RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY

VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism

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In previously published experiments of this series [1] radioactive iodine was used as an indicator in the study of animal and human thyroid physiology and iodine metabolism. Much of this preliminary work was done with a view to the discovery of the conditions under which radioactive iodine might be administered with maximum radiational effect in the pathologic thyroid of patients ill with hyperthyroidism. The present paper is a progress report on our early experiences (1941-1946) with such "internal irradiation" in the treatment of 29 cases of hyperthyroidism. It is, indeed, a three to five year follow-up report on these cases.

PROCEDURE

Patients were selected who had had no previous iodine treatment and who were judged clinically to have hyperthyroidism. The usual clinical tests were made and the patients were presented to the Thyroid Clinic of the Massachusetts General Hospital for discussion and determination of their suitability for this type of treatment. In each instance a dose of radioactive iodine, which had been made by the cyclotron at the Massachusetts Institute of Technology or by the Harvard University cyclotron, and separated chemically as sodium iodide, was then orally administered.

The samples of radioactive iodine used were obtained by deuteron bombardment of tellurium and at the time of administration consisted of a mixture of different radioactive isotopes of iodine. Over 90 per cent of the activity at this time consisted of the 12.6 hour isotope I^{130} and most of the remainder of the 8 day isotope I^{131}. The total activity administered varied between 0.7 and 28 millicuries. In 19 cases the total dose was administered to the individual patients as one dose; in 10 cases divided dosages were employed.

From the data already obtained from tracer studies it was considered desirable to keep the total amount of iodide administered below 2 mg. of iodine in order to insure maximum collection by the thyroid.

Urinary iodine excretion was determined during the first seventy-two hours after the administration of radio-iodine. An indirect estimate of the thyroid retention of radioactive iodine was thereby obtained, since an approximate balance exists between administered iodine on the one hand and the sum of thyroid iodine retention and urinary excretion on the other.

Urinary studies were carried out on aliquot portions of carefully collected twenty-four hour specimens, which were kept iced and corked during the collection periods.

It was early found [2] that significant amounts of the original dose were to be found only in the first three days' specimens. Fecal excretion was tested and was found to be so low as to be negligible for the purpose of these experiments.

In a few cases external gamma ray counter measurements were made of the activity of the thyroid of patients following the administration of radioactive iodine. Such measurements are difficult, for obvious reasons, to evaluate quantitatively. However, day to day measurements of this type can give good data on the variation of thyroid iodine content. They were performed in order to follow the loss of iodine from the thyroid following the initial uptake and to evaluate the effect of routine iodinization following the administration of radioactive iodine.

External counter measurements were roughly calibrated against actual direct measurements on the thyroid glands at operation and after chemical separation [2] in 2 patients, previously scheduled for surgery, who received therapeutic amounts of radioactive iodine.

Following the administration of radioactive iodine, routine iodine (nonradioactive) in the usual dosage of saturated solution of potassium iodide 5 minims (0.3 cc.) twice a day was begun at periods varying from one day to several weeks after the radioactive iodine dose.

The basal metabolic rate of the patients treated was tested frequently both before and after the radioactive iodine administration. Basal metabolic levels were taken prior to treatment to establish a measure of the degree of thyrotoxicosis present. In addition to the basal metabolic rate, weights, pulse rates and physical findings were recorded and the total clinical picture was used to evaluate the effects of treatment. No adverse effects, such as fever, nausea or irradiation sickness, were noted in this series of patients. No complaints were recorded regarding the taste of the medicament (since it is tasteless), nor were any local effects, either in the oral cavity or over the thyroid, encountered at the dosage levels used. No increase in the degree of thyrotoxicosis following the radioactive iodine treatment, per se, was recorded, although several test patients were kept uniodinized for three to four weeks prior to routine iodinization.

In most cases, after a period of two to four months following the radio-iodine administration, routine iodine therapy was stopped when an essentially normal basal metabolic rate had been maintained on iodine for a few weeks or months. Such basal metabolic rate response was taken to be indicative of good control of

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This work was performed at the Massachusetts General Hospital and the Massachusetts Institute of Technology under a grant from the John and Mary R. Markle Fund. Cooperation and assistance in this work were given by Professor J. H. Means, Professor J. W. Irvine, Dr. Wendell C. Peacock, Professor M. Stanley Livingston, Professor Robley D. Evans, Drs. R. W. Rawson and Jacob Lerman, the technical assistants Mrs. Phyllis Brown Shattuck, Miss Ann Gaurdo and Miss Mary Lennon as well as the nursing, surgical and medical staffs of the Massachusetts General Hospital. The speech of President Karl T. Compton of the Massachusetts Institute of Technology before a Harvard Medical School colloquium in the fall of 1936 served to inspire the senior author in the initiation of this investigative program.

1. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38**: 510 (May) 1938. Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive Iodine as an Indicator in Thyroid Physiology: II. Iodine Collection by Normal and Hyperplastic Thyroids in Rabbits, Am. J. Physiol. **128**: 565 (Feb.) 1940; Tr. Am. A. Study Goiter, 1939, p. 260. Hertz, S.: Radioactive Iodine as an Indicator in Thyroid Physiology: III. Observations on Rabbits and on Goiter Patients, Am. J. Roentgenol. **46**: 467 (Oct.) 1941. Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: VI. Application of Radioactive Iodine in Therapy of Graves' Disease, J. Clin. Investigation **21**: 624 (Sept.) 1942. Hertz, Roberts and Salter.[2] Hertz and Roberts.[6]

2. Hertz, S.; Roberts, A., and Salter, W. T.: Radioactive Iodine as an Indicator in Thyroid Physiology: IV. The Metabolism of Iodine in Graves' Disease, J. Clin. Investigation **21**: 25 (Jan.) 1942.

the thyrotoxicosis at that time. Failure of the basal metabolic rate to rise on the cessation of iodine treatment was then interpreted as positive evidence of remission of the disease. A rise of the basal metabolic rate on cessation of iodine therapy was considered evidence of failure of the regimen of internal irradiation. A lowered basal metabolic level, with weight gain, symptomatic relief and lowered pulse, were considered indicative of a decrease of the severity of the disease.

As with other forms of treatment for hyperthyroidism, a prolonged follow-up of six months to one year (or more ideally two to five years) following, clinical evidence of remission was required before classification of cases as "cures."

CALCULATION OF RADIATION DOSAGE

In order to obtain a basis of comparison among patients and between radioactive iodine on the one hand and x-ray therapy on the other, the probable values of radiation dosage delivered in the thyroid were calculated. Such calculations are based on the following data:

1. Fractional uptake of radioactive iodine by the thyroid.
2. The known energy of the radiations from I^{130} and I^{131}.
3. The clinical estimation of the weight of the thyroid of the patient.
4. The known pattern of uptake and retention of radioactive iodine [3] by the hyperplastic thyroid gland of hyperthyroidism.[2]

By using the known values of ionization produced by 1 millicurie of radiation and the properties of I^{130} and I^{131} the following formulas can be derived for the total radiation delivered in decaying to zero:

$$\text{Radiation (in roentgen units)} = \frac{10{,}000 \text{ (dose of } I^{130} \text{ in mc) (fractional uptake in thyroid)}}{\text{weight of thyroid in grams}}$$

For I^{131} the constant 10,000 is replaced by 117,000.

Thus for I^{130} a net collection of 3 millicuries in a 30 Gm. thyroid will give a total of 1,000 roentgens in decaying to zero.[4]

The effectiveness of radiation therapy is known to depend on the rate of delivery, especially at low rates. In the case of I^{130} the initial rate of delivery of a 1,000 roentgen dose is 55 roentgens per hour. For I^{131} it is only 3.6 roentgens per hour. Thus, while in these experiments the total radiations delivered by the two isotopes are comparable, the rate is so much slower for the long-period isotope that its effectiveness is at least open to question. Furthermore, an appreciable fraction of the activity leaves the thyroid during the decay of the long period iodine.[2] We shall assume throughout that it is the I^{130} radiation which is most effective.

Calculations of the type described are subject to large errors. These arise mainly in the estimate of the thyroid weight, in the determination of thyroid iodine uptake and in the assumption of a uniform picture of iodine retention.[2] Errors of 50 per cent or more in the estimate of the thyroid radiation are therefore to be expected.

3. This pattern was determined by the use of tracer quantities of radioactive iodine. It is not strictly correct to assume, as we have, that the pattern will be the same when quantities of activity sufficient to have a biologic irradiation effect on the thyroid are present. However, in the absence of other data we have assumed that the pattern is the same. If this is in error it will introduce another error into the calculation, already admittedly approximate, of the dosage delivered to the thyroid.

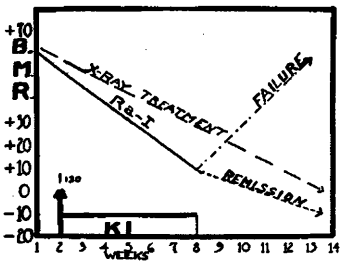
4. The millicurie values of activities cited in this paper are absolute values based on the number of disintegrations occurring in the radioactive substance, determined by methods like those described by Deutsch, M.; Downing, J. R.; Elliott, L. G.; Irvine, J. W., Jr., and Roberts, A.: Physiol. Rev. **62**: 4, 1942.

