

THE RATES OF UTILIZATION OF THYROXINE AND OF DESICCATED THYROID IN MAN: THE RELATION BETWEEN THE IODINE IN DESICCATED THYROID AND IN THYROXINE

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(Received for publication September 1, 1932)

INTRODUCTION

These observations were made in an effort to determine the rate of production of thyroxine in normal man. Boothby, Sandiford, Sandiford and Slosse (1925) have shown that when thyroxine is injected intravenously at intervals of from two to fourteen days, the average daily dose required to maintain the basal metabolism of a "thyroidless" individual at the normal level is 0.25 mgm. Since the injections were not given daily, the possibility remained that some of the thyroxine administered may have been excreted unused. We have accordingly determined the minimum amount of thyroxine which must be injected intravenously or subcutaneously every day in order to accomplish the same result.

DATA

Our observations have been made on two patients with marked myxedema, the basal metabolism during rest in bed before treatment was started being minus 33 per cent and minus 41 per cent respectively (Charts 1 and 2). In view of the low level of the basal metabolism and the intensity of the signs and symptoms of myxedema, it is assumed that these patients had little or no functioning thyroid tissue. The figures obtained, therefore, represent as close an approximation as can be made at the present time to the daily rate of formation of the thyroid hormone in man.

The routine procedure was to weigh out small amounts (usually from 1 to 4 mgm.) of Squibb's thyroxine on a microbalance. A slightly alkaline solution was then made up in the usual manner, sterilized, and an aliquot portion promptly injected. The solution was sterilized by placing the test tube which contained it in a beaker of boiling water for fifteen minutes, except during the period from the one hundred and seventy-sixth day to the two hundred and fourteenth day in Case 1, and from the

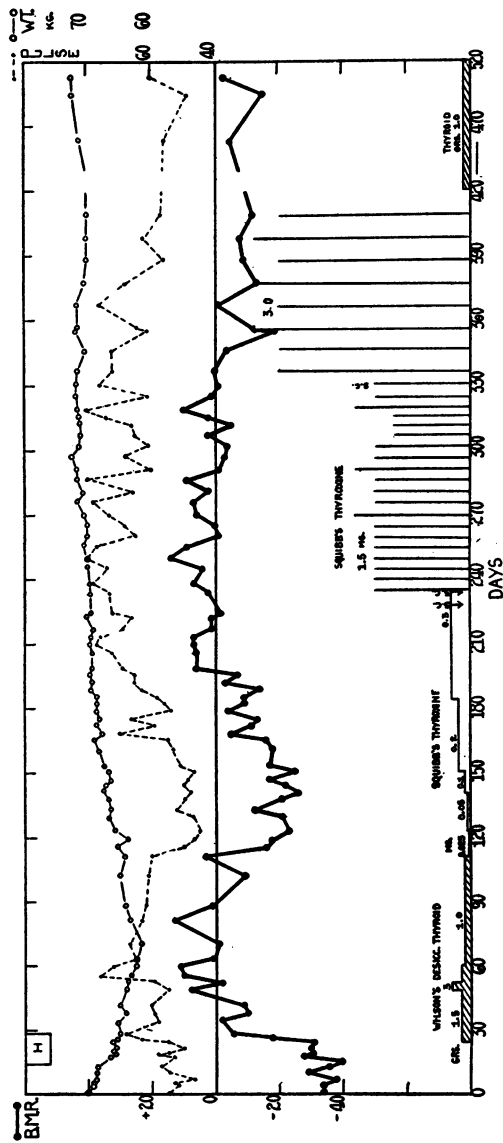


CHART 1. MISS M. F., LABORATORY NUMBER 276, AGE 42, HEIGHT 159 CM.
The effect of various doses of thyroxine and of desiccated thyroid in a patient with marked myxedema (Case 1). "H" denotes a period in the hospital. All injections of thyroxine were given by the intravenous route ("I.V.") except three which were given subcutaneously ("S.C.").

eighty-ninth to the one hundred and twenty-seventh day in Case 2, when it was sterilized by the addition of merthiolate solution¹ in a dilution of 1 : 4. The mixture was allowed to stand ten minutes before injection. In Case 1, all of the injections except three were given intravenously. In Case 2, about the first two-thirds of the injections were given intravenously and all of the remainder except one, subcutaneously. The data show that the effect was the same in either case.

