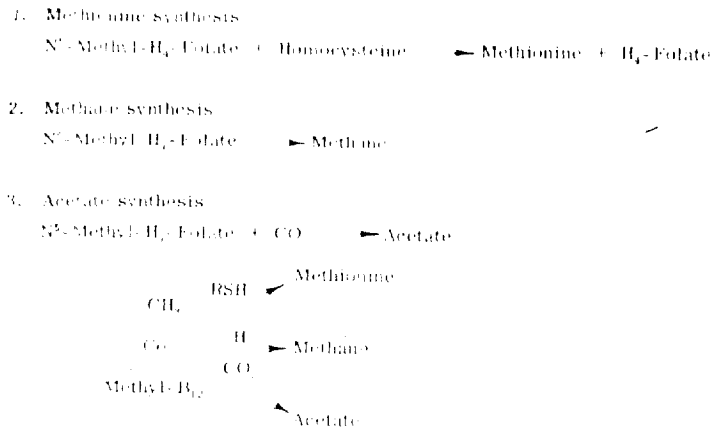
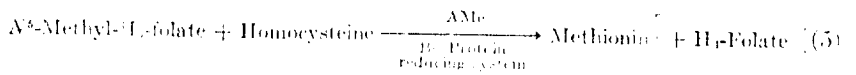
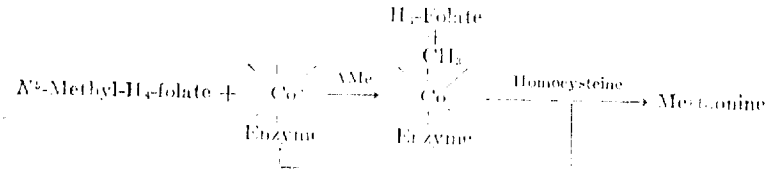
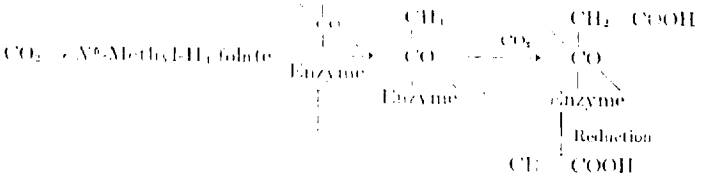


Figure 41. Cobamide-dependent Methyltransferase Reactions (2955)

Notes:

1. 

2. 

3. 

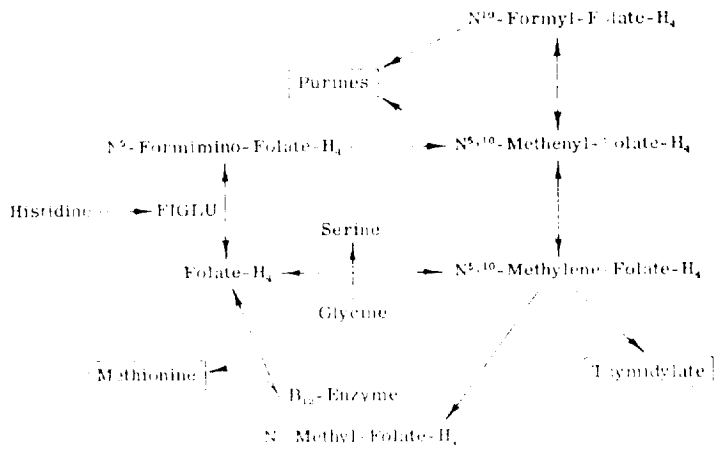


Figure 42. Metabolism of Folic Acid Derivatives (2955)

In 1968 Girdwood (0963) listed the practical causes of clinical B_{12} deficiency as:

1. Dietary deficiency, as in vegans (faddists who eat no animal products).
2. Lack of intrinsic factor, as in pernicious anemia, or after partial or total gastrectomy.
3. Malabsorption syndrome; dysfunction or removal of ileum.
4. Bacterial flora in small intestine, or tapeworms, that deprive the patient of B_{12}.

A major sign of B_{12} deficiency in man was increased urinary excretion of methylmalonate. Other suggested biochemical signs included aminoaciduria with taurine and excessive phenols.

Clinical results of B_{12} deficiency were mainly neurological, such as:

1. Peripheral neuropathy.
2. Posterior column degeneration.
3. Postero-lateral degeneration (characteristic of vegan diets).
4. Psychiatric disorders that responded to B_{12}.
5. Hemorrhagic retinopathy with visual impairment including color vision.

The author reviewed several series of patients with pernicious anemia in which the incidences of neuropathy varied from 12 to 100%.

Table 72. Vitamin B_{12} Levels in the Cerebrospinal Fluid of Seventeen Non-anemic Hospital Patients (0963)

Method of determination	Vitamin B_{12} concentration (pg/ml)								
Euglena gracilis	3	6	7	9	10	14	14	20	
Lactobacillus leichmannii	N	N	10	10	13	14	17	20	27

N, negligible.

The above values are only approximate since, particularly with L. leichmannii, it is not possible to measure such small concentrations with any degree of precision.

(b) Growth and Utilization of Diet

In 1953 Dammers (0608) reported trials involving 312 pigs fed rations with or without added B_{12}. The author concluded that growth was retarded when most animal protein in the pig ration was replaced by vegetable protein, and that B_{12} supplements partly reversed this effect; therefore, it could be considered as one component of the "animal protein factor" beneficial to young pigs. However, he also concluded that little benefit could be expected from adding B_{12} to rations currently used in the Netherlands.

In 1959 Yesair et al. (3074) found in B_{12}-deficient chick embryos, decreases of total phospholipids and of the lecithin, cephalin, and sphingomyelin fractions. Lecithin decreases were proportional to growth retardation; the other two fractions decreased more. Sphingosine decreased in proportion to growth retardation, and was judged not to be a limiting factor for sphingomyelin formation.

In 1959 Ralli et al. (2236) conducted a series of experiments with female rats, fed a 12% protein soymeal diet with either water or ethanol to drink, injected or not with 7.5 μg/day B_{12}, and pair-fed or ad libitum fed. B_{12} increased appetite and food utilization with or without ethanol, and produced lower liver fat and higher N with or without ethanol. Growth was better with B_{12} except in pair-fed rats. B_{12} did not affect total plasma proteins, albumin fraction, or adrenal weights; nor did it lower adrenal cholesterol when the rats were pair-fed.

(c) B_{12}-Deficiency from Vegan Diet

In 1963 Connor and Pirole (0550) described what they claimed to be the first

two cases of B_{12} deficiency among vegans reported in Australia. Both had normal B_{12} absorption and low serum B_{12}; one presented with anemia, the other with limb weakness. Serum folate was normal in the anemic patient, high in the other.

In 1969 Lampkin and Saunders (1558) reported a case of nutritional B_{12} deficiency in a male infant breast-fed by a mother without pernicious anemia but with low milk B_{12} attributed to near-vegan diet, despite vitamin supplements that included B_{12} 1 μg/day during pregnancy. The supplements were restricted to pregnancy, and the authors emphasized the importance of B_{12} supplements to vegetarian mothers; however, they pointed to several unusual features of this particular case.

(d) Experimental Anemias

In 1968 Stokstad (2655) reviewed experimental anemias in animals with reference to B_{12}, folic acid, and ascorbic acid.

1. Rats showed B_{12}-deficiency blood changes only if their dams also had been fed B_{12}-deficient diet. The author attributed this to dynamics of blood cell maturation.
2. Guinea-pigs showed megaloblastic anemia from dietary deficiency of B_{12}, folate, or both. Ascorbic acid deficiency produced non-megaloblastic anemia in some animals, and ascorbic acid supplementation did not affect induced megaloblastosis.
3. Chicks did not show blood changes from B_{12} deficiency alone, but B_{12} deficiency might lower the threshold for responses to other inducers of blood changes.
4. Ruminants given cobalt-deficient diets showed normocytic, normochromic anemia that responded to B_{12}, but not to folic acid.
5. Pigs fed B_{12}-deficient diets (necessitating vegetable protein) showed diminished growth but only moderate, normocytic anemia; then B_{12} produced a positive reticulocyte response that was unrelated to the presence or degree of anemia, and the author concluded that the hematology of B_{12} deficiency in pigs was not the same as in man.
6. Monkeys developed megaloblastic anemia from C-deficiency but not from B_{12}-deficiency, and responded to supplements of C but not B_{12}. Serum B_{12} levels, nevertheless responded to B_{12}, folic acid, or C.

The author commented that the complete hematological response of man to B_{12} could not be duplicated in any experimental animal.

(e) Nervous System Effects

In 1957 Schneider et al. (2435) found that the susceptibility of homozygous BSVS mice to acute disseminated encephalomyelitis, previously thought to be entirely genetic, was part-dependent on nutrition. Susceptibility was 100% on a stock diet, 15% on a semisynthetic diet with minimal vitamins added, and 70% when the latter was enriched with biotin, folate, and B_{12}, or B_{12} alone, or folate alone. No further change was seen when the amounts of B_{12} were increased ten-fold, and the authors speculated that the disease could have an immunological cause.

In 1958 Sobotka et al. (2584) determined B_{12} in serum and CSF of over 300 neurological patients; values were high in one-third of multiple sclerosis patients, and upper-normal in another third. Folic acid was high in four-fifths of the CSF's of the multiple sclerosis patients. The authors inferred that these values were "of etiological significance".

In 1961 Grann and Glass (1028) studied serum B_{12} and intestinal absorption of it in 21 patients with multiple sclerosis. According to microbioassay (serum) and double-label (hepatic uptake) data, no deficiency of B_{12} stores or absorption was discernible in these patients.

In 1963 Jenkins (1351) reported two cases of middle-aged White women who developed neuropathy after taking B_{12} orally for pernicious anemia; intrinsic factor was not mentioned among the described medications. The patients responded to parenteral B_{12}. The author commented, "The oral route is condemned."

In 1964 Simpson (2529) detected no significant difference of serum or CSF B_{12} or in the serum/CSF ratio, between a group of 46 patients with multiple sclerosis and 23 controls. Serum B_{12} was correlated with CSF B_{12}, but CSF protein and B_{12} values were not interrelated. Isolated patients with low serum B_{12} levels and multiple sclerosis were not statistically significant.

In 1968 McNicholl and Egan (1794) studied three Irish children (two were siblings) who developed megaloblastic anemia at about one year of age, and who lacked intrinsic factor according to Schilling tests and assays of gastric juice. The lack was presumed congenital. Growth retardation and acceleration

were related to B_{12} deficiency and treatment respectively. IQ of about 70 in each child was attributed to B_{12} deficiency effects on cerebral growth. The authors concluded that early diagnosis and treatment might prevent brain damage.

In 1969 Torres et al. (2777) studied 43 zoo monkeys fed standard diet and free from gastrointestinal lesions and parasitism. Neuropathology in the animals captive for 11 months to 19 years, and either treated or not with B_{12}, is shown in Table 73. Group I had been fed vegetarian diet without B_{12}; group II a vegetable diet, then B_{12} parenteral, then "normal" diet for 1-4 years; group III were recently captive and B_{12} supplemented. The authors interpreted their nerve damage data to random involvement of Schwann cells, not to selective distal axon degeneration. Since remyelination was observed in some B_{12}-deficient animals, the authors could no longer associate it significantly with B_{12} therapy. They concluded that the primary B_{12} deficiency was dietary.

Table 73. Incidence of Neurological Lesions in Groups I-III (2777)

Group (total No of animals)	Functional status		Histological findings						
	Normal	Paralysed	No. of animals with lesions	Distribution of lesions					
				Cerebrum	Cerebellum	Brain stem	Spinal cord	Posterior nerve roots and/or posterior root ganglia	Peripheral nerve (lower limbs)
I (12)	11	1	12	3	1	3	12	3	10
II (14)	10	4	13	2	1	1	11	6	11
III (17)	17	0	4 (slight)	0	0	0	2	1	3

The nerve roots and the posterior root ganglia were not examined in 2 cases in group I, neither was the brain-stem in one of these cases.

In 1970 Sullivan (2682) noted an absence of correlation in B_{12} deficiency in man, between neuropathology and amounts of urinary methylmalonate, but considered this might be partly due to inadequate analytical techniques. He discriminated between physiological excretion and excretion of "flushing" doses used for excretion tests.

He listed the causes of B_{12} deficiency as:

1. Lack of intrinsic factor, the immediate cause often being gastric atrophy; in children endocrine disorders could also be present.
2. Small bowel malabsorption.