RESULTS

The accompanying graph is a schematic representation of the expected course of the basal metabolic rate in successfully and unsuccessfully treated cases. The upper broken line represents the course of the basal metabolic rate of a patient treated successfully by means of orthodox external x-ray therapy. The latter is given as a basis for comparison of the time interval required for obtaining a remission by the internal and external forms of thyroid irradiation in typical cases of hyperthyroidism.

The results obtained with 29 patients are summarized in tables 1 and 2. Table 1 affords an analysis of 9 cases in which cure was not obtained by the radiational effect of radio-iodine. Table 2 gives an analysis for 20 cases considered to be cures. These cases are so classified after follow-ups and examinations extending to March 1946.

The excretion studies and the external gamma ray counter measurements showed early in these experiments that there is no peak in the excretion of iodine in any of 14 cases tested, nor is there any sudden drop in the radioactive iodine content of the thyroid when a patient who has been given radioactive iodine is started on routine iodinization. On the contrary, these experiments showed that iodinization either has no effect on the normal slow loss of iodine from the thyroid or tends to "freeze" the radioactive iodine collected by the gland, i. e. to foster its longer retention therein. As much as 25 per cent of the initially collected radioactive iodine may remain in the thyroid twenty-five days after an initial collection and subsequent iodinization.[2] It is clear that such prolonged retention is advantageous from the standpoint of efficient use of the radioactive isotopes administered. Urinary studies in a typical case gave the results recorded in table 3.



Course of the basal metabolic rate in successfully and unsuccessfully treated cases of hyperthyroidism: solid line, treatment by radioactive iodine; upper broken line, treatment by external x-irradiation. The arrow indicates the point at which I^{130} was administered to the patients treated with radioactive iodine. The lower rectangle indicates the administration of ordinary iodides. A rise in the basal metabolic rate on omission of iodide therapy is significant of continued thyrotoxicity and failure of the therapeutic program; the absence of any such rise in any case is interpreted as evidence of remission of the disease as a result of the type of treatment received by the patient.

The reasons for adopting the procedure of full iodinization following the radioactive iodine dose were, in the main concern, that if the radioactive iodine was not effective the patients might be injured by uncontrolled thyrotoxicosis. In addition, no adequate control was possible of the iodine intake of patients (from extraneous sources) while ambulatory and awaiting the radiotherapeutic effect.

In spite of the fact that the interpretation with regard to cure might be rendered slightly less unequivocal with the use of this procedure, one can depend on the familiar fact that routine iodinization, per se, has been known for years to be a rather unsatisfactory sole treatment for the great majority of unselected thyrotoxic patients.[5]

5. Thompson, W. O.: Toxic Goitre: The Present Status of Treatment, Canad. M. A. J. **42**: 224 (March) 1940.

COMMENT ON RESULTS OF TREATMENT

A total of 29 patients were given radio-iodine in quantities which might be presumed, a priori, to have a therapeutic effect. As might be expected, in the earlier cases the dosage administered was not uniformly effective. At the time of starting these experiments there was no accumulated experience as to the possible adverse general effects of the administration of radioactive isotopes of iodine on the internal human economy. As our experience became extended, the total activity administered was increased from values in the vicinity of 1 millicurie to a maximum of 28 millicuries in 1 case without the occurrence of even temporary immediate reaction. As the series was followed, no clinical evidence has appeared to make us consider that there are any such undesirable effects or dangers in the range of activities used. No case of cancer of the thyroid has occurred; it appears unlikely that any such condition will arise from the internal irradiation involved in this form of treatment at the activity levels used.

Although the error in the estimation of the actual dosage delivered to the thyroid on the basis of the method of estimation used is necessarily large, it is possible, from the clinical behavior of the latter part of our series, to select the region near 1,000 roentgens (of the 12 hour isotope) as the minimum biologically effective range of dosage. In case 2 four separate doses of 1.4, 0.9, 2.4 and 0.8 millicurie were given to a patient with an uniodinized thyroid, with a frank failure of this regimen. The total dose in this case was 5.5 millicuries and the thyroid irradiation 500 roentgens (of 12 hour radio-iodine).

FAILURES

In case 10 (0.7 millicurie), in which operation was performed, the failure of the regimen may be attributed to the use of subminimal doses of radio-iodine. In cases 1, 5, 14, 16 and 19 of table 1 operations were performed following the administration of 3.3, 5.7, 15, 10 and 28 millicuries respectively. These were the only cases in the series in which operations were performed, and in every 1 of these 5 cases postoperative myxedema or hypometabolism ensued. In case 14 the basal metabolic rate was —15 the day before operation; it was essentially normal in the others (on iodides).

