MEDICAL GRAND ROUNDS

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IODINE INDUCED THYROID DYSFUNCTION. RECENT DEVELOPMENTS IN THYROID HORMONES.

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P.P. is a 60 y/o black man admitted to the Medicine Service at Parkland with a history of repeated episodes of palpitations highly suggestive of supraventricular tachycardia. The most recent episode resulted in his losing consciousness and being admitted. In the Emergency Room he had ECG evidence of runs of supraventricular tachycardia alternating with normal sinus rhythm with frequent PAC's. He has a 10-year history of hypertension, treated intermittently with intermittent control. In addition, history of angina pectoris and COPD is present. The work-up in the hospital included thyroid function test which indicated a T_4 of 11.4 (NL = 4.8-10.4) and T_3 renin uptake of 41.3% (NL = 33.5-46.5) and free T_4 index of 7.87 (NL = 3.3-6.5). ^{131}I uptake was 2.4%. Atthis time, a history of an oral cholecystogram done a month before was obtained which could explain the uptake. He was labelled as having apathetic hyperthyroidism and treatment was started with Inderal 10 mg qid and Propylthiouracil 50 mg qid. It is said that he improved, but soon after discharge he was lost to follow-up for six months. At the end of this time he showed up at the Endocrine Clinic where he gave a history of running out of medications several months before without noting any difference. At the time his ^{131}I uptake was 15%, T_4 was 8.4 µg/dl, and T_3 renin uptake was 33.2%, and he was clinically euthyroid.

This case and multiple others in recent years have prompted me to review selected aspects of old and new topics with respect to the thyroid. I am going to concentrate initially on the effect of iodine and later on review some aspects of recent developments in thyroid physiology.

Historical Notes: Control of endemic goiter for the most part was accomplished by the introduction of iodine supplementation to the diet. However, iodine proved to be a mixed blessing in spite of its usefulness.

I want to review the effect of iodine on thyroid dysfunction, concentrating mainly on the effect of excess iodine and not considering the area of iodine deficiency.

Early in 1820 Jean-Francois Coindet of Geneva reported that iodine shrank goiter (1). Coindet was a prominent physician who trained at Edinburgh and practiced in Geneva. He tried sea sponge ash, an old but never popular remedy for goiter, and observed that it shrank goiters. It had been recently found that sea sponge ash contained iodine. Within a year over a thousand Genevans had tried iodine with good results. It was Coindet, again, who warned against some "annoying symptoms that had been noted among prominent citizens" and that "a definite fear had been invoked against the use of iodine" (2). He was very careful in his administration of iodine; but when consulted about patients who had not been treated carefully, he observed tremor, tachycardia, rapid loss of strength and weight in spite of increased apetite, and insomnia. The goiters had usually decreased in size. His treatment is of some interest. It consisted of stopping iodine, administration of ass's milk, warm baths, and opium. As a rule, recovery was fast.

This seems to be the first description of iodine-induced hyperthyroidism--or as it is called, Jodbasedow.

The administration of iodine initially as a supplement in iodized salt (1:10,000) and, more recently, in many food products and in the medical world as contrast materials has produced, in general, a benefit to humanity, but has created a few problems that, unfortunately, are not well described in the medical textbooks. From 40 to 100 µg of hormonal iodine are metabolized daily by peripheral tissues (3). The requirements vary according to numerous physiological and pathological conditions--such as, environmental temperature, physical activity, fever, etc. The intake of iodine varies widely between different areas of the world. For example, in a coastal population in Japan, intake varied between 0.175 to 29.8 mg daily. In other areas the intake can be as low as 50 µg a day. In spite of this variation, euthyroidism is maintained, which indicates that the thyroid regulates somewhat hormone synthesis in the presence of wide fluctuations in iodine intake.

The daily requirements are approximately 200 µg. We can divide iodine excess into four degrees (4,5,6,7):

(1) Relatively low levels which lead to temporary increases in absolute iodine uptake. In this range the percentage uptake, organification, and incorporation into iodinated aminoacids is unaltered. Positive balances over a long period of time can be associated with increased hormone stores.

(2) A moderate dose of iodine which leads to a decrease in percentage uptake of administered iodide, proportionate organification of thyroid iodide, and proportion of newly formed iodinated iodoaminoacids, but causes an increase in the absolute rate of organic iodination and thyroid hormone synthesis.

(3) A large dose of iodide which decreases both the percentage of administered iodine incorporation and the absolute rate of organic iodine formation--the so-called Wolff-Chaikoff effect.

(4) A very large dose of iodide which saturates the mechanism for active transport of iodide. An acute pharmacologic effect of iodide can be detected before saturation occurs.

The Wolff-Chaikoff effect is temporary. Inhibition of organic iodine formation disappears spontaneously despite continued administration of iodine and the formation of organic iodine increases (escape from the Wolff-Chaikoff effect). Abnormalities in these mechanisms can produce disease processes.

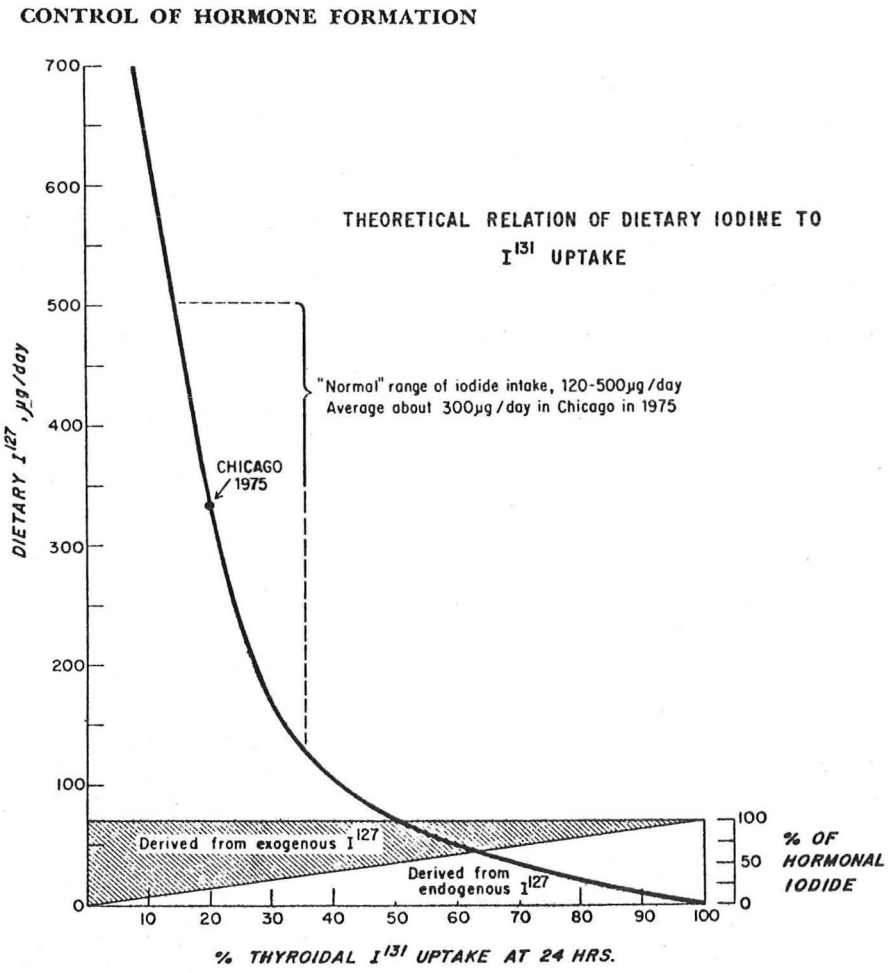
TABLE I: Classification of the Effects of Iodide on Thyroid Function

