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ATOMIC ENERGY PROJECT
Contract No. AT-11-1-GEN-10, Project No. 2
Under the supervision of Robert S. Stone, M.D.

Experience at the University of California with the
Treatment of Patients with Hyperthyroidism by I^{131}

Earl R. Miller, M.D.

with the assistance of:

A. V. Holmes, M.D.
M. E. Dailey, M.D.
G. L. Alexander, M.D.
G. E. Sheline, M.D.

and with the technical assistance of:

Marian Feigentaum
Enid Moor
Louise Prestidge

(September, 1945 to November 1, 1949)

October, 1950

Radiation Laboratory
Berkeley, California

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Experience at the University of California with the
Treatment of Patients with Hyperthyroidism by I¹³¹

Earl R. Miller, M.D.

with the assistance of:

A. V. Holmes, M.D., M. E. Dailey, M.D.,
G. L. Alexander, M.D., and G. E. Sheline, M.D.

and with the technical assistance of:

Marian Feigenbaum, Enid Moor, and Louise Prestidge

University Hospital and School of Medicine
University of California, Berkeley, California

(September, 1945 to November 1, 1949)

October, 1950

This paper deals with the treatment with I¹³¹ of patients who have hyperthyroidism. It is written for the purpose of presenting our concepts with regard to the place of I¹³¹ in the treatment of hyperthyroidism, the methods employed in treating such patients, and the results on patients that we have so treated. The subjects will be treated under the following headings:

1. Introduction: A History of Clinical Use of Radioiodine at the University of California.
2. Discussion of dose and how it is measured.
3. Description of the group of patients on whom we worked with this agent.
4. Methods of carrying out the treatments.
5. Presentation and discussion of results.
6. The place of I¹³¹ among the various methods available for the treatment of hyperthyroidism.

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Experience at the University of California with the Treatment of Patients with Hyperthyroidism by I^{131}

Earl R. Miller, M.D.

with the assistance of:

A. V. Holmes, M.D., M. E. Dailey, M.D., G. L. Alexander, M.D., and G. E. Sheline, M.D.

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University Hospital and School of Medicine
University of California, Berkeley, California

(September, 1945 to November 1, 1949)

October, 1950

1. INTRODUCTION: A History of the Development of the Clinical Use of Radioiodine at the University of California.

Interest in the clinical use of radioiodine for therapy of hyperthyroidism at the University of California began in 1938 with the studies of Dr. Joseph G. Hamilton and the late Dr. Mayo H. Soley. The studies with radioiodine were interrupted by the war and later resumed in the Radiology Division of the Medical School by the author. Dr. Soley started his collaboration with the author in studies of patients in 1945.

It became apparent that the accurate measurement of the radiation from radioiodine constituted a major problem. A study of various factors which affect these measurements was undertaken. It was realized that for clinical work measurements of the radiation from radioiodine depended upon its gamma-radiation. Since the thyroid is of unknown size and depth, the measurements have to be carried out at relatively long distances and with considerable filtration if they are to have meaning. Initially, in 1945, a distance of 53 cm and filtration with lead 4 gm/cm² were adopted. The measurement of the radiation from the thigh as a means of estimating the non-thyroid neck radiation was initiated at

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this time. During the first few months of the work, we undertook studies of the effect of the size of the source, the distance at which it is measured, and the amount of filtration over the counter on the measurement of the gamma-rays from radium and I^{131} . Originally when patients were accepted for study and treatment, end-window, lead-shielded, horizontal Geiger counters were used for making measurements and the measurements were standardized against uranium. When space became available, an x-ray holder was used for the verticle mounting of the Geiger counter and the present technique of measurement evolved. The techniques of measuring patients have remained nearly constant since early in 1946. Techniques for routine handling of radioiodine safely by remote control burettes were in use early in 1946. The uranium standard was abandoned in 1945 and since that time the same radium standard has been used throughout the entire work. Since 1946 the use of glass bottles containing 35 cc of the radioiodine solution have acted as the source of radiation with which the radiation from the thyroid is compared.

With the difficulty of knowing precisely what a millicurie of iodine was and with the lack of assurance that the supply of I^{131} would have a constant calibration, a University of California unit of radioiodine was developed.

Later, the Oak Ridge unit was adopted. The details about this will be described under the discussion of dose.

In the early work very small doses, approximately 250 microcuries at weekly intervals, were used for the treatment of thyrotoxicosis. These doses were used because of insufficient knowledge of the size of the dose required to control the disease and be safe, and the radioiodine supply was limited. As our information and confidence grew, the doses were increased considerably in size. At first it was hoped that the dose might be more directly related to the severity of hyperthyroidism than it was to the size of the thyroid gland. If true this

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would have permitted us to avoid the difficulty of estimating the size of the thyroid. Dr. Robley Evans of Massachusetts Institute of Technology convinced me of the value of considering the thyroid size in the calculation of the dose. Since the middle of 1947, attempts have been made to calculate the doses in radiation units, taking account of thyroid size.

In the early part of this work Dr. Mayo Soley and other members of the University of California Thyroid Clinic handled the clinical phase of the work. Dr. Soley later left the University of California and Dr. Morris Dailey assumed the direction of the Thyroid Clinic. All the radiation aspects were handled in the Division of Radiology. With the establishment of the Atomic Energy Commission contract with the Division of Radiology, assistance became available. Dr. Fred Kreutzer, Dr. Nadine Foreman, Dr. Alden V. Holmes, Dr. George L. Alexander, Mrs. Marian Feigenbaum and Miss Enid Moor have worked on the project.

In 1946 studies on animals were carried out with particular reference to destructive effect of radioiodine on the thyroid and its surrounding structures, the liver and the kidneys. These studies led us to believe that we could use radioiodine with relative safety in the treatment of patients with thyrotoxicosis.

Dr. Edith Quimby, of the Columbia University School of Medicine in New York, and others have emphasized the importance of the effective half-life in determining the dosage of radiation administered to the thyroid from radioiodine. We have leaned heavily on her work and that of Leo Marinelli in the calculations of radiation dosages to the thyroid.

