THE IODINE METABOLISM IN EXOPHTHALMIC GOITER*

GEORGE M. CURTIS, M.D., AND ITALO D. PUPPEL, M.D.
COLUMBUS, OHIO
FROM THE DEPARTMENT OF RESEARCH SURGERY OF THE OHIO STATE UNIVERSITY, COLUMBUS, OHIO

IODINE and thyroid function are inseparably related. The thyroid gland is a principal storehouse for iodine. The thyroid hormone has a high iodine content. The utilization of iodine to form thyroid hormone is thus an integral part of thyroid activity. As a consequence the metabolism of iodine becomes of fundamental significance in the investigation of thyroid physiology, and of the changes in function incident to the development of thyroid disease. The use of iodine in the prevention of goiter has long been known. Since the contributions of Plummer, its use in the preoperative management of exophthalmic goiter has become common clinical knowledge.

Nevertheless, during the past decade newer facts have been added to the iodine story. It is established that iodine is constantly present in human blood. In what form it circulates is not yet clear, although presumably a part, at least, actually exists as thyroid hormone. There is a variable daily loss of iodine in the urine, feces and sweat. The level of the blood iodine fluctuates; likewise the daily excretion in the urine. These findings have gradually assumed clinical significance.

During the past eight years a group of us, including Davis, Cole, Phillips, Barron and Matthews, have investigated various phases of iodine metabolism in over 200 patients with exophthalmic goiter. For determining the minute amounts of iodine present in the blood and urine we have employed three methods: First, an adaptation of the von Fellenberg procedure which was developed by Davis.[1] Second, a similar basic ashing method which was further refined by Phillips.[2] Third, our present method is a closed, chromic acid oxidation procedure derived by Matthews[3] from the Leipert principles, which yields lower values for the blood iodine.

It is difficult to adequately condense the available material. However, further details, together with other tables and charts, are available in current publications.[4, 5, 6, 7] In the present communication we wish to present four features of the metabolism of iodine in exophthalmic goiter. These concern: (1) the iodine content of the goitrous thyroid gland, which is decreased; (2) the blood iodine, which is usually increased; (3) the urinary excretion of iodine, which is usually increased; and (4) the iodine balance, which reveals a depletion of the patient's usual reserve store of iodine.

In order better to understand the pathologic iodine metabolism which exophthalmic goiter presents, it is clarifying to consider its two principal features. Our studies[6] have clearly demonstrated a greatly increased mobilization of iodine with a subsequent depletion. This is comparable to the increased

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mobilization of calcium and the ensuing calcium depletion which occurs in hyperparathyroidism.

THE THYROID GLAND IODINE.—*The Thyroid Gland Iodine Is Decreased in Untreated Exophthalmic Goiter:* The normal iodine content of the human thyroid gland varies from 8 to 10 mg. The wet weight concentration varies around 40 mg. per cent, while the dry weight concentration ranges around 200 mg. per cent. It is significant that this iodine is contained principally in the colloid substance. Variations occur, physiologically, seasonally and geographically. Thus, the iodine content is lower during the winter months, and higher in persons living in coastal cities where the iodine intake is greater.

Since the original contributions of Baumann it has been known that the diffuse hyperplastic gland, characteristic of exophthalmic goiter, has a diminished iodine content. This observation has been repeatedly confirmed, and more recently by Lunde. It signifies iodine loss and is directly correlated with the loss of colloid substance from the more cellular, hyperplastic alveoli.

Thyroid iodine depletion may also ensue during the course of severe infectious diseases. It may be produced experimentally by the administration of the thyreotropic hormone.

THE BLOOD IODINE.—*The Blood Iodine Is Usually Increased in Untreated Exophthalmic Goiter:* Extensive clinical investigation, subsequent to the studies of Veil and Sturm, has established the value of the blood iodine as a measure of thyroid function. It is usually increased in patients presenting hyperthyroidism, and decreased in those with hypothyroidism. It has become a clinical aid in recognizing hyperthyroidism. In those unusual instances where it is not increased, it has been shown to have prognostic value. Its clinical significance has consequently become similar to that of the blood sugar in recognizing functional variations of the islets of Langerhans, or of the blood calcium in determining changes in parathyroid activity.

