

Monograph on Iodine & Iodine Salts

#65

5/9/73

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ON  
IODINE  
AND  
IODINE SALTS

TR-72-1552-26

Submitted Under:  
Contract No. FDA 72-104

May 9, 1973

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# IODINE SALTS USED IN FOODS

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## IODINE AND IODINE SALTS

### Summary

Elemental iodine is classed as a rare element, occurring in the earth's crust as about one part per 15 million; there are no natural isotopes. The chief sources of iodine are Chilean Caliche (a nitrate-bearing rock) and seaweed. Radioactive isotopes of iodine have been obtained from uranium fission, by proton bombardment of elemental iodine, or by neutron irradiation of tellurium or xenon; the most familiar isotope widely used experimentally is  $^{131}$ , a beta emitter with a half-life of 8 days.

Cuprous iodide occurs in nature as the mineral "marshite," but the discovery of iodine itself was incidental to the manufacture of nitrates for gun powder from seaweed ash by Napoleon's scientists, in the early nineteenth century. Seaweed and other marine forms had been used strictly on an empirical basis since ancient times as a treatment for goiter, long before iodine was known or the nature of the disease understood. By the 1820's, iodine and the disease, goiter had become inseparably associated; during the last thirty-five years of the century, however, the use of iodine as a treatment for goiter fell into disrepute and was abandoned in favor of the germ-theory popularized by Pasteur. The demonstration of the presence of iodine in the thyroid gland in 1895 renewed the interest in iodine therapy, and subsequent investigations revealed the thyroid utilization of iodine in the production of the hormone thyroxine. Only after microtechniques of sufficient refinement had evolved was the study of human metabolism of iodine possible; the quantities of iodine involved are minute, of the order of micrograms. G. M. Curtis (64) in an excellent review of the history of "biologic iodine", the human requirements and metabolism of iodine, cites the basal human adult iodine requirement as ranging from 44-75 micrograms daily - or an average of about 1 microgram per kilogram of body weight. Optimally, the daily requirement of iodine for ordinary activities would range between 100 and 200 micrograms daily. Thus, 200 micrograms should satisfy the daily requirements, including some reserve iodine, for an adult weighing 70 kilograms; this need would be more than amply supplied by the daily use of iodized salt containing 0.01% KI.

Information concerning the acute toxicity of iodine salts has been largely acquired from the investigations of Webster et al. (399, 400, 398) who studied the effects of potassium and sodium iodates and iodides in mice, guinea pigs and dogs. The degree of toxicity varies with the salt, the manner in which it is administered and the condition of the animal with regard to diet, as may be seen in the table presented in this monograph under Biological Data, Acute Toxicity. The iodates, potassium and sodium, given orally to fasted mice, produced LD<sub>50</sub>'s of 531 and 505 mg/kg body weight; the iodides similarly administered showed LD<sub>50</sub>'s of 1862 and 1650 mg/kg. The iodates appeared considerably more toxic than the iodides. Small doses of KIO<sub>3</sub> given mice over a period of several months for a total dose of about 1231 mg/kg/day showed minimal toxic effects, due to an increased tolerance for doses actually exceeding the single dose LD<sub>50</sub> of about 1100 mg/kg in animals not fasted. A comparable dose for a 70 kg human would amount to 5-20 grams of KIO<sub>3</sub> given in a single day, a dose 14,000-

56,000 times that of the daily iodine requirement for man. (NRC recommended daily iodine allowance is 0.003 mg/kg body weight). Frey (95) reported a case of a man who used an expectorant containing KI for about 10 years; calculations indicated that the man had ingested more than 500 grams of KI per year.

Little information is available regarding the toxicity in animals of cuprous iodide, ( $\text{Cu}_2\text{I}_2$ , Lange: Cul, Merck). Oral doses of 2000 mg/kg given rats were not fatal; doses of 500 mg/kg produced no ill effects according to studies by Mittler and Benham (247). A dose of 125 mg of  $\text{Cu}_2\text{I}_2$  fed to a 250 gm rat is 30,000 times the daily iodine requirement for normal thyroid activity. The authors concluded that  $\text{Cu}_2\text{I}_2$  can be considered non-toxic at levels meeting the requirements for iodine. Cuprous iodide is included in the GRAS listing as a dietary supplement added to table salt in concentrations of 0.01%.

Potassium iodate has been granted "prior sanction via clearance" for optional use in bakery products up to 0.0075 parts per 100 of flour used. Webster et al. (399) observed that large doses of  $\text{KIO}_3$  in mice caused intoxication and death; hemoglobinuria, hemosiderin deposits in the kidneys and fatty visceral changes were seen. Oral doses of  $\text{KIO}_3$  of 14-500 mg/kg increased gastric pH and produced degenerative changes in the parietal cells. The subacute studies in mice using  $\text{KIO}_3$  by Webster et al. (400) have been noted already. Their studies of guinea pigs using divided doses of  $\text{KIO}_3$  as high as 485 mg/kg for five days, (exceeding the single dose LD50), showed a tolerance in the animals for iodine which the authors stated to be of considerable interest in the light of the proposed use of iodate in salt for human use. Dogs were also subjected to iodate experiments: at doses of 100 mg/kg  $\text{KIO}_3$ , no animals died of four tested; at 200 mg/kg, one of three dogs died; and at 250 mg/kg, all three animals tested died. At the lower doses, emesis, slight anorexia and general listlessness were observed, but at cessation of treatment, normal appetite and behavior returned. The maximum dose well-tolerated by the dogs was estimated to be about 60 mg/kg when given for about 80 days.

Perdomo et al. (283) tested mature Leghorn hens with various doses of potassium iodide in the diet and reported the effects on egg production, fertility, embryonic mortality and hatchability. At dosages of 1250 ppm KI in the diet, egg production was slightly reduced; at 2500 and 5000 ppm, production ceased or nearly so. The KI did not influence egg fertility, but early embryonic death and delayed or reduced hatching did occur. The mode of action of KI was suggested to be due to hormonal effects. Arrington et al. (17) performed a similar study, but included pullets. The results were essentially the same as those seen by Perdomo et al.; when the pullets, however, ceased to lay, it was noted that mature ova were present, but ovulation did not occur.

Acute and chronic iodide intoxication in man was discussed in a paper by Bianco et al. (38). The acute form is rare; the symptoms, angioneurotic edema, fever, arthralgia, lymph-adenopathy, eosinophilia and occasional multiple petechiae of skin and mucous membranes. Chronic

iodism is characterized by gingivitis, increased salivation with a metallic taste, coryza, eye irritation and puffy lids. Salivary glands may enlarge, and the throat become inflamed. Diarrhea, fever and headache often accompany chronic iodism. A case was described of a patient having taken a multivitamin preparation containing 0.15 mg KI for 10 days; symptoms of chronic iodism were present. Removal of the iodine-containing preparation restored the patient to normal conditions. Iodism was observed to mimic numerous other diseases or conditions.

A general attitude that continuous ingestion of iodine is not harmful was questioned by Frey (95) who presented five case histories of hypothyroidism due to excessive use of KI chiefly as an expectorant in the treatment of asthma. Myxoedema and enlarged thyroid glands characterized these patients who had long histories of iodine intake; why iodine behaves in this manner was indicated as being poorly understood, and probable causes, speculative.

An abstract of investigations by Wada (397), without experimental details, of treatment of rabbits with sodium iodate intravenously administered, confirmed the results of other studies in which black pigmentation of the retina of the eyes together with retinal atrophy is seen in iodate toxicity. The rabbits also showed atrophy of the liver and heart muscle; lungs were damaged, and adrenal and spleen abnormalities appeared.

Cuprous iodide was shown to have anti-inflammatory properties in experiments on rats by Sutter et al. (363). Granuloma pouches were developed in rats by injecting subcutaneously 25 cc of air and 1 cc of 1% croton oil in corn oil; the animals to be treated with CuI received oral doses of 250 mg/kg CuI/day for 12 days. Contents of the pouches and the pouch tissues were weighed after sacrifice; CuI given orally showed anti-inflammatory properties in the treatment of granuloma pouches.

Spindle-cell sarcomas implanted in white rats by Oberhauser et al. (265) had their growth inhibited by treatment with oral doses of 0.2 mg/100 g body weight solution containing 0.482 M KI and 0.083 M  $KIO_3$  three times daily (daily dose of KI of (480) mg/kg plus about 100 mg/kg of  $KIO_3$ ). All controls implanted with the tumors died within 64 days; none of the treated died but rather actually showed no traces of the sarcomas, due to regression.

Seelich and Karrer (316) repeated essentially the same experiment reported by Oberhauser, but nearly all animals (Wistar rats) died within 30 days from either the tumor or from hemorrhagic gastritis or broncho pneumonia. No inhibition of tumor (Jensen sarcoma) growth was observed. The iodate-iodide treatment appeared completely ineffectual.

The suitability of  $KIO_3$  for the iodization of table salt in the place of KI used at that time in Bulgaria (1969) led Penchev et al. (282) to test the toxicity of the iodate on rats. Oral doses in distilled water of one microgram of  $KIO_3$  per ml. and 5 micrograms of  $KIO_3$ /ml  $H_2O$  produced no evidence of toxic changes in the animals; a single dose of 5 g  $KIO_3$  in 1 ml  $H_2O$  was injected peritoneally with 5 micrograms of  $^{131}I$  and again produced no adverse effects. The

authors concluded that  $KIO_3$  might be safely used for iodizing table salt for mass iodine prophylaxis.

A comprehensive report of the prevalence and treatment of goiter in Tasmamia was presented by Clements et al. (59). Tablets containing 10 mg KI had been available to school children over a 16-year period, with considerable reduction in the incidence of goiter, but some regions remained high in the prevalence of goiter. In 1955,  $KIO_3$  was introduced into the bread flour at about 2 ppm and proved more effective in overcoming goiter than the distribution of iodide in tablets.

The radioactive isotope  $I^{131}$  has for some time been a useful experimental tool in studies of the thyroid and the metabolism of iodine; as a by-product of the nuclear age in reactor operations, however,  $I^{131}$  could constitute a serious hazard in the event of reactor accident or in the testing of nuclear devices. The use of stable KI and methyl thiouracil as therapeutic treatment in reducing the effects of  $I^{131}$  uptake in the thyroid were tested on rats by Takeuchi and Yoshizawa (368). Oral doses of  $I^{131}$  were accompanied by intraperitoneal injections of KI and methyl thiouracil at intervals; thyroid uptake of  $I^{131}$  was reduced some 90% and the whole-body burden about 70% of that in the controls.

Mielens et al. (241) demonstrated that iodides are effective anti-inflammatory drugs, as had Sutler et al. ten years earlier with Cul. They administered oral doses of 29-466 mg/kg/day of aqueous KI to rats previously induced with granuloma pouches. After nine days of treatment, pouch exudate and wall formation were reduced by 70% and 50% respectively. Rhesus monkeys with induced subcutaneous abscesses similarly treated with KI did not respond favorably. The treatment appeared to be "anti-fibrotic" in the successful applications.

Large doses of KI given orally to rabbits in the diet were shown to be anti-atherogenic in a study by Moyer et al. (250). The diet contained 2% cholesterol and 6% corn oil, augmented by KI or diiodotyrosine. Thyroxine was injected intraperitoneally several times weekly. At eight weeks, the sacrificed animals were examined for atheromata and for serum or liver cholesterol. Significant reduction in the formation of atheromata was observed.

A dose of 100-200 mg of stable KI given to humans before exposure to  $I^{131}$  was shown by Blum and Eisenbird (40) to largely prevent uptake of the radioactive isotope. The authors were motivated in the experiment by the same concern over the hazards of accidental exposure to  $I^{131}$  as noted in the paper by Takeuchi and Yoshizawa (368).

Davis and Saunders (72) described a medical case of tabes dorsalis treated with KI, orally administered one gram three times daily. Purpura of the lower extremities appeared after several weeks of treatment and proved to result from the iodide. Subsequent tests with doses as low as 0.3 g KI produced purpura, an evidence of toxic reaction to iodine.

Segal (332) discussed the use of KI in therapy of asthma, citing ten case-histories of patients given 2.4 KI/day over a period of

of years without ill-effect and with complete remission of asthmatic symptoms. These patients were considered atypical-however, and Siegal estimated that KI therapy was effective in only about 5-10% of bronchial asthma cases. Several undesirable side effects of KI therapy were noted. The paper was the subject of a discussion by various medical practitioners, with differing viewpoints of the usefulness of iodide therapy in asthma.

Oral sodium iodide and sodium iodate were observed to markedly reduce the hypoglycemia reaction in rats induced by injected thiourea in studies by McCreesh and Mann (235). The iodide was somewhat more effective than the iodate. Potassium iodate was shown in an earlier experiment by Mann (223) to be similarly effective in preventing thiourea-induced hypoglycemia in rats.

The availability of iodine from several compounds which might be used in animal salt blocks was investigated by Mittler and Benham (247) using rats and four iodine sources: KI, CuI, diiodothymol and 3-5-diiodosalicylic acid. All the iodine compounds at dose levels of 265 micrograms/kg body weight were effectively utilized, the CuI most effective. Further studies of CuI showed that as little as 1.5 micrograms of iodine per day prevented thyroid enlargement. A third test of all four iodine compounds at a dose level of 5.25 micrograms weekly for 8 weeks showed a protective influence; again CuI was most effective.

Experiments upon rats and human patients by Small et al. (349) demonstrated that the small intestine is the principal site of iodine absorption in both rats and humans. In the rat studies, a solution of KI was gastrically intubated and duodenally intubated in separate groups of animals. Comparisons were made of the degree of absorption from each rat. In human subjects, a saliva test was applied to patients given KI orally or by duodenal administration. A positive iodine saliva test appeared within 6-10 minutes after oral ingestion of KI; only 2-4 minutes elapsed after duodenal intubation.

Harrison et al. (119) in observations of human patients, some with normal thyroid function and others with abnormalities, demonstrated that a fixed dietary level of iodine leads to a fecal iodine excretion varying with thyroid activity, and a urinary excretion of iodine essentially normal in thyrotoxic and hypothyroid patients but low in non-toxic goiter patients. They also investigated fish as a chief dietary source of iodine in Great Britain. The fish were injected with  $^{131}$ I and after 48 hours were fed to patients who were shown to have completely absorbed the iodine from the fish. Boiling the fish loses 50-80% of the available iodine; grilling or frying retains about 80% of the iodine.

The influence of diverse environmental conditions, particularly temperature - upon the excretion of iodine from the human body was studied by Spector et al. (355). Five young men spent 8 hours a day, 5 days a week for eight weeks in a room alternately comfortable for a week and "hot moist" a week. Food consumed was measured, feces, urine and sweat were collected and iodine concentrations measured. Doses of KI, 2 mg daily were given. No evidence was gathered to indicate that sweating increased the iodine requirement; about 75% of

of the total iodine lost from the body was by urine excretion. Increased iodine intake increased urine output of iodine; fecal iodine excretion increased under "hot-moist" conditions with increased intake, but not under comfortable conditions.

The Silberbergs (337) reported that intraperitoneal injections of 0.1 cc of 2.5% solution KI in H<sub>2</sub>O stimulated skeletal tissue development in growing mice. The effects of KI were such to resemble those caused by administration by anterior hypophyseal hormone and of thyroxin, but to a lesser degree.

In order to test the findings of earlier investigators who noted that KI given to guinea pigs stimulated thyroid activity but affected only slightly the basal metabolism, Siebert (327) thyroidectomized guinea pigs, gave them KI orally and tested basal metabolisms. Respiratory quotients in the KI-fed group were higher, and basal metabolisms distinctly lower than in controls.

The relative effectiveness in maintaining blood iodine of KI, NaI and iod-ethamine when given orally 1 g/km to rabbits was tested by Boyd and Blanchaer (45). Inorganic and protein-bound iodine concentrations were measured; the inorganic iodine rose rapidly after administration and fell rapidly; the protein iodine rose more slowly and decreased slowly. The highest levels of blood iodine (both inorganic and protein) were observed from iod-ethamine, but KI maintained high levels longer. NaI was least effective.

Homer (132) showed that 200 mg KI per day fed to rats on a sterol-free diet produced moderate hypercholesteremia. The plasma cholesterol concentration in a group of rats fed KI rose from a pretreatment level of 50 mg % to 92 mg %; that of the groups given water rose to 60 mg % and a third group of animals given KCl showed an increase to 64 mg %. It was not known how the iodide influences the cholesterol blood levels.

The question of how such a large molecule as thyroglobulin (mol. wt. about 700,000) passes through cell membranes was the subject of an investigation by Dziemian (82). To test an hypothesis that thyroid proteolytic enzymes hydrolyze thyroglobulin into smaller polypeptides or peptones which are later recombined into the large molecules, Dziemian fed rats KI, sulfaguandine and thyrotropic pituitary hormone. Hypophysectomies were performed, and the thyroid glands removed after sacrifice of the animals; the amount of protein digestion in the whole thyroid tissue was determined. Similar treatment was given guinea pigs and the thyroid proteolytic activity also determined. In both animals, the thyroid activity was increased by the thyrotropic pituitary factor and by the KI; sulfaguandine and hypophysectomy both decreased the thyroid proteolytic activity.

The effect of a combined thiouracil and iodide diet upon the growth of young rats was studied by Taylor and Barrett (372). Thiouracil, KI or NaI, singly or in combinations, were fed to rats for 14 weeks, after which the animals were sacrificed. (A typical diet contained 0.0384% thiouracil and 0.0498% KI). Body and organ weights were measured and iodine concentrations determined. Growth was repressed

by combined thiouracil-KI, though neither substance singly affected growth; the action of the combination appeared to be synergistic. The mechanisms involved were unknown.

The action of goitrogens, that interfere with the thyroid production of thyroxine, can be overcome or prevented by adding certain animal tissues to the diet, as was demonstrated by Ackerman (3). Thiouracil and sulfaguanidine are goitrogenic. The influence of iodine on the growth of weanling rats fed a diet of thiouracil or sulfaguanidine and a duodenal powder was also observed. Both goitrogens inhibited growth, the thiouracil more so than sulfaguanidine; 10-30 micrograms of KI added to the diet enhanced the inhibitory influence of the goitrogens. Duodenal powder in the diet of the rats fed the goitrogens maintained normal growth, possibly due to the presence of a thyroid hormone-active component. High levels of iodine appear to function synergistically with goitrogens in blocking the thyroid synthesis of thyroxine.

The stimulating effect of KI on thyroid, parathyroid and adrenal glands as measured by the mitotic activity of those tissues was investigated by Blumenthal (41) in guinea pigs. Various diets, with or without iodine, were fed to the animals at different age levels from 2 weeks old to 4 months; one group received KI in daily doses of 0.01 or 0.05 g for 5-50 days. At sacrifice, the three glands were removed and cytological determinations of mitotic activity were made. The younger animals, up to 6 weeks of age, showed an increased mitotic activity in thyroid and parathyroid tissues due to very small amounts of KI in the diet; older animals showed no effect. There was evidence of a slight increase in mitotic activity in the adrenal cortex during a part of the KI treatment. Two other similar experiments with guinea pigs, using KI and determining mitotic activity of the thyroid, were performed by Gray and Loeb (107) and Margolin (226), with much the same results.

The difference between trace quantities of iodine and large doses of iodine in the phagocytosis of leukocytes in guinea pigs was studied by Gerasimova (102). Oral doses of KI given at a level of 1 gamma/kg increased phagocytosis; larger doses of 1600 gamma/kg inhibited phagocytosis.

Danowski and Greenman (65) investigated the effects of moderate and massive doses of KI on the protein-bound iodine in the blood of hospital patients. Moderate doses of KI, 0.2cc of a saturated solution daily, produced no significant changes in serum iodine; daily doses of 3-7 g KI given daily for from 1 to 4 months greatly increased the total iodine serum levels. No evidence of hyperthyroidism or toxic reactions were observed, despite the massive doses of KI.

A determination of the minimal KI dose completely inhibiting thyroidal uptake of iodine in humans was made by Koutras and Livadas (173). Doses of KI ranging from 5 to 80 mg and accompanied by 10 microcuries of I131 were given orally to 60 volunteers (10 additional persons served as controls and received only the I131). The minimal dose found was 40 mg of KI. In the event of accidental exposure to I131, an initial dose of 40 mg KI should be given to minimize the uptake of the radioactive isotope, and subsequent daily doses of 3.3 mg given to maintain protection.

Several early studies of the effects of KI on human subjects were performed by McEachern (237) and McEachern and Baker (236). Two grams of KI were given daily to hospital patients for 8 to 140 days and pulse rates measured. Some patients showed a gradual increase in pulse rate; others showed decreased rates. The second paper dealt with gradual weekly increases in KI doses of from 1 g daily per week to 3 g daily per week. Periodic electrocardiograph records were made; the results were negative. A few patients suffered from severe iodide reactions; the remainder showed no significant changes attributable to the iodide ingested.

No consistent changes in serum lipoproteins or cholesterol concentrations were observed in patients given daily doses of either 30 g tyrosine or 30 mg KI over a period of several months in a study by Strisower et al. (360). The study was motivated by the observation that inorganic iodine and tyrosine were the only known precursors of thyroxine synthesis, and that administering these substances might alter the concentration of serum lipoproteins.

# CUPROUS IODIDE

## Chemical Information

### I. Nomenclature

#### A. Common Names

1. Cuprous Iodide
2. Marshite (mineral)

#### B. Chemical Name

Cuprous Iodide

#### C. Trade Name

None

#### D. Chemical Abstracts Services Unique Registry Number

007681-65-4

### II. Empirical Formula

CuI (Merck Index:  $\text{Cu}_2\text{I}_2$ , Lange's Hndbk)

### III. Structural Formula

Not applicable

### IV. Molecular Weight

190.46

### V. Specifications

(GRAS as dietary supplement in table salt as source of dietary iodine up to 0.01% under 121.101)

### IV. Description

#### A. General Characteristics

Dense powder or cubic crystals (zinc-blende structure).

#### B. Physical Properties

Less photosensitive than CuBr or CuCl mp 588-606 degrees; bp about 1290 degrees;  $d_4^{25}$  5.63; extremely insoluble in water;

practically insoluble in dilute acids, alcohol; soluble in aqueous solutions of  $\text{NH}_3$ , alkali cyanides, thiosulfates, iodides; decomposed by concentrated  $\text{H}_2\text{SO}_4$  and  $\text{HNO}_3$ .

VII. Analytical Methods: From AOAC (21), pg. 529-530.

Iodide and bromide can be determined by A.O.A.C. 31.039 (21).

VIII. Occurrence

Occurs in nature as the mineral marshite (red-brown crystals).

POTASSIUM IODATE

Chemical Information

I. Nomenclature

A. Common Name

Potassium Iodate

B. Chemical Name

Potassium Iodate

C. Trade Name

None

D. Chemical Abstracts Services Unique Registry Number

007758-05-6

II. Empirical Formula

$KIO_3$

III. Structural Formula

Not applicable

IV. Molecular Weight

214.00

V. Specifications

Food Chemicals Codex  
Assay

Not less than 99.0% and not more  
than the equivalent of 101.0%  
of  $KIO_3$  after drying.

Limits of Impurities

Arsenic (as As)

Not more than 3 ppm (0.0003%)

Chlorate

Passes test (limit about 0.01%)

Heavy metals (as Pb)

Not more than 10 ppm (0.001%)

Iodide

Passes test (limit about 20 ppm)

Loss on drying

Not more than 0.5%

\*Insoluble matter

0.005%

pH of 5% solution at 25°C

5.0 to 8.0

Chloride and bromide

(as Cl)

0.01%

Nitrogen compounds (as N)	0.002%
Sulfate (SO <sub>4</sub> )	0.005%
Iron (Fe)	0.001%
Sodium (Na)	0.005%

\* This and succeeding items from NAS/NRC (256) information (Prior sanction for use in bakery products, up to 0.0075 pp 100 parts by weight of flour used)

## VI. Description

### A. General Characteristics

White, odorless, crystalline powder

### B. Physical Properties

Soluble in water (1 g/15 ml H<sub>2</sub>O); insoluble in alcohol; pH of 1 in 20 solution between 5 and 8.

### C. Stability

Store in well-closed containers

## VII. Analytical Methods

To 1 ml of a 1 in 10 solution of the sample add 1 drop of starch T.S. and a few drops of 20% hypophosphorous acid. A transient blue color appears. (Food Chemical Codex)

Iodates in white and whole wheat flour can be determined according to A.O.A.C. methods 13.045, 13.046, and 13.048.

## VIII. Occurrence

Granted prior sanction via clearance for optional use in flour: up to 0.0075 parts per 100 parts flour.

POTASSIUM IODIDE

Chemical Information

I. Nomenclature

A. Common Name

Potassium Iodide

B. Chemical Name

Potassium Iodide

C. Trade Names

None

D. Chemical Abstracts Services Unique Registry Number

007681-11-0

II. Empirical Formula

KI

III. Structural Formula

Not applicable

IV. Molecular Weight

166.02

V. Specifications

Food Chemicals Codex  
Assay

Not less than 99.0% and not more  
than the equivalent of 101.5% of  
KI after drying

Limits of impurities

Arsenic (as As)

Not more than 3 ppm (0.0003%)

Heavy metals (as Pb)

Not more than 10 ppm (0.001%)

Iodate

Not more than 4 ppm (0.0004%)

Loss on drying

Not more than 1%

Nitrate, nitrite, ammonia

Passes test

Thiosulfate and barium

Passes test

\*Insoluble matter

0.005%

pH of 5% solution at 25°C

7.0 to 9.2

Chloride and bromide

(as Cl)

0.010%

Nitrogen compounds (as N)

0.001%

Phosphate (PO <sub>4</sub> )	0.001%
Sulfate (SO <sub>4</sub> ) <sup>4</sup>	0.005%
Barium (Ba) <sup>4</sup>	0.002%
Calcium, magnesium and R <sub>2</sub> O <sub>3</sub> precipitate	0.005%
Iron (Fe)	0.0002%
Sodium (Na)	0.005%

\* This and succeeding items from NAS/NRC (256) information (GRAS as nutrient and/or dietary supplement in table salt up to 0.01%)

## VI. Description

### A. General Characteristics

Hexahedral (cubical) crystals colorless or white, white granules or powder

### B. Physical Properties

Colorless or white, cubical crystals, white granules, or powder. Slightly deliquescent in moist air; or long exposure to air becomes yellow due to liberation of iodine, and small quantities of iodate may be formed; light and moisture accelerate the decompn. Aq solns also become yellow in time due to oxidation, but a small amount of alkali prevents it. d 3.12. mp 680 degrees; volatilizes at higher temp. One gram dissolves in 0.7 ml water, 0.5 ml boiling water, 22 ml alcohol, 8 ml boiling alcohol, 51 ml abs alcohol, 8 ml methanol, 75 ml acetone, 2 ml glycerol, about 2.5 ml glycol. Potassium iodide solns readily dissolve elemental iodine. The aq soln is neutral or, usually, slightly alkaline. pH: 7-9. Thirty g KI with 21 ml water gives 30 ml of a saturated soln at 25 degrees C.

### C. Stability

Store in well-closed containers

## VII. Analytical Methods

See this section under cuprous iodide

## VIII. Occurrence

KI is prepared according to equation:  $HI + KHCO_3 = KI + H_2O + CO_2$

GRAS as nutrient and/or dietary supplement in table salt up to 0.01%.

Cleared for use as a nutritional supplement in mineral and vitamin-mineral preparations marketed under labeling which provides that the maximum daily intake of the additive does not exceed 0.15 mg of iodine, under section 121.1073. The label of the additive shall bear: (A) The name of the additive; (b) A statement of the concentration of the additive in any mixture.

# SODIUM IODATE

## Chemical Information

### I. Nomenclature

#### A. Common Name

Sodium Iodate

#### B. Chemical Name

Sodium Iodate

#### C. Trade Names

None

#### D. Chemical Abstracts Services Unique Registry Number

007681-55-2

### II. Empirical Formula

$\text{NaIO}_3$

### III. Structural Formula

Not applicable

### IV. Molecular Weight

197.90

### V. Specifications

Not Found

### VI. Description

#### A. General Characteristics

White, crystalline powder

#### B. Physical Properties

Density 4.28. Soluble in about 11 parts water, 3 parts boiling water; insoluble in alcohol; aqueous solution neutral.

### VII. Analytical Methods

Add 1 drop of starch T.S. to 1 ml of a 1 in 10 solution of the sample; addition of several drops of 20% hypophosphorous acid produces a transient blue color.

### VIII. Occurrence

Not found

## Biological Data

### I. Acute Toxicity

Substance	Animal	Sex & No.	Route	Dosage (Body Wt. mg/kg)	Measurement	Ref.
KIO <sub>3</sub>	Mice	140	i.p.	136 ± 5	LD <sub>50</sub>	399
KIO <sub>3</sub>	Mice	90	oral	1177 (not fasted)	LD <sub>50</sub>	399
KIO <sub>3</sub>	Mice	110	oral	531 (fasted)	LD <sub>50</sub>	399
KIO <sub>3</sub>	Guinea pig	-	oral	400 (fasted)	LD <sub>50</sub>	400
KIO <sub>3</sub>	Dog	3	oral	200-250	Min. LD	398
KI	Mice	110	i.p.	1177 ± 30	LD <sub>50</sub>	399
KI	Mice	80	oral	2068	LD <sub>50</sub>	399
KI	Mice	90	oral	1862 (fasted)	LD <sub>50</sub>	399
KI	Rat	-	i.v.	285	Lethal Dose	239
NaIO <sub>3</sub>	Mice	100	i.p.	119 ± 4	LD <sub>50</sub>	399
NaIO <sub>3</sub>	Mice	90	i.v.	108 ± 4	LD <sub>50</sub>	399
NaIO <sub>3</sub>	Mice	140	oral	505 (fasted)	LD <sub>50</sub>	399
NaIO <sub>3</sub>	Dog	-	i.v.	200	Lethal Dose	239
Nal	Mice	110	i.p.	1690 ± 85	LD <sub>50</sub>	399
Nal	Mice	50	i.v.	1500	LD <sub>50</sub>	399
Nal	Mice	130	oral	1650 (fasted)	LD <sub>50</sub>	399
Nal	Rat	-	i.v.	1300	LD <sub>50</sub>	239

### II. Short Term Studies

#### Cuprous iodide

##### Rat

Acute and chronic toxicity studies were made by Cu<sub>2</sub>I<sub>2</sub> and 3-5-diiodosalicylic acid by Mittler and Benham (247) using Sprague-Dawley female albino rats reared on a low-iodine diet (other experiments by these authors on absorption and retention of iodine compounds are discussed in this monograph under the heading of Biochemistry II - Absorption and Excretion).

Oral doses of 2000 mg/kg body weight of Cu<sub>2</sub>I<sub>2</sub> fed to 5 rats produced diarrhea but no fatalities; doses of 500 mg/kg Cu<sub>2</sub>I<sub>2</sub> in 5 rats produced no ill effects. A dose of 125 mg Cu<sub>2</sub>I<sub>2</sub> fed to a 250 gm rat is 30,000 times the daily requirement such a rat would need to maintain normal thyroid glands, thus the rat would require only 0.0000039 gm/day. Autopsies on rats fed 0.1 and 1.0 gm Cu<sub>2</sub>I<sub>2</sub>/kg of diet for 5 months showed no gross liver, kidney or intestinal abnormalities. At the dose levels

necessary to supply iodine needed for normal thyroid activity,  $Cu_2I_2$  can be considered non-toxic.

### Potassium iodate

#### Mice

Early investigators in the 19th century, observed the toxicity of iodates appearing as contaminants in iodides used in therapy. Webster et al. (399) made a comparative study of the acute, single-dose toxicity of potassium and sodium iodides and iodates. Female white Swiss mice of the NIH strain were fasted for 17-20 hours and were injected intravenously or intraperitoneally with iodate and iodide solutions and the  $LD_{50}$  determined. The results appear in tables following:

**TABLE 1**  
*Comparative toxicities of iodates and iodides*  
Intraperitoneal injection of 15 to 20 gm. female white Swiss mice fasted overnight on sawdust and for 1 hour after injection.

	3% $KIO_3$	3% $NaIO_3$	3% KI	2.3% NaI
Number of mice used.....	140	100	110	110
$LD_{50}$ in mgm./kgm.....	$136 \pm 5$	$119 \pm 4$	$1117 \pm 30$	$1690 \pm 85$
$LD_{50}$ in millimoles/kgm.....	$0.635 \pm 0.023$	$0.601 \pm 0.020$	$6.73 \pm 0.18$	$11.27 \pm 0.57$
Range in survival time (hr.)*....	2-47	1-32	16-57	8-52
Average survival time (hr.)*....	23	21	36	16
Highest dosage tolerated by 10/10 mice without death (mgm./kgm.).....	100	90	756	1200
Dosage range in mgm./kgm.....	76-265	81-245	658-2010	1000-3500

\* Based on dosage near  $LD_{50}$  level.

**TABLE 2**  
*Comparative toxicities of iodates and iodides*  
Intravenous injection of 15 to 20 gm. female white Swiss mice fasted overnight on sawdust and for 1 hour after injection.

	3% $NaIO_3$	2.3% NaI
Number of mice used.....	90	50
$LD_{50}$ in mgm./kgm.....	$108 \pm 4$	>1500
$LD_{50}$ in millimoles per kgm.....	$0.546 \pm 0.020$	>10
Range in survival time (hr.).....	16-29*	13-61**
Average survival time (hr.).....	cir. 21*	cir. 40**
Highest dosage tolerated by 10/10 mice without death (mgm. per kgm.).....	70	700
Dosage range in mgm. per kgm.....	70-150	700-1500

\* Based on dosage near  $LD_{50}$  level.

\*\* Based on dosage near  $LD_{50}$  level.

Six percent solutions of  $KIO_3$ , KI,  $NaIO_3$  and NaI were given orally by tube; the mortalities and  $LD_{50}$  values are presented in the following table:

TABLE 3  
Comparative toxicities of iodates and iodides  
Oral administration to 15 to 20 gm. female white Swiss mice.

	Mice not fasted**		Mice fasted on screens***		Mice fasted on sawdust***		Mice fasted on screens***	
	6% $KIO_3$	6% $KIO_3$	6% $KIO_3$	6% $NaIO_3$	6% KI	6% KI	6% KI	6% NaI
Number of mice used.....	90	140	110	140	80	130	90	130
$LD_{50}$ in mgm. per kgm.....	1177 ±61	815 ±20	531 ±21	505 ±26	2063 ±140	1982 ±90	1662 ±100	1650 ±90
$LD_{50}$ in millimoles per kgm.....	5.50 ±0.29	3.31 ±0.14	2.48 ±0.10	2.55 ±0.13	12.46 ±0.34	11.94 ±0.54	11.22 ±0.60	11.01 ±0.63
Range in survival time (hr.)*.....	3-16	2-14	2-53	2-14	13-64	10-18	13-39	8-46
Average survival time (hr.)*.....	9	10	13	7	47	15	23	21
Highest dosage tolerated by 10/10 mice without death (mgm. per kgm.).....	819	513	359	—	1750	1420	1260	—
Dosage range in mgm. per kgm.....	737-1750	447-1240	316-861	261-824	1380-3500	1120-3500	1120-2920	603-2820

\* Based on dosages near  $LD_{50}$  level.

\*\* Mice were in non fasted condition when injection was made. Dose was based on fasted body weight measured 24 hr. before injection.

\*\*\* Mice were fasted overnight and 1 hr. after injection.

Given in sufficient quantities, the iodates cause intoxication and death in mice. The hemolytic effects appear as hemoglobinuria, and histologically hemoglobin casts and hemosiderin deposits show in the kidneys. Fatty visceral changes are seen within 24 hours after ingestion of both iodates and iodides. The iodates in oral doses of 140-500 mg/kg often increase the gastric pH, and create degenerative changes in the parietal cells. The toxicity of potassium iodate varies greatly with the route of administration, as does that of the iodide.

Webster, et al. (400) experimented with mice and guinea pigs to determine the subacute toxicity of potassium iodate, which has been used as a prophylactic agent for anemic goiter. Seventy-six weanling female white Swiss mice, consisting of 19 sets of four litter mates each, were separated into four lots. These lots were variously administered the iodate in the drinking water; a 0.65% KI solution, equivalent to an iodine content of 0.84%  $KIO_3$ , served as a base for comparison with the concentrations given the mice, which were: 0.05%, 0.10%, 0.25%, 0.50% and 0.75%. Liquid consumption and weights of the animals were noted

twice weekly. Three mice in the 0.75% group died during the first week; the remaining 73 mice survived the 15-16 weeks of experimentation. After 12-13 weeks, all survivors were subjected to hematologic studies; at 15 weeks, half the animals were challenged by an oral dose of  $KIO_3$  at the  $LD_{50}$  level (1120 mg/kg). Survivors were sacrificed and autopsies performed; tissues were preserved for microscopic studies. No gross abnormalities were observed, but microscopic examination showed hemosiderin deposits in the renal convoluted tubules in nearly all mice receiving 0.50%  $KIO_3$  for 16 weeks. During the experiment, significantly lower values for red blood cells or hemoglobin in the higher dosage groups were observed, which together with the hemosiderin observations, suggest an increased hemolysis due to the iodate. A tolerance for small doses administered for several months along with food was shown by those mice receiving totals of 1231 mg/kg/day with only minimal toxic effects. As single doses, this exceeds the  $LD_{50}$ . To receive the same dosage as that given to mice, a 70 kg human being would have to ingest 5-20 g of  $KIO_3$  in one day, or in excess by 14,000 to 56,000 times as much as the daily requirement of iodine for man.

### Guinea pigs

Experiments similar to those with mice previously described in the paper by Webster et al. (400), were performed on guinea pigs by the same investigators. Thirty-six guinea pigs weighing from 200-250 g were divided into six groups of six each: 2 groups received  $H_2O$  only, 2 groups received 0.05%  $KIO_3$  in the drinking water, and 2 groups 0.25-0.50%. For 4 weeks, all animals remained in good physical condition and showed no striking changes in the blood. Postmortem examination revealed no gross abnormalities or significant histologic changes. Maximal intake of  $KIO_3$  reached values as high as 485 mg/kg/day for 5 days, which exceeds the estimated  $LD_{50}$  dose of  $KIO_3$  of something less than 400 mg/kg for fasted animals (Webster, 1954, unpublished). As observed in the mice similarly treated, guinea pigs can tolerate large doses of  $KIO_3$  when administered in divided doses over a period of time. This is of considerable interest in light of the use of iodate in salt for human use (author's statement).

### Dogs

The addition of potassium iodate to table salt as a prophylactic for endemic goiter has created a need for testing the substance for possible toxicity. Webster et al. (398) studied the toxicity of  $KIO_3$  on dogs, to determine the minimum lethal dose, the maximum allowable dosage of  $KIO_3$  consistent with maintenance of weight and appetite, and the acute and subacute toxic effects of the drug.

Three groups of fasted, mongrel dogs (not further described) were given powdered potassium iodate in gelatin capsules in single doses with the following results (number of animals that died/number dosed): 0/4 at 100 mg/kg; 1/3 at 200 mg/kg; 3/3 at 250 mg/kg. Based on deaths occurring within a week, the minimum lethal dose of  $KIO_3$  in dogs appeared to be between 200-250 mg/kg. Retinal changes were noted in one dog given 200 mg/kg. In subacute studies, four dogs (3 females, 1 male) weighing 8-16 kg were given iodate usually added to milk or given by capsule at levels of 6-100 mg/kg for 68-192 days. When appetite or weight of an animal declined markedly, the treatment was suspended until

recovery occurred. Periodic checks of the urine were made for iodate, iodine and hemoglobin. At the end of the experiment determinations of pH, specific gravity, protein, bilirubin, acetone bodies and sugar were made. Numerous blood examinations were performed, and following sacrifice of the animals, gross and microscopic studies were carried out. Pathological changes were confined largely to deposits of hemosiderin in the spleen, liver and kidneys and mild inflammation of the mucosa of the gastrointestinal tract. During the subacute treatment, occasional emesis, slight anorexia and listlessness were observed, but normal appetite and weight returned upon suspending treatment. It appeared that the maximum dosage level for dogs for protracted periods would be less than 60 mg/kg.

#### Potassium iodide

#### Chickens

The production, fertility, embryonic mortality and hatchability of eggs when hens were fed various levels of dietary iodine were the subjects of experiments by Perdomo et al. (283). Eighty mature White Leghorn hens were used in 2 trials: in the first trial, KI was added to the basal laying diet in amounts to provide 0, 2500 and 5000 ppm; the second trial added levels of 0, 312, 625, 1250 and 2500 ppm. The basal diets contained 17% protein and 0.4% iodized salt which contributed 0.3 ppm iodine to the diet. Potassium carbonate was added to the control diets to furnish potassium equivalent to the 2500 ppm iodine. Three groups of 10 hens each were in the first trial; five groups of 10 each in the second. On the day prior to iodine feeding and weekly thereafter the hens were artificially inseminated using pooled semen from normal males. Eggs were collected daily, identified and incubated periodically. On the 2nd, 4th, 9th and 14th days of incubation, eggs were candled to determine fertility and embryonic death. Hatchability was calculated as a percent of fertile eggs. The table below shows the results:

Production, Fertility and Hatchability of Eggs from Hens Fed Iodine (10 Hens per Treatment).

ppm iodine	No. eggs				Total eggs	% Fertile	% Embryonic deaths*	% Died in shell*	% Hatched*	Delayed incubation, No.	
	1	2	3	4						24-36	36+†
Trial 1											
0	31	26	29	32	118	94	5	6	88	—	—
2500	31	4	4	3	42	81	38	6	56	7	3
5000	22	0	1	0	23	83	11	32	58	4	1
Trial 2											
0	44	35	37	37	153	86	13	4	83	—	—
312	36	39	36	36	147	86	44	8	47	10	5
625	34	28	35	32	129	78	66	6	28	5	5
1250	37	32	27	28	124	77	62	7	31	4	6
2500	30	13	9	7	59	83	59	10	31	2	3

\* Based on fertile eggs.

† Hours beyond average for control.

At levels of 2500 and 5000 ppm iodine in the diet, egg production ceased or nearly so and production was slightly reduced at 1250 ppm. Within a week after the iodine treatment ceased, all hens resumed laying. Fertility of the eggs was not affected by the iodine, but early embryonic death, reduced hatchability and delayed hatching were observed. The mode of action of the iodine is unknown, but hormonal effects are suggested.

Arrington et al. (17) in a study very much like that of Perdomo et al., reviewed above, varied the experimental procedure in using 27-week-old White Leghorn pullets in addition to laying hens. Dosages of KI were virtually the same, as were the results. The two following figures show the effects of KI on egg production:

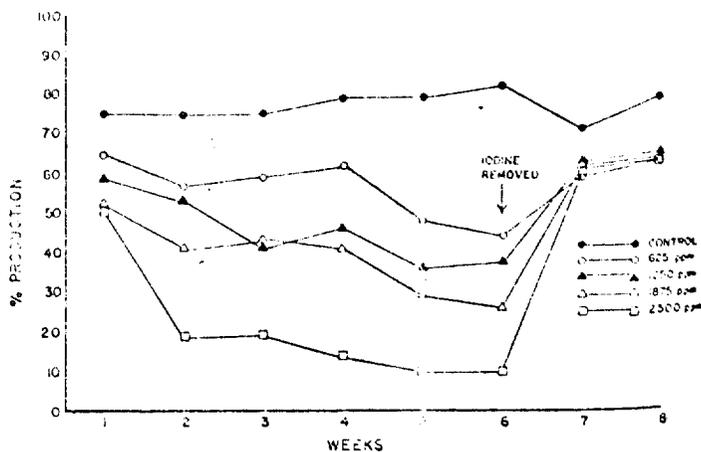


Fig. 1 Egg production of pullets during period of iodine feeding and after removal of dietary iodine

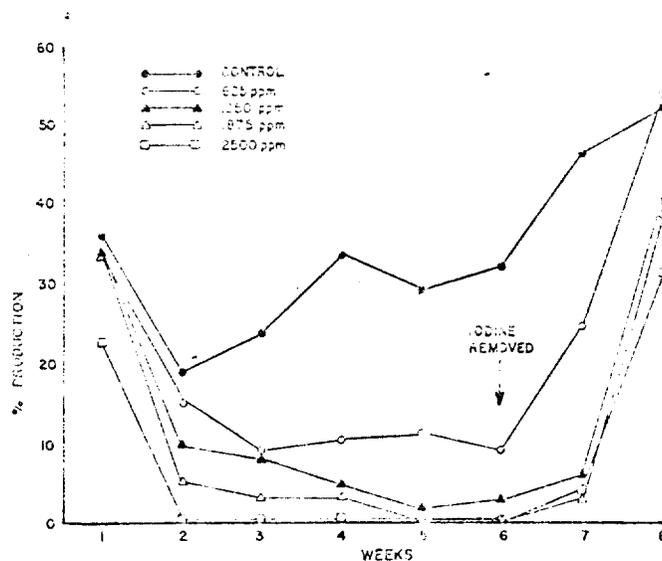


Fig. 2 Egg production of hens during period of iodine feeding and after removal of dietary iodine.

When pullets ceased to lay, they did not undergo moulting; a few mature hens moulted. Mature ova were present, but ovulation did not occur. Fertility of the egg was not affected by KI but there was high embryonic mortality, low hatchability and delayed hatching.

### Man

Branco et al (38) discussed the clinical manifestations of acute and chronic iodide intoxication. The acute form is rare and the symptoms usually appear within a few hours after the initial dose: angioneurotic edema, fever, arthralgia, lymphadenopathy, eosinophilia and occasionally multiple petechiae of skin and mucous membranes. The chronic form usually first presents a metallic or brassy taste in the mouth, gingivitis and a burning sensation of the oral mucosa, increased salivation, coryza, sneezing, irritation of conjunctivae and edema of the eyelids. Parotid and submaxillary salivary glands enlarge; pharynx and larynx may become inflamed in chronic cases. Skin lesions, diarrhea, fever and headache often accompany chronic iodism.

A case was described in which many of the symptoms of chronic iodism were present; the patient, a 54-year-old white male, had been taking a multivitamin preparation containing 0.15 mg KI for about 10 days. With the removal of the iodine-containing preparation, and a little more than a week of hospital treatment, the patient lost the iodine symptoms to a large degree, eventually fully recovering.

The case was presented chiefly as a caution to oral surgeons and others because iodism has marked similarities to numerous other "entities" with which it might easily be confused.

Frey (95) reported five cases of hypofunction of the thyroid gland in human patients due to extensive use of excessive doses of potassium iodide. Continuous consumption of iodine has not been generally considered harmful to a healthy thyroid, but Frey considers that idea not entirely true. The ingestion of large doses of iodine over prolonged periods of time may lead to goiter, and even to myxoedema.

Five case reports were given: (1) A 72-old male suffered from chronic bronchial asthma for 20 years during the last 10 of which he took an expectorant containing KI. It was calculated that he ingested more than 500 g/year. Examined in 1957 he was euthyroid; in March, 1962 he was still clinically euthyroid but the thyroid was slightly enlarged. By June the thyroid had increased in size, and in October, 1962, he appeared myxoedematous, and the thyroid was greatly enlarged. A thyroid biopsy showed parenchymatous hyperplasia. Iodine determinations showed blood serum values of over 100 micrograms/100 ml; after stopping the iodine therapy, the value fell to 15 micrograms/100 ml in 3 weeks time. Two months later the patient was clinically euthyroid, the thyroid having decreased in size to normal.

(2) Similar to above, however, after stopping the iodine and becoming euthyroid he returned to iodine therapy for his asthma and began to slide back into overt hypothyroidism.

(3), (4), and (5) All similar stories, the point being made that hypothyroidism and myxoedema occurred in patients with long histories

of iodine intake, and cessation of iodine restored all to normal or euthyroid condition. The author discussed probable causes for the inhibitory effect of iodine without conclusions beyond speculation; the factors influencing the thyroid gland behavior in the presence of heavy iodine loads are poorly understood.

#### Sodium iodate

#### Rabbits

An abstract of studies performed by Wada (397) presented information without experimental details of the effects of intravenous-injected  $\text{NaIO}_3$  on rabbits sacrificed on 4, 20 or 80 days after treatment and the organs examined histologically and histochemically for abnormalities. Other investigators have noted that the iodate causes black pigmentation of the retina of the eye; Wada found retinal atrophy and marked pigmentation also in the rabbit eye. Pycnosis, granulation and atrophy of the liver was observed. Atrophy of cardiac muscle, lung damage, spleen and adrenal gland abnormalities were also seen in the treated rabbits. Simultaneous administration of helenien, ACTH, methionin and pantothenic acid with the  $\text{NaIO}_3$  reduced the toxic effects of the iodate.

#### Sodium iodide

None

### III. Long Term Studies

None

### IV. Special Studies

#### Therapy

In veterinary medicine, iodine is used in the therapy of various nonspecific or chronic ailments. Sutter et al. (363) investigated the possibility that cuprous iodide possessed anti-inflammatory properties which explained the mechanism of its activity in therapeutic treatments.

Thirty rats of about 150 gm weight were divided into 3 groups of 10 each. A granuloma pouch was developed under the clipped skin of the back of each animal by injecting subcutaneously 25 cc of air and 1 cc of 1% croton oil in corn oil. The anesthetized rats were treated as follows: Group I received, orally, distilled water (0.02 cc/gm); Group II received orally 250 mg/kg body weight  $\text{CuI}$ /day; and Group III was injected subcutaneously with cortisone acetate (1 mg/day). Three of the animals in Group II died during anesthesia. After 12 days the animals were sacrificed and the pouches dissected free of adhering tissues. The fluid contents of each pouch were collected and the pouch tissue preserved and weighed. The findings are shown on the following page.

Effect of Various Treatments on Fluid Volume and Tissue Weight of Granuloma Pouches of Rats

Group	Treatment	No. of animals	Fluid volume <sup>1</sup>	Tissue weight
1	Distilled H <sub>2</sub> O oral daily injection	10	12.3 ± 5.08 cc.	2.1 ± 0.22 Gm.
2	CuI <sub>2</sub> , 250 mg./kg. oral daily administration	7 <sup>2</sup>	1.7 ± 0.28 cc. <sup>3</sup>	.83 ± 0.084 Gm. <sup>4</sup>
3	Cortisone acetate 1.0 mg./rat/day subcutaneous injection	10	7.4 ± 0.62 cc.	1.68 ± 0.14 Gm.

<sup>1</sup>Mean ± standard error S.E. =  $\sqrt{\frac{\sum(x^2 - \bar{x})^2}{(n-1)n}}$ ; <sup>2</sup>3 of 10 animals died of anesthetic accidents; <sup>3</sup>significantly lower than control value (p<0.01) and cortisone treated value (p<0.01); <sup>4</sup>significantly lower than control value (p<0.01) and cortisone value (p<0.01).

It appeared that CuI given orally to rats shows anti-inflammatory properties in the treatment of granuloma pouches.

Oberhauser et al. (265) on the basis of observations that cancer patients received favorable results from administration of aqueous solutions of KI-KIO<sub>3</sub>, performed experimental studies using white rats and solutions of potassium iodide-iodate. The rats were implanted with a spindle-cell sarcoma and then dosed with 0.2 ml/100 g body weight of a solution containing 0.482 M KI and 0.083 M KIO<sub>3</sub>, three times daily by gastric intubation. This treatment on 19 animals given two weeks before, or simultaneously, with tumor implantation showed a marked inhibition of tumor growth. Two more groups of 38 rats each were similarly treated, the non-treated animals except 4, died of tumors within the 64 days of observation, none of the treated animals died. The survivors all showed no traces of the tumor, due to regression occasioned by the iodide-iodate treatment.

A report (see preceding paper by Oberhauser, et al.) of presumed tumor-inhibiting influence of a potassium iodide solution containing potassium iodate in the treatment of Jensen sarcoma in rats led to a repetition of the experiment by Seelich and Karrer (316). Male Wistar rats, ages 3-3 1/2 months, weighing about 200 gm were implanted with 5-10 mm<sup>3</sup> samples of Jensen sarcoma. Some of the animals were implanted with tumor only, some treated only with the iodine solution (concentration not given), some pretreated with iodine and then implanted with the tumor, others pre- and posttreated with iodine before and after implantation, and some given only posttreatment after implantation. One hundred animals in all were used. Nearly all animals died within about 30 days, either from the tumor, or from hemorrhagic gastritis or bronchopneumonia. No inhibition of tumor growth was observed, and the high rate of mortality among those animals treated with the iodine rendered continued experimentation useless under the given circumstances.

The prophylactic and toxic effects of KIO<sub>3</sub> were studied by Penchev et al. (282) using rats; the experiment was performed to demonstrate that KIO<sub>3</sub> could be better used in the iodization of table salt than the iodide, KI, which was used in Bulgaria at that time (1969). The lower

solubility of  $KIO_3$ , in view of the hygroscopic nature of  $NaCl$ , would make a more stable mixture than the  $KI + MgCO_3$  added to  $NaCl$ . The possible danger of a toxicity associated with the iodate, however, required further experimental data than that already available.

White male rats, weighing 120-130 g were divided into three groups; Group 1 served as controls; all animals received a food briquette with 360 micrograms/kg iodine, and were given daily by intubation: Group 1 (10 rats) 1 ml distilled  $H_2O$ ; Group 2 (15 rats), 1 microgram  $KIO_3$  in 1 ml  $H_2O$ ; Group 3, (14 rats) 5 micrograms  $KIO_3$  in 1 ml  $H_2O$ . A second series of experiments of 2 groups of animals, one control (10 rats) and one fed an iodine-poor diet for a month (10 rats) and then given 5 g  $KIO_3$  in 1 ml  $H_2O$  was performed. This last group was injected peritoneally with 5 micrograms of  $I^{131}$  and the amount of the radioisotope in the thyroid was counted for 2, 4, 6 and 24 hours following injection. All animals at the termination of the experiments were exsanguinated and thyroid glands weighed and prepared for cytological examination. Myocardial, liver and kidney tissues were also subjected to histological studies for possible parenchymal toxic changes. Neither the 1 nor the 5 microgram  $KIO_3$ -fed animals showed marked decrease in the thyroid size or cytological evidence of injury to parenchymal organs. The 5 g  $KIO_3$ -treated rats showed a significantly lower absorption of  $I^{131}$  in the thyroid than in the controls, but not evidence of toxicity; such a decrease is noted in normal iodine diets given higher doses of iodine in any form. The authors concluded that  $KIO_3$  could be safely used for iodizing table salt for mass iodine prophylaxis.

Clements et al. (54) have presented an interesting report from Sidney, Australia, discussing the prevalence and treatment of goiter in Tasmania, which has long been recognized as an endemic goitrous region. After a preliminary survey in 1949 which revealed widespread goiter in the Tasmanian population, tablets containing 10 mg  $KI$  were made available to infants, preschool children and school children. These tablets were available in schools and child-health centers for weekly use over a period of about 16 years. Surveys made at 5-year intervals state-wide showed slow steady reduction in the prevalence of goiter; some regions remained high in goiter incidence, however, and the assumption was that the iodide tablets were not being properly utilized, even though some 36 million tablets had been distributed during the 16-year period.

In 1966, potassium iodate was substituted for some potassium bromate in the bread flour used throughout Tasmania as a universal prophylactic against endemic goiter. Studies have shown that 2 parts per million of the iodate in bread is effective, more so than the use of tablets, which were phased out by the end of 1967. The effectiveness of the supplemented bread in meeting the daily requirements for iodine, and the decrease in the prevalence of goiter in Tasmania are shown in the two following tables:

TABLE I—ESTIMATED MEAN IODINE INTAKE BY PERSONS OF DIFFERENT AGES BASED ON BREAD CONSUMPTION, COMPARED WITH RECOMMENDED DIETARY ALLOWANCE \*

Age	Males				Females			
	Bread intake (oz./day)		Iodine intake (µg./day)		Bread intake (oz./day)		Iodine intake (µg./day)	
	Mean	Range	Mean	R.D.A.	Mean	Range	Mean	R.D.A.
1-3	2.5	0-9	81	55-60	2.5	0-8	81	55-60
3-7	4.1	1-19	130	70-80	4.1	0-13	130	70-80
7-11	5.8	0-18	187	100-125	5.1	0-17	163	100-125
11-15	7.3	1-22	235	135	6.1	0-22	196	115
15-18	8.3	0-20	270	150	5.3	0-17	170	120
18-35	6.9	0-21	218	140	3.6	0-14	113	100
35-64	6.0	0-23	194	110	3.5	0-11	113	90

\*Adapted from data of Howeler-Coy.<sup>1</sup>  
 R.D.A. = Recommended dietary allowances.<sup>2</sup>

TABLE II—PREVALENCE OF GOITRE IN TASMANIA FROM 1949 to 1969 BY AGE

Year	4-5		6-8		9-11		12-14		15-17	
	P.G.	V.G.	P.G.	V.G.	P.G.	V.G.	P.G.	V.G.	P.G.	V.G.
<i>Boys</i>										
1949	23.5	0.0	27.9	1.2	34.8	3.7	38.3	6.4	37.4	3.5
1954	24.2	5.0	30.4	8.1	29.7	9.0	31.1	9.9	27.2	5.9
1960	21.5	5.0	22.9	7.2	21.7	7.2	19.2	6.5	18.4	3.7
1965	10.1	2.3	14.4	3.5	17.3	5.6	16.6	5.0	13.8	3.5
1969	8.2	0.2	11.0	1.6	14.3	3.4	15.6	2.1	9.2	1.1
<i>Girls</i>										
1949	20.1	2.7	28.8	3.1	41.5	8.4	44.7	20.8	49.0	23.3
1954	24.9	5.9	30.0	9.6	26.2	12.6	33.3	16.7	29.1	23.3
1960	26.4	7.5	25.7	9.1	24.9	10.5	23.3	14.6	22.9	15.6
1965	11.6	2.5	15.6	4.0	18.2	6.9	18.7	10.1	20.0	9.5
1969	8.6	0.3	12.7	1.2	17.4	3.6	18.1	5.1	16.2	3.8

P.G. = Palpable goitre. V.G. = Visible goitre.

A concern for the dangers inherent in the growing use of nuclear reactors led to a study of the  $^{131}\text{I}$  hazard (similar to that of Blum and Eisenbud) by Takeuchi and Yoshizawa (368). Considerable amounts of radioactive iodine are released in reactor accidents and the iodine is selectively absorbed by the thyroid gland and retained for relatively long periods. Stable iodine and methyl thiouracil were studied in rats as a possible first aid treatment in the event of a reactor accident exposing personnel to  $^{131}\text{I}$ . Female Wistar rats, 2 months old, weighing 150-200 g were used in groups of 5-10 animals, intubated orally with 0.3-1 microcuries per 0.1-0.5 ml of carrier-free  $^{131}\text{I}$ . A scintillation counter for whole-body radiation was used, and thyroid glands were removed at the end of the experiments for determination of iodine uptake. Stable KI and methylthiouracil were injected intraperitoneally at intervals and the effects in reducing  $^{131}\text{I}$  in the thyroid were observed. The two drugs, given in doses of 1.0 mg/kg of KI and 10.0 mg/kg of methylthiouracil, reduced the thyroid uptake of  $^{131}\text{I}$  to about 10% of the control animals; they were less effective in reducing the whole-body burden of  $^{131}\text{I}$ , lowering it to about 30%. Of the two drugs, methylthiouracil was more effective than KI, particularly when longer periods between  $^{131}\text{I}$  and drug application were studied.

A study similar to that described by Sutler et al. was performed by Mielens et al. (241) in somewhat more detail. It is noted that "iodides have been used against chronic inflammation during the past 100 years solely on an empirical basis". Textbooks describe the effects of iodides vaguely as "fibrolytic or histolytic". The following experiments were done in order to determine whether orally administered iodides have anti-inflammatory properties against a number of chronic and acute inflammations in experimental animals.

Sprague-Dawley rats of 125 g weight (12-18 rats in control groups and 6 rats in treated groups) were given granuloma pouches by the subcutaneous air pocket and croton oil technique described in the Sutter paper. Aqueous solutions of KI in doses ranging from 29-466 mg/kg/day were administered orally in the test animals; controls received water. Nine days after the croton oil injections the animals were sacrificed and the exudates in the pouch and the tissues of the pouch walls were measured. Three separate experiments in this manner were performed. The results are shown in the following table:

*Effect of KI against granuloma pouch formation*

A. Inhibition of exudate production							
Daily dose mg/kg	ml	Exp. 1 % Inh.	ml	Exp. 2 % Inh.	ml	Exp. 3 % Inh.	Av. % Inh.
— (controls)	8.9 ± 1.8	..	14.0 ± 1.8	..	15.5 ± 1.0	..	..
29	.....	..	9.5 ± 2.6	32	15.3 ± 1.8	1	16
116	4.3 ± 1.8	52	6.2 ± 1.3	56**	8.2 ± 1.3	47**	52
233	3.7 ± 1.3	58*	.....	..	.....	..	..
466	1.7 ± 0.4	81**	5.4 ± 1.3	61**	5.0 ± 2.4	68**	70

B. Inhibition of wall formation							
Daily dose mg/kg	ml	Exp. 1 % Inh.	ml	Exp. 2 % Inh.	ml	Exp. 3 % Inh.	Av. % Inh.
— (controls)	1.91 ± 0.26	..	2.92 ± 0.17	..	3.06 ± 0.14	..	..
29	.....	..	2.46 ± 0.32	16	3.19 ± 0.20	0	8
116	1.32 ± 0.36	31	2.04 ± 0.27	30*	1.88 ± 0.30	39**	33
233	1.26 ± 0.24	34	.....	..	.....	..	..
466	0.93 ± 0.11	51**	1.87 ± 0.21	36**	1.53 ± 0.40	50**	46

† rats/medicated group, 12-18 rats/control group.  
 \* Significant at  $p < 0.05$ .  
 \*\* Significant at  $p < 0.01$ .

The inhibition of exudate formation and of granuloma pouch wall formation were clearly indicated; exudate was reduced by 70% and wall formation by nearly 50% at the highest doses of KI.

A series of similar studies involving cotton granuloma, carageenan edema and croton oil edema produced results which failed to demonstrate an effective reduction of inflammation by the KI treatment, as shown in the table below:

*Effect of KI against cotton granuloma, carrageenan and croton oil edema, and turpentine inflammation*

Experiment	Dose mg/kg of KI	No. of animals	Quantitation of inflammation	% Inh.	
Cotton granuloma formation in rats	466	9	54.1 ± 5.2*	7	
	— (controls)	9	58.1 ± 4.6	..	
Carrageenan edema in rats	800	5	476 ± 45†	4	
	— (controls)	10	495 ± 32	..	
Croton oil edema in rats	800	6	251 ± 20‡	13	
	— (controls)	6	290 ± 24	..	
Turpentine inflammation in monkeys	a) 5-hour edema	100	71 ± 15‡	0	
		— (controls)	3	64 ± 14	..
	b) 7-day abscess	100	2	352 ± 63§	0
		— (controls)	3	338 ± 63	..

\* mg of dry granulomatous tissue.  
 † mg of edema.  
 ‡ size indices.  
 § sums of 6 measurements of abscesses (size indices) over 7 days.

Five Rhesus monkeys (2 treated with KI, 100 mg/kg/day; 3 controls), with induced subcutaneous abscesses due to intradermal injections of 0.1 ml of 25% turpentine, were included in the experiments, the results of which were shown above. Two of the animals were treated with KI, 100 mg/kg/day and three served as controls, receiving only water daily. Periodic measurements of the size of the abscesses were noted during a week of treatment. The KI did not produce a measurable reduction in abscess size. All the data from five types of induced inflammation indicate an "anti-fibrotic" effect of the KI treatment.

The anti-atherogenic effects of large doses of KI in rabbits was confirmed by experiments performed by Moyer et al. (250). Male rabbits of the Dutch belted strain were fed a diet containing 2% cholesterol and 6% corn oil, augmented by KI or diiodotyrosine. Thyroxine was intraperitoneally injected in doses of 0.05 mg 3 times weekly. After 8 weeks the animals were sacrificed and aortas examined for atheromata, sera were assayed for cholesterol and lipoproteins, and livers were excised and analyzed for cholesterol. The results are shown below:

TABLE I. Autopsy Findings on Rabbits Fed Cholesterol Diets Augmented by KI, Diiodotyrosine and Thyroxine.

Group*	No. of animals	Wt change (g)	Atheromata		Serum chol. (mg %)	Liver wt (g)	Liver chol. (%)
Exp. 1							
1% KI	9	—	.55†		.2170	70	2.9†
B†	10	—	1.55		2260	98	8.3
Exp. 2							
1% KI	8	106	1.00§		3830	—	—
B	14	212	2.70		3150	—	—
Exp. 3			Arch Thoracic				
.001% KI	10	132	2.20	1.40	2520	89	4.1
.01% "	9	60	2.11	1.44	2610	81	3.9
.1% "	8	-3	1.94	1.00	2490	75	3.6
1 % "	7	-59	.98§	.14	2400	63	2.3†
DIT	10	117	2.65	1.40	2360	67	3.7
T	10	-51	1.75	.75	2270	88	4.0
B	7	81	2.43	.93	2800	80	4.0

\* All diets contain 2% cholesterol, 6% oil. † B = Basic diet. ‡ p < .0001.  
 § p < .001. || 0.1% diiodotyrosine. ¶ Thyroxine, 0.15 mg/wk, i.p.

TABLE II. Serum Lipoprotein Levels of Rabbits Fed Cholesterol Augmented by KI, Diiodotyrosine and Thyroxine.

Group*	Serum lipoproteins, S <sub>i</sub> mg %					Total
	0-12	12-20	20-35	35-100	100-400	
Exp. 1						
1% KI	480	727	528	650	461	2846
B†	165	550	851	650	411	2627
Exp. 2						
1% KI	998	649	616	1064	1209	4536
B	362	750	1223	1309	682	4326
Exp. 3						
.001% KI	261	555	1006	1388	696	4006
.01% "	158	490	864	1000	546	3058
.1% "	208	491	786	1106	816	3407
1 % "	367	464	522	956	1050	3359
DIT‡	186	448	773	1202	829	3438
T‡	115	274	675	933	861	2858
B	241	481	845	1301	1073	3941

\* All diets contain 2% cholesterol, 6% oil. † B = Basic diet. ‡ 0.1% diiodotyrosine.  
 § Thyroxine, 0.15 mg/wk, i.p.

From the data observed, only large amounts of KI given orally in the diet of the rabbits had significant effect in reducing the formation of atheromata. Serum cholesterol and lipoprotein levels were elevated in all animals, but on the whole, levels of liver cholesterol were lowest.

Blum and Eisenbird (40) reported that a potential hazard of the application of nuclear energy lies in the exposure to  $^{131}\text{I}$  as a result of nuclear weapons testing, or from industrial, medical or research use of this radioisotope of iodine. Accidental exposures have been reported, and in at least one instance resulted in thyroid nodules, hypothyroidism and short stature. Of several radioisotopes of iodine,  $^{131}\text{I}$  is of greatest concern because of its long half-life and energetic beta and gamma emissions. Atmospheric radioactive iodine is deposited on foliage and areas grazed by cows, and cow's milk is the principle route for human absorption of the iodine particularly by children. The sequestering of iodine by the thyroid has led investigators to study the effect (therapeutic) of administering stable  $^{127}\text{I}$  in the form of KI before exposure to the radioactive iodine in order to reduce the uptake of  $^{131}\text{I}$ .

Sixty-two healthy volunteers, 37 men and 25 women, of ages 21-72 years were given a standard dose of 1.5 nanocuries ( $1.5 \times 10^{-3}$  microcuries, carrier free) of  $\text{Na}^{131}\text{I}$  in 10 ml water. Thallium activated sodium iodide scintillation crystals were placed on the neck of the subject over the thyroid gland, and a counter was used to determine the iodine uptake by the thyroid. Doses of stable  $\text{KI}^{127}$  in amounts of 5-1000 mg were administered prior to, with, or following radioactive doses under various conditions. The data are shown in the following table:

KI Dose, mg	Time of KI Dose, hr*	Subject No.	24-Hour Uptake, %		Reduction in Uptake, %
			Before KI	After KI	
5	0	1	33	7.3	78
25	0	2	41	14	66
25	1	3	31	7.1	77
25	2	4	18	11.3	36
25	6	5	24	7.5	69
50	0	6	28	0.8	97
50	1	7	41	6.1	85
50	2	8	34	6.8	80
50	3	9	35	9.0	75
50	4	10	36	6.0	83
50	5	11	17	0.1	100
100	0	12	25	0.0	100
100	0	13	34	1.3	96
100	0	14	37	0.1	100
100	1	15	32	0.7	98
100	1	16	36	0.5	99
100	1	17	25	1.1	95
100	1	18	52	1.2	98
100	1	19	31	0.1	100
100	1	20	29	0.5	98
100	1	21	13	1.1	92
100	1	22	32	0.8	97
100	1	23	13	0.4	97
100	1	Average ± SD	29 ± 11	0.6 ± 0.5	98 ± 3
100	1	24	28	3.1	89
100	1	25	44	2.9	93
100	1	Average ± SD	36 ± 11	3.0 ± 0.1	91 ± 3
100	2	26	28	5.7	80
100	2	27	18	2.3	88
100	2	Average ± SD	23 ± 7	4.0 ± 2.4	84 ± 6
100	3	28	17	6.8	60
200	0	8	16	0.8	100
200	0	29	18	0.3	100
200	0	30	36	0.6	98
200	0	31	13	0.2	94
200	0	19	31	0.4	94
200	0	32	20	0.5	97
200	0	21	13	1.3	90
200	0	22	32	0.8	97
200	0	23	21	0.1	100
200	0	34	32	0.5	98
200	0	Average ± SD	25 ± 8	0.3 ± 0.3	99 ± 4
200	1	25	26	3.1	88
200	2	16	14	3.5	74
200	3	23	20	7.0	64
200	4	37	13	8.3	34
1000	0	19	31	0.2	99
1000	1	26	31	1.1	96
1000	2	29	24	7.2	70
1000	3	10	36	6.0	83

\*Hours after administration of sodium iodide  $^{131}\text{I}$ .

A dose of 100-200 mg of KI given before exposure to  $^{131}\text{I}$  largely prevents the uptake of  $^{131}\text{I}$ ; even shortly after exposure it minimizes the radiation dose.

No toxicity of the KI was observed, but some patients have shown allergic reactions to the iodide, and should avoid its use. Given as a single dose, KI is both harmless and highly effective in treating  $^{131}\text{I}$  exposure.

Davis and Saunders (72) reported a medical case involving a 48-year-old man diagnosed as suffering from tabes dorsalis (locomotor ataxia). A gram of KI was given 3 times daily together with intramuscular bismuth subsalicylate. After several weeks of treatment, purpura of the lower extremities appeared. The bismuth was suspect and was discontinued; the purpura persisted. Discontinuation of the KI caused the purpura to disappear. Subsequent experiments produced purpura by a single dose of 0.3 gm of KI. The authors recommended that use of KI in therapy should be closely watched for the appearance of purpura as evidence of a toxic reaction.

Ten case-histories of potassium iodide therapy of asthma were described by Siegal (332). The typical therapeutic dose of KI used to suppress the symptoms of asthma consisted of 2 tablets of 0.3 gm, 4 times a day (total 2.4 gm/day) over a period of years without ill-effect and with complete remission of asthmatic symptoms. These groups of patients, however, were atypical; several hundred other asthmatics showed slight or no benefit from iodide therapy. Siegal noted that iodide therapy in bronchial asthma is probably effective in only 5-10% of the cases; side-effects frequently appear in the form of gastrointestinal upset, epigastric pain and minor skin eruption. Some instances of iodide causing a flare-up of tuberculous lesions were observed and the treatment is contraindicated in tuberculosis. The mechanism of the asthma-suppressive action of iodide was said to be "obscure". Following the presentation of Siegal's paper, a discussion by various medical practitioners with differing viewpoints of the utility of iodide therapy in asthma was reported.

Mann (223) studied the possible therapeutic effect of orally administered potassium iodate on the blood sugar response of rats injected intraperitoneally with thiourea. Twenty-four rats of both sexes were separated into 2 groups of 12 each. Rats of group I weighing from 148 to 398 g were bled for glucose determination then injected with 10 mg/kg thiourea intraperitoneally; 2 1/2 hours later a second blood sugar determination was made. The 12 rats of group II ranging in weight from 147 to 392 g received 0.2% potassium iodate in the drinking water "ad libitum" for 2 days after which blood sugar was determined and thiourea (10 mg/kg) injected as in group I. Two and a half hours later a second blood sugar determination was made. The following tables show the results:

**TABLE I.**  
Effect of Thiourea on Blood Sugar Level of 12 Non-fasted Rats. Second blood sugar reading (B) was taken 2½ hr after rats received 10 mg/kg thiourea intraperitoneally.

Sex	Wt g	Blood Sugar (A) mg/100 cc	Blood Sugar (B) mg/100 cc	Difference (B-A)
M	379	90	165	75
M	387	90	187	97
M	398	86	165	79
M	358	86	117	31
M	148	83	225	142
F	322	86	165	79
F	372	90	186	96
F	348	79	165	86
F	324	66	140	74
F	317	79	300	221
F	342	109	140	31
F	168	105	186	81
Avg Blood Sugar Incr.				91

**TABLE II.**  
Effect of Thiourea on Blood Sugar Level of 12 Non-fasted Rats Previously Fed KIO<sub>3</sub>. Sugar reading (B) was taken 2½ hr after rats received 10 mg/kg thiourea intraperitoneally.

Sex	Wt g	Blood Sugar (A) mg/100 cc	Blood Sugar (B) mg/100 cc	Difference (B-A)
M	383	63	79	16
M	392	59	86	27
M	366	76	90	14
M	333	90	93	3
M	319	63	97	34
F	285	93	105	12
F	315	105	122	17
F	186	102	97	-5
F	147	69	86	17
M	193	83	97	14
M	201	90	97	7
M	150	73	93	20
Avg Blood Sugar Incr.				14.7

The average rise in blood sugar in group I of 91 mg/100 cc compared to only 14.7 mg/100 cc in group II, shows the iodate to be an effective agent in preventing hyperglycemia following thiourea injection in rats.

McCreesh and Mann (235) demonstrated that sodium iodide and sodium iodate fed to rats injected intraperitoneally with thiourea solution (10 mg/kg body weight of 0.5% aqueous) would greatly diminish the hyperglycemia which normally follows injections of thiourea. Male albino rats of the Wistar strain were used in the experiment; 27 were given 10 mg/kg thiourea intraperitoneally, serving as controls; 12 were given NaI in the drinking water for 2 days, then were injected; 12 were given NaIO<sub>3</sub> as above and injected with thiourea. The rats in the first group weighed 182-270 g; in the second group, 138-182 g, and in the third, 125-252 g. In each instance, blood samples were taken after the 2-day pretreatment and at 2 1/2 hours following injection of thiourea. Blood glucose in each sample was determined. The first group receiving no iodine showed an average blood sugar rise of 69.85 (± 33.39) mg/100 ml of blood at 2 1/2 hours after injection; the average blood sugar rise in the iodide-treated group was 16.21 (± 13.62) mg/100 ml of blood; and in the iodate-treated group, 20.53 (± 12.54) mg/100 ml of blood. The sodium iodide and iodate both reduced the hyperglycemia characteristic of thiourea injection.

### III. Metabolism and Excretion

The Silberbergs (337) reported that the three phases in the life cycle of skeletal tissue development in growing mice were stimulated by intraperitoneal injections of 0.1 cc of 2.5% solution of potassium iodide in water. Twenty-eight male mice, 8 of the closely inbred strain C57 and 20 of the C3H strain were used in the experiment. Of the C57 mice, 2 were injected for 4 consecutive days and then sacrificed; the remaining 6 animals were injected for 5 consecutive days, then untreated for 2 days. Pairs were sacrificed after 1, 2 and 4 weeks following the first injection. The C3H mice were similarly treated but allowed to grow for 2, 3, 4, 5 and 11 months. Four untreated males of the C57 strain and 10 of the C3H strain served as controls. At necropsy, tibia and femur were removed and the upper tibial growth zone was selected for histological study. A temporary increase in the proliferation of the epiphyseal and articular cartilages was observed, with accelerated regression of the articular cartilage. Stimulation of bone formation is subsequently followed by more rapid resorption of bone. The skeletal effects of KI treatment resemble those caused by administration of anterior hypophyseal hormone and of thyroxin, but to a lesser degree.

Siebert (327) noted that previous investigators had found that potassium iodide given guinea pigs stimulated the thyroid gland and affected only very slightly the basal metabolism, which should have been stimulated by the increased thyroxin. The author thyroidectomized 12 male guinea pigs weighing between 400 and 450 gm, and 3 weeks later, 8 of the animals were given 0.05 gm of KI by mouth daily; the remaining 4 served as controls and were untreated (thyroidectomized, but no KI). Biweekly metabolism tests were made, showing basal metabolism values of from 2.0 to 3.14 calories/kilo/hour in controls, and 1.91 to 3.42 calories/kilo/hour in the animals to be treated before KI was administered. During the 14-30 days of the experiment the KI-fed animals showed basal metabolism values of from 1.52 to 3.30, and in all but a few determinations the rates were distinctly lower than those of the controls. The respiratory quotients were distinctly higher in the KI-fed group than in the control animals.

A three-fold investigation of the effects of KI, NaI and Iod-Ethamine on blood iodine was reported by Boyd and Blanchaer (45): first, give rabbits by stomach tube doses of 1 gm/kg body weight of these three iodides and note the changes in concentration of alcohol-soluble ("inorganic") iodine and alcohol-insoluble ("protein") iodine in the blood; second, compare KI and NaI effects on the level of blood "protein" iodine; and third, determine whether organic iodide, Iod-Ethamine is better in prolonging post absorptive blood iodine than are the inorganic iodides, KI and NaI.