Early studies of the blood of patients who had received I^{131} were carried out under the direction of Dr. B. V. A. Low-Beer along with his other studies of radiation effects. Direction of this part of the work is now shared with Dr. Paul Aggeler. A succession of extremely high-caliber technicians has kept this blood program on a very high plane.

Dr. Mayo Soley, Dr. Horace McCorkle, Dr. Kenneth G. Scott, PhD., and the

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author have worked together in studying the problem of postoperative thyroid regeneration in animals and its relation to thyroid function as measured by I^{131} uptake.

This work has been supported generously by the Atomic Energy Commission.

Without this support the projects would not have been carried out.

Dr. Robert E. Stone, Chairman of the Division of Radiology at the University of California School of Medicine and Hospital, has aided immeasurably in his constructive and helpful criticisms and in making the time available to the author for carrying out the work reported.

CALCULATION OF THE BETA-RAY DOSE DELIVERED TO THE THYROID FROM I^{131} .

It is desirable that there be a unit which will express the dose of radiation actually delivered to the thyroid from I^{131} , and that it be familiar to those carrying out other types of clinical radiation therapy. Although I^{131} emits both beta- and gamma-rays, the local effect from the gamma-rays is relatively small and will not be considered here. In work with beta-radiation it has become conventional to speak of doses in terms of the beta-roentgen equivalent. An amount of a radioisotope that emits beta-particles will deliver to a gram of air in which it is present a beta-roentgen equivalent when it delivers to it the same amount of energy as will a roentgen of x-ray. A beta-roentgen equivalent delivers essentially the same amount of energy to a gram of tissue as it does to a gram of air.

1 r produces 1.62×10^{12} ion pairs per gram of air.

1 μ c of a radioisotope is that amount whose atoms are disintegrating at the rate of 37000/sec.

Each beta-particle from I^{131} can be considered to have 205,000 electron volts of energy on the average. It requires 32 electron volts (this value is variously quoted from 32 to 32.5) to produce an ion pair.

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Therefore, each beta-particle from I^{131} when completely absorbed will produce on the average $\frac{205000}{32}$ ion pairs. Thus the absorption of the beta-particles from 1 μ c of I^{131} will produce in 1 second $\frac{37000 \times 205000}{1.62 \times 10^{12} \times 32}$ beta-roentgen equivalent/sec.

A different number of microcuries of I^{131} (μc_1) acting for a different number of seconds (t_1) in a different number of grams (gm) of tissue will give to that tissue $\frac{(\mu c_1) \times (t_1)}{(gm)} \times \frac{37000 \times 205000}{1.62 \times 10^{12} \times 32}$ beta-roentgens equivalent (B.r.e.) during time interval t_1 .

This reduces to:

$$\begin{aligned} \text{B.r.e.} &= \frac{\mu c_1 \times \text{seconds}}{\text{gm}} \times 0.000142 \text{ when } t_1 \text{ is in seconds} \\ &= \frac{\mu c_1 \times \text{hours}}{\text{gm}} \times 0.5267 \text{ when } t_1 \text{ is in hours} \\ &= \frac{\mu c_1 \times \text{days}}{\text{gm}} \times 12.6417 \text{ when } t_1 \text{ is in days} \end{aligned}$$

This is strictly valid only if the number of disintegrations per unit time does not change during the interval used. It can be used practically when the time intervals are short as compared with the half-life. The use of this type of approximation is demonstrated in the calculations given below and is applicable to parts A and B of Fig. 1a and parts 1 through 6 of Fig. 1b. The value of μc_1 is taken as the numerical average of number of microcuries present for the interval under consideration.

Dosage Calculation: Weight of thyroid assumed to be 30 grams for purposes of calculation.

For Fig. 1a:

PART A. Average $\mu c_1 = \frac{70}{2} = 35$ Time = 16 hours.

B.r.e. = $\frac{35 \times 16 \times 0.5267}{30} = 9.83$

PART B. Average $\mu c_1 = 70 + \frac{76-70}{2} = 70 + 3 = 73$ Time = 6 hours.

B.r.e. = $\frac{73 \times 6 \times 0.5267}{30} = 7.69$

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Fig. 1b:

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| Part 1 | $\frac{32.5 \times 12.5 \times 0.5267}{30}$ | = | 7.42 |
| Part 2 | $\frac{70 \times 9 \times 0.5267}{30}$ | = | 11.06 |
| Part 3 | $\frac{72 \times 10 \times 0.5267}{30}$ | = | 12.82 |
| Part 4 | $\frac{55 \times 20 \times 0.5267}{30}$ | = | 19.31 |
| Part 5 | $\frac{33 \times 22 \times 0.5267}{30}$ | = | 12.75 |
| Part 6 | $\frac{23 \times 23 \times 0.5267}{30}$ | = | 9.29 |
| Total | | | 72.65 B.r.e. |

In those cases where the descending portion of the uptake curve is straight when plotted on semi-logarithmic paper, the dosage calculation is modified. The basic formula then becomes:

$$\text{Beta-roentgen equivalent} = \frac{18 \times \mu\text{Ci} \times \text{EHL}}{\text{gm (thyroid)}}$$

where μCi is the number of microcuries present at the start of the time for which the calculation is made. EHL is the effective half-life as determined from the curve of I^{131} uptake in the thyroid and is the time interval between two points, on the straight part of the curve, so chosen that the amount of I^{131} in the thyroid at one point is twice the amount at the other. See Part C of Fig. 1a.

Application of this type of calculation to:

Part C Fig. 1a

$$\text{B.r.e.} = \frac{18 \times 76 \times 3.87}{30} = 190.9 \quad \text{where EHL} = 3.87 \text{ days}$$

Part 7 Fig. 1b

$$\text{B.r.e.} = \frac{18 \times 20 \times 4.0}{30} = 48.0 \quad \text{where EHL} = 4.0 \text{ days}$$

Addition of the doses determined for the several parts of each curve gives

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the total dose.

For Fig. 1a the total dose is:

$$\text{Parts A + B + C} = 9.83 + 7.69 + 190.9 = 208.4 \text{ B.r.e.}$$

For Fig. 1b:

$$\text{Parts 1 through 6 + Part 7} = 72.65 + 48.0 = 120.65 \text{ B.r.e.}$$

It should be noted for the two patients whose uptakes are illustrated in Fig. 1 that although the oral doses, the thyroid sizes, the maximum uptakes and the time at which the maxima occurred are the same, one patient's thyroid received much more radiation than the other.

