TEN YEAR RESULTS OF I-131 THERAPY OF HYPERTHYROIDISM*

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RADIOIODINE, I-131, eight day half-life, made in the atomic pile at Oak Ridge was released for general use by the U. S. Atomic Energy Commission, July 1946. It was employed almost immediately in the treatment of hyperthyroidism, following the lead gained from the few patients treated earlier with this agent by Soley working with Hamilton and Lawrence,[1] and the small series of patients given I-131, 12 hr. half-life isotope, by Hertz and Roberts[2] and by Chapman and Evans.[3] The present report summarizes our ten year experience with I-131 given for this purpose.

During these past ten years, the results of various groups have been presented after varying intervals of experience. Also, a serious effort has been made to define the relative roles of radioiodine, surgery, and chronic antithyroid drugs in the treatment of toxic goiter.[4] Nevertheless, as pointed out in a recent editorial,[5] there is need for the presentation of results with I-131 on a wide scale, to permit both the advantages and the drawbacks of the method to be defined and to be compared with those of the other modalities of treatment.

The present report is based on the results in a series of 525 hyperthyroid patients treated and followed by the senior author at the Presbyterian Hospital in New York between October 1946 and July 1955, and observed through June 1956. Throughout the study, the physical aspects pertaining to I-131 therapy were supervised by Dr. Quimby. At the follow-up visits, the eyes were examined routinely; the majority by Dr. Day, the rest by Drs. J. Kennedy and R. Nichols who collaborated in the initial phases of the study.

The results presented herein confirm the already established fact

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that I-131 is a highly efficacious agent for the medical treatment of hyperthyroidism. Unfortunately, however, the adverse features of the use of the method still remain a source of trouble.

Methods

All patients initially were subjected to a complete medical work-up. Only patients with well-documented hyperthyroidism were treated with radioiodine, and these were selected for therapy with this modality essentially according to principles outlined elsewhere.[4] Patients younger than 40 years of age were not treated with I-131 except when there was recurrence of toxicity following surgery or when other methods were contraindicated.

During the first two years of the study, a standard dose of 3 or 4 mc. I-131 was given to all patients.[6] Only two doses were provided to any one patient, and the second dose was not administered until four months or more after the first. In subsequent years, a dose range of I-131 was established, between 1 and 8 mc. for each of the first two doses but up to 25 mc. when a third dose or more was necessary.[7] Doses were repeated at two month intervals, provided toxicity remained severe and I-131 uptake elevated. Otherwise, the patients were observed for four months or longer according to earlier practice. According to this schedule, the smaller dose levels were employed for patients with small glands and low toxicity, the larger ones for big glands and high toxicity. Maximal doses were given only when biological resistance to radiation effect was evident from failure of the preceding doses. Withal, the average initial dose throughout the study for the great majority of patients was approximately 6 mc.

Subsequent to 1950, antithyroid drugs were given routinely in conjunction with I-131.[8, 9] As a rule, drug therapy was begun two to seven days after I-131 administration, and was continued for five to six weeks, in an effort to control toxicity during the latent period until I-131 effect becomes evident. In the past two years, thyroid by mouth has been added to the regimen. The latter drug has been given in an effort to prevent the rate and extent of reduction in level of thyroid hormone thought to provoke onset of, or exacerbation of, complicating severe infiltrative ophthalmopathy.

Changes were made in the standardization of the millicurie of I-131 several times during the ten years of the study. The present "standard"

millicurie of the Bureau of Standards is 80 per cent of the "New York" millicurie in use until January, 1955, i.e., the patients received 1.2 present "standard" mc. per tabulated mc. prior to January, 1955. All doses were given orally; the usual precautions for the safety of patient and personnel necessary for the use of these large quantities of I-131 were observed. Twenty-four hour uptake readings were made routinely for the first five years of the study but are done now only when a preliminary uptake determination with a test dose has not already been made. Effective half-life of the isotope within the gland was estimated routinely from weekly measurements over the neck but this practice was also discontinued five years ago. Calculations of the radiation dose provided to the gland were also made routinely from this value, from the dose of I-131, from estimated gland size and from the I-131 uptake. However, since the radiation dose to the thyroid was not found to correlate satisfactorily with the therapeutic result,[6] this calculation was not attempted further.

Once remission had been achieved and sustained for a year, the patients were seen annually in follow-up. At these visits, a clinical appraisal of their general and thyroid status was made. In the laboratory, B.M.R. and fasting cholesterol determinations were performed routinely; in case of doubt, the 24 hour I-131 uptake and serum precipitable iodine (SPI) level chemically were also measured. The SPI test has now replaced the former two tests as the routine. The eyes were examined by the ophthalmologist from the beginning of the study, and were measured with the Hertel exophthalmometer.

When hypothyroidism resulted from I-131 therapy, the patients were treated with thyroid for six months or more. Therapy was then discontinued in order to exclude the possibility that the hypothyroidism might have been only transient. In some instances, treatment was resumed and discontinued several times in this effort to establish the correct diagnosis.