Three groups of 18 rabbits each were given 1 gm/kg, by stomach tube, of the iodides: Group A, KI; Group B, NaI and Group C, Iod-Ethamine. Blood samples were taken at intervals of 0, 0.5, 1.5, 2.5, 3.5, 6, 9, 15, 18, and 24 hours after administering the iodides. Extraction with alcohol yielded the alcohol-soluble, non-protein blood iodine; the remaining residue contained the alcohol-insoluble fraction, or protein iodine. The iodine content of the two fractions was determined; the following figures show the results:

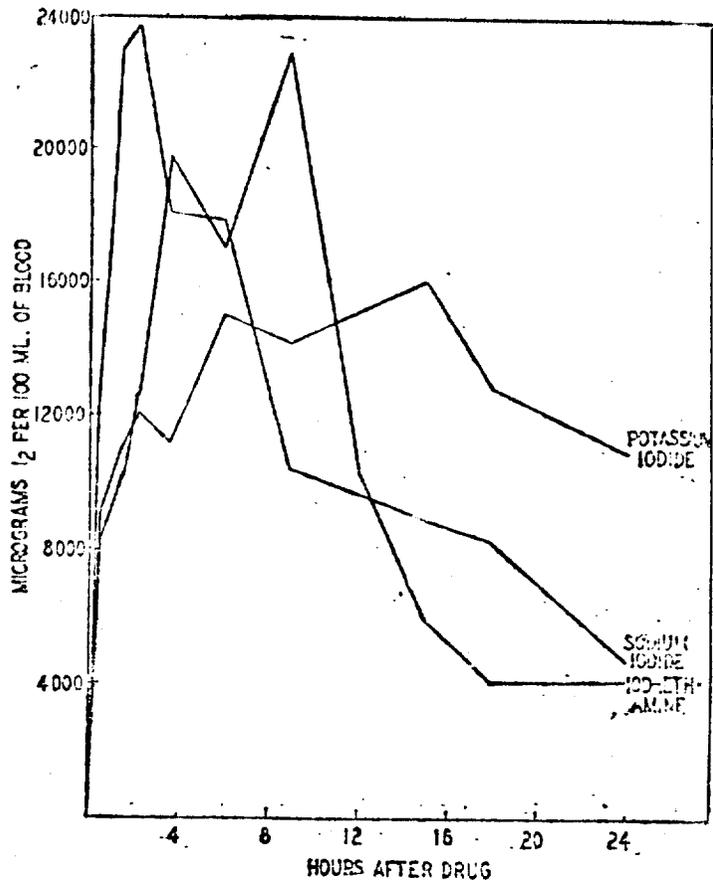


FIG. 1. The effect of administration by stomach tube of potassium iodide, sodium iodide, and Iod-Ethamine, in doses of 1 gm. per kgm. body weight, upon the concentration of cold-alcohol-soluble or "non-protein" blood iodine of rabbits.

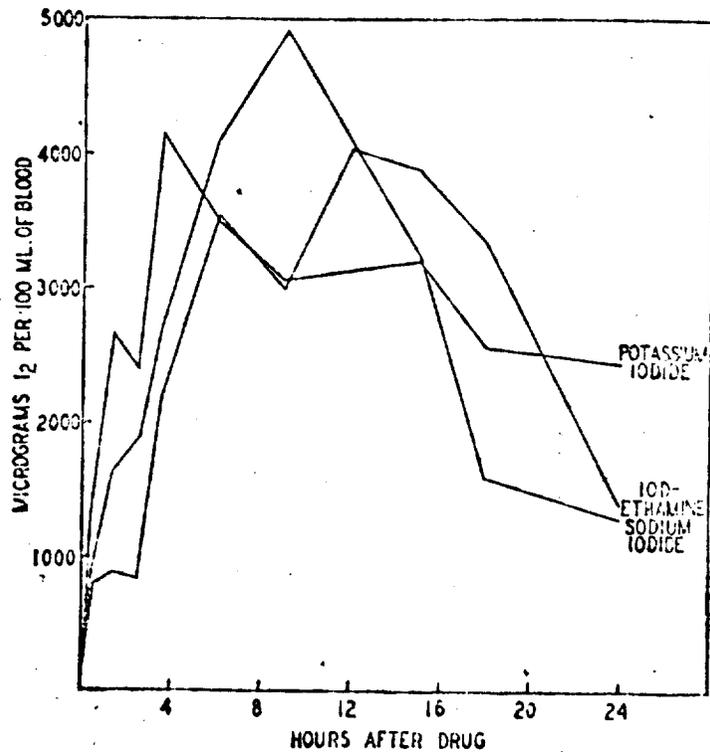


FIG. 2. The effect of administration by stomach tube of potassium iodide, sodium iodide, and Iod-Ethamine, in doses of 1 gm. per kgm. body weight, upon the concentration of cold-alcohol-insoluble, or "protein," blood iodine of rabbits.

All three iodides produced a rise and fall in both fractions of blood iodine; the values for alcohol-soluble (inorganic) blood iodine rose higher but fell more rapidly than values for the protein iodine fraction. Both fractions were maintained at high levels longer with KI than after NaI. Iod-Ethamine produced high levels in both fractions for shorter periods than KI, but longer periods than for NaI. Blood iodine concentration and respiratory-tract fluid iodine concentration were of the same order; the latter appeared to be of the nature of a simple diffusion from the blood (author's conclusion).

## Biochemical Aspects

### I. Breakdown

None

### II. Absorption - Distribution

Mittler and Benham (247) investigated the availability of iodine from several iodine compounds as might be used in animal salt blocks; such a source should be insoluble to prevent leaching out through exposure to moisture. Potassium iodide, cuprous iodide, diiodothymol and 3-5-diiodosalicylic acid were tested for available iodine in the diet of 4-week old Sprague Dawley female albino rats (35-50 gm). Controls (5) Group A, were raised on a low-iodine test diet, four other groups of 10 rats each were given one of the four iodine compounds in the diet. Group B received 265 micrograms of iodine (as KI); group C received the same amount in the form of  $\text{Cu}_2\text{I}_2$ ; group D, diiododithymol and group E, 3-5-diiodosalicylic acid. After 5 weeks of these diets, the animals were sacrificed and the thyroid glands dissected and weighed. The results are shown in the table below:

**TABLE**  
*Availability of iodine from several sources*  
(Female albino rats given 10 gm of food daily for 5 weeks)

GROUP	ADDITION TO IODINE-FREE DIET	IODINE SOURCE	NUMBER OF ANIMALS	AVERAGE WEIGHTS	
				Body	Thyroid gland
	<i>µg/kg</i>			<i>gm</i>	<i>mg/100 gm of body weight</i>
A (control)	none	none	5	111.4	15.4 ± 3.5 <sup>1</sup>
B	265	KI	10	105.2	10.0 ± 1.1
C	265	$\text{Cu}_2\text{I}_2$	10	100.1	9.8 ± 1.9
D	265	diiododithymol	10	101.6	12.5 ± 2.4
E	265	3-5-diiodosalicylic acid	10	99.0	11.9 ± 1.4

<sup>1</sup> Standard deviation.

A second experiment showed the influence of different doses of  $\text{Cu}_2\text{I}_2$  in protecting the thyroid gland of albino rats raised on an iodine-deficient diet. Dosage levels studied were 150 micrograms iodine from  $\text{Cu}_2\text{I}_2/\text{kg}$  iodine-free diet, 200 and 265 micrograms. Since the rats consumed about 10 gm of food daily, as little as 1.5 micrograms of iodine per day from  $\text{Cu}_2\text{I}_2$  prevented thyroid enlargement. The results of this experiment are shown on the following page.

*Availability of iodine from Cu<sub>2</sub>I<sub>2</sub>*  
(Female albino rats allowed feed at will for 6 weeks)

GROUP	ADDITION TO IODINE-FREE DIET	NUMBER OF ANIMALS	AVERAGE WEIGHTS	
			Body	Thyroid gland
	<i>µg/kg</i>		<i>gm</i>	<i>mg/100 gm of body weight</i>
F (control)	none	5	138.2	18.1 ± 2.1 <sup>1</sup>
G	265	10	141.3	7.3 ± 1.8
H	200	10	140.1	8.5 ± 2.2
I	150	9	139.8	9.2 ± 2.4

<sup>1</sup> Standard deviation.

A third test using the Cu<sub>2</sub>I<sub>2</sub>, KI, and the two goitrogens at very low doses over 8 weeks time demonstrated a protective influence of the four iodine sources even when given only twice a week; apparently the iodine is retained in the body and not too rapidly excreted. The retention of the iodine is shown in the following table:

*Retention of iodine from several iodides*  
(Albino rats given 5.25 µg of iodine weekly for 8 weeks)

GROUP	IODINE SOURCE	NUMBER OF ANIMALS	AVERAGE WEIGHTS	
			Body	Thyroid gland
			<i>gm</i>	<i>mg/100 gm of body weight</i>
J (control)	none	9	155.6	40.86 ± 5.2 <sup>1</sup>
K	KI	10	148.2	12.48 ± 2.47
L	Cu <sub>2</sub> I <sub>2</sub>	10	149.5	9.62 ± 2.06
M	diiododithymol	9	150.2	14.34 ± 2.05
N	3-5-diiodosalicylic acid	10	149.7	13.53 ± 2.6

<sup>1</sup> Standard deviation.

The absorption of potassium iodide from the gastrointestinal tract of man and rat was the subject of experiments performed by Small et al. (349). Those studies using rats are described here.

Wistar strain male rats weighing between 147 and 181 g were divided into two groups, one of 11 rats and one of 12. The animals of the first group were secured to boards, shaved and the abdomen infiltrated with 1% xylocaine hydrochloride. A polyvinyl tube was inserted into the stomach through a midline incision and the stomach washed with distilled water. Two ml of 25% solution potassium iodide (in 0.01 N HCl) was then injected into the stomach, the tube removed and the incision closed. After one hour, the animals were sacrificed, the stomachs removed and contents extracted with demineralized water. A second group of 12 animals was similarly treated, but the iodide was injected into the duodenum. After one hour these rats were sacrificed, the entire gastrointestinal tract removed and the intestine examined for retained iodine. Absorption of iodine in group I was 14.9%, in group II,

48.9%. It appears that the small intestine is the principal site of iodine absorption in rats.

As was previously described under rat experiments with potassium iodide absorption by Small et al. (349), the small intestine in human patients given potassium iodide appears to be the site of absorption. A number of subjects (not given) were administered orally a solution of 0.25 g of potassium iodide after a 14-16 hour fast. Mouths were rinsed, and saliva collected and tested every 2 minutes for iodine (1 ml saliva added to 1 ml, 1% starch solution containing 4 drops 10%  $\text{FeCl}_2$  solution, a test sensitive to as little as 0.0027 mg iodine). Ten normal subjects showed a positive test for iodine in from 6 to 10 minutes after ingestion; seven of these were retested with the addition of  $\text{BaSO}_4$  to the iodide solution ingested and the subjects observed under fluoroscope control. No iodine appeared in the saliva until the radio-opaque  $\text{BaSO}_4$  medium had been seen to pass into the duodenum. Several previously tested subjects were instilled with the iodide directly into the duodenum whereupon the saliva tested positively for iodine within 2-4 minutes after intubation. Similar tests upon four alcoholic patients gave the same results when intravenously injected with iodide, or given the iodide- $\text{BaSO}_4$  mixture and observed fluoroscopically.

The fate of iodine in the intestinal tract and its subsequent excretion and availability were studied by Harrison et al. (119). Seventeen hospital patients were observed. A diet fixed at a low level of 35-40 micrograms of iodine per day was supplemented with tablets of KI to bring the total intake to about 100 micrograms/day. After allowing 10 days on this diet to establish an equilibrium between intake and excretion, feces and urine were collected and analyzed for iodine content.

Seven individuals with normal thyroid function showed a mean fecal excretion of 15.0 micrograms/day and urinary iodine of 61.8 micrograms/day. Five patients with thyrotoxicosis showed fecal excretion of 37.2 micrograms/day and urinary, 53.6. Three hypothyroid patients showed low fecal levels of iodine; urinary iodine was normal in 2 patients, high in the third. Two patients with non-toxic goitre showed normal fecal levels and low urinary iodine.

All results indicated that when the dietary iodine level is fixed, fecal excretion varies with the thyroid activity; urinary iodine excretion in thyrotoxic and hypothyroid patients was essentially normal, but low in the non-toxic goitre patients.

Since fish is the chief source of iodine in Great Britain (iodized salt is not widely used), studies similar to those described for humans were performed on haddock and plaice. The fish were injected in the coelomic cavity with  $^{131}\text{I}$  (100 microcuries) and after 48 hours, the fish were fed to patients. Urine and fecal samples indicated that the iodine in fish was completely absorbed from the alimentary tract of the patients. Cooking the fish resulted in iodine losses of 50-82% in boiled fish, and about 20% in grilled or fried fish. These are important data when considering dietary sources of iodine.

The effect of environmental temperature and potassium iodide

supplementation on the excretion of iodine by normal human subjects was studied by Spector et al. (355). Five young men, 20-28 years of age, for 8 hours a day, 5 days a week for 8 weeks were kept in an air-conditioned room alternately "comfortable" for a week and "hot moist" a week, unclothed. Each day was begun with a thorough cleansing and rinsing of the body. All perspiration (sweat) was carefully collected in various manners; food was measured, feces and urine were collected for analysis of iodine, as was the sweat. Body weights to the nearest gram were noted before and after entering the chamber. The net loss of body weight under comfortable conditions (28.9 degrees, 50% relative humidity) averaged 92 gm/hr, largely unsensible vapor; the net loss under hot moist conditions (38.3 degrees, 69% relative humidity) averaged 676 gm/hr., largely sweat. At one point, undiluted sweat was collected in a beaker held to the body; the concentration of iodine measured 0.95 gamma per 100 cc. A single dose of 2 mg KI (presumably oral, but not stated by the authors) increased the average concentration of iodine to 3.18 gamma/100 cc; 14 daily doses of 2 mg KI produced no significant increase beyond that of the single 2 mg dose. No evidence was gathered showing that sweating increased the iodine requirements of the body. About three-fourths of the total iodine lost from the body was by urine excretion. Increased iodine intake resulted in increased urine excretion of iodine.

#### IV. Effects on Enzymes and Other Biochemical Parameters

Homer (132) presented evidence that potassium iodide (200 mg/day for 3 days), administered to rats on a sterol-free diet, produces a moderate hypercholesteremia. Male Long-Evans rats about 12 weeks old were divided into 3 groups of 25, 23 and 10 rats, and placed on a fat and sterol-free diet. After 24 hours of this diet, blood samples were taken for initial plasma cholesterol determinations. For 3 days the animals were anesthetized and fed the test materials by stomach tube. The 25 experimental rats received 200 mg KI (200 mg/cc) daily; the 23 controls received 1 cc H<sub>2</sub>O daily; the 10 rats were given 200 mg KCl (200 mg/cc). Three hours after the last tube feeding, blood samples were again collected and analyzed for cholesterol. The average plasma cholesterol concentration in the KI-fed group rose from the pretreatment level of 50 mg % to 92 mg %; the H<sub>2</sub>O-fed animals rose to 60 mg %; and the KCl-fed group rose to 64 mg %. The mechanism by which the iodide influences the cholesterol levels in the blood was not known.

Cell membranes are not normally permeable to large protein molecules as represented by thyroglobulin with a molecular weight of about 700,000. It has been suggested that thyroid enzymes hydrolyze thyroglobulin into smaller polypeptides or peptones capable of passing through cell membranes, after which they would be recombined into the large molecules by other enzyme activity. Dziemian (82) devised experiments on rats and guinea pigs to determine variations in the proteolytic activity of whole thyroid tissue in various physiological states. He fed the animals potassium iodide, sulfaguanidine and thyrotropic pituitary factor and performed hypophysectomies.

Ten rats (not described) were fed Purina dog chow and greens, ground and mixed with 1% by weight KI; 14 rats were injected intraperitoneally with a 0.2% solution in 0.85% NaCl of a thyrotropic factor containing 1 mg of the pituitary factor; 12 rats were given 2% sulfaguanidine by weight in the diet; 10 rats were hypophysectomized; and 10 were first fed 2% sulfaguanidine for 3 weeks and then hypophysectomized.

After sacrifice, the thyroid glands were weighed, minced and treated for analysis of the amount of protein digestion. The results are shown below:

TABLE

	TIME OF TREATMENT	NO OF RATS	CMM. N/20 HCl/MG. THYROID	% CHANGE FROM NORMAL	MG. THYROID PER 100 GM. BODY WEIGHT
	<i>days</i>				
Rats on KI diet	7	2	13.50	+ 30.9	6.5
	14	2	11.88	+ 15.2	
	16	2	12.73	+ 23.4	
	38	2	10.94	+ 6.1	
	40	2	9.29	- 9.9	
	<i>hours</i>				
Rats treated with thyrotropic pituitary factor 10 g. p. u.	2.5	8	13.36	+ 29.6	6.6
	21	2	13.33	+ 29.3	
	48	2	13.40	+ 30.0	
	72	2	11.03	+ 7.0	
	<i>days</i>				
Rats on sulfaguanidine diet	1	2	10.36	+ 0.5	9.9
	3	2	7.62	- 26.1	8.6
	5	2	8.22	- 20.2	14.3
	7	2	7.96	- 22.8	16.4
	14	2	7.19	- 30.2	24.8
	21	2	8.80	- 14.7	20.4
	<i>days</i>				
Hypophysectomized rats on normal diet	21	10	8.01	- 22.3	5.6
Hypophysectomized rats on sulfaguanidine diet	21	10	11.61	+ 12.6	3.8

Ten guinea pigs were similarly treated, receiving injections of 0.1 cc thyrotropic pituitary factor twice daily for five days; the higher dose were injected with 0.5 cc of the factor. After sacrifice, the thyroid proteolytic activity was determined in the same manner as for rats. The results are shown below:

TABLE

	NO. OF GUINEA PIGS	NO. OF GUINEA PIG UNITS INJECTED	CMM. N/20 HCl/MG. THYROID	% CHANGE FROM NORMAL	MG. THYROID PER 100 GM. BODY WEIGHT
Guinea pigs treated with thyrotropic pituitary factor	2	50	8.60	- 0.6	15.9
	4	250	9.70	+ 12.2	37.3
	4	450	10.64	+ 23.0	54.2

Both rat and guinea pigs showed increased proteolytic activity for some 48 hours after injection of the thyrotropic pituitary factor. The KI treatment also increased proteolytic activity of the thyroid up to about 38 days of feeding, after which the activity became normal or below normal. Sulfaquanidine feeding decreased the thyroid tissue proteolytic activity, as did hypophysectomy.

An experiment to test the effect of thiouracil-iodide mixtures on the growth of young rats, and to compare this effect with the thiouracil used alone, was reported by Taylor and Barrett (372). Male Sprague-Dawley rats, 25-65 days of age, were grouped by weight and fed diets of ground Purina Fox Chow (1.3 ppm iodine) mixed with powdered thiouracil, NaI or KI singly or in combination at a level of 3 micromoles/g of feed (0.0384% thiouracil, 0.0497% KI). Amounts of food and drug consumed were recorded daily and weights of the animals taken weekly. After 14 weeks the rats were sacrificed, lengths measured, organs removed and weighed. Some organs were analyzed for iodine, others were prepared for histological examination. The results are shown below:

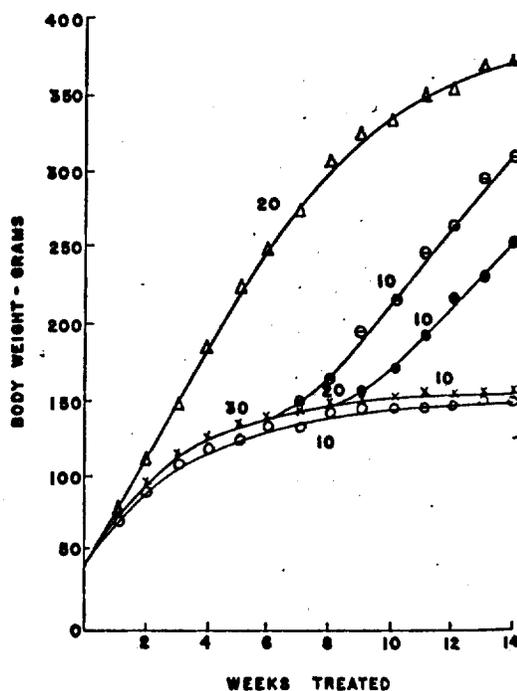


FIG. 1. Effect of antithyroid treatment on weight gain.  $\Delta$ - $\Delta$  Control.  $\times$ - $\times$  Thiouracil + KI.  $\ominus$ - $\ominus$  Thiouracil + KI 6 wk, KI 8 wk.  $\bullet$ - $\bullet$  Thiouracil + KI 8 wk, plus thyroid powder 6 wk (1 mg/g diet).  $\circ$ - $\circ$  Thiouracil + KI 6 wk, thiouracil 8 wk. Drug concentration 3  $\mu$ moles/g feed. Number of animals shown on curves.

TABLE Effect of Antithyroid Treatment on Feed Consumption, Body Weights and Organs of Rats, Starting Age 24 Days; Treated 14 Weeks.\*

	Dietary additive, 3 $\mu$ moles/g feed			
	Controls	KI	Thiouracil	Thiouracil + KI
Feed consumed, g/rat/day	16.5	17	16.6	10.3
Drug intake, mg/rat/day	—	8.5	6.4	4 (Thiouracil) 5.1 (KI)
Wt gain, g	336	340	330	112
Length in cm, breech to nose	23.3	23.4	23.3	19.4
Organ wt, mg/100 g body wt				
Thyroid	6.5 (74)†	7.0 (121)	16.0 (6.0)	15.6 (21.0)
Pituitary	2.4	2.4	2.8	4.5
Spleen	185 (.2)	190 (2.0)	170 (.3)	133 (2.0)
Heart	278 (.4)	270 (1.1)	265 (.6)	246 (3.3)
Testes	946 (<.1)	940 (.2)	981 (<.1)	1622 (.5)

\* For italicized values compared with controls,  $P \leq .05$ .

† Total iodine, in parentheses, as  $\mu$ g/100 mg fresh tissue; 6-16 tissues of each kind analyzed. Values of less than 1  $\mu$ g for a whole tissue are approximate only.

The combination thiouracil-KI diet repressed growth, but neither substance singly affected growth of the rats. The combination diet effect could be reversed by adding thyroid powder to the diet (1 mg/g) or by removing the thiouracil; thiouracil alone could maintain growth repression once established. As others have reported, the action of the thiouracil-KI appeared to be synergistic; this synergism may operate by causing a prolonged and greatly increased sensitivity toward thiouracil. The actual mechanisms involved in antithyroid action are unknown (author).

Goitrogens, substances that apparently interfere with the thyroid production of thyroxine, a growth regulator, can be overcome, or their action prevented, by the addition to the diet of certain animal tissues according to some investigators. Ackerman (3) reported that the diet had profound effect on the response of rats to the goitrogens thiouracil and sulfaguanidine. Duodenal tissue was selected as representative of animal tissue found to be capable of reinstating growth in goitrogen-fed rats. An effort was also made to determine the relationship of the iodide level of the diet and the unexplained fatal effects of goitrogens.

Weanling male Sprague-Dawley rats (35-45 gm) were fed a basal diet including 0.13 micrograms iodine/gm diet. Thiouracil and sulfaguanidine were added to the diet. Duodenal powder replaced the diet in part in some cases, and KI in aqueous solution (3.0 gm/liter) was added to the diets in experiments to determine the effect of KI on growth and organ weights of sulfaguanidine and thiouracil-fed rats. The following figure shows the results and is self-explanatory: (8 groups of 6 rats each provided the data).

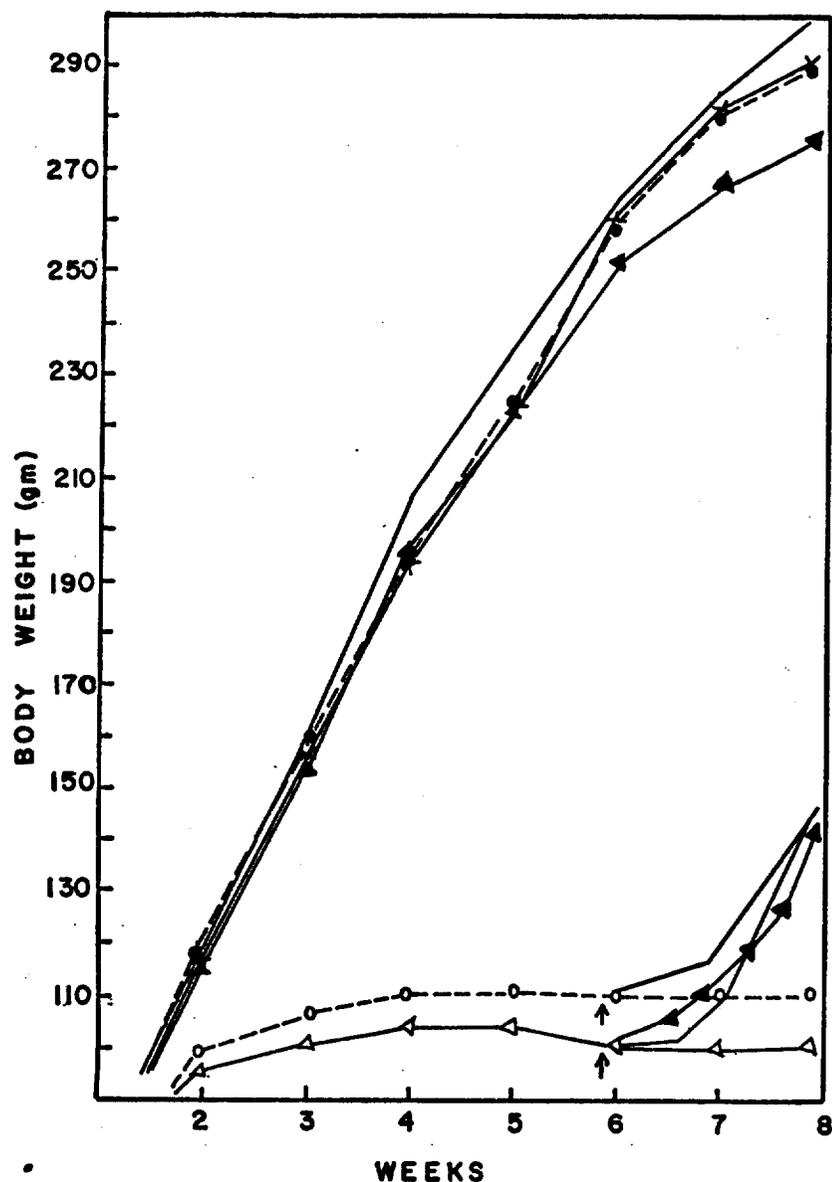


Fig. 2 The ability of duodenal powder to maintain and reinstate growth of thiouracil and sulfaguanidine-fed rats. All diets contained  $30 \mu\text{g}$  of KI/gm. Normal, —; normal + 4% of duodenal powder, ×—×; 1% of sulfaguanidine ○—○; 0.1% of thiouracil, △—△; solid symbols indicate that 4% of duodenal powder was added to the diet. Goitrogens were removed or duodenal powder was added on the forty-first day (arrow).

Additional experiments with commercial laboratory chow and also with radioiodide in the form of  $\text{NaI}^{131}$  were performed. The author notes that the role played by iodide appears to be complex. High levels of iodide seem to function synergistically with goitrogens in blocking the synthesis of the thyroid hormone. Animal tissues such as those of the duodenum used in these experiments, it is suggested, contain thyroid hormone-active material.

The stimulating effect of KI on the thyroid gland, parathyroids and adrenal gland, as evidenced by mitotic activity of those tissues, was the subject of investigations performed by Blumenthal (41). The

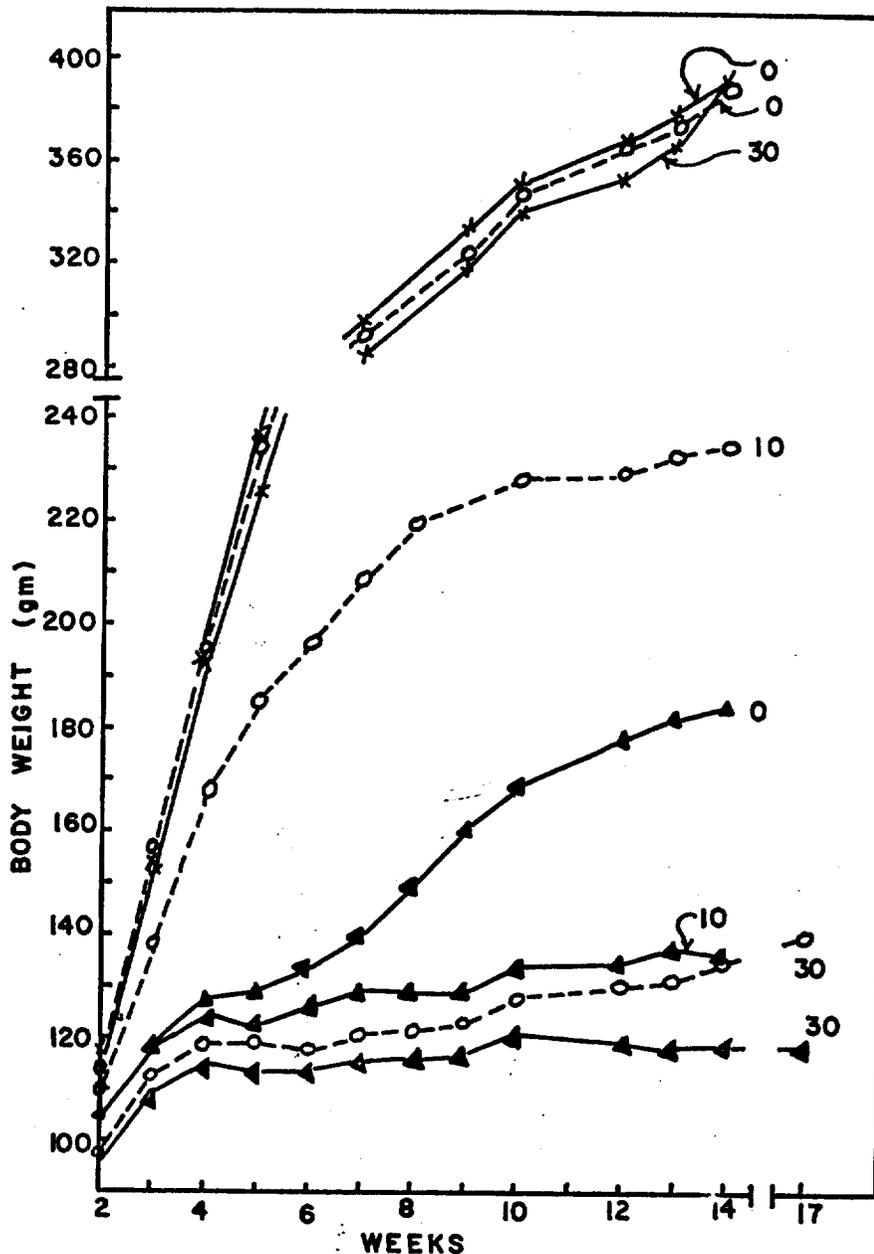


Fig. 1 Effect of zero, 10, and 30  $\mu$ g of KI on growth of sulfaguanidine or thiouracil-fed rats. Basal diet,  $\times$ — $\times$ ; 1% of sulfaguanidine — $\circ$ — $\circ$ —; 0.1% of thiouracil,  $\leftarrow$ — $\leftarrow$ . The figures at the termination of each curve indicate the amount of KI added to the diet in micrograms per gram of diet.

Thiouracil alone was more effective as a growth inhibitor than was sulfaguanidine; the addition of 1-30 micrograms KI/gm of diet enhanced the growth retardation effect of the goitrogens.

A second experiment basically similar, but adding duodenal powder to the diet showed that the powder (4% of the diet) was effective in maintaining the growth of rats fed either thiouracil or sulfaguanidine. Normal thyroid function is restored when the goitrogens are removed from the diet. The results of this experiment are shown in the figure on the following page.

influence of age, diet and dosage as factors were also included in the study.

Two experiments are described: in the first, three groups of guinea pigs were used; group I, 52 males just weaned (about 2 weeks old, weighing 100-115 gm; group II, 46 guinea pigs of 4-6 weeks old, 180-200 gm weight; and group III, 24 animals, 390-420 gm, 3.5-4 months old. In the second experiment 123 guinea pigs were similarly divided by age, weight and diet. In the first experiment three further subdivisions of each group were made on the basis of diet; all received a basal diet of lettuce, carrots and oats. One subdivision was fed only the basal diet; one received Purina rabbit chow including iodine-free salts as supplement; and the last subdivision received the same diet as the second, except that 0.5% iodized salt replaced the iodine-free salt. In the second experiment, KI in daily doses of 0.01 or 0.05 gm were intubated gastrically for periods ranging from 5-50 days.

At the termination of the experimental feedings, the guinea pigs were sacrificed, the thyroid, parathyroid and adrenal glands were removed and prepared for cytological examination. The number of mitoses seen in tissue sections were recorded as mitoses/total gland in thyroid; mitoses/10,000 cells in the parathyroid; and mitoses/section in the adrenals. The results indicated that the addition of very small amounts of KI in iodized chow to the diet of 2-6 week old male guinea pigs increased the growth (mitotic) activity in thyroid and parathyroid glands. Older guinea pigs (3-4 months old) do not show this effect. The animals maintained on iodized chow showed a greater response to subsequent larger doses of KI than those on iodine-free diets. The administration of larger doses of KI (0.01-0.05 gm) show maximal response in thyroid and parathyroid glands at about the 15th day, followed by a decreased effect. Confirmation of observations showing a parallelism between the effect of KI on thyroid and parathyroid glands resulted from these experiments; there was also evidence of a slight increase in mitotic activity in the adrenal cortex from the 8th to the 15th day of treatment with KI.

Gray and Loeb (107) in an early paper on the thyroid gland and the effects of iodine on the thyroid, discuss the somewhat anomalous results of various investigators. Loeb concluded that thyroid tissue might respond to both a deficit and a surplus of iodine, as though the thyroid gland is adapted to a definite amount of iodine for normal function and that any change - diminution or increase - disturbs the normal cell equilibrium and acts as a stimulus.

The question is raised whether or not the administration of iodine on an intact, normal thyroid gland will serve as a stimulus and induce proliferation of the thyroid tissue (produce a goiter). In order to determine in a definite and quantitative manner the effect of iodine on the thyroid, the authors estimated from cytological examination of tissue sections, the number of mitoses present at a given time in the gland.

Several series of experiments were performed. In one, 5 guinea pigs served as controls, 6 animals were fed daily with 0.05 gm KI

and 4 were fed dessicated thyroid gland. The basic diet was the same for all animals. At the end of the test, the animals were sacrificed, thyroid glands were removed, fixed in Zenker's solution and serially sectioned. Every tenth or eleventh section was examined and the number of mitotic cells counted. An estimate of the total number of mitoses for the thyroid gland was then made. An average of 192 mitoses was found in the controls, 719 mitoses in the animals fed potassium iodide, and 64 for those fed 0.1 gm thyroid gland daily for 18-30 days. Additional similar experiments gave much the same result; the number of dividing cells in the KI groups was about 3 1/2 times that of the controls and 2-3 times that of the thyroid-fed animals. During the early stages of the experiments, cytological examination of the acini showed little difference between controls and KI-fed; in later stages, after several months, the acini of the KI group tended to become larger with the colloid content markedly retracted, and the epithelium flattened and cell walls thinner.

The administration of thyroid gland material substituted, as it were, for the activity of the normal gland and depressed its activity; the KI provided more of the precursor of thyroid hormone and stimulated the growth of the gland.

These experiments were followed in 1937 by a study of Margolin (226) in which very small oral doses of KI, as small as 0.0001 g, daily produced in guinea pigs a slight stimulating effect on the thyroid as measured by mitotic counts and increased average size of the acinus cells.

A study of an "inactive zone" between the action of small, trace quantities of iodine and of large doses in phagocytosis of leukocytes in guinea pigs was performed by Gerasimova (102). Thirty guinea pigs were divided into three groups: the control group received water; the experimental animals were given orally aqueous solutions of KI daily at levels of 1 gamma/kg, 40 gamma/kg or 160 gamma/kg body weight. Phagocytosis of leukocytes was determined before administration of KI and at 5 and 15 days after administration. The large dose, 1600 gamma/kg, inhibited phagocytosis, small doses of 1 gamma/kg increased it; the 40 gamma dose had no effect on phagocytosis even after 15 days of daily administration.

It has been observed that the iodine of blood plasma or serum exists primarily as a protein-bound form associated with thyroxine, and in healthy person the concentration remains constant with the normal intake of iodine present in the diet. Increases or decreases of thyroid activity produce corresponding changes in the level of protein-bound iodine in the serum. The effects of moderate and of massive doses of potassium iodide in human subjects was studied by Danowski and Greenman (65). Moderate doses of KI were given to four healthy male adults, 0.2 cc of a saturated solution daily, later increased to 0.4 cc. Measurements of the protein-bound iodine in the sera showed no significant change after two weeks of the iodine supplement. After two weeks, however, the same or doubled doses of KI showed a distinct increase in serum iodine, attributable to organically combined iodine and not to free or inorganic iodine.

The limited evidence of the moderate dose effects led the

authors to study the results of much larger doses of KI; five hospital patients, 3 female and 2 male, were given daily doses of KI, up to 3.0 g or as much as 7.0 cc of iodide solution, over intervals ranging up to 5 months in length. In these cases, described in some detail - the total iodine serum levels were greatly increased. No toxicosis or evidence of hyperthyroidism were observed, despite the doses of 3 to more than 7 g KI administered daily for from 1 to 4 months.

Koutras and Livadas (173) determined the minimum amount of KI which served to inhibit further uptake by the thyroid. Tracer doses of  $^{131}\text{I}$  of 10 microcurie activity were given orally, with doses of KI varying between 5 and 80 mg. The subjects were adults of either sex with no evidence of thyroid or other disease likely to influence iodine metabolism. Ten persons served as controls, receiving only the radioiodine; 60 persons in 10 groups of 6 each made up the experimental groups. The KI was given in water, 15 mg/ml. The results are shown in the following table:

Table (Results)

	2 h Uptake %			24 h Uptake %		
	Mean	S. E.	Median	Mean	S. E.	Median
Control	9.6	2.1	9.6	32.1	3.8	32.0
1. 5 mg KI with tracer	8.4	2.0	8.1	14.2	2.7	11.6
2. 10 mg KI with tracer	5.9	2.5	6.0	4.9	2.4	4.5
3. 20 mg KI with tracer	6.1	2.7	5.3	2.5	0.5	2.9
4. 40 mg KI with tracer	3.7	0.9	4.2	2.6	0.4	2.7
5. 80 mg KI with tracer	4.1	1.7	3.8	1.4	0.6	1.1
6. 40 mg KI 2 h before tracer	3.6	1.2	3.3	1.5	0.2	1.5
7. 80 mg KI 2 h before tracer	2.6	0.6	3.0	1.4	0.4	1.6
8. 40 mg 12 h before and 10 mg with tracer	1.8	0.6	1.3	2.2	0.6	2.0
9. 80 mg 12 h before and 10 mg with tracer	1.7	0.8	1.8	2.1	0.6	0.6
10. 40 mg KI 1 h after tracer	9.7	1.9	11.5	8.6	2.2	8.0

The minimal KI dose completely inhibiting thyroidal uptake is 40 mg, as shown by the experimental results. The authors suggested that in cases where it is desirable to block entirely the uptake of radioactive isotopes of iodine by the human thyroid, initial dose of 40 mg KI should be given, with minimal maintenance dose of 3.3 mg/day.

Two papers, one by McEachern (236) and another by McEachern and Baker (237) represent early studies (1930) of the effects of KI on human subjects. In the first study, 34 hospital patients ranging in age from 3 to 80 years were given 2 g KI daily for from 8 to 140 days and their pulse rates noted. Twelve patients showed a significant increase in pulse rate; 5 showed a decrease. The

change was gradual, reaching a maximum at about the tenth day of treatment. Rates returned to normal within a week after the KI was discontinued.

The second paper involved 14 normal hospital staff members who ingested daily doses of KI of 1 g for a week; 2 g KI/day during the second week; and 3 g/day during the third week. Four subjects dropped out due to severe iodide reactions. Before the KI treatment, and every five days during treatment, electrocardiographic records were made. No change of any consequence was observed that could be attributed to taking the iodide.

Tyrosine and inorganic iodine were noted as the only known precursors for thyroidal synthesis of thyroxine, in a paper by Strisower et al (360), which led to an investigation of the effect of administration of tyrosine and iodide on human serum lipoproteins.

The tyrosine study of 11 male hospitalized chronic schizophrenic patients, given daily doses of 30 g tyrosine in water for 18 weeks, produced negative results in blood tests for serum lipoprotein and cholesterol when compared with 5 patients serving as controls.

Five ambulatory office patients with various illnesses were given a daily oral dose of 30 mg KI over a period of from 10 to 36 weeks, during which 5-15 blood samples were obtained for serum lipoprotein and cholesterol analyses. The results of the tests are shown below:

**TABLE** Effect of Potassium Iodide on Serum Lipoprotein and Total Serum Cholesterol Concentrations.

	Time interval (wk)	Serum lipoprotein conc., mg/100 ml serum				Cholesterol, mg/100 ml	Diagnosis	Age, sex
		s <sub>1</sub> : 0-12	s <sub>2</sub> : 12-20	s <sub>3</sub> : 20-100	s <sub>4</sub> : 100-400			
Off ( 2)*		96	70	525	801	604	Xanthoma	47 ♂
On ( 9)	16	110	89	582	488	417	tuberosum	
Off ( 2)		141	107	361	34	268	Xanthoma	41 ♀
On ( 8)	14	154	121	355	51	270	tuberosum	
Off ( 4)		439	30	58	20	247	CVA, hyper-	64 ♂
On (13)	36	450	40	68	24	259	tension	
Off ( 7)		356	38	71	22	223	Myocardial in-	55 ♂
On (15)	35	343	42	67	16	223	farcction (old)	
Off ( 7)		1135	118	44	0	618	Xanthoma	52 ♀
On ( 5)	10	1071	106	36	0	567	tendinosum	

\* All lipoprotein and cholesterol data represent mean values derived from number of blood samples indicated in parentheses.

Potassium iodide produced no consistent changes in serum lipoprotein distribution or in cholesterol concentration in the patients studied.

## V. Drug Interaction

None

## VI. Consumer Exposure Information

The addition of iodine to foodstuffs has been motivated almost exclusively by the necessity for the inclusion of very small amounts of iodine in the diet for normal thyroid gland production of the hormone thyroxin, an important growth, development, and metabolic regulator. Most of the available iodine is concentrated in the algae and fish of the seas, and where seafood is a common part of the diet, iodine supplements are not significant. Many geographical regions of the world lack iodine-rich sources, as seafood in the diet, and peoples suffer from goiter or malfunction of the thyroid. Potassium and sodium iodates or iodides are added to the table salt or bakery flour to provide iodine, and goiter may be avoided. Animal feed is also frequently supplemented by salts of iodine. Mineral waters containing iodine are also available. There is nothing in the literature examined to suggest any hazard in the present supplementation of foodstuffs with iodine salts.

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

Table 2 reports the usage of iodine and iodine salts in foods and table 3 their use in infant formulas and baby foods. Table 11 reports the annual poundage data and table 13 reports the possible daily intake per food category and total dietary based on food consumption by total sample.

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

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# FIRMS REPORTING	*** USUAL USE *** WTD MEAN, %	*** MAXIMUM USE *** WTD MEAN, %
POTASSIUM IODIDE NAS 0155	05 MILK PRODS(R)	5	.00002	.00007
	00 PROCSD FRUT(R)	*	.00010	.00010
	23 BEV TYPE I(R)	*	.00000	.00000
	28 IMIT DAIRY(R)	*	.00043	.00043
	48 SEAS FLAVRS(R)	6	.00866	.00726

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

SURVEY NO. SUBSTANCE NAME	FOOD CATEGORY NO. NAME	# FIRMS REPORTING	*** USUAL USE *** WTD MEAN, %	*** MAXIMUM USE *** WTD MEAN, %
CLASS POTASSIUM IODIDE	05 POTASSIUM(R)	6	.00013	.00015

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

SUBSTANCE NAME (SURVEY NO.)	# REPORTS TO NAS 1960/1970	POUNDAGE REPORTED TO NAS (MATCHING REPORTS FOR BOTH YEARS)		TOTAL 1970 POUNDAGE REPORTED TO NAS	# REPORTS TO FEMA	POUNDAGE REPORTED TO FEMA-- 1970 ONLY	TOTAL 1970 POUNDAGE NAS + FEMA
		1960	1970				
POTASSIUM IODIDE NAS 0155	21/ 23	51,850	37,035	37,060			37,050

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

SUBSTANCE NAME (SURVEY NO.)	FOOD CATEGORY NO. NAME	# OF FIRMS	***** POSSIBLE DAILY INTAKE, MG. *****			
			(AGE)	AVERAGE	HIGH A	HIGH B
POTASSIUM IODIDE NAS 0155	05 MILK PRDGS(R)	5	0-5 MO.	.001080	.000000	.000780
			6-11 MO.	.012480	.050020	.143600
			12-23 MO.	.010900	.000000	.000000
			2-65+ YR.	.007900	.000000	.000000
POTASSIUM IODIDE NAS 0155	08 PROCSC FRUT(R)	*	0-5 MO.	.004700	.012000	.004700
			6-11 MO.	.051900	.129000	.051900
			12-23 MO.	.100600	.199700	.100600
			2-65+ YR.	.116300	.260600	.116300
POTASSIUM IODIDE NAS 0155	23 BEV TYPE I(R)	*	0-5 MO.	.000000	.000000	.000000
			6-11 MO.	.000000	.000000	.000000
			12-23 MO.	.000000	.000000	.000000
			2-65+ YR.	.000000	.000000	.000000
POTASSIUM IODIDE NAS 0155	28 IMIT DAIRY(R)	*	0-5 MO.	.000000	.000000	.000000
			6-11 MO.	.006020	.009890	.006020
			12-23 MO.	.003440	.014520	.003440
			2-65+ YR.	.003870	.006450	.003870
POTASSIUM IODIDE NAS 0155	46 SEAS FLAVRS(R)	6	0-5 MO.	*****	*****	*****
			6-11 MO.	*****	.000865	*****
			12-23 MO.	*****	.001732	*****
			2-65+ YR.	.000865	.004330	.000865
POTASSIUM IODIDE NAS 0155	83 FERFULAS(R)	6	0-5 MO.	.436410	.755500	.436410
			6-11 MO.	.088920	.423070	.088920
			12-23 MO.	.028500	.000000	.000000
POTASSIUM IODIDE NAS 0155	ALL CATEGORIES	20	0-5 MO.	.442190	.812500	.442190
			6-11 MO.	.159220	.623440	.159220
			12-23 MO.	.143540	.250992	.143540
			2-65+ YR.	.130936	.225500	.130936

## IODINE AND IODINE SALTS

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# Effect of Potassium Iodide and Duodenal Powder on the Growth and Organ Weights of Goitrogen-fed Rats<sup>1</sup>

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It has been reported that growth arrest induced by the ingestion of goitrogens, could be prevented or overcome by the addition to the diet of certain animal tissues (Ackerman, '59). An assay based on the reinstatement of growth of growth-arrested rats, was used to screen a variety of tissues for their growth-promoting activity, and it was observed that duodenal powder consistently evoked a growth response under these conditions (Ackerman and Tsou, '61). This suggested that duodenal powder and other tissues contained thyroid-active material since goitrogens are considered to exert their effect primarily by an inhibition of thyroid hormone synthesis (Mackenzie and Mackenzie, '43; Astwood et al., '43). Observations made in other laboratories suggest that thyroid-active material may be present in meat (Griesbach and Purves, '43; Goldberg and Chaikoff, '52), in liver (Ershoff, '54), and in casein (Van Middlesworth, '52). The thyroid-active material in these foods has not been characterized, and it appeared desirable to investigate the nature of the growth-promoting activity of duodenal tissue.

During the course of this investigation, it was observed that growth arrest could not be induced by thiouracil when it was fed in commercial laboratory chow.<sup>2</sup> Also, growth arrest could not be induced in sulfaguanidine-fed rats when the iodide level of the diet was less than 10 µg/gm and that prolonged feeding of either sulfaguanidine or thiouracil in purified diets was fatal to rats. When these drugs were fed in more natural-type diets, death did not occur.

The diet, therefore, had a profound effect on the response of rats to goitrogens and these experiments were initiated to determine the effect of KI and animal tis-

sue on the response of rats to sulfaguanidine and thiouracil. As a representative of animal tissue, duodenal tissue was selected from those tissues that had been found capable of reinstating growth of sulfaguanidine-fed rats for further studies on its ability to maintain normalcy in goitrogen-fed rats. In addition, it was hoped to determine whether the unexplained fatal effects of goitrogens could be linked to the iodide level of the diet.

## EXPERIMENTAL AND RESULTS

**Materials and methods.** Weanling male Sprague-Dawley rats (35 to 45 gm) were housed in screen-wire cages and were fed food and water ad libitum. The basal diet for the experiments 1, 2, and 4 consisted of the following: (in grams) ground wheat, 55; crude casein, 8.5; alfalfa leaf meal, 2.0; peanut oil meal, 13.0; brewer's yeast, 0.5; refined hydrogenated cottonseed oil,<sup>3</sup> 10.0; sucrose, 8.75; sodium chloride, 0.75; calcium carbonate, 1.0; and crystalline vitamins (in mg); menadione, 0.5; biotin, 0.1; vitamin B<sub>12</sub>, 0.004. This diet contained 19.3% of protein (Kjeldahl N × 6.25) and 0.13 µg of iodine/gm of diet. The total iodine was determined by the method of Grossman and Grossman ('55) on three aliquots of the diet that had been prepared with the hydrogenated cottonseed oil.

Thiouracil and sulfaguanidine were added to the diet at the expense of sucrose. Duodenal powder<sup>4</sup> was added

Received for publication August 13, 1962.

<sup>1</sup> Supported in part by a grant from the National Science Foundation, NSF-G-13165.

<sup>2</sup> Purina Laboratory Chow, The Ralston Purina Company, St. Louis. According to the manufacturer, this diet contains meat meal. The exact composition of the diet is unknown.

<sup>3</sup> Crisco, Procter and Gamble, Cincinnati.

<sup>4</sup> Duodenal powder was purchased from Cutter Laboratories, Omaha, Nebraska, and was a partially defatted dry preparation whose origin and processing treatment is unknown.

the expense of the entire diet. Potassium iodide in aqueous solution (3.0 gm/liter) was added to the diets after they had been prepared and then thoroughly mixed.

Carrier-free  $\text{NaI}^{131}$  was obtained from the Union Carbide Nuclear Company, Oak Ridge, Tennessee. Suitably diluted aliquots in sterile saline were injected intraperitoneally. Samples were counted in a Nuclear-Chicago, well-type scintillation counter and corrected for background and radioactive decay.

The standard error (SE) was calculated from  $\text{SE} = \sqrt{\frac{\sum d^2}{n(n-1)}}$ , where  $d$  = deviation from the mean and  $n$  = number of observations.

#### Experiment 1

*The effect of KI on growth and organ weights of sulfaguanidine and thiouracil-fed rats.* Three groups of 6 rats each were fed the basal diet containing 1% of sulfaguanidine and zero, 10, or 30  $\mu\text{g}$  of additional KI/gm of diet. Three other groups of 6 rats each were fed diets containing 0.1% of thiouracil and zero, 10, or 30  $\mu\text{g}$  of additional KI/gm of diet. Two additional groups of 6 rats each served as controls. One was fed the basal diet without further supplementation. The other was fed the basal diet containing 30  $\mu\text{g}$  of additional KI/gm. When the experiment was terminated, the rats were exsanguinated. Certain organs were removed, cleaned of adventitious tissue and weighed to the nearest 0.1 mg on a Roller-Smith Torsion Balance.

The growth response of thiouracil and sulfaguanidine-fed rats to various levels of KI added to the basal diet is shown in figure 1. The final body weights and organ weights are summarized in table 1. In the absence of a goitrogen, KI (30  $\mu\text{g}/\text{gm}$  of diet) had no effect on growth or organ weights. Sulfaguanidine, without additional KI had no effect on growth, and only the thyroid gland exhibited a moderate increase in weight (table 1, group 3). The addition of 10  $\mu\text{g}$  of KI/gm to the sulfaguanidine diet resulted in growth inhibition and 30  $\mu\text{g}$  of KI/gm resulted in growth arrest. The latter group weighed 120 gm at 28 days and gained 15 gm during the subsequent 13 weeks. As the iodide level

increased, the relative weight of the thyroid, the adrenals, the testes, and pituitary increased (table 1, groups 4 and 5). The effect on the thymus was marked. The thymus glands from rats in group 3 were firm and well-formed. Those from group 4 were visibly more diffuse and fragile, requiring great care in handling. Those in group 5 were small, extremely diffuse, and fragile. This was true also of the thymus glands from rats in groups 7 and 8 (table 1). The reliability of this data was questionable and was, therefore, omitted from the table. The omission of these figures is intended to indicate an advanced stage of thymic involution.

Thiouracil alone was a more effective growth inhibitor than was sulfaguanidine, and growth arrest was observed in those rats receiving 10  $\mu\text{g}$  of KI/gm. Those rats receiving 30  $\mu\text{g}$  of KI/gm of diet gained only 2 gm between the fourth and seventeenth week (fig. 1). However, the pattern of response to additional dietary KI was similar to that observed with sulfaguanidine. As the iodide level increased, growth was progressively inhibited and the relative weights of the thyroid and the adrenal glands increased. The testes and the pituitary appeared to have been maximally affected by thiouracil alone (table 1, group 6) since the addition of 10 or 30  $\mu\text{g}$  of KI/gm did not effect a further increase in the relative weight of these two glands (groups 7 and 8).

Thirty micrograms of KI/gm were fatal to rats fed both thiouracil and sulfaguanidine. On the ninety-seventh day, one rat in group 8 (table 1) developed tremors and was unusually sensitive when touched. It was moribund on the one-hundredth day and died on the one-hundred-first day. It had lost only 3 gm in body weight during this 4-day period. Its stomach and cecum were filled with food, and 6 firm and well-formed fecal pellets were in the intestinal tract indicating that inanition was not a factor contributing to its death. Only the adrenal glands appeared abnormal. These were almost black in color.

The rats in groups 5 and 8 were maintained for 17 weeks after these symptoms appeared. Identical toxic symptoms appeared in another rat of group 8 on the one-hundred-fifteenth day, and in two

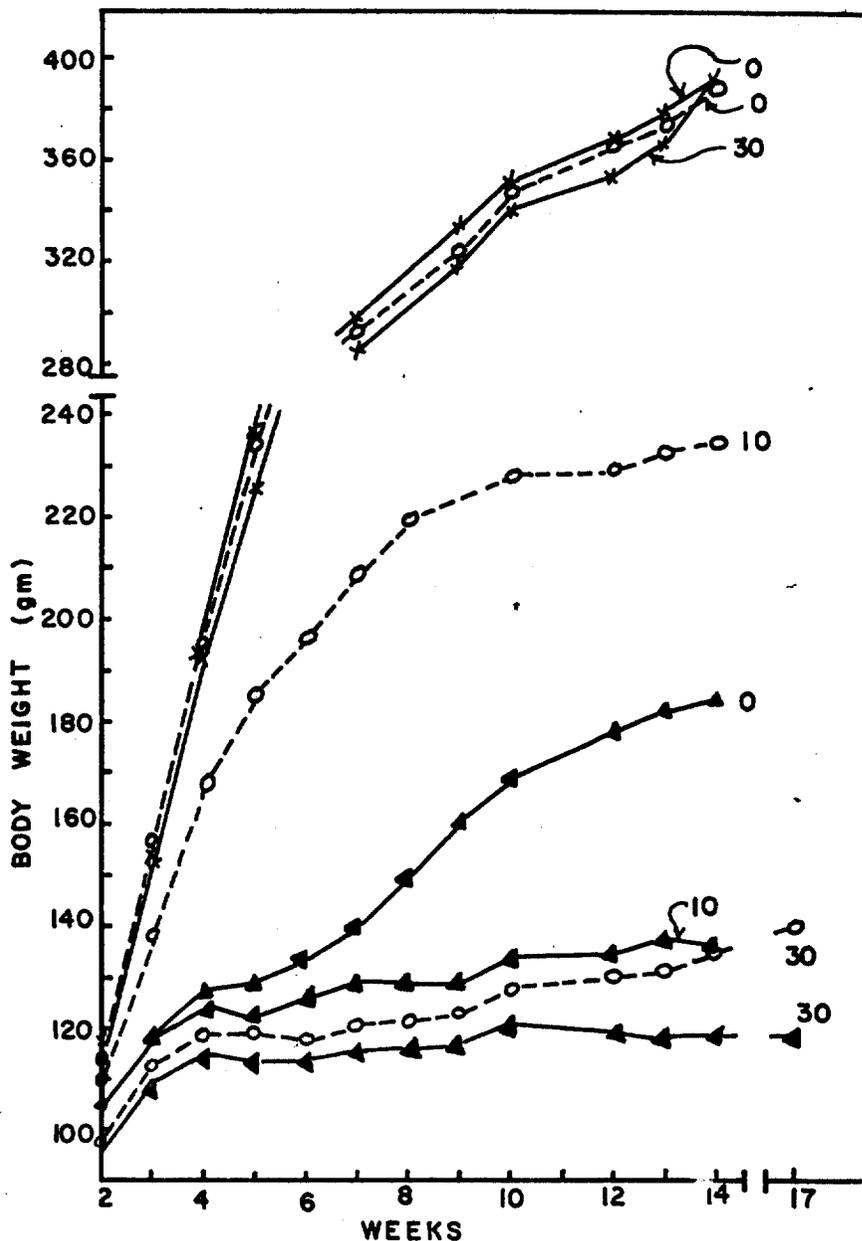


Fig. 1 Effect of zero, 10, and 30  $\mu\text{g}$  of KI on growth of sulfaguanidine or thiouracil-fed rats. Basal diet,  $\times$ — $\times$ ; 1% of sulfaguanidine — $\circ$ — $\circ$ —; 0.1% of thiouracil,  $\leftarrow$ — $\leftarrow$ . The figures at the termination of each curve indicate the amount of KI added to the diet in micrograms per gram of diet.

rats of group 5 on the one-hundred-seventh and one-hundred-fourteenth day. Two of these were killed when they became moribund and the adrenal glands of these two rats were also dark in

color indicating that this change in color was not due to postmortem changes. The remaining rats in groups 5 and 8 were alert and active exhibiting only severe exophthalmos. They were killed on the

TABLE 1  
Effect of potassium iodide on the growth and organ weights of goitrogen-fed rats

Group <sup>1</sup>	Additions to basal diet		Final body wt <sup>2</sup>	Organ weights				
	Drug	KI		Thyroid	Thymus	Adrenal	Testes	Pituitary
	$\mu\text{g}/\text{gm}$		gm	mg/100 gm	mg/100 gm	mg/100 gm	mg/100 gm	mg/100 gm
1	0	0	396 ± 3 <sup>3</sup>	6.09 ± 0.2	134 ± 3.5	12.0 ± 0.8	934 ± 15	2.6 ± 0.2
2	0	30	397 ± 13	7.02 ± 0.4	164 ± 13	11.8 ± 0.5	923 ± 19	2.5 ± 0.2
3 (5)	Sulfaguani- dine, 1%	0	391 ± 9	11.6 ± 0.7	149 ± 9.7	11.7 ± 0.2	958 ± 36	2.3 ± 0.07
4	Sulfaguani- dine, 1%	10	235 ± 19	31.3 ± 3.4	120 ± 7.2	13.2 ± 2.1	1086 ± 196	4.3 ± 0.3
5	Sulfaguani- dine, 1%	30	135 ± 8	54.3 ± 6.6	—	15.1 ± 1.1	1417 ± 136	4.5 ± 0.2
6 (5)	Thio- uracil, 0.1%	0	184 ± 18	55.9 ± 8.1	181 ± 32	12.1 ± 0.8	1458 ± 107	4.8 ± 0.1
7	Thio- uracil, 0.1%	10	138 ± 8	77.5 ± 10	—	14.7 ± 0.5	1536 ± 120	6.3 ± 0.1
8	Thio- uracil, 0.1%	30	121 ± 8	87.6 ± 16	—	15.9 ± 1.0	1459 ± 198	4.7 ± 0.2

<sup>1</sup> Six male rats except where indicated by numbers in parentheses.

<sup>2</sup> Body weight at the end of the 14th week except for groups 5 and 8 which were maintained for 17 weeks. See text.

<sup>3</sup> Mean ± SE.

one-hundred-nineteenth day and their adrenal glands were normal in color. The organ weights of the rats that had died were included with the data of the surviving rats in their respective groups since no differences in their organ weights were noted.

#### Experiment 2

The ability of duodenal powder to maintain and reinstate growth of goitrogen-fed rats. Nine groups of weanling rats were fed the basal diet supplemented with 30  $\mu\text{g}$  of KI/gm, and the following: (1) none; (2) 4% of duodenal powder; (3) 1% of sulfaguani-  
dine; (4) 1% of sulfaguani-  
dine plus 4% of duodenal powder; (5) 0.1% of thiouracil; (6) 0.1% of thiouracil plus 4% of duodenal powder; (7) 1% of sulfaguani-  
dine for 41 days at which time the drug was omitted from the diet; (8) 0.1% of thiouracil for 41 days at which time the drug was omitted from the diet; and (9)

0.1% of thiouracil. On the forty-first day, 2, 4, and 8% of duodenal powder was added to the diet of three rats each. All rats were weighed weekly but rats in groups 7 to 9 were weighed every two days from the forty-first to the fifty-fifth day. All rats were killed on the fifty-fifth day, and certain organs were removed and weighed.

Figure 2 illustrates that growth arrest again occurred after the twenty-eighth day in rats fed either thiouracil or sulfaguani-  
dine with 30  $\mu\text{g}$  of KI/gm, but 4% of duodenal powder in the diet was effective in maintaining growth of rats fed either goitrogen. Duodenal powder had no appreciable stimulatory effect on growth when it was included in the control diet (fig. 2). With the exception of the thyroid glands, whose increase in weight was inhibited but not prevented, duodenal powder also maintained organ weights at or near normal values when it was included

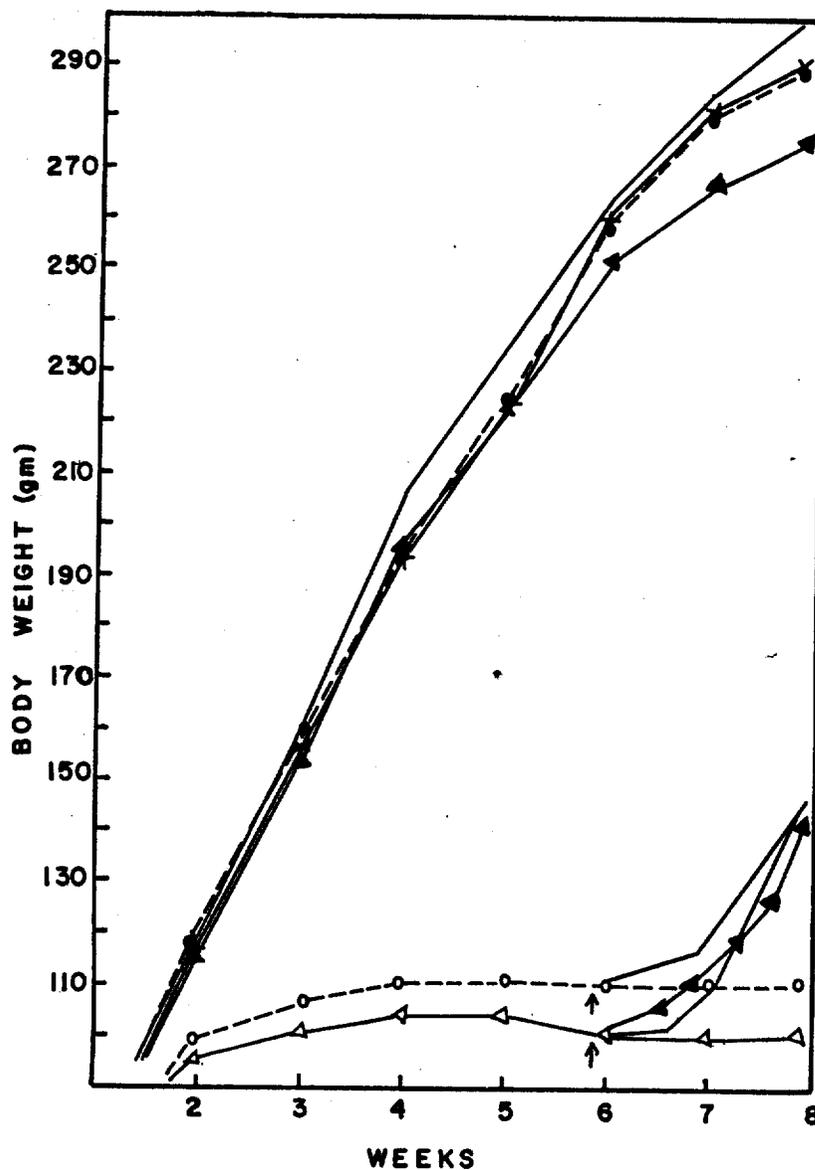


Fig. 2 The ability of duodenal powder to maintain and reinstate growth of thiouracil and sulfaguanidine-fed rats. All diets contained  $30 \mu\text{g}$  of KI/gm. Normal, —; normal + 4% of duodenal powder,  $\times$ — $\times$ ; 1% of sulfaguanidine  $\circ$ — $\circ$ ; 0.1% of thiouracil,  $\triangle$ — $\triangle$ ; solid symbols indicate that 4% of duodenal powder was added to the diet. Goitrogens were removed or duodenal powder was added on the forty-first day (arrow).

in the goitrogen-containing diets from the first day (table 2, groups 4 and 6).

Growth was reinstated when the goitrogens were removed from the diet on the forty-first day (fig. 2 and groups 7 and 8 of table 2). Normal thyroid function is

restored under these conditions, and comparison of groups 7 and 8 with the corresponding groups 3 and 5, shows that growth resumption was accompanied by a decrease in the relative weight of the thyroid gland and an increase toward normal

TABLE 2  
Effect of duodenal powder on growth of goitrogen-fed rats

Group (no. rats)	Diet <sup>1</sup>		Final body wt.	Wt. gain 41-55th day	Organ weights				
	Drug	Duodenal powder			Thyroid	Thymus	Adrenal	Testes	Pituitary
		%	gm	gm	mg/100 gm	mg/100 gm	mg/100 gm	mg/100 gm	mg/100 gm
1 (5)	0	0	293 ± 9 <sup>2</sup>	32	4.4 ± 0.2	256 ± 22	11.6 ± 0.5	1116 ± 34	2.3 ± 0.3
2 (6)	0	4	303 ± 8	38	4.2 ± 0.3	213 ± 9	15.4 ± 0.8	1146 ± 16	3.2 ± 0.1
3 (6)	Sulfa- guanidine, 1%	0	110 ± 5	-1	55.6 ± 2.7	133 ± 11	19.5 ± 0.6	1205 ± 309	4.6 ± 0.2
4 (7)	Sulfa- guanidine, 1%	4	290 ± 6	31	10.2 ± 0.6	242 ± 14	11.7 ± 0.5	1146 ± 36	2.0 ± 0.2
5 (5)	Thiouracil, 0.1%	0	100 ± 1	0	100 ± 11	126 ± 12	15.6 ± 0.5	1958 ± 216	5.1 ± 0.9
6 (7)	Thiouracil, 0.1%	4	278 ± 11	25	17.1 ± 1.1	190 ± 12	11.3 ± 0.4	1154 ± 35	2.6 ± 0.2
7 (6)	Sulfa- guanidine, 1% <sup>4</sup>	0	149 ± 2	35 ± 3	16.8 ± 0.8	263 ± 14	19.7 ± 0.7	1381 ± 81	3.4 ± 0.5
8 (6)	Thiouracil, 0.1% <sup>4</sup>	0	149 ± 3	44 ± 2	24.4 ± 1.4	181 ± 11	17.3 ± 0.1	1037 ± 147	3.6 ± 0.3
9 (3)	Thiouracil, 0.1%	2 <sup>5</sup>	143 ± 9	36 ± 4	73.4 ± 8	174 ± 26	16.2 ± 0.8	1752 ± 203	4.8 ± 1.2
(3)	Thiouracil, 0.1%	4 <sup>5</sup>	149 ± 2	43 ± 7	53.6 ± 11	185 ± 29	17.1 ± 1.0	1531 ± 150	3.6 ± 0.1
(3)	Thiouracil, 0.1%	8 <sup>5</sup>	164 ± 18	56 ± 3	23.3 ± 3	209 ± 32	16.2 ± 2.5	1508 ± 261	3.3 ± 0.3

<sup>1</sup> The diets of all rats contained 30 µg of KI/gm.

<sup>2</sup> Body weight on the 55th day.

<sup>3</sup> Mean ± SE.

<sup>4</sup> Sulfaguanidine and thiouracil were omitted from the diets on the 41st day.

<sup>5</sup> Duodenal powder was added to the thiouracil diet on the 41st day. The data for these groups is recorded as mean ± range.

GROWTH OF GOITROGEN-FED RATS

mal of the thymus gland. The adrenal glands did not respond by a change in weight during this two-week period. A marked reduction in the relative weight of the testes was observed in those rats which had been fed thiouracil (group 8).

The addition of duodenal powder to the thiouracil diet on the forty-first day evoked a response similar to that observed in group 8. This is shown in group 9 (table 2) where the addition of 2, 4, and 8% of duodenal powder to the diet resulted in a progressive increase in body weight gain and a definite trend toward normal values

of the thyroid, thymus, and the pituitary. The adrenal glands and the testes did not respond by a change in weight during this two-week period. Figure 2 depicts the growth response of those rats in group 9 which were fed the thiouracil diet supplemented with 4% of duodenal powder.

### Experiment 3

Growth of rats fed thiouracil in a commercial ration. Commercial laboratory chow<sup>5</sup> was finely ground and then supplied

<sup>5</sup> See footnote 2.

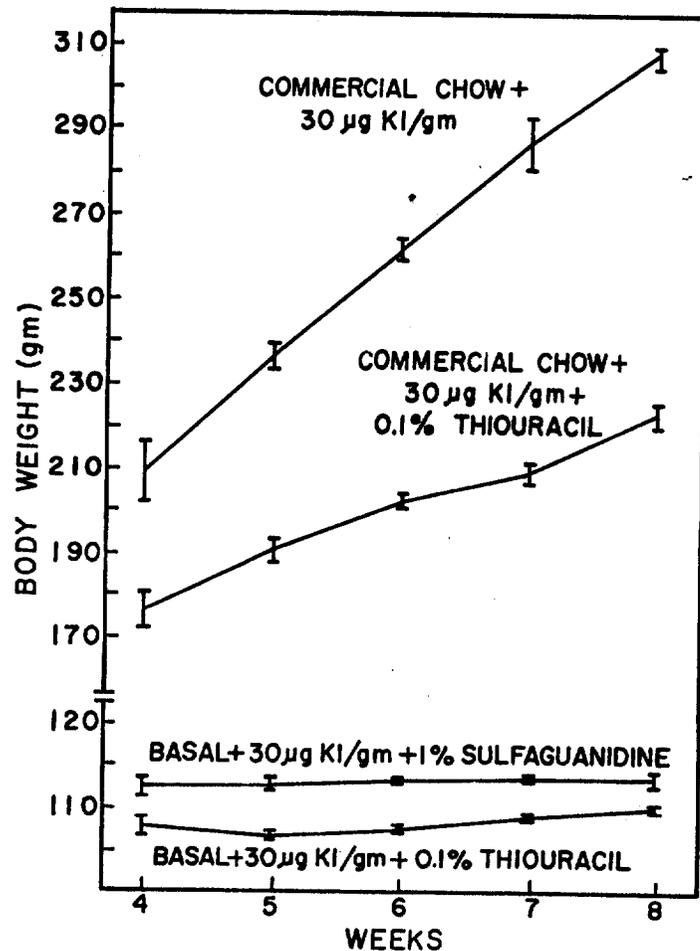


Fig. 3 Growth of rats fed 0.1% of thiouracil in commercial laboratory chow compared with rats in experiments 1, 2, and 4 which were fed goitrogen plus 30 µg of KI/gm of diet. Vertical bars represent the standard error of the weight gain for the previous week. From the fourth to the eighth week, the points on the sulfaguanidine curve represent the average of 18, 18, 12, 12, and 12 rats, respectively. The points on the thiouracil curve represent the average of 24, 24, 12, 12, 12, and 6 rats, respectively.

mented with 30 µg of KI/gm. One group of 6 rats was fed this diet without further supplementation. Another group of 6 rats was fed the same diet supplemented with 0.1% of thiouracil. The experiment was terminated on the fifty-fifth day. Organ weights were not determined.

The laboratory chow, containing 0.1% of thiouracil and additional KI (30 µg/gm), did not produce the severe growth inhibition that was observed in experiments 1 and 2. This is illustrated in figure 3. For comparison, the growth data of those rats fed 1% of sulfaguanidine or 0.1% of thiouracil with 30 µg of KI/gm of diet in experiments 1, 2, and 4 were pooled and plotted in figure 3. The actual body weight attained in 28 days by an individual rat may vary from 90 to 140 gm, but the subsequent weight gain is negligible. This is illustrated in figure 3 by the vertical bars which represent the standard error of the average weight gain for each week. The various components of the commercial laboratory chow were not available for a more critical study, but it is inferred from these experiments that the meat meal component of this chow is responsible for the failure to observe growth arrest.

Experiment 4

The effect of duodenal powder on the uptake and protein binding of radiotiodide by goitrogen-fed rats. Five groups of 5 rats each were fed diets indentical to those fed to groups 1, 3 and 5 of experiment 2. After growth arrest was established (35 days), 5 µc of NaI<sup>131</sup> was administered to each rat. Twenty-four hours later, blood was collected by heart puncture. The thyroid glands were removed, weighed, and homogenized with 5.0 ml of 0.001 M thiouracil in 0.01 N NaOH. An aliquot was removed and counted to determine total radioactivity in the gland. Four milliliters of the remaining thyroid homogenate were added to 4 ml of 20% trichloroacetic acid which contained 10 µg of KI/gm. The precipitate was washed three times with 5% trichloroacetic acid containing 5 µg of KI/ml. The precipitate was counted for radioactivity and this represented protein bound I<sup>131</sup> (PBI<sup>131</sup>). The protein from one milliliter of serum was precipitated and washed with trichloroacetic acid exactly as

TABLE 3  
Effect of duodenal powder on the incorporation of I<sup>131</sup> into thyroid and serum protein

Group <sup>1</sup>	Diet <sup>2</sup>		Final body wt <sup>3</sup> gm	Thyroid weight mg	Thyroid I <sup>131</sup>		Serum I <sup>131</sup>	
	Drug	Duodenal powder %			Total I <sup>131</sup> / 100 mg	PBI <sup>131</sup>	Total I <sup>131</sup> / 100 ml	% of dose
1	0	0	267 ± 7 <sup>3</sup>	10.0 ± 0.25	23.1 ± 2.1	18.0 ± 2.1	68.9 ± 6.1	0.51 ± 0.04
2	Sulfa-guanidine, 1%	0	109 ± 7	32.5 ± 1.7	0.95 ± 0.09	0.006 ± 0.001	0.42 ± 0.02	0.53 ± 0.05
3	Sulfa-guanidine, 1%	4	248 ± 11	17.2 ± 1.7	0.63 ± 0.03	0.30 ± 0.02	54.8 ± 3.6	0.25 ± 0.03
4	Thiouracil, 0.1%	0	107 ± 4	55.7 ± 3.4	1.33 ± 0.12	0.0012 ± 0.0002	0.34 ± 0.01	0.48 ± 0.04
5	Thiouracil, 0.1%	4	217 ± 4	17.1 ± 0.40	0.10 ± 0.02	0.014 ± 0.003	15.9 ± 4.9	0.18 ± 0.01

<sup>1</sup> Five male rats per group.  
<sup>2</sup> Thirty micrograms of KI/gm added to all diets.  
<sup>3</sup> At 35 days.  
<sup>4</sup> Percentage of total thyroid I<sup>131</sup> =  $\frac{\text{PBI}^{131} \text{ count}/\text{min} \times 5/4}{\text{Thyroid I}^{131} \text{ count}/\text{min} \times 5} \times 100$ .  
<sup>5</sup> Mean ± SE.

described for the thyroid homogenate and then counted to determine the serum PBI<sup>131</sup>.

The uptake of radioiodide and its incorporation into thyroid protein is markedly inhibited in rats fed sulfaguanidine or thiouracil with 30 µg of KI/gm of diet (table 3, groups 2 and 4) which provides additional evidence that under the conditions used in these experiments, both goitrogens effectively block thyroid hormone synthesis. When 4% of duodenal powder was included in these diets, growth was maintained, thyroid weight decreased, and the total uptake of I<sup>131</sup> decreased.

Although the total uptake of I<sup>131</sup> decreased, the incorporation into thyroid protein increased 50-fold in sulfaguanidine-fed rats and 10-fold in thiouracil-fed rats. Only 0.42% of the total thyroid I<sup>131</sup> was protein bound in those rats fed sulfaguanidine alone, but the addition of duodenal powder to the diet increased this to 54.8%. In thiouracil-fed rats, the thyroid I<sup>131</sup> bound as protein increased from 0.34 to 15.9% when duodenal powder was added to the diet.

Whether this increase in thyroid PBI<sup>131</sup> could account for the growth-promoting effects of duodenal powder is not clear since this increase is not reflected in the serum PBI<sup>131</sup>. Duodenal powder resulted in a decrease in serum PBI<sup>131</sup>.

#### DISCUSSION

Growth arrest has not always been observed in rats fed goitrogens for prolonged periods of time (Mackenzie and Mackenzie, '43; Astwood et al., '43; Astwood and Bissell, '44) and inconsistencies with the expected response to goitrogens have been observed when other parameters of thyroid function were measured (Williams et al., '44; Mayer, '47; Stasili et al., '60). A consideration of these reports suggests that the diet may have been a primary factor responsible for these inconsistencies. For example, Welch and Wright ('43) reported that the unusually high level of 10% succinylsulfathiazole in commercial<sup>6</sup> diets had no effect on growth of rats, yet 1 and 2% of this drug in a purified diet resulted in growth failure. In contrast, 2% of sulfaguanidine in commercial fox chow<sup>7</sup> had only a slight inhibitory effect on growth (Astwood et al., '43).

