A STUDY OF METHODS TO EVALUATE THYROID FUNCTION
AND THEIR APPLICATION IN PATIENTS WITH
CHRONIC ULCERATIVE COLITIS

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A STUDY OF METHODS TO EVALUATE THYROID FUNCTION AND THEIR APPLICATION IN PATIENTS WITH CHRONIC ULCERATIVE COLITIS

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CHAPTER I

INTRODUCTION

In the late nineteenth century, Sir William Wilkes (3) first described an idiopathic ulceration of the colon, which is known today as chronic ulcerative colitis. As the term "idiopathic" implies, the cause of the disease was unknown and has remained so until the present time.

In the effort to discover the etiology of the disease, it has been found that certain of the endocrine glands, such as the adrenals, gonads, and possibly the pituitary, are functionally depressed with this disease (1,2,4). Bensen and Bargen (2) have shown the sexual and somatic development to be retarded in adolescents with chronic ulcerative colitis. They also noted a depression in adrenocorticosteroid and prolan excretion levels. This was thought by Bargen (1) to be a stress reaction produced by the disease.

It was felt that other endocrine glands should be evaluated to determine the extent of involvement of the endocrine system. The possibility that increased thyroid activity might affect colon motility and thus, be a predisposing factor to ulceration of the colon was considered. A search of the literature revealed that no study had been made of thyroid activity in such cases.

It was the purpose of this thesis to establish the functional level of the thyroid gland in patients with chronic ulcerative colitis. The problem was approached by applying a series of eight tests of thyroid function to a normal control group and a group of patients with chronic ulcerative colitis. The tests employed were a basal metabolism test, a serum cholesterol determination, a protein-bound iodine determination, as well as various studies employing tracer doses of radioiodine. The tracer study consisted of a determination of the six-hour I^{131} uptake, twenty-four-hour protein-bound I^{131}, a twenty-four-hour conversion ratio, and a twenty-four-hour urinary I^{131} excretion rate.

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CHAPTER II

REVIEW OF THE LITERATURE

Historical

A number of tests of thyroid physiology have been devised in an effort to fully evaluate the status of the thyroid in various disease conditions. The first of these tests was the determination of the basal metabolic rate. The determination of the basal metabolic rate may be done by measuring directly the amount of heat produced by the body. This is termed "direct calorimetry." However, direct calorimetry is a very difficult and cumbersome technique to perform. The basal metabolic rate is therefore best determined by indirect means. This is most easily done by measuring the rate of oxygen consumption. Oxygen consumption can be converted into calories since it is known that 4.825 calories are produced when one liter of oxygen is used to oxidize the foodstuffs found in the average diet.

The first device designed for measuring oxygen consumption was described by Regnault and Reiset in 1849 (22). This device consisted of a glass vessel containing a liquid carbon dioxide absorber and a means of supplying oxygen from glass bottles. The glass vessel was small and could be used only for small animals. Later, chambers large enough to accommodate a man

and a bed were constructed. These chambers had circulating systems which provided a steady flow of air into and out of the chamber. These gases were then analyzed for oxygen and carbon dioxide content. Water was also circulated through the walls of the chamber and the amount of heat produced by the body was measured. Thus, the metabolic rate could be determined.

In 1904, Tissot described a respiration chamber for measuring oxygen consumption and carbon dioxide elimination. The device consisted of a large metal spirometer which collected all of the gases expired by the subject during a given period of time, usually ten to fifteen minutes. The collected gases were then analyzed. A similar method was the Douglas Bag method, which provided for the collection of the respiratory gases in a large rubber bag. Both techniques required the analysis of gases (22).

Benedict, in 1909, constructed a closed-circuit spirometer, which recorded the respiratory movements on a kymograph. The subject breathed into the spirometer, where the exhaled gases were circulated by a blower through a series of water absorbers and a carbon dioxide absorber. Oxygen was administered by means of an oxygen meter. The production of carbon dioxide was measured by the gain in weight of the carbon dioxide absorber. In 1919 (11), data were published which were based upon the use of the Benedict machine. Then in 1922,

Roth (22) modified the Benedict apparatus by replacing the blower with low-resistance valves. Oxygen consumption was measured from the kymograph tracing. This is the basic machine which, with only minor changes, is still in use today and is referred to as the Benedict-Roth spirometer.

Another test of thyroid function to receive considerable popularity was the determination of total serum cholesterol. One of the earliest to correlate cholesterol levels with thyroid activity was Epstein (8) in 1922. Many others made similar studies and in 1930, Mason, Hunt, and Hurxthal reviewed these works and confirmed them (16). This technique of thyroid study is still employed today (20,21), although it is not as popular as it was a few years ago.

Recent

In 1940, Chaney (5) applied the determination of protein-bound iodine to biological studies. One year later, Salter, Bassett, and Sappington (23) made a study of the protein-bound iodine in the blood and its relation to the thyroid state. Interest in the determination of protein-bound iodine lagged until it was revived by Taurog and Chaikoff (24) in 1946. The method they employed was a modification of the method described by Chaney (5). In 1948, Barker (1) described a method of determination of protein-bound iodine by ashing the protein and dissolving the ash in acid. That same year, Curtis and Swinson (7) found the protein-bound iodine level to rise after the administration of thyroid stimulating hormone (TSH).

They were also able to correlate the symptoms of hyperthyroidism with protein-bound iodine levels and the basal metabolic rate.

The technique of determining protein-bound iodine was somewhat simplified in 1952 by the introduction of the chloric acid method by Zak (26). The chloric acid method was then improved in 1953 by O'Neal and Simms (18) and further simplified by Leffler (15) in 1954. Thus, several techniques were made available for the determination of protein-bound iodine on a clinical basis. However, these techniques are still far from being simple and many hospitals and clinics cannot afford them.

Hertz, Roberts, and Evans (12) in 1938, were the first to suggest the use of radioactive iodine in the study of thyroid physiology. Then in 1939, Hamilton and Soley (10) made a study of the metabolism of the radioactive isotope of iodine and followed its excretion. This was followed by a second study by Hertz and Roberts (13) on the use of I^{131} in thyroid physiology. They found that the collection of I^{131} by the thyroid was dependent upon the amount of TSH present. In 1947, Chaikoff and Taurog (4) found that the conversion of inorganic I^{131} into the protein-bound state increased upon administration of TSH and fell rapidly upon thyroidectomy. The following year, Clark, Moe, and Adams (6) determined the ratio of inorganic I^{131} to protein-bound I^{131} in serum twenty-four hours after the oral administration of radioiodine. The resulting

figure was termed a "conversion ratio." They concluded that the conversion ratio was a useful guide to thyroid activity.