There are several limiting assumptions inherent in the above method of calculation. Important among these are the assumptions that: 1. the I^{131} is uniformly distributed in the thyroid; 2. none of the beta-particles escapes from the periphery of the gland; and 3. the weight of the thyroid is known.

The procedure of determining the EHL is one that takes several days. It would be advantageous if it were not necessary to determine it for each patient and still be able to estimate the dose. With this in view, we studied the distribution of the EHL in the data from patients with Graves' disease who were tested with I^{131} to see if the average EHL might be used. Fig. 2 gives the results of that study and shows that there is wide spread in the EHL in different patients. The dose of radiation to the thyroid is dependent directly on the EHL. Because of the wide spread of the data, we have felt that it is important to determine the EHL for each patient rather than to accept some average value.

In 1946 a platinum needle containing 600 micrograms of Ra was adopted as the gamma-ray standard in the radioiodine laboratory at the University of California Medical School. It was used throughout our work as a source of radiation and as a means of checking the constancy of our measuring apparatus. In the spring of 1946, the microcuries of I^{131} as determined by the Oak Ridge standardization of a particular shipment was accepted as our unit. It remained constant

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throughout the work which followed. On January 1, 1950 the new Oak Ridge definition of the microcurie was accepted. All the data relating to I¹³¹ dosage was corrected to this new standard. They are reported in this paper in terms of the microcurie.

DESCRIPTION OF THE GROUP OF PATIENTS TO WHOM I¹³¹ WAS GIVEN FOR THE TREATMENT OF HYPERTHYROIDISM.

This report presents the data on the first 100 consecutive patients to whom I¹³¹ was given for the treatment of hyperthyroidism.

The diagnosis of hyperthyroidism was made by the evaluation of the clinical status and the laboratory findings of the patients. During the clinical examination of the patient, particular attention was paid to any recent change in appetite and weight of the patient, to the basal pulse, thyroid size and character, thyroid bruit, character of the skin, tremor, change in bowel habits and menstrual cycle, pulse pressure, history of previous thyroid surgery or radiation, history of taking anti-thyroid drugs, nervousness, irritability, sweating, heat intolerance, palpitation, evidence of local pressure by the thyroid and the eye signs associated with hyperthyroidism. Laboratory studies included the determinations of the basal metabolic rate, serum protein-bound iodine, and cholesterol.

Most of the patients came initially from the Thyroid Committee of the University of California Medical School, San Francisco. Many of the rest were sent to the Committee for clinical study.

Patients were accepted for treatment when the author was satisfied with the diagnosis of hyperthyroidism by his own evaluation. In general, patients with nodular thyroids were not accepted for treatment.

Dr. Morris E. Dailey and Dr. Alden V. Holmes devoted much time and effort re-evaluating the charts of these patients in an attempt to be as certain as

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possible of their clinical status. With few exceptions the patients would be accepted for treatment again if they were present with the same evidence of hyperthyroidism.

4. METHODS OF CARRYING OUT THE TREATMENT OF PATIENTS WITH HYPERTHYROIDISM BY I¹³¹.

The patients to be treated are evaluated as described in Section 3. As the first step in treatment a test dose of I¹³¹, usually 100 µc, is administered to the fasting patient. Uptake data are then collected at 1, 3, 6, 24, 48, 72, 96 120 hours and the I¹³¹ uptake curve drawn. The weight of the thyroid gland is estimated. From the thyroid weight and the uptake curve for the test dose, the amount of I¹³¹ necessary to deliver 6000 beta-roentgen equivalents to the thyroid is calculated (see Section 2 on dose calculation). This amount is given as an oral therapy dose and its uptake by the thyroid gland determined. Since the uptake curve for the therapy dose may vary somewhat from the one obtained for the test dose, the amount of radiation to the thyroid gland is then recalculated. It is considered that the recalculated value more accurately reflects the amount of radiation to the thyroid from the therapeutic dose of I¹³¹. Thereafter, when possible, the patient is examined at weekly intervals. Basal metabolic rate and serum protein-bound iodine tests are done occasionally during this initial follow-up period. Six weeks following the initial treatment dose, the patient is re-examined and an uptake curve of a test dose of I¹³¹ is obtained. On the basis of the findings at this time, the patient may be retreated. The estimation of the number of beta-roentgen equivalents to be delivered to the thyroid by such a retreatment dose of I¹³¹ is based on the clinical response the patient obtained from the former therapeutic dose and on the present clinical state of the patient. If retreated, the uptake curve on this therapy dose is also determined. The follow-up visits are continued. About 12 weeks after the initial

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therapy dose, the uptake curve is again obtained and treatment given as indicated. When the patient reaches a state of clinical remission, follow-up visits are placed at longer intervals. An attempt is made to follow the patients continuously from the time of their first treatment.

RESULTS OF TREATMENTS IN PATIENTS TO WHOM WE GAVE I¹³¹ FOR HYPERTHYROIDISM.

Since September 1945, 114 patients received I¹³¹ for treatment of hyperthyroidism. One hundred of these started treatment before the middle of July 1949. The data are analysed as of November 1, 1949. Fig. 3 gives a composite picture of the time of beginning treatment of the first 100 consecutive patients, the length of their illness, the length of time of follow-up, how long they remained well, how many required thyroid medication for hypothyroidism, how many had clinically significant exophthalmos and the number and time relationships of pregnancies.

Of these 100 patients, the results for 90 will be discussed at this time. The following 10 cases are not included in the analysis for the indicated reasons:

- No. 6 Patient not heard from after initial therapeutic dose of I¹³¹.
- No. 13 Became pregnant after second dose. Patient was aborted, did not finish treatment and was lost to follow-up.
- No. 18 Was psychotic at time of treatment. Within 2 months became unmanageable and was lost to follow-up. *ultimately died of Tb at Napa.*
- No. 26 Developed rheumatic pancarditis. Treatment changed to propylthiouracil and patient lost to follow-up.
- No. 47 Patient did not understand that he had been treated. He thought he had been tested only. Was operated upon elsewhere.
- No. 51 Lost after one month.
- No. 73 Complicated by mixed therapy and unable to evaluate.

