

PHYSIOLOGY OF ENDEMIC GOITRE

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Insight into the nature of thyroid disease, as regards both cause and pathologic physiology, has developed through an understanding of the normal function of the thyroid gland. This chapter will be concerned first with a brief account of the physiology of the thyroid and of the metabolic circuit of iodine, and then with a review of the information which is available regarding the functional abnormalities of the human gland when it is deprived of iodine. Comprehensive reviews of thyroid physiology and iodine metabolism are available elsewhere.^{3, 31, 32, 52}

The mean daily human consumption of iodine in those parts of the world where endemic goitre does not occur lies above 75 μg . Most of this is in inorganic form. Generally, the organic iodine of the diet is reduced to inorganic iodide prior to absorption, but thyroxine, triiodothyronine, and diiodotyrosine may be absorbed intact. Iodate is rapidly reduced to iodide after intravenous injection.

The iodide concentration of the blood is extremely low, except after ingestion of large amounts. Absorbed iodide has a volume of distribution of 20% to 30% of the body-weight. It does not enter into cells in significant amounts, with the exception of the red blood cells and the cells of the thyroid gland. Soon after absorption, thyroxine (T_4) and 3,3',5-triiodothyronine (T_3) become confined to the vascular compartment of the body as the result of binding to carrier proteins in the plasma. Certain iodinated dyes, such as those used for X-ray visualization of the biliary tree, are also absorbed unchanged and are bound to plasma proteins. A simplified diagram of the metabolic circuit of iodine appears in Fig. 1.

The inorganic iodide of the blood is either excreted by the kidney or taken up by the thyroid. The relative efficiency of these two processes determines the fraction of the iodine of the diet which enters the gland. Application of this principle is the basis of the familiar uptake test of

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Trapping depends upon cellular integrity and respiration,^{41, 54} and upon the presence of sulfhydryl groups.¹³ Oxidative phosphorylation is also involved in the trapping of iodide.¹³

Thiocyanate and perchlorate ions prevent iodide trapping,^{49, 55} perchlorate being about ten times as potent as thiocyanate. If either of these substances is administered after trapping has occurred, trapped iodide is rapidly released from the gland, but iodine which has been chemically bound to iodinated tyrosines or thyronines is retained. Chronic administration of thiocyanate may cause goitre, a result that has been observed in certain patients treated with this substance for hypertension. It is not known whether thiocyanate and perchlorate ions block trapping by interfering with cell-membrane transport, or by competing for binding sites within the gland.

The trapped iodide of the gland is oxidized by an oxidative system of the thyroid cell and immediately attaches itself at the 3-position or at the 3- and 5-positions of the benzene ring of tyrosyl residues, which are present in peptide linkages. This step is specifically blocked by the antithyroid drugs related to thiourea. Fawcett and Kirkwood¹² have described a tyrosine-oxidase system which they believe to be responsible for the formation of moniodotyrosine. Moniodotyrosine appears in homogenates of thyroid tissue incubated with added ¹³¹I.^{8, 18, 44} Under normal circumstances, neither moniodotyrosine nor diiodotyrosine escapes into the circulation.⁴⁵ The oxidation of iodide and iodination of the tyrosyl residues may simply proceed side by side, or the iodide may first be activated to an intermediate storage form of iodine which requires the presence of a transferring enzyme before it can react with the tyrosine. Free or peptide-linked tyrosine is iodinated by iodine without the agency of enzymes *in vitro*, but it is probable that, in the gland, the rate at which iodination proceeds is governed enzymatically.

There is evidence that peroxidase is concerned in iodide oxidation. Not only has peroxidase activity been demonstrated many times in thyroid tissue, but the oxidation of iodide, which is rather specific to thyroid tissue, is inhibited by catalase. Further, a variety of substances, such as thiourea and resorcinol, which inhibit the conversion of iodide to organic compounds by thyroid slices or *in vivo*, either inhibit the peroxide-peroxidase system or act as competitive substrates for it.³⁸

It has been suggested that the only requirements for iodide oxidation are oxidizing conditions and the presence of large amounts of iodide; this implies that there may be no specific iodide oxidizing system in the thyroid gland. The colloid has a high oxidation-reduction potential, but this is lowered by substances which have antithyroid activity, such as thiouracil.¹⁰ The possibility remains that a specific electron-transfer system exists for converting iodide to iodine.