TABLE I

IODINE METABOLISM IN EXOPHTHALMIC GOITER

Case No.	Sex	Age	B.M.R.	Blood Iodine Micrograms %	Urinary Iodine Micrograms Daily	Days Observed
332556	F.	17	Plus 18	30.9	169	8
331377	F.	18	Plus 47	21.2	65	13
326974	F.	32	Plus 32	29.1	106	5
326035	M.	34	Plus 75	26.7	196	2
332609	F.	35	Plus 95	13.5	159	7
326431	F.	35	Plus 50	35.0	111	2
331567	M.	38	Plus 50	22.7	105	7
335185	M.	39	Plus 44	18.0	146	4
335167	M.	48	Plus 53	20.8	310	3
335262	F.	51	Plus 109	27.5	133	1
335262	F.	51	Plus 93	30.6	230	3
Averages			Plus 69	26.0	157	5
Normal Averages			Plus Minus 10	12.0	51	18

The majority of patients with untreated exophthalmic goiter present an increased blood iodine (Tables I and II). Results obtained from the earlier methods of analysis yielded higher values for the blood iodine than are now found (Table I). These older methods, however, revealed that the blood iodine averaged more than twice normal in patients with exophthalmic goiter. Newer methods reveal a lower normal blood iodine (Table II). Nevertheless, they also show that it is increased to more than twice normal in exophthalmic goiter. The proportional increase in exophthalmic goiter is similar by either method.

TABLE II

THE IODINE BALANCE IN EXOPHTHALMIC GOITER

As Compared with Normal Individuals and Patients with Nodular Goiter

Type of Goiter	Number of Patients	Total days of Investigation	Average B.M.R. %	Average Blood Iodine Mcg.* %	Average Daily Output				Average Daily Intake Mcg.	Average Daily Balance Mcg.
					Urine Mcg.	Feces Mcg.	Sweat Mcg.	Total Mcg.		
1. None: normal persons	3	24	Minus 7	4.3	51	11	9	71	29	−42
2. Nontoxic nodular....	2	18	Minus 8	3.0	40	10	10	60	25	−35
3. Toxic nodular.....	2	15	Plus 28	8.5	107	50	13	170	39	−131
4. Exophthalmic.....	3	33	Plus 40	9.0	68	55	15	138	29	−109

* Mcg. denotes a microgram (0.001 mg.).

The nature of this increased blood iodine is not clear. It appears to be principally in the alcohol insoluble fraction, which has been designated "organic." Presumably it represents a greater circulation of the high iodine-containing thyroid hormone or of its metabolic products.

There is no direct parallelism between the blood iodine, the urinary excretion of iodine and the basal metabolic rate in patients with exophthalmic goiter (Table I). As a rule, however, all three are increased. Each of the three, however, dependent upon the phase of the disease, may lie within the normal range. Thus, in a late stage of untreated exophthalmic goiter we would ordinarily expect a resultant pronounced iodine depletion to have occurred. This should have an effect upon the blood and urinary iodine.

Iodine tolerance tests have been applied to the diagnosis of exophthalmic goiter. These depend upon the rate at which the injected iodine is removed from the blood stream, as shown by subsequent blood iodine determinations. The progressive iodine depletion of exophthalmic goiter is a significant factor in the evaluation of these procedures. The depleted tissues and particularly the depleted thyroid gland appear to remove more rapidly the increased circulating iodine.

The prognostic value of a low blood iodine in patients with exophthalmic goiter is brought out by the studies of Perkin and Hurxthal.[8] It has been our experience that the increased blood iodine usually found in exophthalmic goiter returns to a normal range subsequent to an adequate thyroidectomy. They have shown in addition that these patients present no evidence of recurrence. On the other hand, in those patients with a normal blood iodine pre-

operatively, they even find a postoperative increase, and point out an increased tendency to recurrence.

THE URINARY EXCRETION OF IODINE.—*The Urinary Excretion of Iodine Is Usually Increased in Exophthalmic Goiter:*[5] Iodine is a normal constituent in human urine. The daily excretion fluctuates, however, and appears to depend principally upon the variable food intake, which is inconstant. When a constant, monotonous food regimen is maintained, the daily urinary loss is more uniform.[9] The age of the individual appears to be a factor. Variable physiologic states, such as menstruation, have a demonstrable effect. The amount of iodine excreted in the urine varies geographically.[10] It is low in those regions where goiter is endemic, as in central Ohio, where it averages 51 micrograms daily. It is increased in localities which are relatively goiter-free, as in New Orleans, where it averages 117 micrograms daily. These latter observations have a definite bearing upon iodine deficiency as related to the incidence of goiter.

The majority of patients with exophthalmic goiter reveal an increased loss of iodine in the urine (Table I). Thus 13 normal persons excreted from 36 to 78 micrograms daily, and averaged 51.[10] In contrast, 24 patients with exophthalmic goiter lost from 46 to 357 micrograms daily in the urine, and averaged 147, which is approximately three times greater than normal.[5]

It is suspected that this increased urinary loss of iodine originates in an increased breakdown of the high iodine-containing thyroid hormone. However, this may not prove to be the only factor since other tissue iodine may play a part. To be correlated with this are the increased blood iodine and the loss of iodine from the hyperplastic thyroid.

The precise form in which iodine is excreted in the urine has not been determined.[11] It does not appear to be in the form of thyroxin, either chemically or biologically, but rather in a more simple compound. Solution of this particular problem is important.

