Radioactive Iodine in the Study of Thyroid Physiology

VII. The Use of Radioactive Iodine Therapy in Graves' Disease*

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INTRODUCTION

IN PREVIOUSLY published experiments of this series,[1-6] 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 Graves' disease. The present paper is a progress report on our early experiences (1941-1946) with such "internal irradiation" in the treatment of 29 cases of Graves' disease. 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 Graves' disease. 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 M.I.T. 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

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of the remainder of the eight 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 ten 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 two milligrams of iodine in order to insure maximum collection by the thyroid.

Urinary iodine excretion was determined during the first 72 hours after the administration of radioiodine. 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 24 hour specimens, which were kept iced and corked during the collection periods. It was early discovered[4] 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 after 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[4] in two 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, minims V. b.i.d., was begun at periods varying from one day to several weeks after the radioactive iodine dose.

The basal metabolic rate (B.M.R.) of the patients treated was tested frequently both before and after the radioactive iodine administration. B.M.R. levels were taken prior to treatment to establish a measure of the degree of thyrotoxicosis present. In addition to the B.M.R., 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 Ra-I administration, routine iodine therapy was stopped when an essentially normal B.M.R. had been maintained on iodine for a few weeks or months. Such B.M.R. response was taken to be indicative of good control of the thyrotoxicosis at that time. Failure of the B.M.R. to rise upon the cessation of iodine treatment was then interpreted as positive evidence of remission of the disease. A rise of the B.M.R. upon cessation of iodine therapy was considered as evidence of failure of the regime of internal irradiation. A lowered B.M.R. level, with weight gain, symptomatic relief and lowered pulse were considered as indicative of a decrease of the severity of the disease.

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

CALCULATION OF RADIATION DOSAGE

In order to obtain a basis of comparison between 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; and (4) the known pattern of uptake and retention of radioactive iodine* by the hyperplastic thyroid gland of Graves' disease[4].*

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

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

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

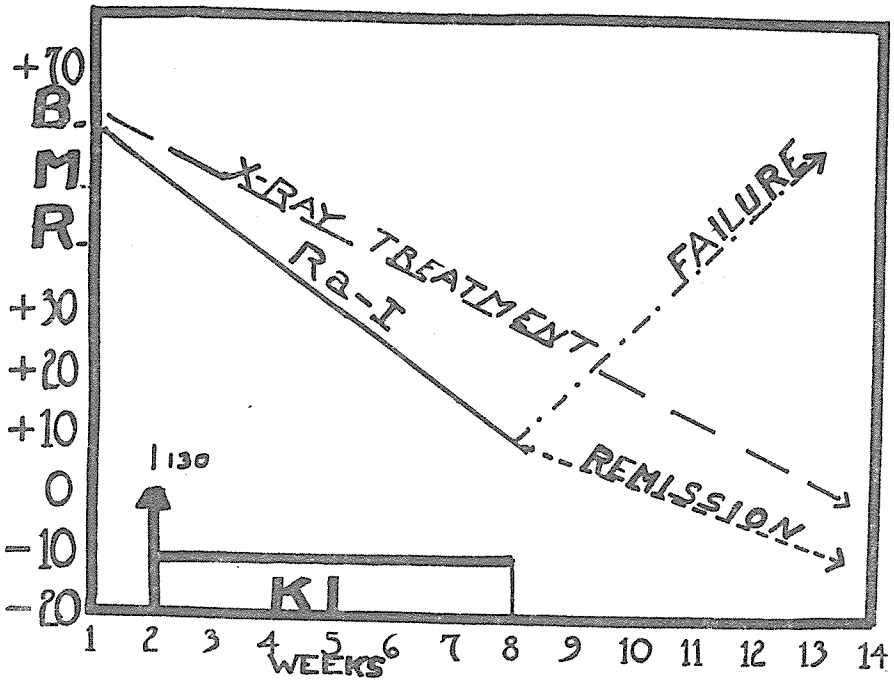
Thus, for I^{130}, a net collection of 3 mC in a 30 gm. thyroid will give a total of 1000 r in decaying a zero.†

*The millicurie values of activities cited in this paper are absolute values based on the number of disiniegrations occurring in the radioactive substance, determined by methods like those described in.[7]

†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.

The effectiveness of radiation therapy is known to depend upon the rate of delivery, especially at low rates. In the case of I^{130}, the initial rate of delivery of a 1000 r dose is 55 r per hour. For I^{131}, it is only 3.6 r 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

Chart I



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.[4] We shall assume throughout that it is the I^{130} radiation which is most effective.

Calculations of the type described above 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.[4] Errors of 50 per cent or more in the estimate of the thyroid radiation are therefore to be expected.