Hormone Formation

The generally accepted pathway of hormone formation is by condensation of two iodotyrosine residues, with extrusion of an alanine group. Conceivably, a variety of substances could be formed, and the number is still greater if one of the condensing residues is tyrosine itself. The possibilities are as follows:

3,5-diiodothyronine
 3',5'- ,,
 3,3'- ,,
 3-monoiodothyronine
 3'- ,,
 3,5,3'-triiodothyronine
 3,3',5' ,,
 3,3',5,5'-tetraiodothyronine (thyroxine)

Thyroxine was the first of these compounds to be identified in the gland. The discovery by Gross & Pitt-Rivers¹⁵ in 1952 that 3,3',5-triiodothyronine is present in the thyroid has been followed by the important studies of Roche and his colleagues³⁵ which have indicated that several other iodinated thyronines may also be found in the gland. Prominent among these is 3,3'-diiodothyronine. It has not yet been shown with certainty that the scheme of formation of the iodinated substances of the gland is indeed that described above, nor is it certain that any substance other than thyroxine is secreted by the gland.

Storage and Release

The iodinated tyrosines and thyronines of the gland are stored in peptide linkages as components of the thyroglobulin. Normally, and under conditions of increased glandular activity, the thyroid cells may secrete hormone directly into the blood without intermediary storage. Thyroglobulin is a compound of high molecular weight which is broken down by the action of cathepsins^{9, 23} into components which are small enough to traverse the epithelial cells of the gland and enter the body. The fate of the monoiodotyrosine (MIT) and diiodotyrosine (DIT) released in the course of proteolysis of thyroglobulin was unknown until Roche et al.³³ postulated and found a specific deiodinase in the gland which removes iodine from these two compounds. Thus, normally, they do not reach the peripheral blood. Several patients with congenital goitre and hypothyroidism have been described who appear to lack the tissue deiodinase.⁴³ Large amounts of monoiodotyrosine and diiodotyrosine were found in the peripheral blood of these patients, and tissue slices from the thyroid gland of one of them were unable to dehalogenate diiodotyrosine, in contrast to

normal thyroid tissue.²⁷ It is interesting and possibly relevant to the problem of endemic goitre that diiodotyrosine has been tentatively identified in the serum of two patients with "endemic cretinism" in northern Italy.⁶

One of the principal unsolved problems of the thyroid is the nature of thyroglobulin with respect to the iodinated amino-acids. There is every reason to suspect that thyroglobulin may contain widely varying amounts of these amino-acids, and yet such variability in amino-acid content and in the sequence of amino-acids is not in keeping with current concepts of the specificity of protein structure. It may be that the amino-acid sequence is fixed but that the degree of iodination can vary, or that the iodinated amino-acids are at N-terminal or C-terminal positions and can vary without altering the backbone of the thyroglobulin molecule. Roche et al.³⁴ have found that in pork thyroglobulin some of the T₄, DIT, and tyrosine residues occupy N-terminal positions. Most of the DIT and T₄ residues were internal. T₃ and MIT were not found at N-terminal positions. Pancreatin released MIT first, followed by DIT, from thyroglobulin. T₃ and T₄ came off more slowly.⁴⁸ Little else is known of the fine structure of thyroglobulin.

It is possible that the strongly stimulated thyroid gland may secrete newly formed thyroid hormones directly into the blood,⁴² but under normal circumstances T₃ and T₄ are released as needed from the thyroglobulin. The proteases and peptidases which have been extracted from the thyroid lack specificity for thyroglobulin. The protease has a pH optimum of 3.5 and is much more effective against haemoglobin than against thyroglobulin. The peptidase has a pH optimum near the neutral point.

Circulating Hormone

Thyroxine comprises 60% to 90% of the circulating iodine. The remainder is triiodothyronine and possibly 3,3'-diiodothyronine. Circulating thyroxine is tightly bound to a specific carrier protein which has an electrophoretic mobility very close to that of α_2 -globulin. A small fraction of thyroxine is also bound to albumin. Triiodothyronine is more loosely bound to protein and is more generally distributed among the various serum components. Thyroxine and triiodothyronine can be removed from the blood by extraction with acid butanol. Significant variations in ratios among the iodinated components of the serum have not been definitely associated with specific disease states.

The quantity of circulating iodine in the serum which is precipitable with the serum proteins (PBI: SPI) serves as a useful measure of thyroid function. Normal values lay between 3.5 and 8 μg per 100 ml. Concentrations below 3.5 suggest hypothyroidism, unless prior administration of certain iodinated substances, such as those used in visualization of the gall

bladder, has obscured the test. The rate at which the circulating hormones are used (and replenished in the equilibrium state) depends at least in part upon their concentration. Normally, the thyroid gland secretes between 100 and 200 μg of hormonal iodine daily, and this is turned over in the periphery at a rate of approximately 10% per day. The secretion rate and the turnover are faster in patients with hyperthyroidism.

Perhaps the most subtle and difficult problem in the study of the thyroid has been the nature of the reaction produced upon cells by the thyroid hormone. It has been suggested that the hormone dissociates (uncouples) oxidative phosphorylation, so that oxidation proceeds without the formation of a proportional amount of phosphate bond energy.^{17, 35, 42} There is perhaps less evidence to support other theories which have been proposed.

