A STUDY OF THYROID FAILURE FOLLOWING RADIOIODINE* THERAPY FOR GRAVES' DISEASE

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THE use of radioactive iodine as a treatment of choice for the hyperthyroidism due to Graves' disease is being increasingly accepted. However, in some patients one consequence of the use of radioiodine, I^{131}, has been the occurrence of permanent thyroid failure. The purpose of this study is to review the circumstances of thyroid failure as a complication of radioiodine therapy in a series of patients having Graves' disease, in order to evaluate factors that may affect the incidence of that complication.

Method of Study and Treatment

Three hundred and thirty-two patients with Graves' disease were treated with radioiodine at Cleveland Clinic between January 1952 and June 1954. The patients constituted five groups (A,B,C,D,E) corresponding to the five physicians who prescribed treatment for them. Two physicians used the same method of calculating the dosages, and the other three each based their estimates of dosage on clinical judgment. Doses for groups A and B were calculated on the basis of estimated weight of the thyroid gland and the initial I^{131} uptake in comparison with tracer studies. The following formula was used to calculate the dose in an attempt to deliver 100 microcuries per gram of gland (normal weight taken as 25 grams) unless the patient had a goiter larger than 75 grams or had symptoms of cardiac failure or angina pectoris, or severe disabling hyperthyroidism, when 150 to 200 microcuries per gram was given.

$$\frac{\text{Estimated weight of gland (Gm.)} \times \text{microcuries/Gm.} \times 100}{\text{Per cent tracer uptake}} = \frac{\text{Microcuries } I^{131}}{1000} = \text{Millicuries } I^{131}$$

The radioactive iodine used in this investigation was supplied by the Abbott Laboratories on authorization from the Isotopes Division, U. S. Atomic Energy Commission, Oakridge, Tennessee.

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If two months after the initial dose of I^{131} the patient was definitely improved but still hyperthyroid and the I^{131} uptake was normal or high, an additional dose, calculated by the above method, was administered. However, if the I^{131} uptake was low (below 15 per cent) in that type of patient, no further I^{131} was given until two more months had elapsed. If the patient was unimproved after the first treatment, a dose of 150 or 200 microcuries per gram was administered. (I^{131} uptakes were measured at the end of 24 hours in the patients of this series.)

The chief concern of all the physicians was to control the hyperthyroidism as quickly as possible; the lesser concern was to try to control the incidence of subsequent thyroid failure.

After the initial dose of I^{131}, patients were seen at two-month intervals until they were euthyroid, and then again two months afterward. If thyroid failure had occurred, there was further observation. The diagnosis of thyroid failure was based upon various typical clinical and laboratory findings: symptoms of hypothyroidism (fatigue, cold intolerance, hoarseness, drowsiness); dry skin, puffiness of the eyes and face, gain in weight, and sluggish reponse of Achilles reflex; posttherapeutic I^{131} uptake (after tracer doses) below 15 per cent of that administered; basal metabolic rate of less than minus 20 per cent with some favorable response to desiccated thyroid treatment; and, usually, plasma cholesterol levels higher than normal.

Follow-up studies were made of some patients with thyroid failure by requesting them to return for examination after discontinuance of the use of desiccated thyroid. Questionnaires were sent to those who could not return, and to a few in whom thyroid failure was doubtful (a total of 42 patients) asking them whether they still were taking desiccated thyroid. Of the 38 patients who replied, 29 stated that they still were taking desiccated thyroid. Those patients who still were taking desiccated thyroid were regarded as having permanent thyroid failure, even though some may have regained normal thyroid function. Those who had discontinued taking desiccated thyroid and who felt well without it were regarded as having had temporary hypothyroidism.

TABLE 1

Analysis Of Results in 332 Cases of Graves' Disease After Radioiodine Therapy

Factor	No. patients treated per year			Series total	Percentage of series total
	1952	1953	1954 (first 6 mo.)		
Yearly total	135	119	78	332	100%
Temporary thyroid failure	3	2	2	7	2.1%
Permanent thyroid failure (percentage of yearly total)	16(11.7%)	9(7.5%)	7(8.9%)	32	9.6%

Results

Incidence and age distribution. Of 332 patients with Graves' disease treated with radioiodine therapy, 32 were classified as having permanent thyroid failure, an incidence of 9.6 per cent; and seven or 2.1 per cent were classified as having had temporary thyroid failure (Table 1). The ages of the patients were from 14 to 65 years.

Weight of thyroid gland. The estimated weights of the toxic thyroid glands before treatment were from 25 to 150 grams. The estimated weights of the toxic thyroid glands of the 32 patients who developed permanent thyroid failure were from 25 to 100 grams before treatment.