Abnormality	Underlying Thyroid Disease
Decrease ^{131}I uptake in normals	None
Goiter and/or Hypothyroidism	Hashimoto's thyroiditis Treated Graves' Subtotal thyroidectomy Metabolic defects in hormone synthesis Cystic fibrosis Synergism with other drugs (Li, etc.)
Newborn goiter	Iodine administration to mother
Hyperthyroidism (Jodbasedow)	None Autonomous nodule Endemic iodine deficiency goiter Nontoxic nodular goiter

TABLE I: (Con't)

Abnormality	Underlying Thyroid Disease
Euthyroidism with elevated T_4	Telepaque administration
Decreased remission rate with PTU therapy	Graves' disease

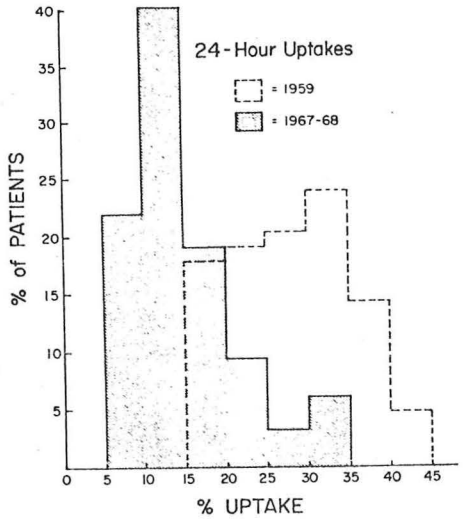
The amount of ^{131}I uptake by the thyroid gland of normal individuals is dependent on the degree of dilution with the pool of stable iodide that is incorporated daily into the thyroid. Such a relationship is shown in Figure 1.



Relation of dietary iodine to ^{131}I uptake. There is an inverse relationship between average dietary iodide and average thyroid ^{131}I uptake at 24 hr. Typical uptakes are now about 20% with iodide intakes of about 100 to 500 µg/day.

figure 1

Iodine intake has greatly increased with the introduction of salt supplemented with iodide and new methods of manufacturing white bread which utilize a mixture of iodides and iodates as dough conditioners in the newer "continuous mix" automated bread making. These breads can vary quite considerably around the country and probably account for the variations in the normal limits for ^{131}I uptakes. For example, in the Bronx normal uptake is reported as 15 to 40% at 24 hours and in Columbia, Missouri, at 5 to 15% (7). In the latter, iodine content in bread was much higher than in the Bronx. Similarly, Figure 2 depicts a situation in Alabama (8) in which the frequency distributions of ^{131}I uptakes in 1959 are compared to those in 1967-68. The average iodine content of the Alabama bread is shown in Table II.



Frequency Distribution of the Uptakes Measured in 1959 and 1967-68.

figure 2

*Total Iodine Content of Bread.**

Variety	Total Content μg
Bread:	
White, sandwich – 1 slice	150±11.2
100 gm	884
Frankfurter bun:	
1 bun	99±9.8
100 gm	246
Cornbread:	
Square	17.4±0.6
100 gm	61

*6 samples of each variety of bread analyzed, & results given as total iodine/common unit used (mean ±SD) & for each 100 gm of such bread.

Table II

Unfortunately, in our technological society methods for everything change and iodine in diet can change when procedures for the manufacture of food changes, which obligates people working in this area to reevaluate normal limits of ^{131}I uptake every few years. We have to realize that there are other unsuspected sources of iodine like the use of iodophores to sterilize cow udders in Tasmania (9) which introduce iodine to the milk.

Iodide Induced Goiter and/or Hypothyroidism: The most frequent use of iodide has been in the treatment of respiratory diseases. Iodide might be one of the few true expectorants and is extensively used for this purpose. In the last few years at Parkland, we have not seen cases of iodide-induced goiter or hypothyroidism since the most popular bronchodilator which we currently utilize has no iodide.

It is curious that this entity was only described about 30 years ago (10). The ingestion of iodide is generally in amounts much greater than the daily requirements.

Classification Modified from Wolff (5):

TABLE III: Iodide Induced Goiter and/or Hypothyroidism

1. Adult iodide goiter
2. Iodide goiter of the newborn
3. Endemic iodide goiter (coastal goiter)
4. Hypothyroidism in diseased glands (Graves', Hashimoto's, etc.)
5. Synergism with other drugs

1. Adult Iodide Goiter: Wolff reviewed the literature (5) and reported on 154 cases. In 80% of them, a goiter was present as shown in Table IV.

TABLE IV: Cases of Non-endemic Goiter

Diagnosis	Number	Percentage
Goiter alone	56 (+ ? 5)†	39
Hypothyroid alone	24 (+ ? 6)†	17
Both	63	
Totals	143 (+ ? 11)†	
	(92 F, 62 M)	

†Description ambiguous

In the course of 18 months Jubig *et al* (11) observed 13 cases with iodide-induced hypothyroidism. They noticed that all these patients were receiving SSKI (one drop = 36 mg of iodide) for COPD. A goiter was found in 7 of the 13 patients. Clinical hypothyroidism was present in about one-third of them. As expected, T_4 was low and TSH was high in all of the patients. Both hormones returned to normal after discontinuation of SSKI.

SSKI was administered (30 drops for 11 weeks) to 4 normal volunteers. T_4 dropped slightly, TSH rose slightly, and T_3 did not change significantly in these subjects. It is unknown why those patients with lung disease developed iodide-induced hypothyroidism and goiter in contrast to the normal subjects. These minor changes have been observed by others (12).

Iodine Preparations: Inorganic iodide is the most common agent, as shown in the Wolff review (5).