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No. 85 Not able to evaluate result. Difficult to be sure the patient had hyperthyroidism at the time of treatment.

No. 96 Left town after one month.

No. 100 Followed for less than 3 months and not seen since.

Among these 100 patients were 13 men and 87 women. The age distribution was as follows:

| AGE | NUMBER | AGE | NUMBER | AGE | NUMBER |
|-------|--------|-------|--------|---------|--------|
| 0-5 | 1 | 26-30 | 14 | 51-55 | 6 |
| 6-10 | 4 | 31-35 | 9 | 56-60 | 7 |
| 11-15 | 3 | 36-40 | 12 | 61-65 | 1 |
| 16-20 | 8 | 41-45 | 11 | over 65 | 3 |
| 21-25 | 8 | 46-50 | 12 | | |

The age of one is unknown.

Forty-nine of these patients had previously had one or more kinds of treatment directed toward their thyroid.

| | |
|------------------|----|
| Operation | 12 |
| Lugol's solution | 29 |
| Propylthiouracil | 11 |
| Thiouracil | 7 |
| X-ray | 3 |
| Thyroid by mouth | 9 |

Although it is difficult to separate the various degrees of severity of hyperthyroidism, Dr. Dailey, Dr. Holmes, Dr. Alexander and the author studied the charts of all the patients treated and on the basis of the clinical and laboratory findings made an estimate of the degree of severity. The following estimates resulted: mild, 23; moderate, 48; severe, 25; and undecided, 4.

The data on oral doses of I¹³¹ given to these patients are given in Fig. 4. No conclusions about the amount of radiation to the thyroid can be drawn from

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These data because the dose of I^{131} given by mouth does not necessarily parallel the radiation dose given to the thyroid. (See Section 2.) Because adequate intake data for the earlier patients are lacking, the radiation doses for those patients cannot be calculated. For the sake of uniformity the oral doses of I^{131} are reported.

Of the 100 patients in whom therapy was started before July 1949, 89 have finished their treatment and one is still under treatment, Table 1 (Nov. 1949). The status of each of the other 10 patients is not certain. Of the 89, 84 are considered "cured". Fig. 5 gives the data on the length of illness of those patients and the intervals between the first and last therapeutic doses are shown in Fig. 6.

Throughout this work the word "cured" is used as an abbreviation for "in clinical remission" or "clinically well". A patient was considered "clinically well" when the signs and symptoms of his disease had disappeared, the thyroid had returned to normal size and his laboratory findings had returned to within normal limits. The decision about the time at which the patients were "cured" was in the hands of Dr. Dailey.

Table I

Status of patients as of November 1949

| Year Therapy Started | Number of Patients | Number "Cured" | Number Lost To Follow-up Or Still Sick | Number Under Treatment | Number Patients Not Able To Evaluate |
|----------------------|--------------------|----------------|--|------------------------|--------------------------------------|
| 1945 | 4 | 4 | 0 | 0 | |
| 1946 | 26 | 20 | 6 | 0 | 4 |
| 1947 | 35 | 32 | 3 | 0 | 2 |
| 1948 | 18 | 16 | 2 | 0 | 2 |
| 1949 | 17 | 12 | 4 | 1 | 2 |
| | 100 | 84 | 15 | 1 | 10 |

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6 THE PLACE OF I¹³¹ AMONG THE VARIOUS METHODS AVAILABLE FOR THE TREATMENT OF
HYPERTHYROIDISM:

The cause of hyperthyroidism is not known, and therefore its treatment is empirical. The present methods of treatment of the disease consist of destruction of a part of the thyroid by surgery, radiation, or the interruption of thyroid function by the administration of anti-thyroid drugs. The first method is the most widely used method of definitive therapy. The use of anti-thyroid drugs has its dangers and difficulties and has not proved to be uniformly successful in producing lasting good results. We await with eagerness the appearance of some drug or method which will attack the disease at its source and make all present approaches to this disease obsolete.

Of the various methods available for destroying a part of the thyroid, surgery has been used longest. The use of radiation therapy permits relatively good control of the rate and amount of thyroid destruction and is done routinely on an ambulatory basis. It spares the patient the pain, fear and dangers, however small, of anesthesia, parathyroid removal, injury to nerves and postoperative hemorrhage.

Externally administered radiation must penetrate the skin in order to reach the thyroid, and does subject the normal structures around the thyroid to radiation. This may produce damage to the skin and other organs. The major difficulty with this mode of treatment has been injury to the larynx and esophagus. However, when the radiation is applied skillfully, this injury is negligible. The results of the external radiation therapy of hyperthyroidism compare favorably with the results of any other method of treatment.

Radiiodine has the advantage of being taken up selectively in the cells of the thyroid that are metabolizing iodine at the greatest rate. Presumably these cells are most concerned with the overproduction of the thyroid hormone. This means that the radiation originates in these cells and has the opportunity to

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destroy them with a minimal effect on the tissue that is not concerned in iodine metabolism. This selective radiation of cells that are thought to be deeply involved in the syndrome recognized as hyperthyroidism is the basis of the use of I¹³¹ for therapy of this condition. The dose of I¹³¹ given to the thyroid depends upon the amount given by mouth and upon the ability of the thyroid to concentrate and to hold radiiodine.

The rest of the body is subjected to some radiation. The kidneys, liver, salivary glands and stomach do receive recognizable amounts of radiation; however, with the dosage levels used in the treatment of hyperthyroidism, both objective and subjective evidence of injury to these organs is not forthcoming. It has been stated that radiiodine is too slow in its action. However, many patients with hyperthyroidism are markedly improved within a few weeks; in some of them, improvement has been so dramatic that the time required for successful treatment with radiiodine is approximately the same as that which would have been required for the preparation of these patients for surgery. It was suggested by Soley that the patients treated by radiation were less likely to be the victims of serious eye complications than those treated by surgery.

It seems that the radiation methods should be able to succeed in bringing the patient to the normal level of thyroid function without danger of recurrence and without necessarily making the patient hypothyroid during the convalescent interval. It is said by some surgeons of our thyroid group that a degree of hypothyroidism is expected during the convalescent period following an adequate subtotal thyroidectomy, if the surgery is radical enough to prevent recurrence.

