Factors Which Influence the Radioactive Iodine Thyroidal Uptake Test*

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THE measurement of the ability of the thyroid gland to accumulate radioactive iodine has become an established diagnostic procedure [*10,126*]. Despite the apparent simplicity of the test, the dynamics of normal iodine metabolism are complicated and the number of factors which can influence the observed results are legion. It is the purpose of this review to compile and evaluate the information concerning the substances and conditions which interfere with the use of this test as an indication of thyroid hormone production.

I^{131} has been used to diagnose thyroid disease in many different ways. The uptake in the thyroid has been measured at various intervals from one to forty-eight hours. The thyroid iodine clearance, the thyroid accumulation rate, the thyroid accumulation gradient, the I^{131} conversion ratio, the I^{131} urinary excretion, and the various thyroid scanning procedures have also been used. Some of these procedures have specific value in the study of thyroid function but the twenty-four-hour uptake has been the standard test in most medical centers and the discussion in this paper will largely be confined to this test. When clinical observations have been inadequate to permit any generalizations, pertinent animal or *in vitro* experiments with possible clinical implications are cited.

NORMAL VALUES

The normal values for the twenty-four-hour radioiodine thyroidal uptake test are generally considered to be as follows: Low, 0 to 15 per cent; normal, 15 to 45 per cent; high, 45 to 100 per cent.

An exact statistical expression of normal values is not possible because of the difference in measuring technics and because of the difference of frequency distribution and range of "normal" uptakes in different geographic areas. Cassidy and Vanderlaan [*25*], for example, compared the radioactive iodine uptake values of ninety-one normal persons in Boston, Massachusetts, and 125 euthyroid people in La Jolla, California, and found that 39.2 per cent of the subjects in La Jolla had uptake values below 20 per cent whereas in Boston only 9.9 per cent of the subjects had values below 20 per cent.

In a survey of 2,477 tests Werner [*127*] found the range of normality for the twenty-four-hour I^{131} uptake to be 15 to 45 per cent. About 16 per cent of all patients had uptake values in the region between 40 and 54 per cent. Virtually no normal persons had values in excess of 55 per cent or below 9 per cent. In 385 cases of hyperthyroidism, values were less than 45 per cent in 14 per cent, but none was less than 40 per cent. In hypothyroidism, the number of patients was small but the overlap into the normal range seemed to be of the same order of magnitude.

GENERAL PATHWAYS OF IODINE METABOLISM

The drugs and toxic substances which affect iodine metabolism usually act at discrete sites in the steps involved in the formation and release of the thyroid hormones. A detailed description of hormonogenesis is beyond the scope of this review but Figure 1, modified from the excellent review of Berson [*11*], schematically presents the prevailing concepts and provides a scheme of reference when the actions of antithyroid substances are specifically considered. Tables I through III provide summaries of factors which influence I^{131} uptake. Table IV lists factors which do not influence I^{131} uptake.

It is helpful to consider thyroid iodine metabolism in three general categories: (1) *Iodide trap-*

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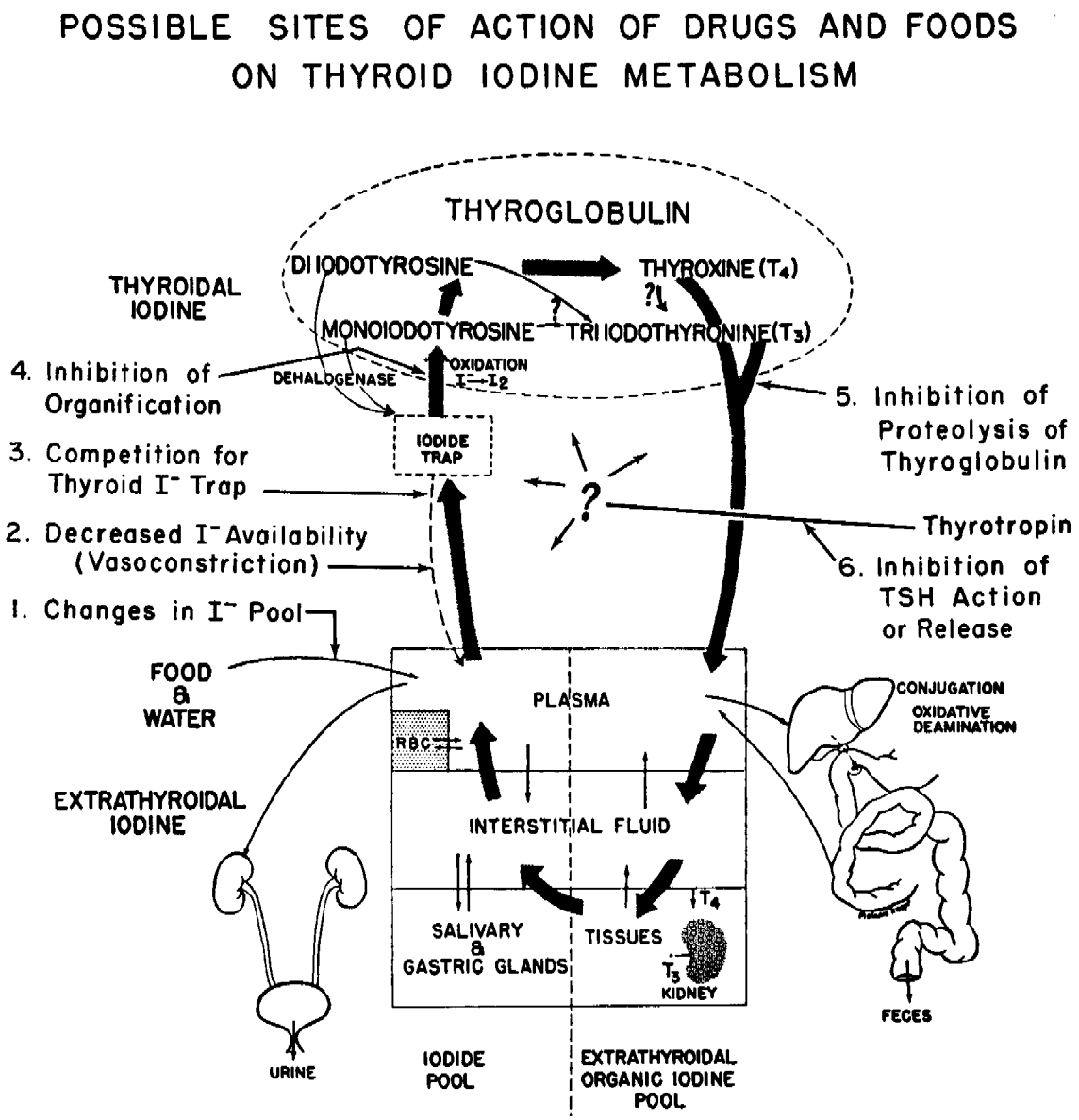


FIG. 1. The pathways of iodine metabolism are shown schematically, adapted from Berson [*11*]. Six possible sites for interference with normal thyroid metabolism are described which may cause variations in the thyroidal uptake of radioactive I^{131}. Examples of drugs which cause interference at these sites are: (1) Changes in size of iodine pool: *iodine;* (2) decrease in iodine availability: vasoconstriction induced by *epinephrine;* (3) competition for iodine trap: *potassium thiocyanate;* (4) interference with "organification": *thiouracil;* (5) changes in rate of proteolysis of thyroglobulin: *iodine;* and (6) change in rate of release or action of thyrotropin: *thyroid hormone.*

ping: Iodide is selectively concentrated within the thyroid cell to provide the substrate for subsequent steps. (2) *Hormonal synthesis:* The next series of reactions involves the activation of iodide by oxidation, with sequential iodination of tyrosine residues of thyroglobulin to form the mono- and diiodotyrosines. Conjugation of the iodotyrosines gives rise to thyroxin, 3, 5, 3′ triiodothyronine and traces of other iodothyronines. (3) *Hormonal release:* The iodinated amino acids are liberated from thyroglobulin by proteolytic enzyme(s) secreted by the thyroid cell. The iodotyrosines are selectively deiodinated within the thyroid follicular cell but thyroxin and triiodothyronine are spared and permitted to enter the blood stream.

