THE DIRECT ESTIMATION OF THE RATE OF THYROID HORMONE FORMATION IN MAN. THE EFFECT OF THE IODIDE ION ON THYROID IODINE UTILIZATION*

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THE interest of thyroidologists was recently aroused by the demonstration by Wolff and Chaikoff (1) that, with levels of serum iodide higher than 20 to 30 micrograms per cent, organic binding of iodine in the rat thyroid was inhibited. Extension of these observations to man was undertaken in view of the paradox thus presented, *i.e.*, that adequate iodide seemed to prevent hormone formation in the rat and yet failed to control thyrotoxicosis completely or to produce myxedema in man.

Although various indirect methods have been used for estimating the rate of hormone formation in man, such as the amount of thyroid necessary to alleviate myxedema, or the urinary excretion of iodine, no direct measurements of this function have been described.

It is the purpose of this paper to present a method for the direct estimation of the rate of iodine utilization by the thyroid in man, and to determine the effects of various amounts of iodide on this process. A simple method for calculating the serum iodide is also described.

METHODS

The principles utilized were, (a) serial quantitative determinations of radioactive iodine uptake by the thyroid, and (b) calculation of the specific activity of the accumulated thyroid iodine by analysis of the simultaneously excreted urine for both I^{131} and I^{127}.

These procedures are based on the assumption that the two isotopes, I^{131} (radioiodine) and I^{127} (stable iodine), chemically identical in the test tube, are metabolized in exactly the same manner in the body. Then, if the quantity of stable iodine accompanying each microcurie of I^{131} into the

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thyroid is known, the calculation of total iodine accumulation is a simple matter. Since the kidneys excrete the isotopes indiscriminately, there will be the same proportion of each in the serum and in the urine. Or, expressed in another fashion, Serum I^{127}/Serum I^{131} = Urine I^{127}/Urine I^{131}. At any time then, the specific activity (I^{131}/I^{127}) of the iodide in the urine being formed will be the same as that of the serum. Since arterial blood from the same source supplies both the thyroid and the kidneys and contains identical amounts of iodide, the specific activity of the iodide of the urine excreted over a short period will accurately reflect the specific activity of the iodide entering the thyroid during this same period.

A group of 31 euthyroid and 13 untreated thyrotoxic subjects were studied by this method. In all instances a tracer dose of 100 microcuries of I^{131} was administered by mouth. Within a few minutes the subject urinated and discarded the specimen. During the course of the test enough water was drunk to provide an adequate urinary output. At approximately hourly intervals for six to twelve or more hours the radioactivity in the thyroid gland was measured with a sensitive gamma (Geiger-Müller) counter at a distance of 35 centimeters from the gland. The background (radioactivity over the lower thigh just above the knee) was subtracted from the thyroid count. The absolute quantity of I^{131} in microcuries was calculated by comparing the net count with that resulting from a standard radioactive iodine solution under similar geometric conditions. Nearly simultaneously with each thyroid count, urine and blood specimens were collected.

Astwood and Bissell's modification (2) of Kendall's method was used for the analyses of the urines for stable iodine, I^{127}. The I^{131} content of the urine and serum was determined by comparing aliquots evaporated on flamed copper planchets with appropriately diluted portions of the administered I^{131}, using a thin window beta counter. In order to compensate for the greater self-absorption of the serum specimens, appropriate quantities of normal serum (containing no radioactivity) were evaporated on the discs with the urines and standard solutions.

When the successive values representing accumulated I^{131} in the thyroid were plotted against a "square root of time" scale, the parabolic curves were converted to straight lines in normal subjects (3). The effect of inhibiting agents administered during the tests was evident as deviations from this linear course of accumulation. Thus, in normal subjects, antithyroid drugs of various types have been quantitatively assayed by this method (3). In this study, also in euthyroid subjects, the method was utilized in ascertaining the action of the iodide ion. The pattern of iodine collection exhibited by very hyperplastic thyroids such as in thyrotoxicosis could not be fitted to a straight line.

CALCULATIONS

The thyroid accumulation of I^{131} (I^{131} *per hour*): The increase in microcuries for each period was divided by the length of the period. The rate of I^{131} collection was greatest within a short time after administration, and progressively decreased after this. (The calculations of Keating *et al.* (4) indicated that this could be expressed as a "collection rate" which was a constant per cent of the radioactive iodine available to the thyroid. However, since some of our subjects were not observed for a long enough period —twenty-four hours or more—so that the asymptotic levels could be estimated, this expression of the rate of uptake was not calculated for them.)

The specific activity of the urine iodine: This was determined from the fraction, Urine I^{131} (microcuries)/Urine I^{127} (micrograms), which, during the course of the uptake, progressively decreased. In other words, each microcurie of I^{131} collected by the gland represented an increasing quantity of I^{127}.

The rate of thyroid accumulation of I^{127} (I^{127} *per hour*): For each period T equalled I^{131} (microcuries/hour)/Urine specific activity.

