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# INTRODUCTION

Early investigations of urinary excretion of iodine followed experiments proving that the distribution of the element varies geographically. Orr and Leitch (46) have pointed out that the presence of iodine was discovered in sponges and other marine products only 4 years after Courtois' identification of the element in 1811. Sponges and seaweeds were commonly used for treatment of goiter in ancient Greece. Chatin between 1850 and 1876 published results of a number of experiments demonstrating the universal presence of varying minute amounts of iodine in water, soil and foodstuffs (11). Curtis and his associates (9) summarized not only their own investigations in Columbus, Ohio, but also the results of early studies of urinary iodine excretion in goitrous and nongoitrous areas. The range of average values in nongoitrous areas was 72 to 343 and in goitrous regions 27 to 64 gamma per day.

In the work on urinary iodine employing chemical quantitative determinations various methods have been used. These were based upon oxidative processes giving free iodine, which was determined either colorimetrically by comparison with known standards or by titration with sodium thiosulfate. Orr and Leitch (46) have discussed the merits of the two basic methods, each subjected to several later modifications. That of Kendall was useful for the estimation of iodine in thyroid tissue, but it was crude, the lower limit of detectable iodine being about 5 gamma. For most other biological substances including blood and urine, von Fellenberg's method was the only one, of sufficient delicacy, its lower limit of detectable iodine being about 0.08 gamma. Phillips and

Curtis (52) devised a modification of von Fellenberg's method which they used in their earlier work, applying it to 10 ml. samples of blood and 25 ml. samples of urine in duplicate. Their experimental error was large as compared with present techniques; 26 analyses of the same sample of beef blood ranged from 12.3 to 16.9 gamma per cent. The minimal detectable iodine by the present technique using the recording colorimeter (28) is approximately one-eighth that of von Fellenberg's method, i.e., as low as 0.01 gamma.

The only long-term study of iodine balance in recent years not employing radioactive iodine has been that of Nelson and associates (45) in 1947, who used large amounts of the element. They administered doses containing 20 to 440 mg. of inorganic iodine daily to healthy soldiers for a period of 45 days under conditions of standardized physical stress and environmental temperatures. It was observed that the iodine concentration in the sweat, like the chloride concentration, was related to the plasma concentration, and that the plasma iodine level decreased rapidly after cessation of intake to basal levels within 72 hours. His calculations for over-all iodine balance were 74 per cent of the ingested iodine in the urine, 6.0 per cent in the sweat, and 0.35 per cent in the feces, a total recovery of 80.35 per cent.

Results of this as well as of early balance studies employing older chemical methods, after administration of either iodide or physiologically active organic iodine compounds, are in close agreement with results of recent investigations employing radioactive iodine. Iodine of sodium or potassium iodide is rapidly absorbed from the gastrointestinal tract. In euthyroid individuals usually less than 2 per cent of

radioactive iodine ingested as iodide is excreted in the feces in 5 days (1, 3, 19, 20). This fecal iodine is almost entirely in organic form, according to Albert and Keating and their group (1, 3). After ingestion of radioactive iodide Hamilton and Soley (20) found 70 to 87 per cent of the radioiodine excreted in the urine of normal subjects within 48 hours with only traces appearing over the next 3 days. Other investigators (4, 25, 37) obtained mean recoveries of 55 to 64 per cent of the radioactive iodine in the urine during the 48 hours following administration of radioiodide. Rall (53) administered radioactive iodine to humans and fractionated the iodine compounds in the urine. In euthyroid individuals 0.3 to 2.0 per cent of the total urinary radioiodine was in the thyroxine fraction, 3 to 10.6 per cent as diiodotyrosine, and 88.8 to 95 per cent as inorganic iodide. He did not report the percentage of administered radioiodide in the urine. The above observations indicated that the simplest measurement of excretion of iodine, namely urinary total iodine, has significance in evaluating iodine balance.

In euthyroid individuals the cumulative urinary excretion of radioiodine administered as iodide is essentially exponential in form, approaching a plateau within 48 hours (25). Hyperthyroid individuals, because their thyroid glands take up more administered iodide that do those of normal subjects (42, 44, 59), tend to excrete a smaller proportion of it in the urine during the same amount of time than do normal persons (4, 10, 23, 36, 37, 47, 59). Conversely, hypothyroid individuals generally excrete a larger percentage of the administered iodide, though more slowly, than do normal persons (4, 10, 20, 25).

Childs and associates (7), who studied the influence of varying amounts of carrier iodide on radioiodide experiments, found that more than 0.1 mg. of carrier significantly reduced the relative thyroidal accumulation of radioactive iodine as measured by extrarenal disposal rate; on the other hand, quantities of carrier as great as 2 gm. had no significant effect upon the renal clearance of radioiodine.

Since the advent of the use of radioactive iodine this tool has been employed almost exclusively for investigation of iodine balance. As mentioned, the recently developed chemical method of iodine determination using the recording colorimeter (28) has a degree of accuracy manyfold that of earlier methods. The present experiment revives investigation in euthyroid subjects of quantitation of urinary iodine, employing these newer techniques. The more recent work on iodine balance, which will be discussed later, using various synthesized physiologically active organic compounds containing radioiodine, has been applied either to laboratory animals (17, 18, 24, 57) or to 1 or 2 humans who had abnormal thyroid function (1, 2, 3, 19). A few early experiments concerned with iodine excretion following administration of desiccated thyroid indicated an apparent difference between the disposition of exogenous thyroid in the body and that of pure thyroxine (5). In view of these facts experiments have been conducted to measure urinary excretion of iodine in 3 subjects receiving physiological amounts of desiccated thyroid.

## MATERIALS AND METHODS

The collection of each 24-hour urine specimen was begun in the morning at a uniform hour soon after arising. With the exception of the specimens from a subject, R.O.2, in southeastern Missouri and of those from a hypothyroid patient, N.C., all urines were collected in containers which had been thoroughly rinsed with distilled water. Yet in those cases in which the containers were cleaned with tap water, which in New Haven frequently has more than 10 gamma of iodine per liter (34) and more recently was found to contain 8 gamma per liter, the minute amount of contamination was negligible when diluted with a 24-hour specimen.

Each 24-hour specimen was in most instances diluted to a round numbered quantity selected so that a 1 ml. aliquot would contain no more than 12 gamma per cent of iodine. Greater concentrations are less accurate when measured with the recording colorimeter. Within this range the standard deviation of duplicate SPI (serum precipitable iodine) analyses on a large series of sera was found to be ±0.55 gamma per cent (28). Most specimens were diluted to a volume of 1 to 2.5 liters, and thus the standard deviation of the total daily iodine value ranged from ±5.5 to ±13.8 gamma. In certain instances in which the iodine content of the specimen was considerably higher than was expected the colorimetric reading was above 12 gamma per cent. On 2 occasions it reached 32.8 and 41.9 gamma per cent, representing the 2 days when the iodine excretion of N.C. was highest. With each of those values, however, the differences between the duplicate determinations were only 2.0 and 1.8 gamma per cent respectively. To have diluted the specimens so that the iodine concentration

would have been less than 12 gamma per cent would have required a further three- or fourfold dilution. Differences between duplicates would then have been magnified 3 or 4 times. Dilution to this extent probably would not have decreased the errors of 2.0 and 1.8 gamma per cent.

In most instances each 24-hour collection was diluted and analyzed on the day of its completion. In every case a 20 ml. portion of the thoroughly mixed dilution was refrigerated in a small bottle which had been rinsed 5 times with redistilled water and again several times with portions of the specimen to be retained. Preservative was never used, in order to avoid possible contamination by that route; since only total iodine was being measured, any organic decomposition should not have affected the final value. In several instances a repeat determination 4 to 13 days later agreed with the initial analysis within the limits of the standard deviation. The 4 specimens of R.O.2 were analyzed 3 to 5 days after their collection because they were mailed to the laboratory. In alkalinized urine specimens McCarrison and associates (39) demonstrated no loss of iodine over a period as long as 23 days.

Duplicate samples of single-distilled water, which was used in making the dilutions, revealed 0.05 gamma per cent of iodine, a concentration which is identical with the value obtained in this same laboratory in 1947 (34). Thus whenever more than 1 liter was used in a dilution 1 gamma was subtracted from the total iodine value. This was an academic correction, as it was only a fraction of the experimental error.

Aliquots of 1 ml. from each diluted specimen were analyzed in duplicate, employing the recent micro-procedure for determining the iodine in as little as 1 ml. of serum (28). Initially 1 ml. aliquots of urine were added to zinc hydroxide precipitates as described for the measurement of blanks in the SPI procedure (28). When the urine was submitted directly to the digestion step, however, the values agreed with those obtained when zinc hydroxide precipitates had been used. Consequently the time-consuming practice of precipitating and washing blanks was abandoned in the analyses of urine. Because urine has a low organic content in comparison with serum only 7 ml. of 2 N potassium permanganate solution were used, followed immediately by the addition of 18 ml. of 27 N sulfuric acid. With these amounts, as opposed to the 12.5 ml. of permanganate solution followed after 20 minutes by the sulfuric acid in the digestion of serum protein precipitate, 3 to 8 ml. of 0.15 N oxalic acid were necessary to decolorize the permanganate in the distillation stage. When 12.5 ml. of permanganate were tried in the digestion of the urine, as much as 20 to 30 ml. of oxalic acid were required for decolorization.