Extensive studies of the urinary excretion of I^{131} were made in 1947 by Keating (14) and in 1948 by McArthur (17). It was thought that the amount of I^{131} taken up by the thyroid could be calculated indirectly from the urinary excretion of the isotope. This was based upon the assumption that the I^{131} not taken up by the gland would be eliminated in the urine. This was found to be an inaccurate procedure.

At that time, Werner, Quimby, and Schmidt (25) employed a Geiger counter placed over the thyroid gland to determine the per cent of the administered radioiodine taken up by the gland in a twenty-four-hour period. They established the range of thyroid uptake in euthyroid individuals and in patients with overactive glands. In 1949, Freedberg, Ureles, and Hertz (9) found the serum level of protein-bound I^{131} to be elevated in patients with thyrotoxicosis and suggested that the serum level of protein-bound I^{131} be used as an aid in the diagnosis of hyperthyroidism.

Much of this earlier work has been repeated many times and the abnormal as well as the normal values for these tests have been well established. Many of these techniques, along with several variations, have been adapted to routine clinical procedures. One such variation is the use of TSH in combination with various tracer techniques to determine if the primary cause of hypothyroidism lies with the thyroid itself or with the pituitary gland (3). Other variations involve

the continuous recording of the uptake of I^{131} by the thyroid and the determination of the rate of clearance of the serum of I^{131} by the thyroid (2,19). Thus, it can readily be seen that there are numerous techniques available for the evaluation of the thyroid state.

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CHAPTER III

MATERIALS USED FOR STUDY

The subjects employed in this study were divided into two groups: a control group and an experimental group. The control group was made up of six euthyroid individuals with no evidence of thyroid or colon disorders. The control group contained four males and two females, ranging from nineteen to fifty-three years of age. Only six control subjects were employed since it was found that the results obtained with the procedures used in this study were in complete accord with data found in the literature.

Ten patients with varying degrees of chronic ulcerative colitis were studied. Of this group, seven were females and three were males. Their ages ranged from thirteen to forty-nine years. These patients were seen in the Scott and White Clinic by the staff physicians and referred to the research laboratory for study.

CHAPTER IV

METHODS

General Procedure

The following procedures were employed in all normal individuals and patients. They were instructed to report to the laboratory at 8:15 A.M. in the fasted state and without having smoked since the previous evening. The first procedure was to determine the basal metabolic rate. Twenty milliliters of blood was then obtained by venipuncture for various chemical tests. The blood was centrifuged and two milliliters of serum was used for the total serum cholesterol determination, and the rest was kept for the determination of the protein-bound iodine. Next, the subject was given thirty micro-curies of radioiodine orally and instructed to collect and preserve all urine during the next twenty-four hours. At six and twenty-four hours after the administration of the radioiodine, the subject returned to the laboratory for measurement of the thyroid uptake of radioiodine. Following the twenty-four-hour uptake determination, another twenty milliliters of venous blood was obtained for various radioactive measurements.

Basal Metabolic Rate

The method and equipment employed in the determination of the basal metabolic rate was similar to that described by Roth and Roth (5). The subject, who had not eaten or smoked for ten to twelve hours, rested quietly on a couch for thirty minutes to attain the basal state. The procedure was explained to the subject and any fears that the subject might have had were dispelled. After the rest period, a sponge nose clamp was applied to prevent nasal breathing. The mouth-piece was introduced and the airways were tested for leaks. The patient was at this time breathing room air. When it was apparent that the subject was accustomed to breathing through the mouth-piece, the respiratory air streams were diverted into the respirometer (See Fig. 1.). The respirometer, which had a capacity of seven liters, contained only oxygen. The rate of oxygen consumption was recorded on a revolving drum by means of an ink writer.

After approximately seven minutes of eupnic breathing, the test was terminated by disconnecting the subject from the machine. The subject's height and weight were recorded on the tracing for use in calculating the basal metabolic rate. The basal metabolic rate was expressed as calories produced per square meter of body surface area per hour. This value was expressed as plus or minus the per cent of normal. The oxygen consumption was determined for a six-minute interval by drawing a straight line along the bottom of the tracing (See Fig. 2.).

The volume of oxygen, expressed in liters, which had been consumed during the six-minute interval, was multiplied by the factor, 4.825, to obtain the calories produced. This value was multiplied by ten to obtain the value for one hour. The calories produced per hour was divided by the body surface area in square meters to obtain the calories per square meter of body surface area, which is the basal metabolic rate. In order to obtain the per cent of normal, the normal value was found in a table of standard values (1). The difference in the two values was divided by the normal value and expressed as per cent. It was a positive figure if the test figure was larger than the normal, and a negative figure if the reverse was true. The body surface in square meters was obtained by applying the subject's height and weight to the DuBois Body Surface Area Chart (1).

Total Serum Cholesterol

The total serum cholesterol determination was done according to the method of Pearson, Stern, and McGavack (4), with slight modification. This technique employs the colormetric determination of a color produced by cholesterol and p-toluenesulfonic acid in the presence of acetic acid, acetic anhydride and sulfuric acid. The procedure consisted of placing 0.2 milliliters of the unknown serum into a test tube and adding 0.2 ml. of glacial acetic acid and 1.0 ml. of p-toluenesulfonic acid. The solution was allowed to cool without stirring. Four tenths of a milliliter of concentrated sulfuric

acid was added and the test tube was shaken vigorously and left to stand at room temperature for twenty minutes. A spectrophotometer, set at 550 millimicrons, was used to assay the unknown. For adjusting the spectrophotometer to the zero point, a solution containing all of the reagents and 0.2 ml. of distilled water in place of the serum was used. An assay blank was prepared with 4.6 ml. of p-toluenesulfonic acid and 0.2 ml. of serum. The standard contained 0.2 ml. of cholesterol standard (made by dissolving 200 milligrams of cholesterol in 100 milliliters of glacial acetic acid), 0.2 ml. of distilled water instead of the acetic acid and then proceeding as with the unknown. The results were expressed as milligrams of cholesterol per 100 milliliters of serum and were calculated by the following formula:

$$\text{mg. cholesterol/100 ml. serum} = \frac{100(a-b)d}{c},$$

where "a" represented optical density of the serum, "b" represented optical density of the assay blank, "c" represented optical density of the standard, and "d" represented the milligrams of cholesterol per milliliter of standard solution.