The occurrence of postoperative hypometabolism in 100 per cent of patients exhibiting essentially normal basal metabolic rates preoperatively is suggestive of a radiational effect on the thyroid tissue remaining after operation. For example, Mrs. R., patient 5, who was operated on after receiving 5.7 millicuries (1,000 roentgens) in a planned experiment for another purpose, developed myxedema despite the fact that one of us was present to advise the surgeon to leave 6 to 7 Gm. of thyroid (a nonradical subtotal thyroidectomy) in view of the previously demonstrated high radio-iodine uptake by this patient's thyroid. It is reasonable to surmise that hypometabolism might not have ensued in such a large percentage of the patients had they not received the radio-iodine prior to operation.

An analysis of preoperative basal metabolic rates of the patients operated on indicates that all 5 so treated were adequately controlled on iodides at the time of operation despite the long period of observation of these patients in a nonoperated state.

TABLE 1.—*Analysis of Nine Cases of Hyperthyroidism in Which Cure Was Not Effected by Administration of I^{130} with Therapeutic Intent*

Number	Patient	Basal Metabolic Rate Level Prior to I^{130}	Dose of I^{130} and Dates of Administration	Basal Metabolic Rate Prior to Subtotal Thyroidectomy	Postoperative Basal Metabolic Rate	Thyroid Weight, Gm.	Histologic	Total Thyroid Irradiation (Roentgens) 12 Hr. I^{130}	Total Thyroid Irradiation (Roentgens) I^{131} 8 Day	Estimated Thyroid Weight	Percentage of Dose of Radio-Iodine Excreted 72 Hours
1	Elizabeth D.	+30	2.1 mc. 3/31/41 1.3 mc. 4/16/41 3.4 mc.	(—5) (—7)	(—29)	34.5	Involution	470 220	660 240	35	20 28
5	Lillian R.	+35	5.7 mc. 7/16/41	Planned experiment	(—20)	31.8	Hyperplasia, no involution	1,000	1,150	40	27
10	Gladys B.	+55	0.7 mc. 2/2/42	Controlled through pregnancy (+3) (12/30/43)	(—26)	26 30 56	Hyperplasia + moderate involution	120	80	60	38
14	Wilfred B.	+50	15 mc. 7/15/42	(—15) (8/17/43) operation (8/18/43)	(—24)	55	Hyperplasia + involution	650	...	60	71 (?)
16	Carmella D.	+25	10 mc. 8/11/42	(—8)	(—24)	28	Involution	1,800	...	45	6
19	Peter C.	+65	15 mc. 8/25/42 8 mc. 3/8/43 5 mc. 3/9/43 28 mc.	(+8) to (+13)	(+36) to (—18)	35	Slight hyperplasia + involution	2,000 (?) 1,500 (?)	...	60	9 15 (?) 7
2	Margaret B.	+35	1.4 mc. 5/10/41 0.9 mc. 41 2.4 mc. 42 0.8 mc. 42 5.6 mc.	Persistent thyrotoxicosis, another radio-iodine dose proposed	....	Not operated on		160 110 120 100	140 100 120 100	40	54 48 78 ..?
4	Camille Sch.*	+30*	3.6 mc. 7/14/41 2.2 mc. 7/31/41 5.8 mc.	Eyes better, no goiter, basal metabolic rate off all medication	(+2) 4 yrs.	Not operated on		270 170	300 180	60	55 56
3	Ruth M.	+50	3.4 mc. 6/6/41 20 mc. 1/9/46	Remission of one year's duration following hemithyroidectomy (6/25/41) (Recently for true recurrence)				430 4,300	410	45 30 (recurrence)	45 35

* Case classified as special ophthalmopathic type of hyperthyroidism (Low intake of I^{130}).
Eight day isotope figures assume no loss of iodine from thyroid during decay; they are therefore excessive. They were not measured for cases 13-29.

Mrs. M. B., patient 2, has been taken off iodine in preparation for a 20 millicurie dose of radio-iodine. She has remained fairly well, at work, on full iodinization but remains chronically thyrotoxic.

Miss R. M., patient 3, who had 3.4 millicuries, was subjected to hemithyroidectomy in June 1941. She was in remission off iodides for twelve months but during the past one and one-half years developed a definite recurrence of hyperthyroidism, for the treatment could have been by subtotal thyroidectomy, since the probability of recurrence is distinctly higher following pregnancy in the postoperative follow-up of surgically treated cases.