The experiments reported here show that growth arrest may be induced in sulfaguanidine-fed rats when the dietary iodide level is between 10 and 30 µg/gm of diet, and that iodide (10 and 30 µg/gm) enhances the growth-inhibitory effect of 0.1% of thiouracil. Under these conditions, the synthesis of thyroid hormones by the thyroid gland was effectively inhibited. However, duodenal powder added to the diet maintained growth and organ weights of both thiouracil- and sulfaguanidine-fed rats. Thus, the failure to observe growth arrest or symptoms typical of a thyroid deficiency when thiouracil or sulfonamides are fed may be due either to insufficient dietary iodide or to the use of diets which contain animal tissues such as the commercial chows used, or to both.

The role played by iodide appears to be complex. Mackenzie ('47) reported that iodide inhibited the goitrogenic effect of thiouracil but enhanced the goitrogenicity of sulfaguanidine. Highley et al. ('54) noted that the growth-inhibitory and goitrogenic effects of low levels of thiouracil (0.025% or less) could be overcome by iodine, but that iodine did not prevent growth inhibition or thyroid hyperplasia caused by 0.1% thiouracil. High levels of iodide have been reported to promote growth of thyroidectomized rats (Evans et al., '60), but it had no effect on growth or other parameters of thyroid function when it was administered to normal rats fed normal diets (Pitt-Rivers, '60). It appears, therefore, that high levels of iodide function synergistically with a goitrogen such as thiouracil or sulfaguanidine to more effectively block thyroid hormone synthesis.

The fatal effects of sulfaguanidine and thiouracil (experiment 1) appear to be linked to the level of dietary iodide and this is now under investigation. That sulfaguanidine in purified diets is fatal to rats has been reported by Axelrod et al. ('53) and Tentori and Vivaldi ('50, '54). The former workers used diets containing 30 µg of KI/gm of diet, and the latter workers reported that sulfaguanidine was not fatal when it was fed in McCollum's stock diet. This diet is relatively low in iodide.

<sup>6</sup> Purina or Wayne Brand.

<sup>7</sup> Purina Fox Chow.

The effect of duodenal powder in these experiments suggests that this tissue contains thyroid hormones at physiologically effective concentrations. This is conceivable in view of the reports which indicate that the thyroxine requirement to maintain growth of thyroidectomized rats (Evans et al., '60a) or thiouracil-fed rats (Stasilli et al., '61) is 0.04 to 0.05  $\mu\text{g}/\text{day}$  when it is administered parenterally.

The relative weights of the thyroid glands from rats fed sulfaguanidine plus 30  $\mu\text{g}$  of KI/gm were consistently lower than those of rats fed thiouracil plus 30  $\mu\text{g}$  of KI/gm (tables 1, 2, and 3). These rats had ceased to grow (fig. 3) due to a depletion of endogenous thyroid hormones. It would be expected then, that thyrotropin secretion would be maximal and that the compensatory response of the thyroid gland would be maximal in both thiouracil and sulfaguanidine-fed rats. This was not the case, indicating that the secretion of thyrotropin or the sensitivity of the thyroid gland to thyrotropin had been inhibited by sulfaguanidine in these experiments.

#### SUMMARY

Two factors which modify the thyroid hormone deficiency produced by the ingestion of thiouracil or sulfaguanidine were studied and certain observations indicate that the mode of action of these two goitrogens are different.

1. The addition of 10  $\mu\text{g}$  of KI/gm of diet markedly inhibited growth, and 30  $\mu\text{g}$  of KI/gm of diet resulted in growth arrest of rats fed 1.0% sulfaguanidine. Growth arrest occurred after 28 days in thiouracil-fed rats when 10  $\mu\text{g}$  of KI/gm were added to the diet. With either goitrogen, growth arrest was accompanied by an increase in the relative weights of the thyroid, adrenals, testes, and the pituitary, and a decrease in that of the thymus gland. The uptake of  $\text{I}^{131}$  and its incorporation into protein by the thyroid gland was markedly reduced. Prolonged feeding of either goitrogen with 30  $\mu\text{g}$  of KI/gm of diet was fatal to some of the rats.

2. Growth and organ weights were maintained at or near normal values when the duodenal powder was added to those diets capable of producing growth arrest. Under such conditions, duodenal powder

decreased the uptake of  $\text{I}^{131}$  by the thyroid gland but increased the incorporation of thyroidal  $\text{I}^{131}$  into protein. The pattern of response to duodenal powder suggests that this tissue contains thyroid hormone-active material. Since growth arrest could not be induced in rats fed thiouracil plus 30  $\mu\text{g}$  of KI/gm of commercial laboratory chow, it was inferred from these experiments that this diet contains thyroid hormone-active material in the meat meal which is a component of this chow.

3. The relative weights of the thyroid glands from growth-arrested, sulfaguanidine-fed rats were consistently less than that of growth-arrested, thiouracil-fed rats indicating that the mechanism which compensates for low levels of circulating thyroid hormones was inhibited by the sulfaguanidine under the conditions of these experiments.

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# Effects of Excess Dietary Iodine upon Pullets and Laying Hens<sup>1,2</sup>

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**ABSTRACT** Iodine as potassium iodide was fed to sexually mature pullets and hens that had completed one year of lay, to study the effects upon egg production, fertility, hatchability, embryonic mortality and incubation time. Dietary intakes at 5 levels from zero to 5000 ppm iodine were fed in a practical-type diet for 6 weeks. Measurement of egg production was continued following the iodine feeding period. Egg production decreased with increasing levels of iodine and ceased with intakes of 5000 ppm. The decreases were greater for hens than for pullets. Production commenced and increased rapidly within one week after change to control diets and was equal to that of control birds during a 27- and 18-week subsequent feeding period for pullets and hens. Molting did not accompany the cessation of lay in pullets but some mature hens molted. Mature ova were present in birds not laying but ovulation did not occur. Weight of eggs produced during the period of iodine feeding was reduced but returned to normal within 3 weeks. Fertility of eggs was not affected but high embryonic death, low hatchability and delayed hatching were observed.

Iodine is recognized as one of the essential elements for poultry and is normally provided in the diet as iodized salt. At the level provided by 0.5 or 1.0% of iodized salt in the diet, no abnormal or harmful effects are produced, but toxic effects have been observed with experimental intakes of excess iodine. Decreased egg production, prolonged hatching, enlarged thyroids of chicks, decreased egg size and appearance of wiry down have been reported (1-3). A more recent study (4) has confirmed these observations and extended them to other effects of iodine. With 5000 ppm iodine as KI in the diet, production ceased within one week and was reduced to 10% at 2500 ppm. Fertility of eggs was not affected, but high embryonic mortality and delayed hatching resulted.

Studies with other species have also demonstrated harmful effects of iodine (5, 6). Rats fed 500 to 2500 ppm iodine were fertile and produced litters, but lactation failed and high mortality of the young resulted. Pregnant rabbits fed 250 to 1000 ppm iodine produced litters but most young died within 48 hours after birth.

The present study was conducted to determine the influence of feeding high levels

of iodine upon subsequent egg production and to compare the effects of iodine on pullets and mature hens.

## EXPERIMENTAL PROCEDURE

**Pullets.** One hundred and fifty 27-week-old White Leghorn pullets were assigned at random to 30 replicates of 5 birds each and housed in individual laying cages. Thirty pullets each were fed diets containing zero, 625, 1250, 1875 or 2500 ppm iodine as potassium iodide. Four additional replicate treatments of 5 pullets each were provided with 5000 ppm iodine for 105 days. The basal diet to which selected levels of iodine were added consisted of the following: (in per cent) ground yellow corn, 67.7; soybean meal, 20.6; alfalfa meal, 3.0; ground limestone, 5.8; defluorinated phosphate, 1.96; iodized salt, 0.4; and microingredients, 0.5. The microingredients supplied per kg diet: vitamin A, 4,400 IU; vitamin D<sub>3</sub>, 1,540 ICU; and (in milligrams) choline, 500; niacin, 13.2; riboflavin, 4.4; Ca pantothenate, 8.8; ethoxyquin, 12.5; MnSO<sub>4</sub>, 220; and (in micrograms) vitamin B<sub>12</sub>, 13.2.

Received for publication February 9, 1967.

<sup>1</sup> Florida Agricultural Experiment Stations, Journal Series no. 2635.

<sup>2</sup> Supported by Public Health Service Research Grant no. AM-08760 from the National Institutes of Arthritis and Metabolic Diseases.

On the second day after iodine feeding started, pullets were artificially inseminated using pooled semen from normal males. Eggs were collected daily and those produced from day 2 through day 14 after insemination were stored and subsequently incubated. Pullets remaining in production at 35 days were again inseminated and the eggs incubated.

Individual egg production records and weight of eggs were determined through the experimental period and for an additional 27-week period after removal of iodine. Fertility of eggs produced during the period of iodine feeding was determined using the conventional candling technique. During incubation, eggs were candled on days 4, 10 and 18 as a measure of embryonic mortality. Records were also made of hatching time, number hatched, eggs pipped without emerging and those which died in the shell.

Representative one-day-old chicks hatched from eggs produced with the control and each experimental diet were weighed, identified and fed a practical-type chick starter diet. Growth of the

chicks as measured by body weight at 2 weeks was determined. Five one-day-old chicks from control pullets and five from those fed 2500 ppm iodine were killed and the thyroids removed, weighed and subsequently examined histologically. At the end of the iodine feeding period, 2 birds from each dietary treatment were killed and the reproductive system was examined.

*Mature hens.* One hundred mature White Leghorn hens which had been in production for 12 months were used in a concurrent study. Four replicates of 5 hens each received the same basal diet and diets with iodine described for pullets. The same procedures for feeding, insemination and incubation described for pullets were followed with the hens. No eggs, however, were available for incubation at the end of the 6-week period. Interior egg quality was determined for control hens and those fed 2500 ppm iodine at 10 weeks after removal of iodine. Quality was based upon Haugh units calculated from albumin height and egg weight. Statistical calculations were based upon analysis of variance (7).

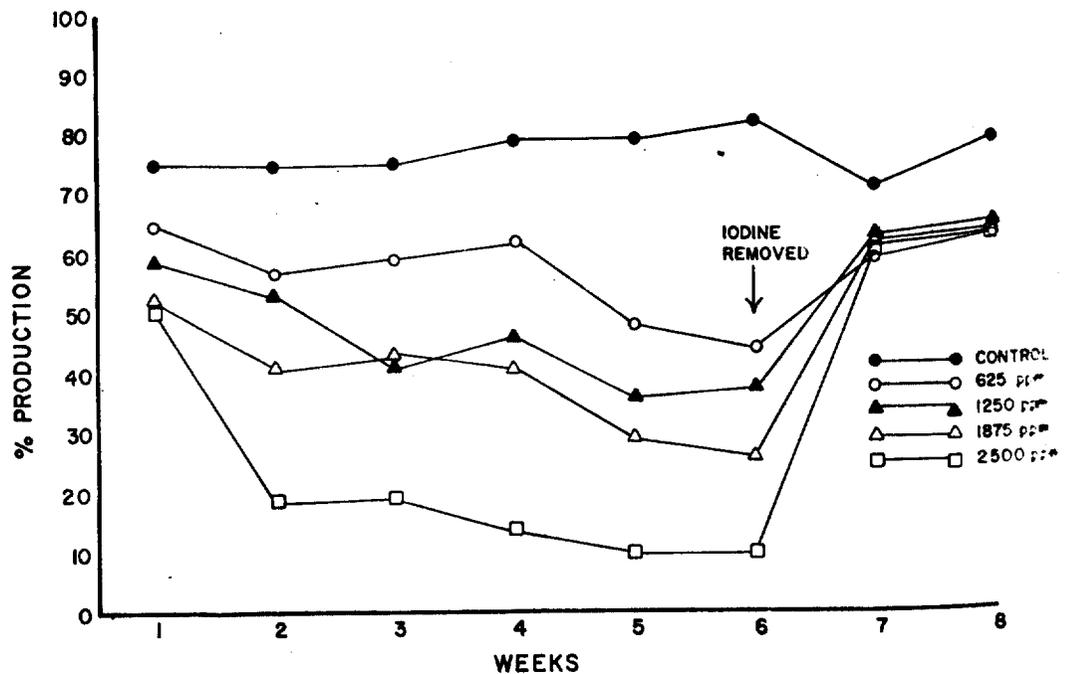


Fig. 1 Egg production of pullets during period of iodine feeding and after removal of dietary iodine.

TABLE 1  
Rate of egg production in pullets and hens following the experimental period of iodine feeding<sup>1</sup>

Dietary iodine ppm	Egg production	
	Pullets %	Hens %
0	58.1	37.8
625	59.7	35.0
1250	60.0	40.7
1875	59.1	40.3
2500	56.3	39.3

<sup>1</sup>Production computed as average of 27 weeks for pullets and 18 weeks for hens, beginning 2 weeks after iodine was removed from feed.

RESULTS

Egg production of pullets fed iodine varied inversely with level of iodine beginning during the first week of treatment (fig. 1). With 5000 ppm iodine, virtually no eggs were produced after the second week. Pullets fed the control diet maintained a production rate of 75% or

more throughout the 6-week experimental period.

No molting accompanied the cessation of lay, and production increased rapidly after removal of dietary iodine. At the end of the 6-week period, production of pullets fed 2500 ppm iodine was 13% that of controls. By one week after iodine was removed, production equaled approximately 80% that of controls. The rate of production during 27 weeks after removal of iodine was not significantly different from controls (table 1). Two pullets in the group fed 2500 ppm iodine failed to return to production. At the end of the 27-week period, they were killed and eggs with several membranes were found in the isthmus. Tumerous growths present were evidently preventing their passage. This condition was not considered to be caused by iodine and these pullets were not included in the calculation of egg production data. If these 2 pullets had been included,

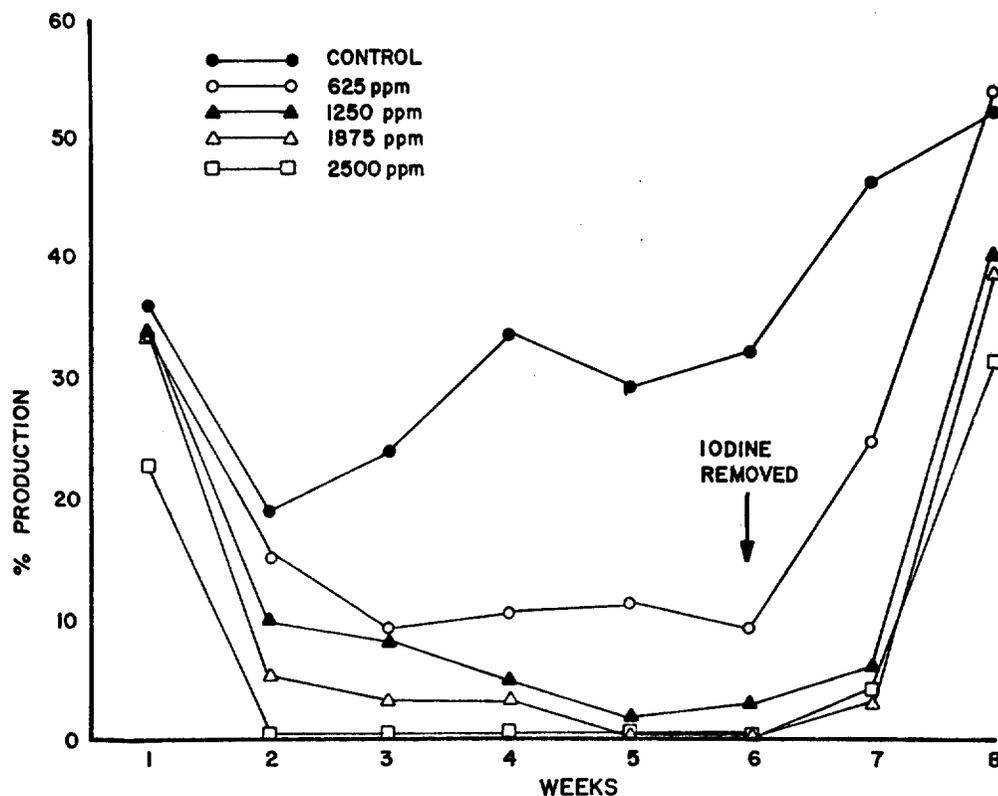


Fig. 2 Egg production of hens during period of iodine feeding and after removal of dietary iodine.

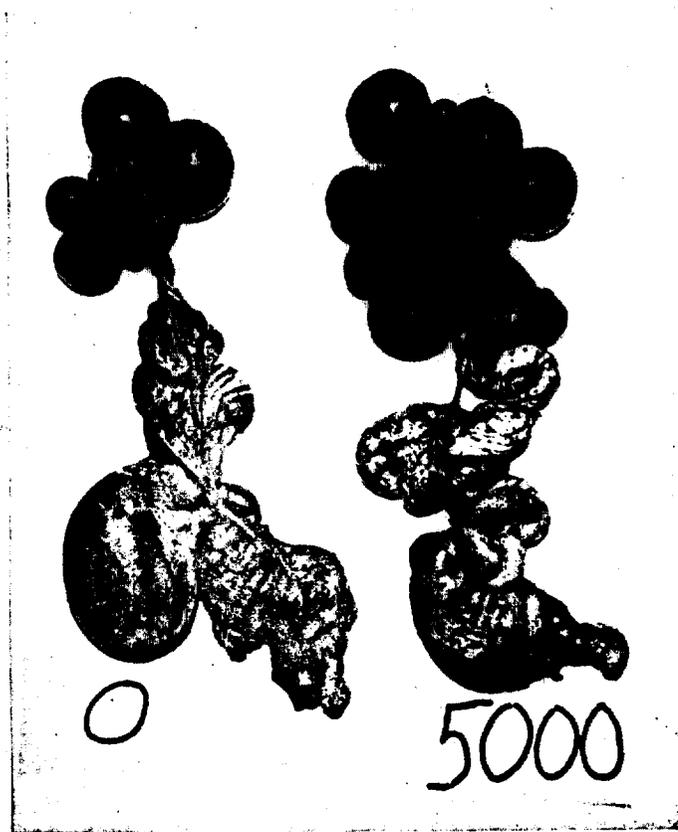


Fig. 3 Reproductive tracts from hens receiving control diet (left) and 5000 ppm iodine for 5 weeks. Note that the ovary was still functioning and ova were present in hen fed 5000 ppm iodine, but hen was not laying.

the rate of production would have been 51.8 instead of 56.3% (table 1).

Pullets provided 5000 ppm iodine were continued for 15 weeks and remained out of production. When returned to the control diet, all except one returned to production within 10 days. The rate of production for 16 weeks, beginning 2 weeks after removal of iodine, was 51.7% compared with 51.6% for the control group.

Mature hens responded somewhat differently to iodine treatment than pullets although the major effects were similar. The hens were removed from floor pens to laying cages at one week before iodine was fed. A small percentage of the hens in each group molted, but the proportion in the control group was less than in the iodine groups. Rates of egg production are shown in figure 2. Sixty-eight per cent of

all hens fed iodine were out of production after one week and by 4 weeks, 95% had ceased laying. Only 40% of the control hens were out of production at that time. When the iodine was removed from the diet, they returned to production in a manner similar to that observed for pullets. The rate of production for these hens was equal to that of the controls for an 18 week period beginning 2 weeks after removal of iodine from the feed (table 1).

Physical condition of pullets and hens out of production was such that they would have been judged to be laying. Position of the pelvic bones indicated production and yellow pigment was absent from beaks and shanks. Ovaries of hens not laying contained many ova in various stages of development but ovulation was not occurring. Some ova appeared to be

regressing. The ovary labeled 5000 ppm (fig. 3) was from a hen which had been out of production for 5 weeks.

Average of individual weights of eggs produced by the pullets fed all levels of iodine were significantly less than that of controls (table 2). At 3 weeks after removal of iodine, egg weights were normal. Interior quality of the eggs was improved following the rest induced by iodine in the mature hens. Average Haugh units of eggs from control hens maintained in continuous production was 62.6. The average value for eggs produced by hens at 10 weeks after removal from 2500 ppm iodine was 70.4.

Fertility of eggs produced was not affected by iodine feeding, but hatchability was decreased and embryonic mortality

and length of hatching time increased (table 3). The percentage hatchability decreased with increasing levels of iodine and was considerably less with eggs produced near the end of the iodine feeding period. Approximately 80% of all embryonic deaths occurred within the first 4 days of incubation. A number of the embryos survived the incubation period and pipped the shell, but were unable to emerge. Hatching time was delayed by 24 hours or more in 20 to 100% of the eggs hatched from hens fed iodine. Some eggs were hatched following a delay of more than 96 hours.

Thyroid weights of the chicks from hens fed 2500 ppm iodine were 3 times larger than those of controls but no specific differences in microstructure were observed.

TABLE 2  
Egg weights from pullets during and following consumption of excess iodine

Dietary iodine	Avg egg wt			
	10 days	3 weeks	6 weeks	3 weeks after return to basal
ppm	g	g	g	g
0	55.0 (195) <sup>1</sup>	56.2 (170)	57.2 (157)	57.9(153)
625	52.9 <sup>2</sup> (180)	50.9 <sup>2</sup> (120)	51.0 <sup>2</sup> ( 92)	57.6(101)
1250	52.1 <sup>2</sup> (171)	49.3 <sup>2</sup> (106)	50.4 <sup>2</sup> ( 74)	57.9(129)
1875	50.8 <sup>2</sup> (146)	46.2 <sup>2</sup> ( 86)	45.8 <sup>2</sup> ( 56)	57.9(141)
2500	53.4 (102)	47.6 <sup>2</sup> ( 32)	48.7 <sup>2</sup> ( 17)	58.6(102)

<sup>1</sup> Figures in parentheses represent number of eggs.

<sup>2</sup> Significantly less than control ( $P < 0.01$ ).

TABLE 3  
Hatchability, incubation time and thyroid weight of chicks from pullets fed excess iodine

Dietary iodine	No. fertile eggs set	Embryonic death, 4 days <sup>1</sup>	Hatched <sup>1</sup>	Pipped, not hatched <sup>1</sup>	Delayed hatch <sup>2</sup>	Thyroid wt
ppm		%	%	%	%	mg
			2-12 Days			
0	145	4.8	82.5	1.4	0.8	2.4
625	145	20.7	55.9	5.5	19.8	—
1250	131	30.5	45.8	12.2	25.0	—
1875	109	27.5	39.4	20.2	39.5	—
2500	80	17.5	40.0	13.8	31.3	7.7
5000	20	5.0	0.0	75.0	—	—
			35-45 Days			
0	195	1.5	91.8	1.0	2.2	—
625	94	47.8	12.8	2.1	83.3	—
1250	84	55.9	13.1	4.8	90.9	—
1875	57	59.6	0.0	1.7	—	—
2500	16	43.7	6.2	6.2	100.0	—

<sup>1</sup> Percentage based on number of fertile eggs set.

<sup>2</sup> Delayed by 24 hours or more; percentage based on numbers of chicks hatched.

Hatching weight of the chicks was not affected by iodine, but the chicks from the iodine group appeared weak and did not grow as well as controls. Control chicks averaged 88.5 g body weight at 2 weeks of age and those from pullets fed 2500 ppm iodine averaged 68.7 g.

Relatively few eggs were available for incubation from mature hens and none were produced near the end of the iodine feeding period. Those which were collected early after iodine feeding was started and were incubated, indicated the same effects upon hatchability as observed in pullets.

#### DISCUSSION

The difference in response of pullets and mature hens to excess dietary iodine is not understood. The change of hens from floor pens to laying cages may have initiated the molting and decrease in production independent of iodine. No molting was observed in mature hens in a former study (4) and did not occur among pullets in the present study. In a subsequent study in progress, high level feeding of iodine has resulted in considerable molting among hens which had been in production for 13 months. The different response observed may have been due to a difference in hormone production at the different age. It is possible that a natural molt and interruption of production was imminent in hens at the time of treatment. A clarification of the mode of action of iodine which permitted formation of ova without release should provide a greater understanding of the ovulation cycle in chickens.

The general absence of molting, physical condition of birds fed iodine and the presence of ova in hens out of production suggest that the action of iodine in causing the cessation of production is different from the action of other substances or

methods of forced resting of hens. A specific effect of iodine in causing these and other effects in poultry and in rats and rabbits (5, 6) has not been identified. The rapid return to normal egg production and normal reproduction and lactation in rats and rabbits after removal of iodine suggest some temporary interference with hormone production or action. The presence of many follicles without ovulation in hens suggests an inhibition of luteinizing hormone. Pullets which had received 5000 ppm iodine for 15 weeks laid as well as controls after removal of the iodine. This rest in production did not, however result in a higher rate of production following the interruption as is observed with some methods of forced resting.

#### ACKNOWLEDGMENT

The authors are indebted to T. C. Beatty, Jr. for technical assistance.

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## Iodide intoxication

### Report of a case

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Iodide sensitivity or intoxication is infrequently encountered in clinical procedure. The following is a brief report of a case of iodide sensitivity, including signs, symptoms, and treatment. The similarity of iodide intoxication and other clinical entities such as Mikulicz's disease, Mikulicz's syndrome, Sjögren's syndrome, malignant lymphomas, and uveoparotitis is mentioned. The importance of taking a thorough history is emphasized.

Iodide sensitivity or intoxication is infrequently encountered in clinical procedures.<sup>1-2</sup> It occurs in two forms, acute and chronic. The manifestations of the two forms differ slightly. In the acute form, the onset of symptoms usually occurs immediately or within several hours after the initial administration of the medication. The outstanding symptoms of acute iodide intoxication are angioneurotic edema, fever, arthralgia, lymphadenopathy, eosinophilia, and, more rarely, multiple petechiae of the skin and mucous membranes.<sup>2-4</sup> Fortunately, the occurrence of acute iodide intoxication is relatively rare. In the chronic form, the first oral symptom may be a metallic or brassy taste. This complaint is usually accompanied by a gingivitis and a burning sensation of the oral mucosa. Increased salivation is usually present with these symptoms.<sup>5</sup> Other more generalized symptoms include coryza, sneezing, and irritation of the conjunctivae with edema of the eyelids. Marked enlargement of the parotid and submaxillary salivary glands and inflammation of the pharynx and larynx may

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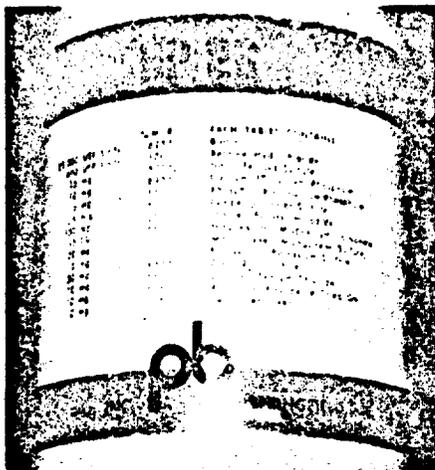


Fig. 1. Vitamin preparation taken by patient. The contents were as follows:

		% MDR*
Vitamin A	25,000 USP units	625%
Vitamin D	400 USP units	100%
Vitamin B <sub>1</sub> (mononitrate)	15 mg.	1,500%
Vitamin B <sub>2</sub>	10 mg.	833%
Vitamin B <sub>6</sub>	5 mg.	†
Vitamin B <sub>12</sub>	5 mg.	†
Vitamin C (sodium)	100 mg.	333%
Vitamin E (d-alpha tocopheryl succinate)	15 I.U.	†
Calcium pantothenate	20 mg.	†
l Lysine monohydrochloride	15 mg.	†
Niacinamide	50 mg.	500%
Choline bitartrate	10 mg.	†
Dl-Methionine	10 mg.	†
Biotin	25 mcg.	†
Betaine hydrochloride	10 mg.	†
Iron (ferrous sulfate)	20 mg.	200%
Calcium (dicalcium phosphate)	58.2 mg.	7.5%
Phosphorus (dicalcium phosphate)	45 mg.	6.0%
Copper (copper sulfate)	1 mg.	†
Iodine (potassium iodide)	0.15 mg.	150%
Magnesium (magnesium carbonate)	65 mg.	†
Manganese (manganese sulfate)	1 mg.	†
Potassium (potassium sulfate)	3 mg.	†
Zinc (zinc sulfate)	1.5 mg.	†
Aluminum hydroxide dried gel	10 mg.	†
Dessicated liver	30 mg.	†

\*%MDR = Per cent minimum adult daily requirement.

†Need in human nutrition established, but MDR not determined.

‡Need in human nutrition not established.

also be present.<sup>6-9</sup> Skin lesions are common and usually are acneiform in nature, involving the hair-bearing areas of the face and chest. Diarrhea, accompanied by bloody stools, fever, and severe headache, may be additional symptoms of chronic iodism. The exact mechanism of iodism is unknown. Various theories, including the antiphylactoid response, antigen-antibody reaction, and a disruption of the colloidal equilibrium of the body fluids, have been proposed to explain the mechanism of action in this condition.<sup>2</sup>

The treatment of iodide sensitivity is empirical. Symptoms of the condition



*Fig. 2.* Patient as seen on admission. Note marked swelling of all major salivary glands, usually disappear after discontinuance of the medication. However, it is often necessary to institute supportive measures as determined by the particular symptom or symptom complex that is present. This condition is rarely fatal, but recognition is essential so that treatment can be instituted.

#### **CASE REPORT**

On Jan. 25, 1976, a 54-year-old white man was seen in the emergency room of the Carle Foundation Hospital with complaints of a sore throat and difficulty in swallowing. He stated that the sore throat had begun 2 days previously, on January 23, and that his face, cheeks, and neck had begun to swell during the afternoon of January 25. That evening the swelling had become marked, he began to have difficulty swallowing, and at that time he reported to the emergency room. On further questioning, he revealed that during the week previous to his present symptoms, he had suffered some burning of the eyes, headache, gastric upset, and diarrhea. He also stated that he had been taking a multivitamin preparation containing 0.15 mg. of potassium iodide for approximately 10 days prior to the onset of his symptoms (Fig. 1). The patient was admitted to the hospital.

#### **Clinical examination**

Clinical examination revealed a 54-year-old, well-developed, slightly obese white man who appeared to be acutely ill. His blood pressure was 160/110 mm. Hg, pulse was 80 beats per minute, oral temperature was 104° F., and respiration rate was 20 per minute. There was induration of the neck and face. Both parotid glands were markedly enlarged, as were the submaxillary glands (Fig. 2).

#### **Physical examination**

The pharynx was injected. Examination of the ears revealed injection and dullness of both tympanic membranes. The remainder of the physical examination findings were within normal limits, with the exception of moderate obesity.



*Fig. 3.* Patient's appearance on day of discharge from hospital showing a marked decrease in the edema and inflammation of the parotid and submaxillary salivary glands.

#### **Laboratory examination**

Hematologic findings were as follows: hemoglobin, 15.7 Gm.; hematocrit, 49.6 per cent; red blood cells, 5,210,000; leukocytes, 17,700 with a differential white count of polymorphonuclear leukocytes, 85 per cent, lymphocytes, 9 per cent, monocytes, 5 per cent, eosinophils, 1 per cent, and basophils, 0 per cent. The sedimentation rate was 28 mm. after 45 minutes. Reaction to a mononucleosis test was negative. The blood chemistry profile was within normal limits. The lupus erythematosus clot test was negative. Routine urinalysis yielded values within normal limits. Protein electrophoresis revealed a slightly elevated beta globulin level of 1.19 (normal being 0.38 to 0.94). Bleeding and coagulation times were within normal limits. Posteroanterior and lateral radiographs of the chest were within normal limits, as was the panoramic laminogram of the teeth and jaws.

#### **Course in the hospital**

Upon admission, the patient was placed on bed rest plus ampicillin, 250 mg., every 6 hours. Frequent saline rinses and a full liquid diet were given. He was febrile for the first 2 hospital days, but his temperature then returned to normal and remained so for the rest of his hospital stay. He improved steadily and at the end of 8 days was discharged from the hospital. At the time of discharge, the edema and inflammation of the parotid and submaxillary glands had decreased markedly (Fig. 3).

The patient has been seen several times since his discharge from the hospital, and he is free of symptoms (Fig. 4).

#### **DISCUSSION**

Iodide intoxication is a condition that occurs infrequently. The oral surgeon should be familiar with it because of its similarities to such entities as Mikulicz's disease, Mikulicz's syndrome, Sjögren's syndrome, malignant lymphoma, and uveoparotitis.<sup>1, 10</sup> This case illustrates the importance of taking a thorough history. Without a correct diagnosis, proper treatment is impossible.



Fig. 4. Patient as seen 6 months after discharge from the hospital. He has remained free of symptoms.

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# Reduction of Thyroid Irradiation From $^{131}\text{I}$ by Potassium Iodide

Manfred Blum, MD, and Merrill Eisenbud, ScD

The prophylactic administration of 100 to 200 mg of potassium iodide in anticipation of radioactive iodine exposure will largely prevent uptake by the thyroid gland, thereby reducing the irradiation dose delivered by more than 98%. The same amount given at intervals after  $^{131}\text{I}$  absorption is progressively less effective, but still reduces uptake to less than half after a delay of three hours. The suppressive effect of one dose is of short duration and daily readministration of the agent is required for prolonged protection. The extent of uptake blockade may be estimated by measuring serum inorganic iodide; concentrations of greater than  $10\mu\text{g}/100\text{ cc}$  correlate with marked uptake arrest. Toxicity is negligible for a single ingestion, as is required in this temporary measure for the reduction of the immediate thyroid irradiation hazard, but the drug must be avoided by those allergic to it.

**R**elease of radioactive iodine to the environment is one of the potential hazards arising out of certain applications of nuclear energy. Thus,  $^{131}\text{I}$  was widely present in the environment in recent years as a consequence of nuclear weapons testing, resulting in low level contamination of milk supplies. Human exposure is also possible as a result of the industrial, medical, or research use of  $^{131}\text{I}$ , and could be particularly significant following reactor or fuel processing plant accidents. Indeed, accidental exposure have been reported,<sup>1,2</sup> and the sequels in one instance of overexposure has recently been shown to include thyroid nodules, hypothyroidism, and short stature.<sup>3</sup>

Ingestion is probably the main route of human exposure to radioactive iodine, but inhalation may be important in some instances. Of the several radioactive isotopes of iodine,  $^{131}\text{I}$  is the focus of concern because of its relatively long half-life and energetic beta and gamma emissions. Other iodine isotopes are of lesser importance except promptly after low level nuclear reactions.

Atmospheric radioactive iodine is deposited on foliage and because of the large area grazed by cows, the physiology of lactation, and the rapidity with which dairy products reach the consumer, the principle route for human absorption is cows' milk. In the case of other food or water moving more

slowly to the consumer, appreciable decay of radioactivity usually occurs. The hazard of  $^{131}\text{I}$  exposure after atmospheric release is particularly relevant to children because of their large milk consumption and small thyroid glands, but the potential risk to adults involved in localized accidents or "spills" may also be substantial.

Iodine is rapidly absorbed from the small intestine or lungs and to some degree from the skin and is distributed to the extracellular fluid from which it is sequestered by the thyroid, synthesized into thyroglobulin, and secreted as thyroxine. Thyroid iodine uptake is depressed when serum iodide concentration is elevated, and therefore inorganic, stable potassium iodide ( $^{127}\text{I}$ ) administration prevents  $^{131}\text{I}$  accumulation by the gland.

The object of our study was to investigate the efficacy of potassium iodide in suppressing thyroid  $^{131}\text{I}$  uptake as a means of reducing the risk of thyroid damage due to single, massive exposures to this isotope. Since exposure might be unavoidable in the event of an accident, it is desirable to have a prophylactic procedure to minimize or prevent absorption of radioactive iodine by the thyroid gland. In contrast, the relatively moderate repeated exposure that might occur among individuals working with radioactive iodine in hospitals or research laboratories can be controlled by proper design of equipment and working habits.

There have been several investigations of blockade of radioactive iodine uptake in the thyroid gland, but little specific information is available regarding the dose of drug, rapidity of onset of effect, or duration of effectiveness.<sup>4-9</sup> We extend the previous observations to a larger number of subjects, confirm the efficiency of 100 to 200 mg of potassium iodide in promptly inhibiting thyroid-concentrating ability, show that a single dose of potassium iodide is progressively less effective as a blocking agent after one or two days, and demonstrate that the extent of thyroid suppression may be predicted from serum inorganic iodide measurements.

## Method

Thyroid  $^{131}\text{I}$  uptake was measured in 62 healthy volunteers, 37 men and 25 women, ranging in age from 21 to 72 years. A total of 110 control determinations were done in these subjects. The percentage of thyroid  $^{131}\text{I}$  accumulation was determined 24 hours after the administration of a standard dose

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of 1.5 nanocuries ( $1.5 \times 10^{-9}$   $\mu$ c carrier free) of sodium iodide I 131 dissolved in 10 ml of water. Studies were carried out in a low background steel room with two 3  $\times$  3-inch thallium-activated sodium iodide scintillation crystals placed in contact with the anterior surface of the neck, from the sternal notch to the thyroid cartilage. The details of the procedure have been reported in previous communications from this laboratory.<sup>7</sup> This method was used because it minimizes the irradiation dose to the subject, the infinity thyroid dose for 30% thyroid uptake of <sup>131</sup>I being 6.8 mrem/1.5 nc.

The volunteers were examined by clinical and laboratory means including determinations of protein-bound iodine (PBI), 24-hour thyroid <sup>131</sup>I uptake, and liothyronine I 131 resin uptake (Triosorb [liothyronine I 131 diagnostic kit]). Two subjects were found to be hypothyroid and were rejected from the study; all others were euthyroid. One, receiving norethynodrel with mestranol (Enovid) for contraceptive purposes, had a low resin uptake, as expected, but was euthyroid and was included in the study.

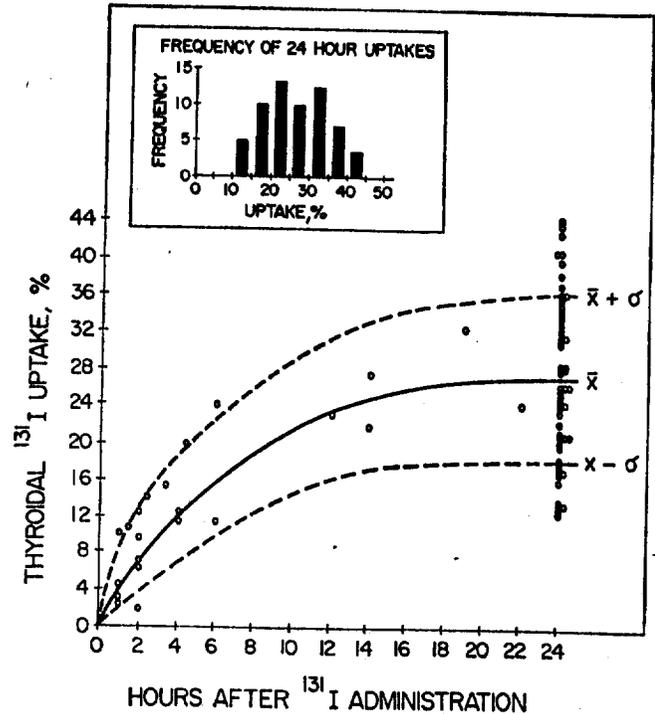
The effect of potassium iodide administration on thyroid <sup>131</sup>I accumulation was investigated in 24 men and 17 women in the group. These subjects received doses of stable potassium iodide (<sup>127</sup>I), ranging from 5 to 1,000 mg, dissolved in cherry syrup, either one hour prior to, with, or at specified times following administration of the radioactive compound. One or two days later, an additional dose of 1.5 to 5 nc of the radioactive agent was administered without a further dose of potassium iodide, and the 24-hour uptake was again measured to evaluate the duration of the suppressive effect.

The uptakes are not corrected for extrathyroid iodine because attempts to measure this component proved to be inaccurate. Since iodide other than that concentrated and organified by the thyroid is cleared by the kidney at a rate about twice that of thyroid clearance, extrathyroid iodide normally accounts for a very small part of the total neck activity at the end of 24 hours.<sup>8</sup> After arrest of thyroid uptake, however, extrathyroid iodide may constitute the largest part of neck activity. Therefore, our neck measurements yield estimates of thyroid concentrations which are somewhat high, particularly when uptake was blocked and during the first few hours in subjects whose uptake was not arrested. This leads to conservative estimates of the efficacy of the blocking regimen.

**Results**

Figure 1 shows the average uptake of the 62 volunteers to have been 27.1% in 24 hours, with a standard deviation of  $\pm 8.9\%$ .

As shown in Fig 2, the ability of the thyroid to accumulate radioactive iodine is progressively reduced when increasing amounts of potassium iodide are administered with the radioactive compound. The data in the Table show that none of the 25 subjects receiving more than 50 mg of potassium iodide

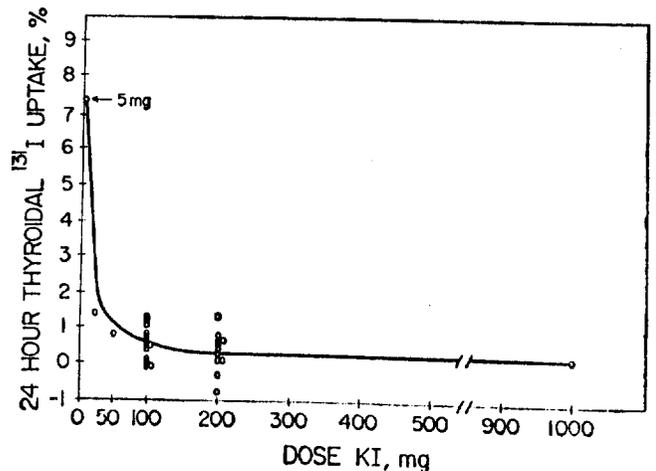


1. Thyroid <sup>131</sup>I uptake in 62 euthyroid volunteers administered sodium iodide I 131 and their frequency distribution.

together with sodium iodide I 131 concentrated more than 1.3% of the dose, and that the average <sup>131</sup>I uptake (percent) after 100 and 200 mg of potassium iodide was  $0.6 \pm 0.5$  ( $n = 14$ ) and  $0.3 \pm 0.3$  ( $n = 10$ ), respectively.

Figure 3 demonstrates that <sup>131</sup>I accumulation ceases promptly after potassium iodide administration. Delayed institution of therapy is progressively less effective in decreasing thyroid isotope burdens, but more than a 50% reduction in uptake occurs even if the countermeasure is started three hours after exposure to <sup>131</sup>I has begun. The Table lists the observations and suggests that 1,000 mg of potassium iodide may be slightly more effective than 100 to 200 mg in suppressing uptake if the drug is given

2. Thyroid 24-hour <sup>131</sup>I uptake when potassium iodide is coadministered with sodium iodide I 131.



Thyroid <sup>131</sup>I Uptake Before and Specified Times After  
Single Dose of Potassium Iodide and Resultant Reduction of Uptake

KI Dose, mg	Time of KI Dose hr*	Subject No.	24-Hour Uptake, %		Reduction in Uptake, %
			Before KI	After KI	
5	0	1	33	7.3	78
25	0	2	41	1.4	96
25	1	3	31	7.1	77
25	2	4	18	11.3	36
25	6	5	24	9.5	60
50	0	6	28	0.8	97
50	1	7	41	6.1	85
50	2	8	34	6.8	80
50	3	9	35	9.0	75
50	4	10	36	6.0	83
100	0	11	17	-0.1	101
100	0	12	25	0.0	100
100	0	13	34	1.3	96
100	0	14	37	-0.1	100
100	0	15	32	0.7	98
100	0	16	36	0.5	99
100	0	17	25	1.1	96
100	0	18	52	1.2	98
100	0	19	31	0.1	100
100	0	20	25	0.5	98
100	0	21	13	1.3	91
100	0	22	32	0.8	97
100	0	23	13	0.4	97
		Average ± SD	29 ± 11	0.6 ± 0.5	98 ± 3
100	1	24	28	3.1	89
100	1	25	44	2.9	93
		Average ± SD	36 ± 11	3.0 ± 0.1	91 ± 3
100	2	26	28	5.7	80
100	2	27	18	2.3	88
		Average ± SD	23 ± 7	4.0 ± 2.4	84 ± 6
100	3	28	17	6.8	60
200	0	8	16	-0.8	105
200	0	29	18	-0.3	102
200	0	30	36	0.6	98
200	0	31	33	0.2	99
200	0	19	31	0.4	99
200	0	32	20	0.5	97
200	0	21	13	1.3	90
200	0	22	32	0.8	97
200	0	33	21	0.1	100
200	0	34	32	0.5	98
		Average ± SD	25 ± 8	0.3 ± 0.3	99 ± 4
200	1	35	26	3.1	88
200	2	36	14	3.5	74
200	3	23	20	7.0	64
200	4	37	13	8.3	34
1,000	0	19	31	0.2	99
1,000	1	38	31	1.1	96
1,000	2	39	24	7.2	70
1,000	3	10	36	6.0	83

\*Hours after administration of sodium iodide I 131.

one hour after the radioactive agent. However, these are single determinations, the variability of which are unknown, and the differences are not great. The variation of thyroid <sup>131</sup>I accumulation in a population one hour after the radioactive compound is given is large, as is seen in Fig 1. Therefore, the only meaning which can be assigned to our observations is that 24-hour thyroid <sup>131</sup>I burdens increase with delay in potassium iodide ingestion. Statements concerning relative effects of various dose levels are not warranted on the basis of these data.

Figure 4 demonstrates that the uptake of <sup>131</sup>I, when the radioactive agent is administered 48 or 72 hours after potassium iodide, varies inversely with the amount of iodide given and is generally reduced. Fifty milligrams or more of potassium iodide lowers <sup>131</sup>I uptake to some degree for 48 hours; marked arrest of uptake 48 hours after po-

tassium iodide ingestion was observed only with the 1,000-mg dose, and even this large amount was largely ineffective in efficiently blocking thyroid <sup>131</sup>I uptake after 72 hours.

Figure 5 shows that the degree of suppression of thyroid <sup>131</sup>I uptake correlates well with serum inorganic iodide levels.

Toxic reactions to iodides were not encountered in this study, although two subjects reported uncomfortable sensations at the angles of the jaw and headache for several hours after ingesting 1,000 mg of potassium iodide.

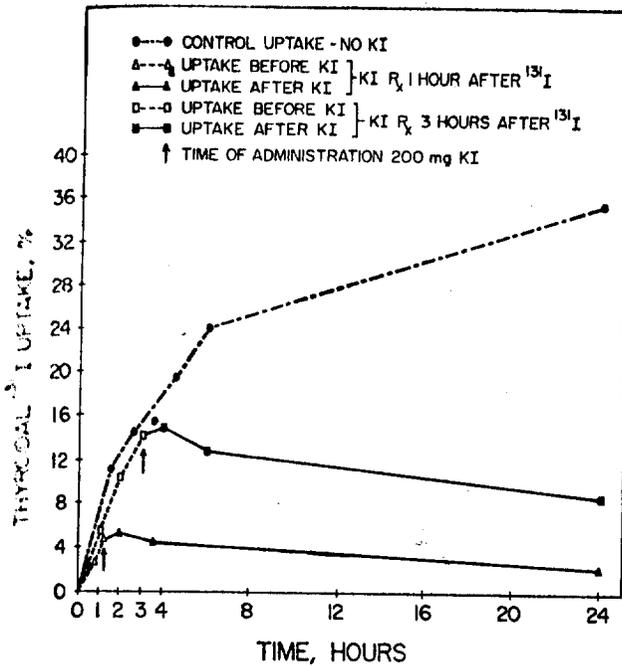
#### Comment

The effect of potassium iodide on thyroid <sup>131</sup>I accumulation was studied in healthy volunteers in order to clarify its optimal use as a countermeasure for massive radioactive iodine exposure, as in the case of occupational exposure following laboratory or industrial accident.

Adams and Bonnell demonstrated in two volunteers that the use of 100 mg of potassium iodide lowers the 24-hour radioactive iodine uptake

from normal values to less than 3% of the amount ingested, and Pochin and Barnaby<sup>8</sup> observed arrest of subsequent thyroid concentration in six subjects when 200 mg of potassium iodide was administered within four hours after a dose of an agent containing radioactive iodine. Saxena et al<sup>9</sup> reported gradual suppression of uptake to 5% after daily administration of 2 mg of potassium iodide per square meter of body surface, with 50% of the reduction taking place in the first 24 hours, and uptakes returning to or above pretreatment levels promptly after drug discontinuation.

Johnson<sup>9</sup> found 50% to 20% reduction in uptake three to four days after cessation of potassium iodide administration, with disappearance of effect after eight days, and Taguchi et al<sup>10</sup> noted population heterogeneity with rebound thyroid hyperavidity for radioactive iodine in three of 24 subjects.

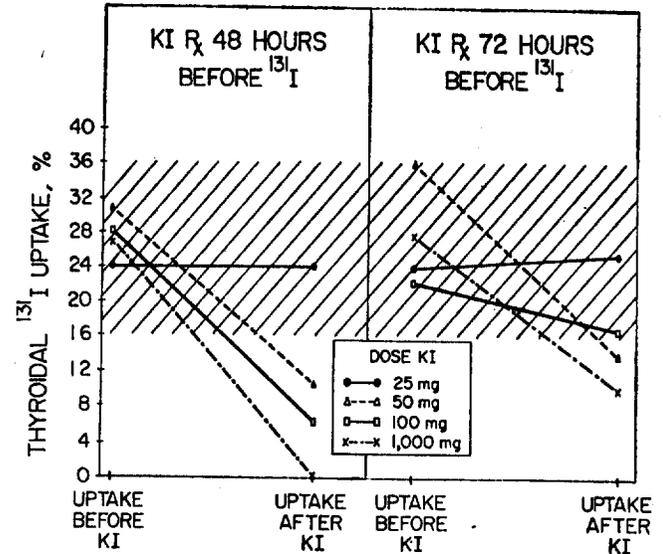


3. Thyroid <sup>131</sup>I uptake when potassium iodide is administered after sodium iodide I 131.

The <sup>131</sup>I uptakes observed in this series are similar to those obtained with conventional clinical methods, except that the number of observations below 20% is somewhat high. Phantom studies have suggested that this may be related to detector position and decreased counting efficiency of the lower poles of the thyroid. Since each individual served as his own control and constancy of geometry was maintained, such variation does not affect the conclusions reported here.

In one of the subjects the initial uptake was only 13%, but he was clearly euthyroid by other indices. This may have been due to normal variation or to counting geometric errors for this subject. Following suppressive therapy, his neck concentrations (1.2% and 1.3%, respectively, after 100 and 200 mg of potassium iodide) were similar to those observed in others under comparable conditions.

There is no doubt that 100 to 200 mg of potassium iodide given at the time of exposure can largely prevent thyroid uptake of radioactive iodine and thereby minimize the radiation dose to the gland. Administration of the drug after exposure to <sup>131</sup>I promptly blocks further accumulation by the thyroid, but previously concentrated isotope remains in the gland to be metabolized and released at a slow rate,<sup>11,12</sup> as is shown in Fig 3. The decrease in radioactive iodine activity in the neck shortly after arrest probably reflects clearance of inorganic <sup>131</sup>I from the blood by the kidneys which, unlike thyroid clearance, is not depressed by elevated serum iodide concentrations. (It should be recalled that extrathyroid iodide is not corrected for, and that this may comprise a part of neck burdens after blockade). Figure 2 demonstrates that increasing the amount of potassium iodide above 100 to 200

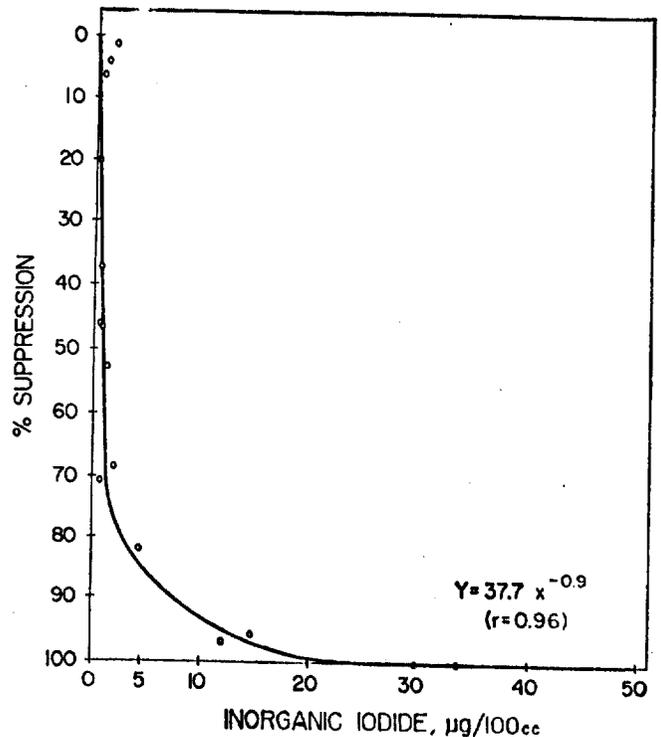


4. Duration of effectiveness of single dose of potassium iodide administered before sodium iodide I 131 in lowering thyroid uptake.

mg does not seem to reduce concentrating ability any further.

The blocking agent is most effective if given with or just before exposure to radioactive iodine. The extent of suppression observed was sharply reduced when the iodide was given 48 hours before the radioactive compound. Iodide is rapidly excreted by the kidney from the extrathyroidal pool, accounting for the short duration of protection afforded by a single ingestion. Therefore, in the event of prolonged exposure to radioactive iodine daily potassium iodide

5. Relationship between suppression of <sup>131</sup>I uptake and iodide concentration in serum.



readministration is required for maintenance of suppression.

Radioactive iodine previously accumulated by the thyroid is not discharged by potassium iodide. The greater the time lag in the institution of the countermeasure after exposure to  $^{131}\text{I}$ , the larger the isotope burden that will result; about 50% protection was noted even if three hours had elapsed between ingestion of the radioactive compound and potassium iodide therapy.

It might be desirable to know the extent to which thyroid uptake has been inhibited without performing actual uptake measurements. Our data show that less than 1.3% uptake may be expected with serum inorganic iodide concentrations of at least  $10\mu\text{g}/100\text{ cc}$ . These levels are achieved by administering at least 50 mg of potassium iodide with, or 200 mg 48 hours prior to, radioactive iodine exposure; these levels correlate with suppression of 95% on the curve in Fig 5 and with the observation that  $98\% \pm 3\%$  suppression occurs after 100 mg of potassium iodide. The techniques for measuring serum iodide concentrations are commonly available and such determinations may serve as a useful index of protection. However, this relationship is only an indirect index of suppression, since the ability to accumulate iodide probably reflects thyroid  $^{127}\text{I}$  burdens rather than serum concentrations. The association can be made with confidence at elevated serum concentrations and is less reliable as physiologic inorganic iodine levels are approached.

The actual thyroid uptakes are somewhat lower than the neck burdens reported due to our inability to correct reliably for extrathyroid iodine. Therefore, the suppressive effect of the countermeasure is slightly underestimated.

Toxicity to iodide was not encountered, and the two subjects who experienced discomfort at the angles of the jaws when taking 1,000 mg of potassium iodide were not incapacitated. Since 100 to 200 mg of potassium iodide was just as effective as 1,000 mg in causing uptake blockade and had the advantage of not eliciting undesirable side effects, the use of larger doses is unnecessary. Toxic reactions from a single dose of the iodide or from short-term administration is most unlikely, except for occasional allergic reactions which are usually mild<sup>13</sup>; nevertheless, those allergic should avoid its use.

A word might be added concerning long-term use of iodide as a countermeasure for prolonged exposure to radioactive iodine. In this circumstance, untoward reactions are uncommon, but there is a small risk of hypersensitivity, goiter, iodine-basedow, hypothyroidism, and iododerma. Neonatal goiter and respiratory distress developing in the offspring of mothers who ingested iodide is an important problem requiring caution in the prolonged use of iodides during pregnancy, and long-term iodide ingestion is unwise in people with renal disease, cardiac failure, and pulmonary tuberculosis.<sup>13</sup> It is to be

stressed that a single ingestion, such as used here, in the suggested dose range is largely harmless.

In view of the possible serious consequences from exposures to large amounts of  $^{131}\text{I}$  and the safety and effectiveness of potassium iodide in blocking thyroid uptake of radioactive iodine, it may be desirable to provide 200-mg capsules of potassium iodide in high-risk areas for immediate use by adults in the event of exposure to massive amounts of radioactive iodine. Large supplies of the drug could be strategically located for population use at the discretion of public health authorities.<sup>14,15</sup> Pediatric dose considerations in this regard have been previously discussed in the literature.<sup>6</sup> This countermeasure would supplement, but not replace, evacuation from a contaminated environment.

This investigation was supported by Defense Atomic Support Agency contract DA-49-146-XZ-153 and Public Health Service research grants ES 00014 (Bureau of State Service) and CA 06699 (National Cancer Institute).

The protein-bound iodine and free iodide measurements were made by Bio-Science Laboratories, Van Nuys, Calif. Linda Rose and Harold T. Peterson performed the other measurements in this investigation.

#### Generic and Trade Names of Drug

Norethynodgel with Mestranol—*Enovid*.

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INFLUENCE OF WEIGHT (AGE), DIET AND DOSAGE ON  
RESPONSE OF THYROID AND PARATHYROID GLANDS OF  
MALE GUINEA PIG TO POTASSIUM IODIDE; EFFECT OF  
THIS SUBSTANCE ON ADRENAL GLAND<sup>1</sup>

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THE RESPONSE OF the thyroid gland to the administration of potassium iodide has been a matter of controversy for many years. It has been maintained by Marine and his co-workers (1-3) that, when the iodine intake is lessened below the normal level, the thyroid gland tends to undergo hyperplasia, and, conversely, that the administration of iodine diminishes the activity of this gland, causing the production of hard colloid and low epithelium. Similarly, Levine, Remington and von Kolnitz (4) and also Chapman (5) have reported that hypertrophy of the thyroid of rats results from a low iodine intake. On the other hand, Loeb and his associates (6-13) have reported, in a large series of investigations, that the administration of KI primarily results in a stimulation of the thyroid gland, which is characterized by an increase in mitotic activity of the acinar epithelium associated with a softening of the colloid, an increase in the number of phagocytes in the colloid, and an increase in height of the cells lining the acini. This response occurs during the first three weeks of administration of this substance and is subsequently followed by an increased storage of colloid, which presses on the acinar epithelium and causes its flattening.

It is the purpose of the present investigations to present further evidence concerning the stimulating effect of KI on the thyroid gland and to define certain variable factors which may, to a certain extent, modify this response. In addition, further evidence is given relating to the parallelism in the response of the thyroid and parathyroid glands to the administration of KI, an observation which has recently been reported by Loeb and the author (14). The effect of this substance on mitotic activity of the adrenal cortex has also been studied.

MATERIALS AND METHODS

In the first experiment, a group of guinea pigs was divided into three groups according to weight (age): *Group I* consisted of 52 male guinea pigs which had just been weaned (approximately 2 weeks old) and which weighed between 100 and 115 gm. at the beginning of the experiment; *Group II* (46 guinea pigs) ranged between 180

Received for publication May 8, 1942.

<sup>1</sup> These investigations were carried out with the aid of grants from The International Cancer Research Foundation, from the Committee on Research in Endocrinology of the National Research Council, and from The Jane Coffin Childs Memorial Fund for Medical Research.

In a preceding paper titled "Further investigations on the proliferative activity of the thyroid gland of the female guinea pig during the sexual cycle," by K. S. Chouke and H. T. Blumenthal, through oversight the statement was omitted that these investigations were carried out with the aid of a grant from the Committee on Research in Endocrinology of the National Research Council.

TABLE I. INFLUENCE OF IODINE CONTENT OF DIET ON MITOTIC ACTIVITY IN THYROID AND PARATHYROID GLANDS OF MALE GUINEA PIGS OF VARIOUS WEIGHTS (AGES)

A, Diet Not Containing Chow						B, Diet Containing Chow Without Iodine						C, Diet Containing Chow With Iodine					
Number of guinea pigs	Average final weight, gm.	Days on diet	Average mitoses/thyroid	Average parathyroid count		Number of guinea pigs	Average final weight, gm.	Days on diet	Average mitoses/thyroid	Average parathyroid count		Number of guinea pigs	Average final weight, gm.	Days on diet	Average mitoses/thyroid	Average parathyroid count	
				Mitoses/10,000 cells	Cells/unit field					Mitoses/10,000 cells	Cells/unit field					Mitoses/10,000 cells	Cells/unit field
Group I. Initial weight 100-115 gm.																	
3	114	0	263	4.8	209 <sup>1</sup>	3	114	0	263	4.8	209 <sup>1</sup>	3	114	0	263	4.8	209 <sup>1</sup>
4	135	5	89	1.4	205	2	150	5	45	1.5	223	2	155	5	180	1.4	218
3	140	10	50	0.8	215	2	215	10	93	1.7	180	4	214	10	189	2.8	190
2	138	15	50	0.9	198	2	263	15	88	1.0	200	2	248	15	198	3.1	198
4	197	20	97	1.1	180	2	280	20	50	1.5	185	5	244	20	303	4.5	178
4	220	30	565	7.0	200	2	330	30	853	6.7	173	5	270	30	331	5.4	140
2	210	40	140	3.4	180	2	340	40	195	4.0	200	3	310	40	985	6.8	153
		Average	186	2.6	197			Average	223	2.6	191			Average	316	4.3	173
Group II. Initial weight 180-200 gm.																	
4	180	0	153	3.7	203 <sup>1</sup>	4	180	0	153	3.7	203 <sup>1</sup>	4	180	0	153	3.7	203 <sup>1</sup>
2	215	5	160	2.1	190	2	218	5	120	1.0	200	2	210	5	130	1.9	180
2	245	10	200	1.0	200	2	230	10	110	0.5	210	2	270	10	160	2.1	171
2	240	15	130	1.1	195	4	237	15	136	1.8	188	6	268	15	210	2.6	176
2	255	25	100	1.4	185	4	288	25	141	1.6	183	6	285	25	254	2.4	175
2	274	40	70	0.6	210	4	339	40	90	0.6	173	4	384	40	156	1.1	190
		Average	132	1.2	196			Average	121	1.2	187			Average	199	2.6	179
Group III. Initial weight 390-420 gm.																	
4	418	10	47	0.8	198							4	408	10	65	0.3	197
4	447	25	52	0.3	205							4	435	25	40	0.5	202
4	495	40	45	0.7	188							4	504	40	20	0	220
		Average	48	0.6	197									Average	42	0.2	206

<sup>1</sup> Counts were made in these guinea pigs before the other animals of the respective groups were placed on the various diets.

TABLE 2. INFLUENCE OF WEIGHT (AGE) AND IODINE CONTENT OF DIET ON MITOTIC RESPONSE OF THE THYROID AND PARATHYROID GLANDS OF MALE GUINEA PIGS TO KI ADMINISTRATION

A, Diet Not Containing Chow						B, Diet Containing Chow Without Iodine						C, Diet Containing Chow With Iodine					
Number of guinea pigs	Average final weight, gm.	Days on KI	Average mitoses/thyroid	Average parathyroid count		Number of guinea pigs	Average final weight, gm.	Days on KI	Average mitoses/thyroid	Average parathyroid count		Number of guinea pigs	Average final weight, gm.	Days on KI	Average mitoses/thyroid	Average parathyroid count	
				Mitoses/10,000 cells	Cells/unit field					Mitoses/10,000 cells	Cells/unit field					Mitoses/10,000 cells	Cells/unit field
<i>Group I. Initial weight 105-115 gm.</i>																	
3	118	5	113	1.0	208	2	116	5	230	1.3	225	2	125	5	430	2.0	200
2	124	10	232	2.2	210	2	126	10	480	1.1	179	2	140	10	650	2.2	180
3	137	15	633	3.1	207	2	145	15	670	2.5	160	2	185	15	820	3.3	158
2	148	20	310	2.0	200	2	170	20	550	1.9	210	2	220	20	560	1.4	145
2	203	30	120	2.1	195	2	235	30	265	0.8	240	2	245	30	190	0	150
2	210	40	40	0.9	230	2	245	40	120	0	230	2	280	40	150	0	180
		Average 273		1.9	208			Average 384		1.3	216			Average 467		1.5	169
<i>Group II. Initial weight 180-200 gm.</i>																	
6	209	4-7	176	2.7	189	6	180	4-7	285	2.4	210	4	229	4-7	460	3.3	190
4	224	10-12	248	2.5	195	10	212	10-12	449	4.3	204	8	251	10-12	812	4.1	195
4	225	15	885	4.2	192	5	225	15	963	6.7	180	6	271	15	1387	9.6	171
4	232	20	500	3.4	190	6	246	20	336	3.4	175	6	282	20	647	5.0	195
		Average 422		3.1	191			Average 483		4.1	194			Average 856		5.5	188
<i>Group III. Initial weight 385-420 gm.</i>																	
2		5	480	2.4	190												
2		10	1620	4.7	160												
4		15	2640	9.5	135												
4		30	1060	3.2	144												
2		40	400	1.9	210												
2		50	280	0.9	217												
		Average 1276		4.6	167												

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and 200 gm. in weight, and between 4 and 6 weeks in age; *Group III* (24 guinea pigs) varied in weight between 390 and 420 gm. and were approximately 3.5 to 4 months of age. Three further subdivisions were made according to the diet given. Each of these three subdivisions received a basic diet consisting of lettuce, carrots and oats. Subdivision *A* received only the basic diet; subdivision *B* received in addition Purina rabbit chow containing wheat germ, soybean oil meal, cracked corn, molasses, 0.5 per cent calcium carbonate, and other salts which were iodine-free, while subdivision *C* received in addition to the basic diet the same Purina Chow, except that 0.5 per cent iodized salt replaced the iodine-free salt. (See table 1.)

In a second experiment, 123 guinea pigs were divided in a similar manner according to weight (age) and diet, and were fed their respective diets for a period of 10 days preceding the administration of KI. The latter substance was then administered either by feeding tablets or in solution through a tube introduced into the stomach, in doses of 0.01 or 0.05 gm., daily for periods varying between 5 and 50 days (see table 2).

The thyroid, parathyroid and adrenal glands were removed, immediately fixed and prepared for study by the paraffin section technique in the usual manner. Mitotic counts were made on these three glands according to methods described in previous publications (14, 15). Thyroid counts were recorded as the number of mitoses per total gland (both lobes), adrenal counts as the average number of mitoses per section, and parathyroid counts as the number of mitoses per 10,000 cells; in the latter instance, an additional figure representing the average number of cells per standard unit field was recorded in order to indicate changes in cell size.

#### EXPERIMENTAL RESULTS

*Influence of very small amounts of iodine in the diet on mitotic activity in thyroid and parathyroid glands of normal male guinea pigs of various weights (ages).* The influence of the iodine content of the diet on mitotic activity in the thyroid and parathyroid glands is shown in table 1. In *Groups I* and *II*, mitotic counts were made in guinea pigs in a manner similar to those used in the experiments in which guinea pigs of a corresponding age were fed with the various diets; these control counts serve as a baseline for the curves indicating the influence of the special diets. It can be seen that in *Groups I* and *II* the guinea pigs which received a diet not containing iodized salt show, on the average, a lower degree of mitotic activity of the thyroid gland than do those receiving the diet containing additional iodine. In *Group III*, in which only two diets were tested, no effect of the added iodine was observed. The reason for this becomes apparent when it is noted that in all three subdivisions there is a decrease in mitotic activity with increasing age, which occurs irrespective of diet. Apparently the factors which bring about this diminution in mitotic activity with increasing age are able to overcome the stimulating effects of iodine when a certain age has been reached. With this interpretation agrees the fact that in *Group II* the average increase in mitoses, resulting from the administration of the iodized-salt diet, is less marked than in *Group I*.

It may be noted further in table 1 that in subdivisions *A* and *B* of the youngest age group (*Group I*), which received diets to which iodine had not been added and which had therefore, a very low iodine content, there is a rapid fall in mitotic activity in the thyroid gland within the first 5 days, and this is maintained for somewhere between 20 and 30 days; at about 30 days there follows a sudden rise in mitotic activity, which subsequently again declines, without, however, reaching the same low level which it had at earlier periods. While the reason for this rapid rise is not definite, it may perhaps be a response of this gland to factors which become active

at the onset of sexual activity. On the other hand, in subdivision C of the lowest age group, there is a steady rise in mitotic activity through the 40 days during which these guinea pigs received the diet containing iodized salt. But even in this group the marked rise in mitotic activity developing between the 30th and 40th day may perhaps be attributed also to the onset of sexual activity. In *Group II*, the fall in mitotic activity of the thyroid gland in guinea pigs kept on non-iodized diets in subdivision A begins between the 10th and 15th day and continues until the 40th day, while in subdivision B there is a fall between the 25th and 40th days. The guinea pigs in *Group II*, subdivision C, which had received the iodized chow diet, show a steady rise in mitotic activity up to the 35th day, when the maximum is reached.

In general, the mitotic activity in the parathyroid gland in these experiments parallels that in the thyroid gland. Thus, in the parathyroid gland in *Groups I* and *II*, in the guinea pigs which received the non-iodized diet, the average number of mitoses is somewhat lower than in subdivision C which received iodized chow; likewise, the averages in age *Group II* are lower than those in the younger age *Group I*. The averages are lowest in the oldest age *Group III*, and here there was no increase in mitotic activity in subdivision C which received iodized chow. There is, furthermore, a correspondence between the average of cell size and the number of mitoses; an increased average number of mitoses is usually associated with an increased average cell size.

In the parathyroid as well as in the thyroid glands of the guinea pigs of the youngest age group (*Group I*) there is in subdivisions A and B the same rapid fall in mitotic activity within the first 5 days, due to a very low iodine intake and here, also it is maintained for about 20 to 30 days and is followed by a sudden rise in mitotic activity at about 30 days. As in the thyroid gland, mitotic activity subsequently declines, but not to the same level as at earlier periods. In subdivisions C of *Group I* in which the guinea pigs received iodized chow, there is a steady rise in mitotic activity, which again closely parallels that observed in the thyroid gland including the marked rise in proliferative activity between the 30th and 40th days, which may perhaps be attributed to the onset of sexual activity.

We may then conclude that in the age *Groups I* and *II*, the iodized chow causes an increase in mitoses in the thyroid and parathyroid glands, which is absolutely and also relatively greater in age *Group I* than in age *Group II*. In age *Group III* the mitotic activity is low in all subdivisions, in accordance with the greater age of these animals. In this latter group, the mitotic activity is not increased by substituting iodized chow for a non-iodized diet. In age *Group I* a maximum in mitotic activity is reached usually somewhere between the 25th and 40th days; at 40 days there occurs a fall from the maximum, which may perhaps be connected with the stage of sexual maturity reached at that time. There is also a decline in mitotic activity between the 1st and 5th days of observation in certain groups; however, the significance of this fall remains doubtful.

*Effect on thyroid and parathyroid of the addition of large amounts of KI to the three basic diets of guinea pigs differing in age.* These guinea pigs received either 0.01 or 0.05 gm. of KI daily for periods ranging from 5 to 50 days. This substance was administered either in the form of tablets orally, or as a solution by means of a tube inserted into the stomach. No significant difference was noted between the two doses used or between the two methods of administration, hence no distinction is made as to dose or method of administration in the discussion of the results (table 2).

In this table is shown the influence on the mitotic response in thyroid and parathyroid glands of the various amounts of KI given to guinea pigs kept on the various diets. Mitotic activity in the thyroid glands of guinea pigs in subdivision A of

Groups I and II was somewhat less than in those in subdivision B, while mitotic activity in the latter was, in turn, somewhat less than that in guinea pigs of subdivision C. Here the average mitotic counts were highest. There was a summation of the effects of iodized chow and of the additional KI. However, in age Group II, subdivision C, the effects were greater than those of the mere summation. This seems to be due to the influence of age (weight) on the response to iodine; the old guinea pigs responded with a greater increase in mitoses to the addition of KI. This comes out most markedly in the oldest age group, in which, even in subdivision A, the averages reach the highest level, namely, 1276 mitoses. In general, it can be seen that the maximum degree of mitotic activity in the thyroid of all groups is reached after about 15 days of KI administration. This corresponds to the former experiments on guinea pigs in which it has been found that the largest number of mitoses were observed after KI had been given orally for a period of 15 days.

The difference in the degree of mitotic activity in the various age groups should especially be noted. The average maximum mitotic response in Group I in the animals receiving iodized chow (subdivision C) was 820 mitoses per thyroid gland and 3.3 per 10,000 cells in the parathyroid, whereas, in Group II it was 1387 in the thyroid and 9.6 per 10,000 cells in the parathyroid. In Group III, in which only one non-iodized diet was given, the maximum response was greater than in the two groups of younger guinea pigs (2640 mitoses per thyroid gland on the average, and 9.5 mitoses per 10,000 cells in the parathyroid gland). There was, then, in response to the administration of KI, an increase in mitotic activity in both the thyroid and parathyroid glands with increasing weight (age) in these experiments. There is a parallelism between the mitotic activity in thyroid and parathyroid in that also in the parathyroid the maximum number of mitoses was found after 15 days and that in Group I, the youngest age group, the number of mitoses reached the lowest average level. Furthermore, in the second age group the number of mitoses increased in the direction from the other two diets to the iodized chow, and among the animals in subdivision A the average counts increased with increasing age. There is, then, in the most essential respects, a parallelism between the effects of iodine on the mitotic activity of thyroid and parathyroid.

*The relationship between the daily dose of KI and the intensity of the mitotic response in the thyroid and parathyroid glands.* In the various experiments carried out by Loeb and his associates, Gray (6), Rabinovitch (7), McCordock (13), and Margolin (12), the results which follow the administration of KI to guinea pigs during the initial period were concordant as far as the increase in mitoses in the thyroid gland is concerned. There is also agreement as to the time when the maximum response of the thyroid is observed, namely, after about 15 days of oral administration of this substance. On the other hand, there are great differences as to the degree with which the mitotic activity was increased in different experiments. Thus, Rabinovitch (7) reported maximum figures for mitotic counts as high as 4000 to 8000 mitoses per thyroid gland when the optimal doses of KI, namely 0.1 gm. daily, was given. The figures found by Gray and Loeb (6), as well as by McCordock (13), were lower; Margolin (12) subsequently reported that guinea pigs fed as little as 0.0005 gm. of KI daily for 15 days showed an average count of 1188 mitoses, a degree of response similar to that observed by other investigators with 0.01 and 0.05 gm. of KI. Our own counts (table 1) indicate that the weight of the guinea pigs used is probably one of the variable factors which is responsible for variations in the mitotic counts. It was also of interest to determine the influence of the daily dose of KI on the mitotic activity of the thyroid gland, in view also of the finding of Rabinovitch (7) that within a certain range the increase in the dose of KI increased with the number of

mitoses. In an additional experiment in which 24 guinea pigs were used, the initial weight of the guinea pigs was approximately the same as that of Group II corresponding to an age of 4 to 6 weeks. These animals were fed the diet given to subdivision A, not containing chow. We added also some of the counts of 16 other guinea pigs shown in table 1. The guinea pigs received KI daily for periods of 15 and 20 or 25 days. The results in table 3 indicate that the maximum is recorded usually after 15 days of administration of this substance and that even a daily dose as low as  $3.5$  to  $7.0 \times 10^{-6}$  gm. of KI still has some effect. There was no essential difference between

TABLE 3. RELATIONSHIP OF THE DAILY AMOUNT OF KI ADMINISTERED TO THE DEGREE OF MITOTIC RESPONSE IN THYROID AND PARATHYROID GLANDS

Number of Guinea Pigs	Daily Amount of KI Fed, gm.	Number of Days Fed KI	Thyroid Count, Mitoses/Gland Num. Aver- ber age		Parathyroid Count			
					Mitoses/10,000 cells		Cells/unit field	
			Num.	Aver- age	Num.	Aver- age	Num.	Aver- age
Initial weight 180-190 gm.; final weight 220-285 gm.								
2	$10^{-1}$	15	580	710	3.4	5.2	193	184
2	$10^{-1}$	20	840		6.9		174	
2	$5 \times 10^{-2}$	15	647	635	3.8	3.4	201	202
2	$5 \times 10^{-2}$	20	600		2.9		203	
2	$10^{-2}$	15	907	752	4.5	3.8	190	194
2	$10^{-2}$	20	520		3.1		198	
3	$5 \times 10^{-3}$	15	913		5.8		158	
3	$10^{-3}$	15	407	324	2.5	2.3	195	189
2	$10^{-3}$	20	200		2.1		181	
2	$10^{-4}$	15	500	370	4.1	3.2	150	168
2	$10^{-4}$	20	240		2.3		185	
6	Chow with KI <sup>1</sup>	15	210	232	2.6	2.5	176	176
6	Chow with KI <sup>1</sup>	25	254		2.4		175	
2	No chow Controls	15	130	115	1.1	1.3	195	190
2	No chow Controls	25	110		1.4		185	

<sup>1</sup> This chow furnishes a daily intake of  $3.5$  to  $7.0 \times 10^{-6}$  gm. of KI per guinea pig.

responses to doses of  $10^{-1}$  and  $5 \times 10^{-2}$  gm.; however, if still smaller amounts of KI are given, the effectiveness decreases, and it reaches the lowest point if the iodized chow is used. These results apply in the case of guinea pigs in the weight and age range chosen in these experiments. It is possible that if heavier and older animals are used, such as those used by Rabinovitch, the results may not be exactly the same.

If we compare the mitotic activity in the parathyroid gland with that in the thyroid, we find a very close parallelism. However, the correspondence is not in every respect complete and this may be taken as an indication that there may be an additional factor determining the intensity of mitotic proliferation which is not identical in thyroid and parathyroid. As to the size of the parathyroid cells in these experiments, the variations were relatively slight and are probably of no significance.