Much of the iodine from the thyroid hormones is split off and returned to the plasma as iodide to re-enter the metabolic cycle. Some of the hormone may be conjugated or partially degraded, and appear in this altered form in the bile and possibly also in the urine.

Control of Function

The thyroid gland is under tripartite control. The best understood of these regulatory mechanisms is the anterior-pituitary—thyroid relationship. The rate of secretion of thyroid-stimulating hormone (TSH) depends upon the concentration of thyroid hormones circulating in the blood. Secretion of TSH can be inhibited by administration of appropriate amounts of thyroxine or of triiodothyronine. When the thyroid is removed, the production of TSH increases, at least for a time. Removal of the hypophysis results in a reduction of thyroid function, and in man thyroid activity may be suppressed completely.²⁴ Thus, the TSH-producing cells of the hypophysis and the thyroid appear to exist in a dynamic state of balance (feed-back).

The circulating thyroid hormones in the plasma may have a direct regulatory effect upon thyroid function. Cortell and Rawson⁵ observed that the size and cell height of the thyroid gland of TSH-treated hypophysectomized rats could be influenced by various doses of thyroxine. Their observations are subject to the alternative explanation that the exogenous thyroxine may have altered the rate of disposal of the exogenous TSH. Halmi¹⁶ has found that the responses of the gland are dependent in part upon the iodine content of the gland. Supporting evidence has been furnished by VanderLaan & Caplan⁵⁰ and by Wahlberg.⁵¹

It can be seen that the regulation of the gland is complex and incompletely understood. The relative contribution of the several regulatory influences is not known, nor is it known to what degree the various metabolic steps in the gland can be separately and independently influenced. TSH stimulates all aspects of glandular activity, such as iodine uptake, phos-

phorus uptake,²⁰ hormone release, etc., but equal stimulation does not always occur because there are states of disequilibrium where the gland is storing iodine faster than it is secreting hormonal iodine, or *vice versa*.

Iodine Deficiency and Endemic Goitre

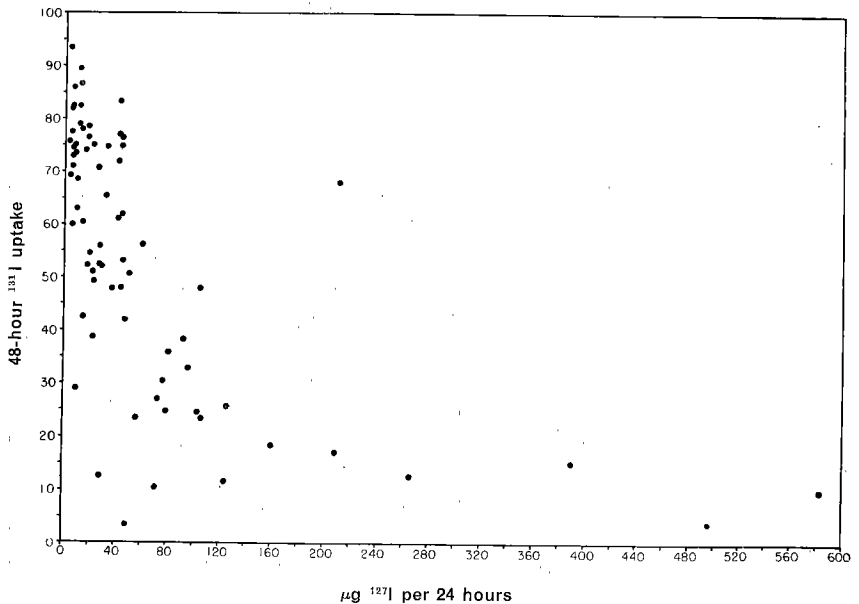
There is a vast amount of information on the effect of iodine deficiency on the function of the rat thyroid. Hyperplasia of the gland can be readily produced,³⁰ and this effect can be enhanced by feeding chloride,¹ but chloride has no similar noteworthy iodouretic effect in man (D. S. Riggs & J. B. Stanbury, unpublished data). Calcium also causes enhanced growth of the iodine-deprived rat thyroid.⁴⁶ Querido et al.²⁶ have found that in rats deprived of iodine there is a relative increase in the amount of labelled iodine which is present in the monoiodotyrosine fraction of the gland. It is beyond the scope of this chapter to review all the findings from animal studies. The reader is referred to the paper of Barker² for an introduction to the literature concerning the general physiology of the thyroid. This chapter will be principally concerned with studies which have been made upon patients and where the weight of evidence has indicated iodine deprivation as the sole predisposing factor. With few exceptions, study of endemic goitre as performed with modern methods has consistently furnished information which has been in accord with a situation of iodine deficiency in the diet.