TABLE I
FACTORS WHICH CAUSE LOW TWENTY-FOUR-HOUR I^{131} UPTAKE

- Excess iodine or iodide
  - Iodine medications (see Table V)
  - Diet
    - Foods (see Table VI)
    - Iodized salt
  - Radiographic media
- Goitrogenic foods
  - Brassica family
    - Turnips
    - Cabbage
    - Kale
    - Rape
  - Milk from cattle eating chou-moullier and certain other fodders
- Thiourylene derivatives
  - Thouracil
  - Propylthiouracil
  - Methimazole
- Aromatic antithyroid drugs
  - Resorcinol
  - Aminobenzenes
    - Para-aminosalicylic acid
    - Para-aminobenzoic acid
  - Sulfonylureas
- Cardiac decompensation
- Sedatives
  - Thiopental
  - Bromides if contaminated with iodine
- Miscellaneous drugs
  - Monovalent anions
    - Perchlorate
    - Thiocyanate
    - Others, vitamin A, phenylbutazone, salicylates
- Hormones
  - Adrenocortical steroids
    - Endogenous steroids activated by adrenocorticotrophic hormone
    - Cortisone and related compounds
    - Desoxycorticosterone
  - Thyroid
  - Progesterone
  - Testosterone

TABLE II*
POTENTIAL CAUSES OF LOW I^{131} UPTAKE

- Heavy metal administration
  - Mercury
  - Cobalt
  - Arsenic
  - Bismuth
- Goitrogenic foods
  - Peach, pear, strawberry, spinach, carrot [*46*]
  - Peanuts
- Antibiotics
  - Penicillin
  - Chlortetracycline
  - Chloramphenicol
  - Sulfonamides
- Morphine
- Epinephrine

* Substances listed in this table are considered to be unconfirmed in man.

TABLE III
CLINICAL AND EXPERIMENTAL FACTORS WHICH MAY INCREASE I^{131} UPTAKE

- Iodine deficiency
- Chronic liver disease with dietary iodine deficiency
- Rebound phenomenon following withdrawal of antithyroid drugs
- Nephrosis
- Estrogens
- Low serum chlorides
- Soy bean meal, cellulose and bulk producers

TABLE IV
FACTORS WHICH APPARENTLY DO NOT INFLUENCE THE TWENTY-FOUR-HOUR THYROIDAL I^{131} UPTAKE

- Mercurial diuresis
- Malabsorption syndrome
- Increased glomerular filtration
- Decreased glomerular filtration
- Sedatives
  - Reserpine
  - Pentobarbital
  - Tribromoethanol

The thyroid gland is under the direct regulation of the anterior pituitary by means of thyrotropin and indirectly subject to hypothalamic control by mechanisms which remain largely undefined.

THE EFFECTS OF EXOGENOUS IODINE AND IODIDES

Normal Requirements. Before consideration of the important subject of exogenous iodine and iodides as a cause of decreased I^{131} thyroidal uptake, it is necessary to define the daily requirements and the average intakes of iodine prevalent in this country.

The recommended iodine intake for adults needed to satisfy physiologic requirements is 2 to 4 μg. grams per kg. of body weight per day [*3*]. No special requirements dependent on sex, physical activity, pregnancy or lactation are recognized. The mean daily normal thyroidal accumulation of iodine is about 75 μg. and the average daily urinary iodide excretion is about 150 μg. [*11*]. It is probable that an intake of 200 μg. in an adult weighing 70 kg. is optimal [*52*].

Actual Normal Daily Intake of Iodine. Iodized salt in the United States contains 0.01 per cent potassium iodide. If an adult takes 6.2 gm. of salt daily, calculated as the usual American salt intake, he therefore ingests 620 μg. of

potassium iodide, equivalent to 474 μg. of iodine. According to Beierwaltes [*10*], the average person living in Michigan and using iodized salt ingests a total of 600 to 800 μg. of iodine a day. Ralls [*83*] estimated the dietary intake of iodine of eight normal persons on an ordinary diet, living in the New York area, to be about 126 μg. a day.

What is Iodine Excess? Intake of iodine in excess of the values quoted will eventually lower the thyroidal I^{131} uptake of a person. The amount of iodine necessary to depress radioactive iodine uptake has been determined in the case of hyperthyroidism [*42*]. One milligram of iodide daily for four days appeared to be the minimal effective dose that will inhibit the thyroid accumulation rate. This value, of course, might not be applicable to euthyroid people.

In acute experiments in which stable iodide was added as a carrier to I^{131} and administered to iodine-deficient people, the proportion of the radioactive dose that was accumulated by the thyroid was independent of total iodine below 1.5 mg., but when larger amounts were given progressively smaller fractions of the radioactive dose were accumulated [*114*].

THE MECHANISMS WHEREBY EXOGENOUS IODINE REDUCES THE THYROIDAL UPTAKE

Iodide Dilution. Iodide added to the total body iodide pool causes a decrease in the thyroidal I^{131} uptake by lowering the specific activity of body iodide. The uptake of the radioiodine by the thyroid gland does not indicate the gravimetric amount of iodine trapped, but simply represents the percentage of the total stable iodide pool trapped in the same period of time [*5,107*]. Thus an enlarged iodide pool due to added iodide results in a lower uptake, and a contracted pool due to iodine deficiency causes an increased uptake of I^{131} [*40*].

Inhibition of Thyroxin Output. In addition to the dilutional effect of iodide upon the radioactive test, iodide inhibits thyroid hormone synthesis and release under certain circumstances. This effect of iodide, of course, has been used therapeutically for a long time in the treatment of hyperthyroidism. Means [*73*] found that the smallest daily dose of iodine which, with any certainty, will produce a maximum inhibition of the basal metabolic rate in thyrotoxic people is 6 mg.

Some of the theories concerning the antithyroid action of iodide follow:

(1) By interfering with the iodination mechanism of tyrosine necessary to form the precursors of tri-iodothyronine and thyroxine [*79,99,115,121*]. Two suggested mechanisms for this are: (a) Decrease in the effective concentration of hypoiodous acid, a postulated active form of iodide [*98*] and (b) trapping of available elemental iodine, I_2, in the inactive form of I_8 [*36,98*].

(2) By chemical action on the thyrotropic hormone at some point after its release from the pituitary gland [*42*]. Some support for this view is found in the *in vitro* inactivation of thyrotropin by iodine [*2*]. It is possible, however, that thyrotropic hormone is not involved in thyrotoxicosis [*35,128*].

(3) Inactivation of proteolytic thyroid enzyme(s) which releases thyroxine from thyroglobulin [*31*].