*The response of the adrenal cortex to KI administration.* One hundred and five guinea pigs received KI tablets by mouth in doses of 0.01 or 0.05 gm. for periods ranging from 4 to 20 days (table 4). The total average number of mitoses per section

of adrenal gland in the KI-fed guinea pigs was 3.1 as compared with 2.7 in 72 control guinea pigs. This difference is not very great and the number of variations in the different groups is considerable and overlapping. However, a statistical analysis of these results, as indicated in the last column of table 4, shows that there is a significant increase in mitotic activity between the 8th and 15th day of KI administration. A further statistical comparison of the results in the group receiving KI for 8 to 10 days with those in the group receiving this substance for 12 to 15 days showed a figure of 1.7, which is not significant. It may therefore be concluded from these results that KI has some effect on mitotic activity in the adrenal cortex of the guinea

TABLE 4. MITOTIC COUNTS IN THE ADRENAL CORTEX OF CONTROL AND KI-FED GUINEA PIGS

Number of Guinea Pigs	Number of Days Fed KI	Average Number of Mitoses per Section	Range of Variation in Average Number of Mitoses per Section	Factor of Statistical Significance as Compared with Controls <sup>1</sup>
Initial weight 180-200 gm.; final weight 185-365 gm.				
25	4-7	2.1	0-6.8	1.0
22	8-10	4.3	0.2-17.2	3.5
36	12-15	3.3	0-11.5	4.3
22	18-20	3.0	0-8.7	1.1
72	Controls	2.7	0-10	
		Av. 3.1		

<sup>1</sup> The factor of statistical significance was calculated according to the relationship  $A_1 - A_2 / SE_{A_1 - A_2}$ , in which  $A$  represents the average mitotic count for a given group and  $SE$  the standard error for the corresponding group. If this factor is less than 2, there is no significant difference between the two groups compared, while if it is greater than 3, it is almost certainly significant. A factor between 2 and 3 indicates a probability greater than merely a chance phenomenon.

pig, and that this increase in proliferative activity is manifested between the 8th and 15th days of KI administration.

#### DISCUSSION

As stated previously, Loeb and his associates (6-13) have observed that the oral administration of KI results in an increase in mitotic activity in the thyroid gland in guinea pigs, which reaches a maximum between the 15th and 20th days. There are, however, considerable variations in the findings of different investigators as to the degree of this maximum response. Rabinovitch (7) noted that the maximum count was sometimes as high as 8000, and quite commonly reached figures of 4000 and 5000 mitoses per thyroid gland; in certain of his experiments the guinea pig weighed between 350 and 450 gm. Similarly, Gray and Rabinovitch (8) subsequently found an average of 3442 mitoses per thyroid gland in two guinea pigs fed KI for 20 days. On the other hand, Gray and Loeb (6) obtained an average maximum figure of only 710 mitoses per thyroid gland in guinea pigs fed KI for 16 to 23 days, and McCordock (12) observed an average count of 1208 mitoses per thyroid gland in guinea pigs which had received KI for 15 to 20 days. In the latter experiments the weight or age of the guinea pigs used was not given.

In the present experiments it has been shown that weight (age) is an important factor in determining the degree of mitotic response to KI administration. The intensity of this response apparently depends to a great extent upon two antagonistic influences, namely, the stimulating action of KI, and the factors concerned in ageing, which tend to lower mitotic activity. In the first group of experiments (table 1), in which certain guinea pigs were fed diets very low in iodine content, the ageing fac-

tors were predominant and there was a gradual diminution in mitotic activity in the thyroid gland with increasing age. Yet, in guinea pigs receiving a diet of iodized chow the small amount of iodine contained in the diet was sufficient to produce an increase in mitotic activity; this applied so far as the two younger age classes were concerned. But in guinea pigs weighing about 400 gm. such a response was no longer obtained; here the ageing factors predominated over the stimulating effects of the small amounts of KI present in the chow diet.

It seems, however, that the depressing effects of ageing can be overcome by increasing the amount of iodine administered, and, indeed, when this is done the response in older animals becomes even greater than in younger ones. This effect of the age of guinea pigs on the degree of mitotic proliferation of the thyroid glands could account in some degree for the variations in the results of the investigators mentioned above, but it does not completely explain the differences, since the maximum mitotic activity in the oldest age group in the present experiments still does not reach the high degree of mitotic response to KI reported by Rabinovitch (7, 9). It may be that still older animals would have yielded results comparable to those observed by the latter investigator. It will be of interest in future experiments to determine the proliferative reaction of the thyroid gland to KI in still older groups of guinea pigs than those we have used so far.

It is also of great interest that the very small amount of iodine available in the chow containing iodized salt was sufficient to result in a measurable increase in mitotic activity in the thyroid gland. Margolin (12) has reported that doses of KI as small as .0001 gm. per day may have a slight stimulating effect on mitosis. We have also shown that amounts as small as  $10^{-4}$  gm. of KI administered daily by mouth are effective, and that even still smaller quantities of KI, such as those present in the diet of iodized chow, may exert a distinct effect. The preparation of chow used in these experiments contained 88 micrograms of KI per 100 gm. of chow. The average daily consumption of chow in addition to the other elements in the diet was approximately 4 to 8 gm. The average daily KI intake from this source was therefore between 3.5 and 7.0  $\mu$ g. While it cannot be excluded that small amounts of iodine may also have been present in the lettuce, carrots and oats used in these diets, still, this very small increase in the daily total iodine intake provided by the chow was sufficient to result in a definite stimulation of the mitotic activity of the thyroid gland. In the present experiments it has been shown that within a rather wide range, larger doses produce a more marked effect than do smaller doses, while the latter also lead to an increase in mitotic activity when compared with control animals receiving a diet which does not contain iodized salt. In this case, also, additional experiments are necessary to determine the minimal amount of KI which will result in an increased mitotic activity in the thyroid gland.

It has, furthermore, been observed in these experiments that guinea pigs maintained on the diet containing iodized chow respond with greater intensity to the subsequent administration of larger doses of KI than do guinea pigs maintained on the diets not containing iodized salt. This may be due to a cumulative effect of the iodine in the diet and the iodine subsequently administered in the form of potassium iodide, or it may be that the thyroid glands of guinea pigs maintained on diets very low in iodine become so depressed functionally that they do not respond with as great an intensity to subsequent stimulation with iodine as glands which have been previously supplied with very small amounts of iodine.

In a general way, the mitotic response of the parathyroid to various daily doses of KI was parallel to that of the thyroid gland, although there were some exceptions. The parallelism in the response of the thyroid and parathyroid glands to various

hormones and hormone-like substances, which has recently been reported by Loeb and the author (14) and which is confirmed in the present experiments as far as KI is concerned, assumes added importance in the light of certain clinical and experimental observations. Beaumont, Dodds and Robertson (16) have reported a number of clinical cases in which there was an alteration of calcium and phosphorus metabolism in thyrotoxicosis, and Mansbacher (17) has recently published a report of cases of osteoporosis in hyperthyroidism. Michaud (18), Hansman and Wilson (19), Puppel and Curtis (20), Cope and Donaldson (21) and others have demonstrated that increased activity of the thyroid gland is associated with an increase in the excretion of calcium and phosphorus. Aub, Bauer, Heath, and Ropes (22), Collip (23), Langdon-Brown (24), and Cope and Donaldson (21) are of the opinion that the increased excretion of calcium in thyrotoxicosis depends on a direct stimulating catabolic effect of the thyroid secretion on the calcium deposits in the bones. On the other hand, according to Beaumont, Dodds and Robertson (16) 'some other cause than the direct action of secretion must be sought to account for the decalcification and excessive calcium and phosphorus loss from the body in thyrotoxicosis.' The experiments of Loeb and the author (14) as well as the present experiments indicate that these alterations in calcium and phosphorus metabolism may perhaps be due to the concomitant increase in parathyroid activity, which occurs, at least in the guinea pig, when the thyroid gland is stimulated to increased proliferative activity. However, further investigations are necessary before any definite conclusions can be drawn as to the mechanism of the altered calcium and phosphorus metabolism which is associated with hyperthyroidism.

Our purpose in including experiments concerning the effect of KI on mitotic activity in the adrenal cortex was to determine whether or not the mitotic activity of the adrenal cortex parallels that of the thyroid gland in a manner similar to that of the parathyroid. That the proliferative activity of the thyroid gland may have some influence on the activity of the adrenal cortex has been indicated by the experiments of McQueen-Williams (25), Emery and Winter (26), Rosen and Marine (27) and others. These workers have reported that there was either an absence or a decreased response of the adrenal cortex to the administration of pituitary substance following thyroidectomy. The present investigations indicate that the increase in proliferative activity of the thyroid gland which results from KI administration is in all probability accompanied by a slight increase in mitotic activity in the adrenal cortex. However, subsequently we shall discuss in greater detail the relationship of the thyroid gland to the adrenal cortex.

#### SUMMARY

1. The addition of very small amounts of KI in the form of iodized chow to the diet of male guinea pigs between the ages of 2 and 6 weeks results in an increase in proliferative activity in the thyroid and parathyroid glands. Older guinea pigs (3 to 4 months old) do not respond to such small doses of KI.
2. Guinea pigs maintained on diets to which no iodine has been added do not respond as intensely to subsequent administration of larger quantities of KI (0.01 and 0.05 gm.) as do guinea pigs maintained on a diet containing iodized chow.
3. When the larger doses of KI (0.01 and 0.05 gm.) are administered daily, a typical maximal response is observed in both thyroid and parathyroid glands at about the 15th day, which is then followed by retrogression. This response increases with increasing age, within the age limits tested in these experiments.
4. No strict parallelism was observed between the amount of KI administered daily and the degree of mitotic activity observed in the thyroid and parathyroid

glands. However, within a rather wide range, larger doses of KI produce more marked activity in the thyroid and parathyroid glands than do smaller doses.

5. These experiments confirm the previous observation that a parallelism exists between the effect of KI on the thyroid and parathyroid glands; in addition, it is shown that potassium iodide causes in all probability a slight increase in the mitotic activity of the adrenal cortex from the 8th to the 15th day of the administration of this substance.

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THE EFFECT OF POTASSIUM IODIDE, SODIUM IODIDE, AND IOD-ETHAMINE UPON THE CONCENTRATION OF ALCOHOL-SOLUBLE AND ALCOHOL-INSOLUBLE FRACTIONS OF BLOOD IODINE<sup>1</sup>

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Abstract

Potassium iodide, sodium iodide, and Iod-Ethamine were given by stomach tube to 54 rabbits and the concentration of alcohol-soluble and -insoluble blood iodine followed for a period up to 24 hr. Following all three iodides, there was a rise and fall in the values of both fractions of blood iodine, the values for the alcohol-soluble fraction rising to the higher levels but declining more rapidly than the values for the alcohol-insoluble fraction. Potassium iodide had the advantage over sodium iodide that after its use the peak levels of both fractions of blood iodine were maintained for a longer period of time. Iod-Ethamine had the advantage over potassium iodide that higher peak levels were reached with both fractions of blood iodine and, while not maintained for as long as after potassium iodide, these peak levels were held for several hours and for a longer period than following sodium iodide. The concentrations of blood iodine were of the same order or higher than those found in respiratory tract fluid following administration of the same dose of iodides, suggesting that the appearance of iodine-containing substances in respiratory tract fluid (*R.T.F.*) after iodide therapy is of the nature of a simple diffusion from blood.

The purpose of the investigation to be reported below was threefold. In the first place, Boyd *et al.* (2) have shown that potassium iodide and Iod-Ethamine, given by stomach tube to rabbits and cats, increase the output of respiratory tract fluid (*R.T.F.*), and hence may be considered to have properties of expectorant drugs. Incidental to the expectorant action, but not causative of it, there was found to occur a marked increase in the concentration of iodine-containing substances in the *R.T.F.* We have found that normal *R.T.F.* of cats and rabbits has about the same concentration of measurable iodine as has blood, that is, from some 10 to 20  $\mu\text{gm. per } 100 \text{ ml.}$  ( $\mu\text{gm. } \%$ ), and we have considered that iodine-containing substances simply diffuse into *R.T.F.* from blood. After giving potassium iodide or Iod-Ethamine by stomach tube in doses of 1 gm. per kgm. body weight, the concentration of measurable iodine rose to values of the order of 5000  $\mu\text{gm. per } 100 \text{ ml.}$  of *R.T.F.* These very high values suggested that iodine-containing compounds might be actually secreted into the *R.T.F.*, unless it could be shown that blood contained values for measurable iodine, under the above conditions, just as high as, or even higher than, was found in the *R.T.F.* Hence it was decided to give these iodides by stomach tube in doses of 1 gm. per kgm. body weight and follow the changes in the concentration of blood alcohol-soluble ("inorganic") iodine and alcohol-insoluble ("protein") iodine.

<sup>1</sup> Manuscript received July 17, 1945.

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In the second place, Dr. E. D. Osborne of the Mayo Clinic reported some years ago (4), that potassium iodide given to patients produced an increase in blood "protein" iodine while administration of sodium iodide had little effect upon the level of blood "protein" iodine. While Osborne's work did not prove that potassium iodide was preferable to sodium iodide therapeutically, it at least indicated that there was apparently a biochemical difference in the action of the two compounds and suggested a foundation in fact for the continued use of potassium iodide, rather than sodium iodide, in such pharmaceutical preparations as *Liquor Iodi Aquosus*, B.P. (1) and *Liquor Iodi Fortis*, U.S.P. (5), both of which are commonly called Lugol's Solution. Osborne also reported that sodium iodide is excreted in urine at a rate faster than that of potassium iodide which suggested that potassium iodide has the advantage of a more prolonged action than sodium iodide. Since we were investigating the effect of potassium iodide upon the two fractions of blood iodine, advantage was taken of this opportunity to include sodium iodide in order to ascertain whether we could confirm Osborne's findings.

In the third place, it was desired to find whether the organic iodide, Iod-Ethamine, has any advantage in the way of prolonged postabsorptive blood iodine curves, over the two inorganic iodides. Of the many organic iodides available, Boyd *et al.* (2) have found only two, namely *Simine* (N.N.R.) and Iod-Ethamine that have expectorant properties like those of the inorganic iodides. Iod-Ethamine was selected as an example of an expectorant organic iodide. Chemically, it is ethylenediamine dihydriodide, containing about the same percentage of iodine as sodium iodide and potassium iodide, and it was kindly provided by the Pitman-Moore Company of Indianapolis, through the courtesy of Dr. Frank B. Fisk. By comparing Figs. 1 and 2 of the paper by Boyd *et al.* (2), it may be seen that Iod-Ethamine had a more prolonged, and, dose for dose, a more marked, expectorant effect than potassium iodide in the rabbit but little difference could be detected in the cat.

Postabsorptive blood iodine curves were determined in the following manner. Three groups of 18 rabbits each were given by stomach tube, 1 gm. per kgm. body weight of the following iodides: Group *a*, potassium iodide; Group *b*, sodium iodide, and Group *c*, Iod-Ethamine. Samples of venous blood were oxalated and taken at intervals of 0, 0.5, 1.5, 2.5, 3.5, 6, 9, 15, 18, and 24 hr. after administration of the iodides. In view of the high values found for blood measurable iodine, a sample of about 2 ml. of blood was found to be sufficient for analysis in all except the sample taken before the iodides were given, when 10 to 15 ml. were required. Blood was then extracted repeatedly with alcohol, which had been especially purified, after the method of Boyd and Clarke (3). It is our custom, in this laboratory, to refer to the iodine contained in this extract as the cold-alcohol-soluble fraction and it is analogous to what is usually referred to as the non-protein blood iodine. Similarly, we refer to the iodine content of the residue after extraction with alcohol at room temperature, as the cold-alcohol-insoluble fraction and this corresponds approximately to what is usually called protein blood iodine. The terms

208 protein and non-protein blood iodine are somewhat ambiguous in so far as they refer to alcohol-separated blood iodine, because some analysts have used alcohol at room temperature, some, alcohol in an extraction apparatus at 78° C., and the length of time and other factors have varied considerably. Boyd and Clarke (3) have shown that the conditions of the experiment must be clearly defined because, under certain conditions, all iodine in blood can be made soluble in hot alcohol. Using alcoholic separation, at least three fractions of blood iodine may be separated (3) but as we have no proof of the exact chemical nature of these fractions, we prefer to use the terms cold-alcohol-soluble and -insoluble in connection with the fractions herein separated, rather than the terms protein and non-protein to which, in past usage, these fractions roughly correspond. The iodine content of the two fractions was then determined with the aid of a Conway microburette after the method in use in this laboratory (3).

Values for the concentration of these two fractions of blood iodine, as determined before and at the stated intervals after the various iodides were given by stomach tube, were tabulated, averaged, and plotted in Figs. 1 and 2. The mean changes in the concentration of cold-alcohol-soluble iodine have been charted in Fig. 1. Rising from low initial pretreatment values that averaged slightly less than one-half the normal total blood iodine, the concentration rose rapidly within an hour or two to values between 12,000 and 24,000  $\mu\text{gm. per } 100 \text{ ml. of whole blood}$  and then fell off gradually until at 24 hr. after administration of the iodides the values were between 4000 and 12,000  $\mu\text{gm. } \%$ . The following differences were noted between the post-absorptive curves after the three iodides. Following the administration of all three iodides, there was a rapid initial rise in the level of cold-alcohol-soluble iodine. The greatest initial rise followed administration of sodium iodide, which reached a peak value of nearly 24,000  $\mu\text{gm. } \%$  in about two hours, the peak value was maintained for only an hour or so and then the level fell rapidly until about nine hours after the drug was given, when the slope of the drop became less precipitous and declined gradually from about 11,000  $\mu\text{gm. } \%$  at nine hours to about 5000  $\mu\text{gm. } \%$  at 24 hr. Following administration of potassium iodide, the concentration of cold-alcohol-soluble blood iodine rose rapidly within half an hour to about 9000  $\mu\text{gm. } \%$ , then more slowly increased to 15,000 to 16,000  $\mu\text{gm. } \%$  at six hours; this level or plateau was held for several hours to 15 to 18 hr. and then declined gradually to about 11,000  $\mu\text{gm. } \%$  at 24 hr. These results indicate that a high blood level of alcohol-soluble iodine is maintained for a longer period of time following the use of potassium iodide than following sodium iodide. The rapid decline in the concentration of cold-alcohol-soluble blood iodine following use of sodium iodide might be interpreted as indicating that the iodide has been changed into an alcohol-insoluble form, or that this fraction of blood iodine has gone into the tissues, or that it has been eliminated in urine. As will be shown below, the first of these possibilities does not occur and in view of the work of Osborne (4), it would appear most likely that a rapid renal excretion

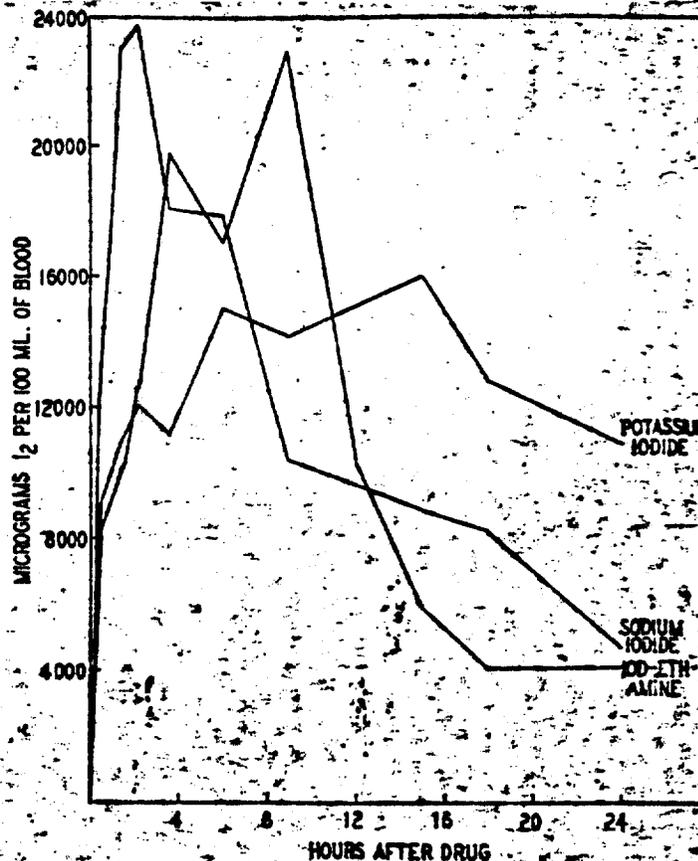


FIG. 1. The effect of administration by stomach tube of potassium iodide, sodium iodide, and Iod-Ethamine, in doses of 1 gm. per kgm. body weight, upon the concentration of cold-alcohol-soluble or "non-protein" blood iodine of rabbits.

of sodium iodide accounted for the rapid fall in the concentration of this fraction. The combination of these various factors would seem to justify, therefore, the continued use of potassium iodide, rather than sodium iodide, in instances where a therapeutic effect of iodide after absorption into the blood stream is desired, as in the preparation of patients for thyroidectomy.

There is good reason to believe that the cold-alcohol-soluble fraction of blood iodine consists mostly of inorganic iodide and water-soluble iodide. As the level of this fraction in blood was even greater than the level in *R.T.F.* following the administration of equivalent doses of the iodides, it becomes unnecessary to postulate that iodide therapy results in a secretion of iodide into *R.T.F.* Simple diffusion from blood to *R.T.F.* could readily account for the high values found by Boyd *et al.* (2) in the *R.T.F.* The evidence herein obtained does not prove that iodine-containing compounds get into *R.T.F.*

by simple diffusion from blood; the evidence is only circumstantial but is strongly suggestive that this is the case.

Is there any evidence, from the data presented in Fig. 1, that the organic iodide Iod-Ethamine has any advantage over the inorganic iodides? The curve for cold-alcohol-soluble blood iodine obtained after administration of Iod-Ethamine differed from that obtained after administration of the inorganic iodides in the following respects: the peak concentration almost equalled that obtained after sodium iodide was given but was maintained not for an hour or so but for five or six hours and the concentration reached the peak concentration, was greater than that following use of potassium iodide though it was not maintained for as long a period of time. It would seem logical to conclude from this that the organic iodide, Iod-Ethamine, has the advantage over sodium iodide that high levels of cold-alcohol-soluble blood iodine could be maintained with longer intervals between dosing, and the advantage over potassium iodide that a higher concentration of cold-alcohol-soluble blood iodine can be attained.

Average changes in the concentration of cold-alcohol-insoluble blood iodine, so-called protein iodine, following administration of the three iodides have been plotted in Fig. 2. Following all three iodides, the concentration of this fraction rose rapidly within one hour of administration of the drugs, to a level of about 1000  $\mu\text{gm. } \%$ , and then more slowly rose to values between 3000 and 5000  $\mu\text{gm. } \%$ . The peak concentration reached was only about one-quarter that attained by the cold-alcohol-soluble blood iodine but it was maintained for a longer period of time.

We were unable to confirm the report of Osborne that the administration of potassium iodide does, but the administration of sodium iodide does not, cause an increase in the concentration of this fraction of blood iodine. In fact, the average concentration of the alcohol-insoluble fraction was increased to a greater extent following sodium iodide than following potassium iodide. On the other hand, following sodium iodide the concentration of this fraction fell more rapidly from its peak value than it did following administration of potassium iodide, which could be harmonized with Osborne's finding that sodium iodide is more readily excreted in urine than potassium iodide.

The postabsorptive curves for cold-alcohol-insoluble iodine reached about the same levels as those found in *R.T.F.* following administration of the same dose of the iodides. It is possible that some, at least, of this fraction of blood iodine could diffuse into the *R.T.F.* If such is so, then the evidence obtained and plotted in Fig. 2 adds further weight to the suggestion that the occurrence of iodine-containing substances in *R.T.F.* is by way of simple diffusion.

Finally, a comparison of the different iodides leads to the conclusion that Iod-Ethamine has the same advantages over sodium iodide and potassium iodide with respect to its effect upon the concentration of the cold-alcohol-insoluble blood iodine as it had upon the concentration of cold-alcohol-

soluble iodine, though not to quite as marked a degree. The peak plateau reached following Iod-Ethamine was almost as great as that following sodium iodide but maintained for a longer period of time and the peak plateau was somewhat greater than that following potassium iodide but not maintained for quite as long.

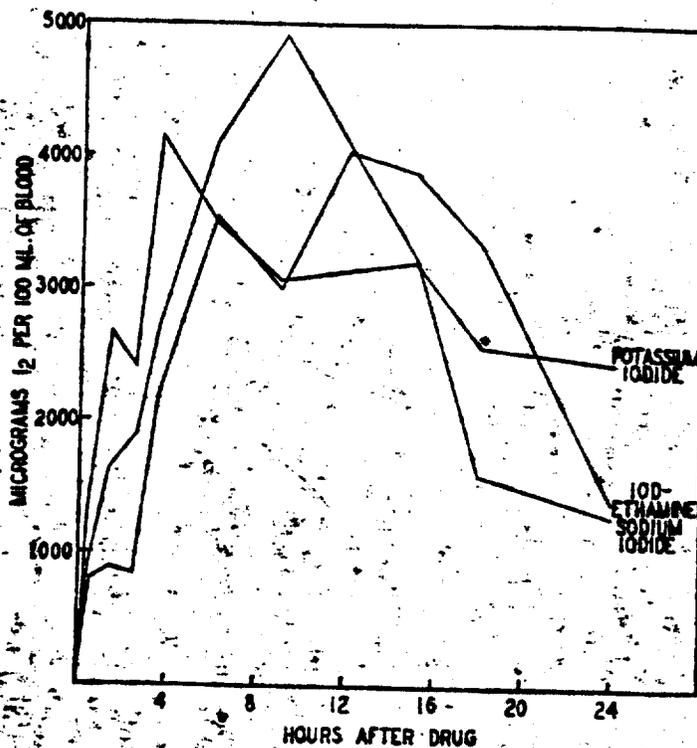


FIG. 2. The effect of administration by stomach tube of potassium iodide, sodium iodide, and Iod-Ethamine, in doses of 1 gm. per kgm. body weight, upon the concentration of cold-alcohol-insoluble, or "protein," blood iodine of rabbits.

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## GOITRE PROPHYLAXIS BY ADDITION OF POTASSIUM IODATE TO BREAD

Experience in Tasmania

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**Summary** In March/April, 1966, potassium iodate was substituted for some potassium bromate in the bread improver used throughout Tasmania, as a universal prophylactic against endemic goitre. The rate of addition of iodate was 2 parts per million of bread by weight. After a preliminary survey in 1949, tablets containing 10 mg. potassium iodide had been made available to infants, preschool children, and schoolchildren through schools and child-health centres for weekly consumption for approximately sixteen years. State-wide surveys at five-year intervals showed a slow steady reduction in the prevalence of goitre, but in some regions the rates remained high. It was presumed that this was due to ineffective distribution of the tablets. Since 1966 there has been a further striking reduction in the prevalence of goitre, and the 1969 rates for the whole State are similar to these in a non-goitrous region. Some unexplained regional variations were noted in the latest survey. It is concluded that the incorporation of 2 parts per million potassium iodate in bread is an effective prophylactic against endemic goitre.

### Introduction

Tasmania has long been recognised as an endemic goitrous region. The intensity of the thyroid enlargement varies from one region to another, probably due to the nature of terrain and the extent of earlier glaciation.

Although there may be other factors in the aetiology of the endemic goitre, the Tasmanian health authorities have accepted that the main factor is iodine deficiency, for in 1950 a programme of iodine prophylaxis was introduced for schoolchildren, infants, and preschool children. Because the mandatory use of iodised salt was unacceptable, the method chosen was the distribution to the selected groups of tablets containing 10 mg. potassium iodide, one tablet to be taken weekly. The distribution was through schools, and child-health centres. Over sixteen years some thirty-six million tablets were distributed.

Surveys were made of a significant percentage of the school population at five-yearly intervals up to 1965 when a report of the results of five State-wide surveys was completed.<sup>1</sup> The prevalence of endemic goitre fell progressively over the sixteen years of the prophylactic programme, but the condition was not eliminated, and there were comparatively large groups of the population, where, because of the lack of co-operation between schoolteachers and health authorities, the distribution of the tablets was so spasmodic as to be apparently non-effective. Furthermore, the distribution through child-health centres to infants

and preschool children was largely ineffective, especially for the preschool children, because of their irregular attendance.

The distribution of the tablets had, however, demonstrated that iodine prophylaxis could reduce, perhaps to vanishing-point, the attack-rate of endemic goitre in the younger age-groups, even if it did little to reduce the size of existing goitres. The Tasmanian public health authorities decided to continue iodine prophylaxis but to change the method from tablets to iodation of bread.

#### Iodation of Bread

The use of potassium iodate as a bread improver up to 20 parts per million (p.p.m.) weight of flour was approved by the National Health and Medical Research Council in May, 1963, and the necessary legislation was passed by the Tasmanian Parliament on Oct. 27, 1964 (Statutory Rule no. 189).

In the early 1960s the average consumption of bread was estimated by the Commonwealth Bureau of Census and Statistics to be approximately 3.3 lb. (1500 g.) per head per week. The improver commonly used at that time was potassium bromate. Since the estimated requirement of iodine for an adult is of the order of 150  $\mu$ g. per day the use of iodate as the sole improver would have yielded much more iodine than was required to prevent

TABLE I—ESTIMATED MEAN IODINE INTAKE BY PERSONS OF DIFFERENT AGES BASED ON BREAD CONSUMPTION, COMPARED WITH RECOMMENDED DIETARY ALLOWANCE\*

Age	Males				Females			
	Bread intake (oz./day)		Iodine intake ( $\mu$ g./day)		Bread intake (oz./day)		Iodine intake ( $\mu$ g./day)	
	Mean	Range	Mean	R.D.A.	Mean	Range	Mean	R.D.A.
1-3	2.5	0-9	81	55-60	2.5	0-8	81	55-60
3-7	4.1	1-19	130	70-80	4.1	0-13	130	70-80
7-11	5.8	0-18	187	100-125	5.1	0-17	163	100-125
11-15	7.3	1-22	235	135	6.1	0-22	196	115
15-18	8.3	0-20	270	150	5.3	0-17	170	120
18-35	6.9	0-21	218	140	3.6	0-14	113	100
35-64	6.0	0-23	194	110	3.5	0-11	113	90

\*Adapted from data of Howeler-Coy.<sup>2</sup>  
R.D.A.—Recommended dietary allowances.<sup>2</sup>

goitre. It was decided to permit the addition of 2 p.p.m. of potassium iodate, and the firm which supplied bread improver to Tasmania agreed to substitute the required amount of potassium iodate for potassium bromate in the improver shipped to Tasmanian bakers. It was estimated that the range of bread consumed by the various age-groups would supply a significant percentage of the estimated daily requirements of iodine.

By the end of April, 1966, practically all areas were being supplied with the new improver, and the distribution of tablets of potassium iodide to infants and children was gradually phased out, so that by the end of 1967 this method of prophylaxis had been abandoned.

#### Results

##### Bread Consumption

A survey of the quantity of bread eaten by different age-groups in Tasmania was undertaken by twenty-two school nurses, who made home visits for this purpose. The survey was planned by one of us (J. F. H.-C.) and ran from March to December 1966. A questionnaire was completed covering a day's intake for each family visited. Nurses recorded sex, age, and the amount of

bread eaten for each meal by each family member from elderly relatives to the youngest child.

The bread intake of 4472 individuals, 1.2% of the total population of Tasmania, was estimated in table 1.

Repeated analyses of bread, by the Australian Microanalytical Service, Division of Organic Chemistry, Commonwealth Scientific and Industrial Research Organisation, have shown that, with one exception in

TABLE II—PREVALENCE OF GOITRE IN TASMANIA FROM 1949 to 1969 BY AGE

Year	4-5		6-8		9-11		12-14		15-17	
	P.G.	V.G.	P.G.	V.G.	P.G.	V.G.	P.G.	V.G.	P.G.	V.G.
<b>Boys</b>										
1949	23.5	0.0	27.9	1.2	34.8	3.7	38.3	6.4	37.4	3.5
1954	24.2	5.0	30.4	8.1	29.7	9.0	31.1	9.9	27.2	5.9
1960	21.5	5.0	22.9	7.2	21.7	7.2	19.2	6.5	18.4	3.7
1965	10.1	2.3	14.4	3.5	17.3	5.6	16.6	5.0	13.8	3.5
1969	8.2	0.2	11.0	1.6	14.3	3.4	15.6	2.1	9.2	1.1
<b>Girls</b>										
1949	20.1	2.7	28.8	3.1	41.5	8.4	44.7	20.8	49.0	23.3
1954	24.9	5.9	30.0	9.6	26.2	12.6	33.3	16.7	29.1	23.3
1960	26.4	7.5	25.7	9.1	24.9	10.5	23.3	14.6	22.9	15.6
1965	11.6	2.5	15.6	4.0	18.2	6.9	18.7	10.1	20.0	9.5
1969	8.6	0.3	12.7	1.2	17.4	3.6	18.1	5.1	16.2	3.8

P.G.—Palpable goitre. V.G.—Visible goitre.

1966, the rate of iodation remains constant at approximately 2 p.p.m.

##### Goitre Survey in 1969

The survey technique and method of assessment of thyroid size were the same as those used in the previous five surveys.<sup>1</sup> The number of children included was determined after a study of the results of the previous surveys, including the regional variations noted, especially in the last survey in 1965, when it became apparent that the method of distribution of the tablets of potassium iodide was defective in some regions.

The main population areas were covered and re-

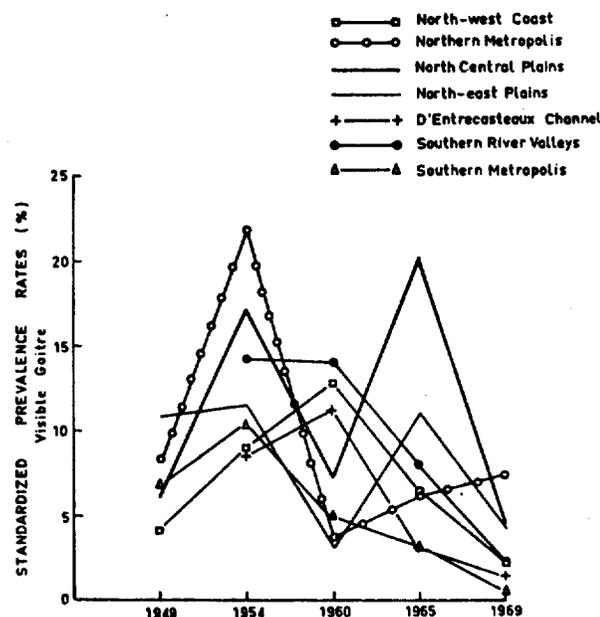


Fig. 1—Standardised prevalence-rates for visible goitre for the regions of Tasmania at five surveys showing the decline over time and the low figures in 1969.

TABLE III—STANDARDISED PREVALENCE-RATES FOR VISIBLE GOITRE IN THE VARIOUS REGIONS OF TASMANIA FROM 1949 TO 1969

Region	1949	1954	1960	1965	1969
North-West Coast	4.1	5.4	12.4	6.5	2.2
Northern Metropolis	8.3	22.9	3.6	6.4	7.5
North-Central Plains	7.1	17.2	7.4	20.0	4.8
North-East Plateau	10.9	11.5	3.1	10.1	4.3
D'Entrecasteaux Channel	N.S.	8.5	11.2	3.1	1.5
Southern-River Valley	N.S.	14.1	14.0	5.3	2.2
Southern Metropolis	6.9	10.1	5.0	3.1	0.6

N.S. = Survey not made that year.

representative samples of each of the age-groups studied in previous surveys were examined.

The State-wide prevalence, expressed as a percentage of those examined, of palpable goitre and of visible goitre for each of the five age-groups, for boys and girls, found at each survey is shown in table II. The age/sex standardised State-wide prevalence-rates for visible goitre for the various regions covered in the 1969 survey, using the 1960 population figures as the standard population, are shown in table III and fig. 1.

*Urinary Iodide Excretion*

Urinary iodide excretion in children was surveyed before and about two years after the introduction of iodate into the bread. The results for three localities, where the prevalence of goitre had been high before enrichment, are compared with results, pre-enrichment, for the whole of Tasmania and two other localities, in fig. 2.

**Discussion**

A feature of the 1949 survey was the high prevalence-rates of large visible goitres, especially in girls, which were prominent and clearly demonstrable to the lay observer. The distribution of the tablets of potassium iodide started in 1950, so the increase in prevalence in

the 1954 survey was unexpected. One feature of the 1954 survey was the substantial increase in the prevalence in children up to 9 years of age; in each age-group from five to eight years inclusive, the prevalence of visible goitre for some regions was almost identical, at about 8%. We suggested<sup>1</sup> that the introduction of a free school-milk scheme in 1951 and the radical change in dairy practice including the introduction of fodder crops of the Brassica family may have resulted in the appearance in the milk of food goitrogens,<sup>4,5</sup> but attempts to isolate a substance with sufficiently strong goitrogenic properties were unsuccessful.<sup>6</sup> Later surveys revealed a progressive fall in prevalence-rates in most regions. However, the North-Central Plains and the North-East Plateau both showed a distinct rise in goitre in 1965. This was attributed to defective distribution of the tablets.

Previous surveys had demonstrated a seasonal variation,<sup>7</sup> and the 1969 survey was done in the autumn, the period chosen for the other surveys (except that made in the spring of 1960) to check on the extent of seasonal variation. The figures in table II show a striking fall in prevalence in all age-groups in 1969 compared with 1965. The visible-goitre rate in the two youngest age-groups is especially encouraging, suggesting that iodation of bread is preventing the appearance of goitre in all but a small percentage of young children. The existence of some goitre in the older age-groups may, in part, be due to residual cases which developed at an earlier age. It must also be appreciated that a small percentage of children and adolescents develop goitre in non-goitrous regions, such as the metropolitan area of Sydney. Kamal et al.,<sup>8</sup> in their recent study of goitre in the Sudan, pointed out that individual susceptibility must always be considered in a goitre survey. A number of ad-hoc surveys of adolescent girls who have lived in Sydney throughout their lives by one of us (F. W. C.) have shown that between 2 and 4% have a small but definite visible goitre. The 1969 survey in Tasmania revealed a prevalence for the older girls not much in excess of that likely to be found in Sydney. Furthermore, in contrast to 1949 when up to 25% of older girls had large visible goitres, the enlargements are just discernible as a bulge filling the space between the two sternomastoid muscles.

Table III shows fluctuations in the age/sex standardised prevalence-rates in the various regions. We have already referred to the high rates in the 1965 survey in both the North-Central Plains and the North-East Plateau. Inquiries made at the schools in these areas, at the time, revealed a lack of cooperation between the teaching staffs and the nurses from the health department responsible for the distribution of the tablets to the schools. In both areas there seemed to be a number of headmasters who influenced other teachers against the prophylactic programme.

Table III shows that regional variations still exist. In view of the uniformity of distribution of iodated bread improver—all bakers in Tasmania draw their supplies from common suppliers in the north and south of the island—and the continuation of the iodation of bread at 2 p.m., the question of the possible operation of some additional aetiological local factors might have to be reconsidered.

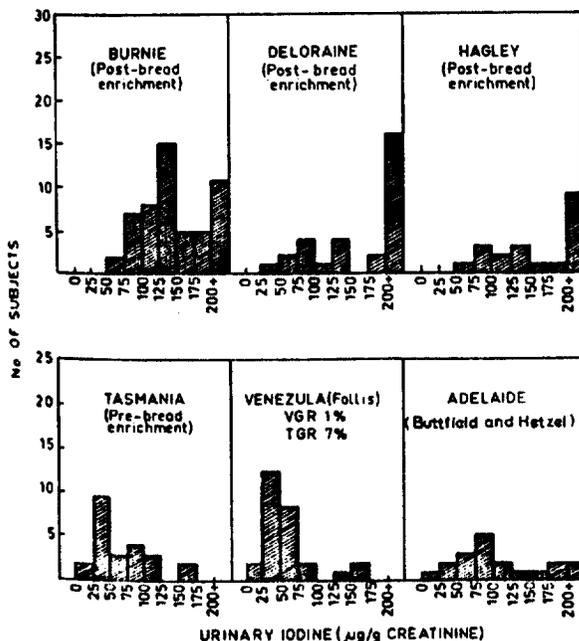


Fig. 2—Urinary iodide excretion; effects of the addition of iodate to bread.

The bread consumption and the estimated mean iodine intake of the people covered by the bread survey, together with the recommended dietary allowance of iodine, are shown in table 1. Some older children, adolescents, and adults may be consuming more than the dietary allowance of iodine. Because of their low consumption of bread some individuals may actually have intakes well below the recommended allowances, and this may account for the continued presentation of some cases of endemic goitre. The urinary excretion of iodide show that most children tested are receiving adequate amounts of iodide.

The results of the 1969 survey indicate that for all regions surveyed iodation of bread has been much more effective in the prevention of goitre than was the distribution of iodide as tablets.

We thank the Minister for Health, Commonwealth of Australia, and the Tasmanian Minister for Health for permission to publish this report.

Requests for reprints should be addressed to F. W. C.

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Scientific Edition

# JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOLUME XL

OCTOBER, 1951

NUMBER 10  
CONSECUTIVE No. 20

## Iodine in the Atomic Age\*†

By GEORGE M. CURTIS

THAT IODINE is of major consequence in any consideration of the essential nature of thyroid activity, or of thyroid disease, long has been a matter of common knowledge. The thyroid gland is a principal storehouse for iodine. The thyroid hormone has a high iodine content. The use of iodine in the prevention, as well as in the treatment of goiter has become even household conversation. In fact, iodine is now generally regarded as a nutritional necessity. Nevertheless, trite as now may sound this older account, newer facts are constantly being added, with the resultant opening of even wider horizons in our understanding of the evolving story of the clinical significance of iodine.

It is established that iodine is constantly present in human blood. A part actually forms a fraction of the circulating thyroid hormone. The intake of food iodine fluctuates. There ensues a consequent variable loss of iodine from the body by excretion. The level of the blood iodine varies. Moreover, by measuring this variation we may obtain some idea of the secretory activity of the thyroid gland. Indeed, that portion of the blood iodine contained within the circulating thyroglobulin may actually be frac-

tionated away and analyzed separately. This determination has become of considerable clinical value in recognizing variation of thyroid function.

After the development of the cyclotron by Lawrence it became possible (1940) to prepare radioactive iodine for experimental purposes. This was created by bombarding elemental iodine or even an entirely different element, tellurium, with high-speed protons. The biologic use of radioiodine has already added greatly to our knowledge of the fundamental physiology of iodine as well as its utilization by the thyroid gland in health and disease. The use of one of the radioactive isotopes of iodine,  $I^{131}$ , as a "tracer" or in the preparation of "autographs," has been most fruitful in adding to our knowledge of endogenous iodine metabolism.

It is the purpose of this address to present a brief sketch of the background history of biologic iodine, thus better to orient ourselves to the more recent developments. Then, to outline those principles underlying the human iodine requirement; to present certain features of the metabolism of iodine as related to nutrition as well as to thyroid function in health and disease; to demonstrate something of the action of radioiodine; and finally to consider certain of the newly discovered principles which underlie the clinical use of radioiodine in the treatment of thyroid disease.

\* Received July 16, 1951, from the Department of Research Surgery, Ohio State University, Columbus, Ohio.

† Presented to the Scientific Section of the A. Ph. A., Atlantic City meeting, May, 1950, by Dr. George M. Curtis, recipient of the second (1949) Chilean Iodine Educational Bureau Award for outstanding research in the chemistry and pharmacology of iodine.

## HISTORIC BACKGROUND

The ancients used burnt sponge and seaweed in the treatment of goiter. This was a fortunate empiricism as the nature of goiter was but little understood and iodine was unknown. Iodine was discovered in 1811 by a French pharmacist, Courtois (1). Napoleon was blockaded in France by the British fleet. It was consequently impossible for him to import sufficient foreign nitrates to make gunpowder. He appealed to his scientific staff who made it possible to process the cruder local supplies of available nitrate by treatment with a lye made from the ash of seaweed. This was carried out in large copper vats. Some unknown substance corroded the vats. Upon investigation this proved to be a new element, iodine. Thus, like the development of the bomb, the discovery of iodine resulted from the stress of military necessity.

Soon afterward Sir Humphrey Davy demonstrated the presence of iodine in sponges, seaweed, and various other forms of marine life. As a logical sequence, a British physician William Prout (2) prescribed the new medication, iodine, as early as 1816 in the treatment of goiter. Two Swiss physicians, Coindet de Genève (3) and Straub von Bern used iodine as early as 1820 for a similar purpose. Since that time *iodine and the goiter problem have become, and remain, inseparable.*

In 1831 a young French chemist, Boussingault, recorded that in the Andes, where goiter is prevalent, the sea salt of Guaca was used as a "cure." Moreover, that the districts in which an iodine-rich salt was used, were free from goiter. This was followed by other similar investigations, resulting in the development of Prevost's theory, and its announcement in 1849. Prevost maintained that there was a direct relation between the supply of iodine and the incidence of goiter. His theory was further substantiated by the subsequent extensive chemical studies of Chatin (4). Chatin published a series of pertinent papers in the "*Comptes Rendus*" between 1850 and 1876. These presented the best supporting evidence available up to that time.

As a consequence of Chatin's findings, three French provinces attempted iodine as a preventive against the development of goiter as early as 1860. The results were not satisfactory. It is not so difficult to understand the ill effects of that extensive experiment in the light of recent investigation. Anyway, the use of iodine as a goiter prophylactic was even denounced before the French Academy of Medicine by Rilliet, and rapidly fell into disrepute. The general use of iodine as a preventive against the development of goiter thus received a severe setback. During the ensuing thirty-five years other theories arose as to the nature of goiter. It was during this thirty-five year period (1860-1895) that the infection theory of the origin of goiter gained credence. This was doubtless due to the wide attention attracted by the contemporary discoveries of Louis Pasteur.

Theodore Kocher (1841-1917), pioneer student of the surgical problems concerning goiter, was well aware of the alleged relation between iodine deficiency and subsequent enlargement of the thyroid gland. In fact, he assigned to one of his assistants the problem of investigating the chemistry of the thyroid gland, to see whether or not it contained

unusual amounts of iodine. The assistant, using inadequate methods of biologic iodine analysis available at that time, failed to find iodine and missed making a discovery of fundamental importance. Sometime later, Kraske, for whom the Kraske operation was named, at that time professor of surgery at the University of Freiburg, asked some of his colleagues to make a similar investigation. Emil Baumann (5) succeeded, and demonstrated in 1895 that there were *quantities* of iodine within the human thyroid gland. As final proof Baumann actually isolated and demonstrated iodine before some of his scientific societies, in its characteristic vapor form, in tubes. The significance of such a major contribution was widely appreciated.

There consequently ensued a widespread renaissance of interest in the interdependence of iodine and the thyroid gland. Again iodine was used preventively in the treatment of goiter. David Marine (6) and his associates obtained significant results in 1917 at Akron, Ohio, by administering small amounts of iodide to schoolgirls. Other investigators in other countries were likewise successful.

Several earlier studies had resulted in the surmise that the thyroid gland actually takes up iodine and fashions it into a hormone, and that probably the thyroid hormone actually contained iodine. These researches were carried to their logical summation by Kendall (7), who actually used *quantities* of beef thyroids in isolating in 1914 a small amount of crystalline substance. After subsequent extensive chemical investigation he called this substance thyroxine and designated it as the secretion of the thyroid gland. Kendall's thyroxine contained 65% iodine. With his associates he attempted the formula of thyroxine but was unsuccessful. As a consequence he could only isolate it by extraction from the thyroid gland and was unable to synthesize it.

Harington and Barger working in London noted certain discrepancies in the given chemical composition (8). As a consequence they first isolated sufficient quantities of pure thyroxine, using methods giving a considerably greater yield, and then determined its true chemical structure. Working from this formula they were actually able to synthesize the hormone of the thyroid gland outside of the animal body.

## NEED OF AN ADEQUATE MICROMETHOD

It thus became clear that, in order to study further the metabolism of iodine in the human body, better chemical micromethods must be developed, so accurate that they would determine quantitatively the minute amounts of iodine ordinarily present biologically. True, the amount of iodine in the thyroid gland was high. On the other hand, the amount normally present within the ingesta, within the blood, the living tissues and excreta was minute. Chatin had learned this in his earlier extensive studies.

The thyroid iodine was readily determined by employment of the older, coarser methods, owing to its relatively high concentration (31). This did not hold, however, for the blood and tissues. Davy had originally separated and determined the iodine present in sponges, by ashing the organic material

The principle of his method has been widely followed. For many years methods were devised for the determination of the iodine content of ordinary foods. None of these, however, was sufficiently delicate *even to detect* the minute amount of iodine present within the quantities of human blood ordinarily used for chemical analysis.

Thus, advancing investigation into the details of human iodine metabolism created an acute demand for an adequate biologic micromethod. In 1922 Theodore von Fellenberg, chemist to the Swiss Government, developed such a procedure (9). This would determine one ten-thousandth of one milligram<sup>1</sup> (0.0001 mg.) or one three hundred-millionth of an ounce of iodine. Facilities were thus available to commence an extensive investigation of iodine as it occurs in nature, and particularly in its relation to man.

### HUMAN REQUIREMENT OF IODINE (17)

The quantity of iodine necessary to answer the daily needs of the human body should be sufficient to meet the daily losses by excretion, as well as maintain within the body such reserves as may be required in the manufacture and distribution of an adequate supply of thyroid hormone. The amount of iodine intake, however, and particularly in certain geographic regions, is not always equal to the physiologic needs. This is in contrast with the organism's chlorine requirement, which is more readily met because of the association of this element with the sensation of taste.

The fundamental question thus arises: How much supplemental iodine is necessary in those regions in which goiter is prevalent, in order to protect the populace from the effects of iodine deficiency? Thus far, three methods have been developed in attempts to answer this question.

By the *geographic method* the iodine intake of the inhabitants of goiter-free areas is determined and compared with that of areas of varying degrees of

goiter incidence. The difference in the amount of average iodine intake is then regarded as the amount of supplemental iodine required. According to von Fellenberg's reckoning the annual iodine intake in one goitrous and one practically goiter-free area in Switzerland was 4.7 and 11.4 mg., respectively (9). Calculating from this, the iodine requirement would be in the neighborhood of 30  $\mu$ g. daily, a figure now regarded as extraordinarily low. Estimating on the basis of determinations of the average daily urinary loss of iodine, which is an unusually accurate barometer of the iodine intake of a given area, the daily iodine requirement would lie somewhere between 100 and 200  $\mu$ g. (10, 15) (Table I).

The principle of *thyroxine formation and decay* was originally outlined by Plummer and Boothby (11) and subsequently developed by Thompson (12). Plummer and Boothby observed that the daily rate of thyroxine decay ranged between 200 and 400  $\mu$ g. Thus, a daily supply of thyroxine in this quantity maintained a normal basal metabolic rate in a "totally myxedematous patient." Thompson and his group concluded that from 300 to 400  $\mu$ g. of thyroxine was necessary to maintain a normal basal metabolic rate in myxedematous patients at bed rest. On the basis of these results the amount of thyroxine supplied daily to the circulation by the thyroid gland, in order to maintain normal metabolic activity, is equivalent to from 130 to 260  $\mu$ g. of iodine. The uncertain factor here, however, is that iodine-containing end products of thyroxine decay may be retained and eventually re-utilized by the thyroid gland in the further synthesis of thyroid hormone.

Studies of the *total iodine balance* (Figs. 1, 2, 3 and Tables II and III) constitute the third principle which has been employed. The iodine balance represents the daily amount of iodine lost or retained by the body, as ascertained by the difference between the amount of iodine intake and excretion (Fig. 1). Pioneer determinations of iodine balance were accomplished by von Fellenberg (9), who reported low values and consequently a *low* daily requirement. The balance studies of Scheffer (13)

<sup>1</sup> 0.001 mg. is designated a microgram, or often a *gamma*.

TABLE I<sup>a</sup>.—THE NORMAL DAILY HUMAN URINARY IODINE EXCRETION IN VARIOUS GEOGRAPHIC REGIONS (10)

Geographic Region	Investigator	Range in Daily Urinary Iodine Excretion, $\mu$ g.	Av. Daily Urinary Iodine Excretion, $\mu$ g.	
Nongoitrogenic Regions				
Danzig	Liek	200-500	343	
Berlin, Germany	Scheringer	(17 women)	66-389	141
		(7 men)	103-214	173
Vik-i-Sogne, Norway	v. Fellenberg	94-240	146	
New Orleans, La.	Moore <sup>b</sup>	60-270	117	
Forte dei Marmi, Italy	v. Fellenberg	30-140	72	
Av. normal 24-hr. urinary iodine (in five "goiter-free" regions)			165	
Goitrogenic Regions				
Efingen, Switzerland	v. Fellenberg	28-108	64	
Columbus, Ohio	The authors	7-196	51	
Sandsvaer, Norway	Lunde	6- 83	38	
Lwow, Poland	Elmer and Scheps	34- 40	36	
Pecs, Hungary	Scheffer	21- 33	27	
Av. normal 24-hr. urinary iodine (in five goitrogenic regions)			42	

<sup>a</sup> Note the great variability in the daily urinary loss; however, the diminished average excretion in the goitrogenic regions.

<sup>b</sup> We are indebted to Margaret C. Moore, of New Orleans, La. for permission to include these data.

TABLE II<sup>a</sup>—THE HUMAN IODINE BALANCE DURING PREGNANCY

Period	Date Started	Weight, Kg.	Output Iodine				Total Intake, $\mu\text{g.}$	Balance, $\mu\text{g.}$	Date	Blood Iodine, $\mu\text{g.}/\%$	BMR, %	Remarks
			Urine, $\mu\text{g.}$	Feces, $\mu\text{g.}$	Sweat, $\mu\text{g.}$	Total, $\mu\text{g.}$						
I	2-13-37	64.5	163	28	25	216	104	-110	2-12-37	7.4	+7	General iodine deficiency
									2-15-37	5.9	+8	
II	2-16-37	64.1	194	18	31	243	105	-138	2-17-37	10.9	+5	"General iodine deficiency"
III	2-19-37	64.5	166	32	18	216	77	-139	2-22-37	5.6	+3	

<sup>a</sup> Woman of 26, pregnant eighth month; dietary intake 2,170 calories with 49 Gm. of protein (14). Note high iodine balance on a low iodine intake.

made in Pecs, Hungary, revealed that 54  $\mu\text{g.}$  of daily iodine intake was sufficient to maintain the iodine balance in a normal person.

Ohio State University studies (Figs. 1, 2, 3 and Tables II and III) were made on normal persons maintained at bed rest on a monotonous diet low in iodine content, under controlled hospital conditions (14). Under these circumstances the basal human adult iodine requirement was found to range from 44 to 75  $\mu\text{g.}$  daily and to average 67  $\mu\text{g.}$ , or approximately 1  $\mu\text{g.}/\text{Kg.}$  of body weight. This average daily requirement is comparable to that determined by Scheffer (13). However, it should be emphasized that it applies to adults maintained under controlled basal conditions. Moreover, to arrive at an optimal iodine requirement, it is necessary to take into account individual activity as well as the varied stress and strain of existence (16).

After consideration of the difference in iodine intake between goitrogenous and nongoitrogenous regions (Table I) and the amount of iodine estimated as necessary to maintain normal metabolic activity, 2  $\mu\text{g.}$  daily per Kg. of body weight, together with the daily basal requirement of 1  $\mu\text{g.}$ , can be reasonably justified as an amount sufficient to account for basal needs, those of ordinary activities, and also some for reserve. The optimal daily requirement would thus be somewhere near 200  $\mu\text{g.}$  for an adult of 70 Kg., a value compatible with Elmer's deduction from various investigations that the human optimal requirement ranges between 100 and 200  $\mu\text{g.}$  daily (16). The pregnant woman should receive additional iodine (Table II). A sufficient amount will be supplied by the daily use of iodized salt (17).

Various methods of supplying supplemental iodine to the inhabitants of iodine-deficient areas have been advanced. These include the use of foods known to

be rich in iodine, iodination of water supplies, administration of iodine at regular intervals in the form of solutions or tablets, the general use of iodized salt, and the consumption of iodized milk (Fig. 2).

The use of iodized salt has thus far proved the most widely adopted method. The nearly universal employment of common salt for seasoning and cooking, as well as the ready preparation and low cost of iodized salt, makes this the popular method. The use of milk with an increased iodine content has also been suggested as suitable, especially for children who ordinarily consume large quantities. Effective iodine prophylaxis should conform to local conditions, since no single method will reach all those persons who need iodine.

The iodized salt originally recommended in 1914 by the Michigan State Medical Society in conjunction with the State Board of Health, and subsequently employed in Michigan with such outstanding results, originally contained 0.02% of sodium iodide (17). However, after careful consideration by the Goiter Study Committee of the American Public Health Association reached the conclusion that the addition of 0.01% of potassium iodide plus a stabilizer should be sufficient. The importance of a stabilizer was emphasized in view of previous experience that iodine may be lost from iodized salt and thus impart a yellowness and a halogen odor on liberation of elemental iodine.

It has been estimated that the average adult requires about 6.2 Gm. of salt daily. Calculated on this basis, the approximate amount of potassium iodide intake would be 620  $\mu\text{g.}$ , which is equivalent to about 474  $\mu\text{g.}$  of iodine. This is more than twice the amount we have suggested as optimal and would amply provide a person with a sufficient reserve (17).

TABLE III<sup>a</sup>—THE IODINE BALANCE IN DISEASES OF THE THYROID GLAND

(A Comparison of the Iodine Balance of Normal Individuals with that of Nodular and Exophthalmic Goiter Patients)

Type of Goiter Present	No. of Patients	Total Days of Investigation	Average BMR, %	Average Blood Iodine $\mu\text{g.}/\%$	Average Output per 3-Day Period				Average Intake per 3-Day Period, $\mu\text{g.}$	Average Balance per 3-Day Period, $\mu\text{g.}$
					Urine, $\mu\text{g.}$	Feces, $\mu\text{g.}$	Sweat, $\mu\text{g.}$	Total, $\mu\text{g.}$		
1. None-normal controls	3	24	Minus 7	4.3	154	31	28	213	87	-126
2. Nontoxic nodular	2	18	Minus 8	3.0	120	31	29	180	74	-106
3. Toxic nodular	2	15	Plus 28	8.5	323	149	38	510	117	-393
4. Exophthalmic	3	33	Plus 40	9.0	204	164	46	414	86	-328

<sup>a</sup> Note the increased negative balance in patients with hyperthyroidism, also the increased BMR and blood iodine level (14).

## THE CIRCULATING THYROID HORMONE

Another problem in which an adequate micro-method of determining biologic iodine has proved of real clinical value is in the estimation of the amount of circulating, iodine-containing, thyroid hormone. The nature and amount of the blood iodine has thus become a useful clinical index of thyroid function. Thus, in patients with toxic nodular and exophthalmic goiter, the whole-blood iodine (18), along with the basal metabolic rate (19), as well as the excretory iodine (15), are significantly higher than normal (Table III). It is important to know how much of this blood iodine is directly resultant to the intake iodine of nutrition (Table II), to the various diagnostic procedures which may have been applied and to any previous therapy; as well as how much is dependent on the daily formation of thyroid hormone and its breakdown products. As a consequence, various fractionation methods have been devised to determine which portion of the blood iodine most nearly coincides with the "circulating thyroid hormone." One of the early problems encountered was to separate the iodine bound to the proteins of the blood from the more soluble "inorganic" fraction. Even more precise steps of delineation have been developed by Salter. Nevertheless, with the simpler clinical methods now available (29), the differential diagnosis of thyroid disease has become more precise. It is now possible actually to differentiate hyperthyroidism from hypermetabolism (30).

After an extensive series of studies, it became evident that in central Ohio the average normal basal metabolic rate was minus  $5 \pm 8\%$  (19) and the corresponding whole-blood iodine  $4.2 \pm 1.2 \mu\text{g. \%}$ . The average normal protein-bound iodine of whole-blood (acetone-insoluble) was  $0.9 \pm 0.2 \mu\text{g. \%}$  (20). This fraction is significantly decreased in patients with hypothyroidism (20). Helpful clinical progress has recently been made in recognizing the early development of hyperthyroidism by correlating the protein-bound blood iodine with the basal metabolic rate as well as the symptoms ordinarily suggestive of hyperthyroidism (30).

Thus, in 178 patients with uncomplicated non-toxic nodular goiter, it was found that the protein-bound blood iodine increases progressively from  $0.51 \mu\text{g. \%}$  in those with basal metabolic rates below minus 21% to  $1.32 \mu\text{g. \%}$  in those exhibiting basal metabolic rates above plus 11% (21). A significant linear relation between the basal metabolic rate and the protein-bound blood iodine was thus established in uncomplicated instances of this disease. Moreover, of the 66.8% of these patients exhibiting hyperthyroid-like symptoms, 60% had elevations of the PBI<sup>2</sup> and only 47% elevation of the BMR, thus demonstrating that the protein-bound blood iodine is a better index of thyroid function than the basal metabolic rate alone (21, 22). However, both taken together are most helpful to the clinician.

The protein-bound blood iodine has thus become an important aid in the differential diagnosis of those diseases which may mimic hyperthyroidism. These include hypertension, organic heart disease, "neuro-circulatory asthenia," anxiety state, psychoneuroses,

<sup>2</sup> The protein-bound blood iodine.

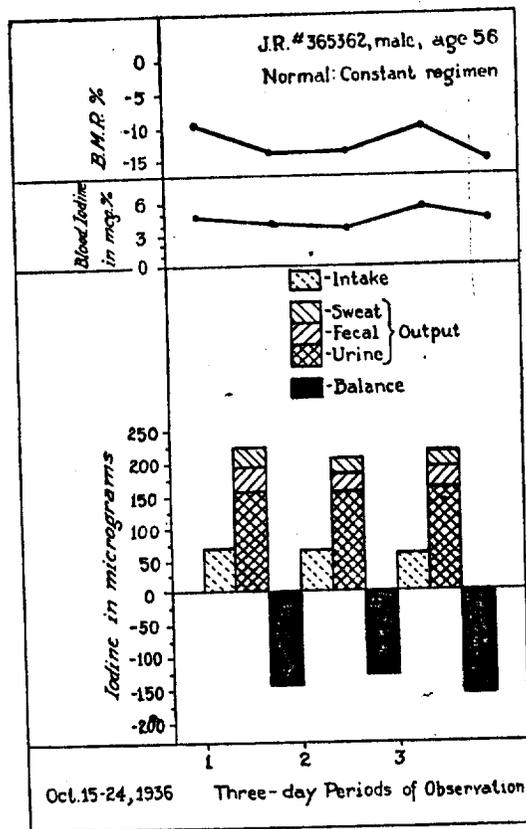


Fig. 1.—Normal iodine balance. Note that the intake is purposely kept low; the urinary excretion is high and the balance consequently negative (14).

neoplastic diseases, and certain endocrine disturbances, such as acromegaly and the adrenocortical syndromes. In hyperthyroidism, the protein-bound blood iodine is increased; however, in the nonhyperthyroid hypermetabolic states the protein-bound blood iodine is normal or may be even subnormal unless hyperthyroidism is also present (30).

## RADIOACTIVE IODINE

Within the decade preceding the development of "atoms" to be used for destruction, iodine, and few elements even before it, had been going "atomic," yet with a scientific intent then purely constructive. Thus, it had been found that these radioactive or "tagged" atoms could be employed to determine the ultimate fate of ingested substances in the body, as well as their intermediate history of absorption, distribution, synthesis, and eventual excretion. Prior to the use of these "radioactive isotopes" there was no method available for differentiating the iodine taken during a given experiment from that already present in the human body and particularly in the thyroid gland. Radioactive iodine, in the truly minute quantities in which it could be employed, lent itself readily to the determination of the fate of intake iodine as well as to the process of the succeeding endogenous iodine metabolism. Studies using radioactive iodine (<sup>131</sup>I) soon demonstrated that iodine was quickly brought to the

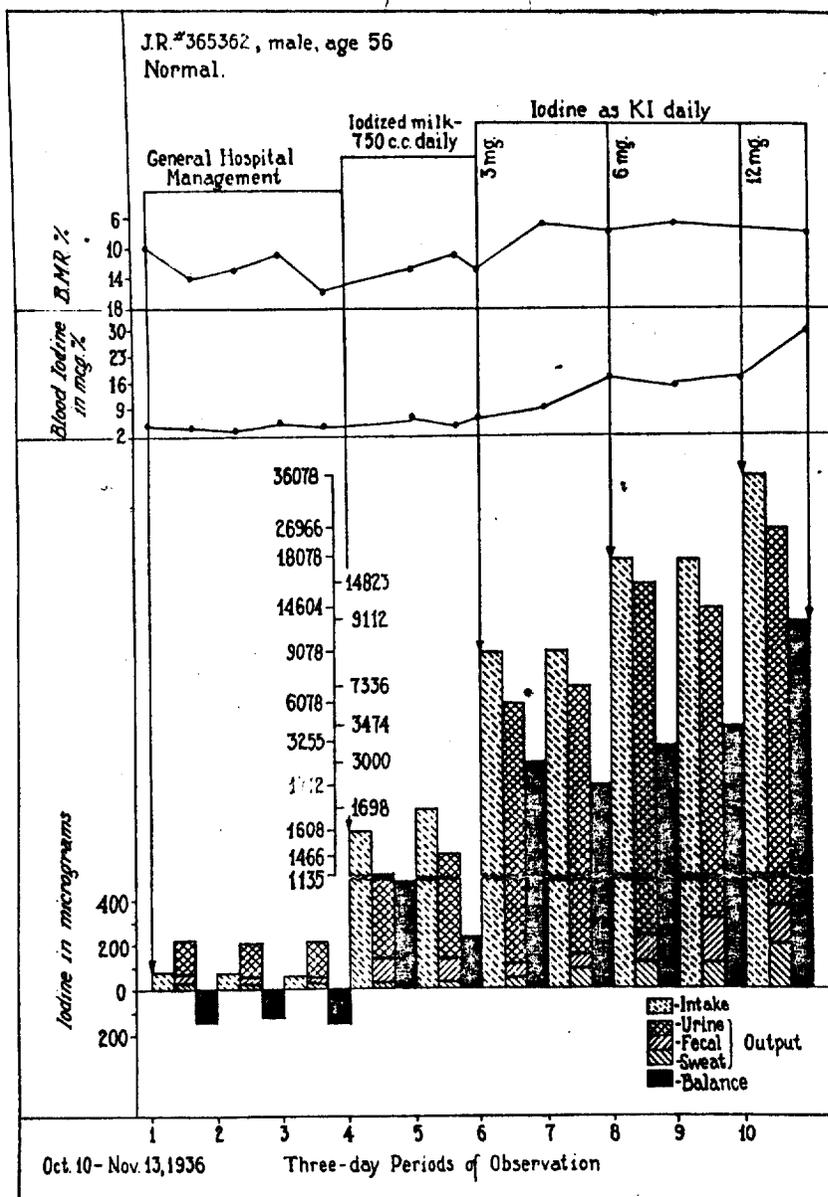


Fig. 2.—The effect of increased iodine intake on the iodine balance. Note the negative balance on a low intake and the storage resultant to adding supplemental iodine (14).

thyroid gland by the blood stream and there rapidly converted by the thyroid cells into diiodotyrosine and eventually thyroxine, the thyroid hormone (Fig. 5), moreover, that within a matter of a few hours these organic iodine compounds returned to the circulation (23-25).

From a consideration of normal thyroid activity, using the "tracer" method, was but a step to a more penetrating investigation of iodine metabolism in thyroid disease. "Labeled" iodine, usually  $I^{131}$ , was used to study the pathologic thyroids of experimental animals. Subsequently the metabolism of radioiodine in human thyroids, later removed at operation, was followed, particularly by "autographs" (26, 28) (Fig. 5).

An investigation of the metabolism of radioactive iodine used as a "tracer" in studying six nodular goiters revealed that the nodular formations, particularly one nodule of a fetal adenomatous type, were less active in their uptake than the surrounding thyroid tissue (24) (Fig. 5). This was demonstrated by the lesser iodine content in the nodules than in the paranodular tissues, a smaller radioiodine fixation and a slower turnover of iodine. Moreover, the formation of thyroxine, isolated chemically and determined by the "tracer" technique, was comparatively slight in the nodular tissue (Fig. 5). These studies were conducted chiefly on nontoxic nodular goiters. A study of toxic nodular goiters revealed that the paranodular tissue rather than

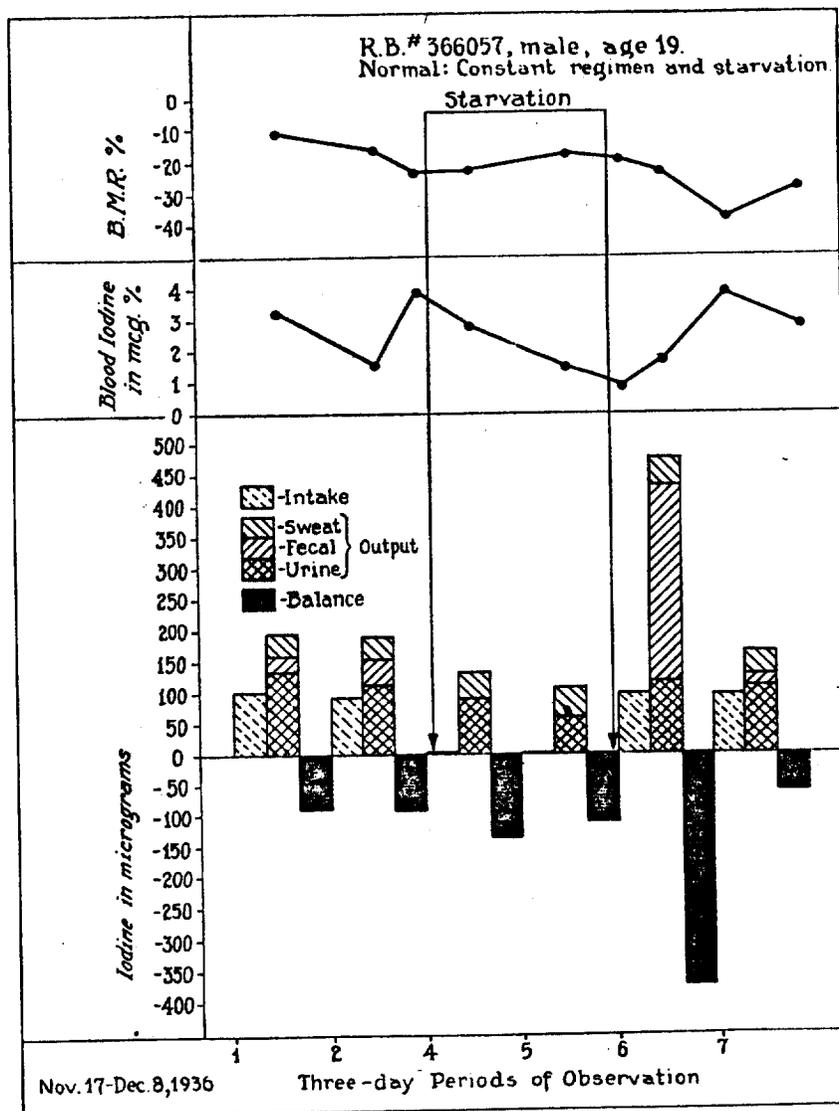


Fig. 3.—Iodine excretion continues during starvation. Note the increased fecal loss during the recovery period (14).

the nodules themselves forms the greater part of the "toxic" secretion (32).

The behavior of the nodular activity revealed that local factors by themselves may affect the iodine metabolism within the thyroid gland. In addition, other influences were demonstrated. Thus, a high level of the blood iodine "saturating" the gland with iodine may result in an increased storage of thyroxine inside the colloid (24). Moreover, that so-important pituitary factor—the thyrotropic hormone—when excessive or deficient, may activate or slow down the iodine turnover (25). The specific activity of the diiodotyrosine fraction has been found intermediary between that in the inorganic fraction and that in thyroxine, at least during the first forty-eight hours, thus possibly indicating that thyroxine is synthesized more slowly than diiodotyrosine, its presumable precursor (24).

The histologic method, or "autograph" technique, by utilizing the radiation effect of radioactive iodine

on the photographic plate has made it possible to trace systematically the various states of the deposition of iodine in the thyroid cell. A comparison of the chemical, biophysical, and histologic results reveals that radioiodine passes through the cellular epithelium of the thyroid follicles rather rapidly, to be stored eventually as diiodotyrosine and thyroxine within the thyroid colloid.

A preferential distribution of radioactive iodine has been demonstrated in the colloid of normal rats (26), as well as in pituitary-treated and hypophysectomized animals (27). It can now be similarly demonstrated in the human thyroid gland, from studies made on surgically removed goiters. Microscopic sections of the diffuse hyperplastic goiter of Graves' disease removed fifteen hours after the administration of radioiodine demonstrate this clearly (28) (Fig. 6). The storage of radioiodine within the colloid is noteworthy. The radioiodine has actually photographed itself, a manifestation of

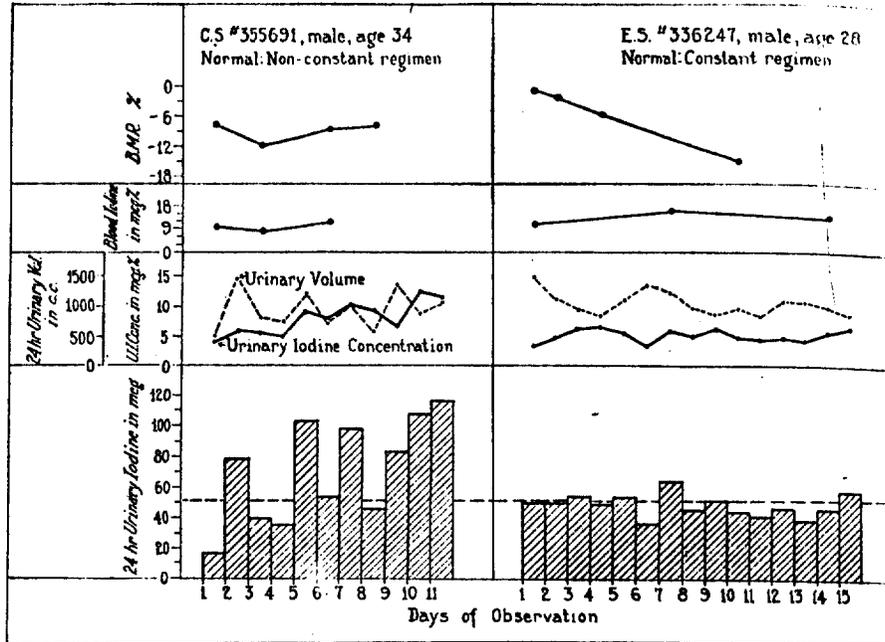


Fig. 4.—The urinary iodine loss. Note the variability on an ordinary diet (C.S.) and the constancy (E.S.) on a monotonous diet (15).

the atomic energy of  $I^{131}$ . It is localized within the colloid, its passage through the cell was only transient (Fig. 6).

A similar study was made of a diffuse colloid goiter (Fig. 5). Again, in any given section, the radioiodine localizes preferentially within the colloid (28). Further comparative study of the different types, as well as the different parts of nodular

goiters, should prove even more revealing. *Strum nodosa trabecularis* is embryonic in character, and quite cellular as well, with little or no colloid formation. It should, therefore, take up but a minimal amount of iodine, since iodine is stored essentially within the colloid. On the other hand, with *strum nodosa microfollicularis* one should usually obtain a significant "autograph."

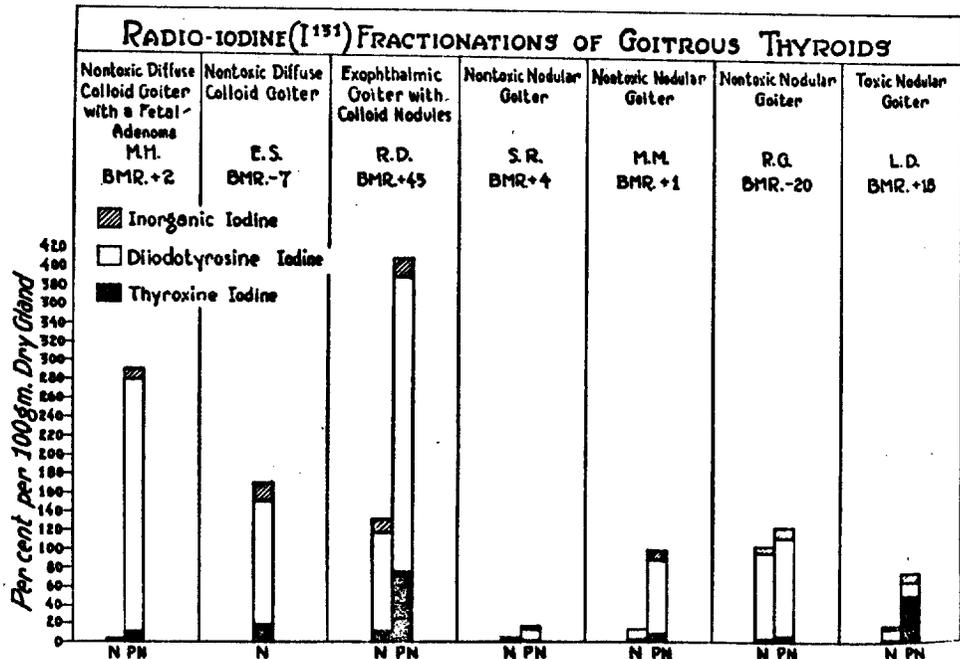


Fig. 5.—The use of radioiodine as a "tracer." Note the variability of hormone formation in the different types of goiter (32).