With few exceptions SPI and BEI (butanol-extractable iodine) were measured in the serum of each blood specimen, using methods previously described (28, 31). In every instance venous blood was drawn in the postabsorptive state in an iodine-free syringe, placed under oil, and centrifuged within 2 hours. It has been demonstrated that whereas the serum precipitate contains virtually all of the iodine in thyroxine or larger organic compounds, it also includes approximately 80 per cent of the diiodotyrosine iodine (35) as well as giving a falsely high

value in patients receiving inorganic iodine (31). With the butanol-extraction process, however, both diiodotyrosine and inorganic iodine are quantitatively removed by the alkali washing (31). The range of SPI values of normal subjects is 3.8 to 7.8 gamma per cent (28). The SPI exceeds the BEI by an average difference of 0.5 gamma per cent when the subject has not received inorganic iodine (33). Therefore the normal BEI range is calculated to be 3.3 to 7.3 gamma per cent.

In 3 subjects receiving desiccated thyroid lipid analyses, where listed, were performed on the same serum specimens as were the iodine determinations. These included analyses of the titratable fatty acids according to the Man and Gildea modification (29, 30) of the Stoddard and Drury method and total cholesterol by the gravimetric digitonin technique (6, 32). Using these methods the mean normal value and standard deviation have been found to be 12.3 $\pm$3.37 mEq. per liter for fatty acids and 202.7 $\pm$35.6 mg. per cent for total cholesterol (50).

One of the 3 subjects, N.C., a hypothyroid patient who was in cardiac decompensation on admission, was treated with desiccated thyroid in daily dosages increasing from 15 mg. to 120 mg. In addition to total iodine, chloride was determined daily on the urine collections, using the principle involved in Harvey's modification (22) of the Volhard method for quantitative urinary chloride determination.

## RESULTS

### 1. Urinary iodine excretion of six normal adults

In consecutive 24-hour urine specimens from 6 young ambulatory euthyroid adults in New Haven, 2 females and 4 males, eating average diets, the total iodine varied from 61 to 272 gamma. In spite of the differences in daily iodine excretion from person to person, the widest individual range of values was only 92 gamma, while the lowest was as narrow as 27 gamma, with one unusual exception, that of F. C. Certain variables occurred in most of the series of determinations, which will be discussed individually. During the periods in which the urinary determinations were being made a serum iodine determination performed on each subject was found to be within the normal range. Also a complete urinalysis in the case of each subject during the collections was within normal limits. The results of the series of determinations are presented in Table I and the iodine values charted in Graph 1.

In the first case, that of B.W., female, a preliminary study of 2 consecutive 24-hour specimens in May, 1951, contained 61 and 78 gamma respectively. Then on October 31, 1951, a series of consecutive analyses over a period of 1 week was begun, 2 weeks following the end of the previous menstrual period. Her serum BEI was 4.6 gamma per cent. She was eating an average diet with the usual variations, seafood excluded, and used plain salt. After the first day the iodine values were remarkably constant. The urinary volumes, varying between 1190 and 1880 ml., and iodine values, ranging from 80 to 133 gamma,

during the 7 consecutive days are presented in Table I and Graph 2. In the case of the 2 determinations made during the warmer weather of May the volumes of 860 and 600 ml. are conspicuously lower than in the later series. The 2 iodine values, 61 and 78 gamma respectively, are not significantly below the later range.

Similarly, in the case of D.S., female, 2 urine collections were analyzed for iodine in the spring. The first specimen, taken May 16, 1951, was completed in its collection approximately 1 day before the onset of the next menstrual period; the iodine content was 226 gamma. Because the question arose as to whether the proximity to the onset of the menstrual period had contributed to the high value, a second determination was done 21 days later. The iodine content was lower, 168 gamma, in spite of the fact that the volume of 1455 ml. was much greater than the previous volume of 580 ml. She had been eating an average diet with the usual daily variations, but, in contrast to B.W., was using iodized salt daily. Her SPI and BEI on April 12, 1951, were 4.4 and 5.4 gamma per cent respectively. Under the same dietary conditions a series of determinations was conducted over a period of a week beginning on November 24, 1951. The iodine values continued to be comparatively high, 134 to 207 gamma (Graph 2). A second serum BEI on November 29, 1951, was 4.0 gamma per cent. During the collection of the November 28 specimen the subject consumed about 3 ounces of frozen cod fish; yet the iodine excretion of that 24-hour period was not elevated, but was the lowest value in the series. Neither were the succeeding values significantly altered.

Ten days after the completion of this series, and 3 days after D.S. had been transferred to plain salt, a series of 4 consecutive determinations were markedly lower than previously, i.e., a range of 63 to 101 gamma per day (bottom of Graph 2) as contrasted with 134 to 226 gamma daily on iodized salt. The average iodine output on plain salt was distinctly less than half of that on iodized salt. The range of iodine excretion by D.S. on plain salt approximated that of B.W., who was similarly on plain salt.

A series of 5 consecutive determinations on J.R., male, in June, 1951, varied between 107 and 175 gamma per day (Graph 3). J.R. similarly ate an average but varied diet, but because his meals were obtained at various restaurants, the possibility of the use of iodized salt cannot be excluded. During the collection of his fifth and final specimen his diet included a cup of clam chowder; whether or not this was responsible for the relatively high iodine excretion of 175 gamma is only a matter of conjecture. According to evidence which will be presented later, the large volume of the final collection probably would not in itself have effected an increased iodine output of that magnitude. A serum BEI on June 13, 1951, was 4.0 gamma per cent.

A similar study on F.C., male, was begun on October 31, 1951 (Graph 3) but was unpredictably interrupted after 3 days when he was in New York for a weekend. On the third day following the interruption he resumed the collection of specimens. As in the case of J.R. he obtained his meals at various restaurants and again the possible use of iodized salt cannot be excluded. His serum BEI on November 13, 1951, was 4.4 gamma per cent. During the first 3 days of the series (Table I)

his iodine excretion varied considerably from 95 to 168 gamma. On the first day after resumption of the series, however, a surprisingly elevated value of 272 gamma was found, which is unexplainable on the basis of anything he had eaten during that day or the 2 preceding days. His diet of both the sixth day and eighth day in Graph 3 included a dozen oysters at supper. The values of both the sixth and ninth days were relatively high; it may have been that any large amount of iodine in the oysters was excreted rapidly on the night of the sixth day but happened not to have been excreted in significant amounts after the second consumption of the shellfish until the following day, i.e., the ninth day. The range of variation of iodine output, 81 to 272 gamma, was the largest among any of these subjects. Yet the average daily excretion, 163 gamma, was not so great as that of D.S. 1, 181 gamma, while taking iodized salt. Iodine excretion did not vary consistently with urinary volume.

A third similar study on R.O. 1 charted also in Graph 3, revealed a much more constant iodine excretion. Once again the diet was obtained at diverse restaurants. His SPI on June 13, 1951 was 5.7 gamma per cent. A preliminary determination of iodine excretion in the urine on May 25, 1951, was 106 gamma. Six serial determinations begun a few days later were remarkably constant, the iodine excretion varying only from 83 to 110 gamma. A separate final determination was performed on a 24-hour specimen collected during a forced water diuresis; again the iodine content, 94 gamma, fell within the previous comparatively low range, although the volume of urine had been essentially doubled to 1700 ml.

A series of 4 consecutive determinations was performed on the same subject, R.O. 2, in August, 1951, during summer residence in southeastern Missouri (Graph 3). Again an uncontrolled diet was followed, with the exclusion of sea food, although it was more liberal in quantity than in the preceding series on the same subject. Plain salt had been used on the table and in the cooking for a period of 3 weeks before the urine collections had been begun, as well as during the collections. In this series the iodine excretions were in a higher range, 129 to 191 gamma per day, while all the volumes were relatively low.

The final 2 series recorded in Table I were the beginnings of more extensive experiments which will be presented in their entirety. They are included here for the sake of comparison with the others, and differ from them in that both were conducted on a basically constant, or monotonous diet. In both cases all sea food was excluded, and only plain salt was used at the table. The first experiment was on the subject of the preceding 2 series. On this constant diet, while the average value was a little higher, the range of values was no less than in the series conducted 4 months previously in New Haven while the subject, R. O. 1, was on an uncontrolled diet. In the second experiment J. L., male, was on a similarly basically constant diet, although from time to time certain unavoidable variations occurred. His values fell into a wider range, 117 to 170 gamma, than did those of R. O. 3, whose range was 95 to 125 gamma.

## 2. Urinary iodine excretion of two normal males before, during and after ingestion of desiccated thyroid

To observe the urinary excretion of iodine in euthyroid individuals following the ingestion of desiccated thyroid 2 subjects, R.O. 3 and J.L., were placed on basically constant diets, with the exclusion of sea food and the use of plain salt at the table. The diet was followed for 6 days in the case of R.O. 3, and 3 days in the case of J.L. prior to the collection of the urine specimens. Then throughout a control period of at least 1 week the daily urinary iodine was measured. During the second week desiccated thyroid U.S.P. (Burroughs Wellcome tablets, uncoated) was ingested at the rate of 60 mg. per day in the form of a 15 mg. tablet with each meal and one at night. Following that period the urinary iodine determinations were continued until they had returned to the previously determined baseline. The results of the experiments with R.O. 3 and J.L. are presented in Tables II and III respectively, and the daily urinary volumes, iodine excretions and thyroid intake are plotted in Graphs 4 and 5 respectively.

Thyroid U.S.P. is desiccated and standardized to contain approximately 0.2 per cent of iodine in active organic compounds from thyroid gland. It is supposed to be free from iodide (27). Therefore 60 mg. of thyroid should have an iodine content of 120 gamma; this figure has been used here to compute iodine intake in the form of desiccated thyroid.