RESULTS

Chart I is a schematic representation of the expected course of the B.M.R. in successfully and unsuccessfully treated cases. The upper dotted line represents the course of the B.M.R. 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 remission

by the internal and external forms of thyroid irradiation in typical cases of Graves' disease.

The results obtained with 29 patients are summarized in Tables I and II. Table I affords an analysis of nine cases which were not cured by the radiational effect of radioiodine. Table II gives an analysis for 20 cases considered to be cures. These patients are so classified after follow-ups and examinations extending to March, 1946.

The excretion studies and the external gamma-ray counter measure-

TABLE I AN ANALYSIS OF CASES "NOT CURED" BY Ra-I+KI (TO MARCH-'46)

SERIES NO.	CASE-HOSP.NO.	BMR PRIOR TO I¹³¹	DOSAGE OF I¹³¹ AND DATES OF ADMINISTRATION	BMR PRIOR TO SUB-TOTAL THYROIDECT.	POST-OP BMR	THYROID WEIGHT	HISTOLOGY	TOTAL THYROID IRRADIATION (r) 12 HR.	TOTAL THYROID IRRADIATION (r) 8 DAY	ESTIMATED THYROID WT. BEFORE I¹³¹	% OF Ra-I (URINE) EXCRETED · 72 HRS. FOLLOWING THE ADMINISTRATION OF I¹³¹
1	ELIZABETH D. MGH-173954	+30	2.1 mC 3-31-'41; 1.3 mC 6-16-'41 — 3.4 mC	(-5)(-7)	(-29)	34	INVOLUTION	470 220	660 240	35	20 28
5	LILLIAN R. MGH-308552	+35	5.7 mC 7-16-'41	PLANNED CARCINOMA	(-20)	31	HYPERPLASIA NO INVOL.	1000	1150	40	27
10	GLADYS B. MGH-121922	+55	0.7 mC 2-2-'42	(+3)	(-24)	26 (30) 56	HYPERPLASIA MOD. INVOL.	120	80	60	38
14	WILFRED B. MGH-363179	+50	1.5 mC 7-15-'42	(-15)	(-24)	55	HYPERPLASIA + INVOLUTION	650	—	60	71
16	CARMELLA D. MGH-255020	+25	1.0 mC 8-11-'42	(-8)	(-24)	28	INVOLUTION	1800	—	45	6
19	PETER C. MGH-369253	+65	1.5 mC 8-25-'42; 8 mC 3-8-'43; 5 mC 3-9-'43 — 28 mC	(+8) (?0) (-13)	(-36) ?0 (-18)	35	SL. HYPERPLAS. + INVOLUTION	2000 1500	—	60	9 15 7
2	MARGARET B. MGH-300230	+35	1.6 mC 5-10-'41; 0.9 mC '41; 2.4 mC '42; 0.8 mC '42 — 5.6 mC	NOT OPERATED — PERSISTENT THYROTOXICOSIS — ANOTHER 20 mC PROPOSED				160 110 120 100	140 100 120 100	40	54* 48 78 — —
4	CAMILLE SCH* MGH-303302	+30	3.6 mC 7-18-'41; 2.1 mC 7-31-'41 — 5.8 mC	EYES BETTER; NO GOITER; BMR (+2) 6½ MO. - 4 YRS				270 170	300 180	60	55 56
3	RUTH M. MGH-304538	+50	3.4 mC 6-6-'41	REMISSION FOR 1 YR - THEN				430	410	45	45
			2.0 mC 1-9-'46	(RECENTLY FOR THY RECURRENCE)				4500	—	30 (RECURRENT)	35

* OPHTHALMOPATHIC TYPE

ments 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 25 days after an initial collection and subsequent iodinization.[4] 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 III.

The reasons for adopting the procedure of full iodinization following the radioactive iodine dose were, in the main, concern that if the radioactive iodine were not effective the patients might be injured by uncontrolled thyrotoxicosis. In addition, no adequate control of the patients' iodine intake (from extraneous sources) was possible while ambulatory and awaiting the radiotherapeutic effect. Despite the fact that the interpretation as to cure might be rendered slightly less unequivocal by this procedure, one may depend upon 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.[12]

DISCUSSION OF RESULTS OF TREATMENT

A total of 29 patients were given Ra-I 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.