We have elsewhere presented extensive data of the urinary excretion of iodine of normal individuals,[10] of patients with exophthalmic goiter,[5] and of patients with other thyroid diseases.[9] From these studies it appears that the urinary iodine is of similar significance in disturbances of thyroid function as is the urinary calcium in parathyroid disease.

Nevertheless, in extending these studies it soon became apparent that the blood or urinary iodine represented but fractions of the entire process of iodine metabolism. The blood iodine, normally less than 1 mg., presented the amount in circulation, although a part of this presumably existed as thyroid hormone or its iodine-containing split products. Another part presumably represented the iodine of nutrition.

Moreover, determinations of the urinary iodine did not present sufficient evidence concerning the intake, utilization or storage of iodine. Therefore, it became increasingly evident that the *iodine balance* should be determined. This meant the institution of carefully controlled hospital conditions for measuring the intake of iodine in the food, water and air, as well as its excretion

in the urine, feces, sweat and expired air. The difference between the determined amount of intake and output would then yield a *balance*. In case storage were occurring, this would be positive. With an excretory loss greater than the intake, it would be negative.

THE IODINE BALANCE.—*Exophthalmic Goiter Presents an Increased Negative Iodine Balance:*[6] It is of advantage to understand something of the normal variables and fluctuations of the iodine balance, in normal individuals as well as in patients with nontoxic goiter, before reviewing the abnormality presented by exophthalmic goiter. Detailed studies of these basic considerations are presented elsewhere.[6, 7, 12]

Normal persons maintained on a low iodine intake reveal a low negative iodine balance (Figs. 1 and 2, Table II). They appear to require a certain amount of intake iodine daily to remain in balance. Thus three normal individuals with a decreased intake of 29 micrograms of iodine daily excreted 71, resulting in a daily negative balance of 42 micrograms. Fifty-one micrograms, or 72 per cent of the iodine, was lost in the urine. Eleven micrograms, or 15 per cent, was excreted in the feces, while nine micrograms daily, or 13 per cent, was lost in the sweat (Table II).

It is possible to increase the intake iodine by adding to the diet milk with an increased iodine content. This has been prepared by giving dairy herds feeds containing supplemental iodine.[13] When maintained on such a diet, containing adequate iodine, normal persons remain in positive balance, and may even store considerable amounts of iodine (Chart 1). Too, this storage may be increased by the addition of potassium iodide to their diet (Chart 1).

During a period of starvation the negative balance is not only maintained, but may even increase somewhat (Chart 2). This further indicates a constant daily requirement of iodine, a part of which is presumably to be used in the formation of the high iodine-containing thyroid hormone.

The iodine balance of patients with nontoxic nodular goiter resembles that of normal persons, with possibly an even greater tendency to storage.[7] It is quite dissimilar to that of exophthalmic goiter patients, since the increased mobilization of iodine is lacking, as well as the subsequent depletion (Table II).

Two patients with nontoxic nodular goiter, maintained on a low iodine intake over a total period of 18 days, showed an average negative iodine balance which was within physiologic limits (Table II). The intake iodine averaged 25 micrograms daily while the output averaged 60 micrograms, resulting in a daily negative balance of 35 micrograms. The greatest excretion was in the urine, averaging 67 per cent. Seventeen per cent was excreted in the feces and 16 per cent was lost in the sweat.

One patient (Chart 3) even showed a greater retention of iodine than normal persons similarly controlled (Table II). This tendency of patients with nontoxic nodular goiter to store iodine, rather than to excrete it, has been noted by Scheffer and v. Megay.[14]

Elsewhere, we have presented extensive data which reveal the great dis-

turbance of iodine metabolism found in exophthalmic goiter.[6] The increased mobilization of iodine is shown in the rise of the blood iodine, and by the

