RADIOACTIVE IODINE THERAPY IN 135 CASES OF THYROTOXICOSIS

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Radioactive iodine (^{131}I) was introduced for the treatment of thyrotoxicosis almost simultaneously by Hertz and Roberts (1942) and by Hamilton and Lawrence (1942). After more than a quarter of a century, the exact place of radioactive iodine in the management of thyrotoxicosis remains undefined (Means, De Groot and Stanbury, 1963; Harvard, 1969; Smith, 1970). In Singapore, radioactive iodine was first used in the treatment of thyrotoxicosis in July 1966. This paper reviews our initial experience of radioactive iodine therapy of thyrotoxicosis.

MATERIALS AND METHODS

The diagnosis of thyrotoxicosis was made clinically and by investigations which include the serum cholesterol, basal metabolic rate, thyroid gland uptake of radioactive iodine and serum protein bound radioactive iodine in all cases and photomotography, thyroid antibodies and serum protein bound iodine in some cases.

The following were considered suitable for radioactive iodine therapy: (i) patient 40 years or older, especially those with small goiters; (ii) relapse after thyroidectomy; (iii) unsuitable for surgery because of heart disease etc. and (iv) hypersensitivity to antithyroid drugs.

All the cases were seen by a panel of physicians and radiotherapists. The chief factors that decide the dosage were: (i) age of patients; (ii) size, nodularity and consistency of the goiter; (iii) uptake and retention of radioactive iodine by the thyroid gland and (iv) presence of complications such as heart disease.

From July 1966 to August 1970, 161 cases were treated at the Department of Medicine, Medical Unit I, Outram Road General Hospital. Twenty six cases are not included in this series mainly because the patients have left the country or are being followed elsewhere. The 135 cases in this series were seen monthly, initially, and at longer periods subsequently.

RESULTS

Of the 135 patients, 107 are females and 28 are males (ratio 3·8:1). The race, sex and age distributions of the patients are shown in Table I. The mean age is 52 years: the youngest patient is 30 years and the oldest patient is 74 years old.

The indications for radioactive iodine therapy are shown in Table II. Only one dose was given to 122 cases: 12 patients received 2 doses and 1 patient received 3 doses. The mean dosage given to a patient was 8·4 millicuries; for a single dose treatment the dosages ranged from 4 to 30 millicuries. The range of the dosages per patient in all the cases is shown in Fig. 1. The type and size of the goiter are shown in Tables III and IV.

Forty-five cases (33·4%) were followed for less than a year while 10 cases (7·4%) were followed for more than 4 years (Table V). The thyroid status of the treated cases at the time of review are shown in Table VI.

Of the 12 cases that became hypothyroid after therapy, 9 are female and 3 are male. Their mean age (48 years) is less than that of all the treated patients (52 years); their ages range from 30 to 59 years. Nine patients received a single dose while 3 had 2 doses each. The mean dose received by each patient (8·0 millicuries) is less than that of the whole series (8·4 millicuries). The details of these 12 hypothyroid cases are shown in Table VII. Five cases became hypothyroid within 6 months of therapy; 3 cases between 6 to 12 months while 4 cases between 1 to 2 years. The number that became hypothyroid in relation to the period of follow-up is shown in Table VIII.

Thyroid antibodies before therapy were determined in only 2 of the 12 hypothyroid patients. In Case 3 (Table VII) antimicrosomal antibody was absent while antibody to thyroglobulin was present in a titre of 1:5; in Case 6 antibody to thyroglobulin was absent. In 32 of the 135 cases in the present series, antibody to thyroglobulin was determined. In 13 cases it was absent; in 4 the titre was 1:5; in 12 it was 1:25; in one each the titre was 1:250, 1:250,000 and 1:400,000. The patient with a titre of 1:400,000 was a 46-year-old lady who was given 4·0 millicuries of radioactive iodine; she was euthyroid 3 months later and has been followed for more than 4 years without evidence of hypothyroidism. The other case with a titre of 1:250,000 was a 52-year-old woman who received 4·0 millicuries; this failed to render her euthyroid and she has been on carbimazole