Occasionally in a patient treated for prolonged periods of time with iodides, in bronchial asthma for example, myxedema and goiter will develop [*79,119,120*]. Radioiodine studies in such cases suggest that the hypothyroidism is due to failure of thyroid hormone synthesis. Inasmuch as in large numbers of asthmatic patients so treated thyroid abnormalities do not develop, it is possible that iodide goiter of this variety occurs only in predisposed subjects on the basis of an idiosyncrasy. In support of this concept is the report of Greer [*49*] that he was unable to detect any effect on the endogenous secretion rate of thyroid hormone by iodide in five euthyroid subjects.

For further details concerning the actions of iodide, the reader is referred to the excellent review by Vanderlaan and Storrie [*122*].

SOURCES OF EXCESS IODINE INTAKE

Exogenous iodine may come from drugs, iodized salt, foodstuffs and x-ray contrast media. Evaluation of all these sources of iodine should be routine in the interpretation of I^{131} thyroid uptake test results. Lugol's solution, for example, contains about 5 to 8 mg. of iodine per drop. Potassium iodide and other iodides are present in many commonly used medications [*80*]. (Table v.) Administration of these preparations, therefore, will produce lower thyroidal uptakes of radioactive iodine (RAI).

Vitamin Tablets and Iodized Salt. Kohn and Nichols [*62*] reported interference with the uptake of RAI during the administration of vitamin-mineral mixtures. Eight euthyroid persons were given Gevral,® which contains 0.5 mg.

TABLE V

IODINE IN DRUGS: A REPRESENTATIVE LIST

Preparation	Usual Dose of Drug	Amount of Available Iodine Daily (μg.)	Hypothetical Absorbed Daily Dose of Drug
	Vitamin-Mineral		
Mi-cebrin® tablets	1 tablet daily	150	.....
Unicap® Therapeutic	1 tablet daily	150	.....
Gevral® capsules	1 capsule daily	500	.....
Gevrabon® liquid	1 ounce daily	100	.....
	Expectorants		
Calcidin	1 to 3 gr. every ½ to 3 hours (15 per cent iodine)	24,000	1.6 gm.
Dainite-KI® tablets	4 tablets daily (320 mg. potassium iodide per tablet)	98,000	1,280 mg. of potassium iodide (77 per cent iodine)
	Topical Agents		
Vioform® ointment, (iodochlorhydroxyquin) cream, suppositories (3 per cent Vioform)	.....	2,460	2 gm. of 3 per cent cream (100 per cent Vioform contains 41 per cent iodine)
Iodex® ointment, (4.7 per cent iodine)	Applied liberally to wounds	9,400	2 gm.
Floraquin® vaginal tablets (100 mg. diiodoquin per tablet; 7.5 per cent per ounce of powder)	2 tablets or 4 to 8 gm. of powder 3 to 7 times per week	38,400	8 gm. of powder
	Miscellaneous Drugs		
Pathilon® (3-diethylamino-1-cyclohexyl-1-phenyl-1-propanol-ethyl-iodide)	25 to 50 mg. 3 to 4 times daily	.....	.....
Diodoquin® (5,7-diiodo-8-hydroxyquinoline)	1 tablet (650 mg.) 3 times daily	128,000	2 gm. (64 per cent iodine)

of potassium iodide per capsule. In only three of these subjects was there a significant difference in the RAI uptake after daily administration, as compared with control values. In the first case the value was 37 per cent before medication and 13 per cent after medication. In the second case, the value was 35 per cent before medication and 24 per cent after medication. In the third case the value was 62 per cent before and 16 per cent after taking one capsule of Gevral daily for one week.

The evidence suggests, therefore, that the amount of iodide present in some vitamin-mineral tablets, administered once daily, is sufficient to lower significantly the I^{131} thyroidal uptake at twenty-four hours if the person is iodine-deficient.

If one compares these result with the RAI uptakes found in the patients described by Kelsey et al. [*61*] before and after the use of iodized salt in cooking, it will be observed that the results are similar. Fifty-four inmates of a mental institution, who had been receiving non-iodized table salt in their diet for a prolonged period of time, were studied. Before the use of iodized salt nineteen of these fifty-four patients had an RAI uptake of over 40 per cent. Of these nineteen patients, eighteen had normal protein-bound iodine values and normal radioactive protein-

TABLE VI
IODINE CONTENT OF FRESH, UNCOOKED FOODSTUFFS
[3,17,47]

Food	Iodine Content (μg./kg. of edible portion of food)	Weight of Average Serving (gm.)	Iodine Content of Average Serving (μg.)
Banana	200	150	30
Cauliflower	1,200	60	72
Spinach	201	100	20.1
Sweet cherry	3,300	100	330
Sardines	284	50	14.2
Halibut	520	100	52
Herring	520	100	52
Cod	1,463	100	146.3
Cod liver oil	8,387	5	41.9
Haddock	3,180	100	318
Oysters	577	100	57.7
Lobster	1,020	100	102
Shrimp	1,300	100	130

bound iodine values in the blood. Twelve of these patients were tested again after iodized salt had been introduced into the cooking at this institution. The median RAI uptake before the use of iodized salt was 49 per cent and the median uptake after the use of iodized salt was 23 per cent. The conclusion reached by these authors was that the initial high values were due to iodine deficiency. The subsequent values, therefore, probably represented 'normal" RAI uptakes.

Iodine in Foodstuffs. An excessive seafood diet has been said to provide enough dietary iodine to lower the thyroidal I^{131} uptake. There apparently have been no studies specifically performed to investigate this question. However, a brief review of the iodine content of certain foods particularly rich in iodine will serve as a reminder that the patient can obtain rather large amounts of this element from this diet. Foods which do not come from the sea, of course, may vary in their iodine content, depending on the iodine concentration of the soil in which they were produced. (Table VI.)

Iodides in X-Ray Contrast Media. Most of the contrast media which are used to demonstrate organs and other spaces radiographically contain large amounts of iodine. In some of these media, iodine is released from its organic binding as iodide, and swells the total body pool; this excess iodide decreases the radioactive iodine uptake by the thyroid.

Even barium sulfate used in gastrointestinal radiography has been incriminated (without documentation) as an inhibitor of the uptake test because of iodide present as an impurity [*10*]. Barium sulfate (U.S.P., for radiologic diagnosis) contains less than five parts of total iodide and iodine per million by weight [*70*]. About 200 gm. of barium sulfate powder used in the routine radiologic examination of the upper gastrointestinal tract would therefore provide less than 1 mg. of iodine per examination. Even if all the iodine were absorbed, this amount of barium sulfate in a single dose probably would not significantly affect the I^{131} thyroidal uptake.

The iodinated compounds used in cholecystography contain large concentrations of iodine (50 to 65 per cent), and despite the fact that these substances are usually excreted shortly after administration, there is a variable moiety which remains in the body for prolonged periods and is deiodinated before excretion, releasing iodide into the iodide pool.

Slingerland [*104*] found that the period of depressed thyroidal uptake of radioactive iodine following the administration of iodoalphionic acid (Priodax®) in the euthyroid subject was usually less than four weeks, and in the hyperthyroid patient, one week or less. There is, however, a wide variation in the response of subjects to the effect of Priodax. Newman and Cupp [*77*] have made similar observations in eleven euthyroid patients; the twenty-four-hour thyroidal uptake was reduced to less than 10 per cent in all of them during the first week after the administration of Priodax. In ten patients the uptake had become normal within thirty days; the other patient required forty-two days to return to normal.