The diet of the first subject, R.O. 3, was as follows: breakfast: two scrambled eggs, two slices of buttered toast and coffee;

lunch: cheese sandwich, milk and apple pie; dinner: orange juice, chopped sirloin steak, corn or peas, lettuce and tomato, roll with butter, vanilla ice cream and coffee; and at night: grilled cheese sandwich and coffee. The diet was adhered to faithfully except for occasional unavoidable minor variations.

The iodine content of the specimens during the initial 8-day control period ranged from 95 to 125 gamma with an average daily output of 107 gamma. The iodine excretion increased during the first 24 hours when thyroid was taken and rose to a plateau by the second day on thyroid. This level of excretion of 165 to 213 gamma obtained throughout the period of thyroid consumption. The iodine output began to fall on the first day after the cessation of thyroid and continued to decrease until it reached the base range by the fourth day off thyroid. The iodine excretion continued in this range throughout the remaining 3 days until the culmination of the experiment on its twenty-second day.

The largest 24-hour urinary volume, 1090 ml. occurred on the second day after thyroid had been begun. This exceeded any other volume by 145 ml., a difference insufficient to indicate any definite diuretic response to thyroid.

A serum BEI on the day before thyroid was begun was 5.2 gamma per cent. This agreed with the SPI of 5.7 gamma per cent obtained 4 months previously. On the morning of the fourth day on thyroid, i. e., after only 3 days of a total of 180 mg. of thyroid, both SPI and BEI were depressed, being respectively 3.9 and 3.8 gamma per cent. These values continued to fall until the BEI reached a low point of 2.5 gamma

per cent 25 days after thyroid had first been ingested and 18 days after the cessation of thyroid. The values throughout the next week, although rising slightly, remained at minimum normal levels. No symptoms such as changes in pulse or weight or subjective phenomena were noted at any time, either during or after thyroid administration.

Because of the persistence of the low serum iodine concentrations total cholesterol and fatty acids were measured in the later serum specimens. Both determinations remained within normal limits.

As mentioned previously, the average daily urinary iodine excretion during the 8 days prior to thyroid administration was 107 gamma. The average excretion during the period in which the iodine output remained elevated (i. e., the ninth through the eighteenth day, a total of 10 days) was 176 gamma. The average excretion after the effect of the exogenous thyroid was no longer apparent (i. e., the nineteenth through the twenty-second day, a total of 4 days) was 103 gamma. By subtracting 107 from 176 the average daily excess of iodine excretion due presumably to the effect of the exogenous thyroid was 69 gamma. Since this effect was apparent for 10 days, the total excess iodine output amounted to 690 gamma. The administered thyroid theoretically contained 120 gamma of iodine for each of the 7 days during which it was taken, or a total of 840 gamma. Thus it is evident that roughly 82 per cent of the iodine ingested in the form of thyroid was excreted in the urine, and that the excretion was complete by the end of the third day after the exogenous thyroid had been withdrawn.

In the case of the second subject, J.L., the basic diet was as follows: breakfast: fruit, 2 eggs, milk and coffee; lunch: soup

or juice, lettuce and tomato sandwich, apple pie and milk; dinner: soup, chopped sirloin steak, potatoes and vegetable, roll with butter, apple pie and milk; late at night: candy bar and coffee. There was somewhat greater daily variation in this diet than in the preceding case, particularly with respect to the soup, juice, fruit, etc. In a few instances there was a gross departure from the diet.

During the initial control period of 9 days the range of iodine excretion was 117 to 170 gamma, with an average daily excretion of 149 gamma. As can be seen in the graph, in the middle of the week during thyroid ingestion there was a discrepancy in the intended plan of 60 mg. of thyroid per day, in so far as five 15 mg. tablets were taken on the third day, only 2 on the fourth, and, in order to compensate, 5 again on the fifth day.

There was no response to the exogenous thyroid until the second day of administration, in contrast to the rise on the first day in the preceding subject. In the present case, however, the increase in iodine excretion on that first day of response was 99 gamma. The iodine level in the urine reached a conspicuous peak on the third day, a day on which 75 mg. of thyroid were taken. Again in contrast with the other subject, the iodine excretion did not reach a plateau, but fell precipitously during the next 2 days to a level at the upper limit of the base range. This low value occurred on a day on which again 75 mg. of thyroid were taken. Then a second lesser but significant rise in iodine output was apparent, reaching its peak on the first day following cessation of the thyroid. From this point the values proceeded to decrease to the base range by the fourth day off thyroid,

as was also true in the case of the first subject. The values remained at the base level for a total of 5 days until the culmination of the experiment at the end of its twenty-fourth day.

With the relatively wide fluctuations in the volume of urine from day to day, this series of determinations illustrates rather clearly the apparent independence of the iodine output from the volume of urine. This fact is particularly evident on the nineteenth day of the experiment, when the volume spiked to a conspicuously high level of 1950 ml. and yet the iodine excretion continued its descent following cessation of thyroid.

Before the thyroid ingestion was begun the SPI and BEI were well within the normal range, being 4.7 and 4.8 gamma per cent respectively. On the morning of the fourth day on thyroid, after 3 days of a total of 195 mg. of thyroid, the SPI dropped to 3.5 gamma per cent, and a BEI analysis on the same serum specimen was 4.3 gamma per cent. On the day after completion of administration of the full 420 mg. of thyroid the values remained essentially unchanged. Three days later they were 4.9 and 3.5 gamma per cent respectively. Both values were well within the normal range after another 3 weeks. This contrasts with the case of the first subject, whose SPI and BEI were slightly below the minimum of normal even after 63 days from the time the thyroid had been begun.

As mentioned above, the average daily urinary iodine excretion during the 9 days prior to the administration of the thyroid was 149 gamma. The average excretion during the period in which thyroid was administered and during which the iodine output remained elevated

(i.e., the tenth through the nineteenth day, a total of 10 days) was 204 gamma. The average excretion after the effect of the exogenous thyroid was no longer apparent (i.e., the 20th through the 24th day, a total of 5 days) was 146 gamma. It can be seen that the average daily excess of iodine excretion due presumably to the effect of the thyroid ingestion was 55 gamma. Since this effect was apparent for 10 days, a total of 550 gamma of iodine in the urine may be attributed to the exogenous thyroid, which contained theoretically 120 times 7, or 840 gamma of iodine. Hence it is evident that 66 per cent of the iodine ingested in the form of thyroid was excreted in the urine, and that the excretion was complete by the end of the third day after the administration of the desiccated thyroid had been terminated. This was true also in the case of the first subject.

### 3. Urinary iodine excretion of a hypothyroid male before and during initiation of therapy with desiccated thyroid

Urinary iodine recovery in a hypothyroid patient was compared with that in the 2 euthyroid subjects discussed.

N.C., C64300, a 75 year old white male, weighing 94 kg., was admitted to the medical service of the New Haven Hospital on Nov. 6, 1951 with a presenting complaint of cough and difficulty in breathing of 4 days duration. He had been essentially well until 4 years previously, when he developed exertional dyspnea, orthopnea, and marked edema of the lower parts of his legs. The symptoms had been progressing with exacerbations during upper respiratory infections, at which times there was also wheezing. During this time he had been treated with digitoxin, ammonium chloride, and parenteral mercurials, with partial relief of symptoms. Over the year preceding this admission the family had noticed marked slowing of movement, speech and

thought, together with a deeper more husky voice, constipation, and sensitivity to cold. He had always been obese with a fairly constant weight around 91 kg. On admission his temperature was 100 degrees rectally, pulse 68, respiration rate 26, and blood pressure 136/80. The patient was a large, obese man appearing chronically ill, with slow ponderous movements, deep hoarse voice, slow speech, and marked orthopnea. The skin was yellowish and thick, although the sclerae were white, and the face had a pasty complexion with some puffiness around the eyes. The thyroid was not felt. The chest was emphysematous with musical rhonchi throughout. The heart was enlarged with a systolic precordial murmur heard loudest in the aortic area. There were multiple varicosities over the lower abdominal wall and legs. The deep tendon reflexes were hypoactive but equal bilaterally with absent Babinski reflexes. The fingers had numerous bony prominences, and there was marked pitting edema of the lower legs. The hemogram and urinalyses were normal except for a one-plus urine albumin noted only on admission. The blood chemistries were within normal limits except for a serum chloride of 91.3 mEq. per liter, and the liver function tests were normal except for a thymol turbidity of 10.0. Chest x-ray revealed enlargment of all cardiac chambers and the electrocardiogram had a P-R interval of 0.26 seconds with digitalis T-wave changes.

The patient was placed on a regular 1000-calorie salt-free diet. A mercurial injection had been given the day before admission. On the morning of the fourth hospital day, 5 days after the last injection of mercuhydrin, serum was drawn which contained a BEI of 0.5 gamma per cent, total cholesterol of 184 mg. per cent and fatty acids of 11.1 mEq. per liter.

The edema and dyspnea markedly decreased on an average of 0.2 mg. of digitoxin per day, and he appeared much more alert at the time of discharge. On the 15th day of the experiment, however, he developed pain, tenderness, swelling, and local heat in the left knee joint, with a temperature of 100.8 degrees by rectum and a white blood cell count of 16,000 per cubic millimeter. X-ray revealed hypertrophic changes. The symptoms gradually subsided over the next few days until discharge, without specific therapy. Three weeks after discharge the patient was noted to have shown great improvement in his mental status as well as cardiac status, although his skin remained quite dry and coarse and his voice coarse, though not to the same degree as on admission. There was still some weakness and stiffness of the left knee. His serum BEI at that time was 2.7 gamma per cent.