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TABLE I

RACE, SEX AND AGE GROUP DISTRIBUTION OF THE 135 CASES

Race	Male						Female						Both Sexes
Sex and Age Group in Years	30-39	40-49	50-59	60-69	70 +	All Ages	30-39	40-49	50-59	60-69	70 +	All Ages	
Chinese	3	3	12	5	1	24	9	29	45	18	1	102	126
Malay	0	1	2	0	0	3	0	3	1	0	0	4	7
Indian	0	0	0	0	0	0	0	0	0	0	0	0	0
Others	0	1	0	0	0	1	0	1	0	0	0	1	2
All Races	3	5	14	5	1	28	9	33	46	18	1	107	135

TABLE II

INDICATIONS FOR RADIOACTIVE IODINE THERAPY

		No. of Cases
1. Elective as first treatment		74
2. Failed medical therapy	Relapse	28
	Irregular treatment	12
	Drug sensitivity	7
3. Relapse after thyroidectomy		14
TOTAL		135

TABLE III

TYPE OF GOITER IN THE SERIES

	No. of Cases
1. Multinodular and firm	95
2. Smooth and soft	29
3. Solitary nodule	3
4. Unclassified	8
TOTAL	135

TABLE IV

SIZE OF THE THYROID GLAND IN THE SERIES

	No. of Cases
Not palpable	8
2 × normal	70
3 × normal	49
4 × normal	6
5 × normal	2
TOTAL	135

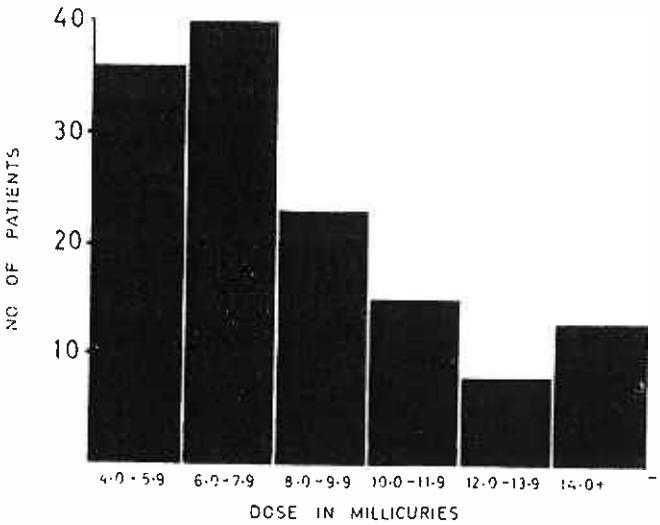

Fig. 1. Range of total dosage received by a patient.

TABLE V

PERIODS OF FOLLOW UP FOR THE 135 CASES

Years	No. of Cases	%
0-0·9	45	33·4
1·0-1·9	22	16·3
2·0-2·9	27	20·0
3·0-3·9	31	22·9
4·0-4·9	10	7·4
TOTAL	135	100·0

TABLE VI

THYROID STATUS AFTER RADIOACTIVE IODINE THERAPY

Thyroid Status	No. of Cases	%
Euthyroid	70	51·8
Hypothyroid	12	8·9
Still toxic	53	39·3
TOTAL	135	100·0