Results of Treatment

As stated, there are 525 patients in the present series. Of these, 282 (54 per cent) had toxic diffuse goiter prior to treatment, 151 (29 per cent) toxic recurrent goiter, and 92 (17 per cent) toxic nodular goiter (Table I). The last diagnosis was made when one or more definite and discrete nodules were palpated within the gland and after every

TABLE I.—TEN YEAR EXPERIENCE WITH I-131 TREATMENT OF HYPERTHYROIDISM

Oct. 1, 1946—May 31, 1956

Sex and age distribution and type of goiter before treatment—525 patients

Type of Goiter	Sex and Age: Male, Under 40	Male, 40 & Over	Female, Under 40	Female, 40 & Over	Total
	(No. Patients)				
Toxic diffuse	13	65	67	137	282 (54%)
Toxic recurrent	6	17	43	85	151 (29%)
Toxic nodular	1	16	3	72	92 (17%)
Total	20	98	113	294	525 (100%)

Summary

Age	
Under 40	133
40 & over	392
Sex	
Men	118
Women	407

TABLE II.—NO. OF DOSES OF I-131 IN PATIENTS ENTERING REMISSION—447 OF 525 PATIENTS

No. of Doses	Type of Goiter: Diffuse	Toxic Recurrent (No. Patients)	Nodular	Total Patients
1	124	78	44	246 (55%)
2	74	32	24	130 (30%)
3	33	9	13	55 (12%)
4	8	1	1	10 (2%)
5	2	2	1	5 (1%)
6	1	0	0	1
Total	242	122	83	447 (100%)

TABLE III.—TOTAL DOSAGE OF I-131 IN PATIENTS ENTERING REMISSION—447 OF 525 PATIENTS

Dosage mc.	Type of Goiter *Diffuse*	*Toxic Recurrent (No. Patients)*	*Nodular*	*Total Patients*
0 - 3	53	29	7	89 (20%)
4 - 6	94	60	36	190 (43%)
7 - 9	38	21	9	68 (15%)
10 - 14	42	6	11	59 (13%)
15 - 25	6	6	15	27 (6%)
Over 25	9	0	5	14 (3%)
Total	242	122	83	447 (100%)
Summary				
0 - 6	147 (61%)	89 (73%)	43 (52%)	
7 - 14	80 (33%)	27 (22%)	20 (24%)	
15 -	15 (6%)	6 (5%)	20 (24%)	
Total	242 (100%)	122 (100%)	83 (100%)	

effort had been made to differentiate nodularity from exaggerations of the normal lobulations of the gland resulting from hypertrophy.

There were 118 men and 407 women in the series with the age distribution shown in the table.

Eighty-five per cent of the patients treated were rendered euthyroid or hypothyroid by the first dose of I-131. The remaining 15 per cent required more than two doses (Tables II and VII). The majority of patients responded to less than 10 mc. total dosage, only 21 per cent requiring more than this (Tables III and VIII). The average total dosage was 6 mc., excluding the 19 highly resistant patients requiring more than 25 mc. to gain remission.

Of the 525 patients in the series, 341 were treated five years to ten years prior to the present review. One hundred fifteen of the 341 were still coming to the follow-up clinic. One patient of the series is known to have died, from metastases of a malignant melanoma noted one and one half years after I-131 therapy.

Incidence of Induced Euthyroidism: In Tables II and III are listed the number of doses, and total dosage, of I-131 required to restore

TABLE IV.—GLAND SIZE* BEFORE I-131 THERAPY AND NUMBER OF DOSES REQUIRED TO INDUCE EUTHYROIDISM—447 OF 525 PATIENTS

Type of Goiter	*Estimated Gland Size*	*No. Doses* 1	2-3 (No. Patients)	Over 3
Toxic diffuse	Small	59	35	1
	Moderate	48	48	4
	Large	17	23	6
	Total	124	106	11
Toxic recurrent	Small	53	21	1
	Moderate	23	16	2
	Large	2	4	0
	Total	78	41	3
Toxic nodular	Small	15	6	0
	Moderate	18	15	0
	Large	11	16	2
	Total	44	37	2

* Small—under 35 Gm. estimated weight; moderate—35-60 Gm.; large—over 60 Gm.

TABLE V.—GLAND SIZE* BEFORE I-131 THERAPY AND TOTAL DOSAGE REQUIRED TO INDUCE EUTHYROIDISM—447 OF 525 PATIENTS

Type of Goiter	*Estimated Gland Size*	*Total Dosage* 0-3	4-9 (No. Patients)	10-25	Over 25
Toxic diffuse	Small	34	40	12	0
	Moderate	17	59	23	1
	Large	2	23	13	0
	Total	53	122	48	1
Toxic recurrent	Small	27	45	3	0
	Moderate	2	31	8	0
	Large	0	5	1	0
	Total	29	81	12	0
Toxic nodular	Small	6	13	1	1
	Moderate	1	22	10	0
	Large	0	10	15	4
	Total	7	45	26	5

* Small—under 35 Gm. estimated weight; moderate—35-60 Gm.; large—over 60 Gm.