Protein-Bound Iodine

The method employed for the determination of protein-bound iodine by chemical means was that described by Leffler (3). The procedure is divided into six steps: (1) precipitation of the protein, (2) washing of the protein, (3) digestion of the protein precipitate, (4) reconstitution of the

digest, (5) colorimetric determination of the iodine, and (6) calculation of the results. Details of the procedure are described below.

The protein in one ml. of serum was precipitated with ten ml. of fifteen per cent trichloroacetic acid in a fifty ml., graduated, pyrex, centrifuge tube. The precipitate was centrifuged and the supernatant poured off and the protein was washed and centrifuged with another ten ml. of trichloroacetic acid. The supernatant was again poured off and the precipitate allowed to drain dry, during which time a series of standards were prepared. There were four standards: (1) a blank which contained only the reagents, (2) a standard with 0.05 micro-grams of iodine and the reagents, (3) a standard with 0.1 micro-grams of iodine and the reagents, and (4) a standard with 0.15 micro-grams of iodine and the reagents. These standards represented 0, 5, 10, and 15 micrograms of iodine per 100 ml. of serum. The digestion reagents consisted of 10 ml. of chloric acid reagent (prepared by the addition of 166 ml. of 70 per cent perchloric acid to 200 grams of potassium chlorate dissolved in 360 ml. of distilled water), and one milliliter of 0.5 per cent sodium chromate solution. These reagents were added to the precipitated protein and stirred with a glass stirring rod, which was left in the tube. A glass bead was added to each tube and all tubes were placed on an electric hot plate inside a fume hood.

The hot plate was regulated to a temperature of about 115°C and the tubes allowed to digest without vigorous boiling or bumping. After about one hour, eight to ten drops of the chloric acid reagent were added to each tube and from one to two drops more were added every fifteen or twenty minutes thereafter until the volume in the digestion tubes reached approximately three ml., at which time one drop was added every seven minutes. The addition of the chloric acid maintained the chromate in an oxidized state. The end point of the digestion arrived when a fine red precipitate formed at the interface of the liquid and the glass. The tubes were then immediately removed from the hot plate and allowed to cool in the fume hood. After cooling, the digest was reconstituted by making the volume up to ten ml. with distilled water. A fine white precipitate of unknown origin, which was present, was allowed to settle to the bottom of the tube.

A three ml. aliquot was taken from each digestion tube and placed in a test tube. Two ml. of arsenious acid reagent were then added to each test tube and mixed by gentle swirling. The arsenious acid reagent was prepared fresh each day by adding two per cent sodium chloride solution to 0.2 N arsenious acid in the ratio of 0.1 ml. of sodium chloride solution to one ml. of arsenious acid. Each tube was then placed in a water bath at thirty degrees centigrade for fifteen minutes. After this period of time, one ml. of the ceric sulfate working solution (prepared each day by adding 0.5 ml. of stock

ceric sulfate solution to ten ml. of concentrated sulfuric acid) was added to each tube at thirty second intervals and replaced immediately in the water bath. The contents of these tubes were then poured into cuvettes which had been maintained at 30°C in a closed beaker in the water bath. Ten minutes after the addition of the ceric sulfate solution to the first tube, the per cent of light transmission at 420 millimicrons, was measured with a Beckman DU spectrophotometer. The remaining tubes were read at thirty second intervals. The values for the standards were plotted on one cycle semi-logarithmic graph paper. The values for the unknown sera, which were always determined in duplicate, were placed on the resulting curve and expressed as micro-grams of iodine per 100 ml. of serum (See Fig. 3).

Radioiodine Tracer Studies

A dose of thirty micro-curies of radioiodine (I^{131}), carrier free, was used for all of the uptake techniques employed in this study. The radioiodine was obtained from the Abbott Laboratories at Oak Ridge, Tennessee. The dose of radioiodine was prepared in such a manner that it was calculated to be at a strength of thirty micro-curies on the date of administration. At the time the dose was prepared, a second dose, used as a standard, was prepared in an identical fashion. Both the dose and the standard were made up in thirty ml. bottles and were counted with the scintillation counter to determine if they contained the same amount of radioiodine. A

difference not greater than one per cent was allowed. The dose of radioiodine was given orally and the bottle containing it was rinsed twice with distilled water in order to administer all of the radioactive isotope. Thyroidal uptake was determined six and twenty-four hours after administration. A twenty-four-hour urine specimen was collected and a twenty-four-hour venous blood sample was taken for the determination of the twenty-four-hour conversion ratio and the twenty-four-hour protein-bound I^{131}.

The radiation counting equipment employed in this study consisted of a well counter (See Fig. 6) and a scaler used in conjunction with a scintillation head mounted on a flexible boom (See Fig. 4). The latter contained a thallium activated sodium iodide crystal and a photomultiplier tube, which was wired to the scaler. The scaler was adjusted in a manner such that one micro-curie of I^{131}, at a sample-crystal distance of 15 centimeters, produced 5,340 counts per minute. The average background count was 630 counts per minute. This piece of equipment was employed in the uptake studies.

The well counter had a similar scintillation head placed in a lead well and was constructed to receive test tubes and centrifuge tubes. The scintillation head was wired to a small scaler which had a sensitivity such that 0.001 micro-curies of I^{131} produced 1,080 counts per minute over a mean background of 141 counts per minute. The well counter was employed in serum and urinary I^{131} determinations.