TABLE II-ANALYSIS OF 20 CASES "CURED" BY Ra-I + K I
ON BASIS OF EXAMINATION MARCH 1, 1946

SERIES NO.	CASE-HOSP. NO.	DOSE OF I^{130} and DATE OF ADMINISTRATION	BMR BEFORE I^{130}	BMR LEVEL OFF IODIDES	TIME OFF IODIDES	THYROID SIZE '46	ESTIMATED THYROID WT. (gm.)	% OF Ra-I EXCRETED 72 HOURS	ESTIMATED IRRIDIATION (r) 12 HOUR	ESTIMATED IRRIDIATION (r) 8 DAYS*
6	MICHAEL K. MGH-227382	2.3mC 7-24-41 } 4.0 1.7mC 7-30-41 } mC	+45	DEC.-'42 (-9) MAY-'43 (-16) JAN.-'46 (-7)	4 YRS.+	N	45	35 22	320 280	390 300
7	ALLISON D. (RET'D.) MGH-319927	1.4mC 8-19-41 } 2.2 0.8mC 3-27-42 } mC	+65	1-8-'46 (-6)	4 YRS.	N	45	? 20 (?)	260 260 (?)	230 220 (?)
8	NAOMI K. (RET'D) MGH-321155	1.8mC 9-24-'41	+30	7-17-'45 (-3)	MOS	FIRM 2 X N	40	15	300	250
9	MILDRED G. MGH 322935	4.9mC 11-26-'41	+30	5-8-'45 (-10)	4 YRS.	N	60	17	650	420
11	FRANCES H MGH-198910	5.8mC 4-9-'42	+37	7-9-'42 (-12) 2-24-'43 (+9) 2-5-'46 (-13)	3.5 YRS.	N	60	17	750	380
12	FERDINAND L. MGH-334350	7.5mC 5-15-'42	+55	'45 (+?) 2-3-'46 (-13)	3 YRS.	HARD 1.5 X N	60-75	26	950	500
13	DOROTHY P. MGH-385541	12mC 6-9-'42	+30	3-'43 (+4) 2-3-'46 (-10)	3 YRS.	N	40	71	750	
15	MARY M. MGH-362811	6mC 8-11-'42 } 10 4mC 8-11-'42 } mC	+35	4-'45 (-1) 2-3-'46 (-2)	MOS.	N	40	10	2000	
17	GEORGE T. BCH-1076956	13mC 8-13-'42	+50	'44 (-15) 1-6-'46 (-9)	3 YRS.+	N	60	14	1300	
18	JENETTE G. MGH-347094	10.5mC 8-15-42	+35	8-22-'44 (+1) 2-16-'46 (+1)	3 YRS.+	N	40	15	2000	
20	ANNE D. MGH-233271	10mC 11-14-'42	+50	4-3-'45 (-1) 2-16-'46 (-5)	2 YRS.+	N	45	20	1600	
21	RICHARD T. BIH-47686	14mC 11-20-'42	+45	1-8-'46 (-13)	3 YRS.+	N	50	15 (?)	2000	
22	ESTHER R. MGH 22094	13mC 3-9-'43	+20	6-30-'43 (-8)	2 YRS.+	?N (LMD)	55	33	2200	
23	MARGARET D. MGH-385741	8mC 3-15-'43 } 18 10mC 3-16-'43 } mC	+55	6-9-'43 (-11) 2-16-'46 (-3)	2 YRS.+	FIRM 1.5 X N	75	76 67	500	
24	JANE ANNE F. MGH-397402	10.5mC 3-26-'43 } 15 4.5mC 3-27-'43 } mC	+40	12-'45 (-5)	2 YRS.+	N (DR. J.C.) (EDWARDT)	50	67? 31	1000	
25	SOPHIE R. MGH-397951	16mC 4-2-'43	+44	9-28-'44 (-7) 4-27-'45 (+9) 3-20-'46 ( )	2 YRS.+	N (DR. J.C.) (AUB)	50	20.6 63.0	750	
26	BESSIE W. METAB.# 23843	12mC 4-6-'43	+39	'45 (-8) 1-16-'46 (+2)	2 YRS.+	N	45	85	350	
27	WINIFRED K. MGH-398698	13mC 4-12-'43	+40	7-17-'45 (-14) 2-15-'46 (-10)	2 YRS.+	N	50	33	1600	
28	MARGARET H. P.P. DR. HERTZ	12.5mC 4-13-'43 } 21 11.0mC 4-13-'43 } mC	+55	12-'45 (-14) 2-3-'46 (+6)	2 YRS+	N	75	---?	2000	
29	JULIA LAF. RY MGH-393852	8mC 3-29-'43 } 12 4mC 3-30-'43 } mC	+30	2-'46 ( )	2 YRS+	N	55	10 53 (?)	1200 250	

* 8 DAY ISOTOPE FIGURES ASSUME NO LOSS OF IODINE FROM THYROID DURING DECAY; THEY ARE THEREFORE EXCESSIVE. THEY WERE NOT MEASURED FOR CASES 13-29 —

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 upon the internal human economy. As our experience became extended, the total activity administered was increased from values in the vicinity of one mC to a maximum of 28 mC, in one 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 1000 r (of the twelve hour isotope) as the minimum biologically effective range of dosage. In Case 2, four separate doses of 1.4 mC, 0.9 mC, 2.4 mC, and 0.8 mC were given to a patient

Table III

Ra-I (20mC of I^{130}) orally administered as a single dose.
37 per cent excreted in a period of four days (I, II, III, IV) = 24 hours' collections of urine following the Ra-I.