TABLE VI.—INCIDENCE OF PERMANENT HYPOTHYROIDISM—78 OF 525 PATIENTS

	Years after I-131 Therapy	*No. of Patients*
	0 - 1	40
	1 - 2	1
	2 - 3	12
	3 - 4	12
	4 - 5	3
	5 - 6	3
	6 - 7	3
	7 - 8	3
	8 - 9	0
	9 -10	1
Summary		
	Within 1st year	40 (7.6% of 525 patients)
	After 1st year	38 (7.2% of 525 patients)
Total		78 (14.8% of 525 patients)

euthyroidism. This status was achieved in 447 of the 525 patients. One dose was sufficient in 246 (55 per cent) of the 447, whereas 16 patients (3 per cent) required more than three doses. Total dosage was less than 10 mc. in 347 patients (78 per cent) but exceeded 25 mc. in 14 (3 per cent).

Gland size prior to I-131 therapy has been correlated with number of doses of I-131, and total dosage, in Tables IV and V. It is clear that the correlations are, at best, rough.

Incidence of Induced Hypothyroidism: Transient hypothyroidism was observed in 11 patients. These patients recovered without need for sustained substitution therapy. A diagnosis of permanent hypothyroidism following I-131 therapy was made in 78, 14.8 per cent of the 525 patients in the series (Table VI). Hypothyroidism became evident within the first year after I-131 therapy in 40 patients, 7.6 per cent of the total series treated (Table VI). However, this incidence rose progressively as the patients were followed subsequent to treatment. Thus, an additional 38 patients (7.2 per cent) became permanently hypothyroid during the ten years after treatment. There was a peak between

TABLE VII.—NO. OF DOSES OF I-131 IN PATIENTS BECOMING HYPOTHYROID—78 OF 525 PATIENTS

	Type of Goiter		
No. of Doses	*Diffuse*	*Toxic Recurrent (No. Patients)*	*Nodular*
1	29	22	4
2	5	5	3
3	3	1	1
4	0	0	1
5	2	0	0
6	0	1	0
Over 6	1	0	0
Total	40	29	9

TABLE VIII.—TOTAL DOSAGE OF I-131 IN PATIENTS BECOMING HYPOTHYROID—78 OF 525 PATIENTS

	Type of Goiter		
Dosage mc.	*Diffuse*	*Toxic Recurrent (No. Patients)*	*Nodular*
0- 3	11	5	0
4- 6	22	17	3
7- 9	4	3	4
10-14	0	3	0
15-25	0	0	1
Over 25	3	1	1
Total	40	29	9

two and four years after therapy; one patient became hypothyroid as late as the tenth year of follow-up. Thus, a total of 14.8 per cent of all patients treated were found to be hypothyroid over the ten year follow-up period, in contrast to the incidence of 7.6 per cent in the first year after therapy.

Whereas all but two of the 40 patients with onset of hypothyroidism in the first year after I-131 therapy had had toxic diffuse or recurrent

TABLE IX.—GLAND SIZE BEFORE I-131 THERAPY AND NUMBER OF DOSES EMPLOYED IN PATIENTS BECOMING HYPOTHYROID—78 OF 525 PATIENTS

Type of Goiter	*Estimated Gland Size*	*No. Doses* 1	2-3	Over 3
		(No. Patients)		
Toxic diffuse	Small	15	5	0
	Moderate	11	2	0
	Large	3	1	2
	Total	29	8	2
Toxic recurrent	Small	13	2	0
	Moderate	7	4	0
	Large	2	0	1
	Total	22	6	1
Toxic nodular	Small	1	0	0
	Moderate	2	2	1
	Large	1	2	0
	Total	4	4	1

* Small—under 35 Gm. estimated weight; moderate—35-60 Gm.; large—over 60 Gm.

goiter before treatment was given, seven of the 38 patients developing hypothyroidism later had had toxic nodular goiter initially.

Number of Doses and Total Dosage of I-131: A single dose of I-131 was given to 55 of the 78 patients becoming hypothyroid (Table VII). Total dosage amounted to 6 mc. or less; in fact, 16 of the 55 patients became hypothyroid after 1 to 3 mc. (Table VIII). In contrast, five patients received more than three doses and five patients received more than 25 mc. before becoming hypothyroid.

Initial Gland Size: An analysis of gland size prior to treatment was made in relation to number of doses and total dosage of I-131, as was done for the patients becoming euthyroid. Tables IX and X show the distributions to be similar to that of the euthyroid group.

Effect of Pregnancy After Therapy: Eighteen patients became pregnant after remission was obtained by I-131 therapy (Table XI). Of these seven became hypothyroid, three during, and four subsequent to, the pregnancy. The offspring at birth were normal and healthy.*

* Three patients received I-131 in the first month of pregnancy when the late mensis was attributed to the hyperthyroidism or was not mentioned. The newborn also were considered healthy and normal, and remained well subsequently.