The Six-Hour Thyroid Uptake

Six hours after the administration of the radioiodine, the subject reported to the laboratory and was instructed to recline, in a supine position, upon a bed. A pillow was placed beneath the shoulders in such a manner that the head was thrown back and the neck fully exposed. The scintillation crystal was placed at a height of fifteen centimeters above the neck at a point just below the larynx (See Fig. 4). A count of one minute duration was made and repeated. The two values were then averaged. A comparison count was made in a similar manner of the thigh, just above the knee. The purpose of this was to evaluate the radiation emitted by the inorganic I^{131} in the blood in an area with a blood flow similar to that of the neck. The value obtained for the thigh was subtracted from that of the thyroid gland, thus giving a more accurate value for the I^{131} in the gland. This procedure also eliminated the need for determination of the background count, since it was a factor common to both values. Immediately following the determination of the counts per minute produced by the thyroid and the thigh, the standard was placed under the scintillation head at the same height and counted for a similar length of time (See Fig. 5). A background count was obtained and subtracted from the value of the standard. The value obtained for the standard was then divided into the value obtained for the thyroid and multiplied by 100 to find the per cent of the radioiodine taken up by the gland in six

hours. This technique was similar to that described by Jaffe and Ottoman (2).

The Twenty-Four-Hour Protein-Bound I^{131}

The twenty-four-hour protein-bound I^{131} value was expressed as per cent of the administered dose per liter of serum. The protein-bound I^{131} was obtained by precipitating the protein in four ml. of serum with five ml. of fifteen per cent trichloroacetic acid and centrifuging for fifteen minutes at a high speed. The supernatant was decanted and the precipitate was washed twice with the acid. This removed the inorganic I^{131}, which was in the serum. The protein was then counted for fifteen minutes in the well counter (See Fig. 6). The background was then subtracted and the resulting value multiplied by 250 in order to obtain the value expected in one liter of serum.

The average counts per minute for the total dose of I^{131} was found by diluting the standard and counting a one ml. aliquot in the well counter and subtracting the background. This figure was then multiplied by the dilution factor. To obtain the final figure, the counts per minute of the protein-bound I^{131} was divided by the counts per minute of the dose and multiplied by 100.

The Twenty-Four-Hour Conversion Ratio

Two four ml. aliquots of serum were counted in the well counter for a period of fifteen minutes each and the average

counts per minute were found. The background was subtracted from these figures. The sera samples were counted in plastic centrifuge tubes which fit in the well counter with all of the serum within the scintillation head. The protein was then precipitated with five ml. of fifteen per cent trichloroacetic acid and centrifuged for fifteen minutes at a high speed. The supernatant was decanted and the precipitate washed twice. The washed protein was counted in the well counter for fifteen minutes and the average counts per minute found. The background was then subtracted. The value obtained for the protein-bound I^{131} was divided by the value obtained for the serum I^{131} and multiplied by 100 to obtain the twenty-four-hour conversion ratio. This technique was performed after the method of van Middlesworth, Nurnberger, and Lipscomb (6).

The Twenty-Four-Hour Excretion of I^{131}

The volume of the twenty-four-hour urine specimen was measured and a one ml. aliquot taken and counted in the well counter. It was counted for two one-minute periods. The background was then subtracted. The standard was diluted up to the volume of the urine and a one ml. aliquot was taken and counted in a similar manner to that of the urine. The average counts per minute of the urine was divided by the average counts per minute of the standard and multiplied by 100 in order to obtain the per cent of the dose of radioiodine excreted in the urine in twenty-four hours.

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CHAPTER V

RESULTS

Eight techniques were employed in the evaluation of thyroid function in a total of sixteen individuals, six of whom were normal euthyroid control subjects and ten of whom were patients with varying degrees of chronic ulcerative colitis.

Two of the patients with ulcerative colitis failed to collect all of the urine excreted during the twenty-four-hour period following the ingestion of the radioiodine. These two results were not included in the final analysis of the data on urinary excretion of I^{131}. The basal metabolic rate was not obtained on one of the patients because of interference with other clinical tests scheduled at that time. The value for protein-bound iodine obtained for one of the patients was too low to be evaluated, while one of the other patients had a value too high to be determined. The latter was explainable on the grounds of a recent cholecystogram. No explanation was evident for the former situation.

The results of these tests of thyroid function may be found summarized in Tables I and II. A comparison of the mean values obtained with each technique for the control group and for the patients with chronic ulcerative colitis may be found in Table III.

Serum Cholesterol

Control Group

The control group was made up of six euthyroid individuals with ages ranging from nineteen to fifty-three years. Two of these were females and four were males. The mean value for the total serum cholesterol was 200 milligrams per 100 milliliters of serum. These values varied from 156 to 316 milligrams per 100 milliliters of serum.

Patients

Of the ten patients studied, seven were females and three were males. Their ages ranged from thirteen to forty-nine years. The total serum cholesterol values varied from 168 to 248 mg. per 100 ml. of serum. The mean value was 205 mg. per 100 ml. of serum. These figures are in agreement with those obtained for the control group.

Basal Metabolic Rate

Controls

Six euthyroid control subjects showed a range in basal metabolic rate from -18.6 to +3.5 per cent. The mean value obtained was -6 per cent.

Patients

Nine patients with chronic ulcerative colitis produced a mean metabolic rate of +1 per cent with a range of from -24 to

$\pm$15 per cent. Only two of the patients were outside of the normal limits of $\pm$ 10 per cent.

Protein-Bound Iodine

Control Group

The six euthyroid controls were found to have a mean protein-bound iodine value of 5.5 micro-grams per 100 ml. of serum. These values varied from 3.8 to 6.5 micro-grams per 100 ml. of serum.

Patients

The variation among eight patients with ulcerative colitis was from 4.2 to 7.8 micro-grams of protein-bound iodine per 100 ml. of serum. The mean value was 6.3 micro-grams per 100 ml. of serum, which is slightly higher than the mean for the controls, but not significantly so.

Radioiodine Techniques

Six-Hour Uptake

Control group.--The mean value for the six euthyroid controls was 13.0 per cent of the administered dose. The individual values varied from 9.2 to 15.7 per cent.

Patients.--Ten patients with ulcerative colitis produced a range from 7.6 to 16.6 per cent with a mean of 12.4 per cent. These values are in agreement with those found in the control group.

Twenty-Four-Hour Uptake

Control group.--The values obtained for six controls varied from 19.0 to 26.2 per cent, with a mean of 22.8 per cent.