One patient (4, Mrs. C. S.) should, in our opinion, be excluded from the series on the grounds of failure to present a picture of typical toxic diffuse goiter. As our experience developed it became evident [6] that patients in the "special ophthalmopathic group" [7] char-

TABLE 2.—*Analysis of Twenty Cases of Hyperthyroidism Successfully Treated with Therapeutically Sufficient Dosage of I^{130} Followed by Ordinary Iodide Administration*

Number	Patient	Dose of I^{130} and Date of Administration	Basal Metabolic Rate Before I^{130}	Basal Metabolic Rate Level Off Iodides	Time Off Iodides	Thyroid Size, 1946	Estimated Thyroid Weight, Gm.	Percentage of Radio-Iodide Excreted, 72 Hours	Estimated Thyroid Irradiation (Roentgens) 12 Hour	8 Day
6	Michael K.	2.3 mc. 7/24/41 1.7 mc. 7/30/41 4.0 mc.	45+	12/—/42 (— 9) 5/—/43 (—16) 1/—/46 (— 7)	4 yrs.+	N	45	35 22	320 280	390 300
7	Allison D. (aged 9)	1.4 mc. 9/19/41 1.5 mc. 9/21/41 2.9 mc.	65+	1/ 8/46 (— 6)	4 yrs.	N	45	9 20 (?)	260 260 (?)	230 220 (?)
8	Naomi K. (aged 9)	1.5 mc. 9/24/41	30+	7/17/45 (— 3)	Months	Firm 2 × N	40	15	300	250
9	Mildred G.	4.9 mc. 11/26/41	30+	5/ 8/45 (—10)	4 yrs.	N	60	17	650	420
11	Frances H.	5.8 mc. 4/ 9/42	37+	7/ 9/42 (—12) 2/24/44 (+ 9) 2/ 3/46 (—21)	3.5 yrs.	N	60	17	750	380
12	Ferdinand L.	7.5 mc. 5/15/42	55+	45 (+11) 2/ 3/46 (—13)	3 yrs.	Hard 1.5 × N	60-75	26	950	500
13	Dorothy P.	12 mc. 6/ 9/42	30+	3/—/43 (+ 6) 2/ 3/46 (—10)	3 yrs.	N	40	71	750	
15	Mary M.	6 mc. 8/11/42 4 mc. 8/11/42 10 mc.	35+	4/—/45 (— 6) 2/ 3/46 (+ 2)	Months	N	40	10	2,000	
17	George T.	13 mc. 8/13/42	50+	44 (—15) 1/ 6/46 (— 9)	3 yrs.+	N	60 (50-75)	14	1,300	
18	Jeanette G.	10.5 mc. 8/15/42	35+	8/22/44 (+11) 2/16/46 (+ 5)	3 yrs.+	N	30-40	15	2,000	
20	Anne D.	10 mc. 11/14/42	50+	4/ 3/45 (— 1) 2/16/46 (— 5)	2 yrs.+	N	45	20	1,600	
21	Richard T.	14 mc. 11/20/42	+45	1/ 8/46 (—13)	3 yrs.+	N (Dr. H. L. Blumgart)	50	15 (?)	2,000	
22	Esther R.	13 mc. 3/ 9/43	+20	6/30/43 (— 8)	2 yrs.+	"? N" (L. M. D.)	35	33	2,200	
23	Margaret D.	8 mc. 3/15/43 10 mc. 3/16/43 18 mc.	+55	6/ 9/43 (—11) 2/16/46 (— 3)	2 yrs.+	Firm 1.5 × N	75	76 67	500	
24	Jane Anne F.	10.5 mc. 3/26/43 4.5 mc. 3/27/43 15 mc.	+40	12/—/45 (— 5)	2 yrs.+	N (Dr. J. C. Zilhardt)	50	57 (?) 31 (?)	1,000 approximately	
25	Sophie R.	16 mc. 4/ 2/43	+44	9/28/44 (— 7) 4/27/45 (+ 9)	2 yrs.+	N (Dr. J. C. Aub)	50	20.6 63.0	750 approximately	
26	Bessie W.	12 mc. 4/ 6/43	+39	45 (— 8) 1/16/46 (+ 2)	2 yrs.+	N	45	85	350	
27	Winifred K.	13 mc. 4/12/43	+40	7/17/45 (—16) 2/15/46 (—10)	2 yrs.+	N	50	33	1,600	
28	Margaret H.	10.5 mc. 4/13/43 11.0 21.0 mc.	+55	12/—/45 (—15) 2/ 3/46 (+ 6)	2 yrs.+	N	75	.. (?)	2,000 approximately	
29	Julia Laf. Ry.	8 mc. 3/29/43 4 mc. 3/30/43 12 mc.	+30	2/—/46 (+ 5)	2 yrs.+	N	55	10 53 (?)	1,200 250	

Eight day isotope figures assume no loss of iodine from thyroid during decay; they are therefore excessive. They were not measured for cases 13-29.

of which she received 20 millicuries of radio-iodine on Jan. 9, 1946.