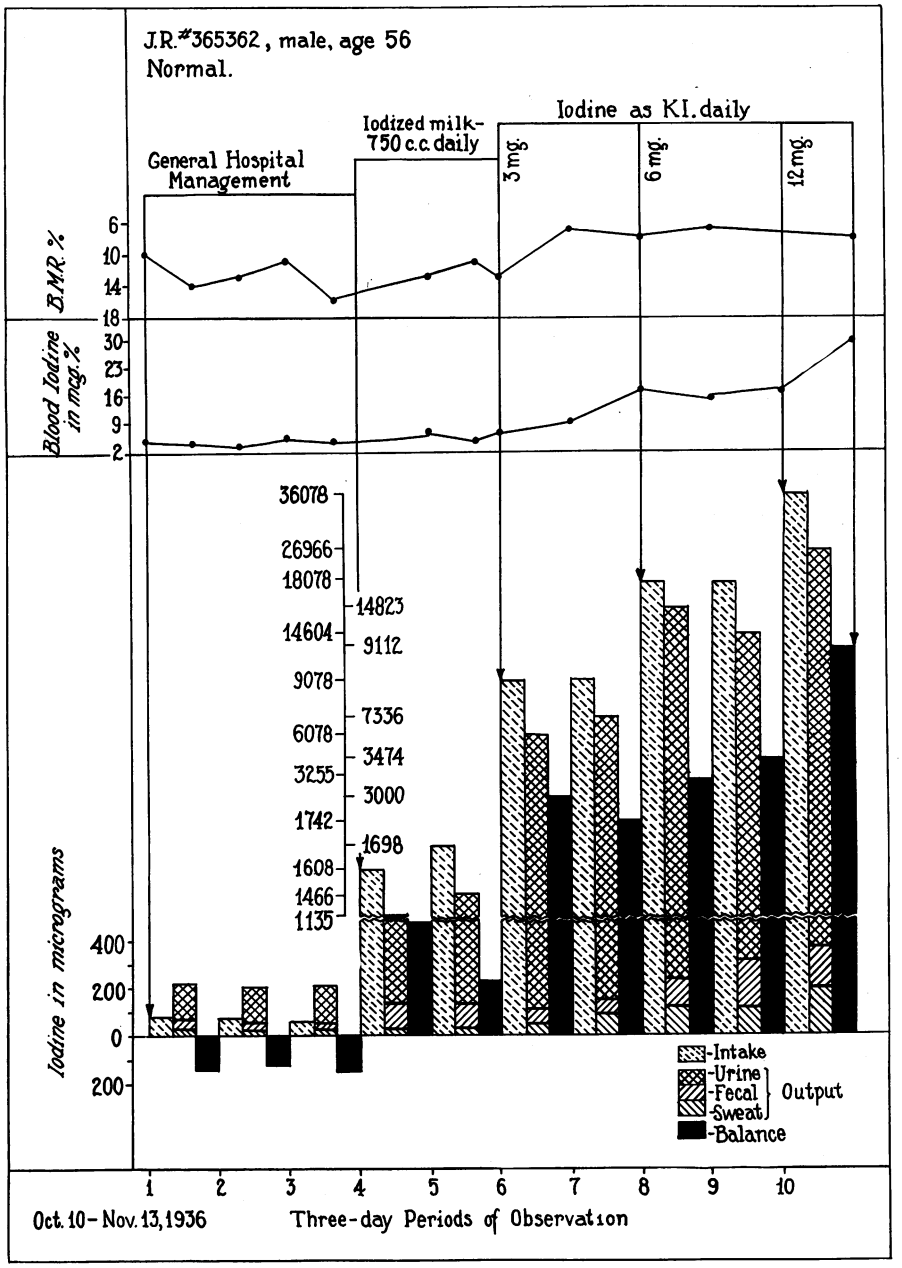

CHART 1.—The iodine balance in a normal individual. Note the negative iodine balance on a low iodine intake and the effect of increasing the intake.

greater excretion of iodine in the urine, feces and sweat. Moreover, subsequent to this increased mobilization, iodine depletion ensues. This is revealed

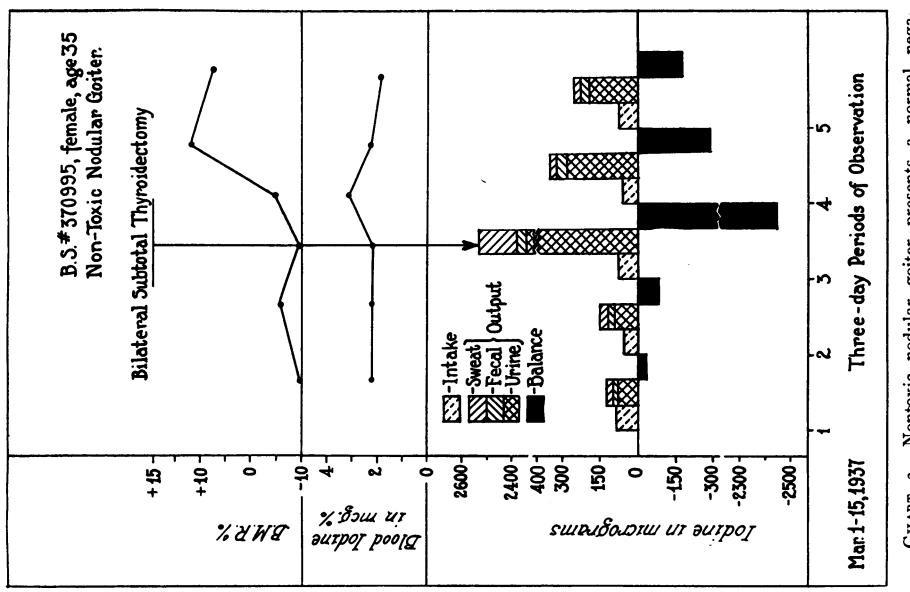

CHART 3.—Nontoxic nodular goiter presents a normal negative iodine balance on a low iodine intake. Note the effect of thyroidectomy.