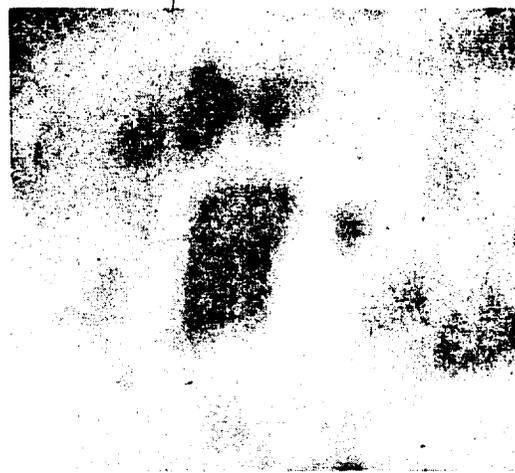


Fig. 6.—The "autograph" effect of radioiodine. The figure at the left is the stained histologic section of the goiter; at the right is its "autograph." Note that fifteen hours after administration the radioiodine has passed through the thyroid cells and is stored in the colloid substance (28).

The use of radioiodine, usually  $I^{131}$ , as a "tracer" under these conditions of varying thyroid disease demonstrates the rate of iodine storage within the thyroid, its rate of synthesis into diiodotyrosine and eventually thyroxine, as well as the subsequent mobilization, circulation, and elimination of these substances and their iodine-containing by-products. Its use as an "autograph" enables a "follow-up" of its quantitative distribution into the various tissues. Radioiodine has more recently taken its place in the therapeutic management of certain forms of thyroid disease and particularly thyroid cancer. Thus, as iodine goes "atomic," our horizons widen, our facilities for learning become greatly augmented, new facts result in new ideas, and our hope for progress in the control of disease is again stimulated.

This autograph (Fig. 6) is prophetic. Bichat demonstrated the significance of the microscopic structure of the various tissues. And Virchow taught us the significance of those changes which take place when disease enters and changes the normal histologic picture. Yet here we see the beginning of new microscopic science, demonstrated by "autographs," which clearly is to follow. For in this we will learn more of histochemistry and the distribution of the various chemical substances so important to human metabolic processes, within the living cells and tissues.

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ALTERATIONS IN SERUM IODINE FRACTIONS  
DURING THE ADMINISTRATION OF  
POTASSIUM IODIDE†

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THE iodine of plasma or of serum in healthy subjects is present largely in a protein-bound form, and only partly as an inorganic iodide (1, 2). The former fraction consists in turn chiefly of thyroxine associated with the serum or plasma proteins (3). It has been shown that in health, with an intake of inorganic iodide limited to that ordinarily present in the diet, the protein-bound or the precipitable iodine of plasma or serum remains quite constant (4). Moreover, it is clear from data on patients with disorders of the thyroid that alterations in the rate of production and release of hormone from the gland induce measurable changes in the level of the protein-bound iodine of serum. Thus in thyroid overactivity the value of this fraction exceeds with great regularity 7.5 or 8.0 gamma per cent, the upper limit encountered in the euthyroid state, using the methods of either Man and Riggs, or of Barker (5, 6, 7). Similarly, with decreasing thyroid function, the concentration of this iodine moiety in serum falls below 4.0 gamma per cent (8). This excellent correlation between clinical and other evidences of the level of thyroid function and the protein-bound iodine is all the more remarkable when it is recalled that the plasma merely serves as a transportation route for the hormone, and insofar as is known, does not itself participate in the metabolism of the thyroid hormone.

Under certain circumstances, however, the protein-bound iodine level may be misleading as an index of thyroid activity. As might be expected, false high values occur in patients who have received organic iodine compounds such as those used in evaluating the biliary, renal, or pulmonary systems (9). The methods available at this time do not differentiate between these substances and the hormone elaborated by the thyroid gland. Furthermore, it is not surprising to find that in certain hypoproteinemic states low protein-bound iodine values are encountered, since the thyroid hormone in the circulation is associated with serum proteins (10). In neither instance is the abnormal concentration indicative of thyroid dysfunction. Finally, it is known that pregnancy is frequently accompanied by increased concentrations of protein-bound iodine, usually without clinical or other evidences of hyperthyroidism (11).

† Read at the Annual Meeting of the American Goiter Association, Madison, Wisconsin, May 26, 1949.

Nonetheless, even when these limitations are taken into account the level of protein-bound iodine of serum remains a remarkably valid index of thyroid activity. It has been the purpose of the studies being reported to you to seek factors, heretofore unidentified, which produce alterations in the serum iodine fractions. Particular emphasis has been placed on the effects of an increased intake of inorganic iodide on the levels of the protein-bound and of the thyroxine iodine.

*Variations induced by potassium iodide in moderate doses.*

Certain studies of Taurog and Chaikoff are of particular interest to us because rises in thyroidal iodine and thyroxine produced by feeding potassium iodide to rats were associated with a slight, but probably definite, increase in the level of protein-bound iodine in serum (12). The small measure of uncertainty on our part in accepting these higher values in plasma as indicative of unequivocal increases is based on the limited number of washings, usually two or three, used in removing inorganic iodide mixed in with the precipitated serum. Obviously, if this separation were incomplete, a false high value for the serum or plasma protein-bound iodine would be obtained.

We have studied certain aspects of this same problem in human subjects. Four healthy male adults have been given a daily supplement of potassium iodide, 0.2 cc. of a saturated solution, later increased to 0.4 cc., in addition to any iodide present in a complete diet. Measurements of the protein-bound iodine at the end of two weeks failed to show any significant change from the pretreatment values. Two weeks later, however, with either the same or a doubled dose of potassium iodide a distinct increase was evident in all subjects. In 2 of the experiments, levels ordinarily associated with hyperthyroidism, *i.e.*, 7.5 to 8.0 gamma per cent or higher, were reached. These changes are all the more striking when it is recalled that in healthy adults the average variation of the protein-bound iodine is less than 1 gamma per cent when determined at weekly intervals (4). Preliminary data based on butanol and NaOH-Na<sub>2</sub>CO<sub>3</sub> treatment of serum (13-15) are available in two of these experiments. These are hardly conclusive in view of the limited number of observations but they do suggest that, with the administration of inorganic iodide, the level of circulating thyroxine does not rise. This change in protein-bound or serum precipitable iodine, though small, must represent an elevation in the nonthyroxine fraction. This does not represent a false rise due to incomplete removal of free iodide or iodine. We have employed a minimum of 6 washings for sera obtained during periods without added intake of iodide, and 14 separate washings with double distilled water whenever the subjects had received iodide. That the values obtained after 14 washings indeed indicate protein-bound iodine and not a combination of inorganic iodide and protein-bound iodine is

clearly demonstrated by the highly satisfactory agreement between duplicate or triplicate aliquots of serum washed 14 and 18 times respectively. It is evident from these data that the additional 4 washings fail to affect significantly the level of protein-bound iodine and hence indicate that the iodide is present in an organic combination.

#### *Effects of massive doses of inorganic iodide*

In view of these suggestive but not conclusive changes in protein-bound iodine of serum observed during administration of a moderate dose of potassium iodide, it should be of interest to describe the serum iodine fractions during periods characterized by a much greater intake of inorganic iodide. In these studies 5 hospitalized patients, 3 female and 2 male, received up to 3.0 grams of potassium iodide or as much as 7.0 cc. of iodide solution daily during intervals ranging in length up to five months.

*Patient E. K.*, a 50-year-old female office clerk, ill with biliary cirrhosis, was found to have a protein-bound or serum precipitable iodine level of 5.7 gamma per cent. At this time a moderate hypoalbuminemia was present, with an elevation of the globulin concentration. Clinically the patient appeared euthyroid in that she was not hyperkinetic, the pulse rate was less than 70, and no stigmata of thyroid disorder were evident. Potassium iodide was then started by mouth, 2.0 grams daily being given in divided doses. Within several days this intake was increased to 3.0 grams, and maintained at this level for twelve weeks, ending nine days before the patient's death in hepatic coma. Measurement of the protein-bound iodine at intervals of several weeks revealed a progressive rise, with a recorded maximum of 31.8 gamma per cent, a value considerably in excess of the upper limits of the euthyroid state, and indeed, higher than most instances of flamboyant hyperthyroidism. As might be predicted, the total iodine during such dosage of KI was tremendously elevated, reaching values as high as 11,000 gamma per cent. Despite those high levels of circulating protein-bound iodine there were no evidences of hypermetabolism. The resting pulse rate only sporadically exceeded 80 per minute and the B.M.R. vacillated but slightly and probably not significantly from the pre-KI treatment range of +29 and +25 per cent. The weight loss observed during this period and the fall in the serum cholesterol can be evaluated only tentatively. The patient had ascites and ate poorly throughout the experimental period. Hence the weight loss which occurred is explicable without postulation of hyperthyroidism. Similarly it seems equally reasonable to suggest that the drop in serum cholesterol can be attributed in part to the rapidly advancing hepatic disease (16). Examination of the thyroid gland post mortem revealed cuboidal epithelium and follicles filled with well-stained colloid.

*Patient M. M.* A study similar to the above was conducted on a 51-year-old housewife hospitalized with a nephrotic syndrome. Potassium iodide was started in a dose of 1.0 gram daily by mouth. This amount was rapidly increased until the total daily intake reached 3.0 grams; she was then maintained on this dosage during a total of four months. As in the previous patient, the total iodine levels measured at intervals were tremendously elevated. It is improbable that any significance can be attached to the variations in this fraction not only because of the errors inherent in determinations of such high values, but also because unavoidable changes occurred in the interval, usually twenty-four hours or less, between withdrawal of a blood sample and the last intake of KI. This would obviously affect the total iodine levels (17). On the other hand, a rather consistent trend of values was obtained in the determinations of protein-bound iodine. The

initial level was low, 3.0 gamma per cent, presumably related to the pronounced hypoalbuminemia which was present as a part of the nephrotic syndrome. With the continued intake of KI a progressive rise in the protein-bound iodine occurred, passing through the euthyroid range and reaching a maximum of 14.5 gamma per cent. At this point, some two months after the beginning of treatment, a plateau was reached and maintained, with only slight fluctuations, until the administration of inorganic iodide was discontinued. Less than one week later the total iodine was diminished to 195 gamma per cent, without any significant drop in the protein-bound fraction. The thyroxine iodine level at this time was 2.8 gamma per cent. One and one-half months following withdrawal of the KI, the total iodine was 5.5 and the protein-bound 5.3 gamma per cent. Despite these marked and persistent increases in the total and the protein-bound iodine, this patient did not develop any symptoms or signs of hyperthyroidism. As a matter of fact, bradycardia appeared during the course of the experiment, but this occurred coincident with changes in the electrocardiogram indicative of a myocardial infarction involving the conduction system. The B.M.R. ranged between +2 and -15 per cent throughout the period of observation; again if any trend were present it was toward a decrease. It is true that the patient lost body weight and that the cholesterol values were at their lowest toward the end of the period of iodide administration. The weight loss represented, however, delivery of edema fluid. Nitrogen studies during this period indicated the existence of equilibrium, or a positive balance (18). The decrease in the cholesterol level coincided with improvement in the nephrotic syndrome characterized by diminished proteinuria and a rising serum albumin concentration. It seems more reasonable therefore to ascribe the body weight changes and lipid fluctuations to alterations in the patient's primary disease rather than to thyrotoxic symptoms produced by high levels of either inorganic or protein-bound iodide. Whether or not the iodide regimen favorably modified the course of this patient's disease cannot be answered unequivocally. It is more likely, however, that her improvement was either spontaneous, or related to bed rest and almost complete sodium restriction.

*Patient L. T.*, a 59-year-old Negress, had been given potassium iodide in the treatment of gummatous syphilis some three months prior to the first serum iodine studies. Hence no pretreatment data are available. However, after receiving 4.0 and subsequently 7.0 cc. of saturated solution of KI daily during a period of three months, in addition to two intravenous injections of sodium iodide, the protein-bound iodine was found to be 21.1 gamma per cent. It remained at approximately this level during the remaining seven weeks of KI therapy, reminiscent of the plateau observed in the previous 2 patients. The total iodine was markedly elevated as well during this period. Following withdrawal of the inorganic iodide these two fractions declined progressively. Thyroxine levels ten days and twenty-five days after the end of the inorganic iodine regimen were 4.9 and 6.4 gamma per cent respectively. At these times the protein-bound iodine values were still elevated considerably above the euthyroid range, and hence the rise in the protein-bound iodine had occurred in the non-thyroxine fraction. Clinically the patient's status was not perceptibly altered insofar as thyroid size and peripheral evidences of its activity were concerned. The weight fluctuated only slightly. Also, if any trend were present in the B.M.R. and pulse variations, it was toward decreased rather than increased values during the time when the protein-bound iodine was greatly elevated.

*Patient S. D.*, a 46-year-old tailor with pulmonary fibrosis, polycythemia, and heart failure had been taking 3.0 cc. of saturated solution of potassium iodide daily for six months when the protein-bound iodine in his serum was measured for the first time and found to be markedly elevated. Pretreatment values are, therefore, not available, but there is nothing in the history to suggest that this patient had any thyroid disorder prior to the administration of inorganic iodide. When the intake of KI was discontinued the pro-

tein-bound iodine declined progressively, and with moderate rapidity, to the euthyroid range, and subsequently even fell to hypothyroid levels—2.4 gamma per cent. The validity of this observation was supported by a confirmatory low protein-bound iodine concentration obtained four weeks later. Since then, this fraction of serum iodine has again risen to euthyroid limits. No evidence of thyrotoxicosis was detected. Maximal improvement in the cardiac status occurred coincidentally with the low protein-bound iodine levels.

*Patient A. S.* This 64-year-old male factory worker, five weeks earlier, had been given potassium iodide in treatment of bronchiectasis and pulmonary insufficiency. The protein-bound iodine had increased to 14.4 gamma per cent after four weeks of iodide therapy. This was unassociated with any discernible change in the patient's clinical status; the pulse rate did not rise and the body weight remained constant.

#### DISCUSSION

The studies which have been presented indicate clearly that an *in vivo* iodination of the serum proteins occurs during the continued administration of moderate to huge doses of potassium iodide by mouth. The repeated washings of the precipitated serum, and the progressive rise and subsequent fall of the serum precipitable or protein-bound iodide following institution and withdrawal, respectively, of the iodide therapy argue strongly against the production of false high values as a result of incomplete removal of inorganic iodide. The plateau phenomenon observed, suggests a saturation of the protein molecule with continued exposure to inorganic iodide. Preliminary observations indicate that, as in other studies, most of the iodine was bound to albumin (15, 18). They differ in that, despite the extensive iodination of protein which took place, no calorogenic material resembling thyroxine was formed (19). This point of view is supported not only by the failure to observe hypermetabolism clinically but also by the results of the butyl alcohol-alkali separation. As a matter of fact if any alteration did develop in the clinical status of the patients it was toward a decrease in metabolic activity. This possibility together with the finding in 1 of our patients of an abnormally low level of protein-bound and hence necessarily of thyroxine iodine after withdrawal of potassium iodide does suggest that this iodine-protein complex may have suppressed thyroid hormone production by inhibiting thyrotropic secretion. This can remain only a speculation in view of the fact that the finding was limited to one patient.

It is of interest that similar elevations of protein-bound iodine have been observed by Dvoskin and by Barker, and their respective co-workers, following subcutaneous injections of elemental iodine (20-22). Their studies suggest that the iodination of protein occurred at the injection site. This does not help identify the site of iodination in our studies in which iodide was given only by mouth.

#### SUMMARY

The administration of inorganic iodide in moderate and in massive doses

to human subjects increases the total and the protein-bound iodine of serum without evidence of hyperthyroidism.

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PURPURA DUE TO IODIDES

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The occurrence of purpuric manifestations following the administration of iodides was recorded in 1877 by Fournier.<sup>1</sup> Other reports were made by Robinson in 1893,<sup>2</sup> Millian in 1899,<sup>3</sup> Mackenzie in 1889,<sup>4</sup> Wilson in 1889,<sup>5</sup> Hudelo and Lebar in 1904<sup>6</sup> and Dennig in 1933.<sup>7</sup> While cutaneous manifestations from the internal use of iodides are common, and, indeed, often anticipated, we feel that purpuric lesions are of sufficient rarity to justify this case report. We consider that purpura resulting from iodides is an ominous sign—if the use of the drug is continued, a fatality might result. Therefore one must recognize the possibility that purpura can be caused by the administration of iodides. In our experience, it occurs so rarely as to make one suspect other causes rather than the obvious (and true) one.

REPORT OF CASE

E. F., a 48 year old man, was first seen by one of us (W. C. D.) in November 1944. He complained of severe headaches, progressive loss of vision in the right eye and some unsteadiness of gait.

Physical examination showed a positive Romberg sign and diminished knee jerks and ankle jerks. The heart and lungs were normal.

Ophthalmologic examination showed 20/50 vision in the left eye and 20/200 vision in the right eye. The pupils were unequal and did not react to light. There was pallor of the optic nerves.

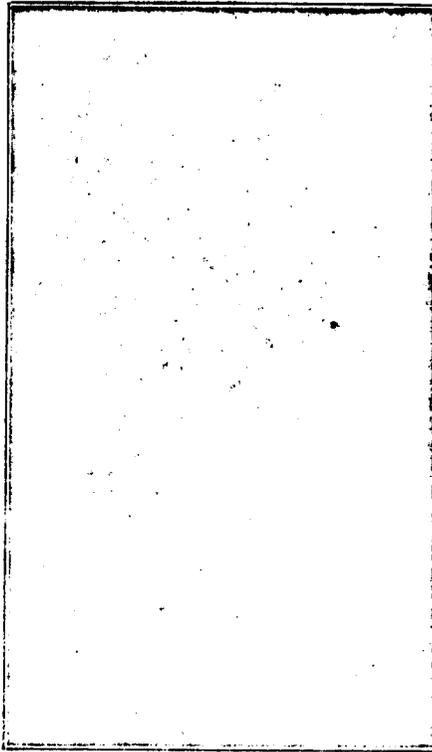
The Kolmer and Kahn serologic reactions of the blood were 4 plus. The Kahn reaction of the spinal fluid was 4 plus; there were 87 cells per cubic millimeter; the total protein level was 80 mg. per hundred cubic centimeters, and the colloidal gold curve (Lange test) was 011231000. A diagnosis of tabes dorsalis (with primary atrophy of the optic nerve) was made.

On November 13 the patient was instructed to take 15 grains (1 Gm.) of potassium iodide three times daily. This was accompanied with weekly intramuscular injections of bismuth subsalicylate (0.2 Gm.). His headaches diminished in severity, and his vision rapidly improved. He reported some soreness in the salivary glands. This was attributed to the potassium iodide, but he was advised to continue taking it.

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On December 1 definite purpura of the lower extremities was noticed by the patient and the physician. No other signs or symptoms were present. Examination of the blood at this time showed a hemoglobin content of 86 per cent (Sahli), 4,560,000 red cells, 12,400 white cells and 100,000 platelets.

Feeling that the bismuth was responsible for the purpura, we discontinued its use and administered oxophenarsine hydrochloride. However, the purpura persisted. Our attention was now drawn to the potassium iodide as a possible cause; hence



Purpuric lesions produced by readministration of potassium iodide.

it was discontinued. The purpuric lesions promptly disappeared. Since they cleared, we have been able to reproduce the lesion experimentally by a single dose of 5 grains (0.3 Gm.) of potassium iodide (fig.).

#### SUMMARY

A case of purpura from the administration of potassium iodide is reported. Because of its ominous import, we feel that the possibility of the production of purpura should be kept in mind whenever iodides are used.

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PROTEOLYTIC ACTIVITY OF THE THYROID GLAND

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The thyroglobulin molecule is of large size, with a molecular weight of about 700,000 (Heidelberger and Pedersen, '35), yet it passes rapidly into and out of the thyroid follicle of the mammal with no apparent intercellular spaces. Since cell membranes are not normally permeable to such large protein molecules, and it is not likely that the cells surrounding the thyroid follicle are specialized in such a way that thyroglobulin will penetrate their membranes, Gersh and Caspersson ('40) suggested that enzymes in the thyroid brought about the hydrolysis of thyroglobulin into polypeptides or peptones which could rapidly pass across the cell membranes. The decomposition products could then possibly be reconstituted by enzyme action into a larger molecule. Lerman and Salter ('36) had already shown that thyroid hormone could be synthesized in vitro from extracts of thyroid tissue by the action of a protease. De Robertis ('41) performed semi-quantitative experiments on proteolytic activity of the colloid withdrawn with a micropipette from individual rat thyroid follicles. He found that the activity of this protease could be made to fluctuate by varying the physiological conditions of the animal.

The present paper concerns experiments performed to determine variations in the proteolytic activity of the whole thyroid tissue in various physiological states, using more quantitative methods than those of De Robertis. Procedures used to bring about these physiological changes were: feeding with potassium iodide, feeding with sulfaguanidine, treatment with thyrotropic pituitary factor, and hypophysectomy.

METHODS

Thyroid glands of rats or guinea pigs were weighed and minced finely. They were then extracted 24 hours in 10 volumes of 60% glycerol (Weil and Jennings, '41) and diluted 1:2 with water. To 7.1 cmm. of the extract were added identical amounts of 1% cysteine hydrochloride,

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This research is part of a project supported by an allotment from the Rockefeller Fluid Research Fund.

veronal-acetate buffer and 4% edestin solution. The last three solutions were all at pH 4. The mixtures were incubated at 40° C. for 4 hours and the amount of protein digestion was determined by the micro-acetone titration method of Linderström-Lang and Holter ('40).

The rats were fed Purina dog chow, with occasional greens. For those on the KI diet, the briquettes were finely ground and mixed with 1% by weight of potassium iodide. The rats treated with thyrotropic factor received it as a 0.2% solution in 0.85% NaCl injected intraperitoneally. The dose contained 1 mg. of the thyrotropic factor, or 10 guinea pig units of thyrotropic activity. The thyrotropic factor was donated by Doctor Jensen.

The rats used in the sulfaguanidine feeding experiments were supplied by Dr. Julia B. MacKenzie. The diet contained 2% sulfaguanidine powder by weight.

Ten rats were hypophysectomized by Dr. James Leatham of Rutgers University, and were fed on a normal diet. Three weeks after the operations, the thyroids were tested for proteolytic activity. Another ten hypophysectomized rats were fed for 3 weeks on a diet containing 2% sulfaguanidine, and then tested for thyroid proteolytic activity.

The guinea pigs receiving thyrotropic pituitary factor were treated with a different preparation of the extract (Ayerst) and were given much larger doses, up to 450 guinea pig units. The guinea pigs receiving 50 guinea pig units were injected with 0.1 cc. amounts of thyrotropic pituitary factor twice a day for 5 days and were killed on the sixth day. Those receiving 250 guinea pig units were treated the same way except that 0.5 cc. injections were given. The animals receiving 450 guinea pig units were injected with 0.5 cc. dose of the thyrotropic factor four times a day, except for the first day, when two injections were made. They were killed on the sixth day.

#### RESULTS

The results of the micro-titrations are given in the number of cmm. of N/20 HCl required to titrate the digestion products of the edestin caused by the proteolytic activity of 1 mg. of thyroid tissue.

Preliminary results showed that the enzyme was activated by cysteine hydrochloride. Without cysteine HCl, a sample of thyroid extract required 4.80 cmm. N/20 HCl; with cysteine HCl added, an identical sample required 8.67 cmm. N/20 HCl. The pH optimum for digestion of edestin was at pH 4.0. Cmm. of N/20 HCl required to titrate iden-

tical samples of thyroid extract at various pH's were: pH 3.75 - 7.85 cmm.; pH 3.88 - 8.06 cmm.; pH 4.0 - 8.67 cmm.; pH 4.13 - 8.12. These results indicate a proteolytic enzyme of the cathepsin type.

The average activity for the thyroids of 20 control rats was 10.31 cmm. of N/20 HCl per milligram thyroid, with a range of 7.92 cmm. to 12.38 cmm. The majority of the results were between 9.5 cmm. and 11.5 cmm. N/20 HCl per milligram thyroid tissue.

TABLE 1

	TIME OF TREATMENT	NO OF RATS	CMM. N/20 HCl/MG. THYROID	% CHANGE FROM NORMAL	MG. THYROID PER 100 GM. BODY WEIGHT
	<i>days</i>				
Rats on KI diet	7	2	13.50	+ 30.9	6.5
	14	2	11.88	+ 15.2	
	16	2	12.73	+ 23.4	
	35	2	10.94	+ 6.1	
	40	2	9.29	- 9.9	
	<i>hours</i>				
Rats treated with thyrotropic pituitary factor 10 g. p. u.	2.5	8	13.36	+ 29.6	6.6
	21	2	13.33	+ 29.3	
	48	2	13.40	+ 30.0	
	72	2	11.03	+ 7.0	
	<i>days</i>				
Rats on sulfaguanidine diet	1	2	10.36	+ 0.5	9.9
	3	2	7.62	- 26.1	8.6
	5	2	8.22	- 20.2	14.3
	7	2	7.96	- 22.8	16.4
	14	2	7.19	- 30.2	24.8
	21	2	8.80	- 14.7	20.4
	<i>days</i>				
Hypophysectomized rats on normal diet	21	10	8.01	- 22.3	5.6
Hypophysectomized rats on sulfaguanidine diet	21	10	11.61	+ 12.6	3.8

Table 1 lists the results obtained on normal rats treated with potassium iodide, thyrotropic pituitary factor, and sulfaguanidine, and also on the hypophysectomized rats fed on control and sulfaguanidine diets. On the average there were 6.4 mg. of thyroid tissue per 100 gm. body weight in the control rats used for the potassium iodide, thyrotropic factor and hypophysectomy experiments. A different strain of rats was used for the sulfaguanidine experiments, and the controls averaged a higher value: 9.1 mg. thyroid tissue per 100 gm. body weight.

Table 2 shows the results on the thyroid proteolytic activity of guinea pigs treated with thyrotropic pituitary factor. The average normal value for the proteolytic activity of the thyroid tissues of six guinea pigs was 8.65 cmm. N/20 HCl per milligram thyroid tissue. In the control guinea pigs there were 13.8 mg. thyroid tissue per 100 gm. body weight.

TABLE 2

	NO. OF GUINEA PIGS	NO. OF GUINEA PIG UNITS INJECTED	CMM. N/20 HCl/MG. THYROID	% CHANGE FROM NORMAL	MG. THYROID PER 100 GM. BODY WEIGHT
Guinea pigs treated	2	50	8.60	- 0.6	15.9
with thyrotropic	4	250	9.70	+ 12.2	37.3
pituitary factor	4	450	10.64	+ 23.0	54.2

#### DISCUSSION

Thyroglobulin has a high molecular weight of approximately 700,000. This material is continually being secreted into the lumen of the follicle and reabsorbed. Mann, Leblond and Warren ('42) estimate that 1.55% of the thyroxine contained in the thyroid gland of the dog is formed per hour. The thyroglobulin absorbed must pass out of the lumen of the follicle either through intercellular spaces or through the walls of the follicular cells. The first method does not seem likely. No intercellular spaces are apparent in mammalian thyroid follicles. Riggs, Laviates and Man ('42) have shown that the organic iodine containing fraction of the blood can be regarded as a compound of the same size as serum albumin, or one of smaller size, which is restrained from diffusion during ultra-centrifugation determinations by the serum albumin. This means that the thyroglobulin with a molecular weight of 700,000 in the follicle is broken into substances with molecular weights of 69,000 or less.

Somewhere the thyroglobulin must be broken down into smaller units through the action of a proteolytic enzyme. Since the iodine containing hormone of the colloid must pass through the membranes of the follicle cells to leave the thyroid gland, it is possible that this breakdown occurs in the thyroid itself, perhaps very largely in the colloid (De Robertis, '41). The proteolytic enzyme found in the thyroid is of the cathepsin type, one found generally in all tissues of the body.

Administration of thyrotropic pituitary hormone causes an increased basal metabolism (Belaseo and Merlin, '41), a decreased viscosity of the thyroid colloid during the first 24 hours after administration (De Robertis, '41) and an increase in mitotic activity in the cells of the

colloid (Salter, '40). There is also an increased efficiency of iodization of the protein of the colloid (Gersh, '43). The present experiments show an increase in the activity of the cathepsin of the thyroid gland of the rat during the first 48 hours after injection of the thyrotropic factor. This may be correlated with the more rapid secretion of the thyroid hormone by the activated gland. By 72 hours after the injection, proteolytic activity of the thyroid tissue has returned to within the normal range. The proteolytic activity of the thyroid tissue of the guinea pig also increased after the administration of the thyrotropic factor, the magnitude of increase being parallel with the dosage given.

Feeding of potassium iodide to rats does not affect the basal metabolism of the animals, but does bring about an increase in mitotic activity of the follicular cells (Rabinowitch, '28), possibly a slight increase in iodine content of the gland (Remington and Remington, '38), and an increased efficiency of iodization (Gersh, '43) of the colloid protein. De Robertis ('41) found that the colloid of thyroid follicles of rats fed for 5 to 12 days on a 1% KI diet was less viscous than normal colloid and its proteolytic activity was increased. Rats fed on the KI diet for 45 to 54 days had thyroid colloid which was more viscous than that of the control rats, and it also had less proteolytic activity. In table 1 the figures show an increase in the proteolytic activity of the thyroid tissue of rats fed on a 1% KI diet for 7, 14 and 16 days. After 38 days of feeding on the special diet there was only a small increase over normal of the proteolytic activity, and after 40 days the activity was somewhat below the average normal level. This data agrees in general with the semiquantitative findings of De Robertis.

MacKenzie and MacKenzie ('43) have shown that a marked enlargement and hyperemia of the thyroid of the rat is caused by the administration of sulfaguanidine. However, this was accompanied by a decrease in the basal metabolism and also decreased protein and organic iodine concentrations in the thyroid colloid (Gersh, '43). The proteolytic activity of the thyroid tissues of sulfaguanidine rats was definitely lower than normal. When rats were hypophysectomized and then fed on a diet containing 2% sulfaguanidine, no enlargement or hyperemia of the thyroid took place, and no decrease in the proteolytic activity of the tissue occurred. In fact, the activity was somewhat above the normal average. Gersh ('43) found that there was a greatly increased efficiency of iodization of the colloid protein in sulfaguanidine fed hypophysectomized rats. The increased catheptic activity of the thyroid tissue seems to parallel this finding.

In hypophysectomized rats, which show an atrophy of the thyroid and a decrease in basal metabolism (Salter, '40), there is a fall in the proteolytic activity of the thyroid tissue. The latter appears to be correlated with a decrease in the output of thyroid hormone from the gland under these conditions.

In summary there is increased proteolytic activity during periods of increased activation of the thyroid gland, as during early treatment of the rat with potassium iodide and after the injection of the rat and guinea pig with thyrotropic pituitary factor. There is a decreased proteolytic activity during periods of decreased activation of the thyroid, as during treatment of the rat with sulfaguanidine after hypophysectomy and in later stages of treatment with potassium iodide. These results confirm the work of De Robertis and suggest that the proteolytic enzyme cathepsin is concerned with the breakdown of the thyroglobulin into units small enough to pass through the cell membranes into the blood stream.

#### SUMMARY

1. After treatment of rats with thyrotropic pituitary factor, the thyroid tissue of such rats showed a proteolytic activity for the first 48 hours after treatment that was greater than that of normal rats. Guinea pig thyroid tissue also showed an increase over normal of proteolytic activity under these conditions.
2. Feeding of potassium iodide to rats for periods up to 16 days caused an increase over normal of the proteolytic activity of the thyroid tissue. After 38 days of KI feeding the thyroid proteolytic activity was normal or somewhat below normal.
3. Feeding of sulfaguanidine to rats caused a decrease in the proteolytic activity of the thyroid tissue.
4. Hypophysectomy of rats caused a decrease in the thyroid tissue proteolytic activity.

The author is grateful for the advice and help of Dr. I. Gersh in the course of this work.

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HYPOFUNCTION OF THE THYROID GLAND,  
DUE TO PROLONGED AND EXCESSIVE INTAKE OF  
POTASSIUM IODIDE

By

*Harald Frey*

ABSTRACT

Five patients are reported, who developed various degrees of thyroid hypofunction and/or goitre while taking iodide-containing mixtures for bronchial asthma. After stopping the iodide treatment, their thyroid condition returned to normal.

The clinical features of the condition are described. Particular attention has been paid to the factors responsible for the development of thyroid hypofunction. Most important among these was the prolonged, regular and high intake of iodides.

It is concluded that patients using iodide-containing medication should interrupt the intake for 2-4 weeks at a time, several times a year.

The mechanism by which iodine depresses the function of the thyroid gland is discussed.

Iodine, the indispensable element for thyroid hormone production, may under certain circumstances exert the paradoxical effect of inhibiting this process. It is well known that even minute doses of iodine seriously hamper the activity of the gland in Graves' disease (*Plummer 1923; Childs et al. 1950*).

There is also evidence that iodine also exerts an inhibitory effect on thyroid hormone production in normal glands. Large doses of iodine interfere with the organic binding of the element both in the human (*Stanley 1949*) and in the rat thyroid. However, in spite of continued high blood levels of iodide, escape from the inhibition occurs after 1-2 days (*Wolff et al. 1949*). Continuous consumption of iodine has therefore generally been considered not harmful to the

healthy thyroid. This, however, is not entirely true. Prolonged ingestion of iodine in rather large doses may lead to the development of goitre and even myxoedema.

The purpose of the present paper is:

1. to draw attention to a condition that is not very well known, in spite of more than 50 recorded cases in the literature (none of which from Scandinavia). It is our belief that the condition is more common than previously thought. The reasons for this are:

a. it is not diagnosed as such,

b. it is possible that the development of iodine myxoedema, under certain circumstances to be described, is the rule rather than the exception.

2. to contribute to the clinical description of the syndrome, which has so far seen presented in short case reports, only 5 authors presenting more than 3 cases.

3. to comment on certain biochemical findings that have so far received scant attention, and in this connection comment on the mechanism and nature of the inhibitory effect.

## METHODS

Serum cholesterol was determined by the method of *Carr & Dreker* (1956). Butanol extractable iodine in serum (BEI) was determined by the method of *Kontaxis & Pickering* (1958). Protein-bound iodine in serum (PBI) was determined by the method of *Foss et al.* (1960). With this method, iodinated tyrosines contribute to the PBI value when the proteins are precipitated with  $Zn(OH)_2$ . The following experiment was performed by Dr. O. P. Foss in order to see whether this is the case when the proteins are precipitated with trichloroacetic acid (TCA):

Mono-iodotyrosine (MIT) and di-iodotyrosine (DIT) were dissolved in 0.01 N NaOH and diluted with distilled water until a final concentration of approximately 1  $\mu g$  iodine/ml was reached. Mixtures of these solutions and serum from a serum pool were prepared as follows:

Sample	Amount	$\mu g$ organic iodine/ml	$\mu g$ organic iodine/11 ml of sample	$\mu g/100$ ml organic iodine in sample
Serum	10 ml	0.064		
+ MIT	1 ml	0.99	1.63	14.8
Serum	10 ml	0.064		
+ DIT	1 ml	0.98	1.62	14.7

PBI was estimated after precipitation of the proteins by  $Zn(OH)_2$  or TCA. All determinations were carried out in duplicate. The PBI value of the serum pool was established by 10 separate determinations, using precipitation with  $Zn(OH)_2$ .

Sample	$\mu\text{g}/100 \text{ ml PBI}$ after precipitation with		$\mu\text{g}/100 \text{ ml}$ organic iodine in the sample
	$\text{Zn}(\text{OH})_2$	TCA	
Serum + MIT	12.0	6.3	14.8
Serum + DIT	13.0	6.2	14.7
Serum	6.0	6.4	6.4

It was concluded that precipitation with  $\text{Zn}(\text{OH})_2$  includes MIT and DIT in the PBI value, while this is not the case when precipitation is done with TCA.

The serum from patients was treated with ion exchange resin before precipitation.

#### CASE REPORTS,

No. 1, A. U., male aged 72 years. He had suffered from chronic asthmatic bronchitis for 20 years, and for the last 10 years had been continually taking an expectorant mixture containing potassium iodide (KI). The yearly intake of KI was calculated to be more than 500 g. He had no known thyroid disease, or serious contributory illness. On examination in 1957 he was euthyroid.

In March 1962 he was clinically euthyroid, but the thyroid gland was slightly en-



Fig. 1.

Thyroid histology in patient A. U. Showing »more or less dilated alveoli lined by a cuboidal epithelium, which in many arcs proliferates into the lumen. The colloid is pale with marked vacuolisation. Thyroid tissue with thyrotoxic changes.«

(Lciv Kreyberg, sign.) Magnification  $\times 192$ .

larged. Serum cholesterol was 237 mg/100 ml. Basal metabolic rate (BMR) 104%, and serum PBI 14.8  $\mu$ g/100 ml.

In June 1962 his thyroid gland had increased in size.

In October 1962 he was admitted to the hospital because of increasing dyspnea. He complained of cold intolerance, spending his day in bed fully dressed, and had stools once a week. On examination he appeared severely myxoedematous with typical changes in skin, voice and tendon reflexes. The thyroid was greatly enlarged, and was estimated to weigh about 80 g. It was soft, with a regular surface and no nodules. The BMR was 77% and 63% on two separate occasions. In addition there was slight cardiac decompensation and evidence of a long-standing bronchial disease.

Thyroid biopsy showed parenchymatous hyperplasia (Fig. 1). Results of determinations of serum cholesterol, PBI, BEI and thyroid uptake of  $^{131}$ I before and after stopping the KI medication are shown in the graphs (Figs. 2, 3, 4, 5). The PBI determination was carried out after ion exchange, and precipitation was done both with  $Zn(OH)_2$  and TCA with almost identical results. Total iodine in the serum was over 100  $\mu$ g/100 ml and fell to 15  $\mu$ g/100 ml after 3 weeks. The iodine determinations were carried out by Dr. Liv Theodorsen.

*Course after stopping KI.* Within one month the patient's ptosis disappeared and the reflexes became normal, but his voice was still hoarse and he still had a goitre. After

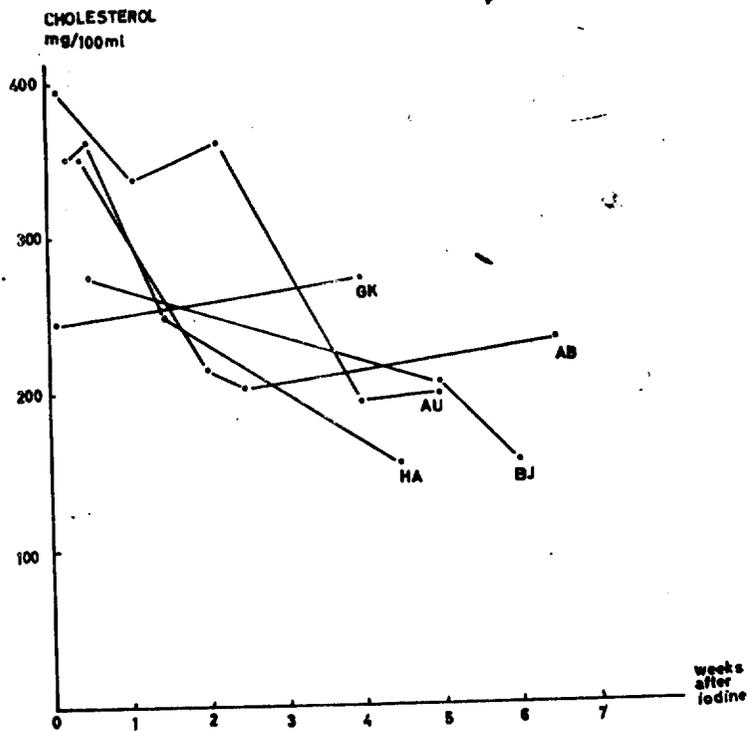


Fig. 2.

Serum cholesterol of patients with iodine hypothyroidism after stopping iodine.

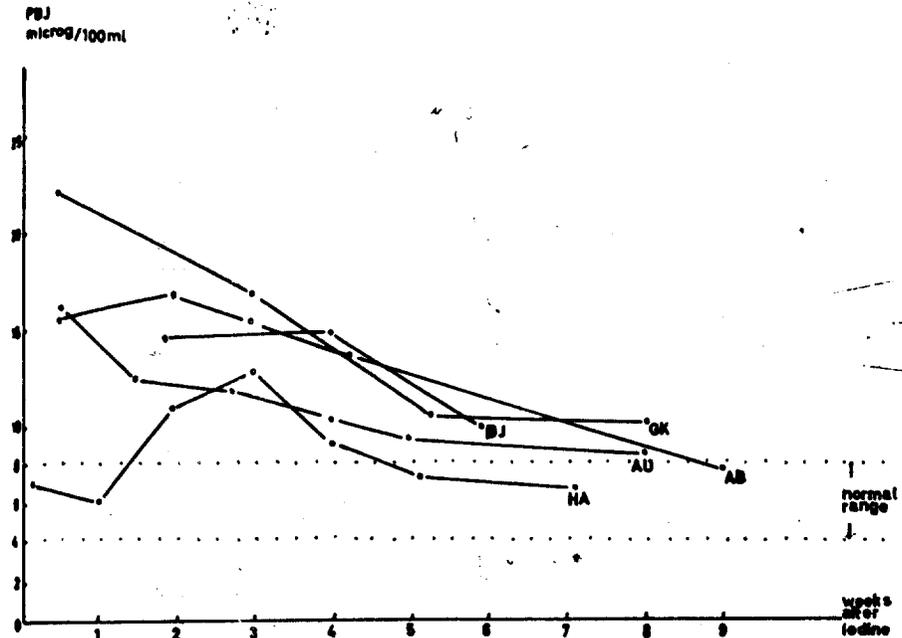


Fig. 3.

Serum protein-bound iodine of patients with iodine hypothyroidism after stopping iodine.

two months he was clinically euthyroid, had lost 5.5 kg in weight, and the thyroid was normal in size and consistency. The BMR increased to 90 and 96%. After seven months he had lost 7.5 kg in weight, the thyroid was normal and the patient euthyroid. Withdrawal of iodide caused no deterioration of his asthma. Serum cholesterol was 221 mg/100 ml and BEI 5.1  $\mu\text{g}/100\text{ ml}$ . With the gradual disappearance of the myxoedema, his bronchial asthma and cardiac condition improved considerably. He stated that he felt «better than ever».

No. 2. B. J., male aged 43 years. He had had asthma since childhood, and for the last 15-20 years chronic asthmatic bronchitis with continual distress. For 15 years he had been taking iodine-containing expectorants every day, with a yearly consumption of KI in excess of 300 g, and possibly 500 g. He had had no thyroid disorder, nor any contributory disease.

In 1957 nothing was said about his thyroid condition.

In September 1962 he complained of loss of energy, loss of libido, loss of hair, swollen legs and constipation. He appeared hypothyroid with hoarseness and typical changes in the skin and hair. The thyroid was enlarged and estimated to weigh about 49 g, with irregular surface, but no distinct nodules. The ECG showed flat T-waves. In addition there was evidence of bronchitis and emphysema. The BMR was 94 and 96%. Thyroid biopsy showed parenchymatous hyperplasia (Fig. 6).

Results of laboratory studies before and after stopping KI are shown in Figs. 2-5.

Course after stopping KI. Within 6 weeks he had lost 7.5 kg in weight and the BMR

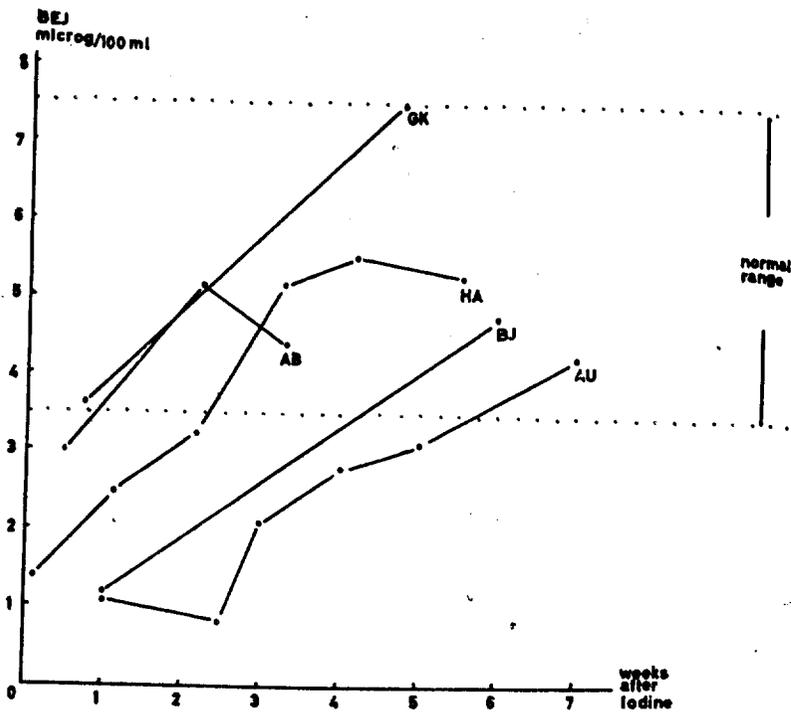


Fig. 4.  
Serum butanol-extractable iodine of patients with iodine hypothyroidism after stopping iodine.

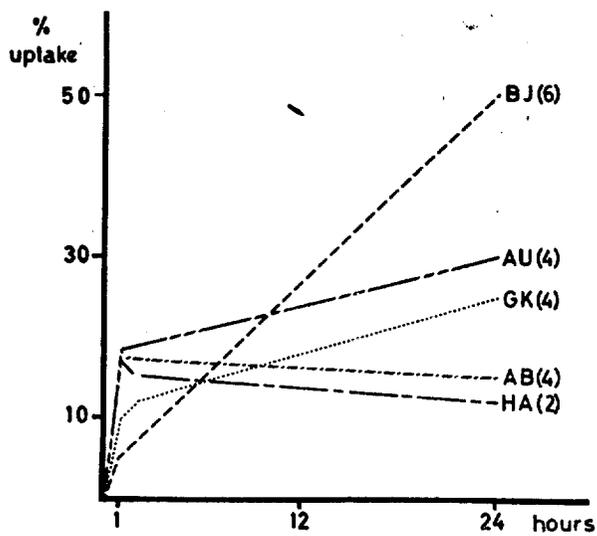


Fig. 5.  
Thyroid uptake of  $^{131}\text{I}$  in patients with iodine hypothyroidism. Figures in brackets indicate number of days after stopping iodine.



*Fig. 6.*

Thyroid histology in pat. B. J. Showing «more or less dilated alveoli lined by a low cuboidal epithelium, which in a few areas is higher and proliferating into the gland lumen. The colloid is rather evenly stained with slight peripheral vacuolization. Thyroid tissue with slight thyreotoxic changes.» (Leiv Kreyberg, sign.)

Magnification  $\times 192$ .

increased to 106 and 119 %. The goitre disappeared. He felt keener, was able to walk without stumbling, and the stools became normal. The skin became softer, and a new crop of soft hairs appeared on the lower arms. The T-waves became higher. As his thyroid condition improved, his asthma improved proportionally. *Five months* later he was euthyroid, had lost altogether 12 kg in weight and had a normal thyroid gland. The BEI was  $5.3 \mu\text{g}/100 \text{ ml}$  and the serum cholesterol  $240 \text{ mg}/100 \text{ ml}$ . At this time the patient requested reinstatement of iodide because of increasing asthmatic distress. The dose was 1 g daily. After 3.5 months on iodides he again experienced cold intolerance and constipation. He appeared mildly hypothyroid and had gained 3.5 kg. The thyroid was normal. BEI was  $2.3 \mu\text{g}/100 \text{ ml}$  (below normal) and serum cholesterol  $284 \text{ mg}/100 \text{ ml}$ . It was apparent that he was sliding back into overt hypothyroidism.

*No. 3, A. B., male aged 56 years.* Asthmatic bronchitis for 30 years. For the last 10 years continual use of iodide-containing mixture, with a calculated yearly consumption of more than 500 g KI. In addition he suffered from cardiac failure of moderate degree, ascribed to previous myocardial infarction and to his bronchial disease.

On examination in 1957, -58 and -59 nothing was said about his thyroid condition. In *November 1962* he complained of troublesome constipation, hoarseness and puffiness of the face. Physical examination revealed a heavy-set subject with signs of chronic bronchitis and emphysema. He appeared slow, had marked hoarseness, oedema of the eyelids and ptosis. The reflex return was slow. His thyroid was enlarged and estimated at 40 g, with a slightly nodular surface. In addition mild cardiac failure was found, and pyuria attributed to chronic prostatitis. Determination of the BMR was not found to be practicable because of dyspnoea.

Results of laboratory studies before and after stopping KI are shown in Figs. 2-5. Total serum iodine was more than  $100 \mu\text{g}/100 \text{ ml}$ .

*Course after stopping KI.* After *one month* he appeared euthyroid, and this condition was maintained. After *two months* his thyroid was no longer palpable, although

scintigram showed the gland to be still enlarged, but smaller than before. The uptake of  $^{131}\text{I}$  was normal.

At this point the patient asked for reinstatement of iodides, and medication was started in the same doses as before, under close supervision. During the ensuing 4 months he appeared to get along well. Control of BEI showed 7.9  $\mu\text{g}/100$  ml (high normal) and serum cholesterol was 265 mg/100 ml. After 4 months on iodides he again started to complain of facial puffiness, constipation, cold intolerance and depression. Clinically he was mildly hypothyroid. The BEI had fallen to 5.0  $\mu\text{g}/100$  ml. and the serum cholesterol had risen to 357 mg/100 ml. Because he felt he could not get along without iodides, he was started on Na-l-thyroxine 0.2 mg daily.

He continued treatment with iodides and thyroxine for three months. His condition again improved, and he soon became euthyroid. BEI was 6.3  $\mu\text{g}/100$  ml and serum cholesterol 287 mg/100 ml. The PBI, however, was still high, 21  $\mu\text{g}/100$  ml.

**No. 4, H. A., male aged 72 years.** Asthmatic bronchitis for 12 years. For the last 10 years he had been taking KI every day, with a yearly consumption in excess of 500 g. In addition he was suffering from polyneuropathy of the lower extremities of unknown aetiology. He had never before shown any evidence of thyroid disease.

In 1958 and -59 nothing was said about his thyroid condition.

In *June 1961* he was clinically hypothyroid, with typical skin and reflex changes. No definite goitre was found. Serum cholesterol was 455 mg/100 ml. BEI was 2.5  $\mu\text{g}/100$  ml and PBI 14.8  $\mu\text{g}/100$  ml. He weighed 65 kg.

KI was stopped, since iodide interfered with the thyroid function studies, but was not at that time held responsible for his hypothyroidism. In *September 1961*, still with no iodides, he was euthyroid with brisk reflexes and normal skin. His thyroid was probably normal. He weighed 60 kg. Serum cholesterol was 253  $\mu\text{g}/100$  ml, BEI 5.2  $\mu\text{g}/100$  ml and PBI 9.2  $\mu\text{g}/100$  ml. Thyroid uptake of  $^{131}\text{I}$  was normal. - Because the causal role of iodides in the production of his symptoms was still not recognized, he was again started on massive doses of KI, in *January 1962*. Before this, in *October 1961*, he had a slight myocardial infarction and later developed heart failure.

In *October 1962* he was seen again and found to have progressive heart failure and flourishing myxoedema. He spent his day dozing in a chair by the stove and was very constipated. His thyroid was still hard to palpate and no definite goitre was found. He had palpebral and ankle oedema, but had normal reflex return and no ptosis, in contrast to the findings in June 1961. (This changing picture of myxoedema in the same patient is very interesting). He weighed 65 kg, and treatment with KI was stopped for good.

The results of the laboratory studies before and after stopping iodides are shown in Figs. 2-5.

The results of the PBI determination was the same both with  $\text{Zn}(\text{OH})_2$  and TCA-precipitation. Total serum iodine fell from 42  $\mu\text{g}/100$  ml to 11  $\mu\text{g}/100$  ml in one week. - Thyrotrophin stimulation did not change the pattern of the  $^{131}\text{I}$  uptake. Thiocyanate administration one hour after the tracer dose was given, resulted in a fall of uptake from 7.6% of the dose at one hour, to 0 at two hours.

*Course after stopping KI.* Within 6 weeks he became euthyroid and lost 10 kg in weight. His bronchial and cardiac condition improved. After 7 months he was seen again; he was euthyroid and weighed 56 kg. No goitre was found. Serum cholesterol was 257 mg/100 ml and BEI 5.7  $\mu\text{g}/100$  ml. His heart and lungs were in a better condition than they had been for a very long time.

No. 5. G. K., female aged 56 years. She had suffered from asthma for more than 20 years. For the last 6-7 years she had been taking iodide-containing expectorants every day, and her yearly consumption amounted to 300 g KI. During the last 4 months before admission she had taken 200 g because of increasing respiratory distress. She had previously not had any known thyroid abnormality, and suffered from no important contributory disease.

In April 1962 she appeared euthyroid and had no complaints except about her asthma. The important finding was an enlarged thyroid gland, estimated to weigh 40 g and firm. Suspecting that her goitre might have been caused by iodides, KI was withdrawn. Figs. 2-5 show the laboratory findings before and after stopping KI. Total serum iodide was 30  $\mu\text{g}/100$  ml.

*Course after stopping KI.* The goitre disappeared within two months, and the gland attained a normal consistency. The patient was last seen 4.5 months after KI was stopped. At that time she was euthyroid and had a thyroid gland that was normal to palpate. Her asthma was unchanged, but she did not miss the iodides.

## DISCUSSION

There appears to be little doubt that the iodine intake was the direct cause of the goitre and/or hypothyroidism in all cases. After stopping iodine intake, manifestations of goitre and hypothyroidism reverted completely to normal within 1-2 months, followed by a short period of slight thyroid hyperactivity, after which the gland returned to normal, leaving no signs of thyroid abnormality. Reinstitution of iodides produced a relapse of symptoms whenever this was tried. The clinical course is in agreement with that reported in the literature.

Particular clinical features of the syndrome deserve more detailed consideration:

The hypothyroidism develops gradually. This feature is well demonstrated in patient A. U., who was examined three times within 7 months. The initial sign was goitre, and later hypothyroidism developed. It apparently takes several months for myxoedema to develop, and during this period various clinical conditions, from goitre via mild hypothyroidism, may be observed. It is also interesting to note how long it takes for the inhibitory effect to become evident. Four of our patients had been followed for years while using KI, and had shown no signs of thyroid inhibition. The above clinical features point to the conclusion that we are concerned with some kind of exhaustion reaction from the thyroid, in response to high and prolonged iodine administration.

The situation seems to be different once thyroid inhibition has been manifest. On reinstitution of iodides, it now takes only a few weeks or months before signs of hypothyroidism are evident, whereas the same patient previously had been able to tolerate iodide loads for years without any ill effect. Both H. A., A. B. and B. J. demonstrate this point clearly. Previous episodes thus

seem to condition the gland to the inhibitory effect of iodides. The phenomena here called »exhaustion« and »conditioning« have not previously been commented upon in the literature, although Nixon (1957) reports a case with four episodes of iodine myxoedema in 5 years.

The size of the thyroid gland varied considerably in our patients and bore no relationship to the severity of the hypothyroidism. Thus G. K. had a goitre with only borderling hypothyroidism, while H. A. had myxoedema with no goitre. The goitre was usually small, in only one case larger than 50 g. It usually had a firm consistency with a somewhat irregular surface, but no distinct nodules. In A. U. it was larger and softer. This erratic nature of the goitre was also noted by Morgans & Trotter (1953), who in one patient found a gland similar to the one usually found in Hashimoto's thyroiditis, and in another no palpable gland at all, while both patients had clinical and biochemical evidence of hypothyroidism. In the case of Dimitriadou & Fraser (1961) the goitre weighed 160 g, and the infants described by Martin & Renton (1962) also had large goitres. In the majority of cases reported, however, the goitre has been of moderate size. The palpation of the gland thus seems to give little information of diagnostic significance.

It has been very satisfactory to observe the beneficial effect on the cardio-respiratory condition of several of our patients as they reached a euthyroid state. This contrasts with the finding of Burrows *et al.* (1960) in one patient and it represents an interesting comment on the widely-accepted treatment of patients with chronic cardiorespiratory failure with radioiodine in order to make them hypothyroid.

#### *Conditions for the syndrome to develop.*

First of all, the syndrome may develop in normal thyroid glands. None of our patients had had thyroid disorders previously, nor did this develop subsequently during the period of observation. It is evident from the literature however, that the syndrome has been described several times in patients with pre-existing thyroid disorders. Bell (1953) was the first to report the syndrome in patients with normal glands. According to Oppenheimer & McPherson (1961), 23 cases with previously normal thyroids had been reported to that time, and the majority of cases reported later had normal glands. Pre-existing thyroid disease was found by some authors (Caplin *et al.* 1961; Dimitriadou & Fraser 1961; Hydovitz & Rose 1956; Laroche & Hirsch 1960; Lukens 1961; Vanderlaan 1956). In conclusion it may be said, that in the majority of cases, the syndrome has developed in previously normal thyroid glands.

In this connection it should be mentioned that the presence of asthma does not seem to be a prerequisite for the syndrome to develop (Martin & Renton 1962; Mornex *et al.* 1960).

The nature of the ingested iodine does not seem to be of importance. Bron

*Table 1.*  
Consumption of KI by 100 asthmatic patients.

Grams KI per year	Number of patients
0 or negligible	58
less than 50	13
50-100	6
100-200	9
200-300	5
300-400	3
400-500	6

chography (*Mornex et al.* 1960) may be the cause, as may Felsol, a combined preparation containing 30 mg of iodopyrin per dose. There is reason to believe that the effect of Felsol on the thyroid gland is a pure iodide effect (*Brownstone & Pitt-Rivers* 1959). In the great majority of cases inorganic KI was the causative agent.

The dose of iodine ingested and the period of administration need closer scrutiny. Our patients were all taking large amounts of KI, and they were taking it every day over a period of years.

In order to get an impression of the pattern of iodine consumption in Akershus county, 100 consecutive cases of asthma or chronic bronchitis as their main or contributory diagnosis were interviewed and examined by the author. The 5 cases reported were included in this group. The age of the patients varied from less than one year to 75 years, and the duration of their disease from acute cases up to 50 years. Only 10 of the patients had had their asthma for less than one year.

Table 1 shows the amounts of iodine ingested. Only 9 patients had been taking more than 300 g of KI per year.

Equally important is the question of regularity of consumption. Of the 100 patients, 90 were taking their medicine intermittently, with intervals of one to several weeks, often many times a year. Only 10 patients were taking it continually, every day the whole year round. Four of these patients used very small doses, mostly in the form of Felsol.

Only 6 patients belonged to both groups, i. e. they were using large doses without interruption. All the 5 patients with iodine hypothyroidism described above were among these 6!

Similar information regarding regularity, dose and time are very scanty in

the literature. Two authors (Folliors 1960; Rubinstein & Oliver 1957) have the impression that most asthmatics take their medicine intermittently. The necessary doses, according to reported cases, are in most instances large, but doses as small as 150 mg iodopyrin daily have been reported as being capable of causing the condition (Ezrin *et al.* 1961; Morgans & Trotter 1959). As for the time necessary for the syndrome to become evident, the quoted figures are usually smaller than in the present material, from 6 months (Toguchi & Skillman 1960) up to several years. Many authors (Mornex *et al.* 1960; Oppenheimer & McPherson 1961; Rubinstein & Oliver 1957; Toguchi & Skillman 1960) have found large iodine intake by the patients, and according to Oppenheimer & McPherson (1961) only 3 out of 23 cases reviewed had been using iodine for less than one year.

In conclusion, it can be said that in the majority of cases high and prolonged exposure to iodine has been encountered, although there are exceptions to this rule, even in patients with no evidence of pre-existing thyroid disorders. The inhibitory effect of iodine can therefore be regarded as an unpredictable event in a few cases, namely those who have been using iodine for only some months and in moderately large doses. To expect and prevent this development in such patients is at the present time outside our ability. On the other hand, our own experience, supported by a body of evidence from the literature, leads us to believe that *high and prolonged exposure to iodine carries a considerable risk of developing iodine goitre and hypothyroidism*. The practical consequence of this must be that these patients stop iodine medication for 2-4 weeks several times a year, starting from the time they begin this form of treatment.

In accordance with the above view, we believe that the syndrome of iodine inhibition of the thyroid gland is rare only because marked and prolonged exposure to iodine is rare.

#### *The mechanism of iodine inhibition.*

Theoretically, iodine might be able to interfere at all stages in the thyroidal iodine cycle, from the trapping of iodide to the release of hormone. Iodine has been found to slow hormone release in thyrotoxic patients, and in subjects made hyperthyroid by exogenous thyrotrophin, but not in normal subjects (Greer & deGroot 1956; Solomon 1956). On the other hand, even in normal glands iodine is able to interfere with the hormone synthesis, as mentioned in the introduction. It is therefore not surprising that study of patients with iodine myxoedema has demonstrated a major defect in hormone synthesis. More specifically, the organic binding of iodine is hampered to a very high degree. Iodine is trapped by the gland, but further binding does not take place or happens on a very limited scale, as demonstrated by autoradiography and thiocyanate block (Paley *et al.* 1958; Paris *et al.* 1960).

The shape of the uptake curve may also point to the presence of an undisturbed iodide trapping mechanism in the presence of diminished organic binding: a high initial uptake which later falls slowly and proportionally to the disappearance of iodide from other tissues in the body (*Paris et al.* 1960). This feature was demonstrated by our patients H. A. and A. B., but not found in the others. The explanation is that the shape of the curve depends on the time that has passed since inhibition has ceased. With time, it approaches normal (Fig. 5). The shape of the uptake curve is not therefore of any diagnostic significance without knowledge of the time factor. More informative is the finding of relatively high initial uptake values (1 and 2 hours) in the presence of a greatly expanded extrathyroidal iodide pool. This points to an enormous extraction of stable iodide from the blood into the thyroid gland (*Paley et al.* 1958; *Toguchi & Skillman* 1960), and is due to compensatory thyrotrophin stimulation. The same pituitary secretions are responsible for the goitre, and would produce the histological picture of a hyperactive gland. This was also found in two of our patients in whom biopsy was performed, and in most of the cases reported by others (*Mornex et al.* 1960; *Paley et al.* 1958; *Paris et al.* 1960; *Toguchi & Skillman* 1960; *Turner & Howard* 1956). Colloid goitre has been found (*Burrows et al.* 1960) but may represent a pre-existing disorder. The above evidence of pituitary hyperactivity does not support an inhibitory action of iodide on the pituitary gland itself.

#### *The elevation of the PBI.*

All patients with iodine myxoedema have elevated values of PBI in the presence of low values of BEI, pointing to the presence of some iodinated substance in the blood that is not hormonally active. It is well known from the work of *Danowski et al.* (1950) that massive doses of iodide increase the PBI, irrespective of the effect on the thyroid gland itself. The cause of this »Danowskiefect« is still not clear (*Danowski*, 1963, personal communication).

In order to study the PBI in euthyroid asthmatic patients receiving comparable doses of KI, serial determinations were done after stopping the iodine medication (Fig. 7). In all patients there was an increase in PBI of the same order as in patients with iodine myxoedema, and this increase persisted for a similar period of time. KI was also given to one patient with primary myxoedema and an initial PBI-value of 1.5  $\mu\text{g}/100$  ml. This patient also had a greatly increased PBI, without any change in his thyroid condition (Fig. 7).

The findings indicate, that an increase in PBI is a uniform feature in subjects using iodide in comparatively large doses, and is thus not confined to patients who develop myxoedema or goitre; and further, that this increase may also take place in subjects with very inactive thyroid glands (primary myxoedema).

Although an increase in the PBI may be caused by the same mechanism in

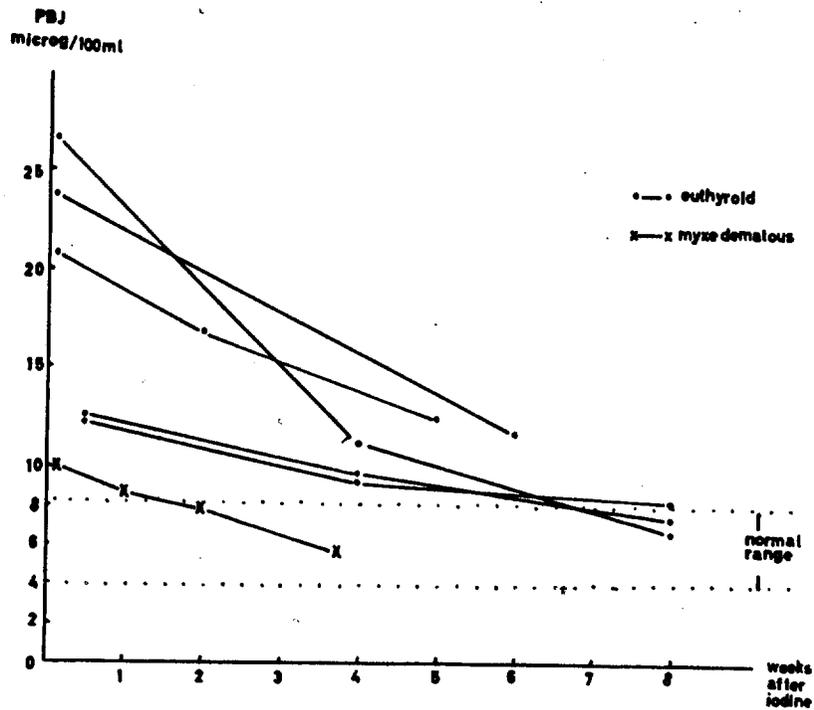


Fig. 7.

Serum protein-bound iodine of 5 euthyroid patients with asthma and 1 patient with primary myxoedema after stopping iodine, which had been given for several weeks in a dose of 1.5 g KI daily.

iodine myxoedema as in euthyroid subjects, other possibilities cannot be excluded. If the block in hormone synthesis caused by iodine is not complete, which is certainly the case as this would be incompatible with life, some iodine would be available throughout the cycle, giving rise to more or less normal products of the thyroid gland. Thus *Paley et al.* (1958) in their careful study calculated that in the presence of a greatly enlarged thyroidal iodine pool, as found in the syndrome, as little as 0.1 % of the iodine in the gland would be necessary to secure a normal production of thyroid hormone. A »leak« of this small magnitude would be very difficult to detect with our present tools.

The present material may shed some light on the question whether the iodine-inhibited gland in addition to small amounts of hormones also produces other products that may increase the PBI. Thus the biochemical findings in H. A. and A. U. tend to exclude iodotyrosines as the cause of the PBI elevation, since the values were the same both with  $Zn(OH)_2$ - and TCA-precipitation. Furthermore, the results of the thyroxine medication in patient A. B. indicate that whatever the nature of the substance that elevate the PBI, it is

not dependent on pituitary stimulation, as it was still present in large amounts during pituitary suppression with exogenous thyroxine.

In conclusion: the chemical composition of the substance responsible for the elevation of the PBI in this syndrome still awaits clarification, as does its eventual role in the pathogenesis. Our own results are all compatible with the view that it may be due to extrathyroidal iodination of serum proteins.

#### *Final remarks.*

We know that some subjects under certain circumstances develop iodine myxoedema. We also partly know how, but not why this happens. The factors governing the fate of the gland working under heavy iodine loads are poorly understood. Increased sensitivity to iodine in susceptible subjects has been demonstrated (*Paris et al.* 1960), but not confirmed (*Dimitriadou & Fraser*, 1961). Some evidence points to the possibility that the compensatory thyrotrophin stimulation, elicited by decreasing amounts of circulating thyroid hormone, may render the gland more sensitive to the inhibitory effect of iodine, thus setting up a vicious circle (*Childs et al.* 1950; *Paley et al.* 1958; *Stanley* 1949).

Future investigations should prove (or disprove) the contention that high and prolonged intake of iodine usually leads to thyroid hypofunction, and throw further light on the intrathyroidal mechanisms operating under these conditions.

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THE EFFECT OF IODINE ON PHAGOCYTOSIS OF LEUKOCYTES IN GUINEA PIGS

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Our studies, conducted on living systems in frogs, have revealed those quantities of iodine in which it enters the systems as a trace element (a biotic factor). In these experiments the effect of different amounts of iodine (in a potassium iodide base) was examined, beginning with the smallest amounts in which it entered the organism or the environment, up to toxic amounts. The study method presented permits verification of the boundary between its toxicopharmacologic action and its effect as a trace element on the organism.

The indicated demarcation between biotic doses and toxicopharmacologic ones was traced during investigations of the work capacity of isolated mice and in experiments with phagocytosis during supplement of differing amounts of iodide salt in water in which frogs were found (Gerasimova, 1960, 1961). The experiments on phagocytosis indicated that the effect of increasing leukocyte activity could be observed with large concentrations of potassium iodide (200 mg %) as well as with very small concentrations (0.003-0.125 mg %). The concentration intermediate between these - 5 mg % potassium iodide - barely altered phagocytosis strength ("inactive zone"). The increase in phagocytosis strength under the influence of potassium iodide at 0.125 and 0.003 mg % may be considered as a manifestation of iodine activity as a trace element (biotic factor). Solutions of potassium iodide at 200 mg % behave mainly as a toxicopharmacologic agent.

It is evident, as our latest experiments have indicated, that during prolonged activity (12-15 days), potassium iodide solutions at 0.125 and 0.003 mg % have the effect of increasing phagocytosis strength. A 200 mg % solution of potassium iodide decreases the phagocytosis of leukocytes, which is characteristic of the action of general, relatively large doses of toxicopharmacologic agents (the transition of a stimulating effect to a depressing effect during prolonged use of the given agent).

The main area of interest is the "inactive zone" which we observed and which is the transition boundary between the action of small quantities of iodine as a trace element and its effect in large doses on the organism as a general toxicopharmacologic agent. The "activity zoning" of trace elements may be considered a phenomenon of an organism's barrier function (Venchikov et al., 1947; Cherkasova, 1952; Venchikov, 1962).

It is necessary to make clear whether the "activity zoning" of iodine" is observed in warm-blooded animals during studies of phagocytosis occurrence.

Method. The experiments were conducted on guinea pigs under the same conditions for experimental and control groups. Iodine (in the form of aqueous solutions of potassium iodide) was given to the experimental animals daily per os in 1 gamma/kg, 40 gamma/kg, or 1600 gamma/kg quantities each. Water was given to the control animals. Thirty guinea pigs were studied in all, divided into three groups. Phagocytosis of leukocytes was determined according to the method of V. A. Almazov and S. I. Ryabov (1963) up to the administration of potassium iodide and then 5 and 15 days after the daily dose. The data obtained were analyzed using variational statistics.

Experimental data. After giving the guinea pigs a 5-day dose from the 1 gamma/kg, 40 gamma/kg, and 16000 gamma/kg quantities, phagocytosis occurred as follows. Under the effect of the large doses (1600 gamma/kg), a 58.3% decrease in phagocytosis was noted ( $M$  (mean) = 24.6,  $m$  (mode) = + or - 5.69, sigma (standard deviation) = 17.07,  $td_{\lambda}$  = 3.89), taking the original amount conditionally at 100 % ( $M$  = 59.3,  $m$  = + or - 3.12, sigma = + or - 9.97). Administration of small doses (1 gamma/kg) evoked an increase in phagocytosis of the leukocytes ( $M$  = 100.5,  $m$  = + or - 3.12, sigma = 22.69,  $td$  = 5.3). An absence of any effect was noted for the 40 gamma/kg sample (variational statistical indices of the original amount of phagocytosis:  $M$  = 64.5,  $m$  = + or - 7.3, sigma = + or - 20.86). After giving the indicated dose of iodine,  $M$  = 61,  $m$  = + or - 4.37, sigma = + or - 13.11,  $td$  = 0.4 (Fig, 1).

As is evident from the data presented, a 40 gamma/kg dose appeared "inactive". In order to verify its "inactivity", we studied the phagocytosis of leukocytes during more lengthy application (15 days) of the indicated iodine dose. The results of these observations showed the absence of a variational statistically significant effect of the quantities of iodine used. The difference between the control ( $M$  = 64.5,  $m$  = + or - 7.3, sigma = + or - 20.86) and the experimental groups ( $M$  = 63.7,  $m$  = + or - 6.6, sigma = + or - 20.7) yielded  $td$  = 0.08.

The presence of a "zone of inactivity" permitted the consideration that iodine, applied in 1 gamma/kg doses, gives rise to a stimulative action on phagocytosis as a trace element (biotic agent). There exist data in the literature which show that under normal conditions, the human organism needs iodine in quantities of about 1 gamma/kg or somewhat more per day (Voynar,

1953).

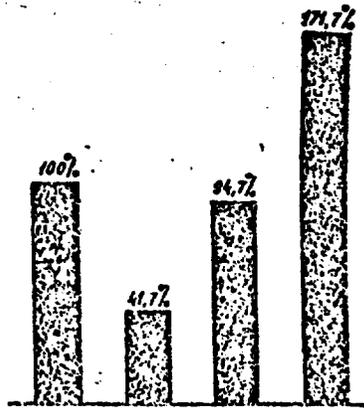


Рис. 1. Изменение фагоцитарной активности лейкоцитов морских свинок под влиянием различных доз йодистого калия.

1. Исходная величина фагоцитарной активности лейкоцитов, принятая за 100%.
2. Фагоцитарная активность лейкоцитов через 5 дней после ежедневной дачи per os йодистого калия из расчета на дозу 1600  $\gamma$ /кг веса.  $t_d = 3.89$ .
3. То же, но доза 40  $\gamma$ /кг.  $t_d = 0.4$ .
4. То же, но доза 1  $\gamma$ /кг.  $t_d = 5.3$ .

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Fig. 1. Variation in phagocytosis of leukocytes in guinea pigs under the influence of different doses of potassium iodide

1. Original amount of leukocyte phagocytosis, taken as 100 %
  2. Phagocytosis of leukocytes over 5 days, after daily doses per os of potassium iodide, 1600 gamma/kg weight of iodine,  $t_d = 3.89$
  3. The same, for 40 gamma/kg iodine,  $t_d = 0.4$
  4. The same, for 1 gamma/kg iodine,  $t_d = 5.3$
- 

If the amounts indicated are transformed for guinea pigs, a sufficient introduction of 1 gamma/kg, naturally, is required to show what we observed in our experiments. The absence of any effect from higher dosages (40 gamma/kg) indicates the presence

of general mechanisms which inhibit the entry of trace elements into the organism (physiological barriers). But just as a regulatory function has a limit, so it is necessary to suppose that in the application of large doses, an opposite transformation occurs in the protective function of the barriers, a penetration of the agent administered to the internal systems of the organism and the onset of a corresponding effect.

Questions of the correctly selected doses have a significant significance in the successful application of trace elements in animal husbandry and medicine as biotic factors.

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THE EFFECT OF THE ORAL ADMINISTRATION OF POTASSIUM IODIDE AND THYROID SUBSTANCE ON THE MITOTIC PROLIFERATION AND STRUCTURE OF ACINI IN THE THYROID GLAND IN GUINEA PIGS\*

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In previous papers Loeb has shown that, contrary to the current view, which is that administration of iodine prevents compensatory hypertrophy, this substance does not exert an inhibiting effect, and it may even increase the hypertrophy. Thus Loeb observed in a very extensive series of experiments that the average of hypertrophy was greater in the iodine-fed than in the control animals.<sup>1,2</sup> This finding suggests that the primary effect of iodine on the thyroid gland is stimulating and that when a depressing effect is noticed, it is of a secondary nature; this conclusion applies to the normal thyroid. It appears that if during development of the organism there is a lack of iodine, this lack may also cause proliferation of the thyroid gland and a goitre develops. This proliferation can be prevented through administration of very small amounts of iodine. In certain cases the proliferation which has already begun can even be stopped through administration of iodine. On the other hand, in some instances, administration of iodine to goitrous individuals exerts a stimulating effect, causing proliferative processes and the appearance of toxic symptoms. Loeb concluded therefore that the thyroid tissue may respond to a deficit of iodine, as well as to a surplus of iodine, with increased activity and in particular with growth processes. Apparently the thyroid gland is adapted to a definite amount of iodine which enables it to function normally, and a diminution as well as an increase of iodine above this amount may disturb the normal cell equilibrium and act as a stimulus.<sup>2</sup>

In continuation of these investigations it seemed of interest to study the effect of administration of iodine on the intact thyroid

\* Received for publication April 6, 1928.

† We are indebted to Miss F. L. Haven for assistance in these experiments.

gland, in which there is no lack of circulating hormone such as is caused by extirpation of a considerable portion of the gland tissue. Would administration of iodine under these conditions likewise act as a stimulus and call forth proliferative processes? In order to determine the effect in a definite and quantitative manner, we estimated the number of mitoses present at a certain time in the thyroid gland. We found that by this means we could establish in an exact degree the stimulating effect of iodine even in the normal gland.<sup>3</sup> The depression in activity which takes place at a later period and under certain other conditions we attributed largely to pressure effects exerted on the epithelium lining the acini by the material contained in the lumina of the latter; but there may in addition be other factors involved. We have reason for assuming such pressure effects, because previously Loeb has observed in the thyroid of the guinea pig a breaking through of the walls of adjoining acini and a flattening of the lining-cells, evidently under the influence of pressure exerted by the colloid material. Thus the colloid of neighboring acini may form, in the end, one continuous mass; and it is very probable that many of the very large acini, which are found especially in the periphery of the thyroid gland, represent really the result of coalesced acini. It is probable that whole acini may thus disappear as a result of pressure and of consequent interference with the circulation. Similar observations can be made also in cases of human goitrous thyroids and pictures of this kind have been described previously by other observers.<sup>4</sup> Furthermore, differences in the activity in the peripheral, middle and central zones of the thyroid of the guinea pig and the resulting differences in the pressures acting on the acinus cells in these areas are responsible for the development of these three zones of acini which Loeb described in the normal thyroid gland of the guinea pig. The factors mentioned, in particular the pressure exerted on the walls of the acini, explain the relative flatness of the epithelium in the peripheral acini.

In the experiments to be described we compared the number of mitoses found and the structural characteristics of the thyroid gland of normal guinea pigs serving as controls and of KI-fed animals; each of the latter received daily a dose of 0.05 gm. KI by mouth in the form of a pill.\* In other experiments we fed a tablet containing

\* In feeding the potassium iodide to guinea pigs care must be taken that the animals actually swallow the pill.

0.1 gr. desiccated thyroid gland (Armour & Co.) to the guinea pigs, a different set of animals serving as controls.