If the assumption is made that patients are nearly in equilibrium with their environment in respect to dietary iodine, then the daily urinary excretion of iodine can serve as a most useful index of the quantity of iodine which the patient is ingesting. Surveys of the urinary excretion of iodine by subjects living in endemic goitre regions have disclosed a mean iodine excretion which is much lower than that of persons in areas where endemic goitre does not exist (the Netherlands,²⁹ Argentina,⁴² Venezuela,³⁷ Finland²¹). Daily excretion rates of less than 10 μg may be a commonplace.

In the limited number of observations which have been made, the serum-precipitable iodine of patients with endemic goitre has not been far different from that of normal control subjects. Lamberg, Wahlberg, and Kuhlback¹⁹ found that certain of their patients with goitre in Finland had subnormal values for SPI. Observations in endemic goitre areas made by Terpstra⁴⁷ using ¹²⁷I showed normal PBI values, both in patients with goitre ($5.2 \pm \text{SD } 0.5$), and in control subjects ($5.6 \pm \text{SD } 1.0$). The statistical dispersion of serum concentrations found among patients in western Argentina was greater than in a control series, but the mean value was very nearly the same.⁴²

The low ingestion of iodine is reflected in the increased avidity of the thyroid gland for iodine. This is illustrated in Fig. 2, which is taken from a study of endemic goitre in western Argentina.⁴² It is seen from the figure that, with considerable uniformity, patients with low amounts of iodine in

FIG. 2. RELATIONSHIP BETWEEN EXCRETION OF IODINE AND UPTAKE OF RADIOACTIVE IODINE IN A GROUP OF PATIENTS FROM WESTERN ARGENTINA

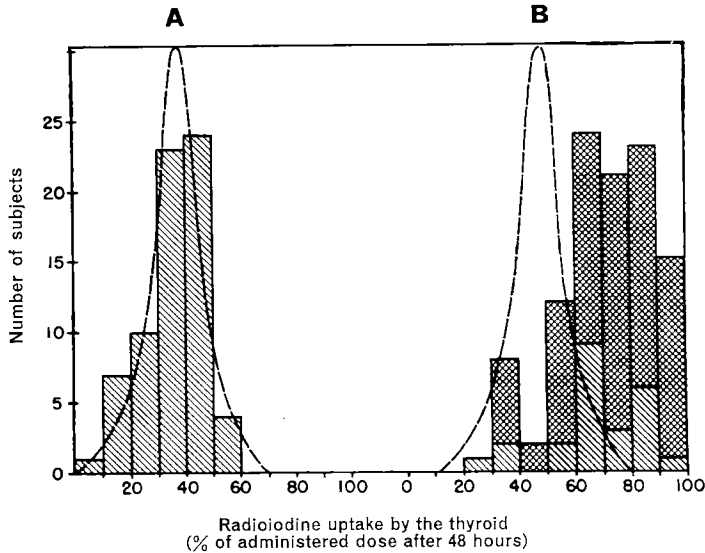


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the urine demonstrated a high avidity for iodine, as indicated by the enhanced uptake of ^{131}I , whereas those patients who had succeeded in obtaining an adequate supply of iodine exhibited uptake values which would be considered normal in non-endemic regions. Entirely similar findings have been obtained in the Netherlands⁴⁷ and in Finland.²¹


The uptake of iodine by the thyroid of the patient with endemic goitre is usually found to be greater than normal. This was recognized long ago from a study carried out with the stable isotope of iodine¹¹ and has been amply confirmed by more direct measurements made recently^{21, 37, 42, 47} with ^{131}I . A typical study illustrating this fact is shown in Fig. 3. The authors³⁷ have compared their findings in an endemic area (Bailadores) and a non-endemic area (Caracas) of Venezuela with those obtained by Skanse⁴⁰ in a group of normal subjects observed in Boston, Massachusetts. While there is an overlap between the two curves of distribution, many patients with endemic goitre have uptake values which would be higher than normal if found in patients from a non-endemic district. In an isolated mountainous area of Venezuela, Roche³⁶ has observed high uptake values of ^{131}I in subjects without goitre. Obviously, the ^{131}I uptake test has serious limitations and may be of no value in patients from a non-endemic district. This has proved


FIG. 3. COMPARISON OF RADIOIODINE UPTAKE BY PATIENTS IN A NON-ENDEMIC ZONE (CARACAS) AND AN ENDEMIC ZONE (BAILADORES) OF VENEZUELA