Twenty-four hour urines were collected, beginning with the third hospital day, 4 days after the last mercuhydrin injection. The urine chlorides and total iodines are in Table IV and Graph 6. Iodine measurement was omitted on the fifth hospital day because on that day 0.5 ml. of mercuhydrin was given. This was the only mercurial injection during the experiment. Following the mercuhydrin, throughout that same 24 hours, the fifth day of hospitalization, the urine output was 2470 ml. with a chloride content of 7.63 grams. On the preceding day and the 2 succeeding days the total daily urinary iodines were 58, 45 and 82 gamma with an average of 62 gamma, an average less than the 96 gamma which was the lowest average for any of the young normal male subjects. The patient's intake was less, however, being limited by his reducing diet.

On the fifth day of urine collections therapy with desiccated thyroid was initiated at the rate of 15 mg. per day. The exact pattern of increase in dosage is recorded in Table IV. On the second and ninth days after the institution of thyroid the urine specimens were not collected in full. There was a rise in iodine output to 136 gamma by the third day on thyroid. Varying levels in this somewhat higher range were maintained until the specimen of the first day on a dosage of 120 mg. of thyroid contained 190 gamma of iodine, followed by a conspicuous rise to 433 gamma on the next day. The excretion of iodine continued at even higher levels on the succeeding days, with a spike to 1048 gamma on the 18th day of the experiment. The excretion was 327 gamma 2 days later, the final day of the experiment, at which time the patient was discharged home, continuing on 120 mg. of

desiccated thyroid per day. The urine volumes were comparatively small when the iodine excretion was undergoing its great increase; for example, the two lowest volumes, 700 and 570 ml. consecutively, contained respectively 433 and 655 gamma of iodine.

Since iodine is a halogen, the question arose as to whether whatever degree of congestive failure the patient had might have seriously influenced the iodine excretion, although the peripheral edema had become markedly reduced by the fifth hospital day. For this reason chloride determinations on the urine specimens were compared with those of the iodine. The chloride values roughly paralleled the volumes, whereas the iodine curve was a marked contrast to both. The patient had received ammonium chloride on the first, second, and third days of the experiment, 9 grams each day, and again on the eighth and ninth days, 9 and 6 grams respectively.

The average of the 3 urinary iodine values obtained before thyroid therapy had been begun was 62 gamma, which represents the baseline for the purposes of calculation. The quantity of iodine excreted in all the succeeding specimens in excess of this daily value amounted to 3518 gamma. The theoretical amount of iodine ingested in the form of desiccated thyroid was 2160 gamma. Thus, as determined by urinary excretion, there was a negative balance of 1358 gamma, even including the total of 150 gamma of iodine ingested during the 2 days for which urine collections were not obtained (November 13 and November 20). This contrasts indeed with the striking positive balances in the 2 euthyroid subjects.

## DISCUSSION

The over-all range of daily total iodine excretion in the 9 series of determinations on normal individuals was 61 to 272 gamma. Excluding the one subject (D.S. 1) who regularly used iodized salt, the range of average total urinary iodine excretion by healthy young adults in New Haven was 73 to 163 gamma per day.

As reported by Curtis and his groups (9), in 6 series of studies in goiter-free areas the range of average urinary iodine excretions was 72 to 343 gamma per 24 hours. A grand average is not justified because of different chemical methods and varying numbers of subjects in different studies. Curtis and his group cited the work of von Fellenberg in 1926 and 1927 in 2 goiter-free regions. In one, on the Ligurian coast of Italy, the daily variation was 30 to 140 gamma with an average of 72 gamma; in the other Vik i Sogn, Norway the range was 94 to 240 gamma per day, averaging 146 gamma. He calculated these values from determinations on nocturnal urines, assuming from previous work that the urinary excretion was approximately constant for each hour. In the coastal city of Danzig, where the water was found to contain an unusually high iodine content of 10 gamma per liter, Liek in 1927 observed in healthy men a range of 200 to 590 gamma, averaging 343 gamma of iodine. In 1931 Scheringer in a series of determinations on 7 normal men in nongoitrous Berlin found 103 to 214 gamma of iodine per day, with an average of 173 gamma, in the urine; 17 normal nonpregnant women excreted from 66 to 389 gamma, with an average of 141 gamma per day. Curtis and associates (9), from unpublished data by Moore, cited an average daily urinary iodine excretion

of 117 gamma in New Orleans, Louisiana. Recently, using newer methods of analysis, Stanbury and associates (56) reported daily urinary excretion of iodide to be 126 and 145 gamma by 2 persons residing in Massachusetts.

The range of average values in New Haven falls within that compiled from these investigations in various other nongoitrous geographical areas, although the early investigators used less accurate methods of analysis. With the exclusion of the exceptionally high values in Danzig, the range of average values was 72 to 173 gamma, as compared with the range of averages of 73 to 163 gamma found in these experiments. The over-all range of individual values obtained in the earlier experiments, excluding those in Danzig, was wider, 30 to 389 gamma, than the range of 61 to 272 gamma in this study. The iodine content of the water in Danzig, 10 gamma per liter, is essentially the same as that in New Haven (34); yet the range of daily urinary iodine as reported there, 200 to 590 gamma, is out of all proportion to that in this series.

The difference between the average daily iodine excretion of D.S. when on iodized salt (181 gamma) and that when on plain salt (73 gamma) is attributed to the iodine in the salt, because other factors remained essentially unchanged. D.S. is a light salt user. Each gram of iodized salt in this country contains 0.1 mg. of potassium iodide (8) or approximately 77 gamma of iodine. If, on the basis of previous investigations (20, 45) about 75 per cent of the ingested iodine is excreted in the urine, this difference in iodine excretion of D.S. could be accounted for by the consumption of an average of 1.9 gm. of iodized

table salt per day. McClendon and coworkers (41) in 1930 found an average content of 9.6 gamma of iodine in eight 24-hour urine specimens of Minnesota men using noniodized salt, whereas 9 specimens from Minnesota men using iodized salt averaged 121.3 gamma. This difference is very similar in magnitude to that noted in D.S., although the absolute values, ocurring in a goitrous region, are considerably lower. Recently Stanbury and associates (56) reported the daily urinary iodide excretion of 293 gamma by an individual ingesting iodized salt in Massachusetts, as contrasted with 2 normal values of 126 and 145 gamma in that region.

The increased average daily urinary iodine excretion in R. O. from 96 to 160 gamma while residing in southeastern Missouri, a region on the fringe of the goiter belt, occurred while the subject abstained from iodized salt and sea food, but did partake of a more generous diet than when in New Haven.

Urinary iodine values found by various authors in goitrous regions of the world contrast sharply with those of this experiment and those of the studies discussed above. In 1923 McClendon and Hathaway (40) noted the extreme paucity of iodine in Lake Superior water. Yet they observed that at least half of the persons drinking that or similar water escaped having goiter, and they became curious as to the role of food in supplying an apparently adequate amount of the element for the physiological needs of these individuals. In a single determination over a 3 day period they found that a young man in the moderately goitrous region of Minneapolis consumed a daily average of 19 gamma of iodine and excreted an average of 7 gamma. As reported by Curtis and his group (9)

von Fellenberg in 1924 demonstrated that in 7 normal persons from the slightly goitrous region of Effingen in Northern Switzerland the daily variation in urinary iodine excretion was 28 to 108 gamma, averaging 64 gamma. His values were calculated from determinations on nocturnal urine specimens. Virtanen and Virtanen (58), on the other hand, in 1940 noted variations in the iodine content of urine excreted during different times of day. Curtis and associates (9) cited Lunde's observation in 1928 that in the Sandsvaer goiter district of Norway, where the incidence of goiter varied between 30 and 60 per cent, 25 nongoitrous healthy men abstaining from sea food excreted daily 6 to 83 gamma of iodine in the urine, with an average of 38 gamma. Again the values had been calculated from analyses of nocturnal urines. McCarrison and associates (38, 39) in 1931 found that in Gilgit in northern India, an area of endemic goiter, nongoitrous persons excreted about 9.0 gamma of iodine per liter. In Coonoor, however, also in northern India, but where true endemic goiter was conspicuously absent, the iodine excretion in 3 persons ranged from 26 to 72 gamma per liter. These workers performed their determinations on single fractional urine specimens, with no note of 24-hour volumes. In the goitrous region of Pécs, Hungary, Scheffer in 1932, as cited by Curtis and his group (9), found a daily urinary iodine range of 21 to 33 gamma, averaging 27 gamma. Elmer and Scheps in 1934 in the goitrous area of Lwów, Poland, recorded 4 average daily urinary iodine values in normal individuals which ranged between 30.7 and 40 gamma, averaging 35 gamma (13, 14).

Curtis and associates (9) in 1937 performed more prolonged studies on 13 normal persons in Columbus, Ohio, a region of moderately

endemic goiter, and found the over-all range of daily iodine excretions to be 7 to 196 gamma; the range of average daily excretions for the 13 subjects was 36 to 78 gamma, with a grand average of 51 gamma.

Virtanen and Virtanen (58) analyzed 24-hour urine specimens with an average output of 1.3 liters. In 144 individuals they found an average of 20.7 gamma of iodine per liter in the district of Sortavala, one of the worst goitrous regions in Finland, but an average of only 25.3 gamma per liter in the district of Turku, in the nongoitrous area. In the 6 studies in goitrous areas of 24-hour urinary iodine excretion, the average values were between 27 and 64 gamma of iodine. Stanbury and his group (56) in 1952 have reported that in many of the euthyroid patients studied in Mendoza, Argentina, an area of intensely endemic goiter, the daily iodide excretion was less than 10 gamma.