TABLE X.—GLAND SIZE* BEFORE I-131 THERAPY AND TOTAL DOSAGE EMPLOYED IN PATIENTS BECOMING HYPOTHYROID—78 OF 525 PATIENTS

Type of Goiter	*Estimated Gland Size*	*Total Dosage in mc.* 0-3	4-9	10-25	Over 25
		(No. Patients)			
Toxic diffuse	Small	9	11	0	0
	Moderate	2	11	0	0
	Large	0	3	0	3
	Total	11	25	0	3
Toxic recurrent	Small	5	10	0	0
	Moderate	0	8	3	0
	Large	0	2	0	1
	Total	5	20	3	1
Toxic nodular	Small	0	1	0	0
	Moderate	0	4	0	0
	Large	0	2	1	0
	Total	0	7	1	0

* Small—under 35 Gm. estimated weight; moderate—35-60 Gm.; large—over 60 Gm.

Incidence of Late Recurrence: Recurrence of hyperthyroidism after one year or more of remission was observed only six times (1.1 per cent) in the series, none later than four years after treatment (Table XI). Remission was readily induced by retreatment with I-131.

Ophthalmopathy: Eye changes were classified into two clinical groups as described elsewhere.[4] The term "non-infiltrative" represents those eyes showing proptosis or widening of the fissures without other ocular manifestations, and the term "infiltrative" represents those eyes showing clinical manifestations suggestive of edematous and cellular infiltration of the ocular structures, such as chemosis, corneal ulceration, lacrimal gland swelling, or ocular muscle weakness. The purpose in classifying the eye changes is discussed later in this paper.

The course of the eye complications was described as "improved", "static", or "worse". By the last is meant progressive ocular involvement leading either to permanent impairment of the motion of the globes (usually with one or both eyes turned down and in) or of vision, or to the need for orbital decompression surgically. No patient in this series however required decompression. If there was transient and

TABLE XI.—RECURRENCE OF HYPERTHYROIDISM 1 YEAR OR MORE AFTER REMISSION—525 PATIENTS

	Year of Recurrence after Therapy					
Type of Goiter	*1*	*2*	*3*	*4*	*Over 4*	*Total (No. Patients)*
		(No. Patients)				
Toxic diffuse	0	2	1	0	0	3
Toxic recurrent	0	0	1	1	0	2
Toxic nodular	0	1	0	0	0	1
Total	0	3	2	1	0	6 (1.1%)

TABLE XII.—EFFECT ON THYROID STATUS OF PREGNANCY COMMENCING AFTER REMISSION INDUCED BY I-131 THERAPY—18 OF 525 PATIENTS

Total becoming pregnant		18
Total becoming hypothyroid with pregnancy		7
During	3	
Following	4	
Initial Goiter		
Toxic diffuse		12
Toxic recurrent		6
Age range	20-39	

TABLE XIII.—INCIDENCE OF OPHTHALMOPATHY—525 PATIENTS

Type of Goiter	*Total Patients*	*Type of Ophthalmopathy*		*Total and % of Group*
		Non-infiltrative	*Infiltrative*	
Toxic diffuse	282	49	48	97 (34%)
Toxic recurrent	151	36	19	55 (36%)
Toxic nodular	92	7	4	11 (12%)
Total	525	92	71	163 (31%)

Summary

Non-infiltrative	92 (18%)
Infiltrative	71 (13%)
Both Types	163 (31%)
Total patients in series	525 (100%)

TABLE XIV.—INCIDENCE OF OPHTHALMOPATHY AND SEX DISTRIBUTION —525 PATIENTS

Type of Goiter	*Type of Ophthalmopathy*	*Sex*		*Total*	
		Male	*Female*		
Toxic diffuse	Non-infiltrative	13	36	49	
	Infiltrative	20	28	48	
Toxic recurrent	Non-infiltrative	9	27	36	
	Infiltrative	2	17	19	
Toxic nodular	Non-infiltrative	0	7	7	
	Infiltrative	2	2	4	
	Total	46	117	163	(31%)

limited advance in chemosis or proptosis followed by return to the original status or better, the patients were not classified as "worse".

Non-infiltrative Ophthalmopathy: There were 92 patients classified as having non-infiltrative ophthalmopathy before operation (Tables XIII-XVI). Of these, 86 either improved or showed no significant change except for 1 or 2 mm. advance in proptosis. Six of the 92, however, made a transition to the infiltrative form, and one of these six ultimately developed severe and permanent muscle function impairment. Following therapy with I-131, two patients with no evident eye changes before the procedure had the onset of non-infiltrative ophthalmopathy. Neither patient in this latter group had an initial diagnosis of toxic nodular goiter. However, an initial diagnosis of toxic nodular goiter was made in seven of the 92 patients with non-infiltrative ophthalmopathy.

Infiltrative Ophthalmopathy: Prior to I-131 therapy, 71 patients were classified as having infiltrative ophthalmopathy (Tables XIII-XVI). Many of these were accepted for treatment after having been rejected by the surgeons for fear of flare-up of the eye complication. Of these, 64 either improved or showed no significant change, except possibly for 1 or 2 mm. advance in proptosis. Eight patients without previous evident eye involvement had onset of infiltrative changes subsequent to I-131 administration.