In case 10 a temporary control of the disease was achieved, but a true recurrence of the disease following an uneventful pregnancy occurred, for which surgical treatment was given at the United States Naval Dependents' Hospital, Boston. As this patient did not remain "cured" for over a year, she is not included in the series of cures. In comparing her case with others in which routine surgical treatment was administered, she might be considered as at least having been temporarily benefited to the same extent by radio-iodine as she acteristically had lower thyroid uptakes of radioactive iodine than patients with typical hyperthyroidism. Although this patient has done well without operation, her improvement cannot be ascribed to the radioactive iodine treatment. In our experience this group does well on medical therapy in any event [8] and rather poorly

6. Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: V. The Use of Radioactive Iodine in the Differential Diagnosis of Two Types of Graves' Disease, J. Clin. Investigation **21**: 31 (Jan.) 1942.

7. Hertz, S.; Means, J. H., and Williams, R. H.: Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy, West. J. Surg. **49**: 493 (Sept.) 1941; Tr. Am. A. Study Goiter, 1941.

8. Means, J. H.: The Eye Problems in Graves' Disease, Illinois M. J. **80**: 135 (Aug.) 1941.

by rapid cure of the thyrotoxic element by operation. It is conceivable, however, that by giving larger dosages of radioactive iodine radiotherapeutic advantage could be obtained even in this class of cases.

In summary, therefore, there were 9 cases which comprise this series of "failures."

In 1 case (10), in which there was a recurrence, the dosage of radio-iodine is known to have been probably inadequate (120 roentgens) for biologic effect. One, patient 4, is grouped in this list because she was a "special ophthalmopathic" patient; the control of her disease cannot be uniquely attributed to the effect of the radio-iodine.

Two patients (3 and 5) had operations as part of planned experiments and gave us the first evidences of possible biologic effect of the radio-iodine which was administered. They are, however, included among the failures because of the complicating factor of operation. Patient 5 developed myxedema; patient 3 suffered a recurrence after hemithyroidectomy.

Five patients (1, 5, 14, 16, 19) were operated on who had received dosages of radio-iodine from which one might expect a cure. All developed postoperative hypometabolism.

Mr. P. C., patient 19, received divided dosage of 15, 8 and 5 millicuries, the largest total dosage in our series. He developed postoperative hypometabolism after a short period of persistent thyrotoxicosis (basal metabolic rate + 36 to — 18). His basal metabolic rate the day prior to operation was + 13.

TABLE 3.—*Urinary Studies*

Radio-iodine (20 mc. of I^{130}) orally administered as a single dose; 37 per cent excreted in a period of four days (I, II, III, IV = twenty-four hours' collections of urine following the radio-iodine).

I. 27.9%. 0.047%/cc./hr.	
II. 3.3%, 0.006%/cc./hr.	
	5 minutes of saturated solution of potassium iodide
III. 3.45%, 0.006%/cc./hr.	
	5 minims of saturated solution of potassium iodide
IV. 2.37%, 0.0001%/cc./hr.	

Finally, patient 2 received a total of 5.5 millicuries of radio-iodine in four divided doses, with a total radiation of 500 roentgens. She has not been operated on but exhibits clear evidence of continued thyrotoxicosis which is only moderately well controlled by iodine.

SUCCESSES

There were a total of 29 cases in this entire series. In 1 case (10) the dosage was subminimal. Of the remaining 28 patients who received radio-iodine of therapeutic intensity, 5 were subtotally thyroidectomized. All 5 developed hypometabolism.

In the remaining 23 cases in which radio-iodine of therapeutic intensity was given, no subtotal thyroidectomy was performed. In 20 of these patients a recent follow-up indicates that they are no longer thyrotoxic. The remaining 3 cases (2, 3 and 4, already discussed) cannot be considered as successes.

The thyroid gland in all but 3 of these patients became normal in size (impalpable). In the 3 patients in whom the thyroid is still palpable, despite general metabolic and clinical cure (off iodine), there were decided reductions in the size of the goiters. They have firm to hard glands which suggest the presence of chronic thyroiditis or fibrosis. These patients had the largest pretreatment goiters. One of them (12) states that his collar size has now returned to the same as he had worn prior to the onset of hyperthyroidism. He had had a large goiter (three times normal size) prior to treatment.