Inhibition by iodinated compounds used for visualization of the gallbladder differs in duration, depending on the type of compound used. The I^{131} uptake in seventy-four subjects before and after the administration of iopanoic acid (Telepaque®) was markedly reduced for the first few days and was restored to within 30 to 40 per cent of control values at the end of one week [*27*]. The subsequent rate of recovery approximated 1 per cent per day. Restoration of the average was about 60 per cent complete at thirty days and about 90 per cent at sixty days. Iodipamide (Cholografin®) administered intravenously to seven euthyroid subjects de-

creased the uptake of I^{131} for an average of about three months [*94*].

The iodinated compounds used in intravenous pyelography may interfere with the RAI uptake for as long as one month [*10*]. The effects of substances such as iodized poppy seed oil (lipiodol) used in myelography and bronchography on the I^{131} uptake test have not been adequately studied, although it is known that in some cases the uptake may be useless as a diagnostic tool for thyroid function for as long as one or more years [*102*]. In one case [*16*] the uptake was still zero one year after a bronchogram had been performed with lipiodol.

Studies [*138*] suggest that the prolonged effects of lipiodol on parameters of thyroid function are not limited to the use of the substance in bronchography and myelography, but include oral administration as well. The material is absorbed and stored in an unknown site. There is a continual release of iodine in quantities sufficient to lower the thyroidal I^{131} uptake and elevate the concentration of serum protein-bound iodine.

The thyroidal I^{131} uptake was depressed for 445 days (the duration of the study) in four subjects who received 10 to 20 cc. lipiodol orally.

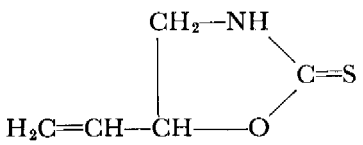
IODINE DEFICIENCY

Iodine deficiency increases the uptake of I^{131} by the thyroid to the range observed in hyperthyroidism. One hundred and three patients with goiter in the endemic goiter area of Mendoza, Argentina, were found by Stanbury and co-workers [*114*] to have a mean twenty-four-hour thyroidal uptake of 58.6 per cent. Well over half of the subjects tested had uptakes greater than 57.7 per cent. A similar group of patients living in the endemic goiter area of Bailadores in the Venezuelan Andes, where the diet is iodine-deficient, was studied by Roche and his group [*92*]. There were eighty-six adults with goiter who had an average forty-eight-hour thyroidal radioiodine uptake of 76 per cent of the dose administered; the uptake was 68 per cent in twenty four non-goitrous adults, and 79 per cent in twenty-eight children. The forty-eight-hour uptake values in seventy euthyroid adults in Caracas, the capital of Venezuela, by comparison, averaged 37 per cent and gave a frequency distribution curve similar to that found in Boston, Massachusetts.

In ten of twenty patients on the Kempner rice regimen, which is low in salt and undoubtedly also in iodine, uptakes increased to 46 per cent or more after three months on the diet [*13*].

GOITROGENIC FOODS

Certain foods eaten by man and animals are known to be goitrogenic because of chemical constituents which interfere with iodine metabolism. The precise mechanism of interference is as yet ill-defined, but appears to be at the level of "organification." Progoitrin is a thioglycoside present in many plants of the Brassica family, including cabbage, turnip, rutabaga, rape, kale and chou-moullier [*6,28,46, 130*]. The probable structure of goitrin isolated from yellow turnip and white turnip root and seed, and from the seed of cabbage, kale and rape, was determined by Astwood, Greer and Ettlinger in 1949 to be L-5-vinyl-2-thio-oxazolidone [*6*]:



This material is liberated from its glycoside complex by a thioglycosidase contained in the plant or seed itself. Cooking destroys this enzyme [*46*]. The consumption of raw vegetables of this class or of vegetables allowed to stand after mashing or freezing before cooking should be looked upon with suspicion in this regard. This chemical is equal in antithyroid potency to thiouracil [*45*]. The plants mentioned contain as much as 400 mg. of vinyl-thioxazolidone per kilogram of wet vegetable.

Recent studies [*137*] by Greer and Deeney indicate that, contrary to expectations, hydrolysis of progoitrin to goitrin occurs within the body in the absence of the exogenous thioglycosidase (myrosin). Progoitrin administered in a single daily dose of 1 gm. was found to be an effective agent in the treatment of thyrotoxicosis in one patient.

Chou-moullier, a forage plant for cattle, appears to be responsible for a significant amount of endemic goiter in Tasmania and Australia by providing a goitrogen which is transmitted in the milk. Clements and Wishart [*28*] injected extracts of chou-moullier into rats and noted a reduction of I^{131} uptake by 94 per cent. Goitrogens from other fodders may also be transmitted in milk.

Cabbage causes goiter in rabbits [*26*], but has not been demonstrated to be goitrogenic in man [*44*]. There are only two reports of goiter in human beings due to the ingestion of foods (other than the milk goiters in Australia and Tasmania): in one patient described by Fisher, Epstein and Pashkis [*39*] in 1952 a goiter (stroma cibaria) developed due to the excessive ingestion of rutabaga, turnips and cabbage. The twenty-four-hour radioactive iodine thyroidal uptake in this case was 8 per cent; seven months later, after removal of the foods in question from the diet, it was 19 per cent. Goiters are said to have developed in a group of Belgian monks in World War I who were forced to eat large amounts of rape seed and cabbage [*73*].

Arachidoside. A newly recognized glycoside, arachidoside, in the red skins of peanuts (groundnuts) causes goiters in rats [*112,113*]. The goitrogenic action of this substance is prevented by the administration of potassium iodide. There is no evidence that thiooxazolidones or cyanogenetic glycosides are present in the peanut. The twenty-four-hour I^{131} excretion in rats fed diets containing groundnut substances was increased, indicating a diminished thyroidal uptake. There are no reported studies on man.

Soy Beans. A new mechanism of goitrogenesis was suggested by Middlesworth [*74*] in a study of the action of soy meal in rats. He noted that soy meal is the only goitrogenic agent known, other than thyrotropic hormone, that produces a high twenty-four-hour radioiodine uptake. The fecal excretion of I^{131} after labeled thyroxine was given intraperitoneally was doubled in rats fed soy flour. Inasmuch as the total fecal mass was also twice that of control animals, the effects of adding cellulose and bran to the control diets were also studied. These substances also increased both fecal mass and labeled iodine excretion. Increased fecal excretion of labeled thyroxine in soya-fed animals has been confirmed [*9*]. It was shown that the increased excretion of labeled iodine was not dependent on increased biliary excretion.

The goitrogenicity of soy flour can be attributed to excessive fecal loss of organic iodine, which increases the requirement for thyroxine synthesis and increases iodine deficiency. It is unlikely that a similar mechanism can induce goiter in man because the relative amount of thyroxine entering the gut is much smaller in man than in the rat [*51,129*]. Studies of this problem in man will be of great interest.

Cyanogenetic Glycosides. The goitrogenic effect of cyanides released from cyanogenetic glycosides in the Brassica and in certain other plants has been suspected but never established [*8*]. Some cyanides probably can act directly on the thyroid gland [*96,105*]. Also, it is known that small amounts of cyanide are transformed by enzymatic action in the liver to thiocyanate [*109,110*]. The goitrogenic effect of potassium thiocyanate is well known [*84,86*]. Plant cyanides [*22,50*] have not yet been implicated in human disease, but cyanide fumes have been blamed for hypothyroidism and goiter following occupational exposure [*54*].