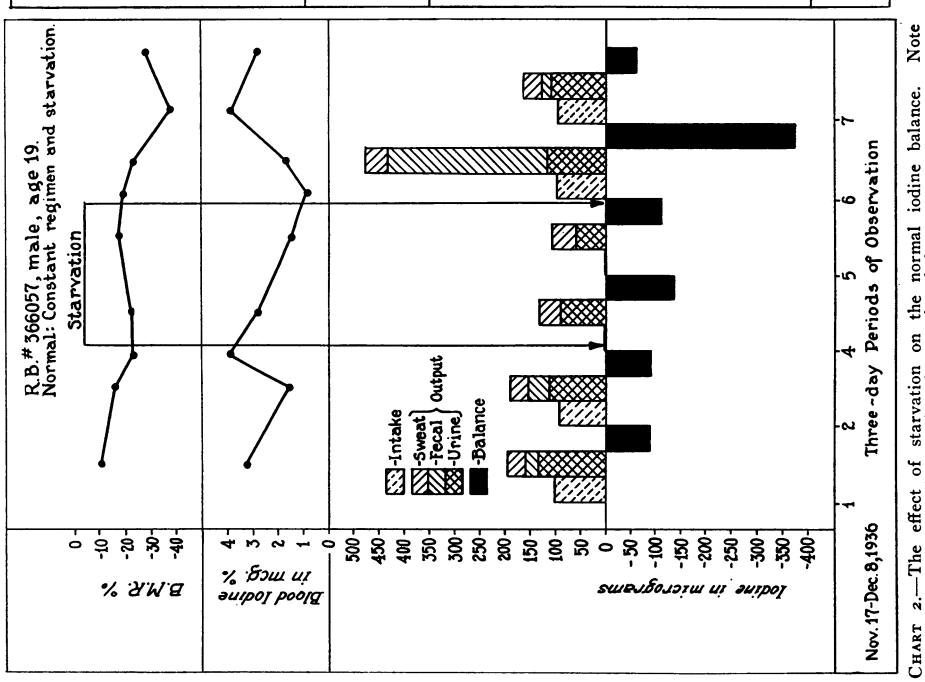

CHART 2.—The effect of starvation on the normal iodine balance. Note the continued negative balance.

in the decrease in the thyroid gland iodine and in the greatly increased negative iodine balance.

Patients with exophthalmic goiter, maintained on a low iodine intake, lose from two to three times the amount of iodine lost by normal persons or by patients with nontoxic nodular goiter similarly controlled (Table II). Thus, the intake of three exophthalmic goiter patients averaged also 29 micrograms

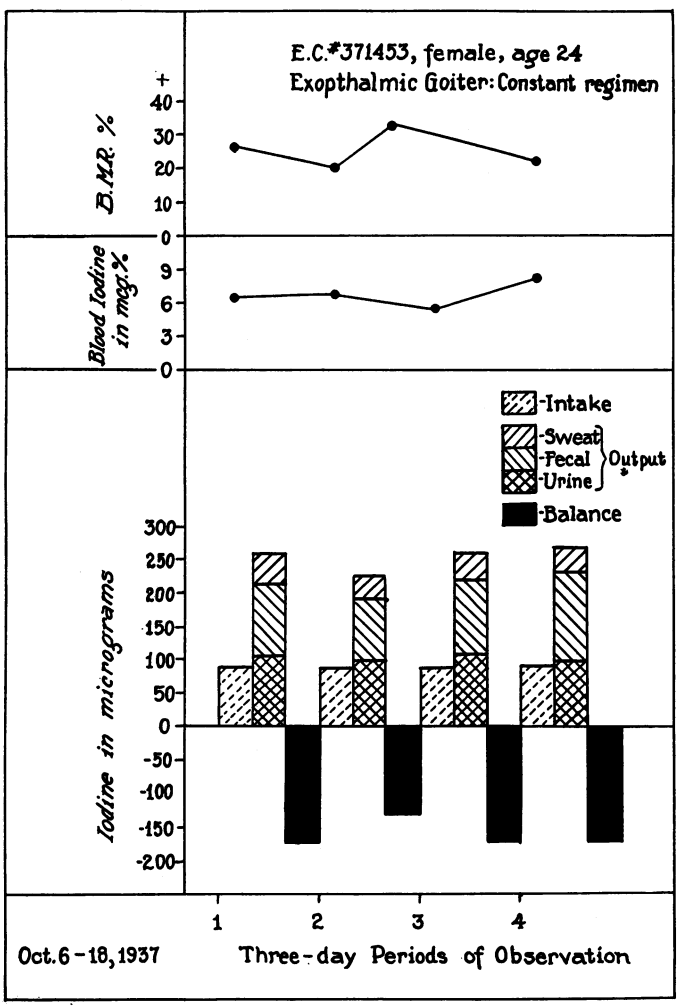

CHART 4.—The increased negative iodine balance of exophthalmic goiter. Note the increased fecal excretion over normal.

daily, while the daily loss was 138 micrograms. This resulted in a daily increased negative iodine balance of 109 micrograms. The greatest excretion of iodine was by way of the urine, averaging 49 per cent. Forty per cent was lost in the feces and 11 per cent in the sweat. The greatly increased fecal loss over normal is shown in Chart 4.