I. 27.9%-0.047%/cc./hr.

II. 3.3%-0.006%/cc./hr.
_____KI mV Sat. Sol.

III. 3.45%-0.006%/cc./hr.
_____KI mV Sat. Sol.

IV. 2.37%-0.0001%/cc./hr.

with an uniodinized thyroid, with a frank failure of this regime. The total dose in this case was 5.5 mC, and the thyroid irradiation 500 r (of twelve hour Ra-I).

FAILURES

In Case 10 (0.7 mC), in which the patient was operated upon, the failure of the regime may be attributed to the use of subminimal dosage of Ra-I. In Cases 1, 5, 14, 16, and 19 of Table I, the patients were operated upon, following the administration of 3.3, 5.7, 15, 10, and 28 mC respectively. These were the only operative cases in the series, and in every one of these five cases postoperative myxedema or hypometabolism ensued. In Case 14, the B.M.R. was -15 the day before surgery; it was essentially normal in the others (on iodides).

The occurrence of postoperative hypometabolism in 100 per cent of patients exhibiting essentially normal B.M.R.'s preoperatively is suggestive of a radiational effect on the thyroid tissue remaining after operation. For example, in Case 5, Mrs. R., who was operated upon after receiving 5.7 mC (1000 r) in a planned experiment for another purpose, the development of myxedema occurred despite the fact that in her case one of us was present to advise the surgeon to leave six to seven grams of thyroid (a nonradical subtotal thyroidectomy), in view of the previously demonstrated high Ra-I uptake by this patient's thyroid. It is reasonable to surmise that hypometabolism may not have ensued in such a large percentage of the patients had they not received the Ra-I prior to operation.

An analysis of preoperative B.M.R.'s of the patients operated upon indicates that all five patients 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.

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

Case 3, Miss R. M., who had 3.4 mC, 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 Graves' disease, for the treatment of which she received 20 mC of Ra-I on January 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 she received surgical treatment at the United States Naval Dependents' Hospital, Boston, Massachusetts. Inasmuch 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 receiving routine surgical treatment, she might be considered as, at least, having been temporarily benefited to the same extent by Ra-I as she could have been by subtotal thyroidectomy, since the probability of the recurrence is distinctly higher following pregnancy in the postoperative follow-up of surgically treated cases.

One patient (Case 4, Mrs. C. S.) should, in our opinion, be excluded from the series on the grounds of failure to present a picture of typical Graves' disease. As our experience developed it became evident that patients in the "special ophthalmopathic group"[10] characteristically had lower thyroid uptakes of radioactive iodine than patients with typical Graves' disease. 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 case,[11] and rather poorly 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 nine cases which comprise this series of "failures."

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

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

Five patients (Cases 1, 5, 14,16 and 19) were operated upon who had received dosages of Ra-I from which one might expect a cure. All developed postoperative hypometabolism.

In Case 19, Mr. P.C. received divided dosage of 15 mC., 8 mC. and 5 mC, the largest total dosage in our series. He developed postoperative hypometabolism after a short period of persistent thyrotoxicosis (B.M.R.'s +36 to -18). His B.M.R. the day prior to operation was +13.

Finally, the patient in Case 2 received a total of 5.5 mC of Ra-I in four divided doses with a total irradiation of 500 r. She has not been operated upon, 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 one case (Case 10) the dosage was subminimal. Of the remaining 28 patients who received Ra-I of therapeutic intensity, five were subtotally thyroidectomized. All five developed hypometabolism.

In the remaining 23 cases in which Ra-I 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 three cases (Cases 2, 3 and 4 discussed above) cannot be considered as successes.

The thyroid gland in all but three of these patients became normal in size (impalpable). In the three patients in whom the thyroid is still palpable, despite general metabolic and clinical cure (off iodine), there were marked reductions in 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 (Case 12) states, "My collar size has now returned to the same as I had worn prior to the onset of Graves' disease." He had had a large goiter (three times normal size) prior to treatment.

In addition to the 20 unoperated cures, there is pathological evidence for cure in one case (Case 16) which was operated upon. A 28 gm. thyroid was removed; it showed histological "involution," and the patient subsequently developed myxedema.

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

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 five of the 20 unoperated cases developed B.M.R. levels of -15 to -20, no case 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