Determination of serum iodide (*serum* I^{127}): From the formula Serum I^{127}/Serum I^{131} = Urine I^{127}/Urine I^{131} this value could be readily calculated as Serum I^{127} = Serum $I^{131} \times$ Urine I^{127}/Urine I^{131}. Since the urine values represented *average* levels for the period, it was evident that the mean serum I^{131} level must be calculated from the quantities at the beginning and at the end of the period. The figures obtained for stable iodide (serum I^{127}) obviously also represented average concentrations during the period.

RESULTS

The rates of I^{127} accumulation in 14 euthyroid subjects who had not received additional iodide fell within rather narrow limits, varying from 3 to 19 micrograms/hour, averaging 10 micrograms/hour for periods of from six to twenty-eight hours (Fig. 1). In these individuals the serum iodide levels were in the vicinity of 1 microgram per cent or (usually) less. Although, in general, the amount of I^{127} collected by the thyroid paralleled the I^{131} uptake, there was considerable deviation; in some instances, thyroids with I^{131} uptakes as much as fourfold different were very similar in their total iodine (I^{127}) accumulations (Fig. 1).

The pattern of total iodine accumulation over periods of six to twenty-four hours was variable. In the majority of fasting subjects the hour-to-hour rates of uptake were relatively constant or decreased slightly over several hours. Following meals, rises occurred frequently, lasting two to three hours, sometimes to three times the fasting rates. These rises presumably were the result of ingestion of iodide with the food, and were particularly striking in hospitalized patients who were served iodized salt.

Small amounts of iodide were given (single doses orally of 10 micrograms of potassium iodide— 7.63 micrograms I^- —/kilogram body weight) to 15 additional euthyroid subjects; in 14, this was added to the I^{131} as carrier, and in the other patient was administered during the course of the uptake. In the instances in which they were determined, the serum iodide values were increased 1 to 3 micrograms per cent by this addition. In all except one person, the amounts of total iodide collected by the thyroid were higher than in those not given iodide, or were increased as a result of the

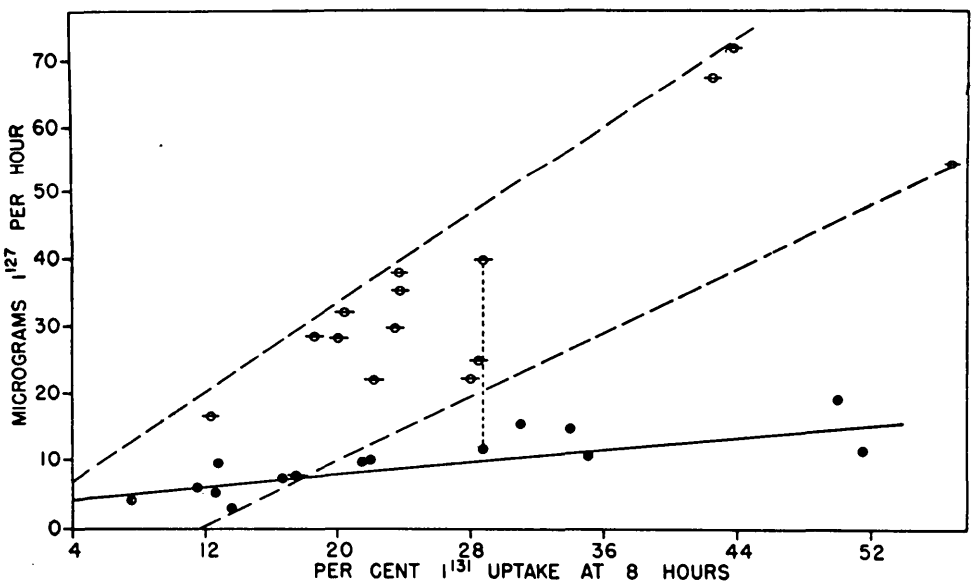


FIG. 1. The rate of total iodine utilization by the thyroid gland plotted against the radioiodine uptake in euthyroid subjects. The per cent of I^{131} collected in the thyroid at eight hours after administration of the dose is selected as an index of radioiodine uptake (abscissa). On the ordinate is represented the rate of I^{127} collection per hour. The solid circles signify that the subjects received no additional iodide; the serum iodide levels were usually less than 1 microgram per cent. The crossed open circles indicate that the subjects received 10 micrograms potassium iodide (7.63 micrograms I^-)/kilogram body weight, either as carrier with the I^{131} or, in one patient, during the course of the uptake (vertical dotted line connecting the solid circle and the crossed open circle).

addition. As a rule, this increase was greater for those individuals with the higher rates of I^{131} accumulation, although some overlapping was evident (Fig. 1).

In those 8 individuals who received additional small doses of iodide there were further increases in the amounts of iodide collected by the thyroid. The iodine accumulation by the thyroid varied directly with the serum levels of iodide, providing the latter were relatively low (Figs. 2 and 3).