TABLE V: Iodine-Containing Preparations in 154 Cases of Iodide-Induced Goiter and/or Hypothyroidism

Preparation	Number of Cases
Inorganic Iodine: SSKI, Lugol, etc.	99
Organic Iodine:	
Iodopyrine	45
Lipiodol	8
Benziodarone	1
Diiodoquin	1
Total:	154

Some of these organic iodines might have additional effects as in the case of iodopyrine, which is a derivative of antipyrine with 40% iodine. This compound is rapidly deiodinated *in vivo*. In rats, antipyrine has been shown to be mildly antithyroid. Most people had received large doses of iodine (18 mg to 1 g/d) for long periods of time and, in some cases, 5 years elapsed before goiter appeared. In other cases it appeared in as short a time as six months. The goiters and/or myxedema subside after discontinuation of iodine, but they can recur promptly after reinitiation of iodine therapy.

As a rule, improvement of thyroid function occurs between several weeks to several months after discontinuation of therapy, and it is not unusual for improvement to occur within three weeks.

An interesting phenomenon seen upon iodine withdrawal is rebound "hyperactivity" of the thyroid gland which can last for weeks. It is seen in most cases manifested by a high ^{131}I uptake.

The Differential Diagnosis: The differential diagnosis of hypothyroidism is shown in Table VI.

TABLE VI: Hypothyroidism and Goiter Differential Diagnosis

1. Iodine-induced goiter
2. Hashimoto's thyroiditis
3. Enzymatic deficiency of thyroid hormone synthesis
4. Neoplastic replacement of the thyroid gland
5. Peripheral resistance to thyroid hormones

2. Iodide Goiter of the Newborn: Iodide is readily transferred across the placenta. Most of the cases reported have been from mothers with asthma or other forms of chronic obstructive lung disease. The mothers usually do not develop either goiter or hypothyroidism. These babies have the additional problem of tracheal obstruction produced by the goiter. Wolff (5) reports that 6 of 25 and 8 of 22 newborns died of tracheal obstruction.

Otherwise, the picture is similar to the adult type.

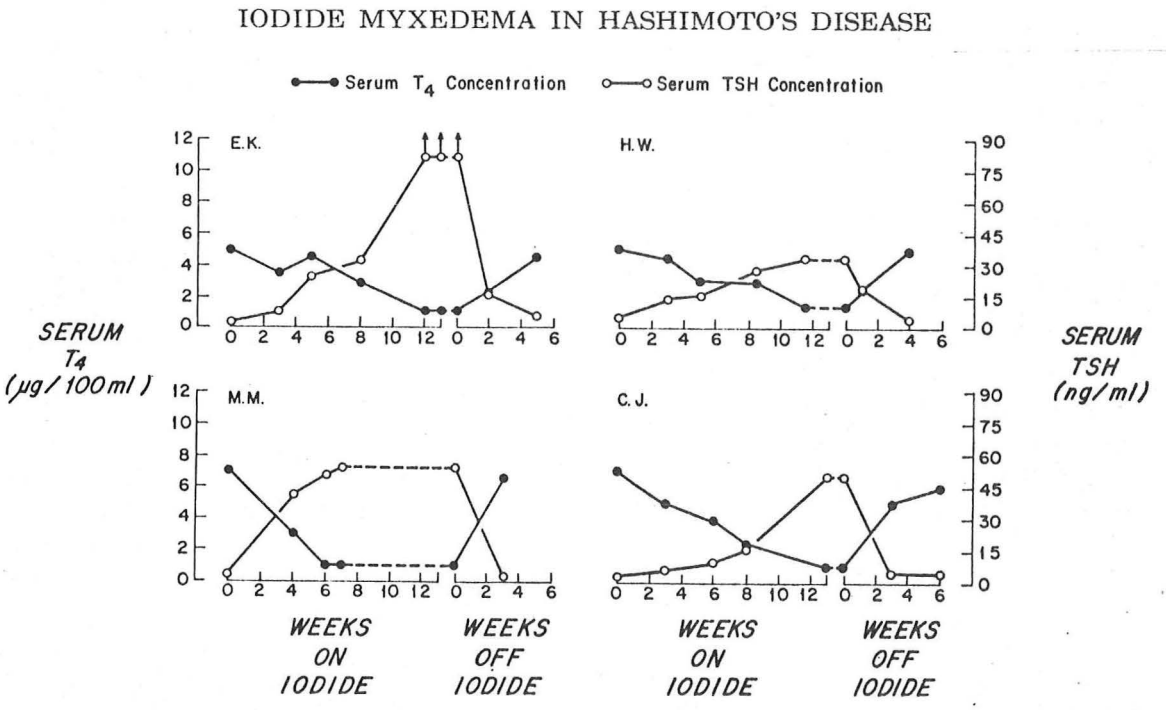
3. Endemic Goiter: In the north island of Japan, Hokkaido, a high incidence of goiter has been recognized for many years. It was noticed to occur mainly among seaweed fishermen who consumed large quantities of "kombu" which contains large quantities of iodine (0.8 to 4.5 g iodine per kg). The average intake of seaweed in 1958 was 31.5 ± 28.9 g per day per capita. In 1968 it had decreased to 13.5 ± 13.4. The incidence of goiter in 1958 among school children varied between 1.1 to 8.9% in the various areas of Hokkaido. Associated with the decreased intake of kombu (as shown above), the incidence of goiter in the island of Rishiri dropped from 8.9 to 2.1% (13).

Almost no hypothyroidism occurs among these patients. This is probably explained by the intermittent consumption of kelp. Apparently, the fishermen consume only the kelp that cannot be sold after the one-day drying procedure. Since this type of kelp grows in deep waters, it cannot be harvested during bad weather and, therefore, consumption will vary with availability.

Recent fadisms have introduced kelp into our diet, especially on the West Coast. Kelp is a good source of bulk with few calories, making it suitable in the mind of some people as adjuvants in weight reduction. It is likely that we will see some cases of iodide-induced goiter from this source, especially in patients having underlying thyroid disease as shown below.

4. Iodide-Induced Hypothyroidism in Patients with Underlying Thyroid Disease: A relationship between Hashimoto's disease and iodine-goiter has been long suspected and discussed. Numerous cases of the latter have been associated with either elevated antithyroid antibodies or histological changes of Hashimoto's (reviewed by 5,14). Patients with Hashimoto's frequently have demonstrable defects in the thyroidal organic binding mechanism, a defect thought to predispose to iodine goiter. And, finally, the frequency of thyroid autoantibodies in serum is higher in patients who develop iodine-hypothyroidism than in either age or sex matched controls (15) or in patients with simple goiters, dyshormogenetic goiters, or goiters induced by other drugs (16).