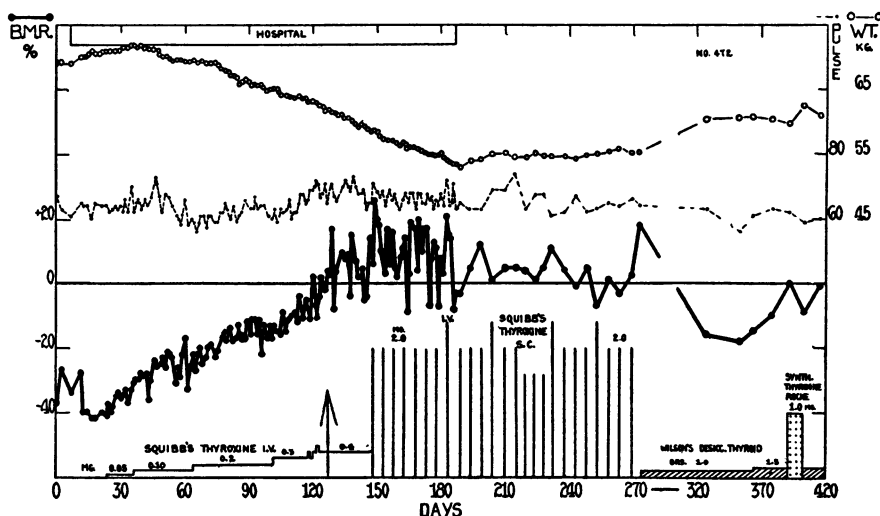


CHART 2. MRS. M. R., LABORATORY NUMBER 472, AGE 38, HEIGHT 153 CM.

The effect of various doses of thyroxine and of desiccated thyroid in another patient with marked myxedema (Case 2). Up to the point denoted by the arrow all injections of thyroxine were given intravenously: after the arrow, all were given subcutaneously ("S.C.") except for the one recorded as being given intravenously ("I.V.").

In the first patient (Chart 1) the basal metabolism was raised to normal by Wilson's desiccated thyroid and the maintenance dose of this preparation determined. Then the injection of thyroxine was substituted, first in an inadequate dose and then in an adequate dose. In the second patient (Chart 2) the daily dose of thyroxine was gradually increased over a period of about four months until an amount was being administered that was about adequate to maintain the basal metabolism at the standard normal level. The amount of desiccated thyroid necessary to

¹ One gram of sodium ethylmercuri thiosalicylate in 1000 cc. of water buffered with 1.4 gram sodium borate in 1000 cc. and containing sodium chloride to make the solution approximately isotonic. This preparation was kindly supplied to us by the manufacturers, Eli Lilly and Company, Indianapolis, Indiana.

accomplish the same result was then determined. The levels of the basal metabolism in each patient after equilibrium had been reached on the various doses of thyroxine and desiccated thyroid used are summarized in Table 1.

TABLE 1

Levels of basal metabolism during the administration of various doses of thyroxine and desiccated thyroid in two cases of myxedema

Medication	Basal metabolic rate*	
	Case 1 <i>Per cent of normal</i>	Case 2 <i>Per cent of normal</i>
None.....	-33	-41
0.05 mgm. Squibb's thyroxine intravenously every day....		-34
0.1 mgm. Squibb's thyroxine intravenously every day.....	-21	-25
0.2 mgm. Squibb's thyroxine intravenously every day.....	-7	-15
0.3 mgm. Squibb's thyroxine intravenously every day.....	+1	-8
0.4 mgm. Squibb's thyroxine intravenously or subcuta- neously every day.....		+5
1.5 mgm. Squibb's thyroxine intravenously every fifth day..	+3	
2.0 mgm. Squibb's thyroxine subcutaneously every fifth day.		+6
3.0 mgm. Squibb's thyroxine intravenously every ten days..	-9	
1 grain Wilson's desiccated thyroid by mouth every day....	-6	-16
1½ grains Wilson's desiccated thyroid by mouth every day..	+7	-1

* Basal metabolic rates were determined with the Sanborn-Benedict apparatus, using Aub-DuBois standards.

In the case of the first patient the data show that the basal metabolism could be maintained at the normal level in the following ways: (1) By injecting 0.3 mgm. of thyroxine every day. (2) By injecting 1.5 mgm. of thyroxine every fifth day. (However, injecting 3.0 mgm. every tenth day did not appear to be as effective as injecting 0.3 mgm. every day.) (3) By administering about 1.25 grain of desiccated thyroid by mouth every day.