AROMATIC ANTITHYROID DRUGS

Many aromatic compounds with an electron-donating group on the ring can inhibit synthesis of thyroid hormone [*36*]. These chemicals include the sulfonamides, the aminobenzenes and resorcinol. Both a free aromatic amine and a free aromatic hydroxyl group are present in the aminobenzenes and have been related to the antithyroid action of these drugs [*116,117*]. These substances may act by binding active iodine formed in the thyroid gland.

Sulfonamides. Most of the sulfonamide drugs are weak goitrogens in animals [*117*]. Neither goitrogenicity nor inhibition of thyroidal I^{131} uptake in man has been demonstrated. Sulfanilamide [*122*] in thyroid tissue slices suppresses the formation of thyroxin and diiodotyrosine almost completely, but the iodide-concentrating capacity remains unaltered. In an experiment in which 2 per cent sulfaguanidine was added to the diet of rats the average weight of the thyroid increased 150 per cent in two weeks [*69*].

Sulfonylureas. Both tolbutamide (Orinase®) and carbutamide possess antithyroid activity in the dose range used in the treatment of diabetes [*19*]. Carbutamide was found to be thirteen times as potent an antithyroid agent in the rat as sulfaguanidine and 1/200th as potent as propylthiouracil. The goiters produced by carbutamide were inhibited by excess iodide [*20*]. Six of nine patients in an acute study [*19*] had a decrease in the twenty-four-hour I^{131} uptake of more than 20 per cent of the control values with carbutamide, and four of the same nine patients when later tested with tolbutamide had a similar 20 per cent decrease. Although carbutamide suppressed the I^{131} uptake little or not at all in some cases, there was a rise in the uptake far above the initial level when the drug was discontinued. It ap-

peared that, in general, carbutamide is twice as potent an antithyroid agent as tolbutamide.

Para-aminosalicylic Acid (PAS). Balint, Fraser and Hanno [7] in 1954 reviewed nine cases of hypothyroidism associated with goiter in tuberculous patients undergoing therapy with PAS. Sutherland [*116*] studied five patients who were receiving 12 gm. of PAS daily and found that the mean I^{131} uptake at twenty-four-hours was reduced from 20 per cent before therapy to 14 per cent after one week of PAS therapy. In three patients receiving PAS for twenty-one to thirty days the mean radioiodine uptake was reduced from 31 per cent to 15 per cent. After the medication was stopped there was an increase in the uptake for three to ten days. Administering 10.5 gm. of PAS intravenously caused complete cessation of I^{131} uptake for a period up to fifteen hours [*53*].

Para-aminobenzoic Acid (PABA). Rats fed 2 per cent PABA in their diet had a 60 per cent increase in thyroid weights as compared to control rats. However, when a similar group of rats was also fed 1 mg. of sodium iodide per 100 gm. of diet, the goitrogenic effect of the PABA was completely nullified [*69*].

Resorcinol. Three cases of myxedema with goiter have been reported in patients treated with resorcinol ointments for leg ulcers [*27*]. In each the urinary excretion of radioiodine was below 10 per cent in forty-eight hours. These excretion rates, however, were all performed more than three days after the use of resorcinol ointment had been discontinued and probably represent the hyperavidity of the thyroid gland which has just been released from inhibitory effects of an antithyroid drug.

Doniach and Frazer [*32*] injected resorcinol into rats prior to administration of radioactive iodine tracer and found the thyroid iodine uptake 10 to 20 per cent of that found in control rats; this was comparable to the maximal reduction in uptake caused by thiouracil under similar experimental conditions. When the resorcinol was administered orally instead of parenterally there was a smaller but still definite antithyroid effect. Rosenberg [*91*] also confirmed the decrease in I^{131} thyroidal uptake in rats given resorcinol.

SEDATIVES

Many sedatives ameliorate to some extent the symptoms of thyrotoxicosis; therefore, it is important to determine whether or not they influence iodine metabolism in such a way as to affect I^{131} uptake. Wase, Repplinger and Foster [*125*] studied I^{131} uptake in rats and found that the administration of thiopental reduced thyroidal uptake of iodine in rats by 82 to 89 per cent. They found no effect with pentobarbital (Nembutal®), vinbarbital (Delvinal®) or tribromoethanol (Avertin®) therapy. The administration of reserpine also has been shown to be without significant effects on I^{131} uptake in thyrotoxicosis [*24*].

Findings in a series of thirty-one euthyroid and twelve hyperthyroid patients [*139*] indicate that the administration of promazine, meprobamate, hydroxyzine, or reserpine in the usual therapeutic doses for a period of ten to twenty-one days does not alter the thyroidal I^{131} uptake or the serum levels of cholesterol and protein-bound iodine in euthyroid or hyperthyroid patients.

Meprobamate. Yohalem [*135*] in a study of the effect of meprobamate (Equanil,® Miltown®) in ten patients with hyperthyroidism found that, despite the symptomatic improvement provided by 400 mg. of the drug taken four times a day, the radioiodine uptake test was not altered. A different conclusion regarding the effect of meprobamate on I^{131} uptake was reached by Friedell [*38*] who did a double blind study on twelve euthyroid people, using a placebo in one group, meprobamate 400 mg. three times a day in the second, and meprobamate plus 0.5 mg. of benactyzine hydrochloride (2-diethyl-aminoethyl-benzilate (Suavitil®)) three times daily in the third series. The average initial twenty-four-hour uptake was 49 per cent. After the placebo therapy, it was 44 per cent; after meprobamate therapy for three weeks, it was 33 per cent; and after the combination of meprobamate and benactyzine therapy, the average uptake was 28 per cent (in seven patients). The range of values initially was from 35 to 62 per cent and in the last group mentioned, the range was from 9 to 38 per cent.

Morphine. Data concerning the effects of the administration of morphine in man are not available. Chronic administration of morphine reduced the thyroidal iodine uptake in rats (two weeks of a daily dose of 2 mg.) approximately 50 per cent [*95*]. The thyroid weights were the same as in the control groups. Histological findings and simultaneous protein-bound I^{131} suggest that morphine interfered with the release of thyroid-stimulating hormone of the

anterior pituitary in some manner. The effects of morphine on iodine metabolism need to be determined in the presence and absence of addiction in man.

Bromides. Bromides are included in the list of inhibitors of RAI uptake not because bromide itself is an inhibitor but because some preparations of bromides may be contaminated with iodine. The bromide ion itself does not interfere with the enzyme systems for iodinating tyrosine [*134*].

Williams and co-workers [*132,133*] administered sodium bromide to rats and found that the thyroid uptake of I^{131} was not affected but an increased rate of excretion of the isotope in the urine occurred. Sodium bromide, 3 gm. daily, given to five patients for four weeks with substandard doses of thiouracil did not cause discernible potentiation of the antithyroid effect of the latter. Sixteen patients tested with radioiodine were given no carrier iodide, but received 2 gm. of sodium bromide. No difference was observed in the response of these patients and the ones given no carrier. No thyroidal I^{131} uptakes were determined however.

Therefore, it seems clear that the bromide ion by itself does not interfere with the collection of iodine by the thyroid.