In a prospective study, Braverman (14) showed that 4 of 7 previously euthyroid patients with Hashimoto's developed clinical and laboratory evidence of hypothyroidism after administration of 5 drops of SSKI (180 mg iodide) for 17 to 30 weeks. Figure 3 shows the individual data for serum T_4 and TSH.



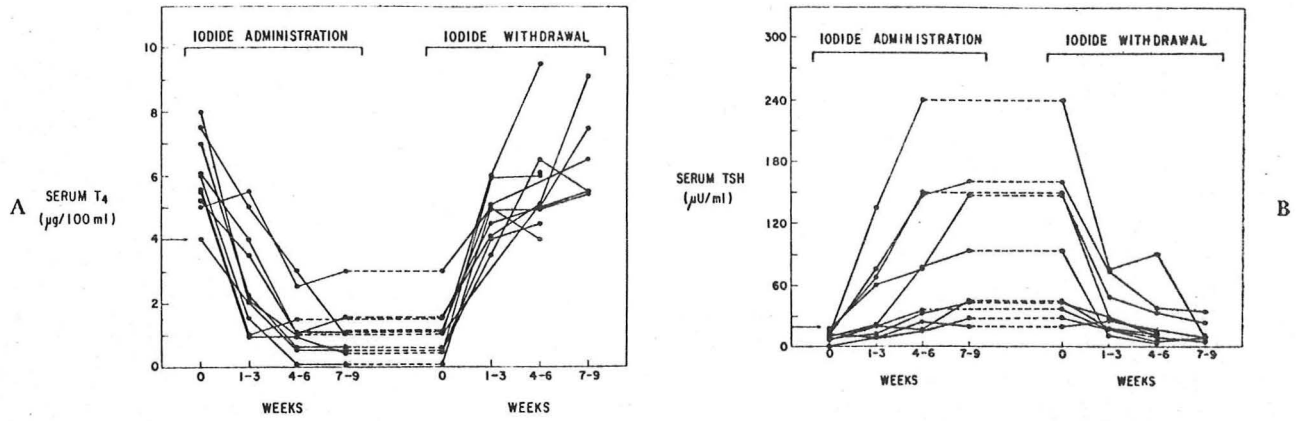
Effects of chronic iodide administration on serum T_4 and TSH concentrations in patients with Hashimoto's disease: patients who developed myxedema. Values for serum TSH concentration indicated by the arrows were greater than 80 ng/ml, the highest value tested for in the immunoassay.

figure 3

This study demonstrates the increased susceptibility to iodine of patients with Hashimoto's thyroiditis similar to the one of treated patients with Graves' disease. No clear explanation is evident.

One of the earliest therapies for Graves' disease was iodine. The beneficial effects of iodine occur very rapidly in comparison to other antithyroidal agents. However, the effects are usually temporary and the effect disappears within a few days or weeks. For this reason iodine was employed only prior to the surgical treatment of Graves' disease. Iodine has been shown to decrease the secretion of thyroxine, and the rapid action suggests that it is the result of an abrupt decrease in the fractional rate of thyroidal T_4 release (17).

In contrast to normal individuals, patients with Graves' disease escape very slowly from the Wolff-Chaikoff effect which explains the therapeutic effect of iodides. On the other hand, patients with treated Grave's disease either after radiation (18) or surgical therapy are very sensitive to the effects of iodides. In this group of euthyroid patients (that is, successfully treated patients), iodides will induce rises of TSH levels and decrease of T_4 to hypothyroid levels and clinical myxedema. In the case of the patients treated with ^{131}I, the changes can be dramatic; but even on the patients treated surgically, changes were found varying from minor to profound decreases of T_4. Figure 4 shows one such study of serum T_4 and TSH.



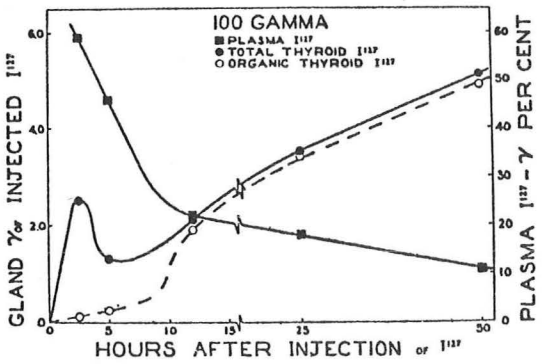
Response of the Serum Thyroxine Concentration (A) *and TSH Concentration* (B) *to Iodide (SSKI, 5 Drops Daily) in Patients with Diffuse Toxic Goiter Who Had Been Rendered Euthyroid by Treatment with Radioiodine.*

figure 4

5. Synergism with other antithyroid agents: As shown before, some iodinated agents (5) can have an antithyroid effect by themselves in addition to their content of iodine. On the other hand, patients can be taking an antithyroid agent for a different purpose and the addition of iodine can induce hypothyroidism. One such case is the chronic administration of lithium. Lithium has been observed to be goitrogenic and to raise TSH levels. Spaulding found iodine administration induced hypothyroidism in 2 of 10 patients on chronic lithium therapy that had been previously euthyroid (19). The exact mechanism of action is not clear, but it has been suggested that it is very similar to that of iodine (20).

Mechanism of Action of Iodide Transport: Chronic administration of excess iodine reduces iodide transport into the thyroid (21). An inverse relationship between glandular organic content and iodide transport activity has been found consistently (21). It is believed to represent an autoregulatory mechanism of the thyroid. It is believed that this is regulated by an intrathyroidal iodinated inhibitor, but no direct evidence exists. At present, its theoretical action to suppress T/S (I^-) ratio (thyroidal/serum) is the only proposed mechanism to explain the escape from the Wolff-Chaikoff effect.

Iodoamino acid synthesis: During acute administration of iodide, there is an inhibition of thyroidal organic iodinations in response to a marked elevation of plasma iodide (Wolff-Chaikoff effect). As can be seen in Figure 5, from Wolff and Chaikoff experiments (22), as long as plasma iodide remained at the 20-35 µg/dl organic binding was blocked. Organification began to occur below this level.



Changes in plasma and thyroid iodine with time, following the injection of 100 µg of iodide in rats. γ, µg.

figure 5

In addition, there is a qualitative alteration of hormonal biosynthesis. During the Wolff-Chaikoff block, the small proportions of organic iodide formed were devoid of iodothyronines and contained an abnormal preponderance of monoiodotyrosine (MIT) over diiodothyrosine (DIT).