The approximate recovery in the urine of 82 and 66 per cent of the iodine ingested as thyroid by the euthyroid males R.O. 3 and J.L. was higher than expected. The few investigations in the past measuring excretion of iodine after thyroid ingestion employed large unphysiological doses of thyroid and dogs as subjects. In the experiments of von Fellenburg on humans and of Asimoff and Estrin on dogs, as reported by Barnes (5), urinary iodine excretion was measured merely during 24 hours subsequent to ingestion of beef thyroid or desiccated thyroid. During these 24 hours only 16 to 35 per cent of the iodine in these substances was recovered in the urine. When Barnes gave dogs as much as 1 to 3 grams of desiccated thyroid per kilogram of body weight daily the iodine excreted in the urine varied between 37 and 57 per cent of

the administered amount in 4 to 9 days. With prolongation of the period of daily feeding to 92 days the excretion reached 60 per cent. Recent investigations on the excretion of iodine after administration of organic iodine compounds which affect metabolism have been made with compounds into which radioactive iodine could be incorporated chemically. The incorporation of radioactive iodine into desiccated thyroid requires physiological synthesis and is not practicable in human experiments. Thyroxine, thyroglobulin and iodocasein containing radioactive iodine have been used by Albert and Keating (1, 3, 19). The early data of Kendall (26) and of Barnes (5), which the latter found comparable to the results of Krayer and of Asimoff and Estrin, suggested that smaller percentages of iodine are excreted by the kidneys and significant amounts (up to 47 per cent) in the bile after the oral or parenteral administration of thyroxine as opposed to the findings when thyroid was ingested. Since the amounts of thyroxine were enormous and unphysiological (20 to 500 mg.), the data are not conclusive. However, it is possible that the compounds and quantities in which iodine is excreted in urine and feces after administration of thyroxine differ from those after administration of desiccated thyroid. There are therefore no comparable data with which the compare the urinary excretion of iodine of J.L. and of R.O. 3 while taking 0.06 gm. of desiccated thyroid.

The experiments most comparable to the studies on J.L. and R.O. 3 when taking thyroid are those of Albert and Keating. After giving orally 45 mg. of thyroglobulin containing 0.1 mg. of iodine and

140 microcuries of radioiodine the kidneys excreted about 58 per cent of the dose of radioiodine within 3 days. In 6 days only 11 per cent appeared in the feces (3). A myxedematous patient given orally 70 and 63 mg. of iodocasein containing respectively 170 and 230 microcuries of radioiodine excreted 41.9 per cent of the isotope in the urine within 3 days and 59.4 per cent in the feces within 40 hours. When the myxedema had been adequately treated 25.7 per cent of the radioiodine was in the urine within 3 days and 51.7 per cent in the feces in a 110 hour period (19). After giving orally about 1 mg. of d-l-thyroxine labelled with 100 microcuries of radioiodine (1, 3) the urinary radioiodine excretion within 72 hours was 28 per cent of the dose when the patient was hypothyroid, and 43 per cent when she had been restored to a euthyroid state. Excretions in the feces were 38 and 23 per cent respectively.

Albert and Keating and associates (1, 3, 19), Gross and Leblond (17, 18), and Taurog, Briggs, and Chaikoff (57) are among the investigators who have tried to correlate thyroid uptake of various compounds of radioactive iodine with concentrations of inorganic and protein bound iodine of plasma, with radioactivity over the liver, and with organic and inorganic iodine of the bile. That the liver is active in the metabolism of thyroid hormone is established. Experiments with labeled thyroglobulin, iodocasein, and thyroxine in man (1, 3, 19) and with oral or parenteral labeled thyroxine in rats (17, 18, 24) have demonstrated that the liver contains a marked concentration of the radioactivity within a few hours after administration. Thyroxine is excreted in the bile. Taurog and his group (57) found that, at least

in rats, a large part of the radioactivity excreted in the bile after giving minute amounts of labeled thyroxine was in the form of a conjugated thyroxine compound which could be hydrolyzed with beta-glucuronidase. Although hydrolyzed to free thyroxine in its passage through the intestines, it was reabsorbed only to a minor extent. Gross and Leblond (17) found in rats that when the bile contained large amounts of thyroxine after injection intravenously of large unphysiological doses of thyroxine, the radioiodine was excreted to a great extent (80 per cent) in the feces in thyroxine-like form. When radioactive iodine was injected as thyroxine in physiologic doses (as low as 0.001 gamma) it was excreted mostly in a nonthyroxine form in both urine and feces, with a much larger proportion (40 per cent of the tracer) in the urine than after the injection of large doses of thyroxine (18). Since, therefore, dosage and speed of absorption influence the quantities of inorganic and thyroxine-like iodine compounds in both urine and feces it is impossible to compare published data with the urinary iodine excretion of R.O. 5 and J.L. when receiving the small amount, 0.06 gm. of desiccated thyroid daily.

It appears that regardless of the type of compound administered, including diiodotyrosine (2, 12, 24), the body is capable of catabolizing it and excreting the contained iodine rapidly, whether large doses or physiological doses are used. This rapid breakdown by the body is evident in the serum, too, as after the administration of labeled thyroglobulin, iodocasein, thyroxine or diiodotyrosine to humans a significant proportion (as much as one-half) of the radioactivity in

the serum within a few hours after administration is in nonprecipitable form (1, 2, 3, 19). On the basis of their findings using physiological doses of thyroxine in rats, Gross and Leblond (18) calculated that the time for complete renewal of the body thyroxine in their animals was 25 to 35 hours. The experiments presented here confirm such a view of rapid catabolism of organic iodine compounds, as in both R.O. 3 and J.L. there appeared to be no cumulative effect by the body over the week-long period of administration of desiccated thyroid. The rate of excretion of the contained iodine decreased on the first day after cessation of thyroid, and within a total of 72 hours all of the detectable excess of iodine had been excreted.

In both of the euthyroid subjects given thyroid in this experiment the serum iodine was depressed significantly after 3 days on desiccated thyroid. Both SPI and BEI of R.O. 3 remained at sub-normal and minimal normal values for at least 8 weeks after cessation of the medication. In the case of J.L. the two values fluctuated between normal and minimal normal but both were well within the normal range by 3 to 4 weeks after cessation of thyroid. It is supposed that this effect may have been mediated through a depressant action on the thyrotrophic hormone production. This seems likely particularly in view of the fact that the sera were drawn at the hour of arising, 8 to 10 hours after ingestion of the last 15 mg. tablet of thyroid, and thus may more truly have represented the level of endogenous hormone production. Neither subject had any symptom of hypothyroidism. It has been shown by other investigators that in contrast to the sensitivity of hypothyroid subjects to desiccated thyroid (61) euthyroid

subjects can tolerate much larger doses without significant effect on the basal metabolic rate or pulse (55, 60). Winkler, Lavietes, Robbins, and Man (60) noted that after cessation of administration of 5 grains of thyroid daily to a nonmyxedemous subject the serum iodine promptly fell to subnormal levels during the next 4 weeks and spontaneously returned to a normal level in 10 weeks. Riggs, Man, and Winkler (55) observed that frankly abnormal SPI values (above 8.0 gamma per cent) in 4 euthyroid individuals, like the basal metabolic rate, were not maintained consistently until a dosage of 10 grains of thyroid daily was attained. When therapy was discontinued the SPI fell within a week to normal or subnormal levels, attaining myxedematous levels in 3 to 4 weeks and returning to normal levels by the fifth week. Farquharson and Squires (15) found that cessation of moderate doses of thyroid which had been given to euthyroid "hypometabolic" individuals produced a rapid decline of the basal metabolic rate to a point below the pretreatment level, with return to that initial level gradually during the next few months. In euthyroid subjects given 3 grains of thyroid daily, Greer (16) observed that in those susceptible to that dosage there was marked depression in radioiodine uptake by the thyroid in approximately a week. One-third of a group of 25 subjects showed marked thyroid depression after receiving 1 grain of desiccated thyroid daily. In most cases, whether thyroid had been given for a few weeks or for several years, there was complete recovery of radioiodine uptake by the thyroid gland within 2 weeks after cessation of therapy, although a few subjects showed depression for 3 to 11 weeks. Rienhoff (54) applied this principle as a therapeutic procedure by giving 4 grains

of thyroid daily to 9 patients with severe hyperthyroidism for 3 weeks preoperatively; in all cases there was symptomatic improvement in 2 to 4 days. Like Greer (16), Perlmutter and his group (48), on the basis of experiments with euthyroid individuals, hypothesize that "ingestion of thyroid substance decreases the function of the thyroid gland primarily through pituitary inhibition." Their data indicate, however, that to a minor degree, ingested thyroid also impairs the responsiveness of the thyroid gland to administered thyrotrophic hormone.

In spite of the persistently low serum iodine values in R.O. 3 during and following administration of the desiccated thyroid, the serum cholesterol and titrated fatty acids showed no tendency toward elevation. Low cholesterol values, however, not infrequently accompany subnormal SPI values as observed clinically (51). Peters, German, and Man (49) reported a series of patients with tumors or other lesions at or adjacent to the pituitary gland who had in most cases SPI values at hypothyroid levels, but in the majority of whom the serum cholesterol was within normal limits and who were all lacking clinical features of hypothyroidism. Assuming that exogenous thyroid mediates its action on the thyroid gland primarily by depressing pituitary thyrotrophin production, a study of serum lipids in euthyroid individuals treated with desiccated thyroid is warranted.