As serum iodide levels above 6 to 12 micrograms per cent were attained with larger amounts of iodide, the organic binding of iodine in the thyroid was halted (Fig. 4). The values for serum iodide with which inhibition of binding was detectable were inversely related to the rate of I^{131} collection. Thus, in subjects with very slow rates of collection, serum iodide values in the upper part of the range were necessary before inhibition occurred,

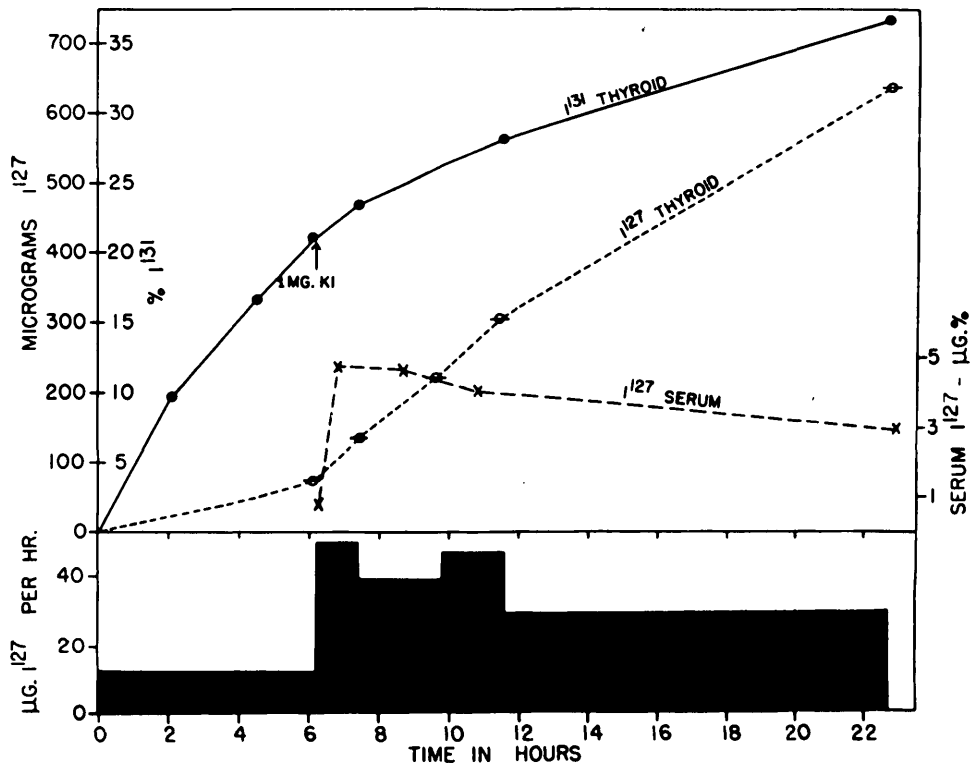


FIG. 2. The iodine utilization by the normal thyroid before and after administration of a small dose of iodide. The I^{131} accumulation curve is plotted against time to show the usual parabolic shape (solid line). The course of the I^{131} uptake was not changed by the dose of 1 milligram of potassium iodide which raised the serum level of iodide by 4 micrograms per cent (five times). However, the total (I^{127}) collection was increased approximately four times, from 11.7 micrograms/hour to 44.9 micrograms/hour, as shown by the dotted line and the bars.

whereas inhibition was attainable with levels around 6 micrograms per cent in others whose glands were very active.

Because of the appreciable amounts of iodine which could be accumulated and held as the iodide ion in the gland (see below), it was difficult to ascertain whether the cessation of organic binding due to iodide was grad-