The author systematized the diagnosis of B_{12} deficiency in Table 74 and the differences between children and adults in Table 75.

He recommended initial therapy with 50-100 μg B_{12} daily for 7-10 days, followed by 50-1000 μg monthly for maintenance, i.m., and either cyano- or hydroxocobalamin. He regarded oral B_{12} as still "experimental". In severe anemia with severe infection, requiring transfusion of packed rbc, venous pressure might rise, and simultaneous phlebotomy was recommended.

Further evidence on immune responses was reviewed. Of pernicious anemia patients 75% had antibodies to gastric parietal cells, and 50% to intrinsic factor. Some of the antibodies had been characterized, but there were conflicting interpretations of the data, and the relationships of these immune responses to pernicious anemia needed clarification.

In 1970 Osuntokun et al. (2086) gave 1 mg hydroxocobalamin, 5 mg riboflavin, or control (1 μg B_{12}) weekly or biweekly for 36 weeks in a double-blind design to a group of 80 patients with Nigerian ataxic neuropathy, a degenerative disorder considered to be related to cassava (high-starch rootstock) diet. Results were negative, but the authors commented that higher doses might have been needed with this high-cyanogen diet.

In 1970 Mahmud et al. (1716) reported the case of a 54-year-old nurse who was B_{12}-deficient but not anemic, with neuropathy typical of pernicious anemia, and paroxysmal positional vertigo, which responded to B_{12} therapy.

(f) Endocrine Effects

In 1953 Chow (0507) concluded that B_{12} was important for fat or carbohydrate metabolism, and less important for protein metabolism. Its retention by the adrenals suggested selective endocrine effects, further suggested by diminished retention of B_{12} by diabetics with retinopathy who excreted more free cortisone than usual. This situation could be normalized by giving the patients testosterone.

Table 74. Comparison of Congenital and Adult Pernicious Anemia (2682)

Type of Anemia	Age at Onset (Yrs.)	Familial Incidence	Gastric Acid Secretion	Instrinsic Factor Secretion	Gastric Mucosal Histology	Associated Endocrinopathy*	Intrinsic Factor Antibody	Parietal Cell Antibody
Congenital	½-16	Siblings	Present	Absent	Normal	Absent	Absent	Absent
Juvenile	10-18	Endocrinopathy in siblings	Absent	Absent	Atrophic	Present	Present	Present
Adult	>18	May occur in any relative	Absent	Absent	Atrophic	Present	Present	Present

*Hypoparathyroidism, hypothyroidism or Addison's disease.

Table 75. Symptoms, Signs and Laboratory Findings in Anemia Due to Vitamin B_{12} Deficiency (2682)

1. Nonspecific symptoms of anemia
   - Easy fatigability
   - Weakness
   - Headache
   - Palpitations
   - Syncope
   - Anorexia
2. Symptoms suggestive of B_{12} deficiency in anemic patients
   - Forgetfulness, irritability
   - Decreased ability to perform simple mathematical calculations
   - Paranoid ideation
   - Depression
   - Sore tongue
   - Paresthesiae
   - Difficulty walking
   - Diarrhea, constipation
3. Signs suggestive of B_{12} deficiency
   - Lemon-yellow cast of skin (pallor plus icterus)
   - Fever
   - Smooth tongue
   - Postural hypotension
   - Hepatomegaly
   - Splenomegaly
   - Increased pigmentation
   - Neurologic dysfunction
     - (a) Impaired mentation, delirium, paranoia
     - (b) Impaired vibratory sensation
     - (c) Impaired position sense
     - (d) Hyporeflexia, hyperreflexia
     - (e) Ataxia, spastic gait
4. Laboratory findings
   - Macrocytic anemia (MCV $> 100\ \mu^3$)
   - Hypersegmented neutrophils in peripheral blood (lobe average > 3.42)
   - Leukopenia
   - Thrombocytopenia especially in severe anemia (Hct < 20 vol. %)
   - Low serum vitamin B_{12} level (< 100 pg./ml.)
   - Elevated serum folate (in 20-35% of patients)
   - Elevated serum lactic dehydrogenase activity
   - Formiminoglutamic aciduria
   - Methylmalonic aciduria
   - Hyperbilirubinemia
   - Increased fecal sterocobilin
   - Elevated plasma iron, with increased saturation of transferrin
   - Accelerated plasma iron clearance, but impaired iron utilization by erythrocytes
   - Achylia gastrica
   - Absent intrinsic factor by in vitro assay of gastric juice

In 1962 Watson (2941) found in 30 consecutive patients at a sterility clinic, that abnormal sperm tended to have B_{12} concentrations less than the serum B_{12} (Figure 43).

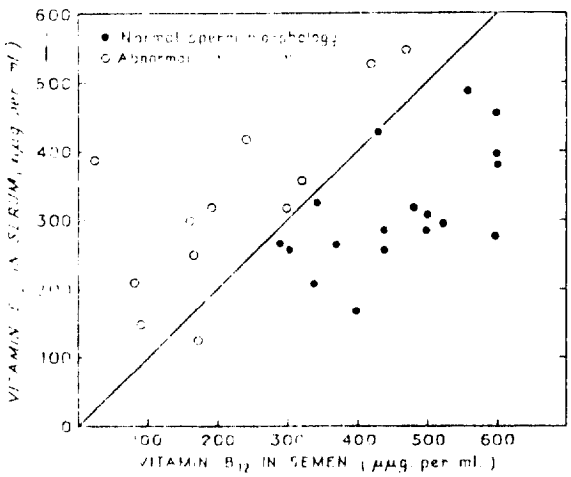


Figure 43. Vitamin B_{12} Levels in Semen and Serum (2941)

In 1968 Blair et al. (0290) reported two cases of improved fertility in men following B_{12} treatment in which other factors did not seem to be involved; hematology was normal throughout, no change in drinking/smoking habits, weekly semen samples through six weeks observation and six months therapy.

1. Baseline sperm count 3 million (range 1-16 million) per ml, complete necrospermia, 50% immature cells, 9% normal appearance. After B_{12}, 140 million average per ml, 80% motile, nil immature, over 50% normal appearance. Somewhat raised APase, SGPT, and bilirubin levels (liver) returned to normal.
2. Baseline sperm 32 (20-43) million/ml in 3 ml volume, 10% motile, 24% normal, 25% immature. After B_{12} 150 million/ml, 75% motile, 60% normal, 5% immature. Liver normal throughout.

The authors would not speculate on causation but urged the acquisition of more data.

In 1970 Alperin et al. (0058) reported the single case of a 67-year-old woman with pernicious anemia and thyrotoxicosis; she responded to B_{12} 10 μg/day but not to 1 μg/day. She was euthyroid 14 months later, and responded to 1 μg/day. Thirty-four hyperthyroid patients in another study had lower serum B_{12} than a normal group, and of 20 who became euthyroid, serum B_{12} rose in 17. Reasons were not determined.

The authors concluded that hyperthyroid patients needed more B_{12} than euthyroid persons.

(g) Skin Pigmentation

In 1963 Baker et al. (0148) attributed to Dr. Bramwell Cook the discovery in 1944 that mycrocytic B_{12}-deficiency anemia resulted in hyperpigmentation of head and neck, fingers, ankles, shins, wrists, and forearms; the pigment responding to crude liver extract.

In 1973 Gilliam and Cox (0954) described the case of a White girl aged 8 with megaloblastic anemia and disturbed skin pigmentation, involving cells with enlarged nuclei resembling those of mucosal epithelial cells in B_{12} deficiency. The authors reviewed earlier reports, concluded that the two conditions were allied (both responded directly to B_{12} therapy), and suggested that the NADP-linked pathway of glutathione metabolism might be involved.

(h) Iron Deficiency

In 1957 Iwamoto et al. (1319) injected Fe^{55} into B_{12}-deficient and B_{12}-replete rats and found that the production of labeled hemin was halved in B_{12} deficiency. B_{12} also increased the formation of labeled hemin from Fe^{55} in cultured bone marrow homogenates.

In 1965 Cook and Valberg (0551) compared the B_{12} status of four iron-deficient subjects with that of six controls, using Co^{58}-B_{12} i.v. The four had normal gastric biopsies and secretions, and had no evidence of B_{12} deficiency or abnormality (such as absorption or excretion), but label disappeared from the plasma more slowly than in the controls. The authors could not explain this. They concluded that when B_{12} deficiency occurred in iron-deficient subjects, it was due to gastric atrophy.

Biochemical Studies

(a) Methylmalonic Acid

In 1968 Rosenberg et al. (2322) identified the metabolic block in the congenital B_{12}-dependent methylmalonic aciduria characterized by neonatal/infantile ketoacidosis. They found that the peripheral blood leucocytes oxidized succinate-1,4-C^{14} but not propionate-3-C^{14} to $C^{14}O_2$, except after parenteral B_{12}. Urinary methylmalonate was then diminished. They inferred a mutation of methylmalonyl-CoA isomerase, catalyzing B_{12}-dependent conversion of methylmalonyl-CoA to succinyl-CoA, and claimed that this was the first B_{12}-dependent condition established in man.

In 1969 Smith et al. (2576) studied the effects of B_{12} on methylmalonate and CoA levels in the livers of pair-fed sheep. Both compounds were two-to-three times higher in B_{12}-deficiency, and CoA was over three times higher than methylmalonate in both deficiency and repletion. The authors concluded that the high CoA of B_{12} deficiency was not due "primarily" to accumulation of methylmalonyl-CoA.

In 1969 DeGrazia et al. (0676) studied the conversion of propionate to methylmalonate in normal and B_{12}-deficient humans. They found that although B_{12}-deficiency affected the amount of the methylmalonate body store, it did not affect the relative contribution of propionate to methylmalonate synthesis.

In 1970 Hsia et al. (1271) issued a second report on their case of congenital methylmalonicaciduria. This was aggravated by diet supplying protein 5 g/kg/day, and oral loads incriminated the methylmalonate precursors isoleucine, valine, methionine, and threonine. Parenteral B_{12} 1 mg/day lowered urine methylmalonate 70% and partly normalized leucocyte and platelet oxidation of methylmalonate and propionate. The patient had "thrived" for two years on protein-restricted diet and B_{12} supplements.

(b) Folic Acid

In 1956 Lear and Castle (1588) concluded that folic acid supplementation of B_{12} therapy was unnecessary in pernicious anemia, and might be harmful. Twenty of 35 patients given B_{12} 15 μg i.m. 4-weekly had serum B_{12} less than 100 pg/ml; doubling the dose was considered adequate. When 22 patients received 30 μg fortnightly, only five had higher hemoglobins than on 15 μg/4 weeks. Folate did not

alter hemoglobins. It lowered the serum B_{12} in 18 of 27 patients receiving the larger B_{12} doses. The authors attributed this to accelerated utilization of B_{12}.

In 1965 Marchetti et al. (1741) showed that B_{12} and biotin had similar effects on the metabolism of folate, interpreted as reflecting common participation in the metabolism of one-carbon compounds, but "the exact nature of the effect is not yet known."

In 1968 Oace et al. (2019) studied the influences of dietary B_{12}, methionine, and thyroid on the urinary output of aminoimidazolecarboxamide in rats. B_{12}-fed controls excreted (average) 20 μg/day, B_{12}-deficient rats 40 or more μg/day, thyroid had no influence, and methionine normalized the deficients without influencing the controls. The authors concluded that B_{12} influenced folic acid metabolism at the level of methionine biosynthesis.

In 1970 Elson et al. (0774) investigated the question of whether B_{12} directly regulated rat liver glutamate formiminotransferase activity. In normal animals B_{12} supplements increased this activity and gave contradictory serum folate data on two different assays. However, in germfree rats both the liver enzyme and the serum folate were shown to be independent of B_{12} supplements.

In 1972 van der Weyden et al. (2860) investigated the metabolic effects of low serum B_{12} in patients with folate deficiency. They studied seven with megaloblastic maturation, low serum folate, but normal serum B_{12}; and five with low serum folate and B_{12}. They measured DNA-thymine synthesis from deoxyuridine in marrow cultures (biopsy) in vitro. Normally, added deoxyuridine suppresses the incorporation of subsequently added ^{3}H-thymidine into DNA. This system is reportedly sensitive to deficiencies of folate or B_{12}. All twelve patients had initial disturbances of this system. The marrow cultures of the seven with normal serum B_{12} levels showed no response of this system to added B_{12}; those of the five with low serum B_{12} showed a partial response to added B_{12} and a complete response to super-added folate.