Patients.--The twenty-four-hour uptake values obtained for the ten patients with chronic ulcerative colitis varied from 15.5 to 47.4 per cent. The mean was 24.9 per cent, which is not statistically slightly higher than the mean of the euthyroid group.

Twenty-Four-Hour Protein-Bound I^{131}

Control group.--The amount of I^{131} found to be protein-bound at the end of 24 hours in 6 euthyroid controls was observed to vary from 0.0414 to 0.1030 per cent of the administered dose per liter of serum. The mean was 0.0676 per cent per liter of serum.

Patients.--The mean protein-bound I^{131} value for 10 patients with chronic ulcerative colitis was 0.1093 per cent of the dose per liter of serum. The individual values ranged from 0.0420 to 0.2150 per cent of the dose per liter of serum. This was a slight, but unimportant deviation from the mean euthyroid value in this group.

Twenty-Four-Hour Conversion Ratio

Control group.--Six euthyroid controls had a mean 24-hour conversion ratio value of 20.2 per cent. The range was from 4.1 to 29.2 per cent.

Patients.--The 24-hour conversion ratio values ranged from 16.3 to 42.3 per cent among 10 patients with ulcerative colitis. The mean value obtained was 31.2 per cent, which was somewhat higher than the mean obtained for the control group, but the difference was insignificant.

Twenty-Four-Hour Urinary I^{131} Excretion

Control group.--The 24-hour urinary excretion of radioiodine among the 6 euthyroid controls varied from 42.6 to 70.0 per cent of the administered dose. The mean value was 54.6 per cent.

Patients.--A mean 24-hour value for urinary excretion of radioiodine for 8 patients with ulcerative colitis was found to be 62.7 per cent. These values varied from 52.2 to 77.0 per cent. These values are in accord with those obtained for the control group.

CHAPTER VI

DISCUSSION

The findings of this study indicate that there was no abnormal function of the thyroid gland in patients with chronic ulcerative colitis. Although there was some tendency for the results to show a slight mean elevation of thyroid activity, it does not appear to be of any great importance. The advantages and disadvantages of each of the techniques employed in the study will now be considered separately.

Serum Cholesterol

The serum cholesterol figures in the present study for both the control and experimental series compare favorably with normal values given in the literature. Zieve, Skanse, and Schultz (17), for example, found the total serum cholesterol values in euthyroid subjects to range from 98 to 390 milligrams per 100 ml. of serum with a mean value of 208 mg. per 100 ml. of serum. This is to be compared with mean values in the present work of 200 and 205 mg. per 100 ml. of serum. It is not felt that too much weight should be given the serum cholesterol levels as a measure of thyroid activity. However, this test is highly unspecific and thus a rather poor diagnostic aid in evaluating the status of the thyroid. It is true that the serum cholesterol level is

elevated in hypothyroidism, but this is only a part of the picture of general hyperlipemia associated with the disease (8). It is also known that the serum cholesterol level may be altered by diseases other than those of the thyroid (8). Its value is further limited by the fact that it is not appreciably altered by hyperthyroidism (11).

Basal Metabolic Rate

It was noted in the results that the range of basal metabolic rates in the control group ran from -18.6 to +3 per cent, while the range in the experimental group ran from -4 to +15 per cent. Thus, certain values exceeded the normally accepted range of from -10 to +10 per cent. However, this does not appear to be an unusual experience. Jaffe and Ottoman (3), in a study of 157 subjects, found that one third had basal metabolic rates outside the normal range. Werner, Hamilton, Liefer, and Goodwin (15) have shown that 50 per cent of their basal metabolic readings were beyond the normal range in a group of 190 euthyroid individuals. Their results show that 21.5 per cent fell above +10 per cent and 28.5 per cent fell below the -10 per cent level. There are several reasons for these deviations. It has been stated that an error of 15 per cent occurs in the estimation of the body surface area and in instrumentation (8).

Other problems arise in applying the technique to people with certain illnesses such as cardiac or pulmonary failure.

Difficulty is often encountered with the young, the aged, and certain nervous or neurotic individuals. Unusually high results may be obtained from shivering, fear of the test, and from visceral activity if the patient is not in the post prandial state for at least twelve hours. Ingestion of thyroid substances will elevate the basal metabolic rate, while flooding the gland with iodine, lowers the rate. The thioureas lower the basal metabolic rate by inhibiting the production of thyroid hormone.

However, with all of the faults listed above, the determination of the basal metabolic rate is still felt by some to be a good routine test for screening purposes (10).

The Protein-Bound Iodine Determination

Determination of the protein-bound iodine gives the most accurate picture of the circulating thyroid hormone. It is, at the same time, the most difficult procedure to perform, requiring some considerable time and a skilled technician, using the highest quality of reagents. If not done frequently, it can become quite expensive.

Its value lies in the fact that it allows the clinician to make repeated observations on the circulating hormone and thus follow the patient's progress. It is also one of the most useful tools in the diagnosis of hypothyroidism, particularly in borderline cases. It is equally valuable in the diagnosis of hyperthyroidism. The normal range is somewhat

well defined, being from 4.0 micro-grams to 8.0 micro-grams of iodine per 100 ml. of serum (7).

Another advantage lies in the fact that conditions such as cardiac or pulmonary failure, which interfere with other tests, have no effect on the protein-bound iodine determination. There need be no difficulty with nervous or neurotic patients since all that is necessary from the patient is a small amount of blood.

A serious disadvantage, other than the difficulty of the technique, is the ease by which it may be invalidated. Such things as the ingestion of Lugol's solution or other iodinated substances leads to abnormally high results. A recent cholecystogram completely ruins the determination. Other tests such as a myelogram, venogram, or arteriogram have a similar effect (1). Therefore, it is imperative that a complete history of the patient's past medication and treatments be obtained. It is rarely altered by diseases other than those involving the thyroid, but it is known to be elevated in infectious hepatitis and lowered by nephrosis, cirrhosis and pituitary failure (5,6).

The results obtained for both groups in this study agree with euthyroid values found in the literature. Zieve, Skanse, and Schultz (17) found in normal individuals that the value of protein-bound iodine varied from 3.1 to 11.7 micro-grams per 100 ml. of serum; the mean value being 5.3 micro-grams per 100 ml. of serum. A mean value of 5.1 micro-grams per

100 ml. of serum with a range of 3.4 to 7.6 micro-grams per 100 ml. of serum was obtained by Owen, McConahey, Keating, and Orvis (9) in a group of 181 euthyroid control subjects.