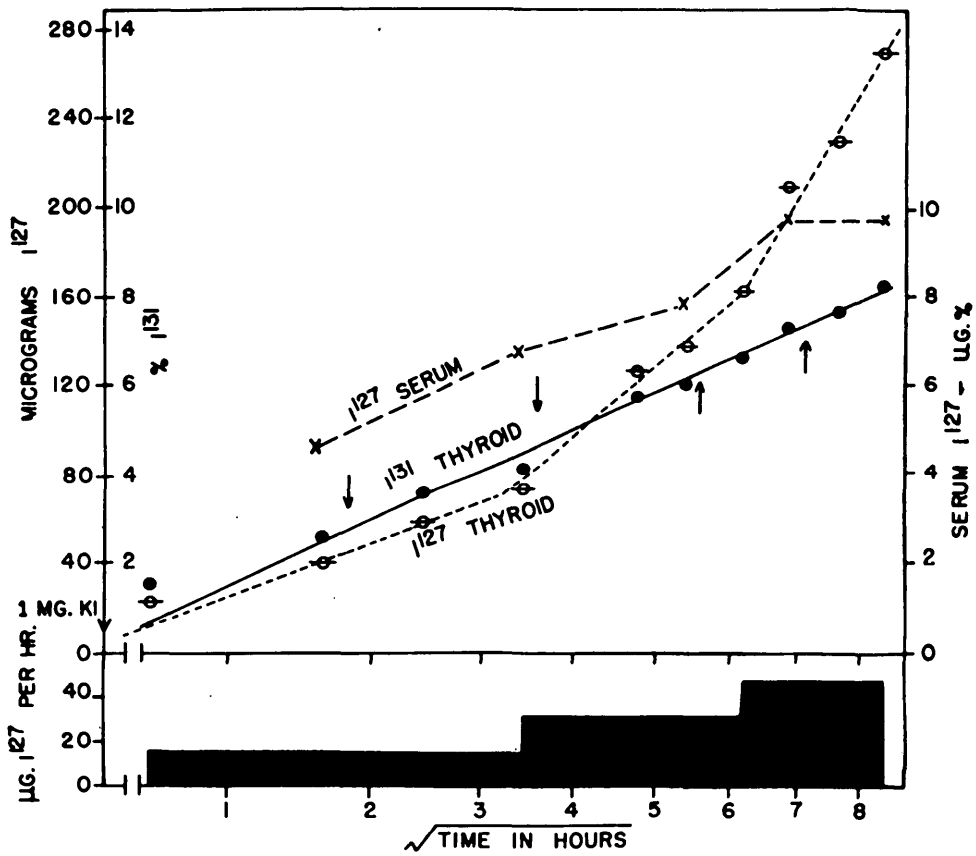


FIG. 3. The influence of several small doses of potassium iodide on the radioiodine and total iodine collection in a normal subject with a relatively inactive thyroid (I^{131} uptake 8 per cent in eight hours). The I^{131} accumulation is plotted against the "square root of time" to demonstrate the linear relationship. One milligram of potassium iodide was given as carrier and, during the test, additional doses of potassium iodide in half-milligram amounts, as indicated by the arrows. Although the serum level was raised to nearly 10 micrograms per cent by the total of 3 milligrams potassium iodide and the total iodine uptake was increased to 48 micrograms/hour, there was no inhibition of binding of iodine in this inactive gland.

ual as it appeared in a few instances, or always abrupt as it seemed in most subjects.

In the 13 thyrotoxic patients studied, there were large variations in the radioiodine collections and usually corresponding differences in total iodine accumulations. The average was 120 micrograms I^{127}/hour, and the range was from 44 to 265 micrograms/hour.

There was in these thyrotoxic glands a very large capacity for accumulating the iodide ion (5); even when organic binding of iodine was virtually completely inhibited by antithyroid drugs of the thiouracil type, such thy-

roids could collect as much as 40 per cent of a dose of I^{131} *as the iodide ion.* It was repeatedly demonstrated that such large quantities as 15 *milligrams* of iodide (I^{127}) could thus be held in glands in which binding had been halted. In such instances the prompt detection of inhibition by iodide was difficult, particularly when the dose was given during the course of accumulation, because of the large size of this "iodide space," which must be