The authors interpreted their data to suggest that, in the presence of folate deficiency, low serum B_{12} reflected a true deficiency for marrow and contributed to megaloblastosis by disturbing the metabolism of folate.

(c) Methionine

In 1963 Baliga et al. (0158) studied the effects of B_{12} on the nutritive value of soybeans. Though containing all essential amino acids, the biological value of soybean protein was low, but could be improved by processing in wet heat. The reason, elucidated by a series of elegant studies starting with Osborne and Mendel in 1917, was the presence of a heat-labile trypsin-inhibitor in the raw soybeans, which delayed the release of methionine. The authors (0158), using rats, found that dietary B_{12} increased the biological value of raw soybean protein to the same extent as did heat-processing. They confirmed their findings by feeding casein plus active soybean inhibitor, and then adding B_{12}, which counteracted the inhibitor when casein was the source of protein. In vitro trypsin digestions of raw soybean protein or casein showed that B_{12} increased the release of α-amino nitrogen and methionine in the presence of added soybean inhibitor.

In 1964 Dickerman et al. (0681) proposed, from their data, that methionine or a derivative might exert a feedback inhibition on enzymes catalyzing synthesis of prefolic acid, because methionine decreased the amount of liver prefolic acid (n^5-methyltetrahydrofolate) more effectively than did B_{12}.

In 1967 Chang and Yokota (0484) found that added B_{12} and folate increased the availability of methionine for rats fed soybean protein and depleted of these vitamins. The depleted rats also excreted more urea and less allantoin in the urine, and the repleted rats grew better and retained more carcass nitrogen.

In 1969 Woodard (3037) produced hydrocephalus, umbilical hernia, spina bifida, and other anomalies in neonatal rats by feeding the dams diets deficient in B_{12} "and other lipotropic substances." Addition of DL-methionine alone increased the frequency of hydrocephalus. No metabolic abnormalities were found when measurements included DNA, RNA, protein, proteolipid, total lipids, and brain phospholipids; tissues were taken within five hours of birth, and no nursing took place. The authors speculated that the failure to find metabolic changes might be due to placental transfer of methyl groups by the mothers at the expense of their own requirements, but the causation of the anomalies was not discussed.

In 1970 Mudd et al. (1915) studied an infant with low plasma methionine and high plasma and urine homocystine and cystathione, by culturing fibroblasts from the patient. They concluded that, probably, the patient's cells could not accumulate active B_{12} coenzymes, so that the patient became deficient in N^5-methyltetrahydrofolate methyltransferase and methylmalonate-CoA isomerase.

(d) Formic Acid

In 1961 Dinning (0689) studied the conversion of formate to methionine methyl in liver homogenates from normal or B_{12}-deficient chicks. The conversion was slower in the deficient chicks, while formaldehyde to methionine methyl occurred faster. The authors concluded that B_{12} might be involved in reduction of formate to formaldehyde (catalyzed by methylene F_4-folate dehydrogenase).

In 1960 Arnstein (0107) studied the metabolism of labeled Na-formate, DL-serine, and L-histidine in the livers of B_{12}-deficient rats from depleted dams. No less serine and histidine was incorporated into visceral total proteins in these animals than in controls. Then B_{12} was given, and:

1. More formate was oxidized to respiratory CO_2, and less was found in the urine.
2. More formate was converted to serine and methionine, and more serine and formate were converted to methyl groups.

(e) Amino Acids

In 1950 Charkey et al. (0488) found that B_{12} fed to B_{12}-deficient chicks decreased blood nonprotein nitrogens and seven amino acids: arginine, lysine, methionine, tryptophan, histidine, threonine, and valine. Growth and utilization of diet were better in the B_{12}-fed chicks. The authors concluded that B_{12} enhanced "utilization of circulating amino acids for building fixed tissues".

In 1957 Henry and Kon (1197) reported some studies of B_{12} and protein metabolism in rats:

1. In B_{12}-deficient rats the biological value of casein was increased equally by adding 1% methionine or 1% homocysteine with B_{12}, but was not increased by homocysteine alone. Conclusion: B_{12} was involved in the synthesis of methyl groups.
2. When the 1% homocysteine was supplemented with 0.5% choline with or without B_{12}, it became equivalent to the 1% methionine. Conclusion: B_{12} was not involved in transmethylation.

3. B_{12} alone did not increase the biological value of casein in B_{12}-deficient rats, nor the value of 100%-extracted wheat flour. Nor did it increase the value of the wheat flour in normal rats, even when lysine, methionine, or both, were also added.
4. In normal rats fed 16% protein diet (soya or casein), added B_{12} did not increase the biological value.

The authors concluded that B_{12} had a role in methyl group synthesis, but not in transmethylation, nor in protein utilization.

(f) Nucleotides

In 1958 Wagle et al. (2916) showed that B_{12} was not directly involved in the synthesis of purines and pyrimidines from 1-carbon precursors such as formaldehyde, formate, glycine, serine, or methionine. Nor was it involved in the conversion of C^{14}-glucose to pentoses, nor in the incorporation of those pentoses into DNA or RNA. The animals used included normal and B_{12}-deficient pigs, chicks, and rats.

In 1960 Marfatia et al. (1743) used B_{12}-depleted rats to study effects of dietary B_{12} on liver cytosol levels of thiamine and riboflavin and their cofactor derivatives. The cofactors and total pyridine nucleotides decreased much in B_{12}-deficiency without corresponding decreases of the free vitamins. Most decreases were in mitochondrial fractions. The authors stated that conversion of the vitamins to their coenzymes was impaired somewhat, but never completely; FAD synthesis was impaired evenly, thiamine pyrophosphate and pyridine nucleotide synthesis was impaired mainly in the cell nuclei. The authors considered that B_{12}-deficiency might damage mitochondria.

In 1962 Marchetti et al. (1739) used day-old chicks to determine the effects of dietary B_{12}, methionine, and orotate on the liver levels of acid-soluble nucleotides, each compound already being known to stimulate RNA production. All three compounds stimulated ADP and GDP. Orotate also stimulated CMP largely, other nucleotides slightly (CDP, IMP, UTP and GTP), and AMP and GMP not at all. Methionine increased UDP and the monophosphates somewhat, but not ATP. B_{12} had "some effect" on adenylic and uridylic acids. These selective effects were attributed to original effects on the free nucleotides.

(g) Protein Metabolism

In 1961 Morse et al. (1913) studied the effect of dietary supplements of B_{12} (1 mg/day) and/or C (200 mg/day) on the protein utilization of 20 young women for six weeks. Their data are given in Table 76 and their interpretations in Table 77. They concluded that B_{12} increased the rbc count; otherwise neither vitamin had any significant effect, separately or together, on their protein data. All subjects had lower serum cholesterol at the end of the study.

Table 76. Means for Erythrocytes, Non-protein Nitrogen, and Amino Acid Nitrogen Obtained with Control and Three Experimental Groups (1913)

PERIOD	GROUP I	GROUP II	GROUP III	GROUP IV	STANDARD DEVIATION*
		Erythrocyte Counts			
			millions/mm.³		
Standardizing period					
Unadjusted mean	4.58 ± 0.06	4.43 ± 0.18	4.50 ± 0.23	4.26 ± 0.21	± 0.31
Comparison period					
Unadjusted mean	4.21 ± 0.25	4.63 ± 0.44	4.52 ± 0.17	4.60 ± 0.32	± 0.32
Adjusted mean	4.15	4.62	4.49	4.72	± 0.26
		Non-Protein Nitrogen			
			mg. per ml. blood		
Standardizing period					
Unadjusted mean	27.9 ± 2.3	24.8 ± 3.8	26.1 ± 1.9	27.1 ± 1.8	± 2.6
Comparison period					
Unadjusted mean	27.1 ± 3.3	25.4 ± 2.8	24.8 ± 1.1	27.6 ± 1.7	± 2.4
Adjusted mean	27.2	26.1	24.7	26.9	± 1.8
		Amino Acid Nitrogen			
Standardizing period					
Unadjusted mean	8.68 ± 0.35	8.80 ± 0.36	8.59 ± 0.84	8.38 ± 0.82	± 0.61
Comparison period					
Unadjusted mean	9.18 ± 0.30	8.62 ± 0.34	8.64 ± 0.41	8.65 ± 0.82	± 0.51
Adjusted mean	9.14	8.52	8.65	8.78	± 0.40

*29 values
Based on 5 values per group

(h) Fat Metabolism

In 1950 Drill and McCormick (0730) fed male Sprague-Dawley rats, 115-149 g, synthetic diets with 6 or 51% lard and gave them a B_{12} concentrate s.c. three times weekly. They found a marked lipotropic effect of the B_{12} concentrate on the high-fat rats, which was not due to small amounts of choline that were in the concentrate.

Table 77. Mean and Differential Responses Based on Adjusted Means Reported in Table (1913)

VITAMIN	MEAN RESPONSE*	DIFFERENTIAL RESPONSE: Ascorbic acid Absent	Ascorbic acid Present	Vitamin B_{12} Absent	Vitamin B_{12} Present	STANDARD ERROR†
			Erythrocyte Counts			
	←		*mill. in mm*			
Ascorbic acid	+0.215			[illegible]	[illegible]	
Vitamin B_{12}	+0.355	+0.48	+0.2[illegible]			+0.16
Standard error†	+0.12					
			Non-Protein Nitrogen			
	←		*mg. [illegible] blood*			
Ascorbic acid	0.85			2.5	+0.8	
Vitamin B_{12}	+0.57	1.1	+2.2			+1.1
			Amino Acid Nitrogen			
Ascorbic acid	0.115			0.49	+0.26	
Vitamin B_{12}	+0.245	+0.62	+0.13			+0.25

*For differential responses.
†For mean response.

In 1950 Gyorgy and Rose (1083) developed hepatic necrosis in rats by offering them yeast as sole source of protein. B_{12} 1 μg/day p.o. made no difference. Nevertheless B_{12} 0.5 μg/day p.o. was significantly lipotropic in rats fed low-protein low-fat diet, and methionine was more effective than B_{12} at preventing fatty liver. When the fat ratio was increased, the lipotropic effect of B_{12} was thought to diminish.

In 1951 Arnstein and Neuberger (0108) studied the effect of dietary B_{12} on the conversion of glycine to choline in rats, and concluded that their findings supported observations by others, that B_{12} was concerned with synthesis of methyl groups.

In 1951 Strength et al. (2668) found that in rats B_{12} and folacin supplements reduced the amounts of choline needed to maintain normal liver lipid levels, and also enhanced the lipotropic efficacy of betaine, DL-methionine, dimethylaminoethanol, or methylaminoethanol as replacements for dietary choline; rats were protected against renal damage. Triethylcholine did not replace choline.

177

The authors concluded that B_{12} and folacin were for the maximal utilization of methionine or betaine in choline synthesis from aminoethanol or methylaminoethanol.

In 1954 Frolich (0888) tested for interactions between B_{12} and D in chicks. Growth was depressed by D 640 or 1400 IU/kg of diet (but not by 200 IU/kg), and restored by adding B_{12} 30 μg/kg of diet.

In 1957 Chakravarti et al. (0479) produced cholesterol-in-olive-oil atherosclerosis in rabbits and stuied the effect of injections of B_{12} and C, alone and in combination. They reported that B_{12} inhibited the development of atheroma more than did C, although it markedly increased the serum free cholesterol and the free/total cholesterol ratio.

In 1961 Fox et al. (0871) studied the effect of B_{12} on the excretion of formiminoglutamate by chicks. Excretion was high when diets contained either 4 or 24% fat, though high fat had previously been found to diminish growth in B_{12}-deficient chicks. B_{12}-deficient chicks excreted more than B_{12}-normals; normality was restored by 1% DL-methionine in the diet, but not by DL-homocysteine thiolactone HCl, DL-homocystine, L-cytsine, choline-Cl, or betaine.

In 1961 Nath and Brahmankar (1953) reported that B_{12} or unsaturated fat or (more effectively) hydrolyzed glucose cycloacetoacetate, added to diets of rats with hyperlipemia from saturated fat, decreased total plasma cholesterol and increased the output of bile acids in feces They concluded that these compounds enhanced metabolism of cholesterol to bile acids.