In the case of the second patient, the data show that the basal metabolism could be maintained at the standard normal level in the following ways: (1) By injecting between 0.3 and 0.4 mgm. of thyroxine every day. (In this patient 0.4 mgm. daily maintained the basal metabolic rate at a level of plus 5 per cent; 0.3 mgm. daily, at a level of minus 8 per cent. Therefore, the amount necessary to maintain it at the normal level may be assumed to be approximately 0.35 mgm. per day.) (2) By injecting somewhat less than 2.0 mgm. of thyroxine every fifth day. A dose of 2.0 mgm. every fifth day held the metabolism at about plus 6 per cent. (3) By administering 1.5 grain of desiccated thyroid by mouth every day.

In the first patient 1 grain of desiccated thyroid per day held the basal metabolism at a level of minus 6 per cent, and 1.5 grain a day at a level of plus 7 per cent, as compared with a level of plus 1 per cent when 0.3 mgm. of thyroxine was given intravenously every day. In the second patient

the basal metabolism was minus 16 per cent during the administration of 1 grain of desiccated thyroid daily and minus 1 per cent during the administration of 1.5 grain daily, as compared with levels of minus 8 per cent and plus 5 per cent respectively during the injection of 0.3 and 0.4 mgm. of thyroxine daily. It would thus appear fair to say that 1.25 grain of desiccated thyroid produced about the same amount of increase in basal metabolism as 0.3 mgm. of thyroxine in the first patient and that 1.5 grain produced about as much as 0.35 mgm. in the second patient.

Relation between dose of thyroxine and basal metabolism

From Chart 3 it may be seen that between the levels of minus 33 per cent and plus 1 per cent in the first case and minus 41 per cent and plus 5 per cent in the second case, there is approximately a linear relationship

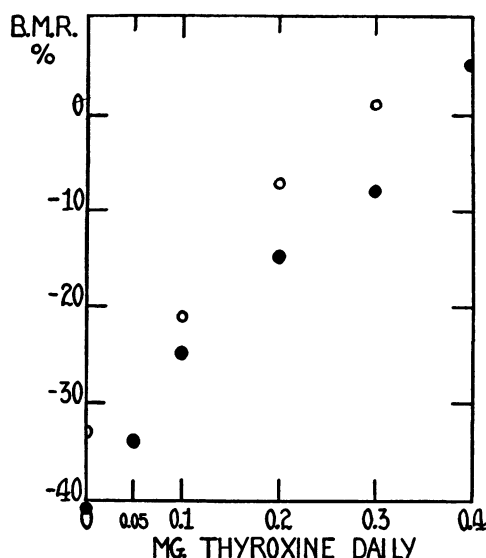


CHART 3. THE RELATIONSHIP BETWEEN THE DAILY DOSE OF THYROXINE AND THE BASAL METABOLISM IN TWO PATIENTS WITH MYXEDEMA

The circles denote Case 1 and the dots Case 2.

between the basal metabolism and the dose of thyroxine. So far as the data go, they suggest that a similar relationship may hold for desiccated thyroid. Whether the same relationship holds for levels above the normal has not been determined, but it appears to be established that the effect of a given dose is less at or above the normal level than below (Boothby, Sandiford, Sandiford and Slosse (1925)) (Thompson, Thompson, Brailey and Cohen (1929)). For example, Thompson and co-workers (1929) have shown that the effect of 10 mgm. of thyroxine at a basal metabolic level of minus 4 per cent is about one-seventh of that at a

level of minus 40 per cent. These results merely emphasize once again that effects obtained with thyroxine in individuals in whom the thyroid function is normal can not be compared with those obtained in individuals in whom the thyroid function is subnormal.