Of all in the infiltrative group, seven became "worse" and had

TABLE XV.—TYPE OF OPHTHALMOPATHY AND TIME OF ONSET—163 OF 525 PATIENTS

Type of Ophthalmopathy	*Before I-131*	Time of Onset *After I-131* *Hyper.*	*Eu.*	*Hypo.* (*No. Patients*)	*Change after I-131 to Infiltrative Ophthalmopathy (No. Patients)*
		Toxic Diffuse			
Non-infiltrative	47	1	1	0	4
Infiltrative	43	2	2	1	—
		Toxic Recurrent			
Non-infiltrative	36	0	0	0	2
Infiltrative	17	1	1	0	—
		Toxic Nodular			
Non-infiltrative	7	0	0	0	0
Infiltrative	3	0	1	0	—
Total	153	4	5	1	6

Summary

Patients with onset after I-131		10
Non-infiltrative	2	
Infiltrative	8	
Non-infiltrative becoming infiltrative after I-131		6
Total with onset of infiltrative ophthalmopathy after I-131		14 (2.7% of 525 patients)

permanent severe ocular muscle damage as a consequence. One of the seven also developed optic neuritis with permanent impairment of vision. This patient had, in addition to his hyperthyroidism, pernicious anemia and diabetes mellitus, although both these were reasonably well-controlled at the time of onset of the optic neuritis. Thus, with the one patient in the non-infiltrative group who developed infiltrative changes and ultimately muscle damage, there were eight patients or 1.8 per cent of the total series who became "worse" by the definition above.

The records of the patients whose ophthalmopathy commenced following I-131 therapy were reviewed to determine the status of the thyroid at the time of onset (Table XV). Of the eight patients, four were euthyroid, none hypothyroid, and three actively hyperthyroid.

An initial diagnosis of toxic nodular goiter was made in four patients of the group with infiltrative ophthalmopathy.

TABLE XVI.—CLINICAL COURSE OF OPHTHALMOPATHY—163 OF 525 PATIENTS

Non-infiltrative—92 patients			
Improved		2	(2% of non-infiltrative group)
Static		84	
Change to infiltrative		6	(6% of non-infiltrative group)
Improved	3		
Static	2		
Worse with muscle fibrosis	1		
Improved or static		91	(93% of non-infiltrative group)
Infiltrative—71 patients			
Improved		6	
Static		58	
Improved or static		64	(90% of infiltrative group)
Worse		7	(10% of infiltrative group)
Muscle fibrosis or weakness	7		
Optic neuritis and amblyopia	1*		
Summary			
Both types of ophthalmopathy			
Improved		8	(1.8% of 525 patients)
Static		148	
Worse		8	(1.8% of 525 patients)

* Also included under "muscle fibrosis"

Miscellaneous Complications: The occurrence of transient thyroiditis and of tracheitis after I-131 therapy for hyperthyroidism has been described in earlier publications.[6, 10] These complications are clinically of minor importance and their incidence has not been quantitated in this paper. Parathyroid injury[11] and leukemia[12] were not observed.* One patient in the series had chronic leukemia as well as hyperthyroidism before I-131 was given. Pericarditis with effusion occurred twice in the series, both times with onset about three weeks after therapy and with no satisfactory etiologic factor elicited.

Recurrent Nodularity: Two patients with toxic nodular goiter treated with I-131 developed readily palpable nodules in the thyroid region several years after thyroid tissue had become impalpable. The recurrent masses were removed surgically for pathologic examination.

* Since this series was reported, acute leukemia developed in one patient, 18 months after she received a total of 2.1 mc. I-131. This patient's record is being reported in detail elsewhere.

Multiple microfollicular adenomata were demonstrated in each instance. The significance of these findings is discussed later in this paper.

Localized Myxedema: This rare, cosmetically disturbing complication occurred twice in the series. Both patients had had toxic diffuse goiter, with onset of the localized myxedema prior to therapy in one, subsequently in the other. Neither patient became hypothyroid. Ophthalmopathy of the non-infiltrative type was present in both.

Thyroid Storm: Flare-up of Toxicity: One instance very suggestive of thyroid crisis or storm occurred in one of the patients in this series who developed pneumonitis about two weeks after I-131 was administered. This patient recovered. One patient treated subsequent to the analysis of the series developed "storm" 24 hours after 4 mc. I-131, with subsequent recovery.

Flare-up in toxicity occurred in six patients, especially serious in three because of exacerbation of cardiac failure. This occurred in the first two weeks after the I-131 was administered.

Hypercholesterinemia: Levels of cholesterol over 300 mg. per cent were maintained in 26 of the 447 patients rendered euthyroid by I-131 therapy. Four of these had been elevated prior to therapy; eight values had not been determined before treatment. The remaining 14 had had normal values. Ten of the 26 patients had not gained weight following remission of hyperthyroidism. Thyroid was ineffective in reducing the elevated levels except transiently.

Radiation Dosage: Calculations of radiation dosage delivered to the thyroid revealed a wide spread of values among the patients in the series. Hypothyroidism was induced by as little as 2700 rads and remission barely induced by more than 30,000 rads, although this patient later became hypothyroid.