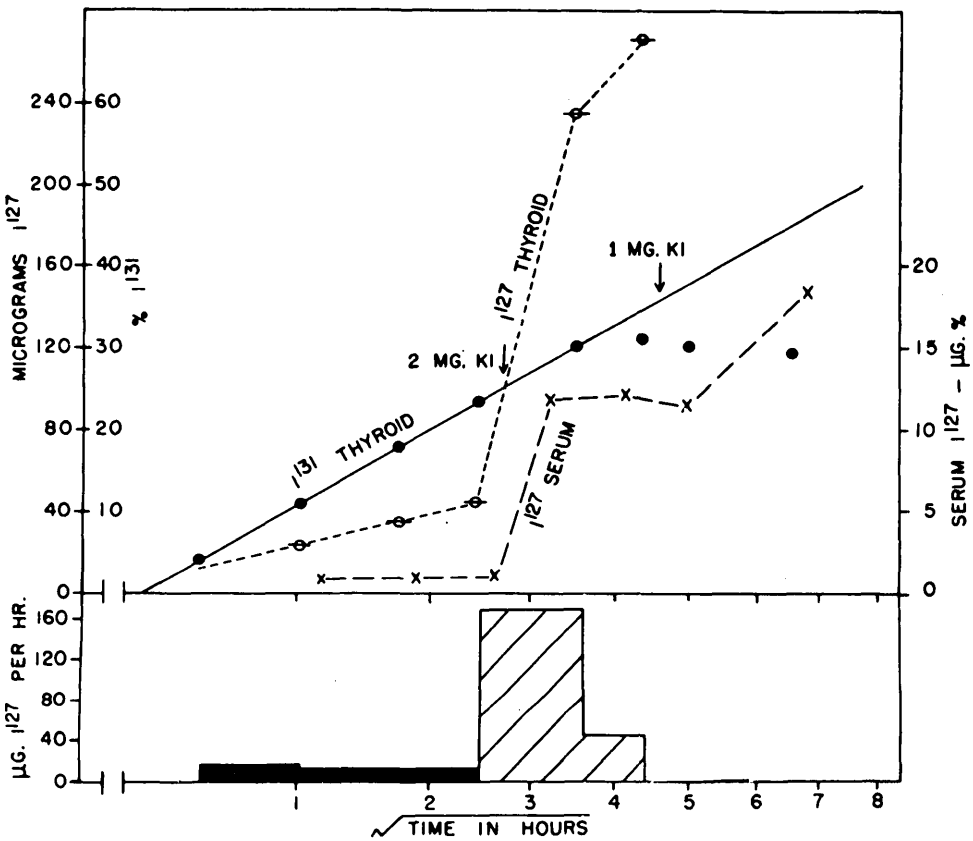


FIG. 4. The influence of a small but inhibitory quantity of iodide (2 milligrams potassium iodide) in a normal subject with a very active thyroid (I^{131} accumulation estimated by extrapolation to be 51 per cent at eight hours). The inhibition is shown by the cessation of accumulation of radioiodine soon after administration of the iodide. The large bars are hatched because the accumulations do not represent organically bound iodine solely. The larger hatched bar is spuriously high and represents a combination of : a) error in calculation (from continued uptake of high activity iodide before and during absorption of the added iodide); b) organic binding while the inhibitory levels were being achieved; and c) iodide ion collected after cessation of binding. The smaller hatched bar indicates an increment of iodide ion almost exclusively. That a part of the accumulated iodine was in the form of the freely diffusible iodide ion (unbound) is shown by the fall in I^{131} in the thyroid which occurred soon after the peak level was attained.

"filled" before blocking was evident. Since the uptake pattern in hyperplastic thyroids could not be fitted to a straight line as in normals, deviations from this line could not be utilized as an index of inhibition.

However, the characteristic pattern of collection exhibited by the inhibited hyperplastic gland was recognizable (5) (Figs. 5 and 6). This con-

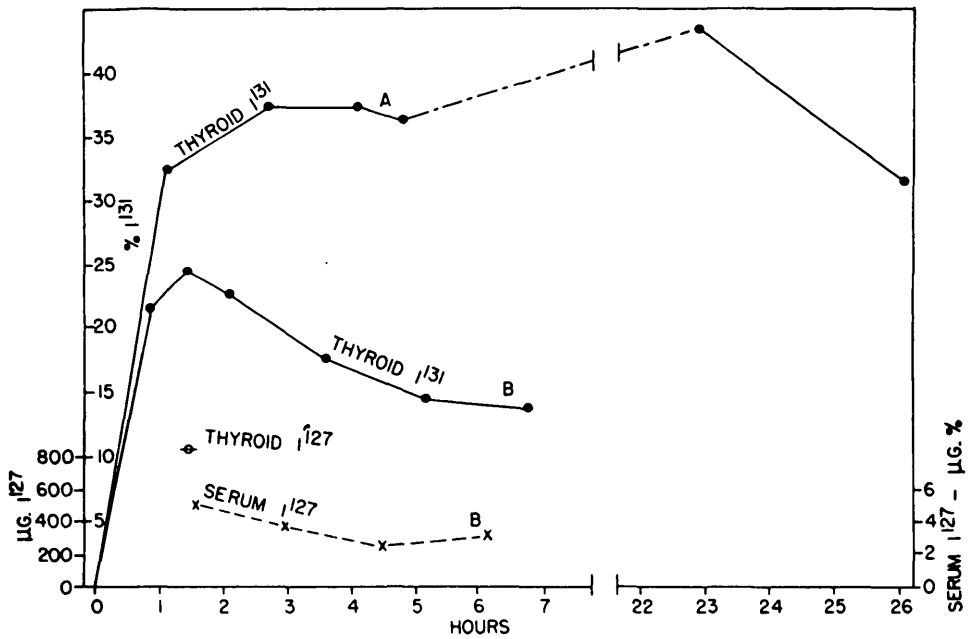


FIG. 5. The influence of small amounts of iodide on organic binding in 2 subjects with untreated thyrotoxicosis. Both received the iodide as carrier. In both, the characteristic shape of the curves denotes that the collection consisted largely of the iodide ion. In A (10 micrograms potassium iodide/kilogram body weight), there was some increase in I^{131} accumulation at the 23-hour interval, indicating that organic binding had occurred to some extent after this prolonged period. The decrease after thiocyanate administration (2 grams, given at the twenty-third hour) showed that an appreciable portion still remained as iodide ion, however. In B, (20 micrograms potassium iodide/kilogram body weight), with levels of serum iodide probably higher, the more rapid spontaneous decrease in the thyroid iodide I^{131} parallels the fall in serum iodide. The quantity of iodine in the thyroid in B, as shown by the crossed circle, was 827 micrograms during the second hour, mostly in the form of the iodide ion. No thiocyanate was given to this patient.

sisted of the rapid accumulation of 10 to 40 per cent of the I^{131}, which was usually at a maximum in two to three hours; following this there was a gradual or rapid fall as the radioactivity remaining in the gland in the form of freely diffusible iodide was diluted with serum iodide of progressively decreasing specific activity. The thiocyanate ion would cause discharge from the thyroid of all, or a large part of, that portion of iodine

which was present as the iodide ion (5, 6); this reaction was employed to identify the relative proportions of these two fractions and, hence, the degree of inhibition at any time (Figs. 5 and 6).