A. Caracas (average: 37%)

B. Bailadores (average: 74%)

 With goitre

 Without goitre

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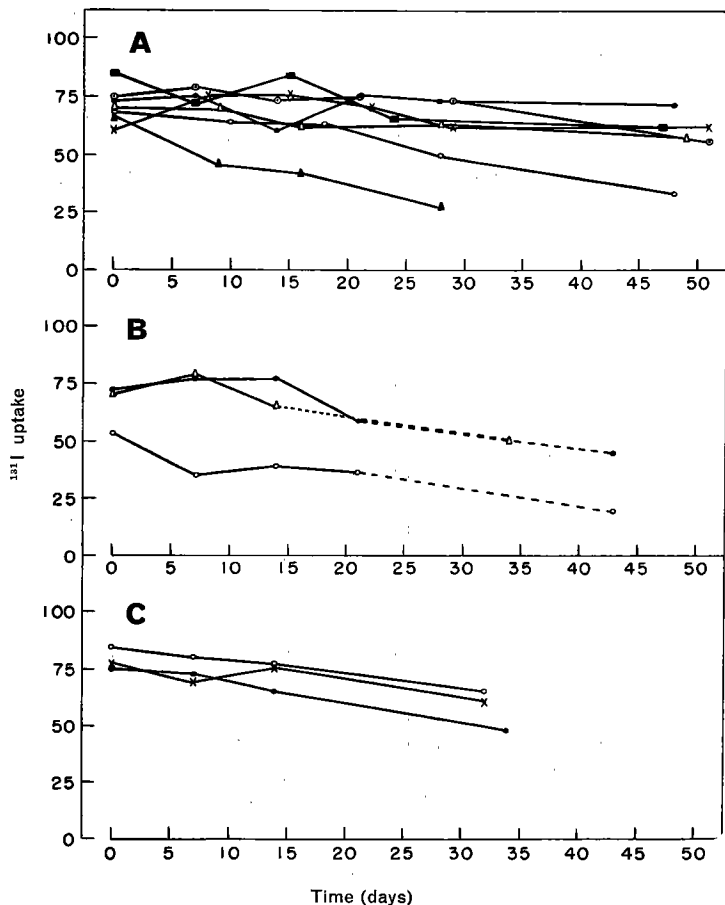
to be an awkward problem in applying the uptake test to clinical situations in endemic regions.

The pioneer work of Greer and his associates¹⁴ on the effect of certain foods on thyroid function has indicated the possibility that in certain cases endemic goitre might be the result of a specific goitrogen in the diet. Such substances inhibit the uptake of iodine by the gland. In Tasmania, Clements⁴ has found that milk from dairy cows fed upon chou-moellier (marrow-stem kale), a plant of the *Brassica* genus, may, upon ingestion, inhibit the accumulation of radioactive iodine in the thyroid gland. On the other hand, A. Costa (personal communication) has found the uptake to be the same in the inhabitants of certain goitrous areas of Italy as in normal control subjects. He has also found high uptake values for ¹³¹I in subjects with endemic cretinism, together with normal to high readings for the protein-bound iodine content of the serum.⁷ On the other hand, Raman & Beierwaltes²⁸ have found the PBI values to be somewhat lower in cretinous than in normal subjects.

If iodine is restored to the daily diet of the iodine-deprived subject, there is a slow readjustment of iodine retention until a new state of balance is

achieved, and during this period there is a net gain of iodine in the thyroid gland. The net gain depends upon the initial degree of depletion and the size of the daily supplement. The adjustment to a new equilibrium state may take several weeks or longer. These principles are illustrated in Fig. 4. Groups of patients with endemic goitre and limited dietary iodine were left on their own household diets and were given supplements of potassium iodide in various amounts. The period of observation was not long enough

FIG. 4. EFFECT OF DAILY SUPPLEMENTARY DOSES OF POTASSIUM IODIDE ON UPTAKE OF RADIOIODINE BY PATIENTS FROM AN ENDEMIC AREA OF ARGENTINA



A. Patients given 150 μg of KI daily

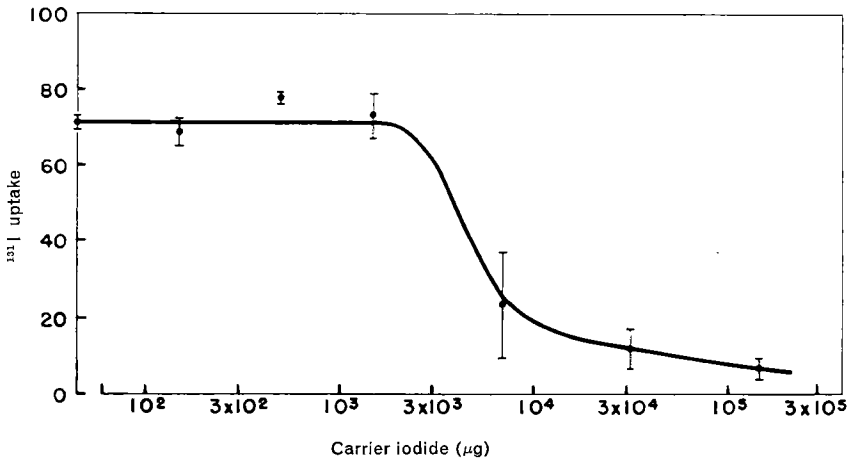
B. Patients given 500 μg (solid line) and 600 μg (broken line) of KI daily