Comparison with effects of a single large dose of thyroxine

In two patients with marked myxedema and basal metabolic rates of minus 40 and minus 45 per cent respectively, Thompson, Thompson, Brailey and Cohen (1929) showed that a single intravenous injection of 10 mgm. of Squibb's thyroxine produced a total increase in calories of 22,455 and 21,075 respectively, assuming for the sake of simplicity that the basal calories represented the total number produced. In the first patient of the present study the basal calories for twenty-four hours were 993 when she was myxedematous and 1515 when her basal metabolism was maintained at the normal level by the intravenous injection of 0.3 mgm. of thyroxine per day. Therefore, the daily injection of 0.3 mgm. resulted in the production of at least 522 calories in twenty-four hours. At this rate, 10 mgm. divided into daily doses of 0.3 mgm. would have produced a total caloric increase of 17,400. In the second patient the daily injection of 0.35 mgm. of thyroxine caused the basal calories for twenty-four hours to increase from 875 to 1383. At this rate, 10 mgm. in divided daily doses of 0.35 mgm. would have produced a total caloric increase of at least 14,510. Comparisons of this sort are not strictly accurate, because, at the standard normal level of basal metabolism with its associated greater activity, the number of calories produced in excess of the basal is probably relatively greater than that at lower levels of basal metabolism with their associated lesser activity. Following an injection of 10 mgm. of thyroxine, the rise of the metabolism to normal is prompt and most of the period of increased heat production is characterized by a gradually diminishing basal metabolic rate. It would be expected, therefore, that our results would turn out as they have, i.e., that the smaller doses (0.3 and 0.35 mgm. daily) would appear to be used at a proportionately more rapid rate than the single large dose of 10 mgm. However, the figures correspond closely enough to those previously obtained to suggest that practically all of the single dose of 10 mgm. of thyroxine given at the low levels of basal metabolism in the previous study, and also all of the single doses of 0.3 and 0.4 mgm. in the present study, were used by the body and little or none excreted unused. A similar conclusion is suggested in the present study by the fact that injecting 1.5 mgm. and 2.0 mgm. every fifth day appeared to have about the same effect as injecting 0.3 mgm. and 0.4 mgm. per day respectively. However, in the two myxedematous patients previously referred to, the intravenous injection of 10 mgm. of thyroxine in one dose when the basal metabolism had risen to minus 4 per cent and minus 6 per cent produced

an increase in basal calories of only 3320 and 2815 respectively. Kendall (1917) has shown that 150 mgm. of thyroxine has much more effect in a goat when it is injected in divided daily doses of 10 mgm. than when it is injected in a single dose. The data, therefore, suggest that when a dose of thyroxine is given which is just adequate to supply a deficiency in the body, it may be used almost quantitatively, in contrast to the prompt excretion of a large part of any excess over this amount. This may explain why Boothby and co-workers (1925), by giving thyroxine at intervals of from 2 to 14 days, secured approximately the same figures for the daily maintenance as we did by daily injections. Since 10 mgm. of thyroxine is just about enough to raise the metabolism of a "thyroidless" individual to the normal level, it is suggested that the amount of thyroxine normally present in the body of an adult man outside of the thyroid gland is approximately 10 mgm., a figure which is in close agreement with that of from 8 to 14 mgm. previously reported by Plummer (1921) and by Boothby (1928). It might then be said that the function of the normal thyroid is to maintain the amount of thyroxine in the other tissues of the body at about 10 mgm. (in terms of Squibb's crystalline thyroxine).

Relation between iodine in desiccated thyroid and iodine in thyroxine

The Wilson's thyroid which we used contained 0.23 per cent of iodine in organic combination, so that 1.5 grain or 100 mgm. contained 0.23 mgm. of iodine, which is the amount of iodine contained in 0.35 mgm. of thyroxine; and 1.25 grain contained 0.19 mgm. of iodine, which is the amount contained in 0.29 mgm. of thyroxine. Therefore, one way of explaining our results would be to assume that all the iodine in desiccated thyroid is active physiologically as thyroxine and is absorbed quantitatively from the gastro-intestinal tract. In a recent conversation with one of the authors (W. O. T.), Kendall did not think this hypothesis was justified, because of the finding by Harington and Randall (1929) of diiodotyrosine in the thyroid and their conclusion that the iodine in the gland is about equally divided between diiodotyrosine and thyroxine. Diiodotyrosine is said to have no effect on the oxygen consumption of normal rats (Gaddum (1930)), none on that of normal man (Hoffmann (1927)) and none in myxedematous individuals (Strouse and Voegtlin (1909), Thompson and Alper (1932)).

Kendall, moreover, is of the opinion that the form and combination in which thyroxine exists in the body may greatly enhance its activity. Gaddum (1930), using material supplied to him by Harington, concluded that levorotatory thyroxine had about two and one-half times as much effect on the oxygen consumption of a normal rat as the dextro-form. Harington and Salter (1930) showed that the levorotatory form, isolated by means of tryptic digestion, was the naturally occurring variety.