Discussion

It is evident from past experience that all patients with hyperthyroidism can be rendered euthyroid or hypothyroid with I-131 therapy. However, it is equally clear that only a little more than half the patients in the present experience responded to a single dose. In fact, a sizable minority were still actively hyperthyroid six months and several doses after starting treatment. This unpredictability of outcome has been

observed by all workers in the field[13] and represents one of the limitations of internal radiation therapy. However, the difficulty is minimized by the use of an adjuvant antithyroid drug or iodine therapy. Thus a patient can be rendered and maintained euthyroid by these agents, except for those brief intervals when drug treatment must be discontinued to establish whether more I-131 is required, or not.

Flare-up of toxicity without fatality shortly after I-131 was administered occurred several times in our series. One death from thyroid storm has been reported in the literature seven days after 4 mc. I-131 was given.[14] The senior author also has seen a fatal outcome in a patient not included in the present series, seven days after 5 mc. I-131 given by another physician. Riggs[15] observed that the serum precipitable iodine level may increase after I-131 therapy for hyperthyroidism. However, Rall[16] states that he has been unable to find thyroglobulin in the serum following I-131 therapy of hyperthyroidism although such material is present five to ten days after the larger doses of I-131 given to patients with thyroid carcinoma or to euthyroid patients with heart disease.

It is thus likely that flare-up of toxicity or "storm" occurring within the first week after the smaller doses given in hyperthyroidism is not related to the therapy, but is an intercurrent event. Nonetheless, patients with cardiac complications, with prolonged thyrotoxicosis and severe wasting, or with big glands, probably should be given relatively small initial doses of I-131, and these should be followed shortly by an antithyroid drug or iodide administration. On occasion, it may be better to give antithyroid drugs prior to I-131 therapy, until the patient's condition is improved. I-131 can then be administered without fear of crisis.

Attention has already been called to the factor within the thyroid of biological variability in sensitivity to radiation affect.[6] The existence of this phenomenon has been amply confirmed in the present experience. Hypothyroidism resulted from as little as 2700 rads and lack of remission from over 30,000 rads, both extremes in patients with toxic diffuse goiter.

In several patients, there was an unquestionable, although limited, initial response to relatively small doses of I-131, followed subsequently by little response to considerably larger doses. It is thus suggested that the thyroid may have developed resistance to radiation effect. There is no method presently available for documenting this hypothesis. One

explanation for this phenomenon would involve differences in cell sensitivity. The radiosensitive cells in the gland would be killed with the early doses. The radio-resistant ones would remain to multiply and sustain the hyperthyroidism.

In some instances of seeming resistance to radiation effect, errors in estimation of gland size may account for the poor success from a given dose. The gland can be considerably larger than was estimated by palpation, due to rotation behind the trachea or to substernal extension. Thus failure of treatment would be due to the miscalculation in dose of I-131 administered.

McCullagh and Richards[17] have observed that patients with toxic nodular goiter are more resistant to I-131 effect than those with toxic diffuse or toxic recurrent goiter. This did not hold entirely in our series. Thus two doses and 9 mc. induced remission in most patients regardless of the initial diagnosis. McCullagh's patients were in an endemic goiter area but Chapman and Maloof in Boston[18] had an experience similar to McCullagh. One patient has been reported with toxic nodular goiter who failed to respond to 100 mc. given in a single dose.[19]

Iodine or antithyroid drugs given in conjunction with I-131 therapy have been thought to increase resistance to I-131 effect.[8] In part, the effect is only apparent since these drugs block recirculated I-131 from entering the gland and slightly shorten the effective half-life of the isotope within the gland.[20] However, these agents may induce changes in thyroid cell height and activity, or in vascularity of the gland, or both. Such changes could truly increase resistance to radiation effect.

Thyroid cancer consequent to radiation effect was not observed in the present series nor in approximately 13,000 patients of the recently pooled experience of a number of clinics.[21] It is dubious however that this can be taken to mean that such malignancies may not develop. It was originally estimated that thyroid cancer after I-131 therapy would occur, if it did so, about 20 years after therapy.[22] However no estimate was made of the range about this mean; and the range could as well be from 18 to 22 years as from 10 to 30 years. Carcinoma of the thyroid has been produced by I-131 in rats,[23] but this work has not yet been confirmed and thyroid cancers have been shown to occur spontaneously with relative frequency in the Long-Evans strain used in the original study.[24]

Persistent bizarre nuclear changes within the thyroid cells have been

described in man as late as five years after I-131 therapy.[25] Two patients of the present series developed multiple adenomata of the thyroid following I-131 therapy for toxic nodular goiter after all palpable thyroid tissue had disappeared for two and one and a half years respectively. These nodules persisted and even increased despite large doses of thyroid by mouth. The occurrence of adenomata is of interest in view of the high association rate of such lesions with thyroid cancer.[26] However, multiple adenomata are seen not infrequently in nodules which have recurred after surgery for toxic nodular goiter. Also, one of the two patients probably had chronic thyroiditis even prior to the administration of I-131, so that it is likely that this disease rather than radiation effect was responsible for the changes observed. Similar histological findings have been described in persistent nodules of toxic nodular goiter not disappearing with I-131 therapy,[27] or remaining postoperatively.