If smaller amounts of iodide capable of increasing plasma iodides moderately are administered to rats (but insufficient to cause acute inhibition of organic binding of thyroid iodide) one can see two phases of response. With small amounts (up to 25 to 50 µg), the percentage uptake, organification, and incorporation into iodoamino acids are unaltered (23). The total quantity of iodine accumulated and incorporated into MIT and DIT and iodothyronines increased proportionally to the dose of iodine administered. In the second phase of administration of larger quantities (above 50 or 100 µg), increasing doses led to progressively severe (1) decreased ^{131}I uptake, (2) decrease in proportionate organification of thyroid iodide, (3) decrease in proportion of DIT and iodothyronines to MIT, and (4) decrease in the absolute rate of organic iodinations and iodothyronine synthesis. These changes are classic sequelae of an inhibition of the organification mechanism.

These results enable us to draw two conclusions: (1) the thyroid appears unable to prevent an acute increase in the formation of active hormones in response to moderate doses of iodide; and (2) the Wolff-Chaikoff effect should be defined, not in terms of the quantity of organic iodine formed, but as the entire phase of iodine metabolism in which iodination decreases in response to increasing doses of iodide.

Chronic Administration of Iodide: Wolff (24) showed that the effect of iodide is transient and lasts for only 26 hours in spite of continuous administration of iodides. This is the so-called escape from the Wolff-Chaikoff effect. The escape may occur through a modification of either iodide transport or organic binding as postulated by Braverman and Ingbar (25).

However, rats given a diet supplemented with large doses of iodide chronically showed evidence of a mild biosynthetic defect similar to the acute administration of iodide and the escape can be overcome partially by very large doses of iodide (26). The development of iodide-induced goiter and hypothyroidism is very similar to the acute Wolff-Chaikoff effect. No clear explanation exists as to why only some patients do not escape from the block and develop the goiter and/or hypothyroidism. For a more extensive review of the effects of iodine, I refer the reader to two excellent reviews (5,21).

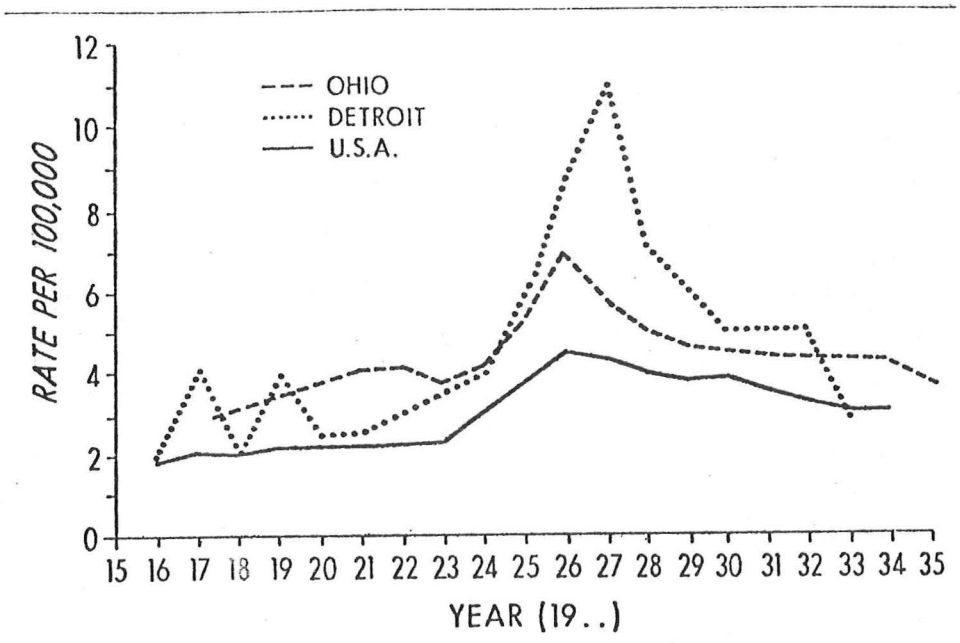
Iodine-Induced Hyperthyroidism: Coindet (2) in 1821 was the first to recognize that iodine could induce hyperthyroidism many years before Graves or Basedow. This syndrome is usually called Jodbasedow--Jod meaning iodine, and Basedow's disease is the non-English term utilized for Graves' disease.

When we talk about Jodbasedow, we refer to cases in which clear cut hyperthyroidism is present clinically and with supporting laboratory evidence. Jodbasedow's accounts for an unknown proportion of cases of hyperthyroidism. The case presented at the beginning could very well represent a case of it. However, as I will discuss later, this case is far from clear.

Iodine supplementation of diet fell in disrepute soon after it was introduced by Coindet, and for about a hundred years it was not utilized. In the second decade of this century O. P. Kimball, then a medical student, attended a lecture by Marine, whose interest was the study of iodine deficiency goiters in dogs, and was struck by the fact that the cause of endemic goiter was known and yet nothing was being done to prevent it. He used his influence with the Akron school system and initiated a program of iodine supplementation which caused a marked decrease in the incidence of goiter among participants (27). A few years later, iodine supplementation of salt was a well-accepted practice in this country.

In 1926-28 there was a sharp rise in the incidence of hyperthyroidism in the Midwest as noted by McClure at Henry Ford Hospital in Detroit, Plummer in the Mayo Clinic, and Crile in the Cleveland Clinic. Mortality figures are shown in Figure 6.

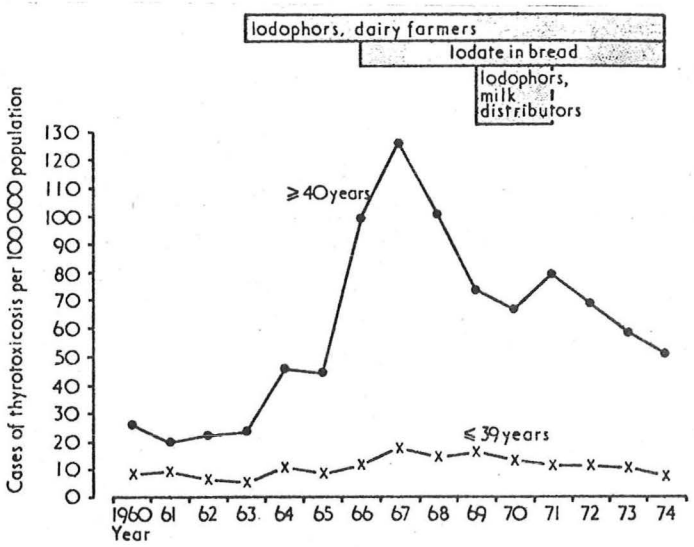
figure 6



Mortality from exophthalmic goiter, 1915 to 1935.