With regard to the conclusion that 50 per cent of the iodine in desiccated thyroid is in the form of diiodotyrosine, it is claimed that thyroxine is relatively stable to hydrolysis with 10 per cent barium hydroxide (Harington and Randall (1929)) or with 5 per cent sodium hydroxide (Kendall (1929)) and that, therefore, any iodine recovered as diiodotyrosine after these procedures represents its original form of combination in the gland. However, we should like to point out that Kendall (1929) has sometimes been unable to recover any thyroxine from glands which were very active physiologically; and Cameron and Carmichael (1926) have shown that sodium hydroxide destroyed at least two-thirds of the activity of iodothyreoglobulin. Harington and Randall (1929) state "As in the case of diiodotyrosine, so with thyroxine, the greatest loss occurs at the stage of the intensive alkaline hydrolysis. This loss consists in part of iodine split off as iodide, and for the rest of iodine which is still in organic combination, but is soluble in acid." In Kendall's words (1929): "The assumption, therefore, that the iodine in the acid-insoluble products after alkaline hydrolysis is a measure of the thyroxine content of the gland is incorrect and the amount of thyroxine which can be isolated from the gland has no significant relation to the physiological activity which the thyroid material may possess before hydrolysis with alkali." Gutman, Benedict, Baxter and Palmer (1932) found a smaller percentage of iodine in the form of thyroxine with Leland and Foster's (1932) butyl alcohol extraction method than with the acid-precipitation method of Kendall. The conclusion is thus suggested that there is no way at present of determining with accuracy the percentage of iodine in the form of thyroxine. Salter, Lerman and Means (1932) have recently made important observations on patients with myxedema which also suggest that all the iodine in desiccated thyroid is in a combination that is physiologically equivalent to thyroxine. Using a polypeptide of thyroxine which Salter (Harington and Salter (1930)) had prepared, and comparing their data with that of the effect of standardized thyroid and with data previously reported by Thompson and co-workers (1929) on the effect of Squibb's thyroxine and of Armour's desiccated thyroid, they found that on the basis of equal iodine contents, about the same results were obtained with desiccated thyroid by mouth, pure thyroxine given intravenously and thyroxine in peptide combination given intravenously. They feel that more data are necessary to determine whether the effect of thyroxine in peptide combination is the same when given by mouth as when given intravenously. Data already collected indicate that the effect is nearly as great.

There is also the consideration of the optical activity of thyroxine. In preparing thyroxine polypeptide by tryptic digestion, Harington and Salter (1930) obtained some free thyroxine which proved to be levorotatory. They, therefore, concluded that the thyroxine in their polypeptide was levorotatory. Since, on the basis of equivalent iodine contents,

the effect of this polypeptide was the same as that of Squibb's thyroxine (Salter, Lerman and Means (1932)), which is racemic (Kendall (1931)), it would seem that optical activity may be disregarded in the interpretation of our data. There remain the observations of Gaddum (1930) on four rats, which led him to the conclusion that l-thyroxine is two and one-half times as effective as d-thyroxine. While we feel that his observations are inadequate to support such an important conclusion, our data, for purposes of completeness, may be considered in the light of his findings. If it be assumed that l-thyroxine is two and one-half times as effective as d-thyroxine, then 0.3 mgm. and 0.35 mgm. of Squibb's thyroxine would be equivalent to approximately 0.21 and 0.25 mgm. of l-thyroxine, respectively. If 50 per cent of the iodine in desiccated thyroid were in the form of diiodotyrosine, then 1.25 grain and 1.5 grain of the desiccated thyroid which we used would have contained only 0.15 and 0.18 mgm. of l-thyroxine, respectively. Thus, provided l-thyroxine is two and one-half times as effective as d-thyroxine and provided Squibb's thyroxine is racemic, it would be necessary to assume that at least 71 to 73 per cent of the iodine in the desiccated thyroid which we used was in the form of thyroxine in order to explain our results. It would also be necessary to assume that the thyroxine in desiccated thyroid is absorbed quantitatively from the gastro-intestinal tract, an assumption which would seem to be supported by the observation of Salter, Lerman and Means that thyroxine in polypeptide combination appears to be absorbed almost quantitatively. Another possibility is that some of the thyroxine in desiccated thyroid is not absorbed from the gastro-intestinal tract and that, even if l-thyroxine were two and one-half times as effective as d-thyroxine, our figures agree about as closely as would be expected in experiments of this sort. However, regardless of whether or not the identity of the effects of desiccated thyroid and thyroxine on the basis of their iodine contents is a coincidence, any difference that may exist is small enough to permit the conclusion that the simplest method of estimating with accuracy the activity of desiccated thyroid is by determining its iodine content. The other more important methods available are the acetonitrile test of Hunt (1905), the metamorphosis of tadpoles (Gudernatsch (1912)), biological assay on patients with myxedema (e.g., present study) and the determination of the amount of iodine in the acid-insoluble fraction after alkaline hydrolysis (Kendall (1929)). As a result of extensive investigations, Hunt (1908) has come to the conclusion that the efficacy of desiccated thyroid in protecting white mice against acetonitrile depends upon its iodine content. The effect of thyroid preparations on the metamorphosis of tadpoles likewise appears to be related to their iodine contents (see summary by Kendall (1929)). The third method is reliable, but, if done well, is very time-consuming. It would probably take several months to standardize any given preparation.