In 1967 Nath and Nath (1956) reported that a 35% fat diet fed to rats for 120 days produced B_{12} deficiency, more so if the fat was highly saturated, and less so if linoleic acid was added to a hydrogenated fat diet.

In 1969 Banerjee and Chakrabarti (0160) found that B_{12} 1 μg/g of diet partly counteracted the tissue cholesterol effects of a high cholesterol diet in rats, by promoting excretion (Table 78).

In 1971 Armstead et al. (0096) studied cholesterol biosynthesis in male rats from mothers that were B_{12}-deficient during pregnancy and lactation. Half of the males were fed B_{12}-deficient diet, and their cholesterols were lower in plasma (especially the ester fractions), higher in adrenals, and no different in

Table 78. Effect of Vitamin B_{12} on Liver and Blood Cholesterol and Fecal Excretion of Bile Acid and Cholesterol of Albino Rats Fed High Cholesterol Diet (0160)

(Number of animals used in the study are 4 and experimental period is 12 weeks. Values are mean ± SE.)

Group	Total cholesterol contents in liver, mg/100 g wet tissue	Total blood cholesterol mg/100 ml	Daily fecal excretion of bile acids mg/rat	Daily fecal excretion of cholesterol mg/rat
I. Normal	253 ±10.5	42.6 ±8.2	11.8 ±1.5	8.4 ±2.7
II. High cholesterol diet	2164 ±210.5	87.6 ±12.5	33.6 ±3.1	17.8 ±5.2
III. High cholesterol diet + Vitamin B_{12}	982 ±70.4	54.6 ±3.9	48.2 ±5.1	19.3 ±3.7

brain and testes, from the B_{12}-fed males. The deficient rats incorporated acetate into cholesterol faster, and mevalonate into cholesterol slower (after an interval) than normals in liver; mevalonate incorporation was also slower in adrenals and testes but not in brain.

The authors suggested that these switches of cholesterol derivation were related to B_{12}, were not limited to liver, and could be related both to reproductive and to neural effects of clinical B_{12} deficiency. They added that other lipid metabolism might also be affected.

In 1974 Loui and Renner (1671, 1672) fed chicks a diet of isolated soybean protein, fat or glucose as energy source, and with limited methionine content. With growth as a criterion, the requirement for B_{12} was greater when fat replaced glucose isocalorically. In either case, growth resulted from stimulation of appetite, not from improved utilization of protein or energy (1672). The

requirement for methionine did not increase or decrease with change of energy source, and the authors suggested that B_{12} might have a methionine-independent role in fat metabolism (1671).

(i) Carbohydrate Metabolism

In 1954 Ling and Chow (1644) found that B_{12}-deficiency in rats disturbed the pattern of carbohydrate metabolism and lowered the phospholipid content of blood and tissues; then B_{12} or glutathione diminished hypoglycemia that had been induced by diet or glucose injections. The authors inferred that B_{12} had a role in blood glutatione metabolism that was important for the rats' carbohydrate metabolism.

They then (1643) inclubated rat rbc for ribose formation in vitro; those from B_{12}-deficient rats made less ribose and used less O_2 than from B_{12}-replete rats, unless GSH was added to the medium.

In 1961 Johnson et al. (1359) reported that in livers of B_{12}-deficient animals the incorporation of C^{14} into glycogen was halved when the source was glucose and was diminished when it was serine or alanine. Serine biosynthesis from glucose was not diminished, nor was formation of deoxyribose by $C_2 + C_3$ condensation.

In 1966 Hadnagy and Horvath (1094) studied the effects of 1 mg parenteral B_{12} (single dose) on glucose absorption in 32 patients with various endocrine disorders. Criteria were blood glucose levels at stated intervals after oral glucose 1 g/kg with or without B_{12} s.c. Tests were conducted 2-3 days apart, in pairs, the first test being without B_{12} and the second with it. In 31 cases B_{12} was associated with increased glucose absorption, attributed by the authors to enhanced phosphorylation. They stated that in rabbits B_{12} had had no effects on peristalsis.

(j) Various Enzymes

In 1958 Wagle et al. (2919) reported that the "pH 5 enzyme" system of rat liver microsomes depended partly on B_{12} for new protein synthesis from amino acids, and that the B_{12} was incorporated into the system.

In 1960 Ranke et al. (2240) reported that in rats, the liver "reserve" of B_{12} was depressed by either deficiency or excess of B_{12} intake. Also, B_{12} deficiency raised serum transaminase activity, indicating an increased B_6 availability, and excessive B_6 lowered the liver B_{12} reserve.

The authors commented that this showed the "importance of a balanced intake" of these vitamins.

In 1960 Szafranski et al. (2706) isolated trytpophan-activating enzyme from ox pancreas acetone powder, and purified the B_{12} content of the powder. They calculated that B_{12} was present as one molecule per 4000-6000 molecules of the enzyme, and concluded that B_{12} took no direct part in tryptophan activation.

In 1961 Gronvall (1056) found greatly elevated levels of lactate dehydrogenase and phosphohexose isomerase enzymes in pernicious anemia serum, which normalized after administration of B_{12}. The author argued that the cause was unlikely to be hemolysis because the rbc levels were not elevated,and there was no evidence of sufficient hemolysis. He speculated that B_{12} might directly or indirectly govern the elimination mechanism for these enzymes, which at that time was not known.

In 1961 Jocelyn (1352) studied the oxidation of glutathione by O_2 in human rbc in vitro and found that it was increased by Cu^{++}, SeO_2, or ascorbic acid. In dialysis experiments it could be inhibited by B_{12} alone at 100-10,000 pg/ml of medium. These actions of Cu^{++} and B_{12} were found to be mutually antagonistic, and B_{12} was inoperative in hemolysates.

The authors concluded that B_{12} might inhibit uptake of Cu^{++} by rbc.

In 1961 Chang et al. (0482) found that when rats were B_{12}-depleted, the NAD/NADH ratio in their livers increased proportionally; this ratio responded but slowly to B_{12} repletion, and the authors inferred that the effect was secondary to decreased GSH levels. They also reported higher blood pyruvate and lactate levels in B_{12}-depleted rats.

In 1963 Bengmark and Olsson (0229) reported that B_{12} had no effect on liver regeneration in part-hepatectomized rats, but significantly stimulated glutamic pyruvic transaminase.

(k) Cyanide Metabolism

In 1965 Matthews et al. (1783) measured plasma and urine cyanide, total serum B_{12}, and serum B_{12} extractable without cyanide in a group of six multiple sclerosis patients and seven controls. Total serum B_{12} was normal in the multiple sclerosis patients, and so was cyanide metabolism under the conditions of this study.

(l) Propanediol Metabolism

In 1966 Yamane et al. (3069) studied the influences of light, temperature, and O_2 on the 5,6-dimethylbenzimidazolylcobamide-dependent conversion of propanediol to propionaldehyde in vitro. The reaction was stimulated by light, but not if it had started and had reached a steady rate in the dark; O_2 was inhibitory. In the cold, B_{12} was photoconverted to hydroxocobalamin. The authors postulated that anerobic cleavage of the Co-C bond resulted in protein-bound B_{12} and a 5'-deoxyadenosyl radical, which was also protein-bound, for added adenosine was seen to inhibit the reaction competitively.

(m) Thiamine

In 1969 Rogers et al. (2309) reported a single, possibly unique, case of megaloblastic anemia resistant to B_{12} but responsive to large doses of thiamine; the history suggested a single-enzyme defect, and the authors claimed that this was first evidence of direct involvement of thiamine in hemopoiesis.

(n) Ascorbic Acid

In 1972 Mohanram (3105) studied the effects of B_{12} supplements on plasma and leucocyte ascorbic acid levels in nine adult volunteers who were vegetarians and had suboptimal B_{12} levels. When these tissues were "saturated" with ascorbic acid, B_{12} did not influence the ascorbic acid levels, and the authors concluded that there was no direct interaction between the two vitamins.

V. Drug Interactions

A number of reports have been condensed from Drug Interactions-NLM vol. 1, 1967-1970 (2818). These preserve the format found, and are prefaced by 5-digit numbers prefixed by a letter, which is A (animals, H (humans), or I (in vitro).

Alcohol

In 1969 Lindenbaum and Lieber (1635) found that ethanol consumption along with adequate diet induced malabsorption of B_{12} (Table 79).

Anesthetics

H.60018. Sakharov L.N., Lotova A.I., Bodatche V.I., Yudelson Ya.B., Klemente V.N. 1966 Zh Nevropat Psikhiat Korsakhov 66:858-860 (Rus). The efficacy of treating lumbar-sacro radiculitis with Novocaine blockades in different blockade modifications and vitamin B_{12}.

A. Procaine HCl 20 ml, 0.5/sol (epidural), 72 patients, 30-50 years, radiculitis.

B. B_{12} 200 μg, 72 patients, 30-50 years, radiculitis.

B upon A significantly increased blockade.

Table 79. Per Cent Urinary Excretion of ^{57}Co-Vitamin B_{12} During Control Periods and Ethanol Administration in Human Volunteers (1635)

Subject	Urinary ^{57}Co-Vitamin B_{12} Excretion (per cent)				Days on ethanol when tested (per cent)	Maximal ethanol dose (total caloric intake)
	Control (pre- and/or post-ethanol)		Ethanol			
	24h	48h	24h	48h		
1	42.4	51.4	27.4	33.0	13	46
	40.7	50.6	11.9	20.6	26	
2	12.1	16.2	5.9	9.1	21	60
	12.1	16.8	6.7	11.0	31	
	11.2	17.5				
3	17.0	21.0	13.1	17.4	21	60
4	10.5	15.4	5.9	10.2	34	66

Antibiotics

I.50006. Dzyobak S.T. 1965 Antibiotiki 10:837-840 (Rus). Development of resistance in Sonnei dysentery microbes to antibiotics and phage under the influence of streptomycin combined with vitamin B_{12}.

A. Cyanocobalamin

B. Streptomycin

Drug resistance was increased by A with B.

A.60080. Yeh S.D.J., Shils M.E. 1966 Proc Soc Exp Biol Med 123:367-370. Effect of tetracycline on intestinal absorption of various nutrients by the rat.

A. Tetracycline HCl 250 mg/kg in 2 doses - rats

B. Triolein p.o. - rats

C. $Fe^{++}SO_4$ 20 μg (0.5 μCi ^{59}Fe) p.o. or i.p. - rats

D. Xylose 150 mg - rats

E. B_{12} 20 and 40 mμc p.o. - rats

A upon B: persistent decrease of absorption.

A upon C: absorption decreased independently of route of administration.

A upon D: excretion increased.

A upon E: no effect.

No data: several mechanisms speculated.

Antitumor Agents

A.60159. Mueller N.R. 1966 Vop Onkol 12(4):69-74 (Rus). Study of combined action of alkylating antitumor substances and vitamin B_{12} on experimental metastasizing tumors.

A. B_{12} 20 μg/kg i.m. starting 10 days before tumor SSK sarcoma transplant - 312 M rats

B. Sarcolysin 5 mg/kg q3d i.p. - 187 M rats

C. Thiotepa 4 mg/kg q2d - 123 M rats

A upon B or C suppressed hematogenic metastasizing effects.

No data. Comment repeated results.

A.80388. Bulkina Z.P., Polyak N.R. 1968 Vop Onkol 14(4):70-75 (Rus). Vitamin B_{12} in chemotherapy of experimental tumors.

A. Thiotepa 3 mg/kg inj. Rats: transplanted sarcoma 45: Heren carcinoma.

B. Embitol 7.5, 8.0 mg/kg inj. Rats: transplanted sarcoma 45: Heren carcinoma.

C. Novembitol 25 mg/kg inj. Rats: transplanted sarcoma 45: Heren carcinoma.

D. B_{12} 20-200 25 mg/kg s.c. or i.v. Rats: transplanted sarcoma 45: Heren carcinoma.

D upon A, B, or C, decreased or eliminated antitumor activity of latter. Table given, no discussion.

B_{12} Analogs and Congeners

H.70044. Tudhope G.R., Swan H.T., Spray G.H. 1967 Br J Haematol 13:216-228. Patient variation in pernicious anemia, as shown in a clinical trial of cyanocobalamin, hydroxocobalamin and cyanocobalamin-zinc tannate.