It seems timely to discuss the conditions under which any radioisotope is usable for the therapy of disease. These are as follows: (1) the disease process must be capable of being treated successfully by radiation; (2) the isotope must have a sufficiently long physical half-life to be useful practically; (3) the physical half-life must not be so long as to make its use dangerous; (4) it must be concentrated in the tissue to be treated; (5) it

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must not be concentrated in other tissues of the body in dangerous quantities; (6) it must remain in the tissues to be treated long enough to insure effective radiation; (7) its radiation components should have either alpha- or beta-particles so that its radiation effects are largely limited to the tissue to be treated; (8) preferably it should have a component of penetrating radiation, a hard gamma-ray, so that the concentration of the isotope in vivo can be determined by measurement of this radiation outside of the patient, and (9) ideally the radiation dose to the tissue should be measurable with certainty, but practical results can be accomplished without perfect measurement. Radioiodine, by these criteria, should be, and is, an excellent therapeutic agent for patients with hyperthyroidism.

Successful and safe conduct of a radioiodine center for treatment of hyperthyroidism requires in its staff the understanding of basic knowledge of radioactivity and technique, of radiation effects on tissue, and of the clinical and pathological manifestations of the disease process to be treated. These areas of knowledge may reside in one or more men. It is unwise and unsafe to embark upon an isotope program unless each of these areas of knowledge are covered adequately by the staff.

SUMMARY: A short history of the clinical use of radioiodine at the University of California Medical School is presented.

One of the most difficult problems facing the radioiodine therapist who is treating hyperthyroidism is the determination of the dose of radiation to the thyroid. One method of attacking this problem is discussed in some detail. The inherent assumptions underlying this method are pointed out. No accurate method of determining the radiation dose to the thyroid is known at present.

The first one hundred consecutive patients treated with radioactive iodine for hyperthyroidism at the University of California Hospital are presented.

Methods of selection and treatment and the results of such treatment are given. The results of radioiodine therapy for hyperthyroidism are found to compare favorably with the results of other methods of treatment of this syndrome. This applies only to the patient who does not have a nodular goiter. Follow-up studies of patients, up to four years in some cases, have shown a striking absence of recurrence. The number of patients rendered hypothyroid by this treatment is not more, and may be less, than is produced by surgery. Further experience may permit us to reduce the incidence of this complication. No untoward effect of the treatment, except hypothyroidism, has become evident in the follow-up of this group of patients.

The place of radioiodine in the therapy of hyperthyroidism is considered.

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LEGENDS

1. The I^{131} uptake curves of two patients who were given the same oral dose of radiiodine. These patients had thyroid glands of the same size. Note that although the maximum uptake and the time at which the maximum occurred were the same for each, the general shape of the two curves are different. Curves of this type are used in calculating the dose of radiation delivered to the thyroid tissue (see text).
2. No legend.
3. Data on the clinical status of 100 consecutive patients treated with I^{131} for hyperthyroidism at the University of California Medical School. The first patient was treated in 1945. The follow-up data are summarized as of November 1949. The chart shows a full dark line for the period the patient was considered to be clinically ill and a lighter broken line for the period the patient was considered to be clinically well.
4. The graph shows distribution of dosage to various patients. The word "cured" as used in this and other charts indicates that at the time of the final follow-up in November 1949, the patient showed no clinical signs of hyperthyroidism. Most of the patients received between 3 and 9 millicuries. It is seen that when doses above 9 millicuries were required, the percentage of patients having clinical remissions decreased.
5. Shows the length of the illness of the patients treated for hyperthyroidism. About two-thirds were well within 6 months. If they remained ill longer than this, their chances of ultimately going into remission were considerably less.
6. Shows the time in months which elapsed between the first and the last doses of radiiodine in the 100 cases presented. Most of these pa-

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tients finished their treatment within 2 months. It will be observed that if we found it necessary to treat a patient longer than 5 months, the chance of bringing about a clinical remission decreased markedly.

Fig. 7. Shows the number of doses of I¹³¹ given to various patients in this series of 100 cases. It will be seen that the great majority of patients received less than 5 doses.

Fig. 8. Shows the estimated weights of the thyroids at various times after patients were treated. "0" time represents the time at which the first dose of iodine was administered. It can be observed that after the administration of radioiodine there is a clear cut downward trend in the weight of the thyroid. The solid lines are used while the patient is considered to be ill and the dashed lines which the patient is considered to be well. Many glands became too small to palpate adequately. Only rarely did an observer believe a thyroid of less than ten grams was palpable.

Fig. 9. Estimated weight of the thyroid gland as a function of time in patients with hyperthyroidism who have been treated with radioiodine. The single dots represent the individual observations and the solid line represents the median of the observations. This figure gives essentially the same information as Fig. 7.

Fig. 10. The composite curve of the basal metabolic rate determinations on hyperthyroid patients treated with radioiodine, as a function of time. It will be observed that in general the higher the basal metabolic rate at the start, the longer is the time before clinical remission is established. As long as the patient was considered ill the line is solid. When the patient was considered to be well the line is dashed. In general, the patients represented by the lines which do not reach the normal range are considered among the unsatisfactory results.

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11. The basal metabolic rate in patients with hyperthyroidism who were treated with radiiodine. The time of the administration of the first dose is taken as "0" time. The dots represent individual observations. The solid line represents the median of these observations. It will be observed that the median reached the "0" level at about 4 months.
12. In this graph the levels of the serum protein-bound iodine in the 100 patients treated for hyperthyroidism with iodine 131 are plotted as a function of time. A solid line represents a patient considered ill and a dashed line represents a patient considered well. A majority of the patients reached normal levels within 3 or 4 months. In general those patients whose protein-bound iodine values did not decrease to within the normal range were considered among the unsatisfactory group. The patients with the higher initial serum protein-bound iodine levels tended to require the longest periods of therapy.
13. The values of the serum protein-bound iodine determinations in patients treated for hyperthyroidism with iodine 131 are shown as a function of time. The dots represent individual observation. The solid line represents the median of the determination. The median decreased to within normal limits and remained within these limits for the duration of the follow-up.