MISCELLANEOUS DRUGS

A large group of unrelated chemicals which affect I^{131} metabolism have been studied. Some of these have been investigated only in the laboratory, however, and it may be that the effects in man differ.

Heavy metals, including arsenic, copper, lead, mercury, silver and zinc, have been found to interfere with iodine uptake *in vitro* by thyroid slices [*105*]. Inhibition of thyroid function *in vivo* has not been similarly produced but the possible effects should be investigated.

The monovalent anions investigated by Wyngaarden and his group [*134*] were shown *in vitro* to inhibit the iodide concentrating mechanism (iodide trap) of the thyroid gland. These substances included perchlorate, chlorate, iodate, bi-iodate, hypochlorite, periodate and nitrate. The action of these compounds was similar to that of thiocyanate.

It is of interest to note that *perchlorate* was ten times as potent and nitrate 1/30th as potent as thiocyanate in causing release of iodide previously collected by the thyroid. The mechanism of action is that of competition with iodide ion for the thyroid iodide concentration mechanism, just as it is for thiocyanate. Potassium perchlorate has been used successfully in the therapy of hyperthyroidism in both adults and children [*75,106*]. Godley and Stanbury [*41*] in 1954 found that the administration of 600 mg. daily of potassium perchlorate to thirteen hyperthyroid patients lowered the twenty-four-hour RAI thyroidal uptake markedly within two weeks after medication was begun. The mean control uptake was 77.5 per cent, with a range from 60.7 to 108 per cent. The mean uptake during perchlorate therapy was 15.9 per cent, with a range from 3.4 to 38.8 per cent. Only three uptakes were above 20 per cent.

Thiocyanate, a monovalent anion, was of more clinical importance in the past when it was used widely as an antihypertensive agent. In nine of fifteen cases of myxedema resulting from the use of thiocyanate [*15*] it was found that the twenty-four-hour I^{131} uptake was less than 10 per cent during the period of high thiocyanate blood levels. Withdrawal of the potassium thiocyanate medication from these patients resulted in a prompt subsidence of myxedema, disappearance of goiter when present, and a marked although temporary increase in the twenty-four-hour thyroidal I^{131} uptake. In seven cases the uptake rose to above 45 per cent of the ingested dose of radioiodine.

Cobalt has been implicated in the production of hypothyroidism with goiter [*63,89*]. Little [*67*], for example, reported five cases of goiter in children receiving a cobalt and iron preparation for anemia. In only one was the I^{131} uptake studied. The twenty-four-hour thyroidal uptake was 44 per cent five days after withdrawal of the drug and 17 per cent six months later. The value recorded initially perhaps represented a rebound phenomenon.

Roche and Layrisse [*93*] measured the twenty-four-hour thyroidal uptake of I^{131} in twelve adult euthyroid subjects receiving cobalt. Within a week after starting administration of cobaltous chloride in a uniform dosage of 50 mg. given orally three times daily the thyroid uptake in most cases was greatly reduced and by the second week was near zero; the values rose toward normal after cobalt was discontinued. These authors subsequently treated two patients with hyperthyroidism with cobaltous chloride successfully prior to thyroidectomy.

There is some dispute about the effects of cobalt, however. Jaimet and Thode [*58*] found

no significant change in thyroid function (thyroid I^{131} uptake, conversion ratio and salivary radioactivity) in fifteen children treated with cobaltous chloride in a dosage up to 6 mg. per kg. per day in the form of a cobalt-iron preparation for ten weeks; two other children showed a lowered thyroidal uptake after one course of cobalt but no effect following a second course. Scott and Reilly [*97*] found no difference in the thyroidal uptake of rats treated with cobaltous chloride in a dosage of 60 mg. per day, as compared to control rats.

Eight patients were treated for hyperthyroidism with cobaltous chloride and improvement in both clinical and laboratory parameters occurred in five [*82*]. The twenty-four-hour I^{131} uptake was lowered by a daily dose of 300 mg. of the drug from hyperthyroid levels to values ranging from 17 per cent of the administered dose down to zero in four subjects. This is convincing evidence that cobalt interferes with uptake and "organification" of iodine.

Phenylbutazone (Butazolidin®) was shown to cause marked depression of the radioactive iodine uptake by Linsk et al. in a study of thirteen patients [*66*]. The twenty-four-hour uptake was measured before and after four days of therapy (800 mg. per day). Uptake varied between 20 and 54 per cent before administration of phenylbutazone and between 5 and 13 per cent after administration of the drug.

Thiourylene Drugs. It is common knowledge that drugs such as thiouracil, propylthiouracil and methimazole depress the twenty-four-hour I^{131} uptake test values. What is less commonly known is the fact that after withdrawal of these drugs there is a period of high RAI uptake, which persists for approximately five days beginning with the second day of withdrawal. For a day or two after the rebound there may be a second low uptake phase before the normal level is regained [*10*]. It would seem wise, then, not to attempt the radioiodine test for a period of at least one week following withdrawal of antithyroid drugs of this class.

Vitamin A. For an as yet unexplained reason, vitamin A depresses the I^{131} uptake. Logan [*68*] tested the effect of the oral administration of 50,000 I. U. of vitamin A acetate daily for twenty-one to seventy-seven days in seven people. The twenty-four-hour uptake before treatment ranged from 21 to 68 per cent and the values after treatment ranged from 14 to 32 per cent. *In vitro*, however, vitamin A at 1×10^{-3} M concentration had no effect on the I^{131} uptake [*105*].

Salicylates. Brief and protracted administration of sodium salicylate in doses up to 9 gm. daily in human subjects produced decreased thyroid function as measured by serum protein-bound iodine levels and radioactive iodine thyroid uptake. The mean reduction in the twenty-four-hour uptake of I^{131} was 43 per cent of the control value in patients who had received 6 to 8.1 gm. of salicylate for eight to fifteen weeks [*4*].

HORMONES

The interrelated functions of the endocrine system are well exemplified by the effects that other hormones have upon the uptake of iodine by the thyroid gland. Hormones that have been studied in this regard include adrenocorticotropic hormone (ACTH), cortisone, epinephrine, desiccated thyroid, thyroxine, triiodothyronine, estrogen, progesterone, desoxycorticosterone, testosterone, and the obvious one, thyrotropin (TSH) [*14*].

ACTH and cortisone decrease the radioiodine thyroidal uptake. Eighteen of twenty-four patients observed by Berson and Yalow [*12*] had an 8 to 34 per cent decrease in the twenty-four-hour I^{131} uptake between the fifth and eleventh days of therapy with doses of 100 to 300 mg. of cortisone daily. Berson [*11*] concluded that, even though the renal clearance of I^{131} was frequently increased during cortisone therapy, the decreased thyroidal uptake was not to be explained on this basis since thyroidal clearances were markedly depressed, frequently to hypothyroid levels.

Although the major effect of corticosteroids might be to suppress TSH formation, Epstein and his group [*34*] provide evidence of a direct action of corticosterone on the thyroid. They administered ACTH and cortisone to groups of hypophysectomized rats and found that there was significant inhibition of the thyroidal I^{131} uptake which had been induced previously by exogenous thyrotropin.