The low urinary iodine values observed in N.C. prior to administration of thyroid have two possible explanations. First, and the most likely, is the fact that he was on a 1000-calorie salt-free diet, thus limiting his iodine intake. Secondly, 3 days before the

urine collections had been begun, and again the day after the collections had been started (for which reason an iodine determination was omitted on that date), the patient received a mercurial injection. Meyers and Man (43) have recently demonstrated an interfering effect of mercuhydrin on SPI determination in subjects which with adequate diuretic response was no longer apparent 24 hours after injection but which without adequate diuretic effect persisted longer. Because the urinary iodine determinations on M.C. had not been initiated until 3 days after the first injection of the mercurial and because a marked diuretic response occurred within the first 24-hour period following the second injection, it may be assumed that the iodine values recorded during the pretreatment period were free of artifactual effect.

The marked negative iodine balance in M.C. during the initiation of his therapy with desiccated thyroid is inexplicable. Contamination of the later specimens during their collection on the ward cannot be excluded, but for such a factor to occur during so many days consecutively and in such similar amounts in very improbable. The iodine content of myxedematous tissue fluid is unknown. No correlation can be drawn, therefore, between the increased iodine excretion and dissipation of myxedematous fluid during initiation of therapy with desiccated thyroid. Another possibility is that mobilization of the edema fluid of the patient's congestive failure may have transported previously retained iodine stores. This seems unlikely for a variety of reasons. First, during the time that the urinary iodine was increasing so rapidly the volume of excretion as well as its chloride content were at the lowest levels of the entire experiment. Secondly, by the time

the great increase in iodine excretion occurred the patient's congestive failure had markedly improved, and mobilization of edema fluid which had been effected earlier in the investigation had failed to transport any such conspicuous quantity of iodine. The only 2 weights taken during the patient's hospital stay were 94 kg. on the second day of the experiment and 92 kg. on the seventh day; this loss of 2 kg. over the period of 5 days, which is not incompatible with the initiation of his low-calorie diet, occurred well in advance of the marked increase in urinary iodine on the fifteenth day of the experiment. Mason and Oliver (36) found that in a case of constrictive pericarditis with serous effusions and some generalized edema the excretion of a tracer dose of radioiodide was normal in all respects; furthermore it was not altered significantly when performed again immediately following the removal of 4 pints of pleural fluid and an injection of "neptal" which doubled the urinary output.

In the experiments on iodine excretion in the euthyroid subjects reported in this paper no consistent relationship existed between volume of output and its iodine content. Curtis and his group (9) and Arnott and associates (4) arrived at the same conclusion. Myant and associates (44) showed that renal clearance rate of iodide, in contrast to thyroid clearance rate, is essentially the same in thyrotoxic patients (27 ml. per minute) as in normal subjects (31 ml. per minute). McConahey and associates (42) found similar values in these two conditions but observed that in myxedematous patients the renal iodide clearance was much less, namely 17.9 ml. per minute. Handley and associates (41) have demonstrated in dogs the diuretic effect of

thyroxine, which causes a marked increase in renal plasma flow, glomerular filtration rate, tubular transport of dextrose and p-amino hippurate, and an increase in renal oxygen consumption.

A possible explanation for the negative balance in N.C. is the mobilization of excess iodine from the tissues of the body. In spite of the high concentration of iodine in the thyroid gland the extrathyroid tissues still contain about 70 per cent of the total iodine of the body. In the case of N. C. it is doubtful that the low grade fever which occurred transiently on each of the first 2 days during which the iodine excretion began to increase could have been responsible for the phenomenon. It seems more likely that the increased metabolic activity attendant upon the administration of the exogenous thyroid may have effected an increased mobilization of iodine from the body's stores. A second patient with a similar degree of hypothyroidism could not be obtained sufficiently early to begin urine collections before therapy. Until further data can be obtained the observations on N.C. need confirmation.

# SUMMARY

(1) Total 24-hour urinary iodine excretion was measured in 9 series of determinations on 2 healthy young women and 4 healthy young men under average dietary conditions in New Haven, Connecticut. The over-all range of daily urinary iodine was 61 to 272 gamma, and the range of average values was 73 to 163 gamma. One subject who regularly used iodized salt excreted a daily average of 181 gamma.

(2) The effect on daily total urinary iodine of ingestion of 60 mg. of desiccated thyroid for 1 week in 2 of the above young men was investigated. Approximately 82 and 66 per cent of the iodine ingested in the form of thyroid, U.S.P., were recovered in the urine. Within 3 days after cessation of the medication the urinary iodine had returned to within the normal range.

(3) The urinary iodine excretion of a hypothyroid man was followed for 16 days during the initiation of therapy with desiccated thyroid. The theoretical amount of iodine ingested in the form of thyroid was 2160 gamma. There was a negative balance of 1358 gamma of iodine on the basis of urinary excretion.

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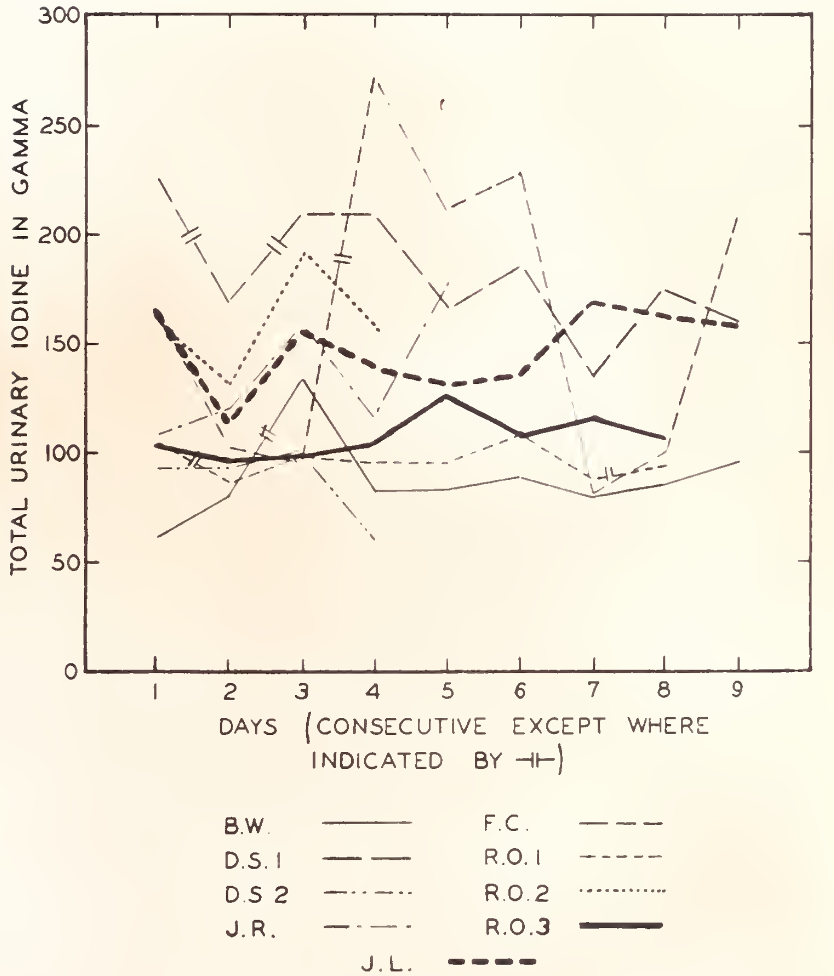
TABLE I