The determination of protein-bound iodine, when practical, is then considered to be the best "single" test of thyroid function.

Radioiodine Techniques

Radioiodine, which is a gamma ray emitter, is known to be utilized by the body in the same manner as the stable isotope and thus the metabolic pathways of iodine can be studied by means of radiation detecting devices. This affords an easy and relatively accurate method of evaluating thyroid function. Its concentration in the gland may be measured, its excretion followed, and its rate of incorporation into the protein-bound state may be calculated. These various techniques will now be discussed individually.

Six-Hour Uptake

According to Owen, McConahey, Keating, and Orvis (9) the six-hour uptake is the most accurate means of differentiating hypothyroidism from euthyroidism. They also noted that there was no overlap between exophthalmic goiter and the euthyroid range. This is the least difficult of the tests to perform and it requires the least amount of time. This is therefore considered to be one of the best radioiodine tests available. It requires only a small dose of

radioiodine (one to two micro-curies), and very little of the patient's time. Nothing is required of the patient but to drink the solution containing the radioiodine and then return six hours later for a count over the thyroid. The disadvantages of uptake determinations include interference by previous medication and the fact that the test cannot be used repeatedly. Medications which lower the uptake are Lugol's solution or any substance containing large amounts of iodine, anti-thyroid agents, and thyroid substances. Iodine starvation and the thyroid stimulating hormone produce an elevated uptake.

The normal range for the six-hour uptake, as reported by Owen, et al.(9), is from 7.5 to 25.0 per cent of the administered dose, and the average six-hour uptake is 14.9 per cent. These figures are in accordance with those obtained in the present study for euthyroid controls and patients with ulcerative colitis.

Twenty-Four Hour Uptake

At twenty-four hours after the ingestion of radioiodine, its concentration in the thyroid gland reaches a plateau and begins a gradual decline (15). Therefore, the value of determining the iodine uptake by the gland at this time is not as great as at the six-hour level. This is particularly true in the case of borderline hypothyroidism. Otherwise, the advantages and disadvantages are the same as those for the six-hour

uptake. Werner, Quimby, and Schmidt (16) found the twenty-four-hour uptake to vary from 9 to 49 per cent for euthyroid subjects. Their mean value was 22.8 per cent. It was noted that there was no deviation from these values in either of the groups studied here.

Protein-Bound I^{131}

The technique of determining protein-bound I^{131} is apparently as accurate as the determination by chemical means and is much easier to perform. The amount of I^{131} which is protein-bound in twenty-four hours has been shown to be a good indication of thyroid activity (2). This technique, however, has the disadvantages of being more time consuming than certain other I^{131} tests and it does not show the relationship between the inorganic I^{131} and the protein-bound form. Nor can the test be repeated frequently. It is also known to produce misleading results in the case of toxic nodular goiter (12).

Seed, Jaffe, and Baumeister (12), in a study of 116 euthyroid individuals, found the protein-bound I^{131} values to vary from 0.0020 to 0.4600 per cent of the dose per liter of serum. The mean value was 0.0540 per cent, which is in very close agreement with the values found in the present study.

Twenty-Four-Hour Conversion Ratio

The twenty-four-hour conversion ratio affords a simple way of expressing the rate at which the radioiodine is converted

from the inorganic form to the protein-bound state. The diagnostic value of this determination is somewhat greater than the preceding one in the separation of euthyroid and hyperthyroid individuals and is felt by some to be the best single radioiodine test of thyroid function (13). However, it is of no value in differentiating hypothyroidism, since the normal range approaches zero. Sheline and Clark (13) found the range to be from 3 to 41 per cent in a group of 26 euthyroid individuals. The mean was 19.6 per cent. The figures obtained in the present study are in agreement with these values. This is also in accordance with other results found in the literature (2,9,12).

Twenty-Four-Hour Urinary Excretion of I^{131}

This technique is not an overly reliable test of thyroid function. It supposedly measures the amount of I^{131} rejected by the gland and should be a function of the thyroid uptake. This does not always seem to be true. One explanation for this is that the excretion depends largely upon the state of the kidneys and the presence or absence of diseases which alter renal function. A second difficulty arises in the complete collection of the urine. However, in situations in which little else can be done, a urinary I^{131} excretion study may be of some value. This occurs when the patient is bedridden and the counting equipment cannot be brought to the patient for uptake studies. In such cases, the conversion

ratio, protein-bound I^{131}, and urinary excretion of I^{131} can give some indication of thyroid activity.

Keating, Power, Berkson, and Haines (4) found the average urinary excretion of I^{131} in 14 euthyroid individuals to be 65 per cent of the administered dose. At a later date, Zieve, Skanse, and Schultz (17), in a study of euthyroid individuals, found the mean urinary excretion of I^{131} to be 60 per cent in twenty-four hours with a range from 43 to 87 per cent. These data are in accordance with those found in the present study for both the control and experimental individuals.

Summary

A series of eight tests of thyroid physiology were applied to six normal individuals and ten patients with ulcerative colitis in an attempt to determine if there was a correlation between this pathological condition and thyroid function. Tests made included determination of serum cholesterol, chemical protein-bound iodine, basal metabolic rate, six-hour and twenty-four-hour thyroid I^{131} uptake, twenty-four-hour protein-bound I^{131}, a twenty-four-hour conversion ratio, and the twenty-four-hour urinary I^{131} excretion rate. None of the mean values obtained for the patients with chronic ulcerative colitis differed significantly from the values for the control series. All of the determinations fell within the normal values quoted in the literature. However, in four of the tests there was a slight

elevation of thyroid activity in the patients with ulcerative colitis. A greater number of cases must be studied before a definite conclusion can be drawn.

Each test was evaluated for usefulness, ease of determination, and accuracy. The uptake studies were the most easily performed and required the least amount of time. They were felt to be the most accurate of the radioiodine techniques. It was concluded that the determination of serum cholesterol is not an accurate measure of thyroid activity although it is easy to perform. The protein-bound iodine determination was felt to be the most accurate and useful of the chemical determinations, although one of the most difficult to carry out.