Epinephrine. Epinephrine increased the four hour I^{131} thyroidal uptake in five euthyroid subjects tested by Reiss, Forsham and Thorn [*88*]. This finding has not been confirmed or explained. Patients with Addison's disease studied the same way showed no change in radioiodine uptake. However, the injection of epinephrine into the intact rat results in a

decrease of the thyroidal uptake of I^{131} of from 45 to 67 per cent as compared with control animals [*107*]. This was in sharp contrast to the results obtained in similarly treated adrenalectomized rats in which there was an increase in the I^{131} uptake of 27 to 56 per cent over that of the control animals.

The work of Brown-Grant and Gibson [*18*] on the effect of exogenous and endogenous epinephrine on the radioiodine uptake in the rabbit may have important clinical implications, particularly in regard to non-specific stress in man. These workers administered epinephrine intravenously to rabbits, both conscious and anesthetized, at a slow rate so that there was no demonstrable rise in the blood pressure. With 2 to 4 μg. of epinephrine per minute, there was intense vasoconstriction of the thyroid blood vessels which apparently caused complete inhibition of the I^{131} thyroidal uptake (measured up to four hours after the intravenous administration of the tracer iodine). The action of Adrenalin® was proved to be unrelated to thyrotropin in these animals; in nine experiments TSH was injected after the administration of Adrenalin was begun and in no instance was any increase in the rate of uptake observed. Other authors have commented on the inhibitory effect of "stress" in animals, including the "emotional" stress of restraint [*124,131*]. This interesting finding should be considered in evaluating not only the design of radioactive iodine tests, but also the test results in man.

In contrast to the effect of epinephrine on I^{131} uptake by the thyroid gland is the related finding by Ackerman [*1*] that the thyroid vein blood in dogs contained increases in protein-bound radioiodine levels of from 1.5 to 17.1 times control values within ninety-five minutes after the intravenous administration of epinephrine or norepinephrine.

The Effects of Thyroid Hormone. During the administration of desiccated thyroid, thyroxin and triiodothyronine, the radioiodine uptake of normal subjects is suppressed [*30*] because of inhibition of the release of thyroid-stimulating hormone by the anterior pituitary. This inhibition is not evident in most patients with Graves' disease [*10*]. The return of normal iodine metabolism following discontinuance of these medications has been investigated by Greer [*48*] in forty-seven normal human subjects. Depression of the RAI uptake to below 10 per cent was noted in ten of eleven subjects after they had received 3 gr. of desiccated thyroid daily for eight days. In one-third of twenty-five subjects depression of the RAI uptake to below 10 per cent was noted after the administration of only 1 gr. of desiccated thyroid daily. After cessation of therapy, complete recovery of the RAI uptake occurred within two weeks in most subjects. Four subjects still showed marked depression at three weeks, two at the end of six weeks and one at eleven weeks following cessation of therapy. There was no significant difference between the rate of recovery of glands depressed only a few days and that of those depressed for several years.

Progesterone. The administration of 25 mg. of progesterone daily for three days to three adult women was found by Zingg and Perry [*136*] to inhibit the radioiodine uptake by the thyroid gland. Prior to administration of the drug the thyroid uptake of I^{131} was from 1.5 to 2.2 per cent per hour, whereas following the course of progesterone the uptake was depressed to 0.6 to 1.2 per cent per hour.

Zingg and Perry [*136*] also studied the effect of *desoxycorticosterone* acetate on the thyroidal radioiodine uptake. They administered 10 mg. daily of this steroid for three days to twelve subjects. Six of the twelve persons responded with a decrease in the I^{131} uptake to below 50 per cent of initial values.

Testosterone was found to lessen the radioactive iodine thyroidal uptake by 6 to 15 per cent of the administered dose in five of six dwarfed prepuberal children receiving 25 mg. of methyltestosterone orally three to four times daily for a period of forty days [*60*].

Seven women with advanced carcinoma of the breast who received 50 mg. of testosterone propionate intramuscularly three times a week for periods from fifteen to fifty-five days were also studied. The twenty-four-hour thyroidal I^{131} uptake of four fell slightly (exact figures not given) during medication, in two patients there was no change, and in one patient there was a rise in the uptake. In twelve of the total of thirteen cases in this study the protein-bound iodine level in the serum fell significantly. In none of the patients was there evidence of hypothyroidism. The cause of these changes is not known.

Estrogens. Studies of the effects of estrogens on the I^{131} thyroidal uptake in a small group of euthyroid patients showed no consistent changes [*136*]. Animal studies, however, suggest

that the administration of estrogen would be expected to raise the twenty-four-hour thyroidal uptake. Increase of the serum precipitable iodine after administration of estrogens was documented in all sixteen patients studied by Engstrom and his group [*33*].

Soliman and Reineke [*108*] determined that the accumulation of iodine by the thyroid in the female rat is at its maximum during estrus, that estrogens in small doses consistently increase the thyroidal iodine collection, and progesterone decreases it. Feldman [*37*] studied the thyroidal I^{131} uptake after administration of estrone to castrated male rats, some of which were also adrenalectomized. The radioiodine thyroidal uptake was more than double in both treatment groups, as compared to control animals receiving saline solution. The presence or absence of the adrenal did not influence the effect.

ANTIBIOTICS

Animal experiments suggest that antibiotics may have important effects on I^{131} thyroidal uptake. Despite the common use of these agents in patients requiring thyroid function studies, this question has received little experimental study.

Grant [*43*] gave chlortetracycline (Aureomycin®) to rats and found no change in the size of the thyroid gland but there was a small increase in the thyroid I^{131} uptake. Colesnick, Harris and Jones [*29*], however, found opposite results in rats tested with iodine tracer after administration of either chlortetracycline or penicillin G. In these rats the thyroidal I^{131} uptake was decreased to 27 per cent of control values and the thyroid glands were increased in weight, suggesting a goitrogenic effect.

Chloramphenicol (Chloromycetin®) added to the diet of rats increased thyroid weight and thyroid iodine content when administered over extended periods [*118*]. No radioiodine studies were performed, however. The antithyroid effect was potentiated by additional dietary iodide and was prevented by adding desiccated thyroid to the diet.

RENAL STATES

It is important to consider the effects of renal disease on the uptake of iodine by the thyroid gland. Topics that can be conveniently grouped under this heading include increased glomerular filtration, mercurial diuresis, low serum chlorides, decreased glomerular filtration caused by renal disease and by congestive heart failure, and the nephrotic syndrome.

Increased Glomerular Filtration. Increased glomerular filtration has been stated, without documentation, to cause an increase in loss of radioactive iodine and a subsequent decrease in the thyroid uptake [*86*]. However, increased glomerular filtration could only cause a net decrease in the total body pool of stable and radioactive iodine in the same proportions, inasmuch as stable iodine and I^{131} are both filtered by the glomerulus and reabsorbed in the tubule at the same rate [*65*]. Relative iodine deficiency so produced could result only in *increased* thyroid uptake.

Diuresis. The effect of therapeutic diuresis on the thyroidal I^{131} uptake has been examined by Spies [*111*]. It was shown that the rate of iodide excretion was totally unaffected by the administration of a mercurial diuretic. He found that the administration of meralluride sodium (Mercuhydrin®) to eight euthyroid patients had no effect on the six- and twenty-four-hour thyroid I^{131} uptake. In all patients the excretion of chloride during the test period following mercurial injection rose to between 250 per cent to 350 per cent of the control values. In contrast, during the same period of time the renal clearances of radioactive iodine were essentially unchanged, remaining within the range of 88 per cent to 98 per cent of the control values. This finding is of great value to the clinician since many patients with cardiac or pulmonary disease in whom the tracer test is employed for the determination of subsequent I^{131} therapy need a mercurial diuretic for treatment of edema during the period of the test.