TABLE VII

DETAILS OF THE 12 PATIENTS RENDERED HYPOTHYROID BY RADIOACTIVE IODINE TREATMENT

NO.	SEX	AGE IN YEARS	THYROID GLAND		THYROID ANTIBODIES		RADIOACTIVE IODINE DOSAGE		PERIOD OF FOLLOW-UP IN MTHS.	HYPOTHYROID: NO. OF MTHS. AFTER THERAPY
			SIZE	NODULART AND CONSISTENCY	TRC*	AMA+	NO.	AMOUNT IN MILLICURIES		
1	F	47	2X NORMAL	SMOOTH/SOFT	ND$^{\phi}$	ND	1	8·1	22	20
2	F	57	NP$^{\bullet}$	–	ND	ND	1	8·0	6	4
3	M	30	NORMAL	SMOOTH/SOFT	1:5	Absent	1	7·9	7	2
4	F	59	2X NORMAL	NODULAR/FIRM	ND	ND	1	6·1	22	10
5	F	55	2X NORMAL	NODULAR/FIRM	ND	ND	2	5·0 6·4	40	24
6	F	46	2X NORMAL	NODULAR/FIRM	Absent	ND	1	6·0	30	2
7	M	51	2X NORMAL	SMOOTH/SOFT	ND	ND	1	5·0	36	24
8	F	55	NP	–	ND	ND	1	8·2	38	8
9	F	59	2X NORMAL	NODULAR/FIRM	ND	ND	1	6·1	24	8
10	F	44	3X NORMAL	NODULAR/FIRM	ND	ND	2	5·0 6·4	40	12
11	M	44	2X NORMAL	NODULAR/FIRM	ND	ND	2	5·5 8·0	40	3
12	F	55	2X NORMAL	SMOOTH/SOFT	ND	ND	1	4·0	5	2

*: TANNED RED CELL AGGLUTINATION. ●: NOT PALPABLE.
+: ANTIMICROSOMAL ANTIBODY. ϕ: NOT DONE

TABLE VIII

RELATIONSHIP BETWEEN THE PERIOD OF FOLLOW-UP AND THE NUMBER OF HYPOTHYROID CASES

Period of Follow-up in Years	No. of Cases	Hypothyroid	
		No.	%
0-0·9	45	3	6·7
1·0-1·9	22	2	9·9
2·0-2·9	27	2	7·4
3·0-3·9	31	4	12·9
4·0-4·9	10	1	10·0

TABLE IX

TYPE OF THYROTOXIC HEART DISEASE IN 61 CASES

Thyrotoxic Heart Disease	No. of Cases	%*
Atrial fibrillation	45	73·8
Cardiac failure	38	62·3
Myocardial infarction	3	4·9
Angina pectoris	2	3·3
Paroxysmal atrial tachycardia	2	3·3
Atrial flutter	1	1·6
Ventricular extrasystole	1	1·6
Right bundle branch block	1	1·6

*Of 61 cases.

supplement for the past 3 years. In 12 of the 135 cases antimicrosomal antibody was determined. It was present in 2 and absent in 10.

Sixty-one cases (45·2%) had thyrotoxic heart disease (2 cases with hypertensive heart disease and 2 cases with mitral valve disease are excluded). There are 15 males and 46 females; their mean age (55 years) is higher than that of the whole series (52 years). The pattern of heart disease in the 61 patients is shown in Table IX.

Atrial fibrillation was the commonest finding; there being 45 cases (73·4%). Cardiac failure occurred in 38 cases (62·3%). Of the 45 cases with atrial fibrillation, 19 (42·2%) reverted to sinus rhythm after radioactive iodine therapy. All the 19 cases reverted in less than a year after therapy; the mean period was 5 months. The mean age of these 19 cases was 56 years; 11 of them received digitalis. At the time of reversion, 10 were euthyroid, 8 were still toxic while 1 was hypothyroid. Twenty-six cases (57·8%) continued to have atrial fibrillation after therapy. Their mean age (53 years) is less than in the 19 that reverted to sinus rhythm. Fifteen of these 26 cases are euthyroid while 11 are still toxic; 16 of them had also been treated with digitalis.