Duration of treatment. More than 90 per cent of the patients were euthyroid within four months following radioiodine therapy; most were definitely improved, if not euthyroid, within two months following radioiodine therapy. The average interval between the date of the last treatment of I^{131} and onset of thyroid failure was 3.7 months (2 to 6 months) (Fig. 1). In two patients (5 per cent) thyroid failure occurred six months after treatment.

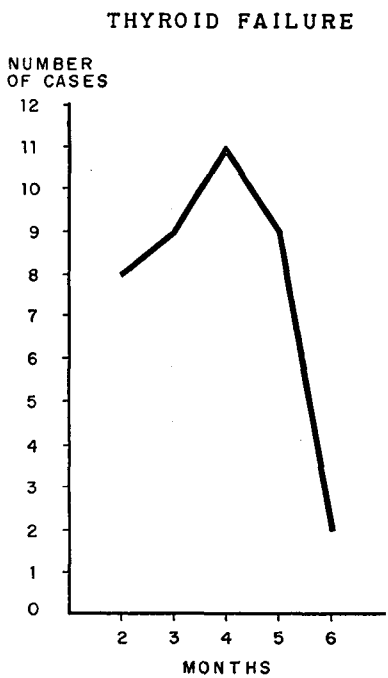

Fig. 1. Thyroid failure in 39 patients, as related to number of months it occurred after last dose of radioiodine.

Size of dose. Doses that produced euthyroidism varied from a single dose of 3 millicuries to multiple doses totaling 75 millicuries. Doses that produced thyroid failure varied from a single dose of 4 millicuries to multiple doses totaling

59 millicuries. The largest single dose producing hypothyroidism was 20 millicuries. Of the 39 patients who developed permanent or temporary thyroid failure, 31 had received single doses of I^{131}; 6 had received two doses of between 5 and 25 millicuries per dose; and 2 patients had received three doses respectively totaling 24 and 59 millicuries.

Temporary thyroid failure. Of the seven patients (2.1 per cent) who developed temporary thyroid failure, five had received single doses of 5 to 10 millicuries of I^{131}; two patients had received two doses totaling 13 and 43 millicuries respectively. All patients in whom thyroid failure was temporary required desiccated thyroid for periods of 3 to 21 months. Subsequently all discontinued the thyroid medication and since have been euthyroid for periods of 2 to 22 months.

Our observations indicate that in a small number of patients the thyroid gland may regain its function after there has been a hypothyroid state. It is possible that some patients who at the present time are considered as having "permanent" thyroid failure eventually will recover thyroid function. Figure 2 illustrates the course in a patient with this temporary thyroid failure due to I^{131}.