C. Patients given 1500 μg of KI daily

for complete readjustment to take place, but the trend was evident. When the daily supplement was 150 μg , the net retention of iodine was estimated to be 5.8 mg in 99 days. When the supplement was 1500 μg daily, the retention was 34.1 mg over a period of 33 days. One of the patients in the latter group subsequently developed thyrotoxicosis.

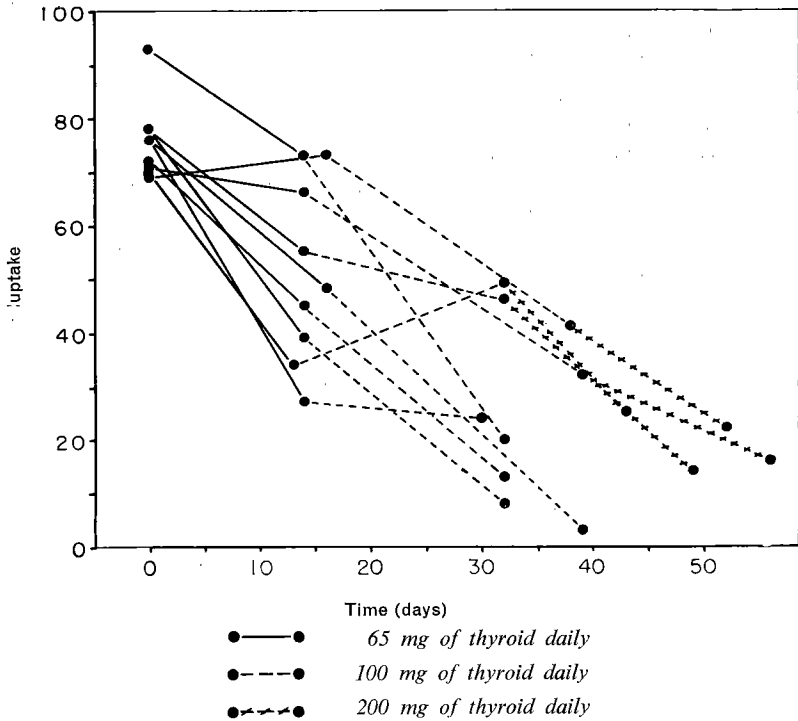
The fraction of a single dose of iodine retained by a patient with endemic goitre is constant over a wide range, but at higher dose levels the fraction decreases as the capacity of the gland to absorb iodine from the blood approaches saturation. A group of patients with endemic goitre were given control tracer doses of ^{131}I , and later tracers of ^{131}I supplemented with widely varying amounts of carrier ^{127}I . The results (Fig. 5) suggest that most of the iodine above 5 mg is rapidly excreted by the kidney.

FIG. 5. EFFECT OF A SINGLE DOSE OF IODINE ON THYROIDAL UPTAKE OF SIMULTANEOUSLY ADMINISTERED RADIOIODINE



Both in normal subjects and in those with endemic goitre, administration of desiccated thyroid inhibits the activity of the gland, presumably by causing diminished production of TSH by the anterior pituitary. Observations on a group of subjects with endemic goitre are illustrated in Fig. 6. In 7 out of 9 patients, 65 mg daily of desiccated thyroid caused a significant fall in uptake of radioiodine. Increasing the daily dose to 100 mg caused a further fall in uptake in all but one patient. These responses are comparable to those observed in normal patients, and much greater than those seen after administration of thyroxine or triiodothyronine to patients with Graves' disease, where initial uptake values are comparable to those seen in endemic goitre patients. These observations are consistent with the interpretation that the thyroid gland of the patient with endemic goitre is under an increased stimulus from

FIG. 6. EFFECT OF ORALLY ADMINISTERED DESICCATED THYROID ON UPTAKE OF RADIOIODINE IN PATIENTS WITH ENDEMIC GOITRE IN WESTERN ARGENTINA