It would consequently appear that untreated exophthalmic goiter is characterized by a tendency to lose iodine. Thus, two patients have been maintained on an iodine intake sufficient to keep a normal individual in positive balance, and to allow for some storage. Both, however, showed a continued negative iodine balance.[6, 12]

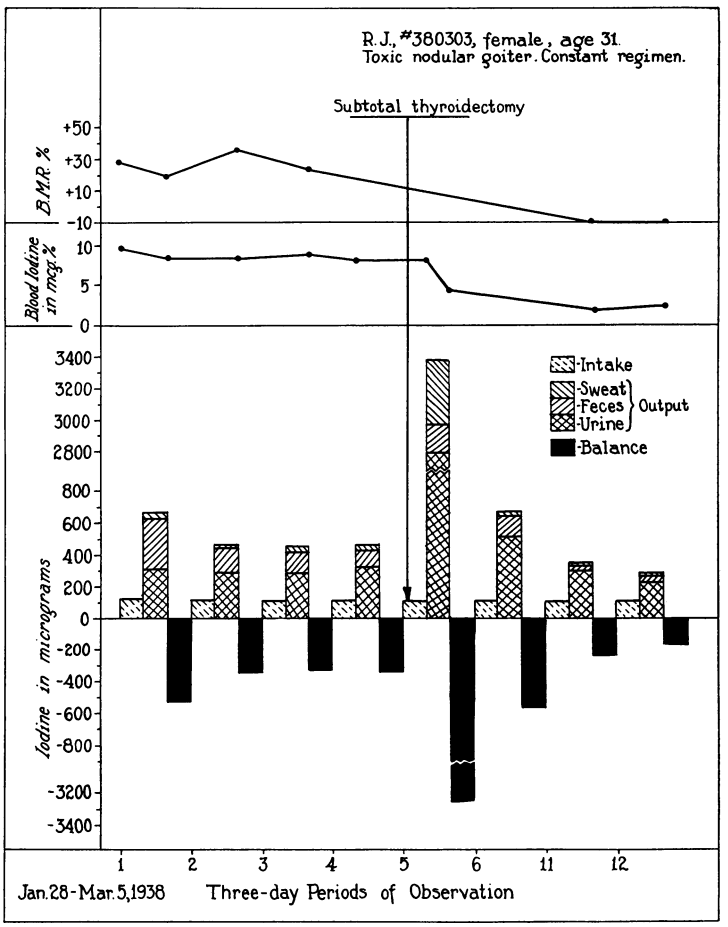

CHART 5.—The increased negative iodine balance of toxic nodular goiter. Note the increased urinary excretion over normal. Note the effect of thyroidectomy.

Nevertheless, *greatly* increasing the intake results in an immediate retention of iodine. Moreover, the resultant positive balance becomes considerably greater than normal (compare Chart 6 of reference 6 with this Chart 1). The diffuse hyperplastic goiter, progressively depleted of iodine during the previous course of the disease, may then rapidly store more than 100 mg. Presumably there is also a lesser repletion of other depleted tissues. This increased storage is maintained for a varying period of time, depending upon the extent to which previous depletion had occurred. However, with the

cessation of the daily administration of 10 mg. of iodine, the former negative balance is soon reestablished, while the stored iodine is then progressively lost.[6] It appears difficult for a patient with untreated exophthalmic goiter to store or to hold iodine.

The true nature of this increased negative iodine balance of exophthalmic goiter needs further investigation. Other tissue-iodine than that of the thyroid gland may play a part. Too, it is possible that iodine has another function in human metabolism besides furnishing two-thirds of the active thyroid hormone, thyroxin. Presumably, however, the increased iodine loss results from an increased secretion and consumption of thyroid hormone with the consequent greater mobilization and excretion of iodine. This problem has been further discussed elsewhere.[6]

Several factors may influence the increased loss of iodine in exophthalmic goiter. On medical management alone, including hospital control with bed rest, a high caloric diet and calcium therapy, one patient showed a remission of the clinical symptoms, and a decrease of the basal metabolic rate to within normal range. There was a corresponding decrease in the excretion of iodine through the various channels, while the iodine balance returned to within normal limits during the sixth three-day period.[6]

Subsequent to adequate thyroidectomy we have found that the disturbed iodine metabolism of exophthalmic goiter returns to normal.[6] The blood iodine decreases. There ensues a lessened urinary excretion of iodine, while the fecal and sweat loss are also diminished. The increased negative balance decreases, and eventually comes to lie within the normal range. This may ensue as early as the sixth postoperative day.