By such means, therefore, it was demonstrated in 8 additional thyrotoxic patients that with very low levels of serum iodine—less than 5 micrograms per cent—organic binding could be prevented in hyperplastic glands. The inverse relationship observed in normal subjects between the level of iodide in the serum at which inhibition occurred and the thyroid iodide-concentrating ability (or rate of uptake) could be extended to include thyrotoxic patients with hyperplastic thyroids. Inhibition could be produced with much lower levels of serum iodide in thyrotoxic patients than were necessary in normal subjects.

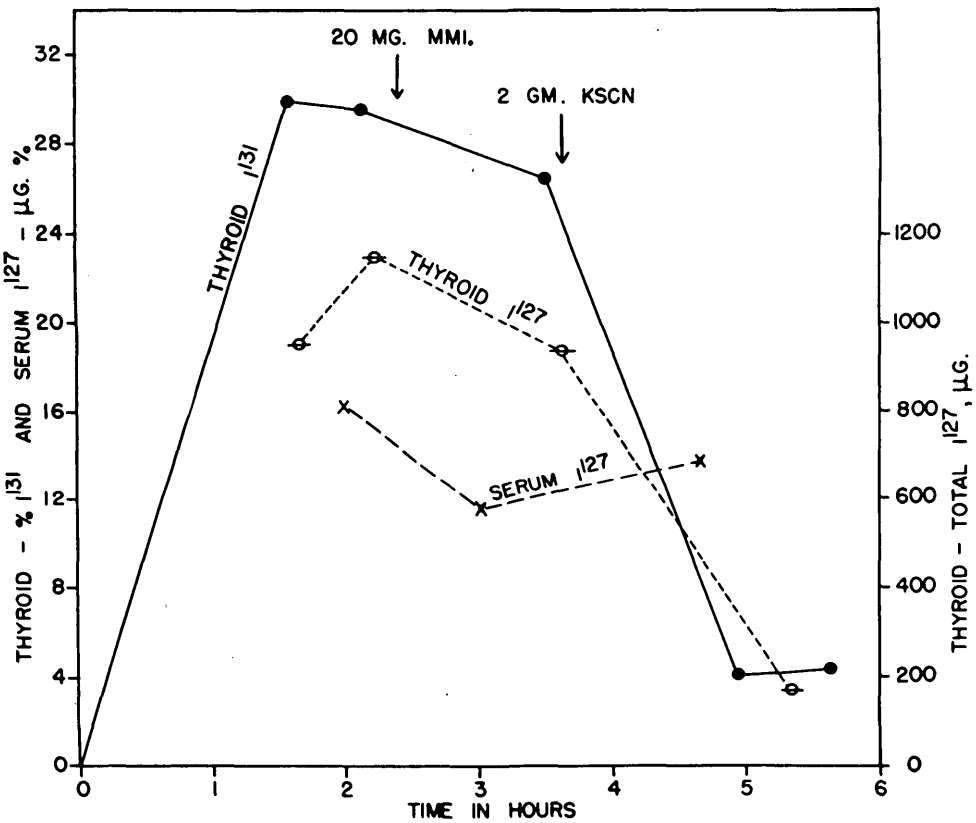
The thyroid *clearance* of serum iodide is readily calculated for each period from the expression: $\frac{\text{Thyroid } I^{131} \text{ accumulation per hour}}{\text{Average } I^{131} \text{ serum concentration}}$. Average values for the 3 normal individuals whose iodine accumulations are illustrated, are shown in Table 1.

TABLE 1. THE AVERAGE THYROID IODIDE CLEARANCES IN 3 NORMAL PERSONS

	Thyroid I^{131} accumulation (per cent at 8 hours)	Thyroid clearance of iodide ml./hour	ml./minute
Fig. 2	24	1115	18.6
Fig. 3	8	430	7.2
Fig. 4	51.5 (by extrapolation)	1720	28.7

DISCUSSION

Without the studies of concurrent serum iodide levels and, especially, of the total iodine entering the gland, the effect of iodide on iodine binding in the thyroid could not be assessed by the radioiodine method because of the uncontrolled factor of chemical dilution. It could not be certainly ascertained in some situations that the total hormone formation was altered —*i.e.*, that apparent blocking was not the result simply of chemical dilution. Thus, a minute quantity of I^{131}, the detection of which could conceivably be beyond the limits of accuracy of the apparatus, would carry with it, if the specific activity of the serum iodide were very low, the same amount of I^{127} as measurable amounts of I^{131} with a higher specific activity of the serum iodide. However, since this factor of chemical dilution was quite