Since, despite all, the possibility remains that late cancer may yet result from treatment with I-131, it appears wise to continue the age restriction upon the use of the isotope in primary toxic goiter currently in effect in many clinics. According to this practice, patients under 40 years of age are regularly treated by other means than I-131, although there are exceptions.[4]

The presence of toxic nodular goiter is held not to contraindicate I-131 therapy in patients over 40. The spontaneous incidence of associated cancer is not much greater than in toxic diffuse goiter,[28] unlike the high rate of association in nontoxic nodular goiter.[29, 30] Thus it is believed that I-131 will not predispose to malignancy more in this group than in toxic diffuse goiter.

Recently, there has been added another objection to treatment with I-131 in younger patients with hyperthyroidism. There is a risk that incidental radiation to the gonads may increase the likelihood of mutant offspring, should these patients become parents.

Glass[31] has estimated the effect of radiation from I-131 therapy upon the mutation rate in the offspring of the population as a whole, and in the progeny of the particular patient. From a liberal estimate of the number of patients of childbearing age who might be treated annually and from the dosages in current use, he has estimated that the increase in mutations from this cause will have virtually no meaning for the population at large. To quote him:

"The average gonadal dose can be estimated to be about six rads per person from data presented at the recent Atomic Energy Commission sponsored conference on I-131 therapy.[32] This indicates an equivalence of about 1 rad to the gonads from 1 millicurie of radioiodine administered. The effect upon the population as a whole must be regarded as negligible because of the small number of individuals being treated. Thus one can assume that 100,000 persons under 40 years of age are given radioiodine in the course of a human generation, a number which is much greater than actually now given such treatment. The product would be 1500 mutations scattered in the descendants of these 100,000 persons in a population of 100 million persons per generation. Ten r, the permissible dose set by the National Academy of Science Committee, administered to the entire population would result in five million mutations. The ratio works out 0.03 per cent or 3/10,000 of what might be considered a critical limit. Even if 100,000 persons were treated per year, this would produce only 45,000 mutations, which works out at 0.9 per cent of the permissible limit. Since the administration of radioiodine is only one of many sources of radiation exposure to which the population is subject, I would think personally that this latter level would begin to be of some significance.

"If the administered dose averaged 36 rads, this would about equal the dose that would double the spontaneous mutation rate from all sources, including the background radiation."

However, the situation for the individual patient is somewhat different. As just seen from Dr. Glass' estimates, the possibility of tangible genetic defects in the progeny of the I-131 treated individual is about 1 to 2 per cent (1500 mutations per 100,000 patients at risk) with the usual doses employed in the treatment of hyperthyroidism, about 10 per cent of which would appear in the first generation. Such a likelihood may be small percentagewise. Yet, if confirmed, it would seem to be too large to warrant I-131 therapy in the younger age groups when only uncomplicated hyperthyroidism is being treated, and not cancer. Surgery in this age group is effective; is presently associated with virtually no mortality; and carries no such genetic risks or fear of carcinogenesis. Chronic antithyroid drug therapy also is available for the younger patient although the method carries a lower permanent remission rate than operation.

Obviously, these arguments against the use of I-131 in younger people are less important when the toxic goiter has recurred after a previous operation. The greater morbidity and sharply decreased efficacy of surgery when a second operation or more is required, make I-131 the method of choice.

The occurrence of acute leukemia after I-131 therapy for thyroid cancer is well-recognized and had been anticipated as a risk of the

doses of I-131 required. With these doses, whole body radiation may reach or exceed the dose level of 30-50 r which is the dose which has been estimated by some to double the spontaneous incidence rate of leukemia in the population as a whole.[21] The doses of I-131 usually employed in hyperthyroidism, however, provide radiation doses well below this doubling dose. Nonetheless, if the effect of radiation is proportional to the dose, there should be an increase in leukemia even with low dose levels, i.e., 10 per cent increase for 5 r. Withal, an occurrence of leukemia at these lower doses would be more apt to be a spontaneous event and not the consequence of the I-131 therapy.

This hypothesis seems borne out by the results presented at the recent Atomic Energy Commission sponsored conference on I-131 therapy.[32] Four patients in the 13,000 followed from one to ten years after I-131 therapy for hyperthyroidism were reported to have developed acute leukemia, i.e., four per 65,000 patient years. This incidence corresponds to the expected spontaneous incidence of acute leukemia in the general population of 1 per 20,000 patients per year, i.e., 1 per 20,000 patient years.