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APPENDIX

TABLE I

THYROID STUDY OF 6 EUTHYROID CONTROLS

Measurement	6 Hour* Uptake	24 Hour* Uptake	24 Hour** Protein-Bound I^{131}	24 Hour Conversion Ratio (%)	24 Hour* Urinary I^{131} Excretion	Protein-Bound Iodine (mcg. %)	Cholesterol mg. Per Cent	Basal Metabolic Rate (% Normal)	Age
Range	9.2 to 15.7	19.0 to 26.2	0.0414 to 0.1030	4.1 to 29.2	42.6 to 70.0	3.8 to 6.5	156 to 316	-18 to + 3	19 to 53
Mean	13.0	22.8	0.0676	20.1	54.6	5.5	200	- 6	30
S. D.	1.7	2.7	0.0279	10.0	9.9	1.8	55	8	--

*Per cent of dose
**Per cent of dose per liter of serum
S. D. = Standard Deviation

TABLE II

THYROID STUDY OF 10 PATIENTS WITH CHRONIC ULCERATIVE COLITIS

Measurement	6 Hour* Uptake	24 Hour* Uptake	24 Hour** Protein-Bound I^{131}	24 Hour Conversion Ratio (%)	24 Hour* Urinary I^{131} Excretion	Protein-Bound Iodine (mcg. %)	Cholesterol mg. Per Cent	Basal Metabolic Rate (% Normal)	Age
Range	9.9 to 15.2	15.5 to 47.4	0.0420 to 0.2150	16.3 to 42.3	52.2 to 77.0	4.2 to 7.8	168 to 248	-24 to +15	13 to 49
Mean	12.4	24.9	0.1095	31.2	62.7	6.3	205	+ 1	26
S. D.	2.6	8.9	0.0535	11.3	15.5	1.3	22	11	--

*Per cent of dose
**Per cent of dose per liter of serum
S. D. = Standard Deviation

TABLE III

COMPARISON OF MEAN RESULTS OF
CONTROLS AND PATIENTS

Group	6 Hour* Uptake	24 Hour* Uptake	24 Hour** Protein-Bound I^{131}	24 Hour Conversion Ratio (%)	24 Hour* Urinary I^{131} Excretion	Protein-Bound Iodine (mcg. %)	Cholesterol mg. Per Cent	Basal Metabolic Rate (% Normal)	Age
Patients	12.4	24.9	0.1095	31.26	62.7	6.3	205	+ 1	26
Controls	13.0	22.8	0.0676	20.18	54.6	5.5	200	- 6	30

*Per cent of dose
**Per cent of dose per liter of serum
S. D. = Standard Deviation

ILLUSTRATIONS

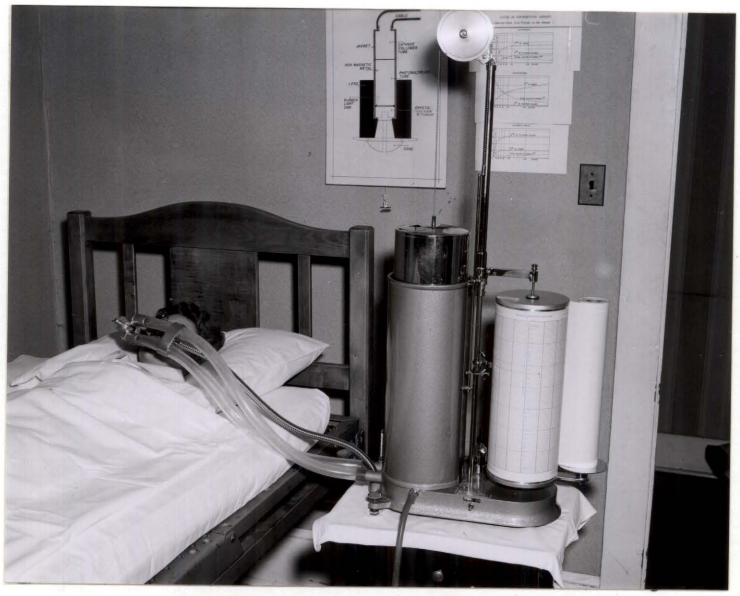

Fig. 1--Benedict-Roth type of spirometer employed in determination of basal metabolic rate.