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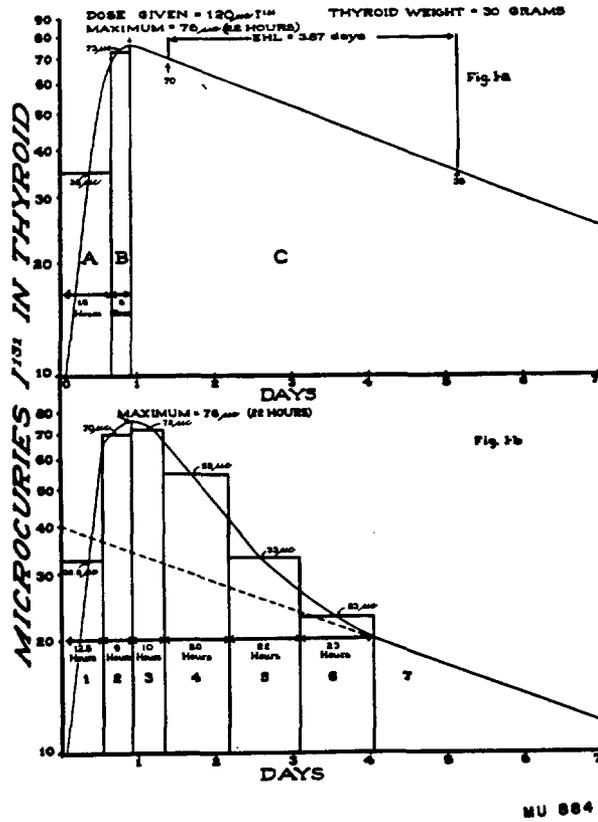
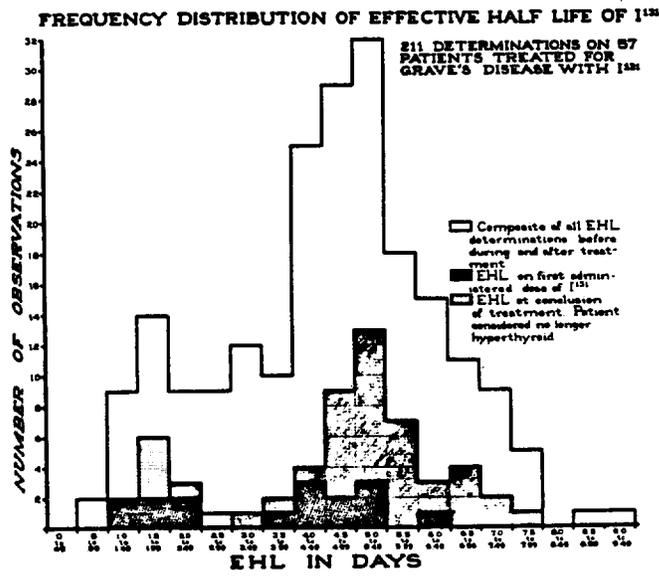


Fig. 1

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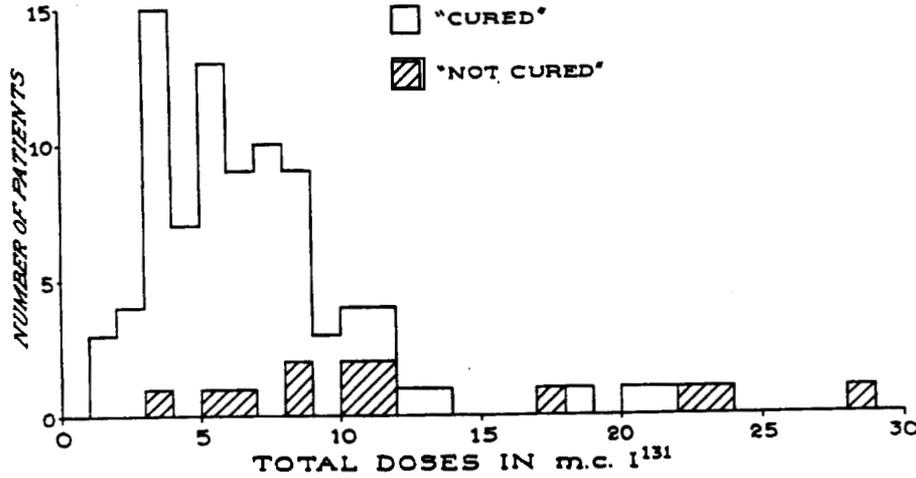
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Fig. 2

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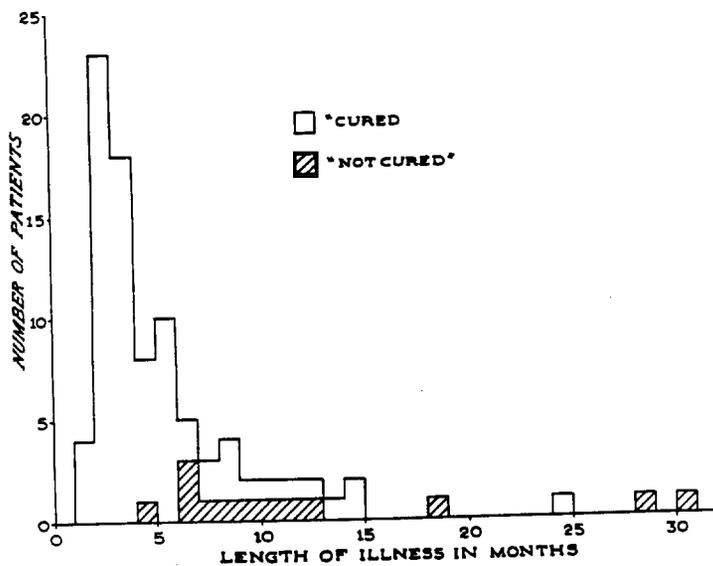
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Fig. 4