Immediately, iodide was blamed for this increase in the morbidity and mortality. The controversy continued for years, but somehow the epidemic subsided in spite of no change in the iodide consumption. The exact cause of the increased incidence of hyperthyroidism or its disappearance is far from clear.

Another epidemic was observed in Tasmania, where a relatively low iodine intake was common before 1964. The epidemic started in 1964 and reached peak levels in 1967. In an initial report (28), it was noted that iodates had been added to bread, as explained before, and was felt to be the cause of increased incidence of hyperthyroidism. However, the epidemic had actually started in 1964--that is, before iodate supplementation of bread was introduced. It was discovered that in 1963 iodophores had been introduced by dairy farmers (9) for sterilization of udders, and the concentration of iodides in milk increased considerably. The incidence is shown in Figure 7.



Age-specific incidence of thyrotoxicosis in northern Tasmania 1960-74. Bars indicate duration, but not magnitude, of various factors adding to dietary iodine.

figure 7

As can be noted, the increased morbidity occurred only in subjects older than 40 years old--the importance of which may be seen later.

Other sources of iodide have also been associated with Jodbasedow's--i.e., pyelography (29), cholecystogram (30), ingestion of kelp (31), and a variety of iodinated compounds (32).

Most cases have been reported to follow iodine supplementation in the diet of patients in areas of iodine deficiency. Ek found an incidence of 7% in euthyroid patients who were given 10 mg of KI daily for two weeks (33), and he attributes the hyperthyroidism as the response of a stimulated gland lacking iodine after the administration of iodides, producing a rapid iodination of iodine-poor thyroglobulin and synthesis and release of T_4 and T_3. However, there have been reports from areas of iodine sufficiency--such as Boston (34)--of patients with multinodular goiter, where the above would not be the case.

Thyrotoxicosis can follow the administration of small doses (35) to patients with autonomous nodular or large doses of iodine (32) to patients with normal thyroids. It should be emphasized again that both reports come from areas where iodide intake is relatively low.

In the cases of abnormal glands (33,34,35), it is feasible that the glands had been the seat of one or more autonomous functioning nodules. Here in the absence of TSH dependency, ingestion of excess iodine may have permitted synthesis and release of quantities of hormones in excess of those possible at ambient iodine intake. We should remember, as outlined in the previous section, that administration of a small to moderate excess of iodine is associated with increased

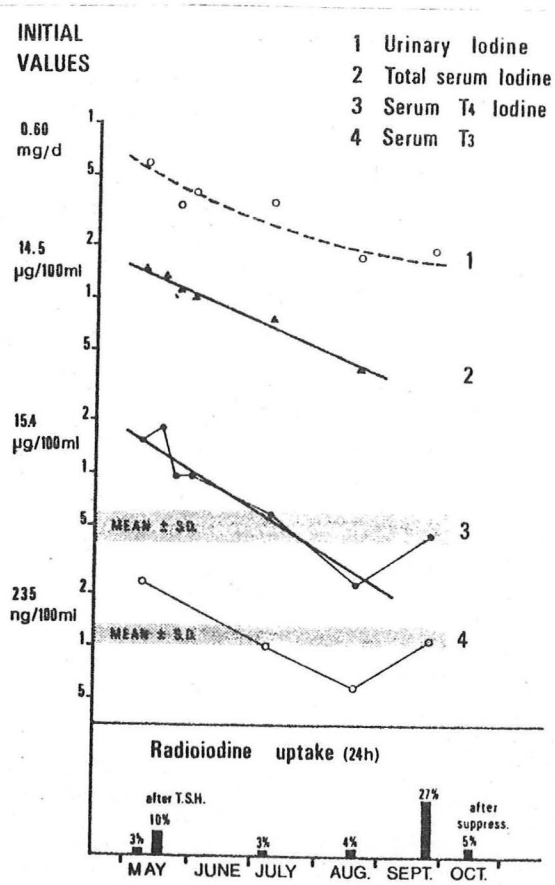
total uptake by the gland, organification, and synthesis of iodothyronines and part of the regulation is dependent on decreasing TSH as a response to this increased secretion, resulting in a new regulation level. However, autonomous tissue will not be regulated by TSH and could conceivably explain hyperthyroidism. It is significant that most patients are in the older category. The incidence of goiter is much greater, especially goiter of the multinodular type.

Iodine excess inducing hyperthyroidism in patients with normal thyroids (32) is somewhat more difficult to explain. The features of the disease are:

(a) development of thyrotoxicosis while an excess of iodine was present for at least one month;
(b) the lack of any earlier recognizable thyroid disorder;
(c) a moderate diffuse goiter recognized when thyrotoxicosis was discovered;
(d) undetected ^{131}I uptake during the course of thyrotoxicosis which was stimulated by exogenous TSH;
(e) parallel regression of the goiter and spontaneous remission of the thyrotoxicosis;
(f) period of latent transitory hypothyroidism preceding recovery; and
(g) no detectable thyroid abnormality, including suppressibility, after remission.

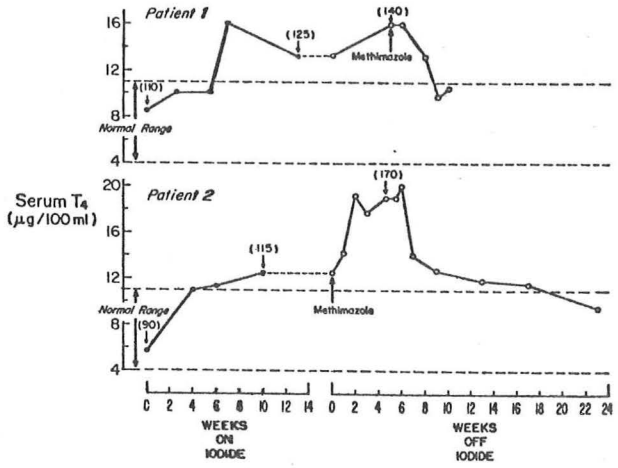
Figure 8 shows one such case. In contrast to patients with Grave's disease occurring in subjects who are exposed to excess iodides (especially for therapy), withdrawal of iodides usually worsens the disease.

figure 8



Consistent patterns of evolution of laboratory parameters from case 7 iodide-induced thyrotoxicosis. Note the first order decline of the data plotted in log scale and the temporary hypothyroidism before recovery.

The incidence of this disorder is not rare, Savoie *et al* having observed 11 cases in one year at their Paris clinic (32). The course of other patients with abnormal thyroid can be more prolonged as indicated in Figure 9.