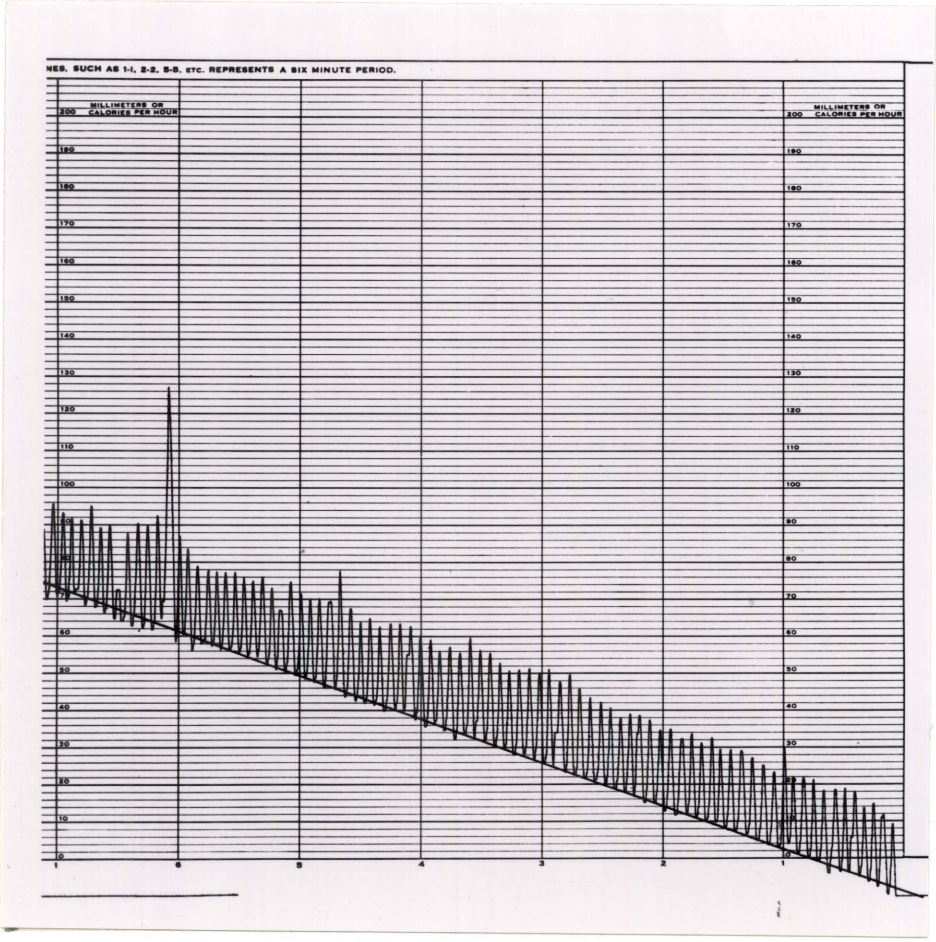

Fig. 2--Typical respiratory tracing showing rate of oxygen consumption.

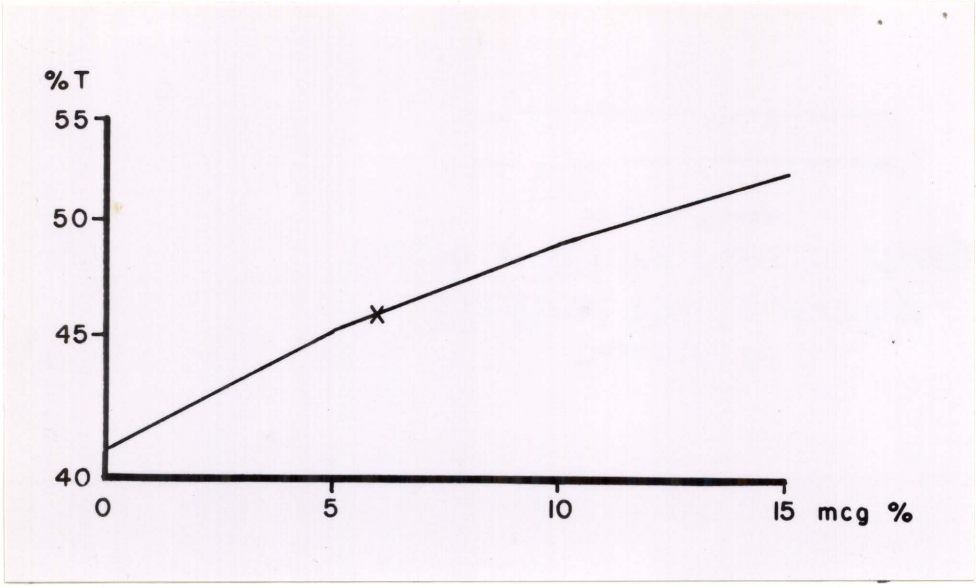

Fig. 3--Graph showing curve produced by four iodine standards. The "X" represents a serum sample.

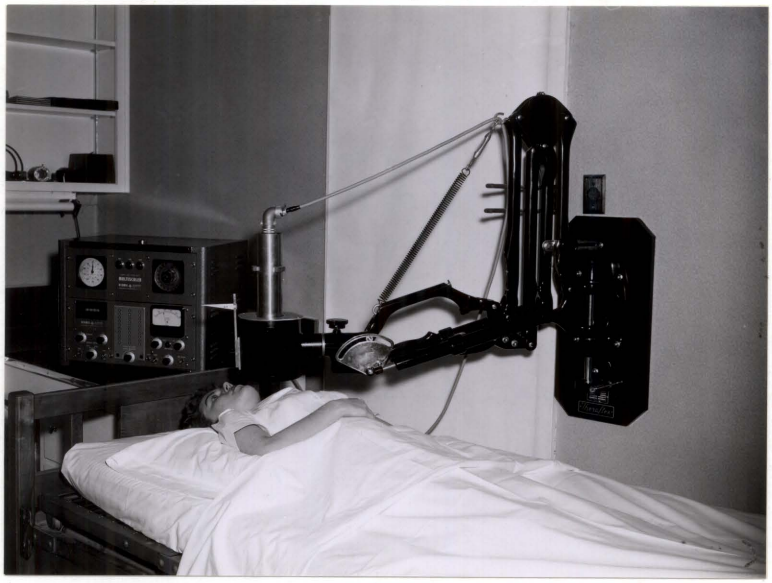

Fig. 4--Scintillation counter employed in uptake studies illustrating relative position of patient.

Fig. 5--Scintillation head and relative position of standard employed in thyroid uptake studies.

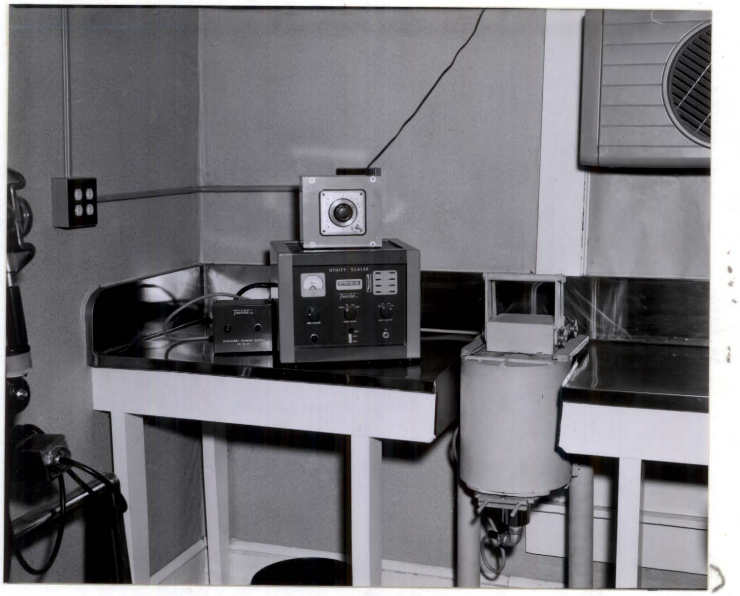

Fig. 6--Well counter and scaler employed in serum and urinary I^{131} studies.

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