In conclusion, we wish to compare the disturbed iodine metabolism of toxic nodular goiter with that of exophthalmic goiter. This will be done briefly, since it has been considered *in extenso* elsewhere.[7] In both, the blood iodine is usually increased; however, in average more so in exophthalmic goiter.[4] In both, the urinary iodine is usually increased; however, more so in toxic nodular goiter.[5] Both present an increased fecal and sweat loss, greater in exophthalmic goiter (Table II). In both, the B.M.R. is usually increased, to a higher range in exophthalmic goiter.

Toxic nodular goiter is thus likewise characterized by an increased negative iodine balance,[7] which is greater than that of exophthalmic goiter. Too, this also returns to a normal range subsequent to an adequate thyroidectomy (Chart 5).[7]

A summary of our balance studies on ten patients[6, 7] is presented in Table II. This reveals, by comparison, the increased negative iodine balance of exophthalmic goiter.[6] However, patients with toxic nodular goiter present an even greater negative iodine balance,[7] due to a greater urinary excretion.[5] Nevertheless, the excretion of iodine in the feces and sweat is greater in exophthalmic goiter.[6] These findings have a direct bearing upon the comparative differences between these two forms of hyperthyroidism.

CONCLUSIONS

Exophthalmic goiter is characterized by an *increased mobilization of iodine.* This is revealed in the elevated blood iodine, and by the increased loss of iodine in the urine, feces and sweat. As a consequence of this increased mobilization, *iodine depletion* ensues. This is demonstrated by the decreased thyroid gland iodine and in the negative iodine balance, which is greatly increased over normal. Exophthalmic goiter thus presents a profound disturbance of iodine metabolism.

There is a striking similarity between the disturbed iodine metabolism of hyperthyroidism and the disturbed calcium metabolism of hyperparathyroidism.

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DISCUSSION.—DR. FRANK H. LAHEY (Boston, Mass.): This problem of iodine metabolism is a very interesting one and we have always been interested in Doctor Curtis' investigations. We have carried on some investigations during the past three years in association with Mr. Perkin, a biochemist, and have learned some very interesting and valuable things.

When one realizes the variation in tissue iodine content, it becomes evident, at once, what an important part the thyroid plays in this iodine problem. For instance, Mr. Perkin has made iodine determinations of 10 Gm. of wet tissue and when the 10 Gm. of brain or any of the remainder of the tissue is approximately 23 micrograms, not infrequently there will be 3,500 micrograms of

iodine in the thyroid. That evidences what a part the thyroid plays in iodine metabolism.

We have tried, for a long time, various methods of demonstrating circulating thyroxin, such as the effect of the serum of the patient with hyperthyroidism upon an electrocardiogram of the six, seven, eight or nine day chicken embryo heart, and we have never been able to demonstrate it. We have been interested in blood iodine, of course, as a possible indicator of the amount of thyroxin in the blood stream because 65 per cent of thyroxin is iodine. The iodine fraction is separable and when separated, thyroxin, of course, no longer elevates metabolism.

It has seemed to us, probably in the beginning before we had some of our disappointments, that when a patient had a high blood iodine preoperatively and low postoperatively, which correlates quite accurately with the basal metabolism, that this was probably evidence of the fact that blood iodine is circulating thyroxin, but we have found that 30 per cent of our cases do not have a high preoperative and low postoperative blood iodine. They did always, however, have a high preoperative metabolism. Thirty per cent of our cases have had a blood iodine preoperatively below normal or normal, which postoperatively went above normal and did not come back to normal for six months. Then we found ourselves a little confused.

I would like to present on the other hand, certain interpretations which have proven of great value to us. I would be very much interested to hear from Doctor Curtis what happens to the urinary iodines in these patients who have low blood iodines in the presence of high metabolism.

We have correlated the basal metabolism and blood iodine preoperatively in 110 proven cases of hyperthyroidism, and have charted the course of both of these figures postoperatively at the end of three months and at the end of six months. In these cases, the average basal metabolism was plus 45 and the average blood iodine 22.8 micrograms, normal in this region being 10 micrograms. At the end of three months the basal metabolism had come to normal, the blood iodine to 10 micrograms, and at the end of six months the basal metabolism was at normal and the blood iodine 7.5 micrograms. It is of interest in this group of cases, in which there is the typical preoperative elevation of blood iodine and return to normal correlated with basal metabolism, to note what the percentage of recurrent hyperthyroidism in this group is. We are particularly interested in this because by means of blood iodine we can, with quite definite certainty, establish in what cases recurrence is most likely to occur. In this typical group with preoperatively elevated blood iodines, there is but one-half of 1 per cent recurrent hyperthyroidism. This type of preoperative elevation of blood iodine correlated with basal metabolism both preoperatively and in postoperative drop, represents 70 per cent of all the cases.