In addition to the 20 cures in which operation was not performed, there is pathologic evidence for cure in 1 case (16) in which operation was performed. A 28 Gm. thyroid was removed; it showed histologic "involution," and myxedema subsequently developed.

There were no mortalities in the series either as a result of thyrotoxicosis or due to operation in the 5 cases. The incidence of myxedema and hypometabolism has been mentioned.

No undesirable complications such as tetany or loss of phonation occurred. No tracheal or laryngeal irritations occurred. No undesirable radiation effects were observed. No anemia ensued in any patient in the series.

Although 5 of the 20 patients not operated on developed basal metabolic levels of —15 to —20, no one suffered the development of permanent myxedema at the dosage level employed in this series.

CONCLUSIONS

From these data it is clear that we are now in a fair position to set down a minimum dosage and a preliminary estimation of the therapeutically effective dosage range in typical cases of hyperthyroidism. This range is from 5 millicuries to 25 millicuries (as a single dose), with the choice of the dose largely a function of the clinical estimation of the size of the goiter of the patient being treated.

The calculated dosages administered in those cases (500 to 2,500 roentgens) (± 50 per cent) in which treatment was successful are in satisfactory agreement with the x-ray dosages which have been successfully used (1,000 to 1,200 roentgens). The apparently greater efficacy of the radio-iodine treatment as compared with orthodox x-ray treatment may perhaps be attributed to the fact that x-ray dosages are sometimes limited by the appearance of undesirable skin reactions; and the intraglandular irradiation within the thyroid cells may conceivably offer certain advantages over external irradiation. On the basis of our experience to date, the following are considered to be important clinical considerations in patients who are to be chosen to undergo treatment by radioactive iodine:

1. No previous iodine therapy; or, if previously treated, iodine treatment to be stopped for at least one month to allow maximum uptake of the radioactive iodine dose.[2]
2. Availability for close follow-up.
3. Administration of routine iodinization, starting one to three days after the administration of radio-iodine, as soon as the uptake is known to be adequate.
4. Unwisdom of treating patients having large goiters with secondary involutional changes at this time by this means, as surgery might be needed by them on a purely mechanical basis, even though detoxification by radioactive iodine could be accomplished. Early diagnosis and early treatment of cases would then appear to offer major advantages in this as in many other forms of treatment.

The treatment of the special cases in the ophthalmopathic group of hyperthyroidism appears to offer special problems, as do cases of large, involutional goiters. However, typical cases of hyperthyroidism respond to this form of treatment in such a manner as to make it possible to venture the prediction that this therapeutic program may in time replace the surgical approach currently in vogue.

Radioactive iodine is produced in enormous quantities in nuclear chain-reacting piles. When radio-iodine from such sources is made readily available to the medical

profession, this form of treatment may well prove itself not only highly effective, safe and noninjurious but also cheap and of least inconvenience to the patient who may receive it while continuing at his normal pursuits. After a short period of hospitalization for the usual preliminary clinical studies and the administration of radio-iodine, the patient may be fully iodinized and released, to be followed as an ambulatory case.

SUMMARY

On the basis of a series of animal and clinical experiments using radioactive isotopes of iodine as a tracer in the study of thyroid physiology and iodine metabolism, the treatment of 29 cases of hyperthyroidism with internal irradiation by radioactive iodine was instituted. By careful excretion studies, external counter measurements over the thyroid gland and by planned operations in 2 cases, data were obtained which allow us to construct a formula for a procedure in treatment.

The addition of ordinary iodine therapy after the administration of radio-iodine offers many advantages in the clinical care of these patients and in the economy and safety of the procedure.

By an analysis, over a long period, of both the failures and successes in this series of 29 cases, it is shown that radioactive iodine when given in the dosage range of 5 to 25 millicuries to uniodinized patients with hyperthyroidism possessing goiters of 60 to 75 Gm. is highly effective as a cure of the disease in about 80 per cent of cases. When appreciable activity has been administered and subtotal thyroidectomy is resorted to, myxedema or hypometabolism may be expected to develop in a large fraction of the cases (100 per cent in 5 cases in this series).

THE TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE

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Roentgen treatment has been used for hyperthyroidism for many years. In 1923 Means and Holmes [1] pointed out that in this form of treatment about one third of the patients are cured, another third improved and another third not affected. Since 1923 ordinary iodine by mouth has been used as a preoperative method of quieting the hyperactive thyroid in preparation for surgery. Under iodine alone occasionally the patient and the doctor have been agreeably surprised to find that the symptoms and signs of hyperthyroidism disappeared, and a permanent remission apparently was effected. That x-ray treatment and iodine treatment sometimes cure hyperthyroidism led to the hope that some day a more effective, nonsurgical agent would be found. Then the MacKenzies [2] and Astwood [3] discovered that several chemical compounds inhibit the function of the thyroid in hyperthyroidism as well as under other circumstances. Several of these agents have been investigated, and until now thiouracil has been found to be most useful in the treatment of thyrotoxicosis.