A. Cyanocobalamin 500 μg in one dose 12 pernicious anemia patients.

B. Zinc tannate 500 μg in one dose 12 pernicious anemia patients.

A with B no effect on serum Zn levels, decreased urinary B_{12}, most excretion occurred after 24 hours. Also compared hydroxo-B_{12} (no results given in abstract). Concluded that Zn tannate decreased urinary excretion and injection-site uptake of B_{12}.

I.70030. Gottlieb C.W., Retief F.P., Herbert V. 1967 BBA 141:560-572. Blockade of vitamin B_{12}-binding sites in gastric juice, serum, and saliva by analogs and derivatives of vitamin B_{12} and by antibody to intrinsic factor.

A. Cyanocobalamin

B. Analogs of cyanocobalamin

B upon A, blocked binding of A.

Biguanides

In 1971 Berchtold et al. (0235) studied the side effects of a biguanide drug, Metformin, in five healthy-appearing volunteers, by jejunal biopsy before and after 2-10 weeks of Metformin 3 g/day, and by Schilling test. Tables 80 and 81 show that B_{12} absorption and serum folate levels were significantly diminished, while brush-border enzymes were affected variously.

Table 80 Schilling Test and Enzyme Activities in Intestinal Biopsy Specimens Before (B) and After (A) Metformin Treatment (0235).

Pat.	Age	Time of treatment (weeks)		Schilling test %	Biopsy specimen enzyme activities in units/g protein (normal values in parentheses*) Maltase (266 70)	Isomaltase (97 30)	Sucrase (87 29)	Trehalase	Lactase (44 22)	Acid β-galactosidase	Neutral β-galactosidase
H.A.	28	10	B	16.8	353	101	84	29	34	**	**
			A	0.8	140	46	36	15	18	3.9	3.0
T.R.	47	2	B	15.3	355	133	99	34	39	4.2	0.1
			A	5.5	135	52	35	15	19	4.1	2.0
D.C.	25	5	B	19.0	183	81	50	24	34	4.1	2.2
			A	7.2	213	61	62	31	51	4.0	0.8
N.E.	50	2	B	17.7	201	78	49	22	34	4.0	2.0
			A	5.5	213	82	57	25	52	4.3	2.8
H.J.	52	2	B	19.2	269	84	67	35	53	5.3	4.9
			A	4.2	165	62	82	30	51	5.6	5.8
Mean			B	17.6	272	95	70	29	39	4.4***	2.3***
			A	4.6	173	61	54	23	38	4.5***	2.6***

* Mean ± SD (n = 22) ** Not analyzed. *** H.A. not included.

Table 81. Means ± SD of serum Vitamin B_{12}, Serum and Whole Blood Folic Acid in 6 Subjects Before (B) and After (A) Treatment for 2 Months with 1.5 g Metformin Daily (Range of Normal Values in Parentheses) (0235)

	Vitamin B_{12} serum (180-700 pg/ml)	Folic acid in whole blood (23-110 ng/ml)	Folic acid in serum (3.0-13.0 ng/ml)
B	398 ± 115	109 ± 41	6.33 ± 0.83
A	405 ± 74	70 ± 21	4.83 ± 0.57
p	n.s.	n.s.	0.01

Cardiac Drugs

H.60208. Klykov N.V. 1966 Ter Arkh 38:57-61 (Rus). The use of vitamin B_{12} and folic acid in complex treatment of patients with cardiac insufficiency.

A. Strophantin 0-5 ml 0-05% sol qd i.v.,43 cardiac insufficiency patients.

B. B_{12} 500 µg q2d i.m.,30 cardiac insufficiency patients.

C. Folic acid 0-02 g td internal,13 cardiac insufficiency patients.

B or C on A affected systole significantly. Table of data. Myocardial contractions improved, along with synthesis of protein and nucleic acids in the myocardinum.

Corticosteroids

In 1964 Hadnagy et al. (1097) found low glucose tolerance in 58% of 70 persons aged over 70 in old folks' homes, and diagnosed diabetes in 4%. Eighty percent had low tolerance to the prednisolone-glucose test. In "most cases" B_{12} 1 mg s.c. reduced the 2-hour blood glucose, and according to the authors diminished the diabetogenic effect of prednisolone.

A.60169. Grosman Yu.S., Kozminykh. 1966 Biull Exp Biol Med 62(10):41-44 (Rus). The combined influence of hydrocortisone and certain water-soluble vitamins on the barrier function of the focus of infection.

A. Hydrocortisone 0-025-60 μg/g mice treated with turpentine and strychine.

B. B_1 0.25-30 μg/g mice treated with turpentine 20-30 test.

C. Ascorbic acid 0.025-40 μg/g mice treated with turpentine 20-30 test.

D. B_6 0.025-20 μg/g mice treated with turpentine 20-30 test.

E. B_2 0.15-30 μg/g mice treated with turpentine 20-30 test.

F. B_{12} 0.05-20 μg/g mice treated with turpentine 20-30 test.

G. Folic acid 10-20 μg/g mice treated with turpentine 20-30 test.

A with B or C: smaller doses increased mortality sharply.
A with D: smaller doses increased mortality.
A with E: reduced mortality.
A with F or G: no significant effect on mortality.
Table of data. Concluded: B-group and C vitamins influence the anti-inflammatory action of hydrocortisone and possibly also its analogs.

A.70006. Hadnagy C.S., Gyergyai F. 1967 Int Z Vitaminforsch 37:354-368 (Ger). Studies on vitamin B_{12} and cortisol antagonism, with regard to lipotropic and immunological properties.

A. B_{12} 50-200 μg i.p. fasting rats, guinea pigs, rabbits.

B. Hydrocortisone 12.5-25 mg i.p. fasting rats, guinea pigs, rabbits.

C. Human serum 1 ml intracardiac, guinea pigs (only).

A upon B counteracted fatty liver.

A upon B + C: no effect on inhibition of antibody formation.

A upon B + C: no effect on antianaphylactic effects.

A upon B + C: no effect on lymphoid tissue depression.

B alone was lipotropic.

Hydantoin

In 1970 Amir et al. (0063) reported what they claimed to be the second case of its kind. Their patient (male, 19) was given hydantoin for epilepsy and developed megaloblastic anemia. When this was treated with parenteral B_{12} 1 mg/week, oral folic acid 30 mg/day, and $FeSO_4$ 0.8 g/day, all doses reduced after one month, he developed polycythemia. This was diagnosed after a year of vitamin therapy, which was halted. Four phlebotomies of 400 ml each were performed during the next eight months, and the patient's condition became normal.

Para-Aminosalicylic Acid

In 1964 Heinivaara and Palve (1164) studied absorption of B_{12} in 10 patients taking para-aminosalicylate for tuberculosis, because of the known side-effects of this drug on hemopoiesis. Two cases of megaloblastic anemia were found to have developed during drug treatment, and all ten Schilling test values were lowered, in seven cases by five-fold or more. Intrinsic factor did not normalize the Schilling test values, and the authors concluded that further studies were needed.

In 1966 Paaby and Norvin (2093) tested 26 patients on para-aminosalicylate therapy for relationships between Schilling test serum B_{12}, iron, and transferrin, and rbc data. No such relationships were found, and the authors stated that they could not corroborate the report of Heinivaara and Palve (1164).

In 1970 Sullivan (2682) reviewed some interactions of B_{12} with various drugs. Both colchicine and para-aminosalicylic acid had been shown to interfere with B_{12} absorption. The effects of steroids on B_{12} absorption, though positive in many reports, were transient, and, according to the author, "steroids have no role in the routine therapy of pernicious anemia." The hematologic response to B_{12} in man was partly suppressed by alcohol as shown in Figure 44. The author speculated that alcohol might have affected folate metabolism.

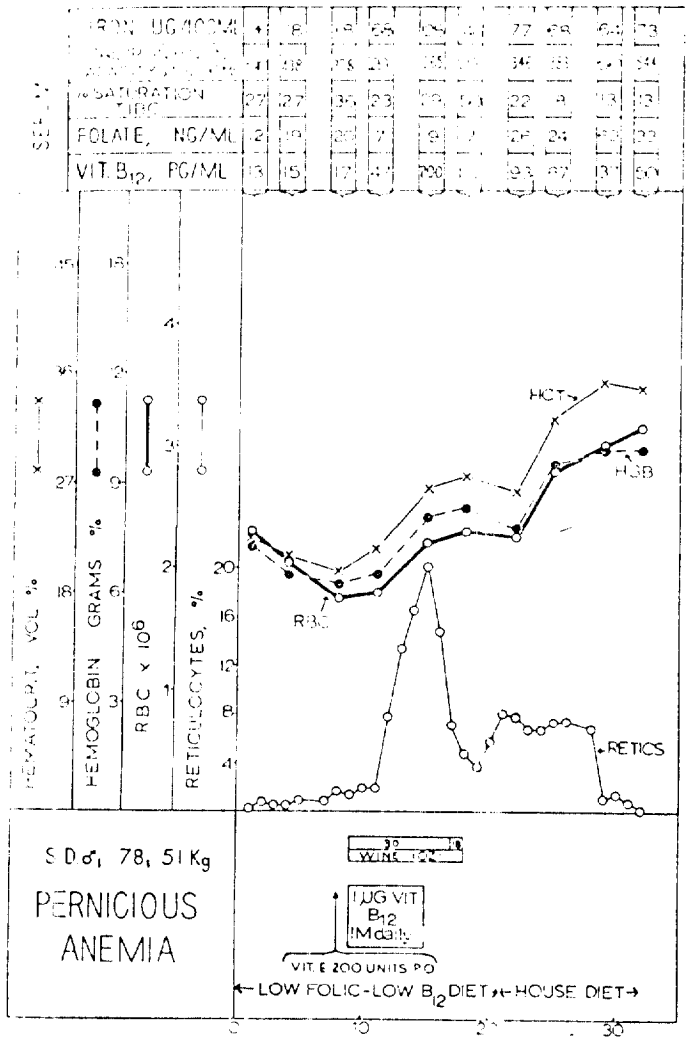


Figure 44. Partial suppression by alcohol (muscatel wine) of erythropoietic response to Vitamin B_{12} in patient with pernicious anemia. Secondary rise in reticulocytes and brisk rise in hemoglobin, hematocrit, and erythrocyte count after discontinuing alcohol indicate initial erythropoietic response to Vitamin B_{12} had been suboptimal.(2782)

Psychotropic Drugs

In 1970 Carney (0453) estimated serum B_{12} in 374 consecutive psychiatric admissions to two hospitals, one general and one mental. Results (Tables 82 , 83, and 84 suggested that low serum B_{12} was common in such patients, unrelated to pernicious anemia, and that B_{12} might be "a useful screening procedure". Of the low B_{12} patients 49% had received drugs as shown in Table 82, 60% had been ill for more than a year, 30% were undernourished, and 28% had other clinical ailments.

Table 82. Diagnoses, Mean Ages and Mean Serum Vitamin B_{12} Levels with Significance Tests for Differences from Organic Psychoses (0453)

Diagnosis	No.	Mean Age	Mean Serum Vit. B_{12} (pg) (± Standard deviations)	Significance Tests
Drug Addiction	10	47.5	418.3 ± 177.8	N.S.
Chronic Alcoholism	22	[illegible]	400.0 ± 193.1	t = 2.1; P < 0.05
Mania	11	51.9	400.0 ± 177.5	t = 1.97; P < 0.05
Neurosis (neurotic depression excepted	[illegible]	45.9	325.0 ± 202.2	t = 2.9; P < 0.05
Epilepsy	8	47.5	383.5 ± 132.9	N.S.*
Abnormal Personality	13	34.5	340.8 ± 132.3	N.S.
Endogenous Depression	68	55.0	338.3 ± 173.6	N.S.*
Schizophrenia	70	41.8	328.0 ± 144.8	N.S.*
Neurotic/Reactive Depression	63	47.7	318.2 ± 182.3	N.S.*
Organic Psychoses	20	73.0	303.4 ± 183.5	
Totals	374	53.7 ± 17.1	340.4 ± 177.1	

*Not Significant

Table 83. Psychiatric Diagnoses and Low Serum B_{12} (0453)

Serum B_{12} (pg)	Organic	Endogenous Depression	Neurotic Depression	Schizo-phrenia	Others	Totals
>150	60	56	55	61	89	321
100-150	13	10	5	6	2	36
<100	7	2	3	3	2	17
Total >150	20	12	8	9	4	53

Table 84. Drugs and Low Serum Vitamin B_{12} (0453)

Drug	*No. of Patients*
Phenothiazines (including Chlorpromazine = 5)	12
Barbiturates	7
Calcium azepoxide	5
Tricyclic antidepressants	5
Monoamine oxidase inhibitors	2
Butazolidine	1
Phenytoin	1
Others	3

Thyroid

A.60261. Dell T.R. 1966 Biull Exp Biol Med 62:91-94 (Rus). Action of vitamin B_{12} and combined action of vitamin B_{12} with thyreoidine on the thyroid gland in rats during reparative regeneration following surgical trauma.