Serum T_4 Concentrations in Two Patients with Nontoxic Goiter (Cases 1 and 2) in Whom Iodide-Induced Thyrotoxicosis Developed.
Numerical values in parentheses represent concentrations of T_3 in serum (in nanograms per 100 ml) at the times indicated.

figure 9

Therapy: Discontinuation of iodine is the most important feature. If the clinical picture requires it, administration of PTU should be done for a short period of time (2-3 months), after which reevaluation is necessary. If ^{131}I uptake becomes high and persistent (rare), then either ^{131}I therapy or radioiodine is necessary.

Iodide-Induced Elevation of T_4 in the Presence of Euthyroidism: By virtue of their high iodide content, radiographic contrast agents suppress thyroidal radioiodine uptake, elevate plasma protein-bound iodine (PBI); but, in general, it is felt that thyroid hormone secretion remains constant. In some cases, as shown in the previous section, thyrotoxicosis can develop.

In a prospective study Bürgi *et al* (36) examined the effect of the administration of three common contrast materials (oral cholecystography, IV cholangiogram, and IV urography) on a group of patients, some of whom had euthyroid goiter.

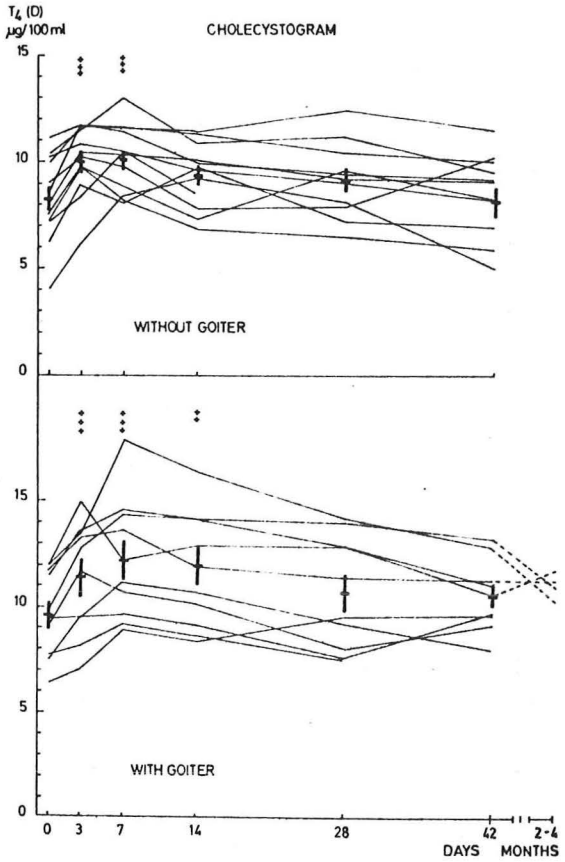
The course of non-hormonal iodine is shown in Table VII.

Non-hormonal iodine in serum, calculated as the difference between total and thyroxine iodine after radiographic examinations; before the radiographic examination the non-hormonal iodine was below the detection limit of the method (below 1 μg/100 ml)

	Non-hormonal iodine of serum Mean ± SEM (μg/100 ml)				
	Day 3	Day 7	Day 14	Day 28	Day 42
Oral cholecystogram with 2 g Na-iopanoate (N = 10)	2,171 ± 1,325	81 ± 28	15.9 ± 5	5.4 ± 1.8	2.0 ± 0.6
Intravenous cholangiogram with 4 g Na-ioglycamate + 6 g methyl-glucamine ioglycamate (N = 10)	2,627 ± 718	192 ± 69	42 ± 7	12 ± 2	12 ± 3
Intravenous urogram with 8.0 g Na-diatrizoate and 52.8 methyl-glucamine diatrizoate (N = 9)	34.3 ± 18.4	2.8 ± 1.6	1.5 ± 1.5	1.2 ± 1.2	1.8 ± .18

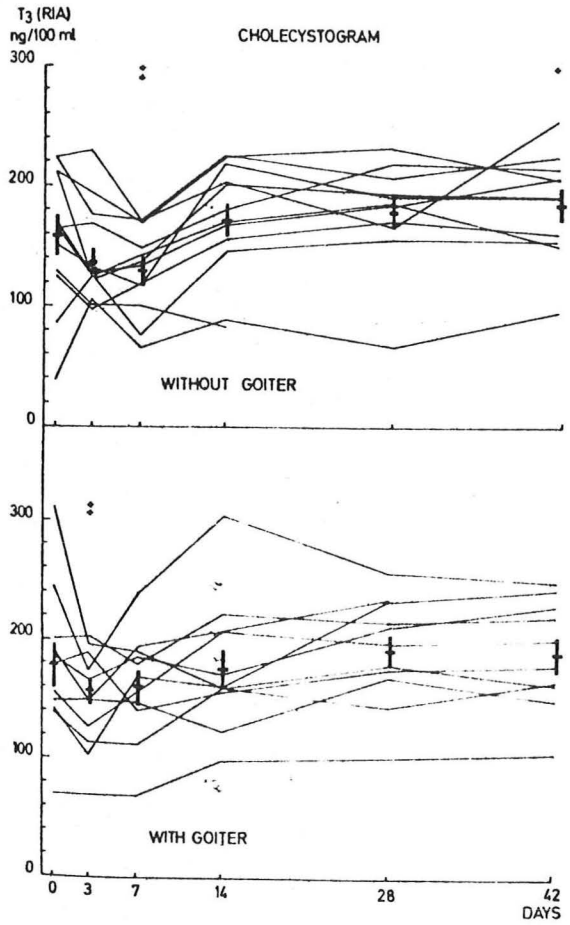
After IV cholangiography there were minor changes, with slight increase in T_4, T_3 or reverse T_3. Changes after IV urogram were similarly nonsignificant. After oral cholecystogram, serum T_4 rose consistently within 3 to 7 days in all 10 patients with and 11 patients without a goiter (Figure 10).

figure 10



Serum thyroxine in 10 patients with euthyroid goiter and in 12 patients without thyroid abnormality after oral cholecystography with Na-iopanoate. The thin lines connect the values of individual patients. The thick bars indicate the mean values with the standard errors. The abscissa gives the days after the cholecystography. The results of Student's *t* test for paired comparisons to the initial measurement are indicated on top: +, ++, and +++ mean $P < 0.05$, 0.01 and 0.001, respectively.

After 42 days the average T_4 had returned to normal in all but 2 patients who took an additional 2 months. T_3 showed the reverse picture. It dropped within 3 to 7 days by an average of 29 ng/dl and after 2 weeks began to return to normal (Figure 11). Reverse T_3 was measured in 7 patients who had shown the most clear cut changes. It increased from a mean of 72 ng/dl to 158 ng/dl after 3 days and correlated inversely with T_3 ($r = -0.946$). TSH levels doubled at 3 days and were above the normal level.