TWENTY-FOUR HOUR URINARY IODINE EXCRETION OF SIX NORMAL YOUNG ADULTS UNDER AVERAGE DIETARY CONDITIONS

| SUBJECT | | TWENTY-FOUR HOUR URINE COLLECTIONS (Dates in 1951, vol. in ml., total iodine in gamma) | | | | | | | | | IODINE RANGE | AVG. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.W., ♀ | | | | | | | | | | | | |
| Age 25 | Date | 5/16 | 5/17 | 10/31 | 11/1 | 11/2 | 11/3 | 11/4 | 11/5 | 11/6 | | |
| 57 kg. | Vol. | 860 | 600 | 1280 | 1583 | 1293 | 1600 | 1360 | 1880 | 1190 | 61- | |
| Avg. diet | I | 61 | 78 | 133 | 82 | 83 | 88 | 80 | 86 | 95 | 133 | 87 |
| Plain salt | | | | | | | | | | | | |
| D.S. 1, ♀ | | | | | | | | | | | | |
| Age 26 | Date | 5/16 | 6/6 | 11/24 | 11/25 | 11/26 | 11/27 | 11/28 | 11/29 | 11/30 | | |
| 57 kg. | Vol. | 580 | 1455 | 1270 | 920 | 1160 | 1465 | 1165 | 1095 | 1015 | 134- | |
| Avg. diet | I | 226 | 168 | 207 | 207 | 165 | 184 | 134 | 174 | 160 | 226 | 181 |
| Iod. salt | | | | | | | | | | | | |
| D.S. 2, ♀ | | | | | | | | | | | | |
| Age 26 | Date | 12/10 | 12/11 | 12/12 | 12/13 | - | - | - | - | - | | |
| 57 kg. | Vol. | 920 | 975 | 1325 | 1230 | - | - | - | - | - | 63- | |
| Avg. diet | I | 93 | 93 | 101 | 63 | - | - | - | - | - | 101 | 73 |
| Plain salt | | | | | | | | | | | | |
| J.R., ♂ | | | | | | | | | | | | |
| Age 25 | Date | 6/3 | 6/4 | 6/5 | 6/6 | 6/7 | - | - | - | - | | |
| 73 kg. | Vol. | 880 | 720 | 1450 | 1080 | 2655 | - | - | - | - | 107- | |
| Avg. diet | I | 107 | 122 | 158 | 117 | 175 | - | - | - | - | 175 | 136 |
| F.C., ♂ | | | | | | | | | | | | |
| Age 24 | Date | 10/31 | 11/1 | 11/2 | 11/5 | 11/6 | 11/7 | 11/8 | 11/9 | 11/10 | | |
| 73 kg. | Vol. | 820 | 830 | 1182 | 1485 | 910 | 1332 | 933 | 840 | 1390 | 81- | |
| Avg. diet | I | 168 | 102 | 95 | 272 | 215 | 227 | 81 | 99 | 210 | 272 | 163 |
| R.O. 1, ♂ | | | | | | | | | | | | |
| Age 24 | Date | 5/25 | 6/3 | 6/4 | 6/5 | 6/6 | 6/7 | 6/8 | 6/14 | - | | |
| 80 kg. | Vol. | 900 | 700 | 730 | 740 | 730 | 815 | 665 | 1700 | - | 83- | |
| Avg. diet | I | 106 | 83 | 98 | 96 | 95 | 110 | 85 | 94 | - | 110 | 96 |
| R.O. 2, ♂ | | | | | | | | | | | | |
| Age 24 | Date | 8/13 | 8/14 | 8/15 | 8/16 | - | - | - | - | - | | |
| 80 kg. | Vol. | 795 | 630 | 695 | 895 | - | - | - | - | - | 129- | |
| Avg. diet | I | 162 | 129 | 191 | 158 | - | - | - | - | - | 191 | 160 |
| Plain salt | | | | | | | | | | | | |
| R.O. 3, ♂ | | | | | | | | | | | | |
| Age 24 | Date | 10/1 | 10/2 | 10/3 | 10/4 | 10/5 | 10/6 | 10/7 | 10/8 | - | | |
| 80 kg. | Vol. | 665 | 620 | 725 | 820 | 770 | 790 | 835 | 800 | - | 95- | |
| Const.diet | I | 103 | 95 | 99 | 104 | 125 | 106 | 118 | 106 | - | 125 | 107 |
| Plain salt | | | | | | | | | | | | |
| J.L., ♂ | | | | | | | | | | | | |
| Age 29 | Date | 10/29 | 10/30 | 10/31 | 11/1 | 11/2 | 11/3 | 11/4 | 11/5 | 11/6 | | |
| 72 kg. | Vol. | 1080 | 1080 | 940 | 1375 | 920 | 1470 | 1375 | 1675 | 1205 | 117- | |
| Const.diet | I | 167 | 117 | 155 | 140 | 132 | 135 | 170 | 164 | 157 | 170 | 149 |
| Plain salt | | | | | | | | | | | | |

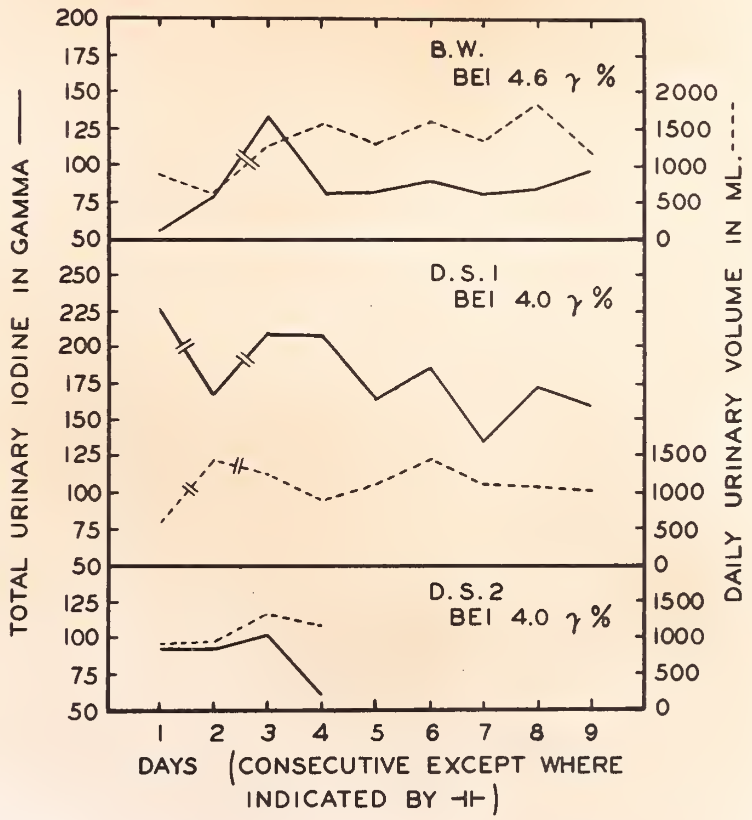
GRAPH I

TWENTY-FOUR HOUR URINARY IODINE EXCRETION OF SIX NORMAL YOUNG ADULTS UNDER AVERAGE DIETARY CONDITIONS (SEE TABLE I)



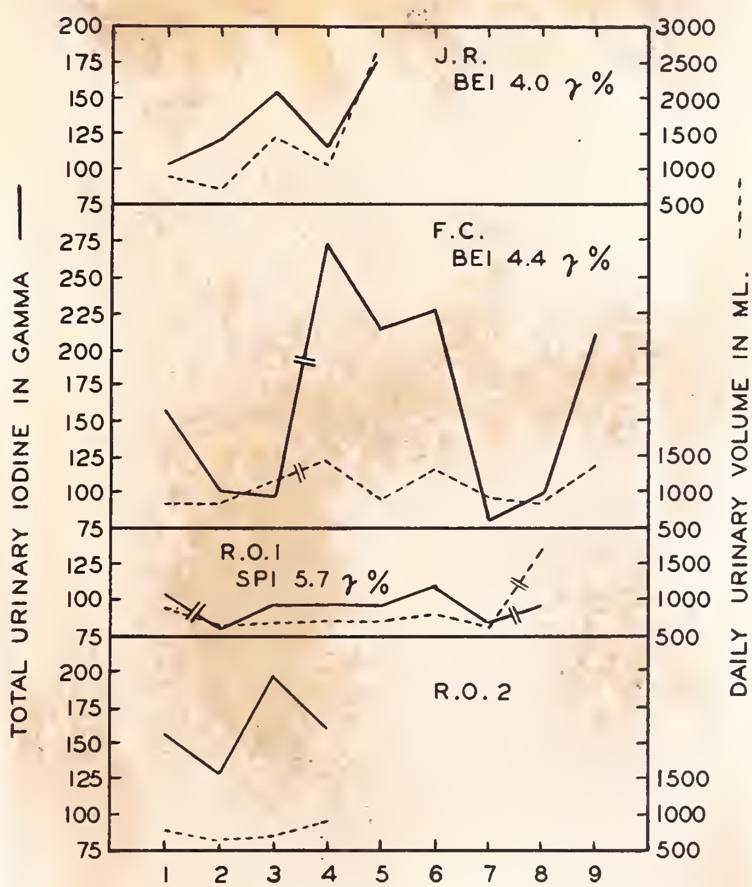
GRAPH 2

TWENTY-FOUR HOUR URINARY IODINE EXCRETION OF TWO NORMAL YOUNG ADULT FEMALES UNDER AVERAGE DIETARY CONDITIONS



GRAPH 3

TWENTY-FOUR HOUR URINARY IODINE EXCRETION OF THREE NORMAL YOUNG ADULT MALES UNDER AVERAGE DIETARY CONDITIONS




DAYS (CONSECUTIVE EXCEPT WHERE INDICATED BY ⊣⊢)

TABLE II

DATA ON EUTHYROID MALE R. O. 3

| Date of Specimen | Day of Expt. | Thyroid, U.S.P. Intake in gm. | Thyroid, U.S.P. Iodine in gamma | Urine Volume (in ml.) | Total Urinary Iodine (in gamma) | Serum Iodine (gamma %) SPI | Serum Iodine (gamma %) BEI | Serum Total Chol. (mg.%) | Serum Fatty Acids (mEq./l.) |
|---|---|---|---|---|---|---|---|---|---|
| Oct.1,1951 | 1 | | | 665 | 103 | | | | |
| 2 | 2 | | | 620 | 95 | | | | |
| 3 | 3 | | | 725 | 99 | | | | |
| 4 | 4 | | | 820 | 104 | | | | |
| 5 | 5 | | | 770 | 125 | | | | |
| 6 | 6 | | | 790 | 106 | | | | |
| 7 | 7 | | | 835 | 118 | | | | |
| 8 | 8 | | | 800 | 106 | | 5.2 | | |
| 9 | 9 | 0.06 | 120 | 705 | 157 | | | | |
| 10 | 10 | 0.06 | 120 | 1090 | 190 | | | | |
| 11 | 11 | 0.06 | 120 | 775 | 194 | | | | |
| 12 | 12 | 0.06 | 120 | 820 | 173 | 3.9 | 3.8 | | |
| 13 | 13 | 0.06 | 120 | 945 | 213 | | | | |
| 14 | 14 | 0.06 | 120 | 855 | 165 | | | | |
| 15 | 15 | 0.06 | 120 | 795 | 213 | | | | |
| 16 | 16 | | | 775 | 163 | 3.6 | 3.5 | | |
| 17 | 17 | | | 825 | 141 | | | | |
| 18 | 18 | | | 755 | 149 | | | | |
| 19 | 19 | | | 780 | 97 | 3.3 | 3.0 | | |
| 20 | 20 | | | 760 | 91 | | | | |
| 21 | 21 | | | 815 | 119 | | | | |
| 22 | 22 | | | 875 | 105 | | | | |
| 26 | 26 | | | | | 3.4 | 2.7 | | |
| Nov.2 | 33 | | | | | | 2.5 | 199 | 10.3 |
| 9 | 40 | | | | | 3.8 | 4.0 | | |
| 16 | 47 | | | | | 3.4 | 3.4 | | |
| 24 | 55 | | | | | 3.4 | 3.7 | 165 | 8.9 |
| Dec.1 | 62 | | | | | 3.9 | 3.5 | 188 | 10.5 |
| 10 | 71 | | | | | 3.6 | 3.0 | 193 | 11.8 |