We carried out two series of experiments; the first series was made in April, May and early June, 1926; the second in December, 1926, and January and February, 1927, for control and potassium iodide-fed animals, while the experiments with feeding of thyroid gland were completed in April and in the early part of May, 1927. Thus we have to deal with three sets of guinea pigs in each series, namely: (a) controls, (b) guinea pigs fed with KI, and (c) guinea pigs fed with desiccated thyroid gland.

### I. THE NUMBER OF MITOSES

We shall first discuss the results obtained in the second series, because here the method used for the determination of the number of mitoses was more satisfactory than in the first series.

**SECOND SERIES:** Five control guinea pigs, six guinea pigs each fed daily with 0.05 gm. KI and four guinea pigs fed with 0.1 gr. desiccated thyroid gland, were studied. The same kind of food was given to all. At the end of the experiment the thyroid glands were removed, immediately after death by chloroform, and fixed in Zenker's solution. Sections were cut serially.

In every tenth or eleventh section, the mitoses were counted and on this basis the approximate number of mitoses in the whole lobe estimated. In some animals an isthmus was present in the thyroid; it was usually small and not included in our counts.

(a) *Control Animals:* The numbers of mitoses found in one lobe of each of the control animals were as follows: 104, 80, 143, 63, 91. Thus an average of 96 mitoses per lobe or of 192 mitoses in the whole thyroid, excluding the isthmus, was obtained (see Table I). This represents the average number of cells which in our experiments were in mitotic division, at a certain time during the winter months, in the normal thyroid gland of guinea pigs, the weight of which varied approximately between 350 and 450 gm.

(b) *Potassium Iodide Animals:* Six guinea pigs which were fed with KI daily showed an average of 355 mitoses in one lobe or 710 mitoses in the whole thyroid, excluding the isthmus (see Table I). The lowest count in this series is more than twice as high as the average count in the controls and quite noticeably higher than the highest count in the control series.

(c) *Thyroid-Fed Animals:* In four guinea pigs, which were fed with 0.1 gr. thyroid gland daily for from 18 to 30 days, the counts of mitoses were as follows: 45, 0, 42, 40. The average count for one lobe was 32; for the whole thyroid, excluding the isthmus, it was 64 mitoses (see Table I).

FIRST SERIES: In the first and larger series, the number of mitoses was estimated in a different and less accurate manner than in

TABLE I  
*Mitotic Activity in Series II*

KI-fed animals			Control animals		Thyroid-fed animals		
Guinea-pig no.	Duration of feeding in days	Mitoses*	Guinea-pig no.	Mitoses*	Guinea-pig no.	Duration of feeding in days	Mitoses*
10	16	868	79(a)	208	233	20	90
11	17	1008	79(b)	160	270	30	0
12	19	962	78	286	250	18	84
13	21	460	57	126	217	20	80
14	21	390	58	182			
15	23	572					
Averages of mitoses		710		192			64

\* Mitoses, per whole gland, excluding isthmus.

the second series. In ten sections of the thyroid of each animal, the mitoses were counted in the central area, characterized by the larger size of the acini and the greater height of the epithelium. These central areas were, on the whole, somewhat smaller in the KI pieces, which were taken out for examination at later periods, than in the controls.

A larger number of sections were used for estimation of the number of mitoses in the thyroid glands of animals fed with thyroid substance than in the others to compensate for the smaller size of the areas in these thyroid glands. While, as stated, this method is less accurate than the method used in the later series, still the results agree fairly well in both and we may therefore consider the results here obtained as corroborative of those obtained in the second series.

(a) *Control Animals*: The results obtained are shown in Table II. The average number of mitoses counted in these 10 guinea pigs was 2.4. There were variations between 0 and 7 mitoses in the individual cases. The weight of the animals varied between 328 gm. and 870

TABLE II  
*Mitotic Activity in Series I*

Control animals		
Guinea-pig no.	Weight in grams	Mitoses
134	695 .....	5
218	660 .....	7
104	580 .....	1
345	515 .....	1
458	620 .....	1
332(a)	870 .....	1
331	665 .....	0
269	650 .....	1
335	445 .....	3
265	328 .....	4
Average number of mitoses		2.4

gm., and the average weight was approximately 550 gm. The thyroid glands of these guinea pigs were removed for examination during the months of April and May.

(b) *Animals Fed with KI*: The average number of mitoses in all the animals in this series which were fed with KI is 6.3. The weight in the KI group varies approximately between 400 and 700 gm. However, there should be omitted from this list Guinea pig 212, which had been fed only during a period of 5 days with KI; the iodine effects were apparently not yet noticeable at this early period. Furthermore, we should omit Guinea pigs 315, 263 and 22 whose thyroids were removed as late as 108 days after the beginning of the

administration of KI. At this time marked retrogressive changes had begun in the thyroid gland. Omitting these four guinea pigs, the average number of mitoses of the remaining 13 guinea pigs is 8.1 (see Table III).

TABLE III  
*Mitotic Activity in Series I*

KI feeding			
Guinea-pig no.	Weight in grams	Duration of feeding in days	Mitoses
212		5	2
216	768-773.....	8	8
217	865-850.....	10	7
264	423.....	12	12
267	390-375.....	15	8
328	520-585.....	21	15
268	520-547.....	25	7
386	465-513.....	30	5
41	485-600.....	30	1
37	535-580.....	30	9
306	465-595.....	40	14
367	525-605.....	40	6
300	415-485.....	60	3
330	393-420.....	60	10
315	735 end weight .....	108	0
263	650 end weight .....	108	1
22	815 end weight .....	108	0
Average number of mitoses (omitting Guinea pigs 212, 315, 263, and 22)			8.1

(c) *Animals Fed with Thyroid Gland:* Seven guinea pigs were fed with thyroid substance. The results obtained are presented in Table IV.

The weight in this group varies approximately between 500 and 600 gm. If we omit Guinea pig 420 in which, after only five days of feeding, the full effect of the thyroid substance had evidently not

TABLE IV  
*Mitotic Activity in Series I*

Thyroid feeding			
Guinea-pig no.	Weight in grams	Duration of feeding in days	Mitoses
420	565-502..... <sup>a</sup>	5	6
474	618-595.....	8	3
484	538-615.....	10	1
246	510 end weight .....	30	2
247	.....	35	0
156	525-543.....	43	0
133	630 end weight .....	48	1
Average number of mitoses (omitting Guinea pig 420)			1.16

yet become apparent, the average number of mitoses in this group is 1.16.

Although the absolute number of mitoses is less accurately determined in the first series, it is of interest to compare the proportion in the number of mitoses in the controls, KI- and thyroid-fed animals in the first and second series. For this purpose we consider the number of mitoses in the thyroid-fed series and refer the number of mitoses in the other series to this unit number. In the first series, the proportions are as follows: Thyroid-fed group = 1; Controls = 2.1; KI group = 7. In the second series the proportions are: Thyroid-fed group = 1; Controls = 3; KI group = 11.

While the proportions found in Series II are more accurate than those obtained in the first series on the whole, the results in

both series agree. The number of mitoses is about three and a half times as great in the KI group as in the control group, and two to three times as great in the controls as in the thyroid-fed group. We may then conclude that during the first three to four weeks, and possibly even somewhat longer, KI feeding increases definitely and considerably the mitotic activity of the thyroid gland, and that on the contrary feeding with thyroid gland diminishes the number of mitoses (see Figs. 1 and 2).

## II. THE SIZE OF THE ACINI AND OF THE CELLS LINING THEM AND THE CHARACTER OF THE COLLOID

(a) *Control Guinea Pigs*: In comparing the acini, the character of the acinus cells and of the colloid in the three series we must take into consideration the fact that noticeable variations may occur even in the control animals. Within the same group of animals the acini and the acinus cells present considerable differences in size. In the average control thyroid gland the acinus cells were medium to low, as far as their height was concerned. The colloid was slightly retracted; there were many vacuoles in the peripheral parts of the colloid; it was of medium consistency. The variations ran from large and medium-sized acini with low epithelium and with harder colloid that was slightly retracted, to acini of variable size, irregular in contour with relatively high epithelium and with colloid that was adherent to the epithelium in various places and separated from the latter merely by vacuoles.

(b) *Guinea Pigs Fed with KI*: If we compare the structure of the thyroid glands of guinea pigs fed with KI with the condition found in control guinea pigs, we find, during a period of approximately the first four weeks following the beginning of the experiment, no very decided differences between these two groups of animals. Again considerable variations in individual cases are present; while in some animals the average height of the acini cells may perhaps be less than in the controls, in others it is equal in the two groups, and in some cases it is even greater in the KI group. In particular, the thyroid of Guinea pig 10 fed with KI for a period of 16 days showed not only a relatively high epithelium but in addition colloid which, on the whole, was very soft and partly liquefied. This gland resembled the thyroids found in some cases of compensatory hypertrophy.

The thyroid of Guinea pig 12, examined after 19 days of daily KI feeding, showed acini with epithelial cells which were slightly higher than medium-sized; some of the acini had prominences extending into the luminae and were irregular in outline. The colloid varied somewhat in different acini; it was fairly hard in some, softer and even partly dissolved in others. In a number of acini it could be shown that the solution was produced, at least in part, through the activity of cells which phagocytosed particles of the colloid. The thyroid of Guinea pig 15, after a period of KI feeding extending over 23 days, was similar, although on the whole, the colloid was here somewhat harder and slightly retracted. Figure 3 (Guinea pig 328) shows the structure of the gland after a period of 21 days during which the animal received a daily dose of KI. The epithelium is of medium height in the majority of the acini, but in a number of the larger acini it is somewhat flatter evidently owing to pressure exerted by the contents of the acini on the layer of epithelial cells. The colloid appears, on the whole, soft and in a number of acini it has been invaded by phagocytic cells which have almost destroyed it.

These examples may serve to show that, for the most part, there is no marked difference in the size and character of the epithelium and of the acini between the control and KI guinea pigs within the first four weeks following the beginning of the KI feeding.

If we now consider the later stages of iodine feeding, we may state in general that there is a tendency for the acinus cells to become low; at the same time the colloid may be solid and be present in the acini in a relatively large quantity, but in other cases solution processes have taken place in it. There is, in addition, a tendency for the acini to become larger. These characteristics are quite definite in the specimens examined 108 days after the beginning of the feeding with KI. Fig. 5 (Guinea pig 315, fed with KI during a period of 108 days) illustrates this stage very clearly. The acini here are large, the epithelium is very low and the walls are thin. What is left of the colloid is very markedly retracted, much more so than in the earlier stages or in the control specimens. This marked retraction is probably a result of the action of fluid on the colloid and indicates softening processes which have taken place in this substance in certain of the acini. There is very little doubt, however, that pressure has been exerted on the walls of the acini by the colloid, or by the substances produced from the colloid through solution processes, and that this

pressure is largely responsible for the greater size of the acini and for the flatness of the epithelium at this period. In addition, we may assume that such an increase in pressure will lead to an interference with the circulation in the spaces between the acini. As a result of the increased intra-acinar pressure, which exists in the later periods of KI feeding, we find here and there that the walls of adjoining acini are flattened and broken through. Thus smaller acini may be united forming larger ones and, as Loeb has stated previously, the very large acini have been produced in many cases as the result of this secondary union of adjoining acini. The colloid of such acini may at first be united by a bridge passing through the openings in their walls, but it may finally form one connected mass. A transition to this condition is found in Fig. 4 (Guinea pig 37), where as early as 30 days after beginning the KI feeding some of the typical effects of the later periods of iodine on the thyroid gland are becoming noticeable. The acini are large, the colloid is correspondingly great in quantity, but still rather solid. The acinus cells, while on the whole fairly low, are distinctly higher than at later stages. The colloid here does not show the marked retraction seen in Fig. 5; in various places it still adheres to the wall of the acinus.

(c) *Effect of Thyroid Feeding on the Structure of the Thyroid Gland:* In the first week of thyroid feeding no definite differences were seen between the structure of normal glands and the glands of the thyroid-fed animals. From the tenth day on, there was on the whole, perhaps, a tendency on the part of the acinus cells to become somewhat flatter and for the colloid to be rather solid; the acini were, on the average, probably somewhat smaller than in the controls. However, these differences as a rule were not very pronounced and not present in all cases. The latest term at which the gland of a thyroid-fed guinea pig was examined by us was 48 days.

We shall cite as an example, the findings in Guinea pig 247, examined after 35 days of thyroid feeding. The acinus cells are here very low; the colloid is hard, almost entirely detached from the wall and rather markedly retracted. In some places the walls separating two adjoining acini have become very thin and they have the appearance of being ready to break through. Similar pictures of the rupture of walls of neighboring acini occur in thyroid glands in other instances and even in the thyroids of control animals, also wherever there is pressure exerted on the tissue separating two acini; this

process is therefore associated with flatness of acinus cells in the area in which such changes are taking place. The majority of the acini represented in this example are still relatively large, and in this respect the picture does not perhaps represent the average findings in the glands of thyroid-fed guinea pigs.

### III. ON CERTAIN SECONDARY CHANGES IN THE THYROID GLAND

In a number of cases we found small accumulations of lymphocytes in the stroma of the thyroid gland. Furthermore, not infrequently, we observed phagocytic cells in the colloid of acini; these take up small particles of colloid into their cell bodies and here destroy it; as a result of this process the colloid may assume a honey-combed appearance. Colloid was also seen, in certain cases, in the interstitial connective tissue that separates the acini. The latter condition seems to depend on the destruction of the walls of some acini, perhaps as the result of pressure, and the subsequent escape of colloid into the interstices of the stroma. However, in interpreting such pictures, we must be aware of the possibility that colloid may be artificially squeezed out from the acini into the connective tissue spaces and we have to distinguish between these two occurrences.

If we now compare the three groups of guinea pigs as to occurrence and frequency of these changes, we find that the latter condition may be seen in all of them; the phagocytic activity, however, seems to be more pronounced in the KI-fed animals than in the controls.

### DISCUSSION

Our experiments have thus shown that in the early stages of administration of iodine to normal guinea pigs, the number of mitoses is quite noticeably increased in the acinus cells of the thyroid gland and we may therefore conclude that iodine exerts primarily a stimulating effect on this gland. While we believe that the number of glands which we have examined is sufficiently large and that the results are sufficiently concordant to justify a general conclusion concerning this formative stimulation exerted by iodine in the case of the guinea pig, still we do not consider our observations will permit us to draw definite conclusions, as yet, as to the intensity of the

increase in cell proliferation, which we find here as the result of iodine feeding, or as to the average number of mitoses found in normal thyroids of guinea pigs. Further investigations, which are being carried out in our laboratory at the present time, may be expected to determine these conditions more definitely.

Of special interest in our investigations is the difference which we found between the action on the thyroid gland of iodine feeding and of the feeding with thyroid gland. Our observations in this respect correspond to the differences established in the influence exerted by these two substances in compensatory hypertrophy of this gland where feeding with thyroid (and to a lesser extent also with anterior pituitary gland) depresses, whereas feeding with KI stimulates, the proliferative processes in the acini. We may explain the difference between the action of these two substances in the following way: Feeding with thyroid gland introduces an excess of the hormone into the circulation and produces the effects observed in the thyroid gland of the animal. Such effects are the opposite of those which follow operative removal of a considerable portion of the thyroid gland tissue; the latter procedure leads to a diminution in the circulating hormone and stimulates growth processes in the remaining part of the thyroid gland; the former procedure depresses the activity of the gland, the function of which is now no longer needed and which might even become injurious. On the other hand, the administration of iodine is not identical with the introduction of ready-made hormone; in the former instance a substance has been introduced which is able to initiate the production of hormone in the gland cells, and it is apparently this stimulating process, set in motion by iodine, which also induces the gland to proliferate; this phase of action is necessarily lacking if we introduce the hormone as such. In a subsequent phase, when possibly an excess of hormone has been produced as a result of this stimulation of the thyroid gland, there may perhaps be added to the primary stimulation exerted by iodine, a secondary inhibiting effect due to the presence of an excess of hormone which may thus, secondarily, cause a depression in the activity of the gland.

However, whether this secondary inhibiting effect of hormone action comes into play at a certain stage and thus causes a depressive action we must consider problematical at the present time. On the other hand, there are definite indications that pressure is exerted

on the walls of the acini which produces the flattening of the epithelial cells, the enlargement of the acini, and in many cases the perforation of the wall of adjoining acini. And we may attribute to this factor, at least in part, the decrease in activity found in later stages of KI administration. This pressure is due to the action of the unchanged or partially liquefied colloid which is not removed from the acini of the gland in the same active manner in case of KI feeding, as it is in the condition found in compensatory hypertrophy where the removal of thyroid gland tissue, in some way, leads to a mobilization of the colloid and where thus neither the colloid as such nor the substance into which the colloid is secondarily transformed is able to the same extent to exert pressure on the inner lining of the acini.

The results formerly obtained by one of us concerning the effect of iodine on compensatory hypertrophy of the thyroid gland and his conclusions as to the primarily stimulating effect of iodine on this organ, as well as our present results regarding the effect of iodine on the normal gland, are at variance with the widely accepted view that iodine in general prevents proliferative changes in the thyroid gland and produces a quiescent condition of this organ. According to Marine and his collaborator,<sup>5</sup> after once a goitrous proliferation and metabolic hyperactivity have started in the thyroid gland, administration of iodine leads to the production of an increased amount of colloid in the acini and thus ultimately a colloid goitre is produced, which under these conditions represents the ultimate resting stage of the abnormal gland.

#### SUMMARY

1. Oral administration of iodine to guinea pigs markedly increases the mitotic activity in the thyroid gland during the first three to four weeks.
2. This first phase of increased activity is followed by a second phase of depression, which is accompanied by definite structural alterations in the thyroid gland. We find indications that this second phase is at least partly due to pressure exerted by the contents on the walls of the acini.
3. In contradistinction to the effect of potassium iodide, administration of thyroid gland substance is not followed by a phase of

stimulation, but in this case, within the first two weeks, a period of depression sets in which may be accompanied by certain structural changes in the gland. As the result of thyroid feeding the mitotic activity is diminished as compared with that found in the controls.

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#### DESCRIPTION OF PLATES

##### PLATE 67

- FIG. 1. Guinea pig 11. 17 days KI feeding. Central part of gland, showing two mitotic figures, tall epithelium, softening of colloid.
- FIG. 2. Guinea pig 11. 17 days KI feeding. Periphery of gland, showing two mitotic figures, one in center slightly out of focus. The epithelium is fairly high.

## Iodine Balance Studies and the Availability of Iodine

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Less is known about the fate of iodine in the intestinal tract than about its urinary excretion and its paths into and out of the thyroid gland. This is perhaps surprising in view of the importance of intake and availability of iodine in determining the development of non-toxic goiter, one of the world's commonest deficiency diseases. The main reason for this lack of knowledge is the difficulty of measuring the very small quantities of iodine in the feces in the presence of much organic material. Data provided by radiiodine excretion studies are incomplete because they are short-term and because the specific activities in the blood and feces are constantly changing.

In Glasgow, we have carried out metabolic balance studies of stable iodine, under controlled conditions of intake, in patients with normal and abnormal thyroid function. This has enabled us to assess the relative importance of exogenous and endogenous sources of iodine in the feces. Also since our most important dietary source of iodine is fish, we have studied the availability of iodine from ingested fish and its chemical nature.

17 patients were studied in a metabolic ward. Dietary intake of iodine was fixed at a low level of 35 to 40  $\mu\text{g}$  per day, and the iodine intake was supplemented with tablets of potassium iodide to bring it to a total of approximately 100  $\mu\text{g}$  per day; errors due to dietary variation were thereby minimized. A low intake was chosen since small changes in fecal iodine excretion can be more easily observed. 10 days were allowed for equilibration after which 2 or more balances were carried out with complete collections of urine and feces. These balance periods averaged 6 days and none was less than 3 days.

To determine the iodine content, fecal and dietary samples were homogenized and desiccated. A portion was then ignited in a Gallenkamp bomb calorimeter and the liberated iodine dissolved in a normal solution of sodium hydroxide inside the bomb. Iodine was determined in this solution and also in urine and serum by chloric acid-digestion method of Farrell and Richmond (1).

Fig. 1 shows the values of fecal and urinary iodine excretion in 7 individuals whose thyroid function was normal. The mean fecal excretion was 15.0  $\mu\text{g}$  of iodine per day, and urinary iodine averaged 61.8  $\mu\text{g}$  day. Figs. 2 and 3 show the iodine balance data in 5 patients with thyrotoxicosis. The mean fecal iodine excretion was 37.2  $\mu\text{g}$  day, and urinary

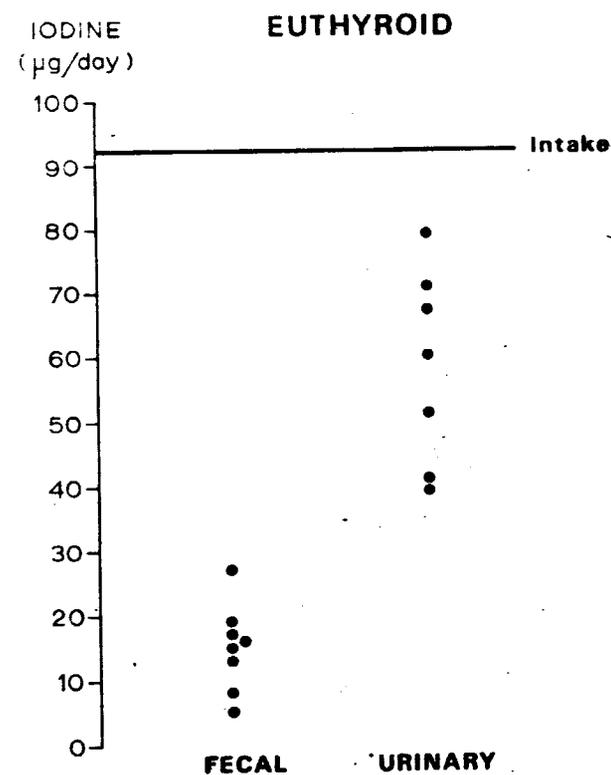


Fig. 1. Fecal and urinary excretion of iodine by euthyroid individuals on intake of 92  $\mu\text{g}$  iodine per day.

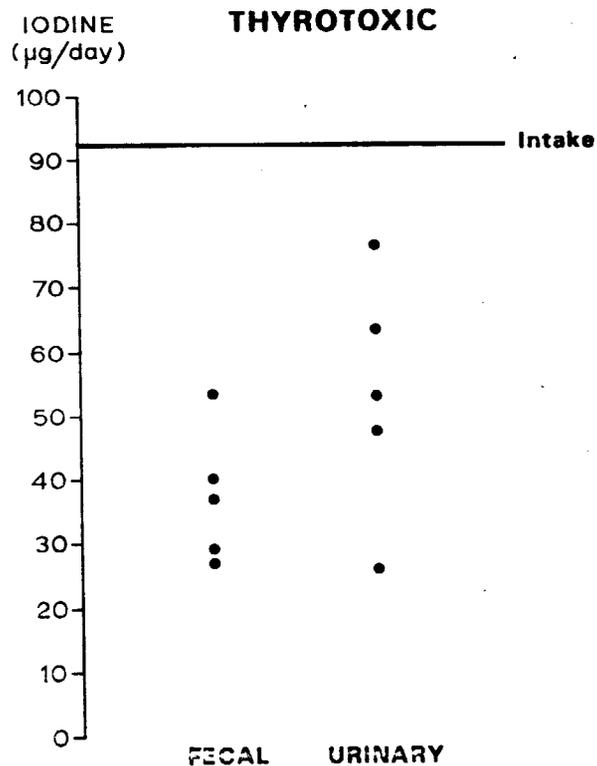


Fig. 2. Fecal and urinary excretion of iodine by thyrotoxic patients on intake of 92 µg iodine per day.

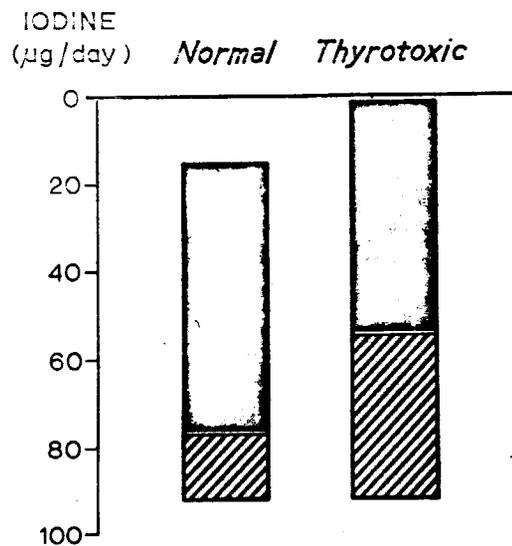


Fig. 3. Mean iodine balance data in euthyroid and thyrotoxic patients. Intake of iodine (92 µg/day) is plotted downwards from the baseline, and fecal (shaded) and urinary (black) excretion of iodine upwards from intake line.

53.6 µg/day. Fecal levels were significantly higher than normal in the thyrotoxic patients ( $p < 0.005$ ).

Fig. 4 compares the mean iodine balance data in 3 patients with hypothyroidism with the mean values in the euthyroid individuals. The level of fecal iodine was low in the hypothyroid patients, while urinary excretion of iodine was normal in two patients and high in the third.

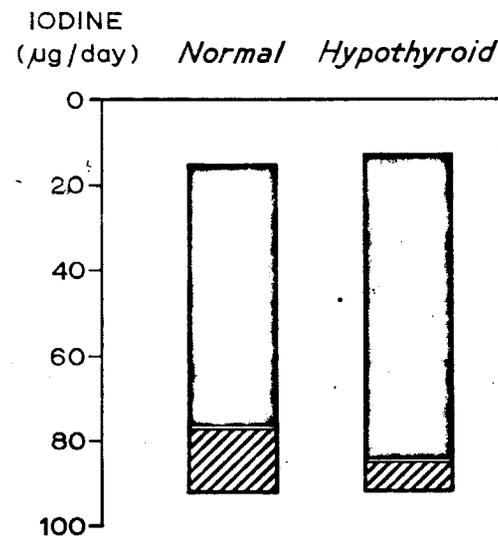


Fig. 4. Mean iodine balance data in euthyroid and hypothyroid patients.

Fig. 5 shows the iodine balance data in two patients with non-toxic goiter, probably due to iodine deficiency. These patients are in strongly positive iodine balance, with low levels of urinary iodine, while fecal levels are within the normal range.

These results indicate that, on a fixed dietary intake, fecal excretion of iodine varies with thyroid activity. The patients with thyrotoxicosis excreted significantly more iodine in the feces than normal, and the patients with hypothyroidism had low levels of fecal iodine. Urinary iodine excretion was not significantly different from normal in the thyrotoxic and hypothyroid patients. The patients with normal thyroid function were, on the average, in positive balance by about 15 µg/day when their iodine intake was 92 µg/day. The thyrotoxic patients on the other hand as a group were in equilibrium, although in one patient, the most severely

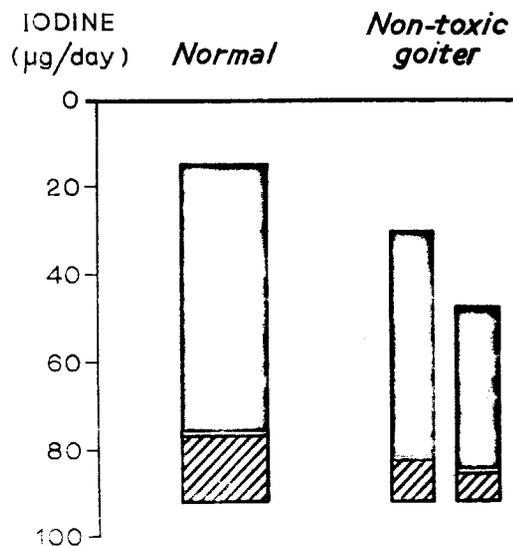


Fig. 5. Mean iodine balance data in euthyroid individuals and in two patients with non-toxic goiter.

thyrotoxic, there was a marked negative balance of 37  $\mu\text{g}$  day. Such a chronic negative iodine balance will result in depletion of the body's stores of iodine, and this may be an explanation of the low levels of plasma inorganic iodine which have been observed in thyrotoxicosis (2).

The patients with non-toxic goiter probably due to iodine deficiency had normal levels of fecal iodine excretion but low urinary iodine, so that they were in strongly positive balance. In states of severe iodine deficiency, however, this relatively constant fecal loss of iodine might lead to a depletion of the body's iodine stores. Our results suggest that fecal iodine excretion is dependent on the secretion rate of thyroid hormone and is partly derived from it. As long as the secretion is maintained at a normal level by the thyroid, there is an inevitable loss of iodine in the feces even if intake of iodine is low.

Endogenous thyroid hormone may not be the sole source of fecal iodine, however, and there is little information on the absorption and availability of the iodine present in foodstuffs. We have therefore studied the nature and fate of iodine in fish, which is the principal source of iodine

in Great Britain, since iodized salt is not widely used. Haddock and plaice were the fish studied. The plaice were injected with 100  $\mu\text{c}$  of  $^{131}\text{I}$  into the celomic cavity, and by 48 hours the radioactivity was distributed throughout the body of the fish. The flesh was then divided into weighed portions, mixed with potato, and fried. The portions were fed to patients whose feces and urine were collected over the next 5 days. Storage of radioiodine by the thyroid was prevented by carbimazole given throughout the collection period. In 10 patients, radioactivity in the feces was between 0 and 1% in every case, and in the patients whose urine collections were complete over 80% of the activity was recovered in the urine over the 5-day period. It is concluded from this that the iodine in fish is completely absorbed from the alimentary tract.

It seemed desirable to find out whether any losses of iodine from fish occurred during the process of cooking. Portions of haddock were cooked by boiling, grilling or frying, and the concentration of iodine measured in the raw fish and after cooking (Fig. 6). This figure shows that substantial losses occur, particularly on boiling, where 50 to 82% of the iodine was lost. The iodine in these cases is lost either into the water used for boiling or in sediment from small fragments of the fish. When fish is grilled or fried the losses are smaller, averaging only 20%. These studies were also carried out on plaice and similar findings were obtained.

As a result of these losses considerable errors will arise in dietary surveys if the intake of iodine is calculated from tables which give the iodine content of uncooked foods. We have previously observed that the iodine intake in a Glasgow population estimated from tables was considerably higher than the urinary excretion of iodine (3), and the losses during cooking are a likely explanation for this.

The chemical nature of iodine in the fish was studied by measurements both of stable iodine and of radioiodine injected into the live fish 48 hours before. Portions of the flesh were homogenized in a Waring blender and centrifuged. It was found that the entire iodine content remained in the supernatant. Tests were carried out on this iodine which showed that it was all inorganic. It was not precipitated by trichloroacetic acid, and none was eluted from Dowex 1 resin at pH 1.4, the pH at which thyroxine and triiodothyronine appear. It was not soluble in butanol after washing with 4N-NaOH, and it was completely dialyzable. The level of inorganic iodine in the serum of the fish was also measured and was the same as that in the flesh, approximately 1,500  $\mu\text{g}\%$ . The finding that all

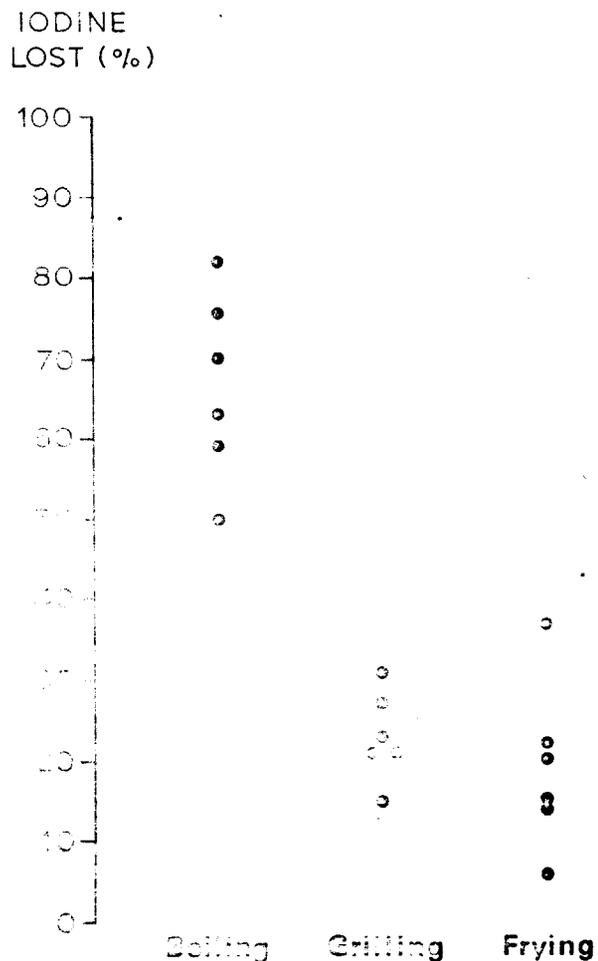


Fig. 8. Percentage losses of iodine from fish (haddock) resulting from different methods of cooking.

the iodine present in the edible part of the fish is inorganic is in accord with the studies on absorption, since it is known that inorganic iodine is completely absorbed from the alimentary tract, in contrast to the iodine in thyroxine.

### CONCLUSIONS

Fecal iodine levels vary with thyroid function, and on an intake of 100  $\mu\text{g/day}$  the iodine is mainly derived from endogenous thyroid hormone. In thyrotoxicosis, levels of fecal iodine are high and in hypothyroidism they are low. In iodine deficiency, loss of iodine in the feces may be an important factor in depleting the body's iodine stores. In fish, the most important source of iodine in Scotland, all the iodine in the edible parts is absorbed after ingestion. Significant losses of iodine occur during cooking, however, and this is important in calculating the dietary iodine intake. The iodine is all present in inorganic form.

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Effect of Potassium Iodide on Plasma Cholesterol of Rats. (21587)

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Liebig(1) observed that administration of iodides (organic or inorganic) to cholesterol fed rabbits appeared to protect them against occurrence of atherosclerosis. This observation has been confirmed by various observers (2), although there has been some disagreement(3). Whatever this mode of protection against atherosclerosis might be, it seems that relative protection of such rabbits against hypercholesteremia is one of the preventive factors(2,4). It is only fair to add that some workers have not found this hypercholesteremia protecting effect of iodides in rabbits (3,5). The possible critical importance of

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dosage(6) may be the reason for these discrepancies. Moreover, this antihypercholesteremic effect of KI could not be confirmed when chickens were used(7).

Since there appear to be fundamental differences in cholesterol metabolism between rats and rabbits(8), it was decided to study the effect of KI on plasma cholesterol of rats under various conditions. As a preliminary step, we determined the effect of KI on plasma cholesterol of rats deprived of external sources of cholesterol.

*Methods.* Male Long-Evans rats approximately 12 weeks old were divided into 3 groups and placed on fat and sterol-free diet for the duration of the experiment. After 24 hours on this diet, all rats were bled from the tail for initial plasma cholesterol determina-

Proc. Soc. Exptl. Biol. and Med. 88(3)354-356. 1955

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TABLE I. Effect of Tube Feeding KI, H<sub>2</sub>O and KCl upon Plasma Cholesterol of Rats on Sterol Free Diet.

Material fed	No. of rats	Avg wt, g	Avg plasma cholesterol	
			First day pre-tube feeding, mg/100 cc	Third day, mg/100 cc
KI*	25	230 (180-260)§	48 (33-67) ± 2.18	92 (67-130) ± 3.45
H <sub>2</sub> O†	23	232 (198-262)	44 (20-65) ± 2.43	60 (42-89) ± 2.53
KCl‡	10	220 (192-232)	51 (37-59) ± 2.93	64 (48-74) ± 2.81

\* KI = 200 mg/day (1 cc), 3 days.

† H<sub>2</sub>O = 1 cc/day, 3 days.

‡ KCl = 200 mg/day (1 cc), 3 days.

§ Range of values.

|| Stand. error of mean.

tion. Beginning that day and for 3 days, the rats were anesthetized and fed test materials by stomach tube. The experimental rats were fed 200 mg KI (200 mg/cc) daily; control rats received 1 cc H<sub>2</sub>O daily; and the third group received 200 mg KCl (200 mg/cc) daily. Three hours after the last tube feeding (third day), the rats were again bled for plasma cholesterol determination.

**Results.** The change in plasma cholesterol concentration following tube feeding of the 3 test materials is shown in Table I. Although plasma cholesterol concentration rose significantly in all 3 series, after feeding period of 3 days, plasma cholesterol rise in the series given KI was considerably greater than in the other 2 series. The series given H<sub>2</sub>O exhibited about as great a rise (16 mg/100 cc) as that observed in the series given KCl (13 mg/100 cc). The rise of plasma cholesterol observed in rats given KI was 44 mg/100 cc. The difference in the rise of plasma cholesterol between rats given KI and either of the other two groups is statistically significant well beyond the 1% level.

**Discussion.** It appears safe to conclude that the rise in plasma cholesterol following feeding of KI to rats, as described, is of such magnitude that iodide must be considered as an important hypercholesteremic agent. The slight rise in plasma cholesterol after administration of either KCl or H<sub>2</sub>O alone is most

likely due to non-specific factors such as repeated anesthesia, intubation, and dietary change rather than to substances fed. Turner also was unable to show any effect in rabbits with halides of potassium other than iodide.

This seemingly paradoxical hypercholesteremic effect of KI is perhaps not too unexpected in view of the fact that Turner and Bidwell (9) and Meeker, Kesten and Jobling (10) have demonstrated that administration of KI could maintain a hypercholesteremic state in hypercholesteremic rabbits, even after removal of dietary cholesterol. Although the actual mechanism by which iodides exert their effect is still unknown, many workers (2,3,6) have held that iodides produce their effect by altering thyroid function. On the other hand, other studies have shown that the effect of KI is unchanged in thyroidectomized rabbits (4,11). If the hypercholesteremic effect of KI in the rat were due to its action on thyroid, then appropriate changes in hepatic synthesis, destruction and intestinal excretion of cholesterol, as found in deranged thyroid states (12), should also be found in KI fed rats. Such possible changes, together with possible alteration of the physical state of plasma cholesterol as observed after administration of Triton WR-1339 (13) and cholic acid (14), are now under investigation.

**Summary.** Evidence is presented which indicates that KI (200 mg/day for 3 days), when administered to rats on a sterol free diet, produces an hypercholesteremia of moderate degree.

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Received January 31, 1955. P.S.E.B.M., 1955, v88.

Nucl. Med. 5(3):256-261. 1966

## The Minimum Dose of Potassium Iodide which Inhibits the Thyroidal Radioiodine Uptake

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(Received: 15. 2. 1966)

There are occasions on which it becomes desirable to inhibit the trapping of radioiodine by the human thyroid. The need for this arises often during studies with  $^{131}\text{I}$ -labelled serum albumin or other compounds labelled with radioactive isotopes of iodine, since in these procedures it is important to make sure that the radioisotope released from the breakdown of the substance studied will not accumulate within the thyroid gland. Poisoning with radioiodine following a nuclear explosion or accident is another indication for inhibiting the uptake of this isotope by the thyroid (10). If the radioiodine is prevented from accumulating in the gland, then most of it is excreted with the urine in one or two days, and so the radiation exposure is minimised.

Pochin and Barnaby (8) have shown that administration of 200 mg of potassium iodide inhibits the trapping of radioiodine by the thyroid. After the administration of this amount of stable iodide the thyroidal uptake curve does not rise any more. This dose of 200 mg is thus effective in blocking the radioiodine uptake, but it is not known whether smaller amounts of stable iodide are equally effective. So, it may be useful to find out which is the minimum amount of potassium iodide which shows the maximum effect, i.e. a more or less complete inhibition of the radioiodine uptake. This forms the subject of the present paper.

### Materials and methods

The thyroidal radioiodine uptake was measured 2 and 24 hrs after an oral tracer dose of  $^{131}\text{I}$ , as described previously by Malamos et al. (6).

All the subjects investigated were adults of either sex, without evidence of thyroid or other disease likely to affect iodine metabolism. Ten persons acted as a control group, while the rest formed ten experimental groups, each of them consisting of six persons.

The control group received only the tracer dose, whereas the 10 experimental groups received in addition potassium iodide. This was in a solution containing 15 mg/ml and was either added to the tracer dose or drunk at another time with half a glass of water. Altogether five groups received potassium iodide simultaneously with the tracer, in doses of 5, 10, 20, 40 or 80 mg, two other groups received 40 or 80 mg 2 h before the tracer, two further groups received 40 or 80 mg 12 h before, together with 10 mg simultaneously with the KI tracer, and finally one group received 40 mg of KI one hour after the tracer.

### Results

The results are summarised in Table I. Together with the mean  $\pm$  S. E. it also shows the median, which in most groups does not differ greatly from the mean. This is evidence that statistically the distribution of the individual values does not differ significantly from a normal one.

Table I: (Results)

	2 h Uptake %			24 h Uptake %		
	Mean	S. E.	Median	Mean	S. E.	Median
Control	9.6	2.1	9.6	32.1	3.3	32.0
1. 5 mg KI with tracer	3.4	2.0	3.1	14.2	2.7	11.6
2. 10 mg KI with tracer	5.9	2.5	6.0	4.9	2.4	4.5
3. 20 mg KI with tracer	6.1	2.7	5.3	2.5	0.8	2.9
4. 40 mg KI with tracer	3.7	0.9	4.2	2.6	0.4	2.7
5. 80 mg KI with tracer	4.1	1.7	3.8	1.4	0.6	1.1
6. 40 mg KI 2 h before tracer	3.6	1.2	3.3	1.5	0.2	1.5
7. 80 mg KI 2 h before tracer	2.6	0.6	3.0	1.4	0.4	1.6
8. 40 mg 12 h before and 10 mg with tracer	1.8	0.6	1.3	2.2	0.8	2.0
9. 80 mg 12 h before and 10 mg with tracer	1.7	0.8	1.8	2.1	0.6	2.6
10. 40 mg KI 1 h after tracer	9.7	1.9	11.5	8.6	2.2	8.0

The mean 2-h uptake is higher in the controls than in any other group, except the one taking 40 mg of KI 1 h after the tracer dose. The difference is statistically significant at the 5% level for the first three groups taking 5 to

20 mg, but it is so with respect to all the other experimental groups except group 10. However, since the values of the groups taking 5 to 20 mg KI are intermediate between the control group and the groups taking 40 or 80 mg, it is possible that even the dose of 5 mg may have a small effect on the 2-h uptake, which can not be firmly established from the present results.

Table I does not show a significant difference between the effect of 40 or 80 mg KI on the 2-h uptake. The lowest values are obtained in the groups receiving 40 or 80 mg 12 h before and another 10 mg simultaneously with the tracer dose. Although the difference with the groups taking only 40 or 80 mg simultaneously is not significant, it is nevertheless suggestive (for groups 4 and 8  $t = 1.73$ ,  $0.10 < p < 0.20$ ).

The 24-h  $^{131}\text{I}$  uptake is definitely depressed in all the experimental groups, and even the difference between the control group and the group receiving only 5 mg KI is highly significant ( $t = 4.64$ ,  $p < 0.001$ ). There is no clear advantage of doses beyond 20 mg, though the group receiving 40 mg 1 h after the tracer dose shows again a smaller depression of the  $^{131}\text{I}$  uptake than the other experimental groups.

An interesting finding is that the groups receiving 10 mg or more of KI together or after the tracer have a higher uptake at 2 h than at 24 h.

### Discussion

The thyroidal radioiodine uptake is normally inversely related to the plasma inorganic iodine (PII) level (3). The minimum dose of potassium iodide which raises the PII to levels high enough to depress the thyroid uptake to virtually zero is 3.3 mg daily (10) or 2 mg per  $\text{m}^2$  of body surface per day (9). The depression of the thyroid uptake, however, does not occur immediately after raising the PII. Koutras et al. (4) have shown that the maximum effect of 0.2 mg KI daily occurs only after 3 weeks of continuous administration, whereas 2 weeks are sufficient when 0.8 mg are given daily. With 3.3 mg/day the depression is more nearly complete, but still several days are required for this.

The present work shows that larger amounts of KI given in a single dose have a prompt and reliable effect. The minimum dose required is of the order of 40 mg. There is no clear advantage of administering larger doses, e.g. 80 or 200 mg.

However, with any dose there still is some radioactivity detectable in the neck, as shown in the present results. This is probably due to the extrathyroidal neck radioactivity (radioiodide in the plasma etc.) and possibly also to iodide trapped by the thyroid but not bound organically (10).

The fact that large doses of stable iodide may act as a thiouracil type of drug and inhibit the binding of iodide in the thyroid has been known for a long time (10). Wolff and Chaikoff (11, 12) have shown that the thyroid gland of animals receiving large doses of iodine traps iodide without binding it organically. A similar defect in organification is found in iodide-treated thyrotoxicosis (2) and in iodide-induced goitre (7). Furthermore, recent work in humans with much smaller doses of iodide, has shown that this is a more or less universal phenomenon (1, 4), and that the thyroid even normally does not bind all the iodide trapped (5). It seems that the proportion of iodide, which is bound after being trapped, is inversely related to the PII level (1). This iodide trapped, but not bound, leaves rapidly the gland, and so the thyroidal uptake curve may show a high initial peak followed by a rapid decline. This, together with the factor of the extrathyroidal neck radioactivity, offers an adequate explanation for the results reported here that in some groups the 2-h thyroidal uptake is higher than the 24 h value.

Although 40 mg of KI inhibit rapidly and completely the thyroidal  $^{131}\text{I}$  uptake, this effect may not be a long lasting one, since the exogenous iodide administered is rapidly excreted with the urine. For this reason it is concluded that when it is desirable to inhibit the thyroidal uptake of radioiodine, the minimum amount of KI required is an initial dose of 40 mg together with a maintenance dose, which has been shown elsewhere to consist of a minimum of 3.3 mg daily in divided doses (10). In this way the inhibition of the thyroidal uptake is both rapid and maintained. Larger doses of iodide are not required, and their use should be discouraged. In addition to side effects, such as iodism or iodide goiter, they may render impracticable for a longer time period the assessment of thyroidal function with either radioiodine or chemical PBI estimations, if this becomes necessary.

### Summary

The thyroidal uptake of  $^{131}\text{I}$  was measured 2 and 24 h after an oral tracer dose in 60 persons receiving potassium iodide in doses ranging from 5 to 80 mg. The results show that 40 mg of KI is the minimal dose which is required for a complete inhibition of thyroidal uptake. In cases when it becomes desirable to block entirely the uptake of radioactive isotopes of iodine by the human thyroidal gland, KI should be given in an initial dose of 40 mg, with a minimal maintenance dose of 3.3 mg/day.

## Résumé

La fixation thyroïdienne a été déterminée après l'administration orale d'une dose traceuse de  $^{131}\text{I}$  à 60 personnes qui ont reçu de l'iodure de potasse à doses variantes entre 5 et 80 mg. Les résultats ont démontré que 40 mg de l'iodure de potasse est la dose minimale qui est nécessaire pour une inhibition complète de la fixation thyroïdienne. Dans le cas qu'une inhibition complète et permanente de la fixation thyroïdienne des isotopes de l'iode est jugée nécessaire, l'iodure de potasse doit être administré à une dose initiale de 40 mg, suivie par une dose d'entretien de 3.3 mg par jour.

## Zusammenfassung

Die Schilddrüsen-Aufnahme wurde 2 und 24 Stunden nach Verabreichung von  $^{131}\text{J}$  an 60 Personen, die Kalium-Jodid in steigenden Dosen von 5 bis 80 mg erhielten, bestimmt. Wie aus den Ergebnissen hervorgeht, ist 40 mg KJ die kleinste Dosis, die für eine vollständige Unterbindung der Schilddrüsen-Aufnahme notwendig ist. Im Falle, daß eine dauernde Unterbindung der Schilddrüsen-Aufnahme radioaktiver Isotopen des Jods gewünscht ist, sollte Potassium-Jodid in einer Anfangsdosis von 40 mg, gefolgt von einer Erhaltungsdosis von 3.3 mg täglich, verabreicht werden.

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(Anschritt der Verff.: Athen 611 [Griechenland], Vas. Sofias and Louren-Str.)

Effect of Orally Administered Potassium Iodate on Blood Sugar Response to Thiourea.\* (17777)

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The profound influence which goitrogenic drugs may exert on carbohydrate metabolism has recently been demonstrated. DuBois, Holm and Doyle(1) observed a marked hyperglycemia with concurrent depletion of liver glycogen 2½ hours after intraperitoneal injection of alpha-naphthylthiourea (ANTU) in adult rats. Previous administration of large doses of cysteine (1000 mg per kg) afforded protection against lethal doses of the goitrogen. Griesbach, Kennedy and Purves(2) have demonstrated that iodide injection in doses of 1.30 mg every fourth day into rats protected them against thiourea toxicity. Byerrum(3) likewise demonstrated the effectiveness of iodine, either as Lugol's solution or as potassium iodide, in protecting rats against the toxic effects of ANTU.

The purpose of this experiment was to determine the effect of orally administered potassium iodate on the blood sugar response of rats injected intraperitoneally with thiourea.

*Experimental.* 24 rats of both sexes of the Wistar strain were separated into 2 groups

of 12 each. Rats of Group I (Table I) ranging in weight from 148 to 398 g were bled from the tail and glucose concentration determined by the Folin-Wu micro method, after which thiourea (10 mg/kg) was injected intraperitoneally. A second blood sugar determination was made 2½ hours later.

The 12 rats in Group II (Table II) ranging in weight from 147 to 392 g received 0.2% potassium iodate in their drinking water *ad libitum* for 2 days, after which blood sugar determinations were made as in Group I. Then thiourea was injected intraperitoneally as in Group I (10 mg/kg) and a second blood sugar determination made after 2½ hours as before.

*Results.* The 12 rats in Group I receiving only thiourea showed an average rise in blood sugar of 91.0 mg per 100 cc 2½ hours following injection. Rats in Group II which had been fed 0.2% KIO<sub>3</sub> when injected with thiourea at the same dosage level as those in Group I showed an average blood sugar increase of only 14.6 mg per 100 cc. Statistically the results are significant, the *t*-value

TABLE I.  
Effect of Thiourea on Blood Sugar Level of 12 Non-fasted Rats. Second blood sugar reading (B) was taken 2½ hr after rats received 10 mg/kg thiourea intraperitoneally.

Sex	Wt g	Blood Sugar (A) mg/100 cc	Blood Sugar (B) mg/100 cc	Difference (B-A)
M	379	90	165	75
M	387	90	187	97
M	398	86	165	79
M	358	86	117	31
M	148	83	225	142
F	322	86	165	79
F	372	90	186	96
F	348	79	165	86
F	324	66	140	74
F	317	79	300	221
F	342	109	140	31
F	168	105	186	81
			Avg Blood Sugar Incr.	91

\* This work was aided by a grant from the Purdue University Alumni Research Foundation.  
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TABLE II.  
Effect of Thiourea on Blood Sugar Level of 12 Non-fasted Rats Previously Fed KIO<sub>3</sub>. Sugar reading (B) was taken 2½ hr after rats received 10 mg/kg thiourea intraperitoneally.

Sex	Wt g	Blood Sugar (A) mg/100 cc	Blood Sugar (B) mg/100 cc	Difference (B-A)
M	383	63	79	16
M	392	59	86	27
M	366	76	90	14
M	333	90	93	3
M	319	63	97	34
F	285	93	105	12
F	315	105	122	17
F	186	102	97	-5
F	147	69	86	17
M	193	83	97	14
M	201	90	97	7
M	150	73	93	20
			Avg Blood Sugar Incr.	14.7

of 5.16 indicating less than one chance in a thousand of the results being accidental.

*Summary.* Oral administration of potassium iodate for a 2-day period in drinking

water prevented the hyperglycemia which followed thiourea injection in rats.

Received March 8, 1950. P.S.E.B.M., 1950, v73.

## THE EFFECT OF SMALL DOSES OF POTASSIUM IODIDE ON THE THYROID GLAND OF THE GUINEA PIG<sup>1</sup>

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Received for publication October 28, 1936

In earlier investigations from this laboratory, it has been shown that if potassium iodide is fed to young adult guinea pigs in doses of 0.01, 0.05, or 0.1 grams daily for a period of 15 to 20 days, the thyroid gland undergoes a definite stimulation as is indicated by a marked increase in the number of mitoses in the acinus cells, by a slight increase in size of the acinus cells, a moderate softening of the colloid, an increase in the number of phagocytes invading and taking up particles of the intraacinar colloid, and also by an increase in the frequency and intensity of compensatory hypertrophy which follows extirpation of a considerable part of the thyroid gland (Loeb (1); Gray and Loeb (2)). It was furthermore possible to show that, within the range of quantities of KI used, the effects mentioned were the greater, the larger the amount of KI which was administered (Rabinovitch (3)). The phase of active thyroid stimulation was followed by a phase of inactivity of the gland. Similar results, which differed only quantitatively from those observed in the guinea pig, were obtained in the rat (Rabinovitch (4)). In principle similar to the effects of KI, although weaker, is the action of sodium bromide on the thyroid gland of the guinea pig (Margolin (5)). In contrast to this stimulating effect of KI, under the conditions stated, is the inhibiting action of KI, which is observed when this substance acts in combination with extracts of anterior pituitary on the thyroid gland (Silberberg (6)); it also diminishes or entirely neu-

tralizes the rise in basal metabolism which extracts of anterior pituitary gland alone would have produced (Siebert and Thurston (7)).

The doses used for stimulation of the thyroid gland of the guinea pig in these earlier experiments were relatively large; they corresponded to daily doses varying between 3 and 30 grams given to a human being weighing about 60 kgm. It was conceivable that much smaller doses might produce only the inhibiting effect of potassium iodide on the thyroid gland, which has been so far considered as the characteristic action of this substance. But, it could be shown by Gray and Rabinovitch (8) that much smaller doses of KI, when fed to guinea pigs during a period of 20 days, did not produce an inhibition of thyroid activity, but either were ineffective or also exerted a stimulation, which was, however, much less marked than that produced by larger doses. In these experiments daily doses as small as 0.0001, 0.001 gram were administered, while other animals received 0.01 gram KI. In control animals which had not been fed KI the average number of mitoses was 152, while in guinea pigs fed with 0.0001 gram KI the average number of mitoses was 560. Even if we omit one guinea pig in which the thyroid showed 2000 mitoses, the average of mitoses was still higher than that of the controls, namely 280. After a daily dose of 0.001 gram KI given for 20 days, the average number of mitoses was 507; if 2 guinea pigs are omitted, one with a very high and one with a very low mitotic activity, the average figure for mitoses was 302. Considerably higher, namely 1045, was the average number of mitoses when a daily dose of 0.01 gram KI was given. If we omit 1 guinea pig which did not react in the usual way, the figure reached as high as 1224 mitoses.

The structure of the thyroid glands of animals receiving the smaller doses of KI was not noticeably changed; the height of the epithelium showed the typical variations which are observed normally in different parts of the gland; the colloid was solid. In those receiving larger doses of KI the average size of the acini was perhaps slightly larger, and somewhat more irregular in shape, the epithelium was on the average slightly higher, the

<sup>1</sup> These investigations were carried out with the aid of a grant for research in science made to Washington University by the Rockefeller Foundation.

colloid somewhat softer, and the phagocytes more numerous than in the controls. However, even in individual control guinea pigs, variations may occur in this respect, and they occur also in the guinea pigs that received the smallest dose. Gray and Rabinovitch concluded that while daily doses of 0.001 and 0.01 gram KI have a stimulating effect on the thyroid gland, the smallest daily dose, namely 0.0001 gram, is ineffective in this respect. But this conclusion does not follow necessarily from their figures. Their counts show a distinct rise in mitoses from an average figure of 152 in the controls to an average figure of 565 in the guinea pigs receiving daily 0.0001 gram KI.

Under these conditions it was of interest to carry out a further series of experiments in which very small doses of KI were fed daily in order to test, whether they may exert a stimulating effect on the thyroid of guinea pigs. We chose for this purpose the smallest dose given by Gray and Rabinovitch, namely 0.0001 gram KI. In additional experiments, 0.0005 gram KI were fed daily to a second series of guinea pigs. These animals weighed on the average 200 grams; they had therefore a lower weight than those used by Gray and Rabinovitch, in which the weight varied between 325 and 450 grams. Furthermore while these investigators studied the glands after administration of KI during a period of 20 days only, we examined the thyroid glands after feeding periods of 5, 10, 15 and 20 days. All the guinea pigs used were males. As usual the thyroid glands were cut into serial sections and the mitoses were counted in every tenth section of one lobe. The average figures obtained were multiplied by the number of sections in both thyroid lobes. Table 1 shows the number of mitoses found in the acini of the controls.

In guinea pig 8, in which the thyroid gland was larger than in the other guinea pigs, the number of mitoses was slightly above the average. The average number of mitoses in the thyroid glands of these 8 animals was 171. This figure is very similar to the average number of mitoses obtained in normal control guinea pigs in former experiments. The acini were generally small and the acinus cells varied as a rule between flat and cuboidal. The size of the acinus cells varied in a characteristic manner in different

areas of the thyroid gland in accordance with the previous findings of Loeb. The colloid was hard. In guinea pig 8, in which the number of mitoses had been somewhat greater, the acinus

TABLE 1

NUMBER OF GUINEA PIG	WEIGHT grams	NUMBER OF MITOSES
1	220	158
2	190	196
3	235	144
4	185	166
5	215	130
6	180	104
7	210	184
8	240	258

TABLE 2

NUMBER OF GUINEA PIG	WEIGHT AT BEGINNING AND END OF EXPERIMENT grams	AMOUNT OF KI FED DAILY grams	NUMBER OF DAYS OF KI FEEDING	NUMBER OF MITOSES	AVERAGE NUMBER OF MITOSES
964	190-205	0.0001	5	350	
965	190-210	0.0001	5	374	362
966	195-225	0.0001	10	188	
967	190-210	0.0001	10	356	262
968	185-225	0.0001	15	706	
969	185-215	0.0001	15	532	619
970	185-225	0.0001	20	282	
971	190-255	0.0001	20	386	334
980	195-285	0.0005	15	1,040	
981	200-290	0.0005	15	1,336	1,188
982	190-300	0.0005	20	580	
983	195-310	0.0005	20	738	659

cells were correspondingly slightly higher than in the average control animals; this applies especially to the central acini; furthermore, the colloid was somewhat softer in this guinea pig, as was

indicated by larger vacuoles in the periphery and by the presence of a few phagocytes observed in the colloid of several acini.

Our findings in the 12 guinea pigs which received KI in the form of pills daily are shown in table 2.

The average number of mitoses in these 12 guinea pigs was 571 as against 171 in the controls. Only in one of the 12 guinea pigs (No. 966) was the number of mitoses as low as in the controls. As early as 5 days after the beginning of the feeding of 0.0001 gram KI, there was noticeable a slight rise in the proliferative activity of the acinus cells. With a dose of 0.0001 gram KI, the maximum figures for mitoses were reached after 15 days administration of this substance. After 20 days feeding there was a slight fall, although the figure at this time was still above the average number in the controls. With a dose of 0.0005 gram KI, the stimulating effect was greater than with the 0.0001 gram dose. In this case also the number of mitoses was greater after 15 days administration of KI than after 20 days. In former experiments, it was found that if larger doses of 0.01 to 0.1 gram KI were fed daily, the maximum stimulation was observed from the fifteenth to the twentieth day after beginning of the experiment. We must therefore consider the possibility that the smaller doses of KI cause an earlier decline in the proliferation of the acinus cells than do the larger doses. In a similar way, Kippen and Loeb (9) observed that if the thyroid gland was stimulated by means of anterior pituitary extract, the maximum of stimulation showed an earlier decline when smaller doses were given.

Counting the number of mitoses represents probably the most exact method for a quantitative estimation of thyroid stimulation which may still show effects when basal metabolism tests prove negative. The other morphological characteristics of the thyroid gland which also indicate a stimulation of this organ, such as an increased average size of the acinus cells, a softening and increased vacuolization of the colloid and an increase in the number of phagocytes in the colloid, which may be used as subsidiary signs, were not on the whole well developed in these experiments. One or the other of these structural signs of stimulation was usually present in the thyroid gland of the animals

which had been fed KI and in some instances there were present several of these indications of increased thyroid activity. This was especially noticeable with animals to which had been administered the larger dose of KI, namely 0.0005 gram daily. It was also more marked in guinea pigs fed during periods of 15 and 20 days with KI than in those which had received this substance only for shorter periods.

#### CONCLUSIONS

We may then conclude that oral doses of KI as small as 0.0001 gram given daily do not exert an inhibiting effect on the thyroid gland of the guinea pig; on the contrary the results obtained by us in counting the mitoses in the acinus cells, together with those obtained formerly by Gray and Rabinovitch, render it very probable that these small quantities of KI exert a slightly stimulating effect on the thyroid gland. The stimulating effect seems to reach a maximum approximately after a period of 15 days during which this dose was administered daily. The stimulating effect is more marked if instead of 0.0001 gram, 0.0005 gram KI is given daily. The doses used in guinea pigs would correspond to doses of 0.03 and 0.15 gram respectively of potassium iodide per day given to a man weighing 60 kgm. These experiments do not justify therefore, the view expressed by some investigators that large doses of KI stimulate the activity of the thyroid gland while small doses inhibit it; but they indicate that with a diminution in the quantity of KI used, the stimulating effect decreases until at last a point will be reached when no effect is noticeable. This applies, if the period during which KI is given, is limited to 3 weeks. In the earlier experiments from this laboratory, indications have been found that this period of stimulation may be followed by a second period during which an inhibition in the activity of the thyroid gland may take the place of the initial stimulation and that this inhibiting effect may be due, at least in part, to the pressure exerted on the acinus cells by an increase in the volume of colloid present in the lumen of the acini.

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J. Am. Pharm. Assn. 47:56-57. 1958

## The Effect of Orally Administered Sodium Iodide and Sodium Iodate on Blood Sugar Response to Thiourea in Rats\*

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Sodium iodide and sodium iodate, when administered in drinking water for a period of two days as a 0.2 per cent solution, greatly diminished the hyperglycemia which normally follows the intraperitoneal injection of thiourea. The mechanism of action is not definitely known, but the protection may result from the prevention of epinephrine release, or the inhibition of hepatic glycogenolysis.

FOLLOWING THE OBSERVATIONS of DuBois, Holm, and Doyle (1), and, later, of Dubois Hermann, and Erway (2) that, following the intraperitoneal injection of thiourea and its derivatives, there occurs in adult rats a marked rise in blood sugar associated with increased hepatic glycogenolysis, several researchers have endeavored to prevent the hyperglycemia induced by these agents and thus, possibly, to uncover their mode of action and develop an antidote for the

toxic effects of pulmonary edema and pleural effusion, as seen in adult rats. The injection of iodide every four days has protected rats (3). Byerrum (4) and Mann (5) have shown that the oral administration of iodine and iodides, either as Lugol's solution, potassium iodide or potassium iodate, will similarly afford protection against the hyperglycemic response, and will enable the animal to withstand normally lethal doses.

This experiment is intended to determine the relative protective activity of sodium iodide and sodium iodate against the hyperglycemia following the intraperitoneal administration of ten milligrams per kilogram of body weight of thiourea to nonfasted, male, albino rats.

### EXPERIMENTAL

Male rats of the Wistar strain were used exclusively in this experiment. The animals were placed in individual cages and were permitted to remain in these cages for periods of five to eight days before being used. All were fed Purina Lab Chow, and were given tap water *ad libitum* through glass tubes attached to drinking bottles until placed on a particular liquid diet. The same drinking bottles

\* Received May 3, 1957, from Temple University, School of Pharmacy, Philadelphia 40, Pa.

Abstracted from a thesis presented to the Graduate School of Temple University, School of Pharmacy, by Arthur H. McCreesh, in partial fulfillment of the requirements for the degree of Master of Science.

Presented to the Scientific Section, A. Ph. A., New York City meeting, May 1957.

TABLE I.—EFFECT OF SODIUM IODIDE AND SODIUM IODATE ON BLOOD SUGAR RESPONSE TO THIOUREA IN NONFASTED, MALE, ALBINO RATS

Group	No. of Animals	Treatment	Av. Blood Sugar before Thiourea, mg./100 ml.	Av. Blood Sugar after Thiourea, mg./100 ml.	Av. Diff. ( $\pm$ )	Av. Change, %
1	27	Thiourea 10 mg./Kg. (controls)	113.63	183.48	69.85 ( $\pm 33.39$ )	63.67
2	12	Sodium Iodide <i>ad libitum</i> for two days, then thiourea	101.72	117.93	16.21 ( $\pm 13.62$ )	19.70
3	12	Sodium Iodate <i>ad libitum</i> for two days, then thiourea	112.20	132.63	20.53 ( $\pm 12.54$ )	18.90

were employed to deliver sodium iodide and sodium iodate solutions throughout the experiment. At the start of the experiment the animals were divided into three groups.

The rats in Group One, all nonfasting, male, albino rats, ranging in weight between 182 and 270 grams, were given tap water *ad libitum* as drinking water for two days, and served as controls in the experiment. After two days, the animals were bled from the tail, and blood glucose determined by the Folin-Malmros method (6). Immediately after withdrawing blood, a thiourea solution (10 mg./Kg. of body weight of a 0.5% aqueous solution) was injected intraperitoneally, and a second blood sample was taken after two and one-half hours. The blood glucose concentration was again determined by the Folin-Malmros method.

Group Two, consisting of nonfasted, male, albino rats, ranging in weight between 138 and 182 grams, was given a solution of sodium iodide (0.2%) *ad libitum* as drinking water for two days, whereupon blood was drawn from the tail, and the blood glucose level determined as above. Thiourea solution (10 mg./Kg. of body weight) was immediately injected intraperitoneally. After two and one-half hours a second blood sample was withdrawn and blood glucose determined.

Group Three consisted of nonfasted, male, albino rats, ranging in weight between 125 and 252 grams. These animals were treated identically as Groups One and Two, except that they received sodium iodate solution (0.2%) as drinking water *ad libitum* for two days. Blood samples were drawn from the tail both immediately before and two and one-half hours following the intraperitoneal injection of thiourea (10 mg./Kg. of body weight). Blood glucose was determined by the Folin-Malmros method as with all groups.

## RESULTS

The rats in Group One, receiving no iodide or iodate therapy prior to the intraperitoneal injection of thiourea, showed an average blood sugar rise of 69.85 ( $\pm 33.39$ ) milligrams per 100 milliliters of blood two and one-half hours following the injection.

The rats in Group Two, receiving a two-day, *ad libitum* administration of sodium iodide prior to an intraperitoneal injection of thiourea, showed an average blood sugar rise of 16.21 ( $\pm 13.62$ ) milligrams per 100 milliliters of blood two and one-half hours after the injection.

The rats in Group Three, receiving a two-day *ad libitum* administration of sodium iodate prior to an intraperitoneal injection of thiourea, showed an average blood sugar rise of 20.53 ( $\pm 12.54$ ) milli-

grams per 100 milliliters of blood two and one-half hours after the injection.

## DISCUSSION

The rodenticidal property of thiourea and its derivatives, proposed by Richter (7), and tested on a controlled scale by MacKenzie and MacKenzie (8), and others in the early and middle forties, is a result of severe pulmonary edema and pleural effusion. Drinker (9) found an eighty-fold increase in lymph flow from the heart and lungs following an injection of alphanaphthylthiourea (ANTU) into rats. Although toxic doses vary greatly among strains of the same animal, and wild rats are much more resistant than laboratory animals, there can be no doubt of the toxicity of these agents.

It was DuBois, Holm, and Doyle (1) who first observed a rise in blood sugar following the administration of thiourea and its congeners, the hyperglycemia being associated with increased liver glycogenolysis; the onset, extent of activity, and duration being dependent upon the quantity given. DuBois, Hermann, and Erway (2) noted that the results were not altered by hypophysectomy, nor was there an inhibition of glycogenolysis or the oxidation of glucose.

Although the mechanism of action is uncertain and as yet no specific antidote has been found for thiourea, it has been observed that drugs which prevent or diminish the hyperglycemic response will also prevent or diminish the toxic effects. Griesbach, Kennedy, and Purves (3) have protected animals by the repeated injection of potassium iodide; and Byerrum (4) enabled rats to withstand many times the lethal dose by feeding the animals a diet rich in iodine, and by administering potassium iodide and iodine in drinking water. Mann (5) showed the protective action of potassium iodide and potassium iodate when administered *ad libitum* in drinking water. In this experiment the protective properties of sodium iodide and sodium iodate against the hyperglycemic response to thiourea have been demonstrated.

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## THE EFFECT OF POTASSIUM IODIDE ON THE PULSE RATES OF NORMAL INDIVIDUALS<sup>1</sup>

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There appears to be no settled opinion concerning the effect of iodine on the pulse rate of normal individuals. Cushny (1) states that no change in the heart, pulse or blood-pressure could be observed even after prolonged treatment with iodides. Nevertheless, in certain Clinics the term "iodine tachycardia" is used to describe the elevated pulse rate occasionally seen in patients under treatment with iodides. There is some evidence to support this view. The statement has also been made that a fall in pulse rate occurs.

Gurewitsch (2), in Basel, studied a series of patients under treatment with potassium iodide and found an increased pulse rate (10 to 50 per minute) in 68 per cent. The tachycardia disappeared in a few days after withdrawal of the drug. Bloom (3), in reporting somewhat similar material from Berne, noted an increase (3 to 33 per minute) in 75 per cent of 23 cases. The majority of the latter subjects had tuberculosis or syphilis which might be considered a modifying factor. Goiter and "Iodine Basedow's" are common in both localities. Stockman and Charteris (4) found no change in the pulse rates of patients treated with sodium iodide and potassium iodide in doses varying from 1 to 20 grams daily. The best study has been made by Read, Walker and McKenney (5) on 12 normal individuals who were placed on 10 drops of Lugol's solution daily for ten days. There was a slight increase in 7, no change in 3 and a slight decrease in 2 cases. The means showed an inconsequential increase.

In a study of the effect of iodine on the electrocardiogram in a series of normal individuals (6) it was found that 8 out of 10 exhibited an increased heart rate after ingestion of potassium iodide and that the means of the series showed a progressive increase during the period of exhibition of the drug. The observations were too few, however, to

<sup>1</sup> Submitted for publication September 20, 1930.

analyze statistically. A review was therefore made of the records of patients who had been treated with iodides over considerable periods of time in the wards of the Johns Hopkins Hospital. Cases of thyroid disease, syphilis, tuberculosis, myocardial insufficiency or of fever due to any cause were rigidly excluded. No patients were accepted who had received other drugs, such as atropine or digitalis, which might have affected the pulse rate. The majority were cases of arteriosclerosis, neuritis and arthritis. The average of seven successive morning pulse rates was taken before administration of the drug and the same for the seven days prior to its discontinuance. When administration of the drug covered sufficient time, the average of each week's morning pulse rates was also noted. The usual dose of potassium iodide was 2.0 grams daily and the duration of its exhibition varied from 8 to 140 days. The youngest patient was 2 years of age and the oldest 80. Potassium iodide was the drug used in all patients.

### RESULTS

The mean of the 34 control pulse figures is found to be 82.6 and that of the iodine pulse figures 87.5, giving a difference in the means of +4.9. The probable error of this difference is  $\pm 2.1$ . It is assumed that a difference, in order to be of significance, must have a ratio, when compared with its probable error, of 3 to 1 or greater. For these figures the ratio is but 2.3 to 1 and the difference cannot therefore be considered as significant. Read, Walker and McKenney (5) treated their figures similarly. Such statistical treatment is based, however, upon the assumption that all individuals in the series react in like manner to the drug, an assumption which the following data show to be incorrect.

Table I shows the data obtained in this study. Each pulse figure represents the average of 7 or more observations. The standard deviation and the probable error of the mean have been calculated for each of these series of variants and the probable error of each difference is included in the table. It will be noted that an apparent increase has occurred in 24 instances, an apparent decrease in 9, and no change in one. When the ratio of each difference to its probable error is calculated, however, it is seen that there is a significant increase in 12 in-

TABLE I

*Effect of potassium iodide on normal pulse rate*

MED. NO.	AGE	DAYS ON KI	TOTAL GRAMS TAKEN	CONTROL PULSE	PULSE DURING IODINE	PULSE DIFFERENCE	PROBABLE ERROR OF DIFFERENCE	RATIO OF DIFFERENCE TO P.E. OF D.	SIGNIFICANT PULSE CHANGE*
3620	45	21	42	75.4	77.1	1.7	3.3	0.5	0
3637	56	27	54	84.0	74.5	9.5	1.4	6.8	-
3640	66	34	68	78.2	96.5	18.3	2.6	7.0	+
3652	42	77	733	64.2	92.0	27.8	2.0	13.9	+
3656	68	13	26	79.4	76.5	2.9	1.9	0.6	0
3671	49	10	20	78.2	58.9	19.3	1.3	14.8	-
3677	38	18	36	81.4	84.5	3.1	2.3	1.3	0
3697	65	12	26	72.0	83.4	11.4	3.1	3.7	+
3721	42	140	280	97.0	110.0	13.0	2.3	5.7	+
3745	33	40	80	72.8	88.5	15.7	2.3	6.8	+
3750	46	61	124	94.2	82.5	11.7	2.3	5.1	-
3859	68	30	60	76.6	79.4	2.8	2.3	1.2	0
3873	56	74	148	75.7	75.7	0	2.8	0.0	0
3878	24	50	253	114.2	101.7	12.5	3.1	4.0	-
3883	66	12	36	85.6	98.5	12.9	2.9	4.5	+
3961	80	16	48	66.6	65.4	1.2	2.1	0.6	0
4047	28	10	30	91.1	91.7	0.6	1.7	0.3	0
4102	80	29	58	95.8	97.8	2.0	4.2	0.5	0
4201	36	8	28	82.8	90.4	7.6	2.8	2.7	0
4320	53	120	240	65.3	82.2	16.9	2.2	7.7	+
10794	38	16	32	70.4	80.2	9.8	4.5	2.2	0
10817	63	20	40	79.4	87.4	8.0	1.8	4.4	+
10820	46	14	20	77.4	84.0	6.6	2.3	2.9	0
10910	61	16	32	77.0	78.2	1.2	3.5	0.3	0
11025	38	30	75	98.3	90.5	7.8	2.0	3.9	-
11028	38	8	37	63.7	89.7	26.0	2.5	10.4	+
11033	47	9	18	85.7	89.1	3.4	2.9	1.2	0
16643	66	15	30	95.5	102.0	6.5	3.3	2.0	0
16648	30	23	182	83.1	79.7	3.4	1.9	1.8	0
16657	44	33	66	97.6	94.2	3.4	1.8	1.9	0
16770	3	35	11	124.8	127.8	3.7	2.5	1.5	0
16898	44	34	105	73.0	86.3	13.3	2.3	5.8	+
16963	34	30	90	80.5	88.0	7.5	2.0	3.7	+
17040	14	25	25	73.2	94.3	21.1	3.8	5.5	+

\* A change is only considered to be significant when the ratio of the difference to the probable error of that difference is 3:1 or greater.

words 35.0 per cent of the 34 cases exhibit an increase pulse rate under iodine, 15.0 per cent a decrease and the remainder no real change. These changes vary from 8 to 28 beats per minute.

Figure 1 illustrates graphically the changes that occurred in cases No. 4320 and No. 11028 of this series following the administration of iodine. In the latter the effect of its discontinuance is also shown.

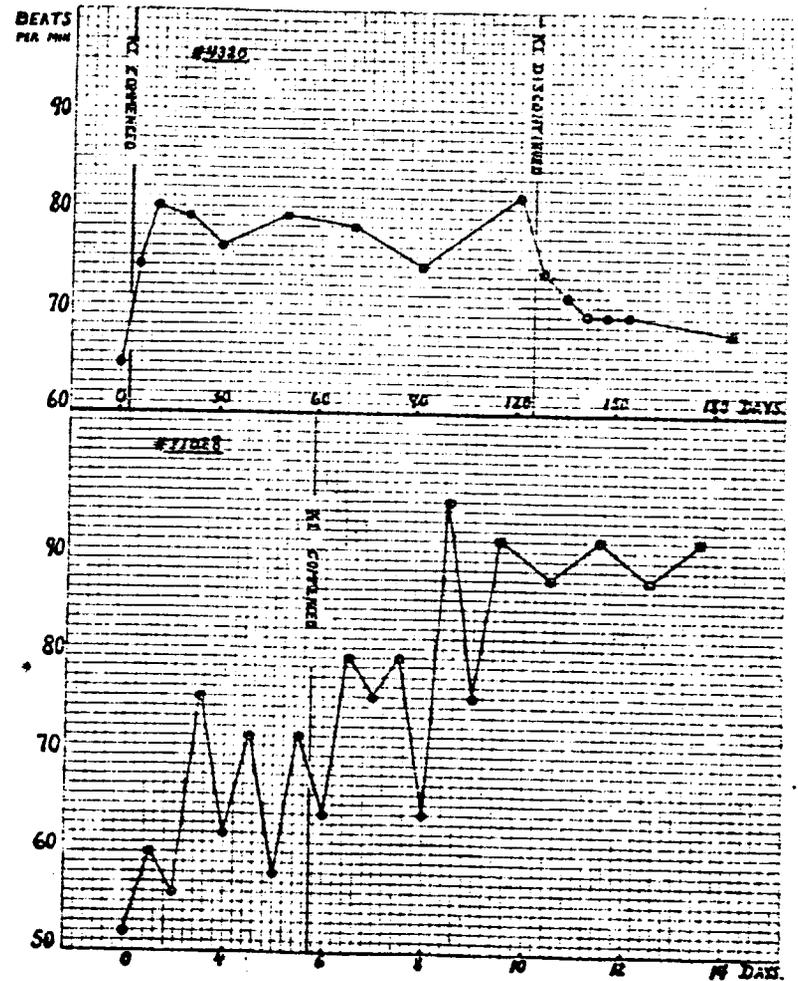


FIG. 1

The upper curve represents a case studied over some 180 days, each point being the average of 7 consecutive daily pulse rates. The rapid elevation of rate, its persistence during iodine therapy and its dis-

appearance after removal of the drug are well shown. The lower curve represents a case followed for 12 days, each point being a separate pulse rate observation. The increase is seen to occur about the third day after the iodine was begun. In all of the cases exhibiting significant alterations in pulse rate, the change occurred gradually at about the third to the seventh day and reached a maximum about the tenth. Upon discontinuance of the drug, the pulse fell to normal within a week or so.