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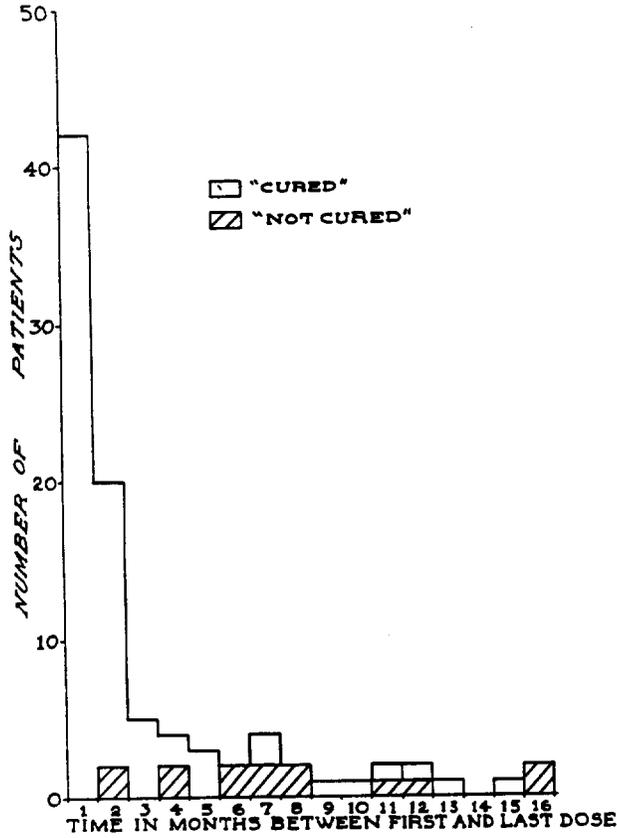
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Fig. 5

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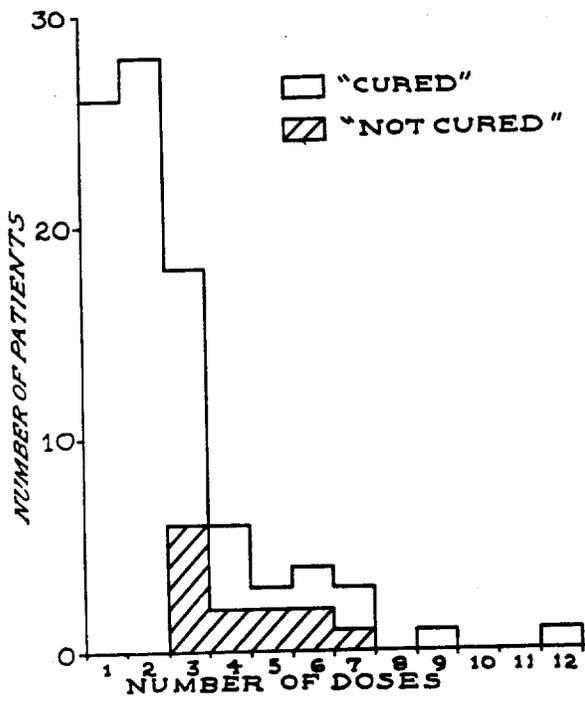
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Fig. 6

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Fig. 7

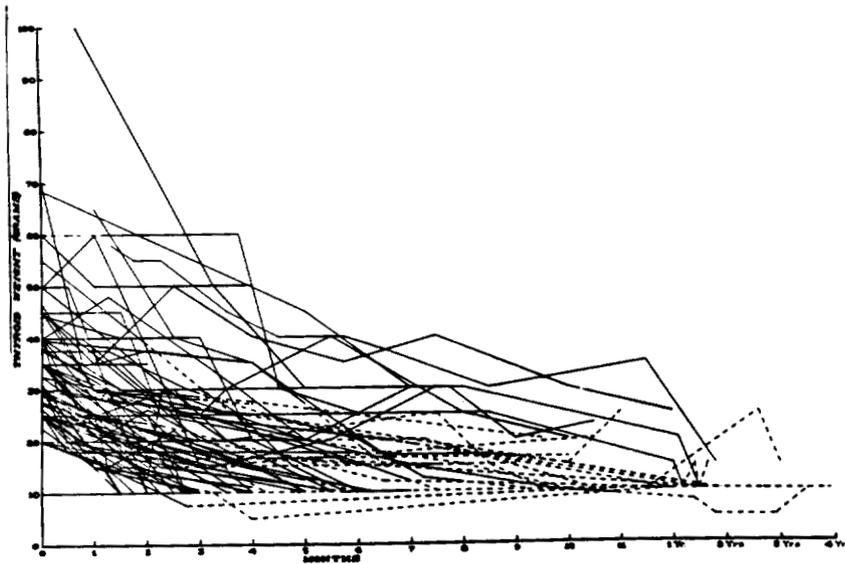
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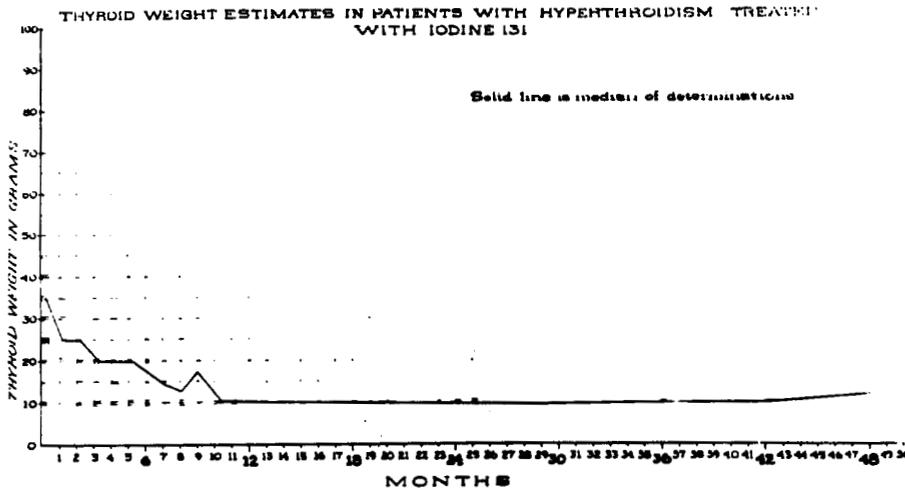
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Fig. 8