GRAPH 4

DAILY URINARY IODINE EXCRETION OF EUTHYROID MALE R.O.3 BEFORE, DURING AND AFTER INGESTION OF DESICCATED THYROID

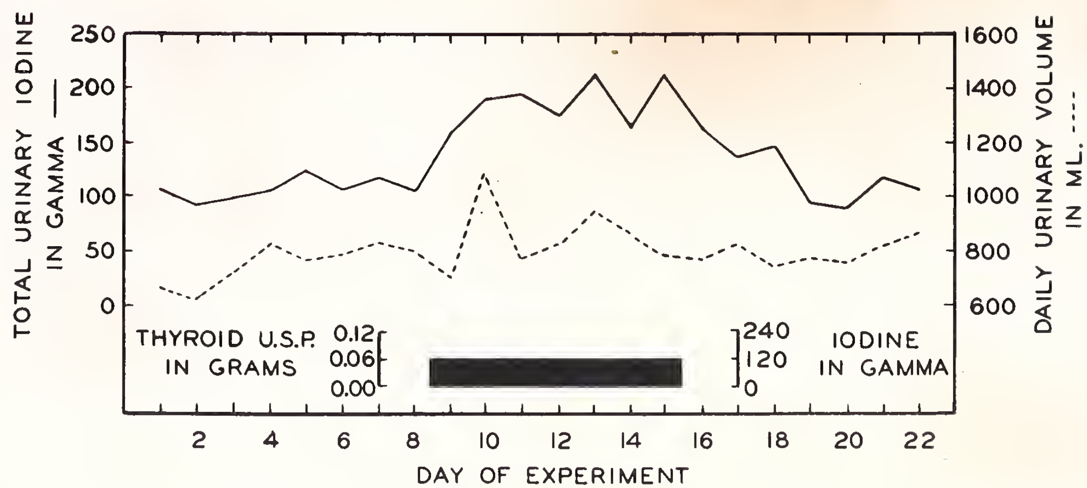


TABLE III

DATA ON EUTHYROID MALE J. L.

| Date of Specimen | Day of Expt. | Thyroid, U.S.P. Intake in gm. | Thyroid, U.S.P. Iodine in gamma | Urine Volume (in ml.) | Total Urinary Iodine (in gamma) | Serum Iodine (gamma %) SPI | Serum Iodine (gamma %) BEI | Serum Total Chol. (mg.%) | Serum Fatty Acids (mEq./l) |
|---|---|---|---|---|---|---|---|---|---|
| Oct.29,1951 | 1 | | | 1080 | 167 | | | | |
| 30 | 2 | | | 1080 | 117 | 4.7 | 4.8 | | |
| 31 | 3 | | | 940 | 155 | | | | |
| Nov. 1 | 4 | | | 1375 | 140 | | | | |
| 2 | 5 | | | 920 | 132 | | | | |
| 3 | 6 | | | 1470 | 135 | | | | |
| 4 | 7 | | | 1375 | 170 | | | | |
| 5 | 8 | | | 1675 | 164 | | | | |
| 6 | 9 | | | 1205 | 157 | | | | |
| 7 | 10 | 0.06 | 120 | 885 | 157 | | | | |
| 8 | 11 | 0.06 | 120 | 1220 | 256 | | | | |
| 9 | 12 | 0.075 | 150 | 1380 | 294 | | | | |
| 10 | 13 | 0.03 | 60 | 1165 | 217 | 3.5 | 4.3 | | |
| 11 | 14 | 0.075 | 150 | 905 | 167 | | | | |
| 12 | 15 | 0.06 | 120 | 1460 | 167 | | | | |
| 13 | 15 | 0.06 | 120 | 1200 | 199 | | | | |
| 14 | 17 | | | 965 | 209 | 3.6 | 4.5 | 162 | 11.3 |
| 15 | 18 | | | 1240 | 199 | | | | |
| 16 | 19 | | | 1950 | 178 | | | | |
| 17 | 20 | | | 1300 | 160 | 4.9 | 3.5 | 142 | 10.6 |
| 18 | 21 | | | 1100 | 108 | | | | |
| 19 | 22 | | | 1100 | 144 | | | | |
| 20 | 23 | | | 1055 | 164 | | | | |
| 21 | 24 | | | 1120 | 156 | | | | |
| 27 | 30 | | | | | 4.4 | 3.8 | 179 | 10.5 |
| Dec. 8 | 41 | | | | | 4.8* | 4.3 | 190 | 10.8 |

*Single determination

GRAPH 5

DAILY URINARY IODINE EXCRETION OF EUTHYROID MALE J.L.
BEFORE, DURING AND AFTER INGESTION OF DESICCATED THYROID

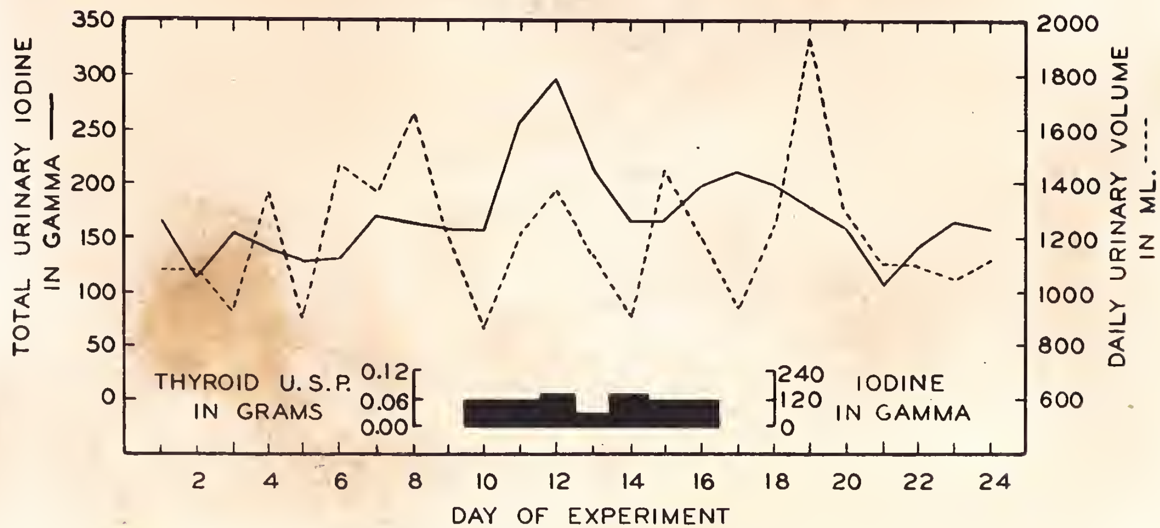


TABLE IV

DATA ON HYPOTHYROID MALE N. C.

| Date of Specimen | Day of Expt. | Thyroid U.S.P. Intake in gm. | Thyroid U.S.P. Iodine in gamma | Urine Volume (in ml.) | Total Urinary Iodine (in gamma) | Total Urinary Chloride (in grams) | Serum BEI (gamma %) | Serum Total Chol. (mg.%) | Serum Fatty Acids (mEq./1) |
|---|---|---|---|---|---|---|---|---|---|
| Nov.8,1951 | 1 | | | 2410 | 58 | 3.05 | | | |
| 9 | 2 | | | 2470 | - | 7.63 | 0.5 | 184 | 11.1 |
| 10 | 3 | | | 1210 | 45 | 2.45 | | | |
| 11 | 4 | | | 1445 | 82 | 3.14 | | | |
| 12 | 5 | 0.015 | 30 | 1023 | 58 | 3.02 | | | |
| 13 | 6 | 0.015 | 30 | - | - | - | | | |
| 14 | 7 | 0.015 | 30 | 2000 | 136 | 2.39 | | | |
| 15 | 8 | | | 1020 | 91 | 1.31 | | | |
| 16 | 9 | 0.015 | 30 | 750 | 51 | 1.44 | | | |
| 17 | 10 | 0.03 | 60 | 1880 | 179 | 3.27 | | | |
| 18 | 11 | 0.03 | 60 | 1730 | 130 | 3.29 | | | |
| 19 | 12 | 0.06 | 120 | 1540 | 92 | 2.99 | 1.1 | 212 | 13.9 |
| 20 | 13 | 0.06 | 120 | - | - | - | | | |
| 21 | 14 | 0.12 | 240 | 1065 | 190 | 1.58 | | | |
| 22 | 15 | 0.12 | 240 | 700 | 433 | 1.30 | | | |
| 23 | 16 | 0.12 | 240 | 570 | 655 | .49 | 2.4 | 184 | 11.1 |
| 24 | 17 | 0.12 | 240 | 1090 | 556 | .43 | | | |
| 25 | 18 | 0.12 | 240 | 1820 | 1048 | .66 | | | |
| 26 | 19 | 0.12 | 240 | 1770 | 440 | 1.18 | | | |
| 27 | 20 | 0.12 | 240 | 2185 | 327 | 2.97 | 1.7 | 119 | 9.4 |
| Dec.19 | 42 | 0.12 | 240 | | | | 2.7 | 133 | 12.2 |

GRAPH 6

DAILY URINARY IODINE AND CHLORIDE EXCRETION OF HYPOTHYROID MALE N. C. BEFORE AND DURING INITIATION OF THERAPY WITH DESICCATED THYROID