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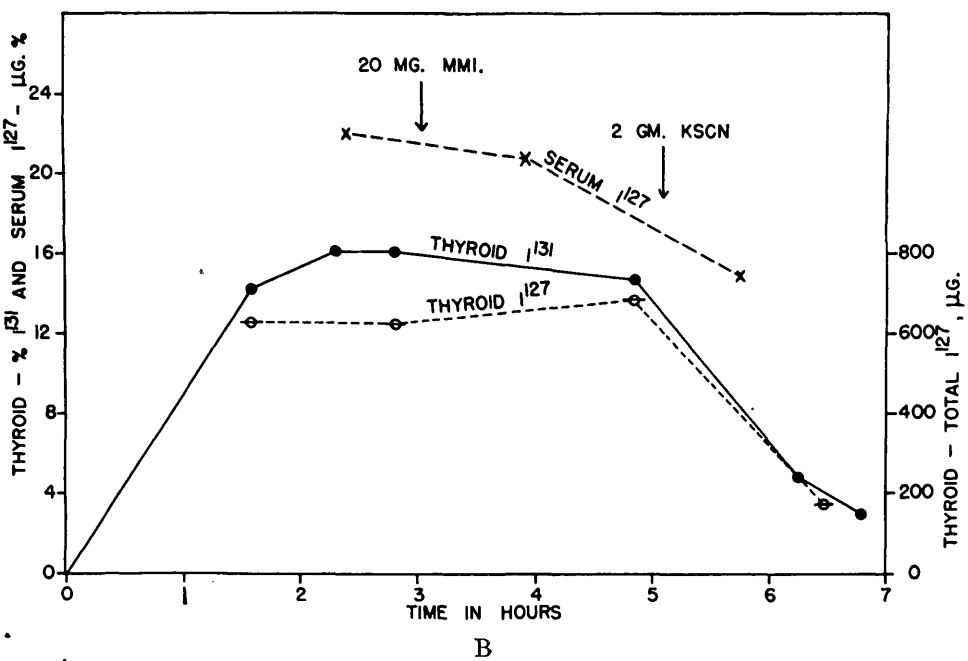

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large in some thyroids (with slow rates of iodine turnover) before the I^{131} accumulation stopped (Fig. 3), whereas it was small in others (with relatively rapid uptakes), it could be inferred that cessation of I^{131} collection indicated actual inhibition of binding. Thus, the observations of Wolfe and Chaikoff in the rat were extended to man.

The observed values for serum iodide in patients who had not received iodine medication, 1 microgram per cent or less, agree well with those obtained by sensitive microchemical methods. Our results depend upon chemical analysis of iodine in the urine, which is a relatively easy chemical procedure. Since the iodine content is usually above 10 micrograms per cent, 10 to 20 cc. of urine can be readily analyzed. Hence it is felt that the results by this indirect method on serum are at least as accurate as those obtained by direct analyses.

From the observations reported here it may be deduced that in each individual the thyroid extracts a certain fraction of the iodide from the blood. This fraction remains constant, at least for a short time, with increasing levels of serum iodide until inhibition is attained. Presumably in euthyroid subjects the quantity of pituitary thyrotropin available is a most important factor in determining the size of the fraction of serum iodide extracted by the thyroid. The rate of I^{131} accumulation is an indication of the magnitude of the fraction, and, hence, of the potential capacity for hormone formation within the limits discussed in the next paragraph. However, in order to know how much iodine is being used for synthesis at any time, it is necessary to determine the specific activity of the metabolized iodine. Therefore the assumption that a rapid accumulation of radioiodine by the thyroid indicates a large total iodine utilization, such as accompanies thyrotoxicosis, may in certain instances be fallacious (Fig. 1). These same limitations are applicable when these functions are expressed as thyroid clearance of serum iodide.

Our data are consistent with the theory (1) that the concentration of iodide ion in the thyroid cells, rather than the serum iodide level, is the ultimate consideration governing the amount of iodide necessary to produce inhibition in a given instance. The thyroid cell iodide concentration is a function, not only of the serum iodide level, but also of the ability of the thryoid to

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FIG. 6. The influence of larger amounts of iodide on organic binding of iodine in the thyroid glands of 2 additional patients with thyrotoxicosis. In both subjects 5 milligrams of potassium iodide were given by mouth (A, 40 minutes; B, 90 minutes) before the I^{131}. In both, the serum levels of iodide were in excess of the concentration required to produce inhibition of binding. The left vertical arrows ("MMI") indicate the administration of large doses of the potent antithyroid drug, 1-methyl,2-mercaptoimidazole; the reasons for this are discussed in the text. In each patient there was a small residual fraction of radioactivity in the gland following the action of thiocyanate. The interpretation of this finding is also undertaken in the text.

concentrate the iodide ion from the serum. This latter is probably largely controlled by pituitary thyrotropin in normal individuals. Further evidence for the above theory was obtained by Raben (7) after he noted that his laboratory rats, with comparatively atrophic glands from a relatively high iodine diet, required much larger amounts of iodide to produce inhibition than the rats described by Wolff and Chaikoff. The only discernible difference in the animals from the two laboratories was that Wolff and Chaikoff's animals had relatively hyperplastic glands, with a high thyroid /serum iodide ratio. Direct confirmation was provided when Raben administered small amounts of thiocyanate to animals with serum iodides above the inhibitory levels. In these amounts this drug had the effect of discharging part of the iodide from the thyroid cells (6) without appreciably altering the serum iodide levels. Following this decrease in the concentration of iodide in the thyroid cell, organic binding was resumed—and in the presence of the formerly inhibitory levels of serum iodide.