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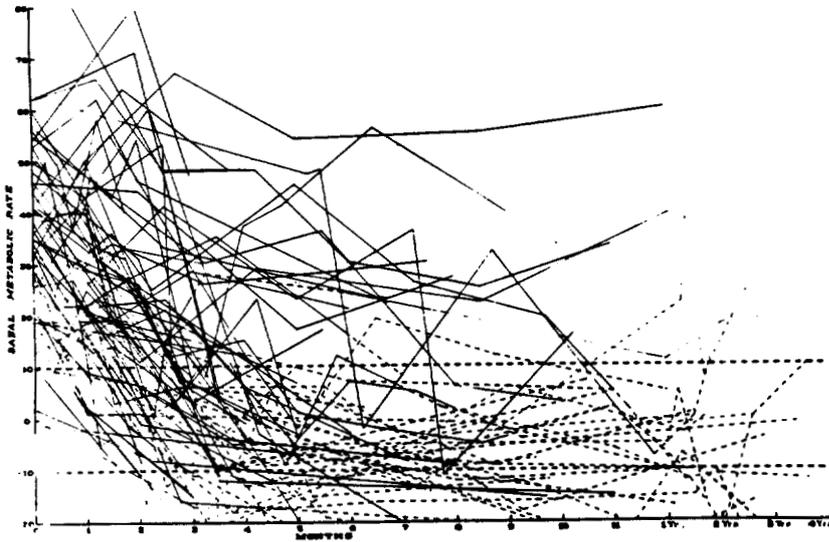
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Fig. 9

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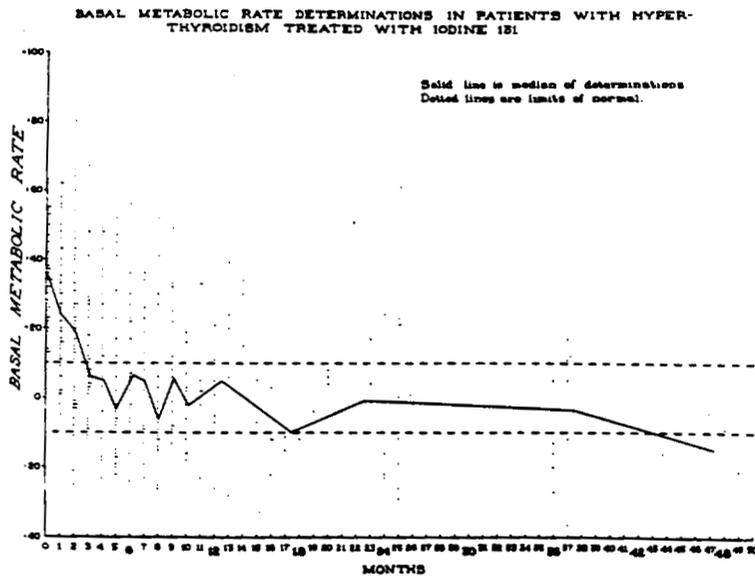
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Fig. 10

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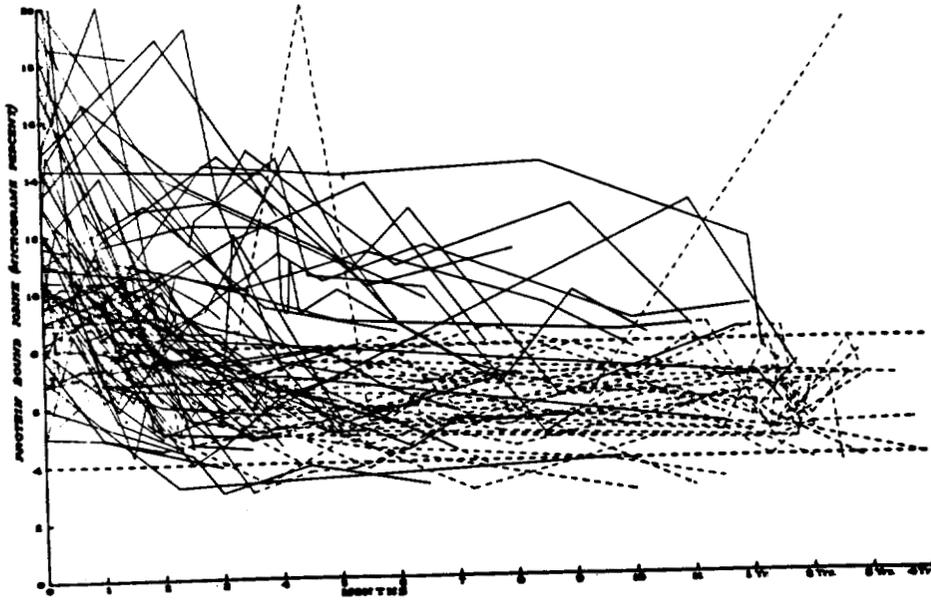
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Fig. 11

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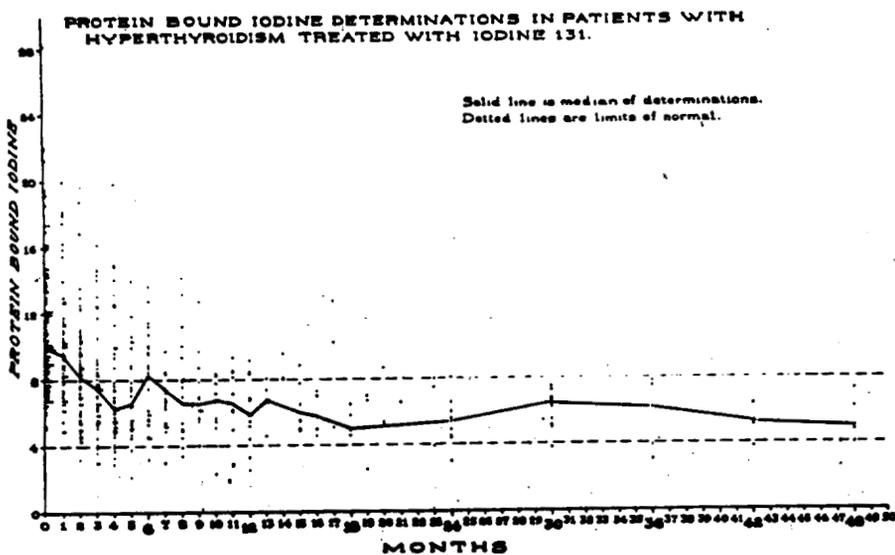
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Fig. 12

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Fig. 13

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