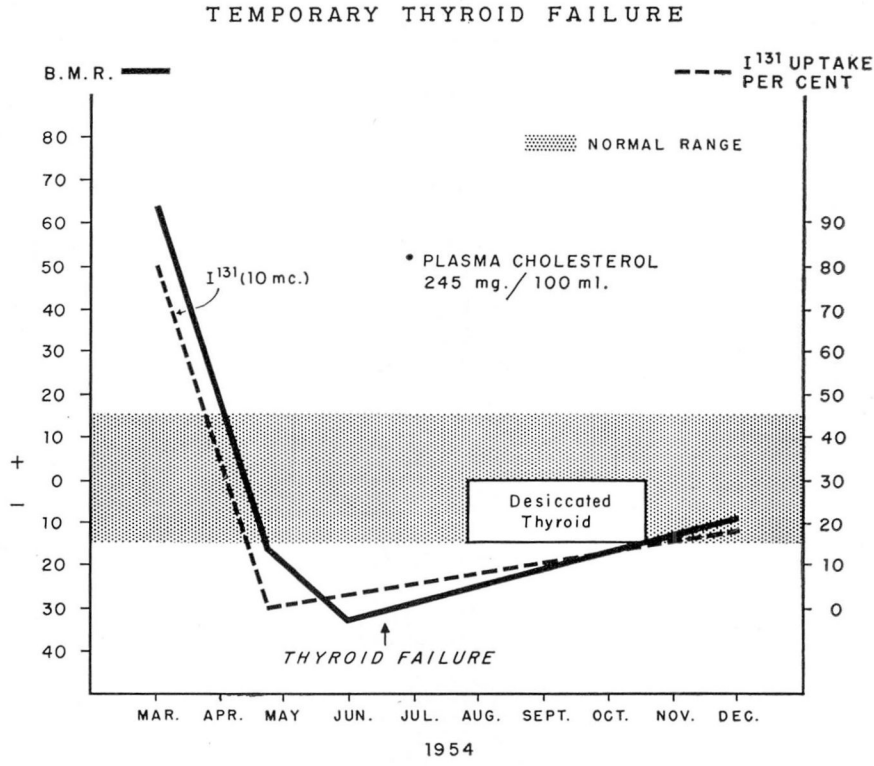

Fig. 2. Chart of data of a case of Graves' disease in a 39-year-old man who was treated with 10 mc. of I^{131}. Thyroid failure occurred four months after administration of radioiodine. He was treated with desiccated thyroid for three months, became euthyroid and remained so after discontinuance of thyroid therapy.

Permanent thyroid failure. Thirty-two patients had permanent thyroid failure and 26 of these were taking desiccated thyroid in doses of 30 to 240 mg. daily. This information was obtained from follow-up questionnaires or from the patients directly who were seen recently. The remaining six patients who were given desiccated thyroid for hypothyroidism, presumed permanent, did not return or reply to the questionnaire. Five of the 32 patients discontinued using desiccated thyroid temporarily and the symptoms of hypothyroidism recurred.

It is of interest to note that the incidence of permanent thyroid failure was lower in the two groups of patients whose doses of I^{131} were calculated on the basis of the weight of the gland (4.4 and 8.5 per cent) than in the other three groups of patients whose doses were based on clinical judgment (13.1, 14, 14.8 per cent) (Table 2).

TABLE 2

Analysis of Results in 332 Cases of Graves' Disease After Radioiodine Therapy

Factor	Number of patients in group					Series total	Percentage of series
	A (Dosage calculated)	B (Dosage calculated)	C (Dosage based on clinical judgment)	D (Dosage based on clinical judgment)	E (Dosage based on clinical judgment)		
Total number	113	70	38	57	54	332	100%
Temporary thyroid failure	2	3	1	1	0	7	
Permanent thyroid failure (percentage of group total)	5(4.4%)	6(8.5%)	5(13.1%)	8(14.0%)	8(14.8%)	32	9.6%

Before any symptoms or signs of thyroid failure were evident, an early laboratory clue as to the likelihood of its occurrence was a low I^{131} uptake. However, a number of patients who had low I^{131} uptakes and euthyroidism did not develop thyroid failure subsequently. The presence of a normal or high I^{131} uptake after the euthyroid state was attained, usually but not always indicated that the patient was not likely to develop thyroid failure.

Figure 3 summarizes the typical course of a patient who developed permanent thyroid failure after radioiodine therapy and who since has been taking desiccated thyroid.

Discussion

In a series of 1720 cases from the literature, Seed and Jaffé[1] reported that hypothyroidism of a more or less persistent nature occurred in 9 per cent of the patients treated with radioactive iodine. Chapman and associates[2] reported an