A. B_{12} 30 µg qd 20 days then 20 µg, 45th day, 6 M rats.

B. Thyroid up to 25 mg p.o., 6 M rats.

B upon A decreased follicle development and non-significantly decreased epithelial thickness. Table given. Concluded: B_{12} decreased the colloid secretion stage: thyreoidine decreased the synthesis stage.

In 1972 McGarry and Andrews (1791) assayed serum B_{12} and inquired about smoking from 847 consecutive antenatal clinic patients and, after excluding stillbirths and multiple births, reported on 826. Serum B_{12} was lower in smokers than in nonsmokers, unrelated to hemoglobin or social levels or parity; the authors speculated that cyanide in tobacco smoke might have degraded the serum B_{12} (they expressed this as body stores of B_{12} but reported only serum data).

Vitamins

A.80134. Lopushansky V.I. 1968 Vop Pitan 27:25-28 (Rus). Effect of vitamins B_{12}, E, and B_1 on the blood content of cholesterol and lecithin during alimentary hypercholesterolemia in rabbits.

A. B_{12} 50 μg, i.m. 2 mos., rabbits, 28 series, fed 0.5 g cholesterol with food.

B. Thiamine HCL 1 ml 5% sol, i.m. 2 mos.,rabbits, 28 series, fed 0.5 g cholesterol with food.

C. E 50 μg, i.m. 2 mos., rabbits, 28 series, fed 0.5 g cholesterol with food.

A with B increased cholesterol-lowering effect, non-significantly increased blood lecithin.
B with C increased cholesterol-lowering effect, decreased blood lecithin.
A with C increased cholesterol-lowering effect, no effect on blood lecithin.
Table given. Explained that B_{12} and (to lesser degree) B, and E facilitate excretion of cholesterol from liver and colon, and "favorably influence the metabolism".

X-Radiation

In 1966 Okuda et al. (2059) found that B_{12} absorption by adult rats was affected by lethal whole-body X-irradiation (1000-1500 r) only indirectly, as the mucosa became impaired. However, absorption increased with diarrhea caused by concomitantly administered $MgSO_4$, attributed to increase of divalent cations. The authors interpreted their data as not supporting a theory of B_{12} absorption by pinocytosis.

Table 85 Etiologic Classification of Vitamin B_{12} and Folate Deficiency in Man* (1015)

I. Vitamin B_{12} Deficiency (normal B_{12} body stores last 3–6 years after cessation of B_{12} absorption)
- A. *Inadequate Ingestion*
  - 1. *Poor diet* (lacking animal protein and microorganisms, the sole B_{12} sources)
    - a. Vegans
    - b. Chronic alcoholism (folate deficiency more common)
    - c. Poverty, religious tenets, ignorance, dietary faddism
- B. *Inadequate Absorption*
  - 1. *Inadequate or absent secretion of gastric intrinsic factor*
    - a. Failure of the stomach to adequately secrete intrinsic factor
      - *1.* Addisonian pernicious anemia
        - *a.* Hereditary failure of intrinsic factor secretion
        - *b.* Hereditary degenerative gastric atrophy
        - *c.* Gastric atrophy as the end result of superficial inflammatory gastritis; superficial gastritis with atrophy
        - *d.* Autoimmunity producing gastric atrophy?
      - *2.* Lesions which destroy the gastric mucosa (ingested corrosives, linitis plastica, etc.)
      - *3.* Endocrine disorders (hypothyroidism, polyendocrinopathy, etc.)
    - b. Gastrectomy
      - *1.* Total
      - *2.* Subtotal
        - *a.* Proximal
        - *b.* Distal
        - c. Intrinsic factor inhibitor in gastric secretion
          - *1.* Antibody to intrinsic factor (in saliva or gastric juice)
            - *a.* Blocking antibody
            - *b.* Binding antibody
  - 2. *Small intestine disorder* (affecting ileum, which is the main site of B_{12} absorption)
    - a. Gluten-induced enteropathy (childhood celiac disease; adult celiac disease) (idiopathic steatorrhea, non-tropical sprue)
    - b. Tropical sprue
    - c. Regional ileitis
    - d. Strictures or anastomoses of the small bowel
    - e. Intestinal resection
    - f. Malignancies and granulomatous lesions involving the small intestine
    - g. Other conditions characterized by chronically disturbed intestinal function
    - h. Drugs
      - *1.* Para-aminosalicylic acid (PAS)
      - *2.* Colchicine
      - *3.* Neomycin
      - *4.* Ethanol
      - *5.* Oral contraceptive agents?
    - i. Specific malabsorption for vitamin B_{12}
      - *1.* Due to long-term ingestion of calcium-chelating agents
      - *2.* Due to inadequately alkaline *pH* in ileum
      - *3.* Unknown causes (absence of intestinal receptors for B_{12}-intrinsic factor complex? absence of "releasing factor"?)
        - *a.* Congenital (Imerslund-Grasbeck syndrome)
        - *b.* Acquired (form fruste of sprue)
      - *4.* Inadequate pancreatic exocrine secretion
  - 3. *Competition for vitamin B_{12} by intestinal parasites or bacteria*
    - a. Fish tapeworm (Diphyllobothrium latum)
    - b. Bacteria: The blind loop syndrome (B_{12}-greedy bacteria)

VI. Consumer Exposure

This section will be divided into:

(a) Purpose of exposure

(b) Research reports

(c) Recommendations by professional and official organizations

(d) Regulatory status

(a) Purpose of Exposure

In 1973 Herbert (1015) stated, in a review, that the only justified use of B_{12} was to remedy its own deficiency. In Table 85 he categorized deficiencies of B_{12} and/or folic acid, and in Table 86 he listed the clinical signs and symptoms of megaloblastic anemias.

Neurological symptoms and signs listed by the author as resulting from B_{12} deficiency include paresthesias of hands and feet, deficits of positional sense, loss of coordination, moodiness, mental slowness, poor memory, confusion, agitation, depression (sometimes with visual disturbances), culminating in delusions, hallucinations and psychoses.

The author emphasized that it was rarely necessary to institute B_{12} treatment before determining the cause of the symptoms, even in critically ill patients. For example, critical anemia would be remedied by transfusion, induced hypertension by phlebotomy. Infections would be treated directly. In the presence of such complications, including severe neuropathy, doses of over 1 μg/day were recommended initially by the author, who added that doses over 30 μg/day parenterally "have no proven therapeutic advantage."

(b) Selected Research Reports Dealing with Exposure to B_{12}

In 1953 Jolliffe et al. (1364) studied 351 underprivileged children of both sexes aged 6-12 at Rome, Italy, whose intakes were 20-30% below RDA for calories and 15-40% below for animal protein. Children given 20 μg/day of oral B_{12} gained significantly more weight than those given a placebo, but there were no differences in height gains.

Table 85. Etiologic Classification of Vitamin B_{12} and Folate Deficiency in Man* (1015) (continued)

C. *Inadequate Utilization*
   1. Vitamin B_{12} antagonists
      a. Substituted B_{12} amides and anilides
      b. Cobaloximes
   2. Protein malnutrition?
   3. Malignancy?
   4. Liver disease?
   5. Renal disease?
   6. Thiocyanate intoxication?
   7. Congenital or acquired enzyme deficiency or deletion
      a. Methylmalonyl-CoA mutase
      b. Methyltetrahydrofolate-homocysteine methyltransferase
      c. B_{12A} reductase
      d. B_{12Y} reductase
      e. Deoxyadenosyltransferase
      f. Other enzyme reduction or deletion
   8. Abnormal B_{12}-binding protein in serum, irreversibly binding B_{12} and making it unavailable to tissues
      a. Abnormal α (myeloproliferative disorders)
      b. Abnormal β (liver disease)
   9. Inadequate serum B_{12}-binding protein
      a. α
      b. β

D. *Increased Requirement*
   1. Hyperthyroidism
   2. Increased hematopoiesis?
   3. Infancy?
   4. Parasitization
      a. By fetus
      b. By malignant tissue?

E. *Increased Excretion*
   1. Inadequate B_{12}-binding protein in serum?
   2. Liver disease (inadequate retention of B_{12})
   3. Renal disease?

II. Folic Acid Deficiency (normal folate body stores will last only 3–6 months after cessation of folate ingestion)

A. *Inadequate Ingestion*
   1. *Poor diet* (lacking unprocessed fresh, uncooked or slightly-cooked food) (folates are heat-labile)
      a. Nutritional megaloblastic anemia
         1. Tropical
         2. Nontropical
         3. Scurvy (diets poor in vitamin C are also poor in folate)
      b. Chronic alcoholism with or without cirrhosis

B. *Inadequate Absorption* (affecting upper $\frac{1}{3}$ of small intestine which is the main site of folate absorption)
   1. *Malabsorption syndromes*
      a. Gluten induced enteropathy (childhood and adult celiac disease) (idiopathic steatorrhea, nontropical sprue)
      b. Any chronic functional or structural disorder involving the upper small intestine
         1. Tropical sprue

Table 85. Etiologic Classification of Vitamin B_{12} and Folate Deficiency in Man* (1015) (continued)

c. Drugs
   1. Diphenylhydantoin (Dilantin)
   2. Primidone
   3. Barbiturates
   4. Oral contraceptive agents (?)
   5. Cycloserine
   6. Ethanol
2. *Specific malabsorption for folate*
   a. Congenital
   b. Acquired
3. *Blind loop syndrome* (folate-greedy bacteria)

C. *Inadequate Utilization* (metabolic block)
1. Folic acid antagonists (dihydrofolate reductase inhibitors)
   a. 4-amino-4-deoxyfolates (*i.e.* methotrexate) — (Chemotherapy, immunosuppression, psoriasis)
   b. 2,4-diaminopyrimidine (*i.e.* pyrimethamine) — (Malaria, toxoplasmosis)
   c. Triamterene — (Diuretic)
   d. Diamidine compounds (*i.e.* pentamidine isethionate) — (Pneumocystis carinii, protozoacidal)
   e. Trimethoprim — (Antibacterial)
2. Anticonvulsants?
3. Enzyme deficiency
   a. Congenital
      1. Formiminotransferase
      2. Dihydrofolate reductase
      3. Methyltetrahydrofolate transmethylase
      4. Other enzymes
   b. Acquired
      1. Liver disease
         a. Formiminotransferase
         b. Other enzymes
4. Vitamin B_{12} deficiency
5. Alcohol
6. Ascorbic acid deficiency?
7. Dietary amino acid excess (glycine, methionine)

D. *Increased Requirement*
1. Parasitization
   a. By fetus (especially in multiple and twin pregnancies)
   b. By malignant tissue (especially lymphoproliferative disorders; myeloproliferative disorders to a lesser extent; extensive carcinomatosis, etc.)
2. Infancy
3. Increased hematopoiesis (hemolytic anemias; chronic blood loss [including scurvy])
4. Increased metabolic activity (*e.g.*, hyperthyroidism)

E. *Increased Excretion*
1. Vitamin B_{12} deficiency? (? of obligatory excretion of folate in urine and bile) (due partly to inability to incorporate folate in cells)
2. Liver disease?

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* Compiled mainly from information in "Symposium on Vitamin B_{12} and Folate" (Herbert, V., guest editor), Am. J. Med. 48:539-670, 1970, and from Herbert, V. "Megaloblastic Anemias—Mechanisms & Management," Disease-a-Month, Year Book Medical Publishers, Chicago, August, 1965.