Our patient whose leukemia was diagnosed subsequent to the AEC conference, received a total of 2.1 mc. I-131. This represents between 1-3 rads general body exposure and a blood dose of between 2-6 rads. The whole body exposure is well below the doubling dose of 30-50 r. Where radiation effect has induced leukemia, onset has been at two years with peak incidence about six years after exposure. The present patient developed leukemia 18 months after I-131 therapy. Pochin's patient[33] included in the four above received 6.8 mc. I-131 and had onset of leukemia at 18 to 24 months after therapy. It is probable that the onset of the leukemia in both was unrelated to I-131 therapy, but it is equally clear that more data need to be collected. It becomes important that an occurrence of leukemia after I-131 therapy be reported with the details of treatment, time of onset, etc.*

The total incidence of permanent hypothyroidism after I-131 therapy is appreciable. The incidence during the first year in the present series, 7.6 per cent, is about as low as has been reported for this method, and is in the range of some surgical series.[4] However, the additional 7.6 per cent with onset during the subsequent years of follow-up makes the

* Since many patients also receive antithyroid drugs, Failla[34] has raised the question whether these latter agents may not in themselves be mutagenic and hence cause, or contribute to, the occurrence of leukemia.

total definitely greater than that of surgery. Since one patient became hypothyroid in the tenth year after therapy, the incidence may become still higher as time goes on. A possible explanation for delayed onset of hypothyroidism may lie in the abnormal pituitary-thyroid relation found to exist in active hyperthyroidism.[35] Euthyroid healthy subjects given tri-iodothyronine show a sharp decrease in I-131 uptake by the thyroid whereas overtly hyperthyroid patients show little or no decrease in uptake.[36] For the first five years following induced remission, tri-iodothyronine still does not decrease uptake in the majority of patients.[37] Subsequently, the majority of patients respond like normals. It is thus possible that the increased secretory rate of the thyroid remnant persists after I-131 therapy, and is thereby able to maintain euthyroidism but not hyperthyroidism. After five years, normal pituitary-thyroid relations may be reestablished. The hyperactivity of the thyroid remnant would end and with a decrease in secretory activity, hypothyroidism would appear.

The relative merits of radioiodine, surgery, and chronic antithyroid drugs must be even more critically scrutinized when complicating ophthalmopathy is present. It is commonly assumed that the non-infiltrative form of the disorder carries a good prognosis following surgery, and the infiltrative form a poor one. Virtually no published data are available however on which to base this assumption. It is, thus, almost impossible to compare the present results obtained with I-131 with those from surgery or antithyroid drugs. However, many of our patients with infiltrative ophthalmopathy were deliberately treated with I-131 after they were rejected by the surgeons on this account. The good results obtained suggest that I-131 may be a better form of treatment in this regard than surgery. Whether I-131 has advantages over antithyroid drugs in respect to ophthalmopathy is not known. Rapidly advancing ocular damage has been seen during antithyroid drug therapy. However, comparisons are not possible because of lack of published data.

The dearth of information about the course of ophthalmopathy after treatment of the hyperthyroidism suggests that the classification of eye changes employed in this study might be used in presenting data from other series and for other methods of therapy. This would provide comparable information so that the relative efficacies of the several methods of treatment could be appraised, or the results among clinics with any

one method evaluated. At worst, the relative incidences of patients winding up their course with severe impairment of ocular function or vision, or need for decompression, could be established.

It is recognized that the criteria employed herein for the classification of eye changes are somewhat arbitrary and that the clinical pictures may frequently not fit clearly into one or the other category. It is also recognized that the several forms of ophthalmopathy may be no more than the different manifestations of a single pathogenetic process, with a range from mild to severe.[38] Nonetheless, separation of the patients into two groups is a time-honored practice,[39,40] and the validity of such distinctions cannot be established unless the effort is made to classify these patients. However, our results would seem to suggest that the separation into two groups is probably meaningless, both prognostically and mechanistically.

Conclusions and Summary

There is no question about the high efficacy of I-131 in the treatment of hyperthyroidism. However, the method carries with it certain risks, such as that of hypothyroidism, or of failure to obtain remission with any given dose. These difficulties are explained by a factor of variability in susceptibility to radiation effect.

The disadvantage of unpredictability of outcome is not too serious since it can be largely offset by the concurrent use of antithyroid drugs. Hypothyroidism too may not be troublesome, since replacement therapy is virtually complete. However, the onset of hypothyroidism may occur years after treatment and may be quite insidious. As a consequence, the relation of the new symptoms to the antecedent I-131 therapy may go unsuspected by both physician and patient, unless the patient has been previously warned of the possibility of such a development.

Uncertainty about late thyroid cancer remains after ten years of I-131 usage. This uncertainty alone probably should continue to limit the use of the isotope in the younger age groups. In addition, however, there is another and equally important reason for restriction of treatment in younger people. The radiation effect to the gonads from I-131 therapy increases the mutation rate to between 1 per cent and 2 per cent in the offspring of the treated patient. Thus, exposure of a potential parent to this risk, however small, or of younger people in general to the possible risk of cancer, seems unjustifiable at the present stage of

information. Surgery in this group is effective and carries a low mortality and morbidity.

There is a dearth of comparable data by which to define the relative success of I-131 therapy in controlling the ophthalmopathy of patients with hyperthyroidism. The present experience suggests that I-131 probably carries less risk of serious ocular damage consequent to therapy than surgery. It is also probable that I-131 therapy is not more risky in this regard than is long-term antithyroid drug therapy, whereas I-131 is a more definitive therapeutic agent for the hyperthyroidism itself.

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