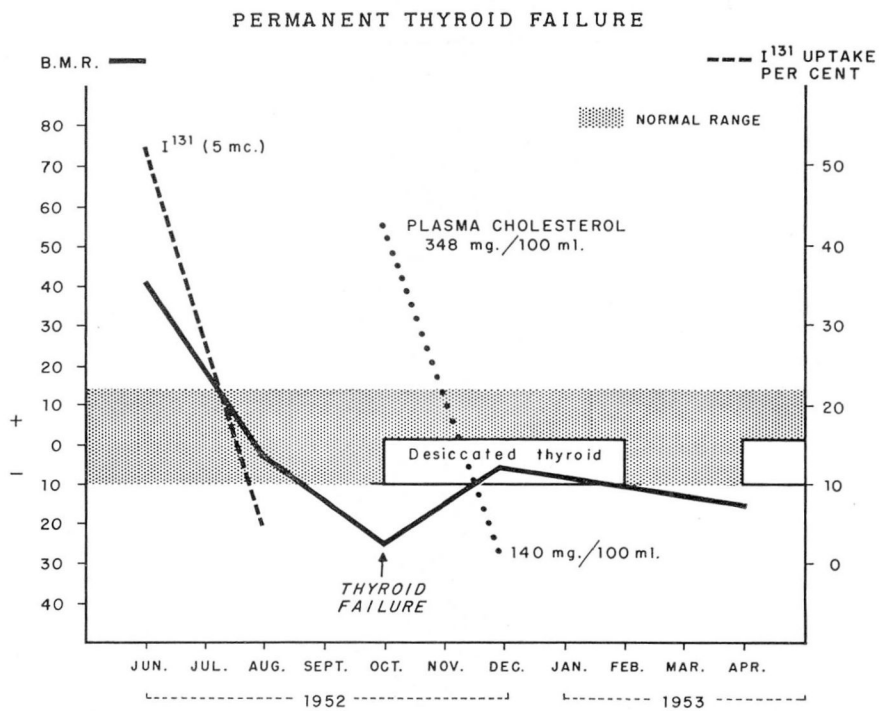

Fig. 3. Chart of data of a case of Graves' disease in a 49-year-old woman who developed a diffusely enlarged thyroid gland (estimated weight 30 Gm.). She was treated with 5 mc. of I^{131} and became euthyroid two months later. Four months after treatment, thyroid failure was evident. Desiccated thyroid was given for four months, and the patient became euthyroid again; treatment was then discontinued for two months and all symptoms of hypothyroidism recurred. Desiccated thyroid therapy was reinstituted, and two and one-half years later the patient still required it to remain euthyroid.

8 per cent incidence of posttreatment myxedema. The incidence of thyroid failure after surgical managemant of hyperthyroidism varies considerably within the individual series. Bartels[3] reviewed several series of surgical cases and found an incidence of hypothyroidism varying from 2.9 to 21 per cent. The latter finding was reported by Crile and McCullagh[4] for radical surgery of the thyroid gland in Graves' disease. They also reported that hypothyroidism occurred in 4.5 per cent of the cases involving conservative surgery. The incidence in Cattell's[5] series varied between 4 and 6 per cent. The incidence of the complication of thyroid failure increases with more radical subtotal thyroidectomy. We have observed the occurrence of thyroid failure in patients years after they had had partial thyroidectomy for Graves' disease, just as undoubtedly will occur years after I^{131} therapy. One of our patients, not included in the series reported here, was treated in 1949 with I^{131} and developed thyroid failure six years later.

There are several factors that apparently affect the incidence of thyroid failure. Overestimation of the dose of I^{131} is one important factor. After studying

the effect of radioiodine in the thyroid gland, Dailey and associates[6] suggested that lymphocytic infiltration, fibrosis, and moderate and diffuse follicular atrophy result from internal irradiation. They noted a higher incidence of lymphocytic infiltration and fibrosis in the thyroids of patients treated with I^{131} than in those patients untreated before surgery.

In our series the smaller the goiter the more likely was the patient to develop thyroid failure. This may be related to difficulty in estimation of dosage, but size alone may be a factor. Previous observations indicate that the larger the goiter the more resistant it is to I^{131}.[7]

The age of the patient was of no etiologic significance.

Perhaps the most important factor is the, as yet unexplained, variation in sensitivity of the thyroid cells in the goiters of different patients to the effects of radiation, despite identical clinical and laboratory findings and the same-sized doses of I^{131}; thus, one patient may develop thyroid failure and another continue to have hyperthyroidism.

It may be that a variation in the duration of retention of I^{131} in the thyroid gland may partially explain this difference in sensitivity, but we have no data verifying or refuting this possible explanation. The histopathologic structure of the hyperplastic thyroid gland before treatment with I^{131} may also be a partial explanation for the variation in sensitivity to I^{131} and occurrence of thyroid failure. We, and others[8] before us, have observed that the thyroid glands of some patients having Graves' disease show focal areas of thyroid cells with oxyphilia in the cytoplasm, which are associated with varying degrees of lymphocytic infiltration and fibrosis; this condition has been called thyroiditis, but we believe it represents focal cellular exhaustion consequent to the stress of overactivity of the cells. This histopathologic condition is observed in only a small percentage of patients with Graves' disease, but the incidence of postoperative thyroid failure is known to be very high in this group.[3,8] Thus, focal thyroid cell exhaustion occurring prior to treatment with radioiodine may be another part of the explanation for the variation in sensitivity to I^{131}. There probably are unknown mechanisms that also may explain this variability in sensitivity to I^{131}.

Summary

Of 332 patients with Graves' disease treated with radioactive iodine, 32 (9.6 per cent) developed permanent thyroid failure. Temporary thyroid failure occurred in 7 patients (2.1 per cent). The incidence of thyroid failure was lower when the I^{131} dosages were calculated on the basis of estimated weight of the thyroid gland than when based on clinical judgment alone. The thyroid failure usually occurred within two months after the patient had become euthyroid. The occurrence of low I^{131} uptake after the patient became euthyroid was often a forewarning of the development of thyroid failure.

Factors that predisposed the development of thyroid failure were overdosage of I^{131}, small size of goiter, and variation in sensitivity of the thyroid cells to I^{131}.

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