In contrast to these findings, a high intake of sodium chloride was found to augment the amount of radioiodine excreted in the urine in both chronic and acute experiments in mice. This was associated with a decrease in the radioiodine content of the thyroid gland [*57*].

Chlorides. Cassidy and Vanderlaan [*25*] have observed two patients with low serum chlorides who had high uptakes of RAI. Additional studies on this problem have not been carried out but it is probable that iodine deficiency due to dietary iodized salt lack is the cause of the high RAI thyroidal uptake in this instance.

Decreased Glomerular Filtration. Renal disease. Decreased renal clearance of iodine was once suspected to be a cause of increased RAI uptake by the thyroid. It is known that decreased

TABLE VII
THE EFFECTS OF THYROID STATES ON RADIOIODINE THYROIDAL UPTAKE

State	Uptake
Subacute thyroiditis	
Active phase	Depressed almost to zero [*56,123*]
Recovery phase	Elevated
Hashimoto's disease	High, normal or low [*103*]
Familial goitrous cretins	High [*64*]
Hypopituitarism	Low (becomes normal after administration of thyrotropin) [*25*]
Thyroidectomized patients	High in 50 per cent of euthyroid patients due to diminished iodine storage capacity [*23,87*]
Primary hypothyroidism	Low
Hyperthyroidism	High; occasionally may be in normal range in severe Graves' disease due to rapid turnover and early peak uptake [*90*]

glomerular filtration in renal disease decreases the renal clearance of iodide [*55*]. This delays RAI excretion and prolongs retention of serum inorganic radioiodine [*16*]. However, when RAI is retained, stable iodine also is retained. Because of the lower specific activity, the thyroid can accumulate the required daily allotment of iodine with a lower uptake of I^{131}. Thus the RAI uptake at twenty-four hours may actually be lower than normal in some cases [*65*]. Perry and Hughes [*81*] observed eleven patients with renal disease: the twenty-six-hour uptake of RAI was within normal limits except in one elderly man in whom it was quite low. They concluded that the twenty-four–twenty-six-hour *in vivo* measurement of thyroid uptake of I^{131} gives reasonably accurate information in patients with decreased glomerular filtration due to renal disease.

Congestive heart failure: It has been suggested [*25*] that congestive heart failure will produce high thyroidal uptakes because of the decreased renal clearance of iodide in this condition. As already indicated, however, it has been shown that decreased glomerular filtration does not elevate the RAI uptake.

Keating and his co-workers [*59*] studied fourteen patients with decompensated heart disease who were euthyroid. The twenty-four-hour thyroidal accumulation of I^{131} averaged 16.6 per cent (±4.3 per cent standard error of the mean). The forty-eight-hour urinary excretion rate averaged 45.7 per cent (±8.8 per cent). The excretion rate was less than the normal (range: 51 to 81 per cent in forty-eight hours). The mean thyroid accumulation rate of 1.4 per cent per hour was significantly less than that of control subjects. It can be concluded, therefore, that cardiac decompensation tends to lower the I^{131} thyroidal uptake at twenty-four hours, not elevate it. The cause of this is unknown.

Nephrosis: In the nephrotic syndrome there may be a low serum protein-bound iodine in the presence of an increased twenty-four-hour thyroidal uptake of radioactive iodine in euthyroid subjects. Recant and Riggs [*85*] carefully studied this problem in sixteen patients. In only three of the sixteen was the uptake above 45 per cent (55 per cent, 71 per cent, 75 per cent). It was concluded that these values reflected hyperactivity of the thyroid due to depletion of the gland of preformed hormone. The depletion was attributed to loss of thyroid hormone in the urine as a result of the proteinuria. In view of the low salt diets these patients usually ingest, it would seem reasonable to suspect chronic iodine deficiency as a major mechanism of the observed elevation in the RAI uptake.

GASTROINTESTINAL STATES AND TECHNICAL ERRORS OF MEASUREMENT

Inasmuch as the radioiodine used in the I^{131} thyroid uptake test usually is administered orally either as a liquid or a capsule, studies relating to the technical details of administration and to the gastrointestinal tract are relevant. It is obvious that vomiting of the test dose shortly after ingestion results in lower uptake. Occasional patients will spill part of a liquid dose during the act of swallowing. Infrequently patients will pass the I^{131} capsule through the entire gastrointestinal tract without dissolution and absorption of the iodine. Furthermore, variations in the amount of the administered dose and in the measuring technics and instrumentation must all be considered [*140*].

The Malabsorption Syndrome. Keating [*59*] found that all radioiodine values in one patient with sprue were normal. A delay of I^{131} absorption was reported in only one of six other patients with sprue [*78*].

Cirrhosis of the Liver. Mueller [*76*] reported that I^{131} uptake was 50 per cent or higher in

twenty of fifty patients who had liver disease with no evidence of thyroid disease. Shipley and Chudzik [*100*] studied thirty-six patients with cirrhosis of the liver and found twenty-four-hour uptake values in excess of 45 per cent in only five of them. Other parameters of thyroid function indicated that these patients were euthyroid. These authors pointed out that hyperavidity for iodine is characteristic in iodine deficiency and that cirrhotic patients may be prone to dietary deficiencies because of prolonged malnutrition and also because of therapeutic restriction of salt. They found that the elevated uptakes seemed to be ameliorated by hospitalization and it was concluded that a pre-existing iodine deficiency, responsible for the high uptakes of I^{131}, had been corrected by diet.

Thyroid Disorders. The effects of various thyroid states upon the I^{131} uptake test are summarized in Table VII. A detailed discussion of the mechanisms of iodine trapping and metabolism in each of these conditions is beyond the scope of this article.

SUMMARY AND CONCLUSIONS

Information concerning the substances and conditions which influence the uptake of radioactive iodine by the thyroid gland has been compiled and evaluated in respect to the known pathways of iodine metabolism.

The factors which determine the normal uptake of radioactive iodine by the thyroid gland are considered and variations due to geographical and nutritional factors are discussed. In particular the dependence of I^{131} thyroidal uptake on iodine intake has been considered. Data concerning the effects of iodine excess and deficiency have been compiled. The duration of the inhibition of thyroidal iodine following the administration of iodinated compounds for radiologic diagnosis is discussed.

Clinical evidence is presented that goitrogenic foods, thiourylene derivatives, aromatic antithyroid drugs, monovalent anions such as perchlorate and thiocyanate, and certain hormonal products may lower the thyroid uptake of iodine. Experimental evidence of other antithyroid agents or dietary states which may prove of eventual clinical importance is discussed. Few conditions other than iodine deficiency, hyperthyroidism and certain unusual thyroid conditions associated with defective hormone synthesis were found to increase iodine uptake by the thyroid. The rebound which occurs following the sudden interruptions of treatment with antithyroid drugs is of particular clinical importance in diagnosis.

The relatively slight effects of mercurial diuresis and other alterations of renal function on radioiodine uptake by the thyroid are documented. Malabsorption states and other gastrointestinal diseases rarely if ever impair the absorption of an oral dose of radioiodine.

Despite the many factors which affect the interpretation of the radioactive iodine thyroidal uptake, this measurement is established as a useful diagnostic procedure.

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