2. Serume triiodothyronine after oral cholecystography in the same patients as shown in Fig. 10.

figure 11

In a further study done on hypothyroid patients on replacement therapy, oral cholecystograms produced similar changes in T_3 and reverse T_3 levels. Similar results were obtained in normal volunteers given 0.2 mg of l-thyroxine daily.

As presented initially, our patient had an oral cholecystogram before he was seen and, as is very common in older individuals with cardiac disease, it can be very difficult to diagnose thyrotoxicosis when there is a worsening of the cardiac status in the presence of several potential causes for this and the patient has had an oral cholecystogram.

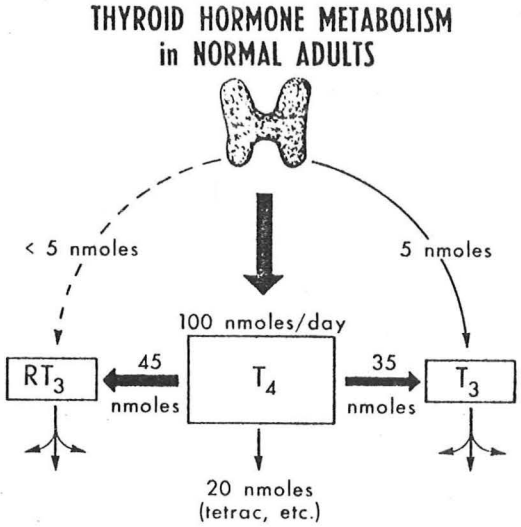
We have currently available both in our hospital and elsewhere in commercial laboratories, measurements of T_3. If T_3 levels are abnormally high, we can assume the patient has thyrotoxicosis and should be treated. If T_3 is completely normal, we should wait and reevaluate.

The above problem is very common in our experience, and knowledge of it can improve our handling of these cases. It has also been reported with amiodarone, an antiarrhythmic and antianginal agent used in Europe (38), that the effects are almost identical to those produced by the oral cholecystograms on the peripheral metabolism of thyroxine.

In a few paragraphs I want to review the main issue in the above discussion. The issue is that peripheral metabolism of thyroxine can be a significant factor in the action of thyroid hormones.

Thyroxine is the main iodothyronine secreted by the thyroid. T_3 and reverse T_3 are also secreted by the thyroid, but the ratio of secretion in the normal thyroid is T_4:T_3:rT_3 85:9:1 (37). Thyroxine (78 µg or 100 nM per day) is metabolized in the periphery following two general routes. Diiodination (80 nM) either by removal of one iodine from the outer ring (phenolic) yielding 3,5,3'-triiodothyronine (T_3) or removal of one iodine from the inner (tyrosyl) ring to yield 3,3',5'-triiodothyronine (r-T_3 or reverse T_3). Non-deiodinative pathways yield several compounds and probably the most important from a functional point of view is tetraiodothyroacetic acid (TETRAC) which retains about 1/3 to 1/4 activity.

The peripheral conversion of T_4 to T_3 has been demonstrated in the human to be the main source of T_3 (80-90%) with the rest coming from thyroidal secretion (39,40,41). Reverse T_3 is almost entirely a product of peripheral conversion from T_4 (Figure 12).



Schematic representation of major pathways of thyroxine metabolism in normal human adults. Rates are expressed in nmole $(24\ hr)^{-1}$ and ought to be considered as approximations, based upon available data. T_4, thyroxine; T_3, 3,4,3'-triiodothyronine; RT_3, 3,3'5'-triiodothyronine (reverse-T_3); tetrac, acetic-acid derivative of T_4.

figure 12

T_3 is several times more active than T4 and reverse T_3 has minimal if any activity (42,43). It is, therefore, important to note that peripheral conversion of thyroxine generates an active and an inactive metabolite. This might be subject to metabolic control with enhancement of one pathway at the expense of the other, resulting either with a more active or less active hormonal status. It has also been found that *in vitro* r-T_3 inhibits the conversion of T_4 to T_3, serving as an additional regulatory factor in the formation of T_3 (44). However, *in vivo* administration of r-T_3 shows no effect (43), which might indicate that either in normal physiology it plays no role in this respect or that *in situ* generation can actually produce the inhibition which cannot be reproduced when administered *in vivo*.

T_4 to T_3 Conversion in Clinical Conditions

Thyroid Disease: It appears that during hyperthyroidism T_3 production rate, which can be as much as 7 times normal (45), comes from secretion from the thyroid. However, T_4 to T_3 peripheral conversion might be slightly increased (40). In untreated hypothyroids, the conversion rate is about twice normal (47), but the absolute amount is small (45).

Age: Serum T_3, but not T_4, declines with age. This is due to decreased conversion rate of T4 to T_3 (40).

Neonates: Reverse T_3 is high and T_3 is low at birth; r-T_3 returns to normal around the tenth day (46). The significance is unknown.

Caloric Restriction: Fasting leads to a fall of T_3 within 24 hours with no change in T_4. This decline in T_3 is sensitive to carbohydrate in the diet (40). At the same time, there is a proportional increase in r-T_3 (48). This phenomenon is probably associated with the decrease BMR during starvation and the decrease in the rate of weight loss during starvation (49).

A similar phenomenon occurs in anorexia nervosa. These patients have normal T_4 and TSH but subnormal T_3 (50,51). Several subtle parameters of hypothyroidism are present in these patients--i.e., the urinary androsterone/etiocholanolone ratio is low in the range characteristic of hypothyroidism (51). Administration of T_3 resulted in a shift of the ratio to normal.

Other Systemic Illness: Serious illness is associated with low T_3 in a significant number of cases (52). Cirrhosis of the liver is also associated with decreased conversion of T_4 to T_3. Nomura (41) found a conversion rate of 15.6% ± 6.6 in 4 patients with advanced cirrhosis (normal = 35.7% ± 3.3). It is the liver that plays the most significant role in the conversion of T_4 to T_3.

Drugs: PTU (propylthiouracil) inhibits T_4 to T_3 conversion, and it is possible that its therapeutic effects as an antithyroidal agent might be a combination of inhibition of thyroxine synthesis in the thyroid and inhibition of the conversion of T_4 to T_3 in the periphery. This inhibition is not complete (53).

Acute dexamethasone administration causes a prompt fall of T_3 and elevation of r-T_3 (54).

Propranolol has also been reported to cause a decrease in T_3 and an increase in r-T_3 (55). However, I doubt that this effect is really significant since the drop of T_3 in hyperthyroid patients was only about 15%, changing T_3 levels from very high to almost as high.

The list of drugs will increase in the future, and their significance will become apparent after further studies are done and our ability to diagnose subclinical degrees of hypothyroidism improves.

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