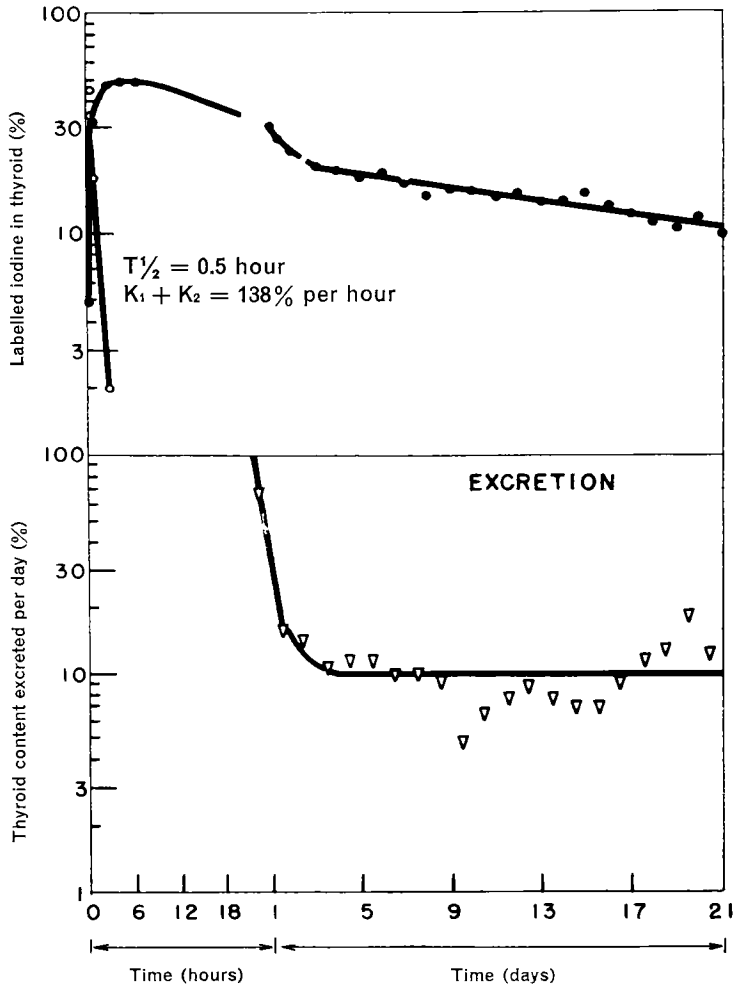


the anterior pituitary gland, or that the thyroid is more susceptible to TSH stimulation.

The iodine content of the endemic goitrous gland varies widely, but the *concentration* of iodine in the gland is usually lower than normal. These observations were made long ago by direct analysis of glands surgically removed.³⁹ The thyroid iodine content has also been calculated from urinary measurements of ¹²⁷I and ¹³¹I after a tracer dose of ¹³¹I, and from *in vivo* data obtained from patients with endemic goitre.⁴² These values varied from 260 to 12 600 μg of iodine in seven patients studied. It was observed that the release of labelled iodine from the gland depended upon the quantity of iodine contained therein. Those patients whose thyroid iodine was high appeared to discharge labelled iodine from the gland at a net rate which was proportional to the contained iodine. No such simple relationship was obtained when the thyroidal iodine was low; in this case, the patients released labelled iodine in such a way as to suggest that it was being given up by two separate and distinct compartments in the gland. One of these was thought to be the cells, which were releasing newly formed

hormone rapidly and directly into the blood. This compartment was small and had a rapid turnover. The other was thought to be a larger compartment with a much slower turnover, possibly the colloid stores. The type of release shown by a patient with low thyroid iodine content is illustrated in Fig. 7. Similar curves may be seen in patients with vigorous thyrotoxicosis. In

FIG. 7. RELEASE OF LABELLED IODINE AND ITS APPEARANCE IN THE URINE OF A PATIENT WITH ENDEMIC GOITRE AND LOW THYROIDAL CONTENT



Note the rapid initial release during the first five days after administration.

$T_{1/2}$ = half-time of iodine disappearance

K_1 = thyroidal uptake constant

K_2 = renal excretion constant

patients with endemic goitre Terpstra ⁴⁷ found that the average PBI values 24 hours after administration of a tracer dose of ¹³¹I were within normal limits (<0.35% of the dose per litre of serum; see table below). These observations led to the conclusion that the total thyroid iodine content in the investigated cases did not differ from the total iodine content of normal glands.