On the other hand, in 30 per cent of the cases, there is quite a different picture. The preoperative metabolism is high but the preoperative blood iodine is not only not elevated, but is below normal. At the end of three months the preoperative metabolism has come to normal, but at this time the blood iodine, previously below normal, has now risen to above normal. At the end of six months the metabolism remains normal, and at that time the blood iodine has become normal. It is in this group of cases that one must look for the recurrent hyperthyroidism because 22 per cent of these cases show a recurrence of hyperthyroidism.

When one realizes that our incidence of recurrent hyperthyroidism has been but 3 per cent and that 22 per cent of this group show recurrence, it is

obvious that it is in this group that very radical removals of the thyroid must be performed.

There is another interesting clinical observation in connection with the patients who have low blood iodines and high metabolisms, and that is that in the group having high metabolisms and high blood iodines, but 17 per cent required multiple stages, while in the group having high metabolisms but low blood iodines, 45 per cent required multiple stage operations. It is, therefore, as important to realize that not only does this atypical group represent the patients in whom recurrence is most likely to occur, but also the group in which mortality is most likely to occur and in which cautious operative approach must be undertaken.

Another interesting development which has been demonstrated by Mr. Perkin in connection with blood iodine is that if one makes a scatter chart of patients' blood iodine in relation to the length of time which they have had the disease, it will be found that in a predominating majority of cases, the blood iodine will be elevated above normal when the disease has been present for a year or less but as soon as the disease has been present for a year or more, a predominating majority of the blood iodine determinations will be found to be below normal. This phenomenon is undoubtedly related to exhaustion of the patient's store of body iodine when the disease has existed a sufficient length of time.

As regards Doctor Smith's paper, we think we will probably always perform thyroidectomy more or less by rule of thumb. It will never be possible, I believe, due to the anatomic variations, the way the lobes go behind the trachea and in the groove between the trachea and the esophagus, to make very accurate decisions about the percentage removed.

There are some very valuable points, however, in this connection, that is, how much thyroid to remove in relation to the patient's reaction to iodine. Doctor Cattell, some years ago, reduced 400 thyroids, surgically removed, to a powder and determined the milligrams of iodine per gram of dried gland, correlating this with the histologic picture, that is, the degree of iodine involution. He found that 90 per cent of the thyroid gland would involute and about 10 per cent would not. He found that the very severe cases were those with small thyroids which were very vascular, very soft and did not involute. You can tell pretty well clinically which patient has involuted and which patient has not, and you can tell very definitely at the operating table which patient has involuted and which patient has not.

The patient whose thyroid gland has involuted under iodine will develop firmness in the thyroid gland, and they will show a drop in metabolism, a gain in weight and a drop in pulse rate. The patients who do not show an involution of their thyroid glands do not show these improvements; and at the operating table when you cut the thyroid gland across, the one that is involuted is pale, firm and nonvascular; the one that has not involuted is red, cellular and vacular. It is in the very small, red, vascular cellular gland that has not involuted that radical removals must be performed if one wishes to prevent recurrence of the hyperthyroidism; and it is in the glands that are pale, firm and nonvascular, and the patients who show marked drops in metabolism, gain in weight, drop in pulse rate after the administration of Lugol's solution, that less radical removals of thyroid tissue need be performed.

DR. GEORGE M. CURTIS (closing): We have also observed low blood iodines in patients with exophthalmic goiter; however, our incidence is not so high as that which Doctor Lahey reports. Too, we have noted a low

urinary excretion of iodine in certain patients with exophthalmic goiter. That is also unusual; I should estimate less than 20 per cent.

Doctor Lahey's "scatter chart" has shown a general decrease in the blood iodine as the disease progresses. On the basis of our studies, a part of which have been presented here, this might have been predicted, since the increased mobilization of iodine in exophthalmic goiter eventually leads to iodine depletion. The increased mobilization is shown in the increased blood iodine, and in the greater than normal iodine loss in the urine, feces and sweat. The resultant iodine depletion is demonstrated by the decreased thyroid gland iodine and particularly by the increased negative iodine balance. Patients with exophthalmic goiter thus progressively deplete themselves of iodine in a similar manner as patients with hyperparathyroidism deplete themselves of calcium.

If we could visualize the onset of exophthalmic goiter, it would appear to commence in a normal thyroid gland with a normal iodine content. Precisely what institutes the hyperplasia or what causes the alveoli progressively to lose colloid and consequently iodine, is not clear. Nevertheless, as the disease continues, depletion ensues and increases. Since Baumann's observations, in 1895, it has been known that the iodine store of the diffuse hyperplastic goiter becomes diminished.

By hypothesis, the "scatter chart" appears to present a similar story of progressive iodine depletion as reflected in the blood iodine. We would expect a similar change in the urinary excretion. The severity of the disease and its duration both modify the variable amount of iodine depletion. If this is severe and if resultant damage has followed, it may explain the tendency of patients with low blood iodines to have recurrence.