From published data it would appear that results with the fourth method are variable. Over all four methods, the determination of the iodine content has the advantage of relative simplicity and is apparently more accurate than any of the four with the exception of biological assay on patients with myxedema.

The large percentage of iodine in the thyroid which is in the form of thyroxine suggests a factor of safety to protect against lack of iodine. If a normal thyroid weighs 25 grams it may store as much as 25 mgm. of iodine when faced with an excess of this element (Marine and Lenhart (1909)). If only 50 per cent of this were stored as thyroxine, the gland would contain 18.75 mgm. of thyroxine, which, if used at the rate of 0.3 mgm. per day, would maintain a normal thyroid function for about 63 days, without any new formation. If all of the iodine is in a form that is active physiologically as thyroxine, then the gland would contain 37.5 mgm. of thyroxine, which, if used at a rate of 0.3 mgm. per day (in terms of Squibb's crystalline thyroxine), would maintain normal thyroid function for 125 days. If these calculations be correct, the maximum total amount of thyroxine that may normally be present in both the thyroid gland and the rest of the body is about 29 to 49 mgm., depending upon the percentage of iodine in the gland that is in the form of thyroxine. Thus, when the supply of iodine is abundant the thyroid gland may store enough of its hormone to keep the gland in a normal state during comparatively long periods when the iodine supply is deficient. This may explain why Kimball and Marine (1918) were able to prevent the development of simple goiter in school children by giving them iodine for periods of from two to three weeks twice a year. In the case of persons living in a goitrous area, a yearly vacation at the seashore with the eating of a large amount of salt water fish and frequent bathing in the salt water might be sufficient to prevent the development of simple goiter.

CONCLUSIONS

1. In two patients with marked myxedema the minimum amount of Squibb's thyroxine which had to be injected intravenously or subcutaneously every day in order to maintain the basal metabolism at the standard normal level was 0.3 and 0.35 mgm. respectively.

2. Injecting 1.5 mgm. and 2.0 mgm. every fifth day appeared to have the same effect as injecting 0.3 mgm. and 0.4 mgm. every day.

3. Desiccated thyroid in a daily oral dose of 1.5 grain, which contained 0.23 mgm. of iodine, the amount present in 0.35 mgm. of thyroxine, had the same effect on basal metabolism as 0.35 mgm. of thyroxine intravenously every day; and 1.25 grain of desiccated thyroid daily had the same effect as 0.3 mgm. of thyroxine intravenously every day. There are two main hypotheses for explaining these results:

- (a) That practically all the iodine in desiccated thyroid is in a com-

ination that is physiologically equivalent to thyroxine and that, when the amount given is not more than adequate to replace a deficiency, it is absorbed almost quantitatively from the gastro-intestinal tract.

(b) That some of the iodine in desiccated thyroid is in a form other than thyroxine, for example, diiodotyrosine; and that differences in the effects of thyroxine as it exists in the body and after separation from the gland by extensive chemical procedures explain the apparent agreement in our results between the effects of desiccated thyroid and thyroxine.

Since optical activity and peptide combination do not appear to alter the magnitude of the response to thyroxine, it seems probable that the first of these hypotheses is correct.

4. When a deficiency of thyroid secretion exists, there is approximately a linear relationship between the dose of thyroxine and the basal metabolism.

5. The intravenous injection of a single dose of 10 mgm. of thyroxine in a patient with marked myxedema produces roughly the same number of excess calories per mgm. of thyroxine as injecting the same amount of thyroxine in divided doses of 0.3 mgm. per day.

6. These results suggest that a dose of thyroxine which is just adequate to supply a deficiency in the body may be used almost completely, whereas any excess above this amount may, in large part, be excreted unused.

7. The amount of thyroxine normally present in the body outside of the thyroid gland appears to be the physiological equivalent of about 10 mgm. of Squibb's crystalline thyroxine, a figure which is approximately the same as that previously estimated by Plummer and Boothby.

8. The best method of standardizing desiccated thyroid at the present time would appear to be a determination of its total iodine content.

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