Table 86. Clinical Picture of the Megaloblastic Anemias (1015)

1. *Symptoms*
   - Weakness, tiredness
   - Dyspnea
   - Sore tongue
   - Paresthesia (B_{12} deficiency only)
   - Diarrhea (especially folate deficiency)
   - Constipation (especially B_{12} deficiency)
   - Irritability and forgetfulness (especially folate deficiency)
   - Anorexia
   - Syncope
   - Headache
   - Palpitation
2. *Signs*
   - Anemia, leukopenia, thrombocytopenia, with macroovalocytes (normal MVC = 87 ± 5 cu. μ) and "hypersegmented polys" (normal "Arneth count"; 2 lobes = 20-40%; 3 lobes = 40-50%; 4 lobes = 15-25%; 5 lobes = 0-5%; 6 lobes = 0-0.1%; more than 6 lobes = 0) (normal "lobe average" = 3.17 ± 0.05) (Rule of Fives! When 100 neutrophils counted, the presence of five or more with five or more lobes means hypersegmentation.)
   - Morphologic "red herrings": congenital hypersegmentation (approx. 1% of population); hypersegmentation with renal disease; twinning deformities; macrocytes of pyruvate kinase deficiency, aplastic anemia, reticulocytosis
   - Fever
   - Icterus
   - Glossitis
     - Acute
     - Chronic atrophic
   - Neurologic damage (only B_{12} deficiency damages myelin)
     - Vibration sense diminished
     - Position sense diminished; ataxia
     - Impaired mentation, paranoid ideation.
   - Malabsorption
   - Achylia gastrica (primary with B_{12} deficiency; secondary with folate deficiency)
   - Splenomegaly (in approximately $\frac{1}{3}$ of cases, if looked for radiologically)
   - Weight loss (especially folate deficiency)
   - Pigmentation
   - Postural hypotension (especially B_{12} deficiency)
   - Low serum vitamin B_{12} or folate level
   - Elevated serum lactic dehydrogenase (LDH)
   - Elevated urine formiminoglutamate
   - Methylmalonic aciduria (B_{12} deficiency only)
   - High serum iron, increased saturation of iron-binding capacity of serum, increased bone marrow iron stores

In 1959 Scrimshaw et al. (2459) gave B_{12} 20 µg/day orally to 50 preschool children and 228 students at four rural schools in Guatemala. No effect was observed on rates of height and weight gain. The authors emphasized that children neither grow nor mature at a steady rate, and cautioned against misinterpreting data by using averages as criteria. They claimed their own data as agreeing with others from children who were somewhat malnourished and slow-growing because of relatively inadequate diets, and concluded that B_{12} would not accelerate growth under these conditions.

In 1963 Bozian et al. (0340) gave 16 subjects Co^{60}-B_{12}; three were normal, one diabetic, one had normocytic anemia, and eleven had pernicious anemia. Follow-up was 8 months to two years, and was performed by "whole body counting", i.e., the patient sat under a single crystal in a standard position, in systems available at that time. The results were interpreted to reflect "a safe, simple and accurate means of assessment of absorption, distribution and excretion" of B_{12}.

Subjects without pernicious anemia absorbed 70% (45-80%) of the dose and those with, 3.25 (0-17) %. Losses of label were 0.09-0.15%/day in normals, and 0.11-0.17% in pernicious anemics, corresponding to bio-halflife of 407-770 days.

The authors concluded that pernicious anemics needed only enough parenteral B_{12} to cover normal losses.

In 1965 Metz et al. (1827) determined serum folate and B_{12}, urinary formiminoglutamate after histidine, hemoglobin, and hematocrit, at intervals in pregnant women eating "good Western type diet" with iron and folate supplements with or without B_{12}. Serum B_{12} decreased during pregnancy and increased again after delivery; this was uninfluenced by B_{12} supplements, which also did not increase hemoglobin or hematocrit significantly.

In 1966 Spector and Metz (2599) fed weanling rats a maize diet and depleted their liver and serum B_{12}; the rats were judged to have accumulated serum N^5-methyl-H_4-folate. Supplements of pteroylglutamic acid maintained liver folate but not B_{12}. B_{12} supplements maintained liver B_{12} and folate, but serum folate

decreased. Stock diet then increased liver B_{12} and folate, and the increase was not accelerated by additions of B_{12} and pteroylglutamate.

In 1966 Herbert (1204) reviewed knowledge of human nutritional requirements for B_{12} and folic acid, in a paper published in 1968, in which he made the following points:

1. Internationally, differences of diet, circumstances, and sizes of the "reference" male and female led to different actual requirements.
2. Parenteral cyanocobalamin, 0.1 μg daily for 2 months, would partly restore hematologic normality in a B_{12}-deficient adult American male, but the neurologic effects were unknown. Serum B_{12} levels were restored by 0.2 μg, but not always by 0.1 μg, and were restored rapidly by 1 μg. Therefore, the MDR for adult males was less than 1 μg, not less than 0.1 μg, and probably less than 0.2 μg daily, in terms of parenteral cyanocobalamin administered to a B_{12}-deficient person.
3. On the other hand, label-turnover experiments indicated that the MDR was 0.5-2.5 μg/day.
4. The optimal therapeutic dose was estimated as between 1 and 40 μg/day. However, much of doses over 10 μg/day was lost in the urine.
5. The optimal adult daily requirement was unknown. The author cited Goodhart's comment that requirements for maximal growth and activity might differ from requirements for maximal longevity.
6. RDA as published might or might not supply a person's nutritional requirements, according to bioavailability of the B_{12} ingested, intrinsic factor activity, and absorption capabilities of the person.
   (a) A standard American diet providing 1 μg/day was "almost certainly adequate".
   (b) Intrinsic factor would transport 2-3 μg/meal, passive diffusion might absorb 3% of the B_{12} present in the gut, and the efficiency of B_{12} reabsorption from bile increased with dietary deficiency: this enterohepatic circulation protected against deprivation.

In 1966 Heyssel et al. (1219) concluded that, in man, B_{12} from food was absorbed comparably to crystalline B_{12}. They further estimated that:

1. Normal adults eating three meals/day supplying 5-15 μg of B_{12}/day probably absorbed at least 5 μg/day.
2. Obligatory B_{12} loss of about 0.1% of the body pool, assumed as 2-5 mg, correlated well with absorption estimates.
3. Therefore, estimates of MDR should not be based on losses or pool size in replete subjects eating high-B_{12} diets, but rather on health-maintenance and B_{12} turnover in depleted subjects whose B_{12} economy would be maximal.
4. Thus, normal subjects with low body stores needed 0.6-1.2 μg/day of B_{12}. Extra needs for growth, pregnancy, or hypermetabolism were unknown. Increased stores had their value, and so 3-5 μg/day was estimated to be "the dietary requirement for a population."
5. Because of heat-degradation, intakes should be assessed on foods after cooking, and, possibly, older people might absorb less B_{12}.

In 1967 Mittal et al. (1877) found that 36 normal formula-fed Indian infants, optimally nourished, had serum B_{12} 714±323 pg/ml, serum folate 18±9 ng/ml, and hemoglobin 10±0.4 g%.

In 1968 an editorial in the British Medical Journal (0082) stated that oral B_{12} with intrinsic factor "had a vogue, particularly in the Scandinavian countries in the 1950s, but is not widely used today. Vitamin B_{12} inhaled as an aerosol is also readily absorbed, but this mode of administration is also not widely practised."

After listing the conditions in which B_{12} deficiency had been recognized (including neuropathies and ophthalmological disorders), the Editor added: "But a lot more vitamin B_{12} is prescribed than could possibly be used for these legitimate reasons, because it is widely used as a "tonic". This has no scientific basis."

In 1970 Edelstein and Guggenheim (0759) reported that when rats were fed unheated soybean flour, instead of heat-processed equivalent, the B_{12} from intestinal flora was less available for absorption, and the disappearance of injected label from kidneys, liver, and spleen was slightly accelerated, attributed to faster turnover.

In 1970 Foulds et al. (0866), ophthalmologists, referred to their evidence that cyanocobalamin could produce rapid optic atrophy, and their more satisfactory experience with hydroxocobalamin ( ). They commented that the chief utility of cyanocobalamin was in the performance of the Schilling test, and "we urge that it would be much safer, and no commercial disadvantage, if manufacturers withdrew cyanocobalamin in favour of hydroxocobalamin for therapeutic use."

In 1970 Hughes et al. (1280) gave 39 elderly subjects, found in a community screening survey to have low serum B_{12} without macrocytic anemia or neuropathy, either B_{12} i.m. or a placebo. The drug was not superior to the placebo at promoting general well-being or psychiatric improvement.

In 1970 Sullivan (2682) stated that inadequate ingestion of B_{12} was rare in the United States. Elsewhere, in India for example, breast-fed infants of mothers who were vegans had magaloblastic anemia and neuropathology due to B_{12}-deficient maternal milk. The author cited a similar case in the United States due to maternal pernicious anemia.

In 1971 Craft et al. (0584) found B_{12} levels in eight brands of British infant milk foods, as in Table 87. All were derived from cows' milk, and the fat content was not thought to have influenced the total B_{12} content. However, when

Table 87 : Total Vitamin B_{12} Content of Infant Milk Foods (0584)

Product	Cream	Total B_{12} Concentration	
		Whole Product	pg/ml Feed[1]
Cow and Gate half cream	Half	24·4 ng/g	2,900
Nestlé dried half cream	Half	36·4 ng/g	4,000
S.M.A.	Full	16·8 ng/g	2,200
Ostermilk One	Full	24·6 ng/g	3,300
Ostermilk Two	Full	35·6 ng/g	3,500
Cow and Gate full cream	Full	22·2 ng/g	2,400
Nestlé dried full cream	Full	29·3 ng/g	3,000
Cow and Gate diluted	Full	1·6 ng/ml	450

[1] Feed prepared as for 1 week infant

the first product was chromatographed, together with fresh cows' milk samples, little was seen but hydroxocobalamin and the authors concluded that this was due to exposure to light during processing and feed preparation.

The authors also concluded from distributional studies (page) that human breast milk supplied an infant with B_{12} in a more readily utilizable form than did formula milks. The authors suggested that 0.5 µg/day of B_{12} in breast milk would be sufficient, compared with the general recommendation of 2.5 µg/day.

In 1973 Herbert (1015), reviewing work by himself and others, stressed that coenzyme B_{12} was more potent than B_{12} itself but only at minimal dosage, which was never employed. At all higher dosages "all forms of B_{12} appear equipotent."

On hydroxocobalamin and other depot or long-lasting forms of B_{12} the author judged that their longer retention at the injection site and in the serum was "a slight therapeutic advantage" that failed to justify their extra costs, and "they may have undesirable side effects."

The author estimated the probable minimum exogenous daily requirement as 0.1 µg, but more in the presence of relevant gastro-intestinal defects. This requirement was expressed as:

$$\text{MDR (units/day)} = \frac{\text{UBS (units)}}{\text{D (days)}}$$

where UBS was utilizable body stores, and D was days needed to develop tissue deficiency after complete stoppage of intake, corrected for any amount of incomplete stoppage.

The formula was also written as:

$$D = \frac{\text{UBS}}{\text{MDR}} \qquad \text{or} \qquad \text{UBS} = D \times \text{MDR}$$

in order to predict when deficiency should develop under such conditions.

The author emphasized that percent losses of labeled cobalt would usually be less than the percent losses of B_{12}, because of continual replacement with unlabeled B_{12} from natural sources.

Some examples of official recommendations were contrasted:

USA -- NAS NRC: 5 µg/day, based solely on turnover of label: adults

FAO/WHO: 2 µg/day, based on this and other measurements: adults,

0.3 μg/day for bottle-fed infants, breast-milk being judged to supply adequate B_{12},

0.9 μg/day for children aged 1-3 years,

1.5 μg/day for children aged 4-9 years,

2.0 μg/day for children of 10 and over,

2.5 μg/day during lactation, and

3.0 μg/day during pregnancy.

These amounts are from all sources, not from supplements only.

In 1974 Adams and Shresta (0027) surveyed the B_{12} folate and hemoglobin status of 52 adult villagers living at 12,000 feet in the Nepal Himalayas (Tables 88 and 89). They commented that although hemoglobins were lower than expected, signs of anemia due to deficiencies of B_{12}, folate or iron were absent, even though iodine deficiency was general.

In 1968 the NAS NRC (3106) stated that "although the minimal requirement of vitamin B_{12} for clinical remission of deficiency states appears reasonably established, further studies are needed to establish the optimal requirements for health." The RDA for replacement of normal losses was set at 5 μg/day for adults, and 15 μg/day to replenish body stores if they had been depleted.

In support of these recommendations the authors cited or stated:

(1) The rate of excretion was 0.1% of total body stores per day, range 0.8-11.9 mg/day, or in another study 1.3 (0.66-2.1) μg/day.