Although the effect of small amounts of iodine in increasing hormone formation is implied in the use of the drug in the prophylactic treatment of simple goiter, the augmentation of iodine utilization has not hitherto been directly demonstrated in man. In animals, on the other hand, this effect has been repeatedly shown (1, 8). It is interesting that Wolff and Chaikoff's data reveal that the level of organic I^{127} binding was very high with a dose of iodide (10 micrograms) below the inhibition level. The studies reported herewith imply that large doses of iodide are undesirable in situations in which it is the purpose to increase hormone production, as in the prevention of iodine-deficiency goiter.

Our results indicate that only very small quantities of iodide are necessary to inhibit organic binding in the thyrotoxic thyroid gland. This correlates well with the observations of Thompson *et al.* (9) that a maximal response in thyrotoxicosis may be regularly obtained by single daily doses of 6 milligrams of iodine. The effective dose could conceivably be smaller if it were divided.

In thyrotoxic subjects (5), even after large doses of potent antithyroid compounds such as 100 milligrams of 2-mercaptoimidazole, a fraction of accumulated radioiodine often remained in the thyroid gland following ingestion of thiocyanate. This portion of radioactivity which was not discharged from the gland amounted to as much as 20 per cent in some instances. There was evidence that organic binding was virtually completely inhibited by these amounts of drug. Hence, it was felt that most of this residual radioactivity was in the form of the iodide ion, but that the thiocyanate had failed to reduce the thyroid/serum iodide ratio to unity in these extremely hyperplastic glands.

In the present study, more than the expected amounts of radioiodine remained in the thyrotoxic thyroid glands after thiocyanate administration.

This occurred with serum iodide levels considered to be inhibitory. In view of Raben's experiments this was thought to be the result of resumption of organic binding as, during the process of discharge, the iodide was decreased to sub-inhibitory levels in the thyroid cells. In order to obviate this difficulty, an inhibiting dose of antithyroid compound was given before the thiocyanate so as to prevent organic binding of iodine *during the period of discharge of iodide* (Fig. 6). Obviously this had no effect on the inhibition of binding by iodide *previous* to administration of the antithyroid drug. With this added precaution, it could be demonstrated that the indicated concentrations of iodide ion produced about the same degree of suppression of the thyroid glands of thyrotoxic subjects as did large doses of antithyroid drugs such as mercaptoimidazole (Fig. 6). However, it could not be stated with certainty that inhibition was complete; it was impossible to exclude the organic binding of a small amount of iodine.

These acute experiments do not provide a clue as to what happens later during the course of the treatment of Graves' disease to prevent a full metabolic response or to explain the relapses which occur while full doses of iodine are being given. The suggestion has been made recently that failure to maintain inhibitory levels of plasma iodide may account for the exacerbation of the hyperthyroid state (10). If this occurred, even for a short period, large amounts of iodine would probably be organically bound, because at iodide levels slightly below those producing inhibition, conditions would be optimal for maximal hormone production. On the other hand, the quantities of iodine customarily prescribed (of the order of 100 milligrams daily) should be adequate to maintain inhibitory blood iodide levels. Therefore, fundamental alterations in the iodine metabolism of the thyrotoxic thyroid gland (or in the urinary excretion of iodine) may take place during treatment of Graves' disease with iodine, which will explain this phenomenon in other ways.

SUMMARY AND CONCLUSIONS

A method is described for the direct measurement of total iodine accumulation by the thyroid, using the thyroid I^{131} uptake and the specific activity of the simultaneously excreted urine. If, at the same time, the radioactivity in the serum is determined, the serum iodide can be calculated:

$$\text{serum } I^{127} = \frac{\text{serum } I^{131} \times \text{urine } I^{127}}{\text{urine } I^{131}}.$$

By this method the iodine collection by the thyroids in 14 euthyroid individuals who had not received added iodide average 10 micrograms /hour. In 13 thyrotoxic persons, the corresponding figure was 120 micrograms/hour. With small amounts of added iodide, the total iodine uptake was increased. With larger quantities, inhibition of organic binding of

iodine in the thyroid gland occurred. In general, inhibition seemed to be determined by the level of iodide in the thyroid cell, which was a function both of the ability of the cell to concentrate iodide from the serum and the amount of iodide available in the serum. The serum iodide levels with which inhibition could be produced in thyrotoxic subjects were 5 micrograms per cent or less, whereas a higher value, between 6 and 12 micrograms per cent, was necessary to stop organic binding in the less hyperplastic glands of euthyroid individuals. These data are the results of acute experiments. No clue is provided to explain the relapses which occur during the course of treatment of Graves' disease with full doses of iodine. Alterations in the above reactions may occur after a period of iodinization.

Acknowledgments

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