#### SUMMARY

A statistical analysis was made of the pulse rates of 34 patients, without thyroid disease or other interfering circumstances, to whom potassium iodide had been administered. Following administration of the drug, 12 showed a significant increase in pulse rate and 5 a significant decrease. These changes came on gradually about the third to the seventh day and reached a maximum at about the tenth day. The rate returned to normal within a week or so after the drug was discontinued.

I am indebted to Miss Rebecca Marshall for assistance with the case-records and calculations.

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THE EFFECT OF THE INGESTION OF POTASSIUM IODIDE  
ON THE ELECTROCARDIOGRAM OF NORMAL  
INDIVIDUALS<sup>1</sup>

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It has been reported by several observers that changes occur in the electrocardiograms of patients with hyperthyroidism following iodine therapy or thyroidectomy. Krumbhaar (1) studied 51 patients with goitre, the majority with hyperthyroidism, and noted unusually high T-waves in the majority of instances. Following operation these returned to normal in half the cases. These records, however, were taken with an Edelmann galvanometer and the string deviations were therefore not standardized. Hamburger and others (3) noted the very high T waves in hyperthyroidism and showed that iodine therapy produced a fall in their amplitude which paralleled the fall in basal metabolic rate. Following thyroidectomy, these changes were even more striking—in three cases proceeding to inversion. The low T waves and QRS complexes found in cretinism and myxedema are well recognized (2, 4, 5, 6, 7, 8). They increase in amplitude upon thyroid administration, the increase paralleling the rise in basal metabolic rate. White and Aub (2) concluded that there was little relationship between the basal metabolic rate and the voltage of the end phase. However, a study of their protocols shows that of 12 cases in which comparison is possible, a parallelism exists between the height of the T waves and the basal metabolic rate in 8 instances.

It seemed of interest, therefore, to determine whether the galvanometric records of normal individuals exhibited changes when iodine was administered in therapeutic doses. Hamburger, and others, (9) attempted to answer this question, but obtained conflicting results. Some writers have claimed on slender evidence, that iodides, in therapeutic doses, exert an injurious influence on the cardiovascular system.

<sup>1</sup> Submitted for publication September 20, 1930.

## METHOD

Iodine, in the form of Potassium Iodide, was administered by mouth to fourteen normal members of the hospital staff each day in doses of 1.0 gram per day during the first week, 2.0 grams per day during the second week and 3.0 grams per day during the third week. Four of the subjects were forced to drop out because of rather severe iodide reactions. The remaining ten took the drug for periods ranging up to 22 days. Lugol's solution was used for the first few days but gave way to Potassium Iodide owing to bitter complaints of the recipients. In this connection it is suggested that enthusiasts for large doses of Lugol's solution try a short course of the drug themselves.

Electrocardiographic records were made before administration of the drug and every five days thereafter till the end of the experiment. They were taken with standard Einthoven leads on a Hindle galvanometer in use for routine purposes. The subjects were made to rest in the sitting posture for ten minutes before records were made and the heart rates were subsequently read in the third lead thus allowing a further short period of rest. Skin resistance was measured in every instance and if above 2000 ohms the electrodes were removed, the skin rubbed with alcohol and remoistened with saline before the written records were made. This procedure effectively brought the resistance below 2000 ohms in every case. The string was standardized in the usual manner to give a deflection of 1.0 cm. with 1.0 millivolt. Records were taken between 4 and 5 P.M. in order to rule out the possible effect of food on the cardiac rate and the written curves.

## DISCUSSION

Table I is a tabulation of the data from each individual before the drug was commenced and at the completion of the course of potassium iodide. The intervening records were examined but showed no significant changes. Measurements were also made of the other deflections in the electrocardiogram, but they showed no alteration and are not included. It is apparent that no change of any consequence occurred as a result of the ingestion of potassium iodide. The T-wave changes said to occur after iodine therapy in patients with hyperthyroidism

TABLE I

	SUBJECT 1		SUBJECT 2		SUBJECT 3		SUBJECT 4		SUBJECT 5		SUBJECT 6		SUBJECT 7		SUBJECT 8		SUBJECT 9		SUBJECT 10	
	Before iodine	After iodine																		
Number of days on KI.....	5		15		19		16		15		21		20		22		20		19	
Total KI taken (gms.).....	9		21		22		23		25		37		40		41		42		45	
Skin resistance (ohms).....	1400-1400		1300-2000		1200-1400		1000-1700		400-1000		1400-1900		1000-1300		-2000		2000-1400		1100-1400	
B. M. R.....	-14	-9	-14		-13	-19	-20	-29	-12	-2	-16	-9	-19	-19	-13	-12	-4	-3	-28	-37
P-R interval (secs.).....	0.20	0.20	0.16	0.17	0.16	0.17	0.15	0.15	0.19	0.20	0.19	0.17	0.18	0.18	0.14	0.14	0.17	0.17	0.19	0.19
R-T interval (secs.).....	0.24	0.23	0.26	0.28	0.24	0.24	0.23	0.23	0.21	0.21	0.25	0.23	0.26	0.24	0.22	0.21	0.24	0.19	0.22	0.20
QRS duration (secs.).....	0.04	0.06	0.08	0.08	0.06	0.06	0.03	0.03	0.04	0.03	0.06	0.05	0.05	0.06	0.04	0.05	0.05	0.05	0.05	0.05
T duration (secs.).....	0.18	0.17	0.21	0.19	0.20	0.19	0.20	0.18	0.18	0.19	0.12	0.13	0.21	0.21	0.20	0.18	0.16	0.13	0.20	0.15
T I -height (mms.).....	5.0	3.5	5.0	4.5	2.5	2.5	2.5	2.0	3.5	3.0	2.0	2.0	2.5	4.0	1.5	1.5	3.0	2.0	2.5	2.0
T II -height (mms.).....	4.0	3.0	5.0	5.5	4.0	4.0	3.5	2.5	3.0	3.0	1.5	1.5	6.5	6.5	5.0	4.0	4.0	2.0	4.5	4.0
T III -height (mms.).....	0*	2.0	2.0	0.5*	1.5	2.0	1.0	1.0	1.0	1.5	1.0	0*	3.5	3.0	4.0	2.0	2.0	0.5	4.0	3.0
Heart rate.....	71	75	68	57	75	79	67	79	83	88	69	75	60	69	59	82	68	63	72	91

\* Biphasic.

diminution in amplitude occurred in six instances and slight increase in two, neither being outside the usual limits of variation. Inversion was not seen, although T III became biphasic in two instances. The skin resistance and the basal metabolic rate showed no alterations that could be attributed to the iodine. The effect on the heart rate is discussed elsewhere (10).

It would appear therefore that the electrocardiographic changes wrought by iodine in hyperthyroidism may be the result of its general effect upon the disease and not of any specific action of the drug on the cardiovascular system.

#### CONCLUSIONS

Potassium Iodide in therapeutic doses has no significant effect upon the electrocardiogram of normal individuals.

We are indebted to Miss J. A. Vickers and to Mr. Wm. M. O'Brien for technical assistance in this study.

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## THE EFFECT OF ORAL IODIDES ON INFLAMMATION\*

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*Iodides; Inflammation*

Iodides have been used against chronic inflammation during the past 100 years solely on an empirical basis. With the advent of new drugs, iodides have fallen into disfavor, and reports on anti-inflammatory effects of iodides are scarce. During the past 15 years, two clinical studies have been reported on the anti-arthritis activity of iodides: one after intravenous administration of colloidal iodide (Hagenbach and Wolsmley, 1953), and the other after balneological treatment with iodide salts (Fortuna, 1960). In textbooks, the anti-inflammatory effects of iodides have been described vaguely as "fibrolytic" or "histiolytic." In experimental animals, inhibition of granuloma pouch formation by 250 mg/kg of cuprous iodide has been reported by Sutter et al. (1958).

In contrast to the concept of iodides as anti-inflammatory agents, Stone and Willis (1967) have presented evidence that iodides enhance rather than inhibit certain types of dermatologic inflammation.

Our investigation was initiated in order to determine whether orally administered iodides have anti-inflammatory properties against different types of acute and chronic inflammation in experimental animals.

### MATERIALS AND METHODS

Potassium iodide (KI)<sup>1</sup> was studied for anti-inflammatory effects against granuloma pouch formation, cotton granuloma formation, carrageenan and croton oil edema in rats, and turpentine abscesses in monkeys.

1. Granuloma pouch formation was induced according to a slightly modified procedure by Selye (1953). Twenty-five ml of air was injected subcutaneously on the backs of 125 g male Sprague-Dawley rats, and 1.0 ml of 1.0% croton oil was injected into this air space. KI was administered orally as an aqueous solution once daily to groups of six rats each, starting one day before the injections of croton oil. The doses ranged from 29 to 466 mg/kg/day and were administered in a volume of 1 ml/100 g body weight. Control rats received equivalent amount of water daily. All rats were sacrificed on the ninth day after the injections of croton oil, and the volume of exudate and the weight of walls for each pouch were determined. The effect of KI on the granuloma pouch formation was studied in three separate experiments because of the inherent variability of this bioassay. In one experiment, the effect of KI upon the thyroid was studied

\* Received for publication October 12, 1967.

<sup>1</sup> "Baker Analyzed" Reagent, Baker Chemical Company, Phillipsburg, N.J.

histologically in rats medicated with 466 mg/kg of KI. The thyroids were fixed in Zenker-formalin, embedded in paraffin, and stained with hematoxylin and eosin.

2. Cotton granuloma formation was induced according to a modified method of Winter et al. (1963). One cotton pellet weighing 46-48 mg was implanted subcutaneously on the back of each rat. KI was administered orally to nine rats at 466 mg/kg/day, starting one day before the implantation of the pellets. Nine control rats received only the vehicle of the medication. All rats were sacrificed on the seventh day after implantation, the pellets with the granulomatous tissue were removed and the dry weight of granuloma was determined.

3. Carrageenan edema was induced in the rat foot according to a modified method of Winter et al. (1963). KI was administered orally at 800 mg/kg to five rats fasted for 18 hours. One hour later, 0.05 ml of 1% aqueous carrageenan<sup>2</sup> suspension was injected into the right hind foot, and 0.05 ml of saline into the left hind foot of each rat. The rats were sacrificed three hours after the carrageenan injections, and the injected feet were cut off and weighed. The difference between the right and left foot weights was taken as the weight of edema.

4. The procedure for croton oil edema in rats was similar to that of carrageenan edema, except that 0.2% croton oil in cottonseed oil instead of the carrageenan suspension was injected into the foot and that six rats were used per group. The dose of KI was 800 mg/kg.

5. Subcutaneous abscesses in Rhesus monkeys were induced by intradermal injections of 0.1 ml of 25% turpentine. Each monkey received two injections, one on each side of the back. The three dimensions of the subcutaneous swellings were determined at 5 hours, 24 hours, and at 2, 3, 6, and 7 days. The lateral and cranial-caudal dimensions of each swelling were determined with a caliper, and the height by a ruler placed on an adjacent noninflamed area. A size index of each abscess of each time interval was obtained by multiplying the three dimensions with each other and dividing by one hundred. The 5-hour readings represented acute, turpentine-induced edema, and sums of the size indices of each abscess over the 7-day period represented the abscess formation. Two monkeys received 100 mg/kg of KI daily starting one day before the injection of turpentine, and three other monkeys served as controls and received equivalent amount of water daily.

The significance of the differences between the results in animals treated with KI as compared to control animals was analyzed according to the t-test.

## RESULTS

KI inhibited granuloma pouch formation (production of exudate and formation of walls) when administered orally at 116, 233, or 466 mg/kg (Table 1). Although significant inhibition could be demonstrated at these dose levels, regression lines of the dose-related responses were not significant due to the flatness of the slopes and the variations within the medicated and control groups. Average of inhibition of exudate formation at 29, 116, and 466 mg/kg in three experiments were 16, 52, and 70%, respectively, and averages of inhibition of wall formation at the same dose levels were 8, 33, and 46%, respectively.

All doses of KI in the granuloma pouch test were well tolerated. The body weight gains were within normal limits, and the thyroids of the rats medicated at 466 mg/kg were normal when studied histologically.

KI did not inhibit cotton granuloma formation at 466 mg/kg, and carrageenan or croton oil edema at 800 mg/kg. Similarly, KI was ineffective at 100 mg/kg against turpentine edema and turpentine abscess formation in monkeys (Table 2).

<sup>2</sup> Viscarin, Marine Colloids, Inc., N.Y., N.Y.

TABLE 1

*Effect of KI against granuloma pouch formation*

A. Inhibition of exudate production							
Daily dose mg/kg	ml	Exp. 1 % Inh.	ml	Exp. 2 % Inh.	ml	Exp. 3 % Inh.	Av. % Inh.
— (controls)	8.9 ± 1.8	..	14.0 ± 1.8	..	15.5 ± 1.0	..	..
29	.....	..	9.5 ± 2.6	32	15.3 ± 1.8	1	16
116	4.3 ± 1.8	52	6.2 ± 1.3	56**	8.2 ± 1.3	47**	52
233	3.7 ± 1.3	58*	.....	.....	.....	.....	..
466	1.7 ± 0.4	81**	5.4 ± 1.3	61**	5.0 ± 2.4	68**	70

B. Inhibition of wall formation							
Daily dose mg/kg	ml	Exp. 1 % Inh.	ml	Exp. 2 % Inh.	ml	Exp. 3 % Inh.	Av. % Inh.
— (controls)	1.91 ± 0.26	..	2.92 ± 0.17	..	3.06 ± 0.14	..	..
29	.....	..	2.46 ± 0.32	16	3.19 ± 0.20	0	8
116	1.32 ± 0.36	31	2.04 ± 0.27	30*	1.88 ± 0.30	39**	33
233	1.26 ± 0.24	34	.....	.....	.....	.....	..
466	0.93 ± 0.11	51**	1.87 ± 0.21	36**	1.53 ± 0.40	50**	46

† rats/medicated group, 12-18 rats/control group.  
 \* Significant at p < 0.05.  
 \*\* Significant at p < 0.01.

TABLE 2

*Effect of KI against cotton granuloma, carrageenan and croton oil edema, and turpentine inflammation*

Experiment	Dose mg/kg of KI	No. of animals	Quantitation of inflammation	% Inh.
Cotton granuloma formation in rats	466	9	54.1 ± 5.2*	7
	— (controls)	9	58.1 ± 4.6	..
Carrageenan edema in rats	800	5	476 ± 45†	4
	— (controls)	10	495 ± 32	..
Croton oil edema in rats	800	6	251 ± 20†	13
	— (controls)	6	290 ± 24	..
Turpentine inflammation in monkeys	a) 5-hour edema	100	71 ± 15‡	0
		— (controls)	64 ± 14	..
	b) 7-day abscess	100	352 ± 63¶	0
		— (controls)	338 ± 63	..

\* mg of dry granulomatous tissue.  
 † mg of edema.  
 ‡ size indices.  
 ¶ sums of 6 measurements of abscesses (size indices) over 7 days.

## DISCUSSION

Examination of KI in five acute and/or chronic models of inflammation revealed significant inhibitory activity only against one model: granuloma pouch formation. Such limited anti-inflammatory activity does not permit a classification of KI as a general anti-inflammatory compound in view of the significant activity that can be obtained with true anti-inflammatory compounds. In our laboratory, anti-inflammatory compounds are active against at least three or four models of inflammation: anti-inflammatory steroids are active against granuloma pouch formation, carrageenan edema, and cotton granuloma formation; and phenylbutazone and indomethacin are active against carrageenan edema, cotton granuloma formation, and turpentine edema and abscesses. The fifth model of inflammation—croton oil edema—is not an anti-inflammatory screening test, and it was used to determine the effect of KI against another croton-oil-induced model of inflammation. Inactivity of KI against this model indicates that the inhibition of granuloma pouch formation is not a specific effect of KI against inflammation induced by croton oil.

Questions can be raised as to the significance of the activity of KI against granuloma pouch formation, and whether the inhibition of granuloma pouch formation by KI is mediated by systemic or local mechanisms.

In considering the systemic effects of KI, the most likely effect of KI is suppression of the thyrotropin-thyroxine axis. Iodides are known to be effective against hyperthyroidism, and Ochi (1961) has reported inactivation of thyrotropin by elemental iodine. However, the activity of thyroids did not appear to be suppressed following administration of KI at granuloma pouch inhibitory doses (11 to 466 mg/kg) in view of the normal appearance and behavior of the rats, and the normal histological appearance of the thyroids. In contrast, severe weight gain suppression due to KI has been noted following administration of a considerably larger dose: 1864 mg/kg/day. Consequently, there appears to be a separation of doses of KI that inhibit granuloma pouch formation from doses that effect the rat adversely.

A stimulation of the thyrotropin-thyroxine axis following administration of KI at lower granuloma pouch inhibitory doses also is not a likely explanation in view of the work by Julezs et al (1964). They administered thyrotropin or excised thyroid in rats, following which they noted that the granuloma pouch formation was increased rather than decreased.

In respect to possible local anti-inflammatory effects of KI, two *in vitro* studies lend support to a concept that KI has anti-inflammatory activity. First, Middlebrook and Szent-Györgyi reported in 1958 that iodide at relatively low concentrations can uncouple oxidative phosphorylation and, later, Boström et al. (1963) and Whitehouse (1964) found that most anti-inflammatory compounds uncouple oxidative phosphorylation. While this is only isolated and indirect *in vitro* evidence of possible anti-inflammatory effect of iodides, further work in other

vitro systems—e.g., on lysosomal stabilization—may provide the necessary additional information.

The activity of KI against granuloma pouch formation, one of the most fibroplastic forms of experimental inflammation, can be considered analogous to the clinical activity of iodides against the granulomatous lesions of tuberculosis, fungal diseases and syphilitic gumma. In both animal and clinical situations the activity of iodides appears to be directed against fibrotic tissue, and a specific "anti-fibrotic" effect of KI can be conceived. Such concept does not appear to be contradictory to the reported enhancement of inflammation by iodides (Stone and Willis, 1967) because the enhancement of inflammation was noted at the acute stages (22–48 hours) of inflammation.

#### SUMMARY

Potassium iodide was studied for its anti-inflammatory effects against five types of experimental inflammation: granuloma pouch formation, cotton granuloma formation, and carrageenan and croton oil edema in rats, and turpentine-induced edema and abscesses in monkeys. Administration of potassium iodide resulted in inhibition of granuloma pouch formation, but in no inhibition of the other types of inflammation. These data are suggestive of a specific "anti-fibrotic" effect of KI.

#### ACKNOWLEDGMENTS

Gratitude is extended to Dr. H. P. Drobeck for his valuable contributions in preparing the manuscript. The skillful technical assistance of Mr. George L. Brown, Jr., is gratefully acknowledged.

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J. Nutrition 53(1): 53-58, 1954

## NUTRITIONAL AVAILABILITY OF IODINE FROM SEVERAL INSOLUBLE IODINE COMPOUNDS<sup>1</sup>

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(Received for publication September 21, 1953)

### INTRODUCTION

The availability of iodine from insoluble iodine compounds is important in the selection of an iodine source to be incorporated into an animal salt block. An insoluble iodine source is desirable in that iodine would not be leached out readily by exposure to moisture. The availability of iodine from cuprous iodide ( $\text{Cu}_2\text{I}_2$ ), from diiododithymol (thymol iodide) and from 3-5-diiodosalicylic acid was compared to the availability of iodine from potassium iodide (KI), using as a criterion the prevention of the enlargement of the thyroid gland in albino rats reared on a rigorously controlled diet. Levine, Remington and von Kalnitz ('33) found that young rats develop a severe goiter within 5 weeks if fed on diets deficient in iodine. Later, Remington ('37) and Remington and Remington ('38) reported that 2 to 3  $\mu\text{g}$  of iodine from KI per day prevented the enlargement of the thyroid gland in albino rats reared on a rigorously controlled diet.

### AVAILABILITY OF IODINE

Four-week-old Sprague-Dawley female albino rats (35-50 gm) were reared on a low-iodine test diet (Remington, '37) which consisted of, in per cent: 18 wheat gluten, 2 Brewer's yeast powder, 78 yellow corn meal, 1 calcium carbonate and 1 sodium chloride. The control animals (group A) were reared

<sup>1</sup> This investigation was supported by Morton Salt Company, Chicago, Illinois.

on this test diet. Another group of 10 animals (group B) was fed the low-iodine diet to which 265  $\mu\text{g}$  of iodine (as KI) per kilogram of test diet was added. In the diet for group C, 265  $\mu\text{g}$  of iodine from  $\text{Cu}_2\text{I}_2$  was added; in D, 265  $\mu\text{g}$  of iodine as diiododithymol was used; and in E 265  $\mu\text{g}$  of iodine as 3-5-diiodosalicylic acid was added. Each group consisted of 10 animals housed in separate cages and fed 10 gm of food daily. At the end of 5 weeks the thyroid glands were carefully dissected and weighed wet. The results of these experiments are given in table 1. The water-insoluble iodine compounds

TABLE 1  
Availability of iodine from several sources  
(Female albino rats given 10 gm of food daily for 5 weeks)

GROUP	ADDITION TO IODINE-FREE DIET	IODINE SOURCE	NUMBER OF ANIMALS	AVERAGE WEIGHTS	
				Body	Thyroid gland
	$\mu\text{g}/\text{kg}$			gm	mg/100 gm of body weight
A (control)	none	none	5	111.4	15.4 $\pm$ 3.5 <sup>1</sup>
B	265	KI	10	105.2	10.0 $\pm$ 1.1
C	265	$\text{Cu}_2\text{I}_2$	10	100.1	9.8 $\pm$ 1.9
D	265	diiododithymol	10	101.6	12.5 $\pm$ 2.4
E	265	3-5-diiodosalicylic acid	10	99.0	11.9 $\pm$ 1.4

<sup>1</sup> Standard deviation.

used provided available iodine and protected the thyroid gland from becoming enlarged.

A second series of experiments was designed to show the influence of various amounts of  $\text{Cu}_2\text{I}_2$  in protecting the thyroid gland of albino rats reared on Remington's iodine deficient diet. Four groups of animals were used to test the following diets during a period of 6 weeks: F, iodine-free diet (control group); G, 265  $\mu\text{g}$  of iodine from  $\text{Cu}_2\text{I}_2/\text{kg}$  of iodine-free diet; H, 200  $\mu\text{g}$  of iodine from  $\text{Cu}_2\text{I}_2/\text{kg}$  of iodine-free diet; and I, 150  $\mu\text{g}$  of iodine from  $\text{Cu}_2\text{I}_2/\text{kg}$  of iodine-free diet. The results are presented in table 2. Cuprous iodide affords protection against enlargement of the thyroid glands. Since the rats eat about 10 gm of food per day, as little as 1.5  $\mu\text{g}$  of iodine

per day from  $\text{Cu}_2\text{I}_2$  prevents this enlargement. When the control animals were kept on the deficient diet for 6 weeks instead of 5 weeks, the average weight of the thyroid gland increased from 15.4 to 18.1 mg/100 gm of body weight.

## RETENTION OF IODINE

Because the iodine was found to be available from  $\text{Cu}_2\text{I}_2$ , 3-5-diiodosalicylic acid, and thymol iodide, the question arose as to whether some of the iodides tested here underwent such a rapid clearance from the body that they were not used as efficiently as others. The intake of the iodine was reduced from

TABLE 2  
*Availability of iodine from  $\text{Cu}_2\text{I}_2$*   
(Female albino rats allowed feed at will for 6 weeks)

GROUP	ADDITION TO IODINE-FREE DIET	NUMBER OF ANIMALS	AVERAGE WEIGHTS	
			Body	Thyroid gland
	$\mu\text{g}/\text{kg}$		gm	mg/100 gm of body weight
F (control)	none	5	138.2	18.1 $\pm$ 2.1 <sup>1</sup>
G	265	10	141.3	7.3 $\pm$ 1.8
H	200	10	140.1	8.5 $\pm$ 2.2
I	150	9	139.8	9.2 $\pm$ 2.4

<sup>1</sup> Standard deviation.

an optimum of 18.55  $\mu\text{g}/\text{wk}$ . (2.65  $\mu\text{g}/\text{day}$ ) to 5.25  $\mu\text{g}/\text{wk}$ . in order to produce a slightly goitrous condition. The 5.25  $\mu\text{g}/\text{wk}$ . of iodine in the compounds to be tested was administered in two feedings (2.625  $\mu\text{g}$  of iodine on Mondays and 2.625  $\mu\text{g}$  on Thursdays), with 10 gm of low-iodine test diet, and the animals were allowed to eat freely as much iodine-free food as they desired for the rest of the week. Because the animals kept on the iodine-free diet for 6 weeks had larger thyroid glands than those on the diet for 5 weeks, the period of feeding on the various diets was extended to 8 weeks. The results of this series of experiments are to be found in table 3. Extending the length of the experiment from 5 to 8 weeks increased the goitrous condition of the control animals. Again

the insoluble iodine compounds tested here provided sufficient iodine to protect the thyroid gland from becoming enlarged.

## DISCUSSION

Iodine is readily available from the insoluble iodine compounds, 3-5-diiodosalicylic acid,  $\text{Cu}_2\text{I}_2$  and thymol iodide. Because of the individual fluctuations in thyroid size and in body weight, it is difficult to compare one iodine compound with another. Nevertheless,  $\text{Cu}_2\text{I}_2$  appears to provide iodine to the thyroid gland as readily as KI, and in one series of experiments in which an amount of iodine less than optimum

TABLE 3.  
*Retention of iodine from several iodides*  
(Albino rats given 5.25  $\mu\text{g}$  of iodine weekly for 8 weeks)

GROUP	IODINE SOURCE	NUMBER OF ANIMALS	AVERAGE WEIGHTS	
			Body	Thyroid gland
			<i>gm</i>	<i>mg/100 gm of body weight</i>
J (control)	none	9	155.6	40.86 $\pm$ 5.2 <sup>1</sup>
K	KI	10	148.2	12.48 $\pm$ 2.47
L	$\text{Cu}_2\text{I}_2$	10	149.5	9.62 $\pm$ 2.06
M	diiododithymol	9	150.2	14.34 $\pm$ 2.05
N	3-5-diiodosalicylic acid	10	149.7	13.53 $\pm$ 2.6

<sup>1</sup> Standard deviation.

was supplied, the  $\text{Cu}_2\text{I}_2$  appeared to afford somewhat better protection. The availability of iodine from thymol iodide agrees with the work of Baldwin, Thiessen and McInroy ('47) who found that 25 to 50% of the radioactive tagged iodine in diiododithymol was concentrated in the thyroid gland.

The weight of the thyroid gland appears to be a sensitive indicator of iodine deficiency, and it can be used as a means of evaluating iodine availability. This change in weight is indirect evidence of the utilization of iodine. The data presented agree with the work of Halverson, Shaw and Hart ('45) and of Levine, Remington and von Kalnitz ('33) who have reported that 2  $\mu\text{g}$  daily of iodine from a readily available

source protects the thyroid gland of a laboratory rat from becoming enlarged. Solubility in water does not play an important role inasmuch as relatively insoluble  $\text{Cu}_2\text{I}_2$  (0.008 gm in 100 ml of water at 18°C.) protects the thyroid gland as well as soluble KI (127.5 gm in 100 ml at 0°C.). It is also probable that some of the insoluble iodides may be absorbed slowly and thus make available a more continuous supply of iodine to the thyroid gland.

#### TOXICITY STUDIES

Acute and chronic toxicity studies were made of  $\text{Cu}_2\text{I}_2$  and 3-5-diiodosalicylic acid. In acute toxicity tests with  $\text{Cu}_2\text{I}_2$ , an oral dose of 2,000 mg/kg of body weight fed to 5 laboratory rats produced diarrhea but did not kill them; with an oral dose of 500 mg of  $\text{Cu}_2\text{I}_2$ /kg 5 other animals suffered no ill effects. A dose of 125 mg of cuprous iodide fed to a 250-gm rat is 30,000 times the daily requirement of iodine to maintain normal thyroid glands and accordingly such a rat would need the low level of 0.0000039 gm/per day.

Rats were fed 1,000 mg of 3-5-diiodosalicylic acid per kilogram of body weight, mixed with meat. Watery stools were the only symptoms, and the rats recovered without any ill effects. This is about 60,000 times the daily requirement of iodine by rats. Five hundred milligrams of 3-5-diiodosalicylic per kilogram produced no apparent symptoms. Autopsies on animals which were fed 0.1 and 1 gm of  $\text{Cu}_2\text{I}_2$ /kg of food and 0.1 and 1 gm of 3-5-diiodosalicylic acid/kg of food for 5 months showed no liver, kidney or intestinal abnormalities. The animals gained weight normally and were in excellent health at the conclusion of the tests. In the amounts necessary to supply iodine needed to protect thyroid glands,  $\text{Cu}_2\text{I}_2$  and 3-5-diiodosalicylic acid can be considered non-toxic.

#### SUMMARY

Iodine was found to be nutritionally available from insoluble cuprous iodide, diiododithymol, and 3-5-diiodosalicylic

acid. Acute and chronic toxicity tests indicated that  $Cu_2I_2$  and 3-5-diiodosalicylic acid were non-toxic in amounts required to protect the thyroid gland.

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Proc. Soc. Exptl. Biol. and Med. 92(2):416-418. 1956.

**Effect of Varying Dosages of Potassium Iodide in Experimental  
Atherosclerosis. (22496)**

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Several investigators have reported that potassium iodide(1,2), organic iodides(3) or desiccated thyroid(3) inhibited formation of atheromatous plaques in cholesterol-fed rabbits. While KI and organic iodides had a tendency to cause hypercholesterolemia, thyroid powder lowered serum cholesterol somewhat. Similar effects of these compounds on serum cholesterol have also been observed in chickens(4), although no anti-atherogenic influence was found. Recently, administration of KI to rats for very short periods was shown to cause a 2-fold increase in serum cholesterol (5).

The present study was designed to examine effects of various dosages of KI as well as of 2 thyroid-active substances (diiodotyrosine and thyroxine) on development of atheromata and on serum cholesterol and b-lipoproteins of rabbits fed cholesterol. The anti-atherogenic effects of large dosages of KI are confirmed.

*Methods.* Male rabbits of the Dutch belted strain were maintained on a diet of rabbit

chow (Wayne Rabbit Ration, Allied Mills, Chicago, Ill.) which had been thoroughly mixed with a suspension of cholesterol in corn-oil so that every 100 g of food contained 2% cholesterol and 6% corn-oil. The basic diet was augmented with amounts of KI or of diiodotyrosine as noted in Tables I and II by spraying the appropriate solution on the pellets while they were tumbled in a concrete mixer. This was done before adding the cholesterol-oil suspension. The thyroxine was administered by the intraperitoneal injection of 0.05 mg, 3 times weekly. After 8 weeks the animals were sacrificed and aortas examined visually for atheromata and graded on a 0-4 scale. Averages for each group are given in Table I. In Exp. 1 and 2 the entire aorta was graded, in Exp. 3 the arch and thoracic portions were graded separately. Sera were assayed for cholesterol(6) and lipoproteins(7) and livers were excised, weighed wet and analyzed for cholesterol content. Average values of these are stated in Tables I and II.

TABLE I. Autopsy Findings on Rabbits Fed Cholesterol Diets Augmented by KI, Diiodotyrosine and Thyroxine.

Group*	No. of animals	Wt change (g)	Atheromata		Serum chol. (mg %)	Liver wt (g)	Liver chol. (%)
Exp. 1							
1% KI	9	—	.55‡		2170	70	2.9‡
B†	10	—	1.55		2260	98	8.3
Exp. 2							
1% KI	8	106	1.00§		3830	—	—
B	14	212	2.70		3150	—	—
Exp. 3							
			Arch	Thoracic			
.001% KI	10	132	2.20	1.40	2520	89	4.1
.01% "	9	60	2.11	1.44	2610	81	3.9
.1% "	8	-3	1.94	1.00	2490	75	3.6
1% "	7	-59	.93§	.14	2400	63	2.3‡
DIT	10	117	2.65	1.40	2360	67	3.7
T¶	10	-51	1.75	.75	2270	88	4.0
B	7	81	2.43	.93	2800	80	4.0

\* All diets contain 2% cholesterol, 6% oil. † B = Basic diet. ‡ p < .0001.  
 § p < .001. || 0.1% diiodotyrosine. ¶ Thyroxine, 0.15 mg/wk, i.p.

TABLE II. Serum Lipoprotein Levels of Rabbits Fed Cholesterol Augmented by KI, Diiodotyrosine and Thyroxine.

Group*	Serum lipoproteins, S <sub>i</sub> mg %					Total
	0-12	12-20	20-35	35-100	100-400	
Exp. 1						
1% KI	480	727	528	650	461	2846
B†	165	550	851	650	411	2627
Exp. 2						
1% KI	998	649	616	1064	1209	4536
B	362	750	1223	1309	682	4326
Exp. 3						
.001% KI	261	555	1006	1388	696	4006
.01% "	158	490	864	1000	546	3058
.1% "	208	491	786	1106	816	3407
1% "	367	464	522	956	1050	3359
DIT‡	186	448	773	1202	829	3438
T§	115	274	675	933	861	2858
B	241	481	845	1301	1073	3941

\* All diets contain 2% cholesterol, 6% oil. † B = Basic diet. ‡ 0.1% diiodotyrosine.  
 § Thyroxine, 0.15 mg/wk, i.p.

*Results.* The data show that only large amounts of KI had any significant effect on formation of atheromata. At levels administered, neither diiodotyrosine nor thyroxine inhibited atherogenesis. None of the compounds produced significant hypocholesterolemia, nor was there a distinct lowering in lipoprotein fractions. In this connection it is of interest that the concentration of the cholesterol-rich 0-12 class lipoproteins(8) was higher in the group receiving 1% KI than in controls. Of groups in Exp. 3, that on thyroxine showed lowest cholesterol and lipoprotein levels al-

though atheromata were considerably higher than those in animals being fed 1% KI.

Moses and Longabaugh(9) observed no significant reduction in atheromata when they administered small dosages of KI to growing rabbits. Groups receiving 325 mg KI daily (plus 15 g cholesterol/week) showed somewhat lower average atheromata than did the control group, while the atheromata of the group fed 20 mg KI were more severe. Rosenthal(10), using very small doses of KI (3-7 mg) in cholesterol-fed rabbits found elevated serum cholesterol levels, and more lipid in

aortas of these animals than in the controls. Greatest protection against atherosclerosis was observed when the cholesterol KI ratio was approximately 2:1. Turner(1,2) fed equal amounts of cholesterol and KI, and Page and Bernhard(3) fed approximately equal amounts of cholesterol and diiodocholesteric acid. Moses and Longabaugh(9) employed ratios of 7:1 and 100:1, with the former giving relatively greater protection.

In Exp. 3 there was a slight weight loss in groups receiving 0.1% KI, 1% KI and thyroxine, but the overall weight difference in all groups was small. Firstbrook(11) has pointed out the high correlation between relative weight gain and severity of lesions in experimental atherosclerosis in rabbits, but the gains and losses recorded in Exp. 3 are too small to have affected the results. Both KI and control groups gained in weight, and there seemed to be no correlation in individual animals between atheromata and weight change. The 1% KI diet, while causing no hypocholesterolemia, lowered average liver cholesterol content significantly.

**Summary.** 1. Groups of rabbits were fed a 2% cholesterol diet augmented with 0.001%, 0.01%, 0.1% and 1% potassium iodide,

0.1% diiodotyrosine, and one group received 0.15 mg of thyroxine weekly by intraperitoneal injection. 2. Serum cholesterol and lipoprotein levels of all animals were elevated, but atheromata were significantly reduced in those on diet containing 1% KI. The S<sub>1</sub> 0-12 lipoprotein levels were also higher in animals of this group than in controls, but on the whole levels of liver cholesterol were lowest.

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Received May 25, 1956. P.S.E.B.M., 1956, v92.

## Anti-tumorigenic Action of Iodinated Compounds

As one of us (F. B. O.) had observed that the administration of a mixture of aqueous solutions of potassium iodide and potassium iodate induced favourable effects in cancer patients, we decided to carry out an experimental study in rats.

White rats received an implant of spindle-cell sarcoma of a strain obtained by courtesy of Prof. E. Cruz Coke, of the Institute of Physiological Chemistry of the University of Chile. Animals were given a dose of 0.2 ml. per 100 gm. body-weight of a solution containing 0.482 M potassium iodide and 0.083 M potassium iodate, three times a day, via cesophageal tube. In this way, 43 mgm. of iodine per 100 gm. of body-weight was administered to each of these animals every 24 hr. Previous experiments with nineteen animals thus treated, giving the iodine solution either two weeks before or on the same day as the implantation of spindle-cell sarcoma, showed that the treatment produces a marked inhibition on the growth of the tumour; in more than 70 per cent the tumours disappeared leaving no traces, whereas twenty-one untreated animals developed large tumours and died. Of the first nine animals treated, six still survive—116 days after treatment was suspended.

We then used another experimental series consisting of two groups of thirty-eight animals each. In one group, the treatment was begun forty-five days before the implantation of the sarcoma. The tumours

Table 1

	Animals		Weeks							
			1st	2nd	3rd	4th	5th	6th	7th	8th
First series	Control	No. of survivors Size of tumours*	11 1.9	11 3.9	8 5.7	5 6.0	3 7.4	1 6.5	1 6.8	0 —
	Treated	No. of survivors Size of tumours*	10 1.8	10 2.0	10 1.9	8 0.6	8 0.2	8 0.1	8 —	8 —
Second series	Control	No. of survivors Size of tumours*	10 —	10 1.4	10 2.6	5 3.3	5 6.8	4 7.5	1 8.2	0 0.5
	Treated	No. of survivors Size of tumours*	9 —	9 1.1	9 1.9	9 2.8	9 2.4	9 2.3	6† 3.0	6 —
Third series	Control	No. of survivors Size of tumours*	35 1.5	35 2.1	30 2.7	26 3.3	22 4.2	14 5.0	9 4.9	— —
	Treated‡	No. of survivors Size of tumours*	34 1.5	34 1.5	34 1.2	34 1.3	34 1.5	34 1.8	34 1.0	— —

\* Average of greatest diameter of the tumour in cm.

† Three animals died accidentally.

‡ In thirty-two animals of this group there were no traces of the tumour by the seventh week of observation.

Nature 176(4479):466-467. 1955

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grew in thirty-four animals of each group. During an observation period of sixty-four days, thirty-four of the non-treated rats died on account of large tumours, ranging from 15 to 45 gm. in weight. All the treated animals are still alive. Besides the four treated rats in which there was no initial tumour growth, all the treated animals of this group show no traces of the tumour at present, due to its regression.

The iodide-iodate solution at the specified dose and rate of administration has been well tolerated, to the extent that it has produced no hindrance of bodily development.

Studies of the metabolism of these and other halogenated substances, their influence on the weight of different organs and their action on various tumours, as well as the effect of smaller doses of the iodinated solution, are being carried out.

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EXPERIMENTAL STUDIES OF THE PROPHYLACTIC AND TOXIC EFFECTS OF  
POTASSIUM IODATE AS A MEANS OF IODIZING TABLE SALT

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Iodized prophylactics in our country are made from table salt, iodized with potassium iodite and an added stabilizer of magnesium carbonate. They are supplied to the populace in special one-kilogram boxes (inside a dark-colored parchment paper). This packaged iodized salt has a useful life of three months. Several experiments have established that due to the moisture and impurities in this salt, it quickly loses its iodine content. In addition the special packing hinders production. Iodized salt stays around for a long time because of its position in endemic regions and the population consuming it receives it long after it has terminated its usefulness. These circumstances have urged the study of questions regarding table salt iodized with potassium iodate, which has significant advantages over iodide, and intake in sufficient quantities may even completely replace it in the biochemical synthesis of thyroid hormones (4,5). In recent years salt has been iodized with potassium iodate in Mexico, Guatemala, Roumania, and other countries (5).

Potassium iodate is consistently stable in content and impurities which occur in the salt, but it is oxidized as quickly as is potassium iodide. An important advantage is its lower solubility in water in comparison to potassium iodite. It is known that the latter absorbs impurity particles with increased humidity and may even be transferred to the packing material (the

box). Thus the iodine content in the salt is lost or decreased. The lesser amount of migration in potassium iodate is associated with its low solubility in water in particular. Because of this property, this salt is more convenient for iodization, especially in an area where it would be exposed to unfavorable chemical and climatic effects (5). Arroyare, Pineda, and Scrimshaw established that under tropic conditions (in high humidity for eight months), the salt, kept in 50 kg cotton bags in open compartments, loses 3.5% iodate at a humidity of 70-84% (5). Our scientists Verbanoz, Khristov, and Staykov also noted that sea salt iodized with potassium iodate was more stable than when prepared with potassium iodide and a stabilizer (2).

Similar studies which have obtained analogous results were verified in Venezuela, Brazil, and other countries, showing the indisputable advantage of potassium iodate for iodizing salt (5).

However there is another question which still prevents the wide application of potassium iodate for iodizing table salt - the danger of a toxic effect on the iodized substance. Information on this behavior is poor, but there is data which affirms one analysis in applying a preparation containing potassium iodate (6,7). In treating rats with large doses of potassium iodate, Tsanev and Dashev noted serious toxic changes in the parenchymal organs. These doses also had an inhibitory effect on the function of the thyroid gland (6,7). Studies of the toxicity of potassium iodate from the Scientific Research Medical Congress in Great Britain and the Board for preserving

products and medical preparations in the Health Protection Department on the USA indicate that this toxicity was low (3).

All the effects of potassium iodate have not been investigated satisfactorily, in relation to the organism during prolonged consumption, although it is already known that large doses taken once do much good, are quickly dissipated, and free iodine needed for synthesis of thyroid hormones (3,5).

In looking at the data indicated and the possibilities for potassium iodate in the iodization of table salt, we undertook an experimental study on the effect of potassium iodate, given continuously, on the function of the thyroid gland for different iodine contents in the diet, as well as any toxic action on the parenchymal organs.

Material and method. White male rats were used in the experiment, originally weighing 120-130 g. The animals in the first series of 5 months received a food briquette with 360  $\mu\text{g}/\text{kg}$  iodine content and were given daily with a stomach probe, the following:

- Group 1 - control - 1 ml distilled water (10 rats)
- Group 2 - 1  $\mu\text{g}$  potassium iodite in 1 ml water (15 rats)
- Group 3 - 5  $\mu\text{g}$  potassium iodate in 1 ml water (14 rats).

The animals in group 2 were fed for 1 month in laboratory preparation food poor in iodine (9), with an iodine content of 240  $\mu\text{g}/\text{kg}$ . After this period they were given, through a clean stomach probe, daily, the following:

- Group 1 - control - 1 ml distilled water (10 rats)
- Group 2 - 5 g potassium iodate in 1 ml water (10 rats).

At the end of the experiment the rats were injected intraperitoneally with 5  $\mu$ K of I-131 and I-131 absorbed from the thyroid gland was traced for 2, 4, 6, and 24 hours without narcosis, using a scintillation counter. The absorbed I-131 was calculated in percent with respect to a standard 5  $\mu$ K I-131, under existing conditions. For the animals in the second series, in a 48-hour trace of I-131, blood was taken during ether narcosis, using a syringe. After determining the albumen content of I-131 (AC I-131), 0.5 ml of plasma was precipitated in two stages with 5 ml 10% trichloroacetic acid, and the trace was washed with distilled water; activity was determined with a scintillator. The following results of the traces, corrected for background, were calculated for 1 ml plasma.

The animal weights were measured at the beginning and end of all the experiments. The animals were killed by exsanguination and the weights of the thyroid glands, noted on a torsion balance, were recorded as a Carnua estimate. Paraffin slices of 3  $\mu$  were studied in periodic acid and Schiff's reagent, according to the method of MacManus and Hotchkiss, with Toluidine Blue at pH 2.8-5.2 as titrated with testicular hyaluronidase and  $\beta$ -glucocoronidase. In addition, there were studies of RNA using Brashe's method of modifying and on DNA, using Folgen's method in comparison with the controls. Material from the myocardium, liver, and kidneys was taken for a histological examination for possible toxic changes in the parenchymal organs.

All the results were analyzed statistically using Student's t-test.

## RESULTS

In the rats from the first series, which had received food with normal iodine content, and were chronically treated with potassium iodate in doses of 1 and 5 mg, there appeared a moderate decrease in absorption of radioiodine from the thyroid gland (Table 1).

Таблица 1

1  
2  
3

Пъзлове, хранени с обикновена брикетна храна

3 Група	7 Телесно тегло г		10 Щитовидна жлеза мг/100 г	11 Поглъщане на <sup>131</sup> I от щитовидната жлеза в процент от дозата			
	8 в началото	9 в края		12 2 ч.	13 4 ч.	14 6 ч.	15 24 ч.
4 Контролни (10)	132±4	180±6	10,6±0,6	19,1±1,1	22,3±1,2	23,4±1,2	32,0±1,8
5 Калиев йодат 1 мг (15)	118±3	168±4	9,0±0,3*	17,1±0,8	18,4±1,2*	19,4±1,2*	28,0±2,0
6 Калиев йодат 5 мг (14)	117±2	160±3	10,0±0,4	16,0±0,7*	17,3±0,9**	18,0±1,0**	27,0±1,8*

16 Дадени са средната аритметична и средната грешка. В скоби е посочен броят на животните в групата; \* -  $p < 0,05$ , \*\* -  $p < 0,01$  в сравнение с контролната група.

## Key

1. Table 1
2. Rats fed usual food briquette
3. Group
4. Controls (10)
5. Potassium iodate 1  $\mu\text{g}$  (15)
6. Potassium iodate 5  $\mu\text{g}$  (14)
7. Body weight, g
8. Original
9. Final
10. Thyroid gland mg/100 g
11. Absorption of I-131 from thyroid gland in percent of dose
12. 2 hours
13. 4 hours

14. 6 hours

15. 24 hours

16. Data were averaged arithmetically and errors were averaged.

In parentheses the number of animals in the group is given.

\* p less than 0.05

\*\* p less than 0.01 in comparison with control group

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The degrees of loss show dependence on the dose received. During treatment of the rats with 1  $\mu$ g, a definite decrease was established in the absorption in the 4- and 6-hour periods. During 5  $\mu$ g treatment, there was a definite decrease before each hour of the study. The thyroid glands did not show any considerable decrease in weight after the final treatment of the animals with 1  $\mu$ g of potassium iodate.

Histologically the thyroid glands from the control rats were characterized by oval follicles with a 45  $\mu$  diameter, covered with cubic epithelial cells 10  $\mu$  in size. The cytoplasm is homogeneous and the nucleus rich in chromatin. Upon illuminating the follicles, a PAS-positive colloid was observed with a normal amount of resorption vacuoles (Fig. 1). In rats which received 1  $\mu$ g of potassium iodate, the follicles were oval, covered with cubic epithelial cells 9  $\mu$  in size. In illuminating them, they had a normal amount of colloidal material with resorption vacuoles. In the group of animals treated with 5  $\mu$ g of potassium iodate, an increase in follicle diameter was noted - up to 60-65  $\mu$  (Fig. 2). In the colloid, there is a tendency toward increased loss of PAS-positive material. The quantity of re-



Фиг. 1      Fig. 1



Фиг. 2      Fig. 2

sorption vacuoles was decreased. Epithelial cells were cubic, with a tendency to be lower in particle separation. Their size was  $8\mu$  (see Fig. 2).

In spite of the length of the treatment with potassium iodate, no changes were established in the behavior and external form of the animals. Increase in weight was the same as in the control group. Macro- and microscopic data did not establish any injury to the parenchymal organs.

Among the rats from the second series of experiments, who received food poor in iodine, two rats were chosen from the control group. Eight rats remaining from this group showed significant acceleration and increased I-131 absorption from the thyroid gland; their weight was also increased (Table 2). The rats in this experimental series which were treated with 5 g of potassium iodate, had, in comparison with the controls, a significantly lower absorption of I-131 from the thyroid and lower thyroid gland weight. In this connection, the results approximated those obtained in the control group of animals who received a normal iodine diet. The AC I-131 activity in the plasma of rats treated with potassium iodate was significantly lower than activity in the controls (p less than 0.001).

2

Таблица 2

Плъхове, хранили с бедна на йод храна

3 Група	6 Телесно тегло в г		9 Щит. жлеза mg/100 г	10 Поглъщане на <sup>131</sup> I от щитовидната жлеза в процент от дозата				15 БС <sup>131</sup> I имп (мин) в хиляди
	7 в нача- лото	8 в края		11 2 ч.	12 4 ч.	13 6 ч.	14 24 ч.	
4 Контролна (8)	126±7	122±9	11,3±0,6	29,4±2,4	43,0±2,8	49,2±3,6	48±2,9	21,9±2,4
5 Калиев йодат 5 мг (10)	122±6	141±8	9,0±0,4**	23,7±1,9	33,5±3,0*	37,5±3,6*	35,3±3,0**	9,6±1,4***

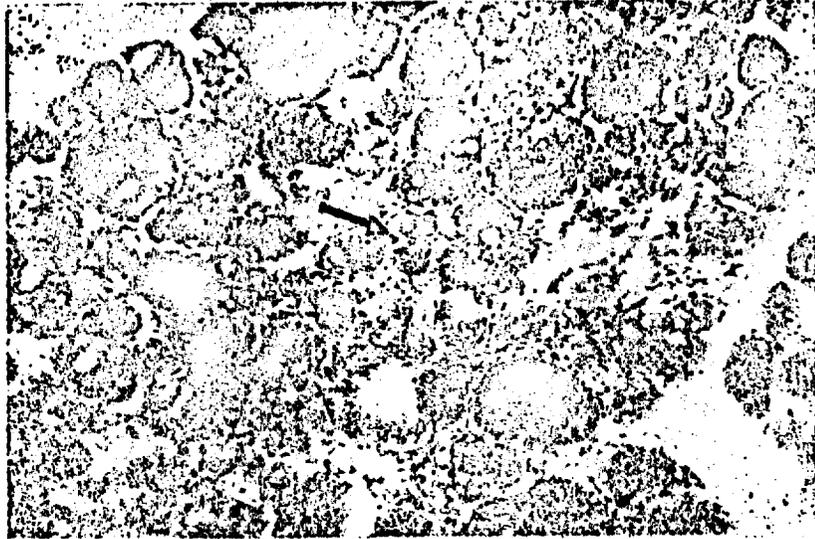
16 Дадени са средната аритметична и средната грешка. В скоби е посочен броят на животните в групата; \* —  $p < 0,05$ , \*\* —  $p < 0,01$  и \*\*\* —  $p < 0,001$  в сравнение с контролната група.

## Key

1. Table 2
  2. Rats fed food poor in iodine
  3. Group
  4. Control (8)
  5. 5 g potassium iodate (10)
  6. Body weight in g
  7. Original
  8. Final
  9. Thyroid gland mg/100g
  10. I-131 absorption from thyroid gland in percent of dose
  11. 2 hours
  12. 4 hours
  13. 6 hours
  14. 24 hours
  15. I-131 AC imp.(min.) in 1000's
  16. Data was averaged arithmetically and errors were averaged.
- Numbers of animals in groups are in parentheses. \*p less than 0.05, \*\*p less than 0.01, \*\*\*p less than 0.001 in comparison with control group
- 

And for this series the data did not establish a toxic effect for potassium iodate. Indeed the reverse - the rats treated with potassium iodate showed an absence of mortality and a significant increase in body weight in comparison to the control group.

A histological study of the thyroid glands of animals which received food poor in iodine showed that, in comparison



Фиг. 3    *Fig. 3*



Фиг. 4    *Fig. 4*

with the control animals from the first series, there was present a majority of microfollicles covered with large cubic cells (12  $\mu$ ), in which a light weakly showed PAS-positive colloids. In the interstitial space ~~was~~ noted epithelial material (Fig. 3). Rats treated with potassium iodate showed a histological pattern for normalcy under these conditions (Fig. 4).

#### DISCUSSION

The results obtained under conditions of chronic treatment with potassium iodate showed that for a normal iodine diet in daily doses of 5  $\mu$ g, the function of the thyroid gland was moderately decreased. The evidence for this is the noted lowering of I-131 absorption from the thyroid gland, which is expressed for increased doses of the preparation. In this connection, the effects of potassium iodate resemble the effects of potassium iodide (10,13). Macro- and microscopic data on the known decrease in thyroid gland weight was not positive, but it nevertheless indicates a tendency of the thyroid gland to rest. A histological pattern coincided with that obtained in our previous experiments on application of such doses of potassium iodate, but for a shorter treatment period (8,7). The absence of toxic changes in the parenchymal organs and in general growth in rats treated with potassium iodate for 5 months may be taken as evidence that at suitable dosages, this prolonged application does not produce a toxic effect on the organism.

The possibility of its use as prophylaxis for iodine-deficient hyperplasia of the thyroid gland is convincingly confirmed from the results obtained from rats which received food poor in

iodine. The control animals in the second series of experiments without the introduction of potassium iodate showed a number of signs of activation of thyroid function, characterized by an iodine deficiency: an increase in thyroid weight with histological changes, indicated by increased thyrotropine stimulation, greatly increasing iodine (I-131) absorption from the thyroid and a high amount of AC I-131 in the plasma. A similar pattern is observed in endemic I-131 goiter (12,14) in experimentally produced iodine deficiency in rats (8,13). Animals treated with potassium iodate in daily doses of  $5\mu\text{g}$  almost completely counteract those patterns, as, morphologically and functionally, the thyroid function approximates that of the control animals which received food with the usual iodine content. It is worthy to note and record normal growth in animals which in the control group was disturbed due to iodine deficiency.

A related mechanism, according to which potassium iodate acts upon the thyroid gland, may be proposed, in reviewing analogous observed changes in rats treated with potassium iodate: iodine content of the preparation determines the effect on the thyroid. It is known that for higher doses of iodine, thyroid function is decreased (11). For a normal iodine diet, this effect is observed even for 1 mg daily doses of potassium iodate. For diets poor in iodine, however, doses of  $5\mu\text{g}$  daily are sufficient to reduce almost completely the function of the thyroid gland. A smaller amount of iodine, in the case of  $1\mu\text{g}$ , which corresponds to the necessary daily amount of iodine for rats (6), has a clear effect and has long been understood as

as sufficient iodine necessary for normal biosynthesis of thyroid hormones. A lower amount of absorption of I-131 and AC I-131, measured in rats treated with potassium iodate, in spite of the given iodine-poor diet, confirmed the similar mechanism for action.

#### CONCLUSIONS

1. In chronic treatment of rats placed on a normal iodine diet of 5 g of potassium iodate daily, a moderate loss of thyroid gland function was observed. Toxic changes disappeared in the parenchymal organs and normal growth was established in the experimental animals.
2. Rats placed on an iodine-poor diet showed signs of activated thyroid gland function, characterized by iodine deficiency. The animals treated with 5  $\mu$ g of potassium iodate daily reversed these signs, as, morphologically and functionally the thyroid gland approximated that in the control animals. Normal growth continued in the animals, but was disturbed in the control group with iodine deficiency.
3. Prolonged (5 months) administration of potassium iodate to rats gave us a basis for concluding that in the doses given, the association provides for completely normal biochemical synthesis of thyroid hormones, without toxic changes in the parenchymal organs being observed. This permitted the possible use of potassium iodate for iodizing table salt for mass iodine prophylaxis.

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*Io. Penčev, T. Stalkev, D. Streshimirov, G. Dashev* — Experimental Studies on the Prophylactic and Toxic Effect of Potassium Iodate as a Means of Iodization of Sodium Chloride

**Summary.** In view of improving mass iodine prophylaxis in patients with endemic goiter in our country the authors propose potassium iodide to be substituted by potassium iodate. The latter preserves its iodine content in the salt longer, but in the literature there are reports that it has toxic effect. We examined this effect on rats for a continuous period of time. The following was established: after chronic treatment of the rats, receiving normal iodine diet with 5 micrograms of potassium iodate daily, a moderate inhibition of the thyroid function was observed. There were no toxic changes of the parenchymatous organs and normal growth of the experimental animals was established. The rats fed by diet poor of iodine revealed signs of activation of thyroid function, characteristic of iodine lack. Treatment of the animals with 5 micrograms of potassium iodate removed the mentioned signs and the thyroid gland was similar to that of the control animals both morphologically and functionally. The normal growth of the animals continued but it was disturbed in the control group with iodate deficit. Continuous administration of potassium iodate (5 months) in rats gives us foundation to think that the compound in a suitable dosage assures complete normal biochemical synthesis of the thyroid hormones without causing toxic changes in the parenchymatous organs. This allows potassium iodate to be used in iodization of salt for mass iodine prophylaxis.

# Effect of Dietary Iodine Upon Egg Production, Fertility and Hatchability.\*† (31245)

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Two recent reports(1,2) have described the toxic effects of excess dietary iodine upon rats and rabbits. The primary effect, when fed to pregnant rats, was a failure of lactation and high mortality of the young. Dietary levels

of iodine from 500 to 2500 ppm as KI caused

\* Florida Agri. Exp. Stations, Journal Series No. 2382.

† This work was supported by Grant AM08760, Nat. Inst. of Health.

TABLE I. Production, Fertility and Hatchability of Eggs from Hens Fed Iodine (10 Hens per Treatment).

ppm iodine	No. eggs				Total eggs	% Fertile	% Embryonic deaths*	% Died in shell*	% Hatched*	Delayed incubation, No.	
	1	2	3	4						24-36	36+†
Trial 1											
0	31	26	20	32	118	94	5	6	88	—	—
2500	31	4	4	3	42	81	38	6	56	7	3
5000	22	0	1	0	23	83	11	32	58	4	1
Trial 2											
0	44	35	37	37	153	86	13	4	83	—	—
312	36	39	36	36	147	86	44	8	47	10	5
625	34	28	35	32	129	78	66	6	28	5	5
1250	37	32	27	28	124	77	62	7	31	4	6
2500	30	13	9	7	59	83	59	10	31	2	3

\* Based on fertile eggs.

† Hours beyond average for control.

increasing mortality of the newborn which approached 100% at the higher level. Ovulation, implantation, number of young born and birth weight of young were not affected. The same levels of iodine fed to pregnant rabbits caused equal or greater mortality of the young but some female rabbits lactated even though all young died. Gestation time of rats was not affected, but prolonged and incomplete parturition and lack of mothering instinct were observed. Hamsters and swine were not affected by the dietary levels of iodine which were toxic to rats and rabbits (2).

Earlier studies with poultry(3,4) indicated harmful effects of excess iodine, but details of the effects upon reproduction were not reported.

The present study was designed to determine production, fertility, embryonic mortality and hatchability of eggs when hens were fed various levels of dietary iodine.

**Methods.** Eighty mature White Leghorn hens were used in 2 trials. Procedures for both trials were similar except for time and levels of iodine fed. In the first trial, iodine as KI was added to a basal laying diet in amounts to provide 0, 2500, and 5000 ppm. Levels of 0, 312, 625, 1250, and 2500 ppm were used in the second trial. The basal diet was composed of natural ingredients and identical to one previously described(5) containing 17% protein and 0.4% iodized salt which contributed 0.3 ppm iodine to the diet. Control diets contained  $K_2CO_3$  to provide po-

tassium equal to that in the diet with 2500 ppm iodine. Experimental diets and tap water were fed for 28 days to groups of 10 hens per treatment. Hens were housed individually in wire laying cages. On the day prior to iodine feeding, and weekly thereafter, hens were artificially inseminated using pooled semen from normal males.

Eggs were collected daily, identified and incubated at periodic intervals. On the 2nd, 4th, 9th, and 14th days of incubation, eggs were candled for determination of fertility and embryonic death. Hatchability was calculated as a percent of fertile eggs.

**Results and discussion.** Data representing egg production, fertility, hatchability and increased incubation are recorded in Table I. Hens fed 5000 ppm iodine ceased production within one week after the initial iodine feeding. Egg production ceased in 90% of the hens fed 2500 ppm in the first trial and rate of production at the same iodine level in the second trial was 21% of the controls. Production was slightly reduced in the third and fourth weeks in hens fed 1250 ppm iodine but not affected at the lower levels. All hens resumed laying within 7 days after removal from the iodine treatment. Molting, which normally accompanies a cessation of egg production, did not occur in hens which were fed iodine and ceased production. Body weight and condition of the hens were not adversely affected by the iodine fed.

Fertility of the eggs produced during the period of iodine feeding was not affected.

During incubation, however, mortality of the embryos was greater in eggs from hens fed iodine. Percent hatchability, based upon number of fertile eggs, was reduced from 85% in controls to an average of 43 and 58% in those fed 2500 and 5000 ppm iodine, respectively. Length of incubation time was increased by 24 hours or more beyond the normal in approximately 20% of the eggs from hens fed the two higher levels of iodine. Delayed hatching was also observed at the lower levels of iodine. Some embryos survived the incubation period but chicks died in the shell, apparently too weak to break the shell.

The adverse effect of iodine upon egg production appears to be temporary since hens resumed production after removal of iodine, but subsequent hatchability has not been determined. Rats and rabbits have produced and nursed litters normally after removal of dietary iodine(2). The absence of any acute gross effects upon hens appears related to similar observations on non-pregnant, non-lactating rats and rabbits. The mode of action of the excess iodine in producing the effects observed is not known, but results suggest an interference with hormone production or function.

A recent study(6) has shown that iodine depressed growth and increased mortality of chicks fed a diet low in chloride and also depressed growth when adequate chloride was fed. Dietary chloride (2400 ppm) in the present study was considered adequate and since little evidence for an interaction between the two elements was observed in the former

study(6), a deficiency of chloride was apparently not a factor in this study. Following the report of chloride deficiency in relation to iodine, an experiment was conducted with rats(7) in which 2 percent additional NaCl was added to diets with toxic levels of iodine. The additional NaCl did not prevent or reduce the harmful effects of iodine.

*Summary.* Laying hens were fed 312 to 5000 ppm iodine as KI in a practical laying diet and egg production and hatchability determined. Production ceased within the first week in hens fed the highest level and production was reduced at the lower levels. Fertility of the eggs produced was not affected but early embryonic death, reduced hatchability and delayed hatching resulted. Hens resumed egg production within seven days after removal from iodine feeding.

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Received March 10, 1966. P.S.E.B.M., 1966, v122

### Tumour-inhibiting Properties of Potassium Iodide Solution containing Potassium Iodate

F. B. OBERHAUSER *et al.*<sup>1</sup> have recently published results of experiments in which they tried to influence the growth of a rat sarcoma by oral treatment of the animals with solutions of potassium iodate in potassium iodide.

The surprising results obtained by these authors seemed to justify a repetition of the experiments using another strain of rats and a sarcoma obtained from another source.

We used male Wistar rats aged 3-3½ months and an average weight of 200 gm. These were implanted with 5-10 mm.<sup>3</sup> samples of rats' Jensen sarcoma subcutaneously in the back. (We owe this tumour to Prof. Lettré from the Cancer Research Institute of the University of Heidelberg.) One hundred animals used in these preliminary experiments were divided into three equal groups. The animals of the first group were implanted with the tumour only, whereas those of the second group were treated only with the solution used by Oberhauser *et al.* by stomach tube. The animals of the third group were treated with 0.2 ml. of this solution three times daily for 20 days preceding the tumour implantation. Those of the fourth group received the same treatment 10 days before and 10 days after the tumour implantation. Finally, the fifth group were treated with 0.2 ml. of the solution for 20 days after the implantation.

The results can be summarized as follows. All animals of the first group, with the exception of two which died from a wound infection on the third and fourth day respectively, died within about 30 days. The majority of the animals in group 2 died from diffuse haemorrhagic gastritis. In these, numerous erosions of the gastric mucous membrane were found and in some cases the stomach was filled with blood. Some animals died from bronchopneumonia. On the thirty-fifth day of the treatment only six survived; these too had lost much weight and were apathetic and without appetite. Most animals of group 3 died before the implantation of tumours, partly from haemorrhagic gastritis and partly from bronchopneumonia, others from unknown reasons (some of the dead animals had been mutilated by their litter mates). Those animals which survived the pre-treatment died from their tumours after an average of 30 days. The experiments of groups 4 and 5 had an analogous result.

The rats used in our experiments can therefore be said to have sustained great damage when treated with the solution described by Oberhauser *et al.* in the way and in the same quantity used by those authors, causing the death of the majority of the animals. Those animals which survived the treat-

ment died from their sarcomas. No inhibition of tumour growth was observed with this treatment. The high mortality of the treated animals rendered it useless to continue these experiments on the basis of the dosage applied by Oberhauser *et al.*

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**Effect of KI upon Basal Metabolism and Respiratory Quotient in Thyroidectomized Guinea Pigs.\***

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Loeb,<sup>1</sup> Gray and Rabinovitch,<sup>2</sup> McCordock,<sup>3</sup> and others have found that the administration of potassium iodide causes a marked stimulation of the thyroid gland in guinea pigs, as shown by a great increase in the number of mitotic figures, a slight softening of the colloid and an increase in the height of the acinar epithelial cells. Cordonnier<sup>4</sup> and the author<sup>5</sup> found that the basal metabolism was only very slightly affected after administration of KI in guinea pigs. In the latter experiments, the majority of the determinations as well as the average for all the animals was at the upper limit of the variations obtained in normal animals. Loeb<sup>1</sup> suggested the following possibilities to explain this discrepancy which exists between the marked degree of stimulation of the thyroid gland and the very slight effect upon basal metabolism after administration of KI. (1) Although KI stimulates the thyroid gland at certain periods of its action at the same time it prevents an excess of thyroxin thus produced from leaving the acini, and instead it is at least partly retained in the gland. (2) The stimulation of the acini does not necessarily lead to an excess production of thyroxin. (3) Peripheral effects counteract the stimulating effect of the thyroid hormone upon the basal metabolism.

The following experiments were carried out to investigate the peripheral action of KI. Twelve male guinea pigs, weighing between 400 and 450 gm., were as completely thyroidectomized as was possible, and 3 weeks after the operation, 8 were given 0.05 gm. of KI by mouth daily and biweekly metabolism tests were made. The remaining 4 guinea pigs served as controls. These were similarly thyroidectomized but were not given KI. At the

\* These investigations were carried out with the aid of a grant for research in science made to Washington University by the Rockefeller Foundation.

<sup>1</sup> Loeb, Leo, *Am. J. Path.*, 1926, 2, 19.

<sup>2</sup> Gray, S. H., and Rabinovitch, J., *PROC. SOC. EXP. BIOL. AND MED.*, 1929, 26, 468.

<sup>3</sup> McCordock, Howard A., *PROC. SOC. EXP. BIOL. AND MED.*, 1928, 26, 109.

<sup>4</sup> Cordonnier, J., *PROC. SOC. EXP. BIOL. AND MED.*, 1929, 26, 636.

<sup>5</sup> Siebert, Walter J., and Smith, Robt. S., *PROC. SOC. EXP. BIOL. AND MED.*, 1930, 27, 629.

operation, a careful effort was made to remove all of the thyroid gland tissue and to leave behind sufficient parathyroid tissue to prevent tetany from occurring. It was found, however, when autopsies were performed and preparations made of suspicious tissue for microscopic confirmation that in the majority of animals small remnants of thyroid tissue could be found. It is very probable that these remnants of thyroid gland tissue become sufficiently large to be seen only after compensatory hypertrophy has occurred. The control animals and the KI fed animals were tested at the same time under similar conditions. The Haldane open circuit respiratory calorimeter was used to make the tests, made after a 24-hour fasting period. Amytal (Lilly) in small doses was injected subcutaneously just prior to the trial periods to keep the animals quiet while determinations were being made. Two hour test periods were used in each case. The basal metabolism values of the 4 control animals ranged from 2.0 to 3.14 calories per kilo per hour; while the KI fed animals showed variations between 1.91 and 3.42 calories per kilo per hour before the administration of KI began. Thus the values for the basal metabolism in these guinea pigs after complete or almost complete thyroidectomy ranged between 0 and 45% below the average for normal guinea pigs. Within a few days following the daily administration of 0.05 gm. KI by mouth all 8 guinea pigs began to show basal metabolism values distinctly lower than those obtained in the animals which were thyroidectomized but to which no KI was administered. This lowering of the basal metabolic rate continued throughout the entire period of the experiments, from 14 to 30 days. The values obtained in the KI fed animals ranged between 1.52 and 3.30 calories per kilo per hour; and in all except a very few determinations the rates were distinctly lower in each individual experiment in this group than in those obtained at the same time in the control animals. This alteration in the basal metabolic rate ranged from 2% above to 55% below the average of those which were thyroidectomized but to which no KI was administered. The total average of the 36 determinations for the control group was 2.87 calories per kilo per hour, which is 18% below the average which we obtained in normal guinea pigs; while the total average for the 50 determinations of those which had received KI was 2.38, 32% below that of normal animals. Thus the average basal metabolism was approximately 14% lower in the 8 thyroidectomized guinea pigs which had received KI than the average of the 4 thyroidectomized guinea pigs to which no KI was administered.

The respiratory quotients of the thyroidectomized guinea pigs

which had received KI were distinctly higher in the large majority of cases as compared with those which did not receive KI. The respiratory quotients varied between 0.706 and 0.819 in the control group, whereas in the KI fed group they ranged between 0.727 and 1.04. The total average of all the respiratory quotients in the controls was 0.747, as compared with 0.859 in the KI fed group. In only 12 out of 50 determinations were the respiratory quotients within the range of the control, while in the remaining 38 tests, the KI fed guinea pigs had respiratory quotients distinctly higher than those of the control experiments. There was no correlation between the lowering of the basal metabolic rate and the rise in the respiratory quotient in individual cases.

*Conclusions.* The administration of KI to completely or almost completely thyroidectomized guinea pigs causes (1) a lowering of the basal metabolic rate and (2) a rise in the respiratory quotient. The peripheral effect of KI in causing a depression in basal metabolism is at least partly responsible for the fact that KI causes only a very slight effect upon the basal metabolism although the thyroid gland shows evidence of a marked degree of stimulation.

THE ASTHMA-SUPPRESSIVE ACTION OF POTASSIUM IODIDE

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OSLER, although reputed to be a therapeutic nihilist, held the view that "in preventing the recurrence of the attacks [of bronchial asthma] there is no remedy so useful as iodide of potassium, which sometimes acts like a specific."<sup>1</sup> Cooke<sup>2</sup> also remarked that this drug is "occasionally surprisingly effective in asthma." Sheldon, Lovell, and Mathews more recently stated that "in addition to their expectorant action iodides sometimes seem to bring about a prolonged remission . . . though the explanation for this phenomenon is obscure."<sup>3</sup> This report presents ten cases which illustrate this exceptional and often striking asthma-suppressive action of potassium iodide, still not widely recognized, and little utilized (Table I). Five cases are described in more detail.

CASE REPORTS

*Case 1.*—E. R., a 34-year-old man, first had bronchial asthma and atopic dermatitis at the age of 2 years. Later he had pollinosis and nasal polyps. At 25, despite many years of multiple desensitization, his previously intermittent asthma became increasingly intractable, and he required cortisone for the first time.

Despite psychoanalysis, he needed continuous oral bronchodilators and epinephrine nebulizer day and night. His total vital capacity was 3,000 to 3,400 ml., 78 per cent of normal. One-second timed vital capacity was reduced to 1,000 to 1,200 ml.

In early 1954, when 27 years of age, he was dyspneic and wheezed audibly. The chest was hyperresonant and distended in inspiration, with typical sibilant rhonchi and diminished breath sounds. Fluoroscopically, there was evidence of emphysema. Results of intracutaneous tests given were: ragweed, timothy (10 protein nitrogen units per milliliter), 3 plus; Hormodendrum, 3 plus; Alternaria, 2 plus; house dust, 4 plus.

Potassium iodide was prescribed in the form of 0.3 Gm. enteric-coated tablets, two tablets four times a day, 2.4 Gm. a day. He reported his asthma improved "after the third dose" and at the end of one week he no longer needed Tedral or the nebulizer. Twenty-eight days later his total vital capacity had risen to 4,300 ml., or 100 per cent of normal, and his one-second vital capacity to 1,800 ml. He could play softball without the use of supplementary medication.

Iodide therapy was continued for five years, with persistent good effect. In addition to a sense of general well-being there was a weight gain of 12 pounds during the first year. Examination of the chest showed signs neither of asthma nor of emphysema.

Occasionally he noted a few pink papules on face or chest which disappeared without

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Received for publication Sept. 9, 1963.

change in iodide dosage. When the dose was reduced to 1.2 Gm. per day there was prompt recurrence of wheezing, relieved by a return to previous dosage. He required higher doses, up to 3.6 Gm. per day, following colds or during the ragweed season. In the third year he went skiing in the bitterest winter cold without need of other medication. His total vital capacity rose to 4,800 ml. (above normal).

In the fourth year he first observed a small adenomatous nodule in the isthmus of the thyroid. He was started on thyroid extract, 60 mg. per day, with diminution in the size of the nodule.

In the fifth year of treatment, iodide was less effective, especially in the ragweed season. When the usual dosage of iodide was ineffective the drug was stopped. He again needed bronchodilators and the nebulizer. Iodide therapy, repeatedly reinstated during the next three years, remained of no help. The thyroid nodule disappeared. Prednisone in short intermittent courses became necessary for control.

*Case 2.*—W. H., a 37-year-old woman, had had bronchial asthma since she was 18. Nasal polypectomy was performed at the age of 15. At 16 she had an acute febrile illness, thought to be polyarteritis nodosa, with purpura, renal damage, and hypertension. Following bilateral splenoethmoidectomy for infected polypoid sinusitis due to *Pneumococcus* type 7, the acute systemic illness subsided, but she developed mitral stenosis. Intracutaneous tests were negative except for a 4 plus reaction to house dust. There was a questionable asthma flare-up in the ragweed pollen season.

From 1949 to 1952 her attacks flared intermittently while she was on antiallergic management. On several occasions she was given the "Dr. Gay mixture," each teaspoonful containing 0.25 Gm. of potassium iodide. She experienced prompt relief for a prolonged period, but her asthma became increasingly severe and required hospitalization. A daily dose of 100 mg. of cortisone was needed until the seventh month of her first pregnancy.

In February, 1954, she was again seen because of a severe flare-up of asthma despite cortisone. She was thin and dyspneic, with diffuse sibilant rhonchi. The blood pressure was 170/110. A murmur and prominence of the pulmonary conus seen on fluoroscopic examination were typical of mitral stenosis.

Potassium iodide, two 0.3 Gm. enteric-coated tablets four times daily, was prescribed, while cortisone dosage was tapered off progressively. One week later she reported that she did not need the isoproterenol hydrochloride inhaler. After one month there was complete freedom from asthma and a gain of 5 pounds in weight. Although cortisone was stopped she remained asthma free while on iodide in her second pregnancy, in contrast to the very severe asthma in her first.

She remained well, never needing steroids. When iodide was stopped the asthma recurred in six weeks. She resumed her regular dosage with good effect until 1959, when she observed decreasing benefit from this medication, and again had to resort to steroids.

*Case 3.*—J. S., a boy of 12, had had rhinitis since infancy, usually worse in the summer. Asthma first appeared in July, 1952, with a one-month flare-up in September. He was clinically allergic to cats and house dust.

There were typical sibilant rhonchi and the nasal membrane was gray and edematous. Results of intracutaneous tests were: ragweed, timothy, house dust, 4 plus; feathers, dog hair, *Aspergillus*, 3 plus; English plantain, mixed trees, horse hair, wool, cottonseed, kapok, *Alternaria*, 2 plus.

On a strict antiallergic regimen with desensitization he was scarcely ever free of asthma and required bronchodilators and frequent use of a nebulizer.

While in status asthmaticus, only partially controlled by cortisone, he was first started on two 0.3 Gm. enteric-coated potassium iodide tablets four times daily, with clear-cut relief apparent in five days. If the dose of potassium iodide was less than three tablets a day, asthma recurred. He remained well for about seven months, needing no other antiasthmatic medication. Potassium iodide was stopped, with only occasional recurrence of asthma during the following two years.

*Case 6.*—G. T., a 55-year-old woman, first had asthma in 1957 at the age of 52, with repeated nasal polyps and vasomotor rhinitis for many years. The asthma was better in

TABLE

CASE	SEX	AGE (YEARS)	AGE AT ONSET OF ASTHMA (YEARS)	CLINICAL TYPE OF ASTHMA	SEVERITY OF ASTHMA
1. E. R.	Male	34	2	Paroxysmal; extrinsic	4+
2. W. H.	Female	37	18	Paroxysmal; intrinsic	4+
3. J. S.	Male	18	11	Paroxysmal; extrinsic	3+
4. L. O.	Female	12	7	Paroxysmal and bronchitic; extrinsic	2+
5. M. C.	Male	62	58	Bronchitic and paroxysmal; intrinsic	2+
6. G. T.	Female	55	52	Paroxysmal; intrinsic	4+
7. M. B.	Male	62	60	Paroxysmal; intrinsic	2+
8. A. S.	Female	59	48	Paroxysmal and bronchitic; intrinsic	2+
9. C. W.	Female	18	14	Paroxysmal; extrinsic	4+
10. F. S.	Female	14	5	Paroxysmal; extrinsic	4+

summer and there was no seasonal hay fever. Intracutaneous tests with inhalants, pollens, molds, and representative foods were negative. She responded well to Quadrinal, containing 0.3 Gm. of potassium iodide per tablet.

Asthma returned during the winter following an upper respiratory infection. Prednisone was needed over a three-month period and reduction in dosage to 5 mg. a day was attended by reappearance of asthma.

In September, 1960, she was first given potassium iodide, two 0.3 Gm. enteric-coated tablets four times daily. After two weeks she was first able to stop prednisone without recurrence of asthma. Despite a slight wheeze on exertion there was no dyspnea. Typical sibilant rhonchi prominent on the first examination were now few, but nasal blocking was more noticeable than when she was taking prednisone.

For over two years she has remained completely well on iodide without supplementary medication. On two occasions deliberate withdrawal of the drug resulted in recurrence of asthma. Each time she again responded to reinstitution of treatment.