(2) Absorption decreased as intake increased, from 70% of 0.5 μg/day down to 30% or less of 5.0 μg/day.

The RDA for infants was set at 1.0-2.0 μg/day during the first year. In support of this the authors stated that the average daily intake from human milk was 0.15-0.25 μg/day.

No RDA were set for pregnant of lactating women. The authors stated that serum B_{12} often declined throughout pregnancy, and in the neonate was approximately twice that of the mother. They attributed this partly to hemodilution, partly to true deficiencies in the presence of normal absorption, and "possibly" to "excessive demand by the fetus."

In 1970, according to the U.S. Tariff Commission, in Synthetic Organic Chemicals (2820), the U.S. production and sales data were:

Table 88. Vitamin B_{12} and Folate Levels in Lang-Tang Village, October 1972 (0027)

Subject no.	Serum B_{12}, pg/ml	Serum folate, ng/ml	Erythrocyte folate, ng/ml
1	640	14.0	392
2	680	29.4	
3	600	16.5	
6	480	6.3	304
9	576	12.2	259
13	220	8.1	235
16	320	9.1	310
17	160	6.2	
18	344	5.6	206
19	240	13.8	289
20	152	7.9	182
21	416	8.4	324
22	370	8.8	
23	520	12.3	216
24	400	16.5	
25	452	8.0	
26	200	13.8	365
27	172	20.5	263
28	400	10.0	248
29	580	11.0	202
31	172	8.1	277
32	360	13.2	265
34	552	10.0	337
35	416	12.2	282
36	480	11.3	326
37	416	13.8	527
38	232	16.9	219
39	1,840	20.0	320
41	520	10.5	149
42	520	9.1	414
43	320	12.2	
44	360	15.0	324
45	128	8.4	163
46	172	11.3	139
48	288	40.0	230
49	420	12.3	342
51	320	15.9	217
52	328	9.9	113
53	268	10.2	297
54	552	7.5	378
55	334	6.7	182
56	504	5.2	145
57	760	7.1	116
58	500	7.6	231
59	360	8.1	160
60	600	7.6	242
61	552	6.7	153
62	560	10.2	177
63	452	8.4	123
64	530	7.5	250
65	552	6.4	126
66	416	5.6	173

Table 89. Vitamin B_{12} and Folate Content of Yak Milk (0027)

	Amount
Folate	31 μg/liter
B_{12}, plain	6,870 pg/ml
B_{12}, papain digested	7,270 pg/ml

Producers of B_{12}:	Grain Processing Corporation Merck Premier Malt Products Wilson Laboratories Division of Wilson and Company	
All Vitamins:	22,815,000 lbs produced Total revenue $84,063,000	17,053,000 lbs sold Revenue/lb $4.93
B Complex Vitamins:	8,079,000 lbs produced Total revenue $31,453,000	6,234,000 lbs sold Revenue/lb $5.01

No separate data were found for B_{12}.

Data from the 1972 NAS NRC Comprehensive GRAS Survey (0854) are shown in Table 90.

Regulation of B_{12} in the United States (0083)

Title 21, 1.32 (CFR 1973, p. 100): No longer does a food to which B_{12} is added have to be labeled "The need for...in human nutrition has not been established" when that food is "offered for special dietary use."

In section 3.40 (p. 102-103) the Commissioner of Food and Drugs found that parenteral B_{12} was fully effective for treatment of pernicious anemia and required a medical prescription. However, not all patients responded, and oral preparations of B_{12} with intrinsic factor "cannot be regarded as safe in all cases." Medical supervision was essential, and inadequate treatment might delay the seeking of medical advice, with potential results of stomach cancer, and permanent damage to the nervous system. The only service rendered by intrinsic factor was to assist gastrointestinal absorption of B_{12}. Therefore, intrinsic factor would be sold on prescription only, and though classed as a food additive

under section 409, would be regarded as an adulterant under section 402(a)(2)(C) of the Federal Food, Drug and Cosmetic Act. Oral B_{12} containing drugs would be permitted to be sold only with specific cautions, to be printed on the label.

In section 3.48, cobalt salts must not be sold for iron-deficiency anemia, and must not be added to other drugs.

In section 100.5, frozen "heat and serve" dinners must contain at least 0.33 μg of B_{12}/100 kcal total components.

In section 121.101, B_{12} is classed as GRAS without restrictions.

In section 125.5, infant foods must be sold so as to contain at least 0.15 μg B_{12}/100 kcal, and must be labeled accordingly.

No mention of B_{12} was found in CRF Title 9.

Table 90. Comprehensive GRAS Survey -- NAS/NRC 1972 (Table 13, Part A) (0854)

POSSIBLE DAILY INTAKES OF NAS APPENDIX A SUBSTANCES (CLASS I & II), PER FOOD CATEGORY AND TOTAL DIETARY, BASED ON FOOD CONSUMPTION BY TOTAL SAMPLE ***** SEE EXPLANATORY NOTES IN [illegible] SECTION

SUBSTANCE NAME (DELANEY NO.)	FOOD CATEGORY NO.	NAME	# OF FIRMS	********** (AGE)	POSSIBLE DAILY INTAKE, MG. ********** AVERAGE	HIGH A	HIGH B
VITAMIN B12 NAS 0244	02	BREAK CEREL(R)	6	0-5 MO.	.000040	.000170	.000340
				6-11 MO.	.002230	.001990	.000070
				12-23 MO.	.002140	.000090	.023490
				2-5+ YR.	.000050	.000100	.000000
VITAMIN B12 NAS 0244	03	OTHER CHAIN(R)	*	0-5 MO.	.001000	.003400	.001000
				6-11 MO.	.019100	.057700	.019400
				12-23 MO.	.032100	.075000	.032000
				2-5+ YR.	.0[illegible]	.120000	.0[illegible]
VITAMIN B12 NAS 0244	05	MILK PROD(R)	*	0-5 MO.	.000041	.000400	.000000
				6-11 MO.	.000[illegible]	.000010	.000240
				12-23 MO.	.000450	.017440	.000450
				2-5+ YR.	.000050	.012000	.000000
VITAMIN B12 NAS 0244	22	SNACK FOOD(R)	*	0-5 MO.	**********	.000000	**********
				6-11 MO.	.000000	.000000	.000000
				12-23 MO.	.000000	.000000	.000000
				2-5+ YR.	.000000	.000000	.000000
VITAMIN B12 NAS 0244	23	BEV TYPE I(P)	*	0-5 MO.	.000000	.000000	.000000
				6-11 MO.	.000000	.000000	.000000
				12-23 MO.	.000000	.000000	.000000
				2-5+ YR.	.000000	.000000	.000000
VITAMIN B12 NAS 0244	24	BEVERAGE VEG(P)	*	0-5 MO.	.000000	.000000	.000000
				6-11 MO.	.000000	.000000	.000000
				12-23 MO.	.000000	.000000	.000000
				2-5+ YR.	.000000	.000000	.000000
VITAMIN B12 NAS 0244	31	BAKED GOODS(R)	*	0-5 MO.	.000000	.000000	.000000
				6-11 MO.	.000000	.000000	.000000
				12-23 MO.	**********	**********	**********
[illegible]	[illegible]	[illegible]	*	0-5 MO.	[illegible]	[illegible]	[illegible]
				6-11 MO.	[illegible]	[illegible]	[illegible]
				12-23 MO.	[illegible]	[illegible]	[illegible]
VITAMIN B12 NAS 0244	ALL CATEGORIES **********		16	0-5 MO.	.[illegible]	1.[illegible]	1.[illegible]
				6-11 MO.	[illegible]	1.[illegible]	[illegible]
				12-23 MO.	[illegible]	[illegible]	[illegible]
				2-5+ YR.	[illegible]	[illegible]	[illegible]

Table 90. Comprehensive GRAS Survey -- NAS/NRC 1972 (Table 2) (0854)

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, %
TRIETHYL CITRATE (CONT.)	20	CELAIN PROD(R)	5	.00077	.00131
NAS 0234 FEMA 3003	23	BEV TYPE I(R)	12	.00120	.00344
	24	BEV TYPE II(R)	*	.00150	.00300
	30	HARD CANDY(R)	*	.00093	.00366
	31	CHEWING GUM(R)	*	.05022	.05022
VITAMIN A NAS 0241	04	FATS OILS(R)	4	.00083	.00083
	05	MILK PRODS(R)	*	.00016	.00066
	23	BEV TYPE I(R)	*	.00300	.00300
VITAMIN A ACETATE NAS 0242	02	BREAK CERLS(R)	*	.00010	.00010
	04	FATS OILS(R)	*	.00095	.00135
	14	PROCSD VEGS(R)	*	.02700	.03000
VITAMIN A PALMITATE NAS 0243	01	BAKED GOODS(R)	5	.00001	.00002
	02	BREAK CERLS(R)	9	.00480	.00760
	03	OTHER GRAIN(R)	*	.00001	.00010
	04	FATS OILS(R)	5	.00157	.00364
	05	MILK PRODS(R)	12	.00047	.00062
	07	FROZN DAIRY(R)	*	.00250	.00250
	10	MEAT PRODS(R)	*	.00061	.00061
	11	POULTRY(R)	*	.00061	.00061
	14	PROCSD VEGS(R)	*	.00019	.00035
	16	SOFT CANDY(R)	*	.00300	.00300
	18	SWEET SAUCES(R)	*	.00001	.00008
	22	SNACK FOODS(R)	*	.00000	.00000
	23	BEV TYPE I(R)	4	.00576	.00576
	25	NUT PRODS(R)	*	.01800	.02000
	28	IMIT DAIRY(R)	*	.00000	.00000
VITAMIN B12 NAS 0244	02	BREAK CERLS(R)	6	.00001	.00009
	03	OTHER GRAIN(R)	*	.00020	.00020
	05	MILK PRODS(R)	*	.00001	.00001
	22	SNACK FOODS(R)	*	.00000	.00000
	23	BEV TYPE I(R)	*	.00000	.00000
	26	BROCRST VEG(R)	*	.00015	.00015
VITAMIN D2 NAS 0245	01	BAKED GOODS(R)	*	.00001	.00010
	02	BREAK CERLS(R)	8	.00002	.00010
	03	OTHER GRAIN(R)	*	.00001	.00010
	04	FATS OILS(R)	4	.00002	.00002
	05	MILK PRODS(R)	14	.00010	.00010

Table 90. Comprehensive GRAS Survey -- NAS/NRC 1972 (Table 3) (0854)

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, %
0182	SODIUM BICARBONATE (CONTINUED)	83	FORMULAS(B)	*	.00510	.00510
0188	SODIUM CHLORIDE	81	BAKED GOODS(B)	*	.50000	.75000
		83	FORMULAS(B)	6	.00000	.00004
		84	PROCSD FRUIT(B)	*	.00000	.00000
		85	MEAT PRODS(B)	*	.25000	.25000
		86	POULTRY(B)	*	.25000	.25000
		87	EGG PRODS(B)	*	.25000	.25000
		89	PROCSD VEGS(B)	*	.25000	.25000
		90	PUDDINGS(B)	*	.25000	.25000
		92	MEAT DINNER(B)	*	.25000	.25000
		93	COMB DINNER(B)	*	.25000	.25000
0189	SODIUM CITRATE	83	FORMULAS(B)	5	.03432	.04631
0192	SODIUM HYDROXIDE	83	FORMULAS(B)	*	.03700	********
0194	SODIUM METAPHOSPHATE	83	FORMULAS(B)	*	.02000	.0400
0197	SODIUM PHOSPHATE DI	83	FORMULAS(B)	*	.01320	.01320
0221	THIAMINE HYDROCHLORIDE	82	CEREALS(B)	*	.00400	.00400
		83	FORMULAS(B)	7	.00012	.00549
		93	COMB DINNER(B)	*	.00030	.00030
0222	THIAMINE MONONITRATE	81	BAKED GOODS(B)	*	.00100	.00120
		82	CEREALS(B)	*	.00018	.00160
0227	TOCOPHEROLS CONC MIXED	83	FORMULAS(B)	*	.00122	.00146
0228	D-ALPHA TOCOPH ACET	83	FORMULAS(B)	5	.00146	.07095
0243	VITAMIN A PALMITATE	83	FORMULAS(B)	8	.00025	.00038
0244	VITAMIN B12	81	BAKED GOODS(B)	*	.00400	.00470
		83	FORMULAS(B)	6	.00023	.00034

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