Induced radioactivity was discovered in 1934, and that same year Fermi and his co-workers [4] in Italy prepared radioactive isotopes of iodine. Because the thyroid absorbs iodine selectively, it seemed likely that beta rays from iodine rendered radioactive would have a greater radiation effect than that derived from roentgen rays delivered through the skin and overlying tissues.

The use of radioactive iodine in the study of thyroid physiology was soon undertaken and reported first in 1938 by Hertz, Roberts and Evans.[5] Subsequently these and other investigators used various isotopes of radioactive iodine as tracers for the study of thyroid function [6] and it was found that in untreated hyperthyroidism the thyroid may take up as much as 80 per cent of a small dose (less than 2 mg.) of iodide within a few hours after oral administration.[7] This established the basis for therapeutic trials of radioactive iodine, and in 1942 Hertz and Roberts [8] published a preliminary report of the treatment in this manner of 10 patients. In this series the procedure was to give the radioactive iodine and follow this with ordinary iodine by mouth for a period of several months. However, our review in the clinic of these 10 cases of Hertz and Roberts, and an additional 18 so treated under the direction of Hertz, has led to the conclusion that it is difficult to decide whether those patients who improved were responding to the ordinary iodine, to the radioactive iodine or to their combination. The dosage of radioactive iodine given to these 28 patients averaged 5 millicuries in 1941, 10 millicuries in 1942 and 14.5 millicuries in 1943, the largest single dose being 21 millicuries. In April 1943 Dr. Hertz went on active duty in the Navy and asked us to continue with this study. The present report is on a series of 22 patients with hyperthyroidism treated only with radioactive iodine and with considerably higher doses. Although both Hertz and Roberts [8] and Hamilton and Lawrence [9] were encouraged by their therapeutic trials, the details of their findings have not yet been published.

METHODS AND DOSAGE

Selection and Care of Patients

The patients selected in the Thyroid Clinic of the Massachusetts General Hospital for radioactive iodine therapy were judged by several physicians to be thyrotoxic on the basis of classic disease pattern accompanied with constantly elevated basal metabolic rates. All patients had thyroids estimated to be at least two to three times normal in size. All but 3 were kept free from all forms of treatment, especially iodine, for at least four weeks prior to giving radioactive iodine. For the administration of the drug they were usually hospitalized for a time adequate to obtain levels of their basal metabolic rate, then given radioactive iodine by mouth—simply a drink of what tastes like rather stale water.

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1. Means, J. H., and Holmes, G. W.: Further Observations on the Roentgen Ray Treatment of Toxic Goiter, Arch. Int. Med. **31**: 303 (March) 1923.

2. MacKenzie, C. G., and MacKenzie, J. B.: Effect of Sulfonamides and Thioureas on the Thyroid Gland and Basal Metabolism, Endocrinology **32**: 185 (Feb.) 1943.

3. Astwood, E. B.: Treatment of Hyperthyroidism with Thiourea and Thiouracil, J. A. M. A. **122**: 78 (May 8) 1943.

4. Fermi, E.: Radioactivity Induced by Neutron Bombardment, Nature, London **133**: 757 (May 19) 1934.

5. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38**: 510 (May) 1938.

6. Rawson, R. W.: Radio Iodine: Its Use as a Tool in the Study of Thyroid Physiology, to be published. Hamilton, J. G., and Soley, M. H.: Studies in Iodine Metabolism by the Use of a New Radioactive Isotope of Iodine, Am. J. Physiol. **127**: 557 (Oct.) 1939. Le Blond, C. P.; Sue P., and Chamorre, A.: Passage de l'iode radi-oactif dans la thyroide d'animaux sans hypophyse, Compt. rend. Soc. de biol. **133**: 540, 1940.

7. Hertz, S.; Roberts, A., and Salter, W. T.: Radioactive Iodine as an Indicator in Thyroid Physiology: IV. The Metabolism of Iodine in Graves' Disease, J. Clin. Investigation **21**: 25 (Jan.) 1942.

8. Hertz, S., and Roberts, A.: Application of Radioactive Iodine in Therapy of Graves' Disease, J. Clin. Investigation **21**: 624 (Sept.) 1942.

9. Hamilton, J. G., and Lawrence, J. H.: Recent Clinical Developments in the Therapeutic Application of Radio-Phosphorus and Radio-Iodine, J. Clin. Investigation **21**: 624 (Sept.) 1942.