*Case 10.*—F. S., a 14-year-old girl, was first seen at age 5 when she developed wheezing and a cough on Labor Day. The chest was full of sibilant rhonchi and showed diminished breath sounds. She required cortisone for a short period when she failed to respond to bronchodilator medication. She had little asthma until the following ragweed season, when she again needed prednisone.

At the age of 8 she reported continuous wheezing throughout the previous year, with intractable cough and dyspnea on slight exertion. Intracutaneous tests showed a 4 plus reaction to ragweed and house dust; 2 plus reactions to grass, mixed tree pollen, feathers, and milk. Systematic manipulation of the diet was of no help.

Prednisone and the nebulizer were used with increasing frequency. After three years,

PREVIOUS STEROID THERAPY	SKIN TEST FINDINGS	POTASSIUM IODIDE EFFECT		
		TIME TO ONSET	DURATION	DEGREE OF CONTROL (%)
Brief	Pollens 3+ Alternaria 2+ House dust 4+	1 day	5 years	90
Repeated, prolonged	House dust 4+ Otherwise negative	7 days	5 years	85
Brief	Pollens 4+ Aspergillus 3+ House dust 4+	5 days	7 months	85
None	Scratch tests: pollens, danders 2+	7 days	12 months	90
None	House dust 2+ Otherwise negative	7 days	12 months	90
Prolonged	Negative	14 days	2 years	95
Brief	House dust 2+ Otherwise negative	14 days	4 months	95
None	House dust 1+ Otherwise negative	7-10 days	10 months	85
Prolonged	Pollens 2+ House dust 4+	14 days	8 months	80
Repeated courses	Ragweed 4+ Other pollens 2+	14 days	10 months	95

desensitization with pollens and house dust was stopped because of distinct asthma flare-ups in the pollen seasons. For two years thereafter prednisone had to be used again and again for control.

In January, 1963, at the age of 14, she was again having asthma. Potassium iodide was prescribed as two 0.3 Gm. enteric-coated tablets four times a day. Within two weeks the asthma was much improved and in the following five months she needed no prednisone. The nebulizer was used occasionally. The patient's rhinitis was also improved on iodide.

On May 27 enteric-coated tablets of potassium chloride were substituted for the potassium iodide without the patient's knowledge. The parents understood this to be "another form of potassium iodide." Within four days there was a severe recurrence of asthma, requiring 40 mg. of prednisone for the first day with tapering dosage for one week. Reinstitution of potassium iodide again brought the asthma under good control during a total of ten months of observation.

#### DISCUSSION

The ten cases of this report (Table I) serve to confirm and document a significant, unusual effect of potassium iodide, that of suppressing attacks of bronchial asthma. These cases alone exhibited this marked effectiveness among those of approximately two hundred asthmatic patients who otherwise showed only slight benefit or for whom it was completely ineffective. There is some variation in the degree of iodide effect even among this favorable group. In Case 1 the response was little short of startling. Cases 1 and 2 illustrate that

the action of iodide in preventing asthma may be prolonged and persistent, lasting up to five years. The results in Cases 3 and 6 were scarcely less dramatic and unexpected, and in each case steroid therapy could be replaced by iodide. Case 9 illustrates a less striking degree of effectiveness.

That this potassium iodide action is more than a placebo effect seems likely for a number of reasons. The remarkably prolonged benefit seen in the first two cases appears unlike the usually more temporary character of placebo action. Moreover, in some cases the dose level appeared to be critical, too sharp a reduction in dosage permitting a relapse of asthma. Three patients responded repeatedly to this drug but to no others in a similar manner, except steroids.

In two cases there is more impressive evidence that the asthma-suppressive action of iodide is pharmacologic and not placebo in character. Case 2 responded not only to iodide in the enteric-coated tablet form but also to the formula of Dr. Gay of Biloxi which she could not know also contained iodide. Most striking is the reaction to sudden withdrawal of iodide in Case 10, although neither the patient, a girl of 14, nor her parents were aware that a change had been made to a noniodide placebo tablet. Within four days asthma had recurred so severely as to require prednisone in full dosage for one week. An extended double-blind study of this exceptional iodide effect might be difficult to interpret, the incidence of responsiveness to iodide being actually far less than to a placebo.

This asthma-suppressive effect of iodide probably cannot be anticipated in more than 5 to 10 per cent of cases. The unpredictability of this action is the drug's most serious limitation. It must nevertheless be emphasized that iodide will occasionally prevent attacks and suppress asthma as well as no other therapy except corticosteroids. Its particular practical value is as an alternative to prolonged steroid therapy.

While this iodide effect usually becomes evident in from one to two weeks, in Case 1 it was noted on the first day and in Case 3 in five days. Two tablets of 0.3 Gm. of potassium iodide were prescribed (enteric-coated to minimize unpleasant taste) four times daily, before meals and at bedtime. This is approximately the equivalent in iodide of ten drops of saturated potassium iodide solution containing 1.0 Gm. of the drug per milliliter. Increased severity of asthma may be benefited by increasing iodide dosage to 3.6 Gm. per day (Case 1). The metallic taste of iodide, annoying to many despite the use of enteric-coated tablets, was scarcely noted by others. Iodide is excreted in the saliva as well as in the gastric secretions, and has been shown by Tuft and Levin<sup>4</sup> to appear also in the bronchial secretions.

This iodide action may be very persistent, lasting for years as in the first two cases, and for several to many months in others. It was a little less predictable in Cases 7 and 8, where some tendency to escape from its effect was noted. The asthma of childhood as well as that of later life may respond (Cases 3, 4, and 10). Male or female patients may be benefited. Whether the patient is skin-test positive or negative appears irrelevant. It may provide striking benefit not only in the cases with severe paroxysms but also where profuse expectoration is outstanding. In Case 5 reduction in sputum was striking, providing a contrast with the usual expectorant action of iodide.

Although generally well tolerated, potassium iodide treatment is not without side effects. Commonest are gastrointestinal upset, epigastric pain, and minor skin eruption. Mild papular erythema was frequent, and readily controlled by temporary reduction in dosage. There was no instance of severe iodide eruption. Three patients had mild "acute iodism" with edema of the lids or face and marked rhinorrhea which required discontinuation of the drug. In two cases pain in the parotid glands was controlled by careful manipulation of dosage.

The most serious side effect observed in this series was the development of a small thyroid adenoma after three years of continuous iodide therapy in Case 1. The nodule diminished somewhat in response to thyroid substance but disappeared completely only when iodide was withdrawn. Adenoma of the thyroid in response to iodide treatment has been reported frequently, and myxedema may also occur.<sup>5, 6</sup> A more serious hazard of iodide therapy which has recently attracted attention is goiter of the newborn, with pressure effects which may result in fatal asphyxia. This has been observed even when the drug has been used in relatively modest dosage, as in Quadrinal tablets which contain 0.3 Gm. of potassium iodide.<sup>7</sup> It is therefore safest to avoid iodide in the treatment of the pregnant asthmatic patient. As illustrated by the experience in Case 2, such an ill effect upon the newborn is not invariable. Severe sensitivity phenomena occasionally ascribed to iodide, such as hypersensitivity angitis, were not seen.

What explains the extraordinary asthma-suppressive effect which potassium iodide exhibits so strikingly but only in certain patients? It has been emphasized that the iodide-responsive asthmatic subject presents no other distinctive clinical features. The history of iodide in medical therapy includes a notoriously wide application in many disorders. Its chief use was formerly in late syphilis for the resolution of gummas, and in acute syphilitic meningitis for which it was administered in huge doses. In sporotrichosis iodide remains the drug of choice and may be used in doses as high as 40 drops of saturated solution three times daily.<sup>8</sup> Such dosage, three times as much as that used in this series, might be tried in bronchial asthma.

The therapeutic effectiveness of iodide is described by Goodman and Gilman<sup>9</sup> as its "histolytic action," the mechanism remaining uncertain. A related observation, to which they refer, was its tendency to cause a flare-up of tuberculous lesions. This warning to avoid iodide in tuberculosis recalls similar current practice as to steroids unless accompanied by specific antituberculosis chemotherapy.

Such observations suggest that the action of potassium iodide in asthma may be part of a more general anti-inflammatory or antiallergic effect. In this series, allergic rhinitis as well as asthma was occasionally observed to improve on iodide. More often, however, there was no effect on rhinitis; rarely, it was aggravated. Iodide was also used in a small series of patients with atopic dermatitis, urticaria, and angioedema, but in no instance was there improvement and in some the condition grew worse. Iodide could not be shown to diminish the immediate skin test response to allergen extracts. In a case of cold urticaria

the edema reaction to topical application of cold was unaffected. In three instances a positive intracutaneous tuberculin test with PPD remained unchanged when the test was repeated during iodide administration. It is possible that some effect might be detectable if a minimal tuberculin stimulus were used, aimed at eliciting a threshold reaction. The fundamental mechanism by which iodide exerts its asthma-suppressive action remains speculative. What insight this exceptional action may provide as to some fundamental difference between iodide-responsive and iodide-unresponsive asthma likewise constitutes a provocative question.

#### SUMMARY

The exceptional asthma-suppressive action of potassium iodide is described as observed in ten cases among approximately two hundred treated with this drug. A high degree of control of asthma may persist for prolonged periods, up to five years. The degree of effectiveness may be such that prolonged steroid therapy can be avoided. The data suggest that this is not a placebo effect.

Potassium iodide was in general well tolerated, but its side effects warrant consideration and their management is discussed. Thyroid adenoma was the most important complication of therapy. Iodide, long considered to possess some anti-inflammatory action, appears to exert little benefit on other common allergy syndromes. It did not diminish either immediate or delayed allergic skin test reactions. The mechanism of the asthma-suppressive action of iodide remains obscure. What accounts for the peculiar iodide-responsiveness of certain cases of bronchial asthma constitutes a related provocative problem.

The author wishes to acknowledge the stimulus of an early observation by Dr. Clifford Spingarn to his continuing interest in this subject.

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## Comments on Dr. Siegal's manuscript

### INTRODUCTION

The preceding paper was accepted for publication in *The Journal of Allergy* because it raised an important question concerning the evaluation of clinical data. The author suggested that only a small fraction of the asthmatic patients respond favorably to potassium iodide. If this is so, then this favorable response might not produce a statistically significant effect on a double-blind study performed on a large group of patients with this disease. Dr. Siegal's manuscript was presented to eight reviewers with the following questions:

1. Is the author's thesis of the heterogeneity of asthma reasonable?
2. If so, do you agree that this reduces the value of the double-blind study in determining the effectiveness of a given drug such as potassium iodide?
3. Has the author exhausted the possibilities other than a double-blind study for establishing the effectiveness of potassium iodide in individual patients?
4. If not, what else could he do?

The answers to these questions provide an instructive analysis of many of the problems of clinical investigation.

*Editor*

*Dr. Francis C. Lowell.*—This issue of the *JOURNAL* contains an article describing strikingly beneficial effects of iodides in relatively large daily doses (2.4 Gm. potassium iodide as an enteric-coated preparation) in 10 patients. These were the only ones among some 200 asthmatic patients in whom a trial with iodides had been successful. As I am sure the author will agree, retrospective selection of cases, without any systematic effort to maintain experimental control (a placebo was given in a single trial, in one case only) and with the single criterion for selection, the very response for which a claim is made, cannot be accepted at face value. The striking response described in these cases may or may not be correctly attributed to an effect of iodides, specific or otherwise—one would like to know.

Can one know? One probably can in spite of substantial obstacles. Admittedly, on the basis of the report presented, one can predict that a study of unselected asthmatic patients will fail to show any significant effect of iodides since the effect was seen in only 10 among 200, or 5 per cent. Therefore one must proceed on the assumption that, with respect to effectiveness of iodides, the asthmatic population is heterogeneous. Pre-selection of suitable, or what seem likely to be suitable, patients would be necessary. One might begin as the author did and try the effect of iodides in a large group. One could thereby identify those who seem to derive benefit. Having made a selection of "indicators" of a therapeutic effect of iodides, the next step would be to conduct a formal study of this group with suitable experimental control.

Another approach would be to survey the iodide-responsive group to determine whether they have one or more clinical features in common which might make preselection possible. For example, nasal polyposis was present in three (Nos. 1, 2, and 6) of the five patients who are described in sufficient detail to allow the reader to know whether polyps were present or not. This information is not given for the remaining five patients. It would be interesting to know, for example, how many among the 10 patients included in the report had nasal polyps and what the incidence of nasal polyps was among the 200 patients from whom the selection of 10 was made. One could perhaps make some estimate of the likelihood that nasal polyposis is related to "iodine responsiveness" and could therefore serve as a means of preselection.

An "informal" clinical observation can have great value, but only if it can be made to "stand on its own two feet." This one cannot, but nevertheless, it may point to a fruitful line of study. Most observations have to be put to a rigorous test and it is the report of this test that deserves priority in our journals, more often than the original observation.

*Dr. Irving H. Itkin.*—Dr. Siegal has made several astute observations of the effect of potassium iodide on the clinical course of ten patients with asthma. Some of the patients who responded favorably may have suffered also from other conditions aggravating bronchial obstruction. Before accepting the idea that the disease asthma should be divided into that sort which is iodide responsive and that which is iodide unresponsive, one must examine the evidence and find that no other explanation is more reasonable, for unnecessary classifications serve only to add confusion.

An interesting report appeared recently in the Italian literature. Rosa and associates studied the effectiveness of potassium iodide when given to 664 patients who wheezed. Clinical observations as well as spirometric readings were obtained during alternating ten-day periods with and without the drug. The usual dose was 1.4 Gm. daily, but on occasion this was raised to 2.8 Gm. or 3.15 Gm. daily. Asthmatic bronchitis (bronchial infection with wheezing), had been diagnosed in 420 patients, 84 with allergic asthma (extrinsic or intrinsic), and 160 with mixed (both allergic asthma and bronchial infection present). Of the 420 bronchitic patients, 85 per cent responded "optimally" to potassium iodide, 14.28 per cent "moderately," and only 0.72 per cent had no response. Of the 84 patients with allergic asthma, no patients responded "optimally," and only 2 responded moderately well. Of the 160 mixed cases, "optimal" response was recorded in 43.75 per cent, "moderate" response in 50 per cent, and "no response" in only 6.25 per cent. Good results were attributed to the expectorant action of the drug, with the abolition of reflex wheezing when the mucus causing bronchial obstruction was reduced. Beneficial results appeared rapidly, in ten days or less, and were lost rapidly when the medication was discontinued.

Considering some of the difficulties involved in differentiating asthma alone from asthma complicated by bronchial infection, it would seem reasonable to suppose that at least some of Dr. Siegal's successfully treated patients were in the latter category. The patient with both conditions is more likely to suffer from cough early in the attack, to note fever during or just before attacks of asthma, to suffer a large number of attacks during the winter season, to find that the usual bronchodilator drugs are relatively ineffective, that the corticosteroids are less dramatic in their effect at some times than at other times, and that antimicrobial drugs are often surprisingly beneficial.

Cytologic examination of the sputum may reveal that polymorphonuclear cells frequently predominate, although eosinophils in great number may be present in a yellow sputum. Cultures of the sputum may reveal the growth of *Haemophilus influenzae*, staphylococci, or pneumococci, although the absence of pathogens on culture does not rule out bronchitis due to infection. Bronchoscopic examination may be helpful not only on the basis of differences in gross appearance, but also because of the opportunity afforded of obtaining mucus from the lower bronchial segments. N-acetylcysteine appears to be singularly ineffective in dissolving the mucus from uncomplicated asthma, while it may influence dissolution of the mucus obtained from infected patients.

Bronchography and cinefluorobronchography may be helpful.

When infection is a complicating factor, blood tests may show elevations of the total white blood count, the polymorphonuclear percentage, the sedimentation rate, the C-reactive protein, the mucoproteins, and the gamma globulin fraction.

Ventilatory studies done over a long period may show a lesser degree of variation in the chronically infected patient. Extreme sensitivity of the bronchial tree to the inhalation of mecholyl chloride is characteristic of the asthmatic patient; lower degrees of sensitivity are found in the bronchitic patient without asthma. The test is helpful in confirming the presence of asthma where infection may overshadow the latter.

After infection has been eliminated as a likely possibility to account for the effectiveness of iodide, more crucial studies of the action of iodides on asthma may be undertaken. These should, indeed, include double-blind studies, using, for example, other expectorants, as well as placebos, for control.

Another method has been in use at the National Jewish Hospital for the past year. After the lowest maintenance dose of steroids has been determined for steroid-dependent patients, airway functions are recorded for several weeks at that dose. Then iodides are

added to the regimen for several weeks, and attempts are made to lower the steroid dose again without producing a corresponding decrease in airway function. At the present writing, none of fifteen patients on whom this has been tried has benefited.

Dr. Siegal has reported convincingly in his paper that the iodide action is unlikely to be directed against the antigen-antibody reaction. Work in progress at National Jewish Hospital with dose-response curves of bronchial reactivity to allergenic extracts as compared with reactivity to solutions of mecholyl chloride using the quantitative inhalation challenge suggests that these may be separate responses. Can it be that iodides interfere with the reaction to mecholyl? We shall attempt to investigate this hypothesis. Other approaches than that by inhalation challenge are also applicable.

The possibility that iodides may have some action upon molds different from that which is recognized should also be entertained. Mold allergy may be more prevalent than has been suspected.

In conclusion, Dr. Siegal deserves great credit for bringing his clinical observations to the attention of a wide circle of readers. Discussion of them cannot but bring more valuable knowledge to light.

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*Dr. Richard S. Farr.*—It is a pleasure to have an opportunity to comment on Dr. Siegal's paper, because I would like to record an opinion in support of his thesis regarding the heterogeneity of the clinical state called asthma. The symptom-complex consisting of bouts of intermittent bronchospasm associated with mucus secretion and difficulty in exchanging air can be caused by a variety of immunologic and nonimmunologic insults to the lung. Generally speaking, these bouts are usually referred to as asthma. Specifically, we can sometimes differentiate between asthmatic attacks primarily caused by such things as (1) bronchial infection, (2) infection associated with structural changes in the lung, (3) antigen-reagin interaction, (4) local tumors, and (5) even tumors located in organs other than the lung but secreting biologically active amines. Unfortunately, however, it is often difficult or impossible to ascertain which of the many possible factors is playing the major role in a given case. Indeed, more often than not, several factors appear to be more or less equal contributors to the symptom complex. The evaluation of a given case of asthma is further complicated by the variation from person to person with respect to end-organ responsiveness when an individual is confronted with a stimulus capable of eliciting asthma. For these reasons, a group of asthmatic patients almost certainly must be heterogeneous with respect to both causal factors and end-organ threshold levels. Although it is possible to select a more homogeneous group of asthmatic patients than those included in Table I of Dr. Siegal's report, a considerable degree of heterogeneity must surely exist in even the most carefully selected cases of asthma due to any specific causal factor one attempts to isolate. Further, because of this heterogeneity and variation from case to case, it is not unexpected that measures designed either to minimize the impact of an asthmatic stimulus to the lungs or to reduce the responsiveness of the lungs to the various stimuli will prove beneficial in some cases and not in others.

In the present study no apparent attempt was made to reduce the heterogeneity of the group of asthmatic patients presented but, under the circumstances, it seems to me that Dr. Siegal has done about all he can do to control his heterogeneous population of patients. In the face of the obvious heterogeneity in his patient population, he used each case as its own control which is a perfectly valid experimental procedure. Perhaps it could be argued that Dr. Siegal should have done more with substitution therapy using placebo tablets and this would be my major criticism of this report. On the other hand, many of

his cases are convincing even without this refinement. It appears that Dr. Siegal has found a few patients with asthma in whom iodide therapy tipped the balance between the state of having asthma and the state of being symptom free when all other factors in these individual cases were held relatively constant. The rationale to justify the concept that the group of conditions which we now call allergies, including asthma, should rightly be looked upon as a medical state of being rather than entities in and of themselves has been partially set forth elsewhere.<sup>1</sup>

Regarding the question about the usefulness of the double-blind technique to evaluate a drug or agent, granted that the given agent to be tested is in fact effective in doing the therapeutic job, then the double-blind study will be able to detect this effectiveness most easily under circumstances when (a) the drug in question is directed toward alleviating a situation which is a dominant causal factor in each of the cases selected for the study, and (b) each case selected for the study must not have a second or third etiologic factor which, if left untreated, is a strong enough stimulus to perpetuate the asthma by itself. If too many cases not in either category (a) or (b) described above are included in a double-blind study, it is not only likely but probable that even a very effective agent being tested as the primary objective of the study will yield only equivocal results.

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*Dr. Paul P. VanArsdel, Jr.*—If potassium iodide were a new drug, subjected to the critical assessment recommended for testing new drugs, it would probably be declared worthless for all conditions except thyroid disease. Unfortunately, or fortunately, depending on one's point of view, iodide therapy has a long clinical tradition. We are confronted then, with a dilemma which Ebert<sup>2</sup> pointed out two years ago in an editorial on evaluation of therapy in chronic illness: "While many of the traditional modes of treatment in medicine would not withstand careful scientific scrutiny, there seems to be no urgency in discarding them."

Yet many physicians with extensive experience in the treatment of asthma would agree with Dr. Siegal that the occasional patient improves dramatically with iodide therapy. This impression, or intuitive association, is reinforced by long-standing tradition. Indeed, the background of such therapy is nicely expressed by the couplet on page 827 of the text by Goodman and Gilman.<sup>3</sup>

"Wenn man nicht weiss Wieso und Warum,

Dann gibt man Jodkalium."

The usual claim for the value of iodide therapy is that it is effective in thinning or altering the volume of bronchial secretions. There is nothing to indicate that such an effect was important in Siegal's patients. This means that only the patients' subjective responses could be utilized; at least no quantitative basis for comparison was mentioned.

Asthma is characterized by wide variations in etiology, morbidity, and response to therapy, not only from patient to patient, but from time to time in the same patient. Except for the patients who react specifically to known extrinsic stimuli, and are free of asthma otherwise, most asthmatic subjects will have some remissions or relapses which are totally unexplained. It is possible that the patients reported upon by Dr. Siegal did respond specifically to some anti-inflammatory effect of iodide as he proposed. This hypothesis, however, cannot be subjected to experiment, and is less tenable than a proposal based on a simple grouping of asthmatic patients:

If group (A + B + C + D) = all asthmatics

and group (A + B) = all asthmatics who get better

and group (B + C) = asthmatics who receive iodide therapy,

then group B includes all patients who get better with iodide.

This is not the same as saying that iodide was responsible for the improvement of

group B. That only ten patients from a total of 200 (B + C) were in this group strengthens the possibility of coincidence.

Clinically, there is nothing unique about Siegal's patients except that they improved with iodide therapy. This means that they provide us with no common denominator which might allow preselecting of other asthmatic patients who would be appropriate candidates for a controlled study. To undertake a controlled double-blind evaluation of iodides in a large group of unselected asthmatic patients is a formidable task, and probably futile, particularly relative to Siegal's hypothesis. As pointed out by Modell and Houde,<sup>3</sup> there are too many factors at work "immaterial to the specific problem at hand." Shure and St. John<sup>4</sup> brought this out in one of the few controlled studies pertaining to iodide therapy in asthma. They were forced to reduce their series for analysis from 126 to 28 patients to get rid of "background noise"—that is, the reports from patients who were unable to discriminate between one agent and another.

Another approach might be to select patients for a controlled study on the basis of their earlier favorable response to iodide. Even if we disregard the fact that some of Siegal's patients became unresponsive to iodide, their responses, as well as those of other patients who have experienced iodide therapy, would be almost impossible to control. There is an unavoidable bias introduced by the distinctive iodide side effects which cannot be duplicated by placebos. One wonders about this bias also in the improvement reported by some patients in the above-mentioned controlled study.<sup>4</sup>

The problem is compounded when one attempts to evaluate the expectorant action of iodide, which is dose related and closely allied to the other physiologic reactions of iodism.<sup>2</sup> Changes in sputum should at least provide a more objective index of the pharmacodynamic action of iodide. Alas, in controlled studies, the observed effects on sputum viscosity or volume have been unimpressive, and the changes that were observed did not correlate with clinical improvement.<sup>5, 6</sup>

The greatest contribution of this paper is the evidence that iodide therapy is worthless for a majority of asthmatic patients, and may be harmful. Considering the casual, and often routine, use of iodides by some physicians, this deserves repeated emphasis. Asthma is a capricious disease and iodide treatment has capricious effects. Only when the occasional patient shows distinct improvement with potassium iodide, can we justifiably resort to an old empirical rule of therapy, "if the patient is improving, keep using it." However, such a practice has not led to the discovery of any general truths about the nature of asthma or the specific action of iodide. Until dependable methods of evaluation become available, this practice should be subjected to continual critical scrutiny during the long-term management of each patient.

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*Dr. George V. LeRoy.*—The fact that complete remission of symptoms lasting from 4 months to 5 years occurred in about 5 per cent of 200 asthmatic patients should not surprise anyone. If we exclude from the category of "asthmatics" those patients with documented chronic bronchial disease—and chronic pulmonary disease, we are left with a group who have paroxysmal or persistent asthma the presumptive causes of which include allergy, psychophysiologic reactions, and hypersensitivity of the respiratory system to en-

environmental agents. We do not expect complete spontaneous remission among patients with disease of the bronchi or the lungs. Any amelioration of their asthmatic symptoms ordinarily is associated with rational therapy and is to a certain extent predictable. However, in dealing with the latter category of asthmatic subjects, I am impressed by my inability to predict the course of the condition. At almost any time after its onset, and for reasons that are rarely clear, the symptoms may disappear entirely. The duration of remission is also unpredictable. It is unfortunate that we do not know the probability that spontaneous remission will occur, or the distribution of the durations of remissions. Nevertheless, the fact that remission occurs is a reality, and the presumption that it is spontaneous is supported by a number of considerations. Iodides are not the only drugs which have received credit for a "cure" of asthma. Arsenic, stramonium, bromides, Lobelia, tobacco, vaccines, and many other substances have been mentioned favorably in the literature. Change of occupation, moving to the city—or to the country, strenuous regimens of exercise (walking 20 miles a day), psychotherapy—the list is long—all have "cured" some asthmatic patients. In addition, it is common knowledge that an unspecified fraction of juvenile asthmatics cease to have symptoms after puberty.

Our inability to distinguish between a spontaneous remission and the effect of a drug—such as potassium iodide—makes it virtually impossible to evaluate Siegal's report. Most physicians recognize the pitfalls involved in attempting to attribute the "cure" of a chronic disorder, such as asthma, to a particular regimen. The fact that *post hoc ergo propter hoc* may be fallacious is accepted, and, in an effort to avoid faulty attribution, statistical methods to evaluate evidence have been employed.

It is not easy to design a satisfactory clinical trial to evaluate the effectiveness of individual drugs in bronchial asthma. There are so many variables in the individual case that most workers hesitate to commit themselves to conventional trials of the double-blind variety. Until a new format is devised we are forced to depend upon clinical judgment in respect to drugs, which means that we can only state that a particular regimen appears to be better, worse, or no different than the one it supplants. This, of course, is a *post hoc* judgment which is necessarily provisional.

Siegal carries the *post hoc ergo propter hoc* reasoning one step further than usual and suggests that there may be some fundamental difference between iodide-responsive and iodide-unresponsive asthma. This kind of reasoning is difficult to categorize. Another physician confronted with the same experience might well say: "Since all my asthmatics were treated with enteric-coated tablets of potassium iodide, and since an unexpectedly long remission failed to occur in 95 per cent, some factor other than iodide must have been responsible for the complete remissions that occurred in these 10 cases." It is possible that a scrupulous investigation of the lucky 10 might provide insights into factors—other than the conventional drugs—that were responsible for the remission. If, as I suspect, such remissions are spontaneous in the sense that the drugs used are not responsible, it would be most helpful if we knew something more about the process. I have the strong impression that a change, perhaps a subtle one, in the total life-situation of the patient is the single most important factor. Unfortunately, we seldom have sufficient information on which to base such a conclusion before a remission occurs. When the patient is free of symptoms he has no further need of the doctor, and it is virtually impossible to investigate the situation retrospectively.

Future studies of asthma would be benefited if reports such as Siegal's were more complete with respect to diagnosis and details. Some day we may have information on the incidence and distribution of symptom-free periods in patients with bronchial asthma. Until we have such data evaluation of therapy must remain subject to the impressions of the clinician.

*Dr. Kenneth P. Mathews.*—Especially since there are a limited number of ways in which bronchioles can react, it seems very possible that a variety of circumstances may eventuate in apparent asthma. If so, certain drugs could produce a beneficial effect in some instances but not others. If, as Dr. Siegal suggests, the percentage of cases where conditions are favorable for demonstrating the action of a drug is less than the usual percentage of

patients responding to a placebo, it would be difficult to demonstrate the efficacy of the drug by the usual type of double-blind study employing unselected asthmatic patients. Theoretically, however, a difference should be demonstrable if a large enough group of subjects were studied. For instance, if 30 per cent of patients improved on a placebo, if a drug actually helped 5 per cent of patients, and if the percentage of placebo responders is the same among those actually benefited, as among those not benefited by the drug, 5 per cent of the 70 per cent not responding to placebos also should be improved on the drug; i.e., in an infinitely large series of patients, 30 per cent would respond to the placebo and 33.5 per cent would benefit from the drug. To demonstrate such a difference at the 5 per cent level of confidence would require between 7,000 and 8,000 patients.

It certainly would be more feasible to study patients selected as prospective responders to the drug under study. In the absence of any clinical or laboratory criteria for selecting this group, a preliminary impression that the patient responded to iodides would have to be the basis of selection. A double-blind cross-over type of study might then be carried out. For instance, randomizing the sequence in which the drugs are administered, each individual might be given two courses of placebos and two courses of iodides and the severity of asthma rated, by appropriate means, toward the end of each treatment period. Gross differences might then be evaluated by the sign test, or an analysis could be carried out by such means as comparing patient days, weeks, or months of mild or severe asthma on the drug or placebo treatment. A difficulty in carrying out this type of study would be the probable impossibility of evaluating all patients simultaneously. The results, of course, would be applicable only to the selected group and not to the universe of asthmatic individuals.

Short of the type of study just mentioned, making objective measurements by appropriate pulmonary function tests helps to substantiate the impression that improvement has occurred, but this does not establish that the improvement is due to the drug rather than to fluctuations in the natural course of the disease or other factors. Finding a rationale for using the drug also would support its administration. In the instance at hand, comparative studies of iodide and potassium metabolism in responders and nonresponders would seem indicated.

*Dr. Constantine J. Falliers.*—The heterogeneity of asthma, with respect to its causative or precipitating factors, is a well-established fact. Dr. Sheppard Siegal has presented further evidence that differences among asthmatic individuals can also be observed in response to certain therapeutic procedures, applied at various times to the same or different patients.

The response of the ten patients to the treatment administered by Dr. Siegal appears dramatic indeed. Is potassium iodide solely responsible for this? The observations reported, although suggestive enough to permit the formulation of an interesting hypothesis, cannot be considered as offering sufficient evidence for definitive conclusions.

The possibility of a placebo effect (whether "pure" or additive to the pharmacologic effect) must be seriously considered. The ten patients reported to have experienced an almost complete control of asthma represent a fraction (5 per cent) of the population surveyed, significantly smaller than the number of patients reported to benefit from specific hyposensitization therapy (74 per cent),<sup>1</sup> environmental change (33 per cent),<sup>2</sup> operative procedures (57 per cent improved, 24 per cent "cured"),<sup>3</sup> or placebos alone, whether injected (26 per cent)<sup>1</sup> or given orally (5 to 12 per cent).<sup>4</sup> Considering that "the question of the time-course of placebo reactivity is still unanswered,"<sup>5</sup> the long duration of the asthma-suppressive effect of KI cannot alone rule out a placebo effect. Neither can the relapses noted after a reduction in dosage from 2.4 to 1.2 Gm. daily\* eliminate this possibility, as it has been shown<sup>7</sup> that the administration of placebos can elicit "dose-response" curves, with "peak" effects, cumulative action, holdover effect, etc., much like a pharmacologically potent preparation.

\*It must be noted in this respect that others<sup>6</sup> have found a daily dose of 200 mg. "in excess of that necessary . . . in the treatment of bronchial asthma."

As Dr. Siegal well recognizes, a "double-blind" design could possibly obscure the remarkable effect of KI, which he has observed in only a few cases, by diluting these cases within his total patient population. A double-blind study among a selected group of patients would naturally be more meaningful, but it does not seem possible, at present, to predetermine which patients are likely to respond to iodide therapy. Some of the difficulties inherent in a double-blind study of unselected cases could be circumvented by following the suggestions of Fisher<sup>8</sup>; a discrimination between placebo and drug effects could thus be accomplished by eliminating from the chi-square analysis patients who appear to respond in a similar fashion to both drug and placebo. An evaluation of the long-term effects of potassium iodide on children with intractable asthma is presently under way at the Children's Asthma Research Institute and Hospital in Denver. A preliminary analysis of the data from the first 12 months of this three-year program<sup>9</sup> suggests that the double-blind design employed did, in fact, permit the detection of certain differences (Table I). It appears that potassium iodide, 300 mg. three times a day, was superior in its effect on asthma to KI, 100 mg. three times a day, and to the placebo. It cannot be stated on the basis of these preliminary findings whether the differences were due to the remarkable response of only a few individuals among the total number of patients, or whether all of them did improve to some extent when they received 900 mg. of KI daily. Definitive statements will be possible only after the completion of the three-year program.

TABLE I. MEAN WEEKLY SCORES\* REFLECTING THE EFFECT OF POTASSIUM IODIDE ON ASTHMA. PRELIMINARY DATA FROM A 12 WEEK, DOUBLE-BLIND STUDY OF 48 CHILDREN AT THE CHILDREN'S ASTHMA RESEARCH INSTITUTE AND HOSPITAL

CLINICAL PARAMETERS*	KI 300 MG. T.I.D.		KI 100 MG. T.I.D.		PLACEBO T.I.D.	
	MEAN	±S.E.	MEAN	±S.E.	MEAN	±S.E.
I Symptoms of asthma reported by patient	7.2	.60	8.8	.67	8.9	.64
II Asthma (wheezing) by physical examination	6.2	.58	7.4	.65	7.3	.57
III Inhalation treatments needed	3.2	.37	4.3	.56	4.1	.52
IV Days in hospital for asthma	.23	.08	.28	.08	.27	.08
V Steroid therapy (prednisone, mg./week)						
a. Intermittent (N=14)	16.5	2.25	25.1	3.66	38.9	4.08
b. Continuous (N=22)	52.7	2.69	55.1	3.26	64.3	3.36

\*A description of the scoring system and a definition of the parameters employed presented elsewhere.<sup>9</sup> S.E. = standard error.

The great dissimilarities of the ten cases reported do not offer any clues as to why KI proved so singularly effective. Pregnancy, adolescence, psychoanalysis, nasal polyposis, connective tissue disease, as well as allergic sensitivities, are among the variables mentioned which are known to influence the course of asthma. The need for corticosteroid therapy was eliminated in many of these cases for certain time intervals when KI was given. It may be hypothesized that KI, through its known thyroid-suppressing effect in some individuals, may result in a prolongation of corticoid turnover time,<sup>9</sup> with a decrease in the reduction of adrenal steroids to the tetrahydro derivatives, perhaps also an increase in the corticoid-binding capacity of serum. On the other hand, the administration of thyroid hormones has been reported<sup>10</sup> to augment immune responses; it would thus have been of interest to know the course of asthma in Case 1, when thyroid extract was prescribed in addition to KI.

Much is yet to be learned regarding the role of anti-inflammatory drugs (which may include potassium iodide, according to Dr. Siegal's study) in the management of asthma and the effect of such agents on hormonal homeostasis. Two points clearly emphasized in Dr. Siegal's article deserve special attention:

1. Significant differences, both quantitative and qualitative, exist among individuals

\*Supported by Grant A-5963 from the National Institutes of Arthritis and Metabolic Diseases, U.S. Public Health Service.

suffering from asthma, not only in their responses to provocative agents, but also in the effect of therapeutic modalities.

2. Simple molecular substances, such as KI (perhaps  $H_2O$  must also be mentioned here) may be of considerable value in the management of asthma, their mode of action (still unknown) being possibly through complex metabolic pathways. The elucidation of such phenomena may eventually lead to a better understanding of asthma itself.

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*Dr. Samuel C. Bukantz.*—For many years I have expressed the opinion that there is little evidence to substantiate the benefits of potassium iodide in treating asthma and have further suggested that additional controlled clinical studies with potassium iodide would be very desirable. Dr. Siegal's interesting paper helps me to understand my negative experiences, which unfortunately I have not documented as well as he, but additionally raises several fundamental issues of considerable importance to the clinical investigator. He has described a heterogeneous clinical response of a complex syndrome (asthma) presumably to the exhibition of a single drug (potassium iodide), in what appears to have been a narrow dose range. He has not measured the pharmacologic response to the iodide itself, but the effect of that response (whether it be on bronchial glands, or on the sputum directly, or on some more complex interrelated endocrine function) on a clinical state. This really complicates the issue of Dr. Siegal's presentation which essentially describes an  $ED_{100}$  in a small segment of the asthmatic population (10 of 200 or 5 per cent of his series.)

Suggested by his observation is the notion that there is a genetic basis for this remarkable response to iodide and it would appear reasonable that such a response would arise from a monofactorial inheritance causing discontinuous variation. The individuals within a population of asthmatic individuals, then, by this notion will not show the usual variance of response to iodides that is usually encountered with other drugs. Variance of response to a given dose of a given drug from individual to individual within a given species has been known for a long time. This matter has been dealt with very nicely by Werner Kalow in his book, *Pharmacogenetics, Heredity and the Response to Drugs* (Saunders, 1962). As Kalow points out, the methods developed to measure and define the potency of a drug have generally been aimed at assessment of the specific kind of individual variation (the

of individual variations) which is given graphic expression in Gauss's distribution curve. What Dr. Siegal points out is what Kalow further states, that methods attempting to deal with the individual variations (such as the iodide response he noted) by the means developed to deal with continuous variations (determinations of dose producing a given effect in 50 per cent of individuals) may lead to misjudgments and failures. I think he may be right, but I do not think his own series alone establishes the point, and it lacks what I am sure he would like to have, some other measure than clinical of what the iodide is doing to the subject as well as not doing to the nonrespondent. One disturbing note in assigning a genetic basis to the described differences of effect of iodides is the temporary nature of the iodide effect in a number of Dr. Siegal's patients. Furthermore, it appeared to me that some of his patients had first failed to respond to iodide, subsequently did so to extraordinary degrees, and finally lost the responsive capacity.

The following comments were made by Dr. John E. Silson, Medical and Pharmaceutical Research Consultant, who is very knowledgeable in the design and analysis of controlled clinical trials with drugs. Although I have gone over the details of Dr. Silson's commentary with him, what follows is essentially his. My own concluding remarks would emphasize what Dr. Silson suggests, that it would be exceedingly useful to compare the historical, physical, and laboratory characteristics of the patients who respond to iodide and those who do not, in an effort to elucidate the nature of the difference. Dr. John Silson's remarks follow:

*Dr. John E. Silson.*—First, the concept of heterogeneity cannot be applied to the evaluation of a primary therapeutic response, since the very basis of the statistical evaluation of a response is its heterogeneity: namely, that some patients respond to the treatment, while others do not. Homogeneity (absence of heterogeneity) tests should be used only to insure that the test and control groups are similar with respect to secondary characteristics, such as severity and duration of illness, age, and sex, which might influence response. This type of testing is intended to insure that the sampling procedure, whether random, stratified, cluster, or card matched, does not introduce any bias factors between the groups being compared (for which correction factors might be necessary, or which in an extreme case might even completely invalidate the results). Tests for homogeneity are necessary only in cross-over studies, in which the same population is used for all groups, when a large order effect is present, in which case the starting groups should be compared.

Second, the factor with which Dr. Siegal is concerned is not heterogeneity, but rather the effect of dilution. If a true therapeutic effect exists, but only in a small percentage of patients, then both test and control groups, assuming proper sampling, become diluted with an approximately equal number of nonrespondents; and the sample size necessary to pick up statistical significance becomes so great as to be impractical. Under these circumstances, it would be inexpedient to run a controlled study in an unselected population to demonstrate effectiveness.

Third, it is unfortunate that "double-blind" has become the *sine qua non* of a controlled study. Actually, blinding is only one of the many tools available to the biostatistician, to be used with discretion to minimize bias factors. In asthma, where evaluation of response is largely subjective, a double-blind check of a medication is normally advisable. It is fully practicable and often preferable, however, first to eliminate the nonresponders by means of an uncontrolled, nonblind clinical trial. A double-blind controlled study only on those showing a favorable response (which will include both drug and placebo respondents) can then be instituted, preferably using a cross-over design. A single-blind check, such as Dr. Siegal used in Case 19, still leaves room for doubt, since the physician may have unconsciously influenced the patient by his knowledge of the change in medication even though patient bias is eliminated and the difference in response observed by the physician appeared too great to be questionable.

Besides its use in validating clinical effectiveness, statistical methodology can play an important role in helping to elucidate the characteristics of the patient likely to respond to the medication, or even the mechanism of its action. Dr. Siegal mentions that "it has been emphasized that the iodine-responsive asthmatic subject presents no other distinctive clinical features," but we wonder how exhaustively all the characteristics of both the patient

and negative reactors have been tabulated and then compared statistically to seek some clue as to their differences. Similarly, how carefully have extensive laboratory studies of the two groups been compared, with particular attention to tests related to iodine metabolism.

*Dr. Siegal.*—It was only after considerable hesitation that I permitted myself to submit for publication these observations on the asthma-suppressive effect of potassium iodide. This experience has been collected over a period of ten years but it was difficult to subject to adequate controlled experiment. I was well aware that any claims for such an unusual degree of effectiveness for so notorious an agent as potassium iodide would automatically meet with disbelief and rejection.

These cases, culled from private practice, made it difficult to resolve the ethical question of upsetting the patient's favorable clinical course by the administration of falsely labeled tablets. Moreover, it is not the custom in this community for a physician to dispense medication to a patient directly. Thus, the control medication would itself raise some doubt in the patient's mind. Furthermore, as indicated by one of the discussants, such an experiment is only an imperfect control.

Fully realizing that clinical observations of this type are in some disrepute, I did not think it right to allow possibly significant observations to remain unreported, permitting a treatment perhaps of real value to remain unrecognized.

I wish to indicate my sincere appreciation both to the Editor of the JOURNAL and to the discussants. I am happy to observe with what seriousness this subject has been considered. My hopes have been fulfilled that the publication of data on this exceptional action of potassium iodide, even though inconclusive, might stimulate the kind of interest that would ultimately lead to a final answer to the problem.

*Dr. VanArsdel* made the very important point that my observations certainly indicate that iodides are worthless for the majority of asthmatic patients. It is also true that they ought not to be used casually. It is the point of this paper that iodides should be prescribed with the purpose of determining whether they will induce an asthma-suppressive action. If not, they should be discontinued. Increased awareness of the thyroid complications of iodide treatment as well as the management of other more minor side effects are also practical considerations of value. However, I would wish to express some disagreement with the statement that "only the patient's subjective responses could be utilized; at least no quantitative basis for comparison was mentioned." In Case 1, timed and total vital capacity measurements changed favorably during therapy. More important, judgment as to improvement was based upon the disappearance of bronchopulmonary physical signs; upon diminution in the requirement for other antiasthmatic medication, even with discontinuance of steroids; upon the observed increased well-being of the patient, as to general appearance, complexion, color of membranes, weight gain; and above all on the patient's increased capacity to perform both normal and even strenuous exertion which had formerly seriously handicapped him. Such observations may be as objective, if not as quantitative, as those that appear on a pulmonary function testing record.

*Dr. VanArsdel* and others have raised the question of spontaneous remissions in asthma as explaining the apparent response to the drug. While well aware of this difficulty, I would suggest that it is precisely our incapacity to provide such patients with prolonged remissions that impels them to shop from doctor to doctor and even from climate to climate to seek relief. This is especially true of well-established asthma. In Case 1, asthma had lasted thirty-two years; in Case 2, nineteen years; in Case 8, eleven years; in Case 10, nine years; in Case 4, five years. Such patients only rarely have spontaneous remissions for an extended period. In more than twenty years of special experience with asthma, I have never been able to induce such remissions with aminophylline. Why did it follow potassium iodide? Can this be coincidence only?

Perhaps too much emphasis in the discussion has been placed upon the auxiliary question of a fundamental differentiation between iodide-responsive and iodide-non-responsive asthma. This concept was after all limited to a provocative one-sentence question. *Dr. LeRoy* was quite correct in implying that such a question is premature, but the reasoning involved

in raising this question is not too difficult to categorize, for it is simply one of curiosity. At this juncture, the fundamental problem is to determine whether iodide does exert the pharmacologic effect claimed for it, and if so, what the mechanism is that underlies this action. For this reason I would agree with Drs. Bukantz and Silson that one cannot now cast light on the fundamental difference which may exist between the iodide-responsive and unresponsive asthmatics. First let it be well established whether there is in fact such a select group who respond so uniquely to this simple compound. Our problem now is not so much one of genetics as of pathogenetics.

Dr. Lowell asks particularly about nasal polyps. Since I was asked to present these cases as compactly as possible, negative observations were omitted. Where nasal polyps were present they were reported; when not reported they were absent.

As to Dr. Itkin's question concerning the role of bronchial infection in relation to the iodide effect, there did not seem to be any relationship. In some patients iodide control appeared to prevent an asthmatic flare-up despite acute respiratory infection. Iodides were helpful when bronchial infection seemed absent. I have no way of knowing whether this action is related to a fungicidal effect of iodide, but I doubt it. Dr. Mathews indicated the difficulties which would be involved in attempting to establish the asthma-suppressive action of the iodides by means of a double-blind study.

I am delighted to learn of the systematic observations of Dr. Falliers and his group in Denver under the favorable controlled conditions available in an asthma institute. While conclusions must await the result of the full three-year program, perhaps it is significant that on preliminary analysis the children on iodide fared more favorably. However, the iodide dosage employed in this study appears to me a little too small for maximum effectiveness. I have previously had the pleasure of discussing this iodide effect with Dr. Falliers and am happy indeed that he has set such a study in motion.

The possible mode of action of the drug as suggested by the various discussants certainly is not elucidated by my observations. I have no data on either potassium or iodide metabolism in these patients. In response to one question, it should be stated that in Case 1 asthma was benefited even though the patient was taking desiccated thyroid for his thyroid adenoma.

Perhaps as a scientist I ought to have presented this problem quite differently: "These are the data; what do they signify?" But as a practicing physician and allergist one inevitably feels the impact of the enthusiasm and gratitude which these patients express in reaction to their unexpected and persistent relief from suffering. As a result of this, I have come to hold the conviction, perhaps wrongly, that there is in fact such an effect as the asthma-suppressive action of potassium iodide.

## EFFECTS OF POTASSIUM IODIDE ON THE SKELETAL TISSUES OF GROWING MICE \*

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In former investigations, we observed<sup>1</sup> that administration of potassium iodide for 20 days stimulated both proliferation and regression of the epiphyseal and articular cartilages in immature guinea-pigs; it also increased the resorption of the primary bony trabeculae during the growth period. These changes resembled in some respects the early changes found in the cartilage of growing mice and guinea-pigs subsequent to the administration of anterior hypophyseal and thyroid hormones.<sup>2</sup>

The present investigation was undertaken in order to determine how prolonged administration of potassium iodide influences skeletal development and ageing in mice, and how these effects compare with those obtained by the administration of anterior hypophyseal and thyroid hormones.

### MATERIAL AND METHODS

Twenty-eight male mice were used in these experiments. Eight mice of the closely inbred strain C57, 4 weeks old, received intraperitoneal injections of 0.1 cc. of a 2.5 per cent solution of potassium iodide in distilled water. Two of these mice were injected for 4 consecutive days and sacrificed the next day; the remaining 6 mice were injected for 5 consecutive days; no injections were given on the sixth and seventh day. The animals were killed in pairs after 1, 2 and 4 weeks following the first injection. Twenty mice of the closely inbred strain C<sub>3</sub>H, 4 to 6 weeks old, were treated in the same way for periods of 4 days, 1, 2 and 4 weeks, and 2, 3, 4, 5 and 11 months. Four untreated male mice of the strain C57 and 10 of the strain C<sub>3</sub>H (when possible, littermates) served as controls.

At necropsy, tibia and femur were removed as a whole. The growth zone at the upper tibia was selected for histological study.

\* These experiments were conducted in the Laboratory of Research Pathology, Washington University, School of Medicine, St. Louis, Mo.

The investigation was carried out by the aid of grants from the Committee on Research in Endocrinology of the National Research Council, the Jane Coffin Childs Memorial Fund for Medical Research and the International Cancer Research Foundation, given to Dr. Leo Loeb; and from the Albion O. Bernstein Fellowship in Pathology, New York University, College of Medicine.

Received for publication, June 25, 1943.

## OBSERVATIONS

The animals stood the injections well. During the first 2 weeks, the mice injected with potassium iodide gained somewhat less weight than the untreated animals. In strain C57, this deviation from the normal was more accentuated than in strain C<sub>3</sub>H. However, after 4 weeks of injection of potassium iodide, there was no difference in the weights of the treated and the control mice.

## HISTOLOGICAL EXAMINATION

## I. In Strain C57

(a) *Epiphyseal Disk.* After 4 days of injection of potassium iodide, the pattern of the growth zone of 4½-weeks-old mice was regular. In a single row, 4 hypertrophic cartilage cells were counted, as is normal for this age; the columnar cartilage cells were slightly increased in number; there were 10 to 12 instead of the usual number of 10. The nonoriented cartilage cells were rounded off and had undergone noticeable proliferation. The columnar cartilage cells likewise showed increased mitotic proliferation, and their conversion into hypertrophic cartilage cells was intensified.

One week after the beginning of the injections of potassium iodide, the epiphyseal disk was narrower than after 4 days of treatment, and also somewhat narrower than in untreated mice of corresponding age. The mitotic proliferation of the cartilage cells was less accentuated than after 4 days of treatment. In a single cartilage row, the number of columnar cells had fallen to 8 to 10, and that of hypertrophic cells to 2 to 3. Simultaneously, the columnar and hypertrophic cartilage cells had decreased in size, while the cartilage ground substance had increased in amount and the calcification of the cartilage was intensified. Moreover, the cartilage cells had undergone karyolysis and karyorrhexis, conditions not seen in control mice of this age. The conversion of columnar into hypertrophic cartilage cells and the replacement of the latter cells by bone were markedly accentuated.

After 2 and 4 weeks of treatment with potassium iodide, the zone of endochondral ossification showed a distinct narrowing and a heavier calcification than ordinarily. The number of columnar cartilage cells in a single row was 6 to 8 instead of 10, that of the hypertrophic cells was 2 instead of 4. Moreover, regressive changes in the cartilage became conspicuous. Several groups of adjoining cartilage cell-rows were thus affected, and thick plugs of amorphous cartilage appeared in the growth zone of 6-weeks-old mice (Figs. 1 and 2). In healthy untreated animals of this strain, a similar condition is not seen before the end of

the fourth month of life. Resorptive processes had likewise increased and had begun, in some places, to dissolve the amorphous plugs. Perforations of the epiphyseal disk, however, were not observed.

(b) *Subepiphyseal Layer.* After 4 days of injection of potassium iodide, the subepiphyseal zone, in which the replacement of cartilage by bone takes place, was congested. Mitotically proliferating spindle cells and epithelioid cells acting as osteoblasts filled the opened cartilage capsules and the peritrabecular tissue. After 1 and 2 weeks of injection, a partly fibrous, partly osteogenic tissue had developed. Numerous trabeculae containing nonossified or incompletely ossified cartilage were linked with each other by transverse bony bridges, but at the same time resorption of bone became accentuated. The activity of increased numbers of osteoclasts and of enlarged capillaries had caused a shortening of the bony spicules that were thickened in their proximal parts.

After 4 weeks of administration of potassium iodide, a thick transverse bony plate delimited the layer of hypertrophic cartilage cells from the bone marrow in 8-weeks-old mice. This condition is ordinarily not found before the end of the fourth month of life in animals of this strain. On account of the increased resorption of osseous tissue, the excessive amount of trabecular bone found at the earlier experimental stages had disappeared.

(c) *Joints.* During the first 2 weeks of injection of potassium iodide, the articular cartilage proliferated markedly by mitoses and underwent increased hypertrophy (Fig. 3).

After 4 weeks of treatment, the hyperplastic processes had decreased, whereas hypertrophy and ossification of the cartilage were still prominent. These changes were followed by, or associated with, an intensive resorption of cartilage and bone. Karyorrhexis and karyolysis of the articular cartilage cells were pronounced.

(d) *The Bony Shaft.* During the early stages the periosteum was vascular and loose. The spindle cells at the inner and outer surfaces of the compacta proliferated very much, and they were, in greater numbers than ordinarily, converted into osteoblastic epithelioid cells. Thus, both endochondral and periosteal ossification were increased, the maximum being reached after 1 and 2 weeks of injection of potassium iodide.

Following this period, increased cellular and vascular resorption caused a solution of the excessive amount of bony tissue seen at the earlier experimental stages. Thus, the histological structure did not differ from that seen in untreated mice of corresponding age. There were no changes in the bone marrow proper.

## II. In Strain C<sub>3</sub>H

The skeletal tissues of mice of strain C<sub>3</sub>H exhibit ordinarily a faster rate of development and ageing than those of strain C57.<sup>8</sup>

(a) *Epiphyseal Disk.* After injections of potassium iodide for 4 days, the epiphyseal growth zone of mice of strain C<sub>3</sub>H, 4½ weeks old, showed a greater narrowing and a heavier calcification, but less stimulation of proliferative processes in the cartilage than the corresponding animals of strain C57. In a single cartilage cell-row of strain C<sub>3</sub>H, 2 or 3 hypertrophic instead of 4, and 6 or 7 columnar cartilage cells instead of 10, were counted. As in strain C57, the conversion of columnar into hypertrophic cartilage cells was intensified, and it began farther proximally than usual. The hypertrophic cartilage cells underwent an accentuated replacement by bone.

After 1 and 2 weeks of treatment, the cartilage cell-rows had shortened still more than after four injections of potassium iodide. The number of hypertrophic cartilage cells in a single row had now fallen to 1 or 2, whereas the number of columnar cartilage cells was unchanged at 6 or 7. The cartilage cells were shrunken and densely calcified (Figs. 4 and 5). The regressive changes had affected several cartilage cell-rows and amorphous plugs of cartilage appeared in the growth zone of mice 5 and 6 weeks old. Breakdown and osseous replacement of the hypertrophic cartilage had progressed so rapidly that after 2 weeks of injections typical hypertrophic cartilage cells were lacking, while the number of columnar cells had decreased to 5. The degenerative plugs had increased in number and extent.

After 1 month's treatment, larger areas of the epiphyseal cartilage had undergone regression and such a degree of calcification that a cell count could not be made. On the other hand, advancing bone marrow began to resorb the amorphous plugs (Fig. 6). Thus, in 2½-months-old mice of strain C<sub>3</sub>H, the structural age of the epiphyseal growth zone was comparable to that of untreated mice of this strain 4 to 6 months of age.

After 2 months of injections of potassium iodide, the conditions were the same as after 1 month.

With prolonged duration of the experiment, the resorption of bone made some further progress, whereas the histological appearance of the cartilage cells had not changed as compared with the preceding stage. Four and 5 months subsequent to the beginning of the treatment, wider perforations of the epiphyseal plate were noted. After 11 months of injection, the structural age of the epiphyseal disk in mice of strain C<sub>3</sub>H did not differ from that of control mice of corresponding age.

(b) *Subepiphyseal Layer.* The subchondral lamella separating the epiphyseal cartilage from the bone marrow was laid down as early as 1 week after administration of potassium iodide had begun, whereas in strain C57 a corresponding state was reached only after 4 weeks of treatment.

After 2 and 4 weeks of injection of potassium iodide, the greater part of the spicules had been dissolved, while the transverse bony plate had become more solid.

After 1 and 2 months of treatment, the thick osseous plate had become corroded on its distal side by bone marrow.

After 3 or more months, the subchondral bony lamella had thinned out, and such bony spicules as were still present were likewise in an advanced stage of resorption. After 11 months of treatment, the conditions did not deviate from those seen in noninjected animals of corresponding age.

(c) *Joints.* The hyperplasia of the articular cartilage was less accentuated, whereas hypertrophy and regressive changes were more pronounced than in strain C57. At later stages, resorption of bone was intensified. Hyalinized homogeneous areas were found in the articular cartilage. They apparently had replaced areas of cartilage that had undergone regression.

(d) *The Bony Shaft.* During the early experimental stages, the compacta was thicker than in strain C57, probably due to the greater amount of bone usually present in strain C<sub>3</sub>H.

After 2 and 4 weeks of treatment, resorption of bone was more pronounced than was seen in strain C57. After 2 and more months of injection of potassium iodide, the resorptive processes were still more accentuated. After 5 months of treatment and later, the equilibrium between formation and resorption of bone was restored. The cortex showed the usual density and thickness.

#### COMMENT

In growing mice, the early effects of potassium iodide on the skeleton consist of a stimulation of the growth of the epiphyseal and articular cartilages. Subsequently, regression, calcification, ossification and resorption of cartilage and bone are increased, and the onset of epiphyseo-diaphyseal union is accelerated.

Potassium iodide thus promotes skeletal development as well as ageing (1) by an intensification of the growth processes, which is however, associated with a shortening of the growth period; (2) by an acceleration of the onset and progress of the second phase, in which

regressive changes predominate; and (3) by hastening the beginning of the third phase, the one during which resorption of cartilage and bone are prominent. However, with prolonged administration the ageing effect of potassium iodide decreases, and at later stages the structural age of the skeletal tissues is not different from that seen in normal old mice. Complete epiphyseo-diaphyseal union was not accomplished.

The present investigation on the effect of prolonged administration of potassium iodide thus supplements the observations made previously in immature guinea-pigs injected for 20 days. In these guinea-pigs, the stimulation of proliferation and regression of the cartilage had reached a maximum after 14 days, after which period it returned to normal.

The scanty reports on the effect of iodine on body growth are not in agreement. Cameron and Carmichael<sup>4</sup> did not observe any influence of sodium iodide on body weight and body length of rabbits and rats. Lipschütz and Morales<sup>5</sup> reported retardation of growth subsequent to the administration of potassium iodide to rats, but Hooker and Newman<sup>6</sup> noted no such retardation in mice. On the other hand, acceleration and increase of body growth were found in rats,<sup>7,8</sup> chickens,<sup>9</sup> pigs<sup>10</sup> and sheep.<sup>11</sup> In growing guinea-pigs, we observed markedly increased mitotic proliferation of the epiphyseal cartilage after a change to an iodine-enriched diet. According to Hunziker,<sup>12</sup> children given iodine were taller than those kept on a normal diet.

The effects of potassium iodide in our guinea-pigs were much more transitory than in our mice. In the guinea-pigs, the treatment was short in relation to the duration of the growth period; it thus might have been too short to cause a more profound alteration of the curve of skeletal growth and ageing. In our mice, on the other hand, the treatment was extended through a large part of the growth period, and in some animals even far into the second and third phases of skeletal development. Furthermore, strain differences may exist in guinea-pigs similar to those observed in mice. These differences play a rôle in determining the responsiveness of tissues to potassium iodide, and the guinea-pigs used in our previous experiments may have belonged to a less responsive strain.

Mice of the slowly ageing strain C57 showed marked skeletal growth changes after treatment with potassium iodide. Conversely, mice of the more rapidly ageing strain C<sub>3</sub>H, whose natural growth capacity was almost exhausted at the time of the beginning of the injections, showed relatively little or no increase of proliferation of cartilage. However,

regression of cartilage and resorption of cartilage and bone, that had been in progress at the beginning of the treatment, could be intensified and accelerated also in mice of strain C<sub>3</sub>H.

The effects of potassium iodide on the skeletal tissues in mice and guinea-pigs decreased with prolonged administration. This may be due to an adaptation to this substance as Loeb<sup>13</sup> and Gray and Loeb<sup>14</sup> have observed to occur in the thyroid of rodents. The data of Mendel and Vickery<sup>15</sup> likewise suggest a gradual decrease in the effectiveness of potassium iodide, although the authors do not comment on this point. Their rats fed with additional potassium iodide showed a greater increase of weight and growth during the earlier stages of the experiments than untreated rats. However, the figures obtained at the end of the experiments were similar in the control and in the treated groups.

The effects of potassium iodide on cartilage and bone are comparable to those caused by the administration of anterior hypophyseal and of thyroid hormones.<sup>2</sup> The differences that do exist are those of degree rather than of kind. The action of potassium iodide was weaker and of shorter duration: there was less proliferation of cartilage during the first phase, the period of growth; regression of cartilage, characteristic of the second phase, was less enhanced than after treatment with either anterior hypophyseal or thyroid hormones; and while the onset of the third phase, that of predominant resorption, was accelerated, resorption did not progress so rapidly, and it was not so intensified as after treatment with the other two hormones. Moreover, potassium iodide caused less bone formation than did anterior hypophyseal hormone.

Although there exists a certain similarity between the skeletal effects of potassium iodide, anterior hypophyseal and thyroid hormones, little can be said as yet about a corresponding similarity in the mechanism underlying the action of these various substances. Potassium iodide seems to affect the cartilage for the most part directly, and not by way of the thyroid gland; in thyroidectomized guinea-pigs, it stimulates the growth of cartilage almost to the same degree as it does in animals with intact thyroids.<sup>16</sup> Other extrathyroidal effects of iodine have been reported by Chapman.<sup>17</sup> Rats show increased food utilization and water intake subsequent to the administration of potassium iodide as they do after injections of anterior hypophyseal hormone.<sup>18</sup> Furthermore, in young pigs, potassium iodide caused an increased retention of nitrogen,<sup>10</sup> a phenomenon also observed under the influence of anterior hypophyseal hormone.<sup>19</sup> Finally, thyroxin-like effects on metabolism and growth have been obtained with iodized proteins.<sup>20, 21</sup>

## SUMMARY

In growing mice, potassium iodide stimulates the progress of the three phases in the life cycle of the skeletal tissues. It increases temporarily the proliferation of the epiphyseal and articular cartilages, accelerates the onset of regression in the latter and stimulates first the formation and subsequently the resorption of bone. The skeletal effects exerted by potassium iodide thus resemble those caused by administration of anterior hypophyseal hormone and of thyroxin; but they are less marked and more transitory than the latter. As is the case also with various hormones, mice of the slowly ageing strain C57 are more responsive to the administration of potassium iodide than are mice of the more rapidly ageing strain C<sub>3</sub>H.

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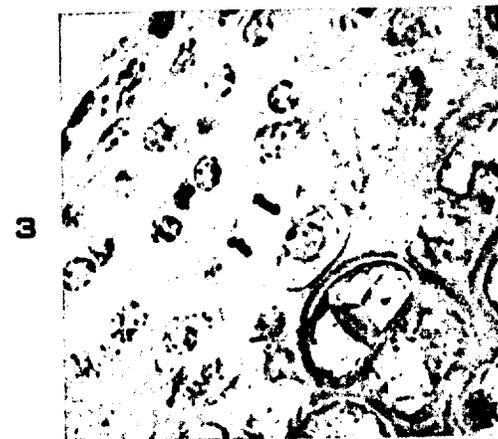
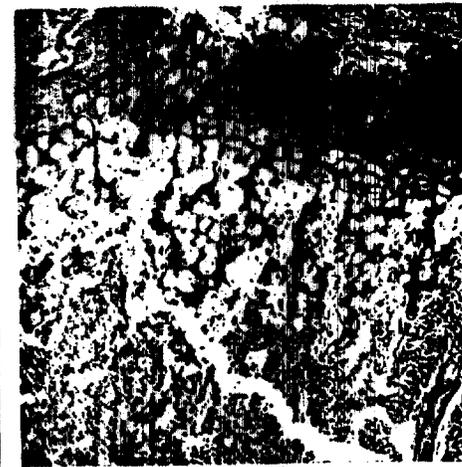
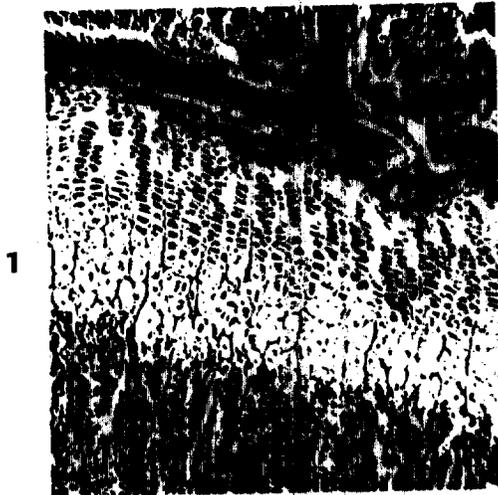
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[ Illustrations follow ]

#### DESCRIPTION OF PLATE

##### PLATE 57

- FIG. 1. Section through the growth zone at the upper tibia of an untreated mouse of strain C<sub>57</sub>, 6 weeks old. Epiphyseal disk shows regular pattern and is wide. × 120.
- FIG. 2. Section through the growth zone at the upper tibia of a mouse of strain C<sub>57</sub>, 6 weeks old, which, from the age of 4 weeks on, had received injections of 0.1 cc. of a 2.5 per cent solution of potassium iodide five times weekly. As compared with Figure 1, the epiphyseal zone is somewhat narrowed, more heavily calcified and exhibits a thick plug of amorphous cartilage. × 120.
- FIG. 3. Section through the articular cartilage of the lower femur of a mouse of strain C<sub>57</sub>, which had received four injections of 0.1 cc. of 2.5 per cent solution of potassium iodide starting at the age of 4 weeks. The articular cartilage is hyperplastic and hypertrophic and shows mitotic figures. × 500.
- FIG. 4. Section through the growth zone at the upper tibia of a mouse of strain C<sub>3</sub>H, 8 weeks old. Epiphyseal disk narrowed as compared with Fig. 1. × 120.
- FIG. 5. Section through the growth zone at the upper tibia of a mouse of strain C<sub>3</sub>H, 7 weeks old, injected for 2 weeks with 0.1 cc. of 2.5 per cent solution of potassium iodide five times weekly. As compared with Figure 4, the epiphyseal growth zone is more heavily calcified, showing formation of a plug of amorphous cartilage. × 120.
- FIG. 6. Section through the growth zone at the upper tibia of a mouse of strain C<sub>3</sub>H, 8 weeks old, injected for 4 weeks with potassium iodide. Beginning resorption of the epiphyseal plate by bone marrow. × 120.



Silberberg and Silberberg

Effects of Potassium Iodide on Skeletal Tissues

Absorption of Potassium Iodide from Gastro-Intestinal Tract.\* (26366)

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Prompt excretion of orally administered iodide by the salivary gland provides a simple measure of the rapidity of its absorption from the gastro-intestinal tract. Salivary iodide excretion is clearly altered in a variety of clinical states in man(1), but the site of its absorption is controversial(1,2,3,4,5,6). In view of its possible utility as a measure of gastrointestinal absorption, it seemed desirable to determine what organ or organ system is involved in its absorption.

*Methods.* 1. *Human:* The potassium iodide absorption test(1) was conducted as follows: Subjects were given a solution of 0.25 g of potassium iodide in water, *per os*, following a 14- to 16-hour fast. Their mouths were then rinsed. Saliva was collected every 2 minutes and tested for presence of iodine (1 ml of saliva added to 1 ml of a 1% starch solution containing 4 drops of a 10% FeCl<sub>2</sub> solution; this test is positive for as little as .0027 mg of iodine). Ten normal subjects were found to have iodine present in their saliva in from 6 to 14 minutes,

\* Supported in part by Grants from U.S.P.H.S., Am. Cancer Soc. (including Massachusetts Division) and Damon Runyon Memorial Fund.

well within the normal limits determined by Heath(1). Seven of these subjects were retested similarly, except that BaSO<sub>4</sub> was added to the potassium iodide solution in sufficient quantity to produce a moderately thick suspension, and the studies were done under fluoroscopic control. The subjects were placed on a fluoroscopy table and were rotated so that all portions of the stomach were exposed to the iodide-containing radio-opaque medium. They then were placed in a supine position, rotated slightly to the left. Saliva was collected and tested for iodine every 2 minutes, and fluoroscopic observations were made at these same intervals. One of the subjects in this group was restudied (after an interval of 3 days) with Urokon<sup>®</sup> (50%) as the opaque substance to obviate the possibility of physical interference with absorption by BaSO<sub>4</sub>. The saliva of all of the above subjects contained no iodide until some of the radio-opaque medium had been seen to pass into the duodenum (Table I).

A solution of potassium iodide was instilled, *via* a tube, directly into the duodenum of 2 of the previously tested subjects. Iodide was detected in their saliva in 2 to 4 min-

TABLE I. Potassium Iodide Absorption in Humans.

Potassium iodide	Min. between intake of KI solution (including contrast media) and		Time from duodenal to salivary appearance
	(a) Duodenal appearance of barium	(b) Salivary appearance of iodine	
	Min.		
In barium sulfate	22	24	2
	12	15	3
	22†	25	3
	*	—	—
	37†	40	3
	35†	39	4
In diodrast†	*	—	—
In barium sulfate instilled directly into duodenum	Direct instillation	3	3
	"	4	4
In barium sulfate given after 7.5 mg I.V. probanthine	110	114	4
	120	123	3
	130	133	3

\* Test discontinued after 20 min.  
† Patients studied twice.

utes. This corresponds to the results obtained when potassium iodide (.25 g in 20 ml sterile distilled H<sub>2</sub>O) was given intravenously to 4 alcoholic patients(7). Three subjects were given .25 g of potassium iodide in a BaSO<sub>4</sub> mixture, *per os*, after they received intravenous probanthine which was given to delay gastric evacuation. Saliva of these subjects was negative until there was fluoroscopic evidence of BaSO<sub>4</sub> in the duodenum.

2. *Wistar strain male rats* weighing between 147 to 181 g were used. Animals were secured to a board; their abdomens were shaved and infiltrated with 1% xylocaine hydrochloride. Group I (11 rats): A midline incision was made and a polyvinyl tube was passed perorally into the stomach. A loose ligature was placed at the cardia, to be tied at termination of experiment, and an occluding ligature was placed at the pylorus. (All major vessels were avoided.) The stomach then was evacuated *via* the tube and washed with 5 ml of distilled water. Two ml of a 25% solution of potassium iodide (in .01N HCl) was injected into the stomach.

The tube then was removed and abdominal incision closed. The animals were sacrificed after a 1-hour absorption period. The stomachs were removed and the contents quantitatively extracted with demineralized water.

Group II (12 rats): A midline incision was made and a polyvinyl tube was passed perorally and manipulated into the duodenum. A loose ligature was placed at the pylorus (excluding all major vessels) and 2 ml of a 25% solution of potassium iodide (in .01N HCl) was slowly (1-1½ min) injected into the intestine. The tube then was removed, the pyloric ligature tied to prevent flow from the stomach, and the abdominal incision was closed. Animals were sacrificed following one hour of absorption. The entire intestinal tract, excluding the stomach, was removed and the contents quantitatively extracted and analyzed for retained iodine by protein bound iodine methods(8). An average of 55 mg potassium iodide/100 g rat/hr was absorbed from the intestine (Table II). The difference is highly significant ( $P > .01$ ).

*Discussion.* The present studies support the contention of several authors that the principal site of absorption of iodide is the small intestine. Heath and Fullerton(1) studied absorption of iodide in human subjects, using the method employed in this present study, and found that iodine could be detected in saliva of normal subjects in 6 to 15 minutes after oral ingestion, while its appearance was markedly delayed in patients with scurvy, myxedema, pernicious anemia and alcoholic cirrhosis. They felt that this delay reflected *intestinal* malabsorption on the basis of the work of Cohn(2), Eisenmann(3) and others. Cohn(2) assessed absorption of iodine in isolated segments of the intestine of anesthetized dogs. He found that 63% of potassium iodide placed in the colon

TABLE II. Potassium Iodide Absorption in Rats.

No. rats	Avg wt, g	Potassium iodide inj, mg	Potassium iodide absorbed		mg/100 g /rat/hr
			mg	%	
11	164	570	85	14.9	55 ± 21
12	163	650	320	48.9	197 ± 36

and from 74 to 80% of the potassium iodide placed in the jejunum was absorbed, while no more than 31% of the iodide placed in the stomach was absorbed. The difficulty in recovering the contents of the stomach, this author suggested, might have caused a loss which would place the percent absorbed higher than the actual amount absorbed. In support of the absorptive role of the stomach are the findings of Rankin(4), Henning(5) and Bertrand(6). Rankin(4) instilled potassium iodide into the rumen of sheep and detected iodine in the saliva in 4 minutes, concluding that the stomach was a principal site of iodine absorption. Henning(5) and Bertrand(6) found that patients with chronic gastritis and gastric ulcer excreted salivary iodine more rapidly than normal subjects, assuming that potassium iodide was absorbed in the stomach.

The difficulty in determining the exact time of pyloric passage may account for the discrepancy between our results and those of Henning(5) and Bertrand(6). Henning assumed that by placing the subject in the left lateral decubitus position, negligible amounts of gastric contents would enter the duodenum, while Bertrand determined time of passage using an air-fluid contrast technic under fluoroscopic control. In the present study, the use of radio-opaque media permitted more accurate determination of the passage of small quantities of potassium iodide into the small intestine. Also, the time

elapsed between passage into the duodenum and salivary appearance of iodide agreed closely with the time required for detection of salivary iodide when potassium iodide was instilled directly into the duodenum.

*Summary.* Potassium iodide mixed with radio-opaque media was administered orally to human subjects studied under fluoroscopic control. Iodide appeared in saliva of these subjects 2-4 minutes after mixture passed into the duodenum. Iodide instilled directly into the duodenum of 2 subjects was detected in their saliva 3-4 minutes later. 14.9% of the iodide placed in the stomach and 48.9% of the iodide placed in the duodenum of rats was absorbed within one hour. It appears that the small intestine is the principal site of absorption in humans and in rats.

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Received November 26, 1960. P.S.E.B.M., 1961, v106.

THE EFFECT OF ENVIRONMENTAL TEMPERATURE AND  
POTASSIUM IODIDE SUPPLEMENTATION ON THE EX-  
CRETION OF IODINE BY NORMAL HUMAN  
SUBJECTS\*

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(Received for publication, June 25, 1945)

Iodine balance studies were carried out for the first time by von Fellenberg (1) on himself in 1926. This was possible only after his fundamental research resulted in the development of a micromethod sensitive enough to determine quantitatively the minute amounts of iodine excreted by the normal human subject. Scheffer (2, 3) studied the iodine balance in normal subjects and patients with thyroid disease. Both of these investigators recognized the importance of the skin as an avenue of excretion in attaining a true balance of iodine. Curtis and associates (4-6) also measured the dermal excretion of iodine in their extensive investigations of the effects of thyroid disease on iodine metabolism.

The dermal excretion in the above mentioned investigations has been loosely termed "sweat," although the environmental temperatures did not exceed 24° and most of the subjects were hospital patients confined to bed. Furthermore, the dermal excretion was obtained only after repeated washing of the body and underclothes, not by a collection of sensible perspiration. These results on the loss of iodine through the skin, however, suggested the importance of studying the dermal excretion of iodine under conditions which would induce profuse sweating.

EXPERIMENTAL

The data to be reported in this paper are taken from a 2 year study of the effects of high environmental temperature and variable humidity upon the dermal losses of certain minerals and vitamins and their metabolites. During eight of the experimental weeks of this study in which the subjects were on a constant adequate diet, iodine was determined in the dermal excretions collected in 8 hour periods in a controlled environment and in the urinary excretions collected in 24 hour periods. During four of these weekly periods, iodine was also determined in the daily food

\* The data presented in this paper were taken from a project covered by a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

of each subject and in the daily fecal collections. For 4 of the 8 weeks the subjects received daily 2 mg. of KI each.

Five young men, 20 to 28 years of age, were used as subjects. For 8 hours each day, Monday through Friday, the subjects were kept in an air-conditioned room maintained on alternate weeks at "comfortable" (about 28.9° dry bulb, 50 per cent relative humidity) and "hot moist" (38.3° dry bulb, 69 per cent relative humidity) conditions.

Before entering the air-conditioned chamber each subject washed his entire body thoroughly with soap and water, then rinsed with distilled water. By means of a preboiled and rinsed piece of cheese-cloth each subject removed all excess rinse water from the surface of his body. The subjects then entered the chamber with no clothing other than klaks.

While in the chamber, the subjects did no work or exercise but sat on chairs or cots which were completely covered with rubber sheeting and towels, the latter preboiled and rinsed in distilled water. Visible body sweat was absorbed on cheese-cloth, preboiled and rinsed thoroughly in distilled water, and collected in a jar containing 10 cc. of glacial acetic acid. At the end of the 8 hour period each subject washed his body first with 600 cc. of distilled water. The second, third, and fourth body washings were made with 300 cc. portions of distilled water each, and these as well as five additional 300 cc. portions of distilled water were used in succession to wash and rinse cheese-cloths, towels, klaks, chairs, and any other surface upon which skin excretion might have collected. All undiluted sweat was combined with the body washings for analysis.

Before entering the exposure chamber, and immediately on leaving it, the men were weighed without clothing to the nearest gm. on a Troemner balance. The final body weight plus the weight of all urinary and fecal excreta subtracted from the initial body weight plus the weight of all food and water ingested gives the "net loss" in body weight. The net loss in body weight under comfortable conditions averaged 92 gm. per hour, representing largely insensible vapor loss. Under hot moist conditions, the net loss in body weight averaged 676 gm. per hour, representing mainly the secretion of the sweat glands.

On three Saturday mornings a 4 hour collection of undiluted sweat was made under hot moist conditions for iodine analysis. On these days each subject stood in a large pan so as to collect all sweat running off the body, and also collected sweat continuously by running the lip of a clean beaker over all readily accessible parts of the body. The samples were preserved by the addition of glacial acetic acid.

The food and feces samples were dried, ground, and kept in tightly stoppered glass jars until analyzed. All samples were analyzed for iodine by the methods described in detail in the previous publication (7).