URINE IODINE EXCRETION AND PBI VALUES OF A GROUP OF PATIENTS WITH ENDEMIC GOITRE IN THE NETHERLANDS

Sex	Age	Thyroid size (times normal)	Total urine ¹²⁷ I excretion per 24 hours * (μg)	PB ¹²⁷ I (μg %)	PB ¹³¹ I after 48 hours (% dose per litre)	Conversion ratio ** after 24 hours (%)
F	31	4-5	43	5.0	0.07	72
F	23	2-3	33	6.0	0.06	64
F	31	3	24	6.0	0.09	79
F	32	4-5	42	4.9	0.078	59
F	21	5	27	5.1	0.026	82
F	18	5	52	4.5	0.025	50
F	16	4-5	32	5.3	0.045	42
F	26	2	14	5.6	0.11	87
F	25	3	17	6.8	0.044	81
M	37	3-4	17	5.8	0.04	65
F	16	6	15	5.3	0.047	50

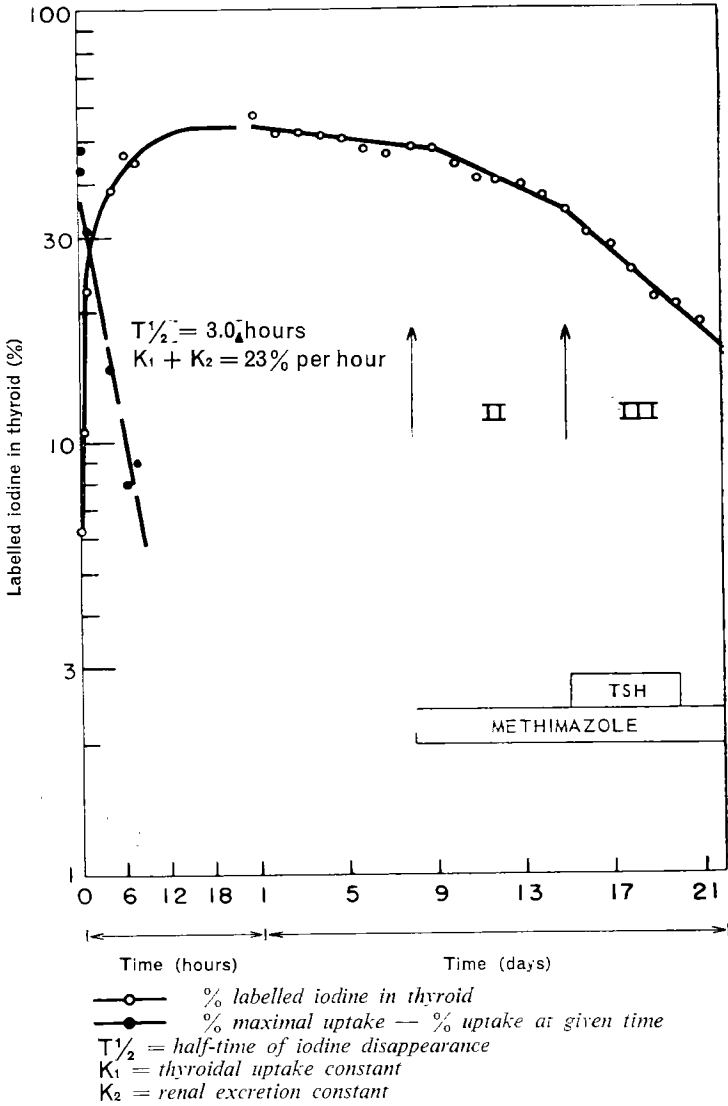
* Average figures of 2-5 observations

** Conversion ratio = $\frac{\text{serum PB}^{131}\text{I}}{\text{total serum }^{131}\text{I}}$
After Terpstra ⁴⁷

The thyroid gland of the endemic goitre patient is responsive to certain antithyroid drugs and to thyrotropic hormone. Administration, for example, of methimazole (1-methyl-2-mercapto-imidazole), causes an accelerated release of labelled iodine from the gland as the drug produces its characteristic inhibition of re-utilization of iodine released through the peripheral degradation of hormone (Fig. 8). Further increase in the rate of release of iodine from the gland occurs when thyrotropin is administered. The latter observation indicates that these glands are responsive to exogenous thyrotropin even though they are already being stimulated by that hormone.

There are fragmentary data which suggest that there may be qualitative abnormalities of iodine metabolism in endemic goitre. G. Escobar & F. Escobar del Rey (personal communication), studying endemic goitre near Granada, Spain, have found that certain patients, although not all, may have a considerable fraction of serum iodine which is precipitable

FIG. 8. EFFECT OF AN ANTI-THYROID DRUG, METHIMAZOLE, AND A THYROTROPIC HORMONE ON THE RELEASE OF LABELLED IODINE FROM THE THYROID OF A PATIENT WITH ENDEMIC GOITRE IN WESTERN ARGENTINA



with the usual protein precipitants and is extractable into acid butanol, but which, unlike thyroxine and triiodothyronine, is extractable from butanol by alkali. The nature of this substance is not known. The observation of Costa et al.⁶ that two out of ten subjects with endemic cretinism had diiodo-

tyrosine in the blood may be important and needs confirmation and further study. Apart from this, there is no evidence that an abnormal iodinated component is present in the blood of patients with endemic goitre.

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