Ophthalmopathy (with exophthalmos) was present in 20 cases (14·8%) before therapy. After treatment, ophthalmopathy remained unchanged in 13 (8 were euthyroid; 5 were still toxic); became worse in 5 (2 were euthyroid; 3 were toxic) while it improved in 2 (both were still toxic). In addition, in 4 cases, exophthalmos was absent before therapy but set in after therapy (2 were euthyroid while 2 were still toxic).

One patient died 8 months after treatment of an unrelated cause. Two patients had carcinoma of the cervix before the onset of thyrotoxicosis. There was no case of leukaemia, thyroid carcinoma or other malignancy following radioactive iodine treatment.

DISCUSSION

From the beginning, there had been fear that the use of radioactive iodine, an ionzing radiation, might lead to an increased incidence of thyroid carcinoma, leukaemia and genetic damage. The thyroid gland in the adult is fairly resistant to irradiation-induced carcinogenesis (Einhorn *et al*, 1967). After treating over 1,500 patients over 20 years, Means, De Groot and Stanbury (1963) found only one case where there is real suspicion that a papillary carcinoma might have been induced by radioiodine given 2 years earlier. Three children are known to have developed suspicious nodules following radiotherapy (Sheline, Lindsay and Bell, 1959). Sheline *et al* (1962) further reported that among 256 cases with toxic diffuse nodules treated with radioiodine, and developed thyroid nodules between 5 and 14 years after the therapy. In view of the above we have limited our patients to those 40 years or older, unless they are not suitable for thyroidectomy or anti-thyroid drug treatment. Means, De Groot and Stanbury (1963) have lowered their age limit from 45 years to 40 years and more recently to 25 years. Crile and Schumacher (1965) have treated 31 thyrotoxicosis children with radioiodine with good results. Kogut *et al* (1965) treated 23 children with radioiodine; one child developed a thyroid nodule which on biopsy showed papillary carcinoma with vascular invasion.

In 60,000 patients who had received radioactive iodine treatment for thyrotoxicosis, Pochin (1960) found no increase in the incidence of leukaemia. In the group of radioiodine treated patients, there has been no evidence of genetic damage, but the problem cannot be disregarded (Means, De Groot and Stanbury, 1963). The observation time is, at present, too short for a definite assessment (Einhorn *et al*, 1967).

Our series have no Indians and only 7 Malays out of 135 cases (Table I). This is probably due to selection; in a comparable series of 137 patients from West Malaysia, there are 18 Malays and 7 Indians (Dharmalingam, Yi and Mahadev, 1970). The female to male ratio in our present study is 3·8:1; this compares with a ratio of 5:1 in the series reported by Dharmalingam, Yi and Mahadev (1970).

We use an empirical regime in the selection of radioiodine dosage: the aim being to give an irradiation dose of 7,000 rads to the thyroid gland. With this practice, two major disadvantages have emerged during recent years. The first is the delay in controlling the hyperthyroidism by radioiodine alone and the second is the rising incidence of hypothyroidism (Smith and Wilson, 1967).

Most of our patients (90·4%) receive only a single dose. The average dose used was 8·0 millicuries; this compares with 8·3 millicuries used by McGirr, Thomson and Murray (1964). Seventy cases (51·8%) were rendered euthyroid; and 53 cases (39·3%) were still toxic and required antithyroid drug supplement. McGirr, Thomson and Murray (1964) reported that 75·6% of their patients were euthyroid after one dose. In contrast Dharmalingam, Yi and Mahadev (1970) only cured one-third of their patients treated with a single dose (most of their patients received 4 to 6 millicuries).

The hypothyroid rate at the end of one year is 6·7%; it was absent in the series of Dharmalingam, Yi and Mahadev (1970) and 18·3% in the series of McGirr, Thomson and Murray (1964). The overall incidence at the end of 5 years in our series is 10·0%; it was 14% and 27·5% in the reports of Dharmalingam, Yi and Mahadev (1970) and McGirr, Thomson and Murray (1964) respectively. The incidence of hypothyroidism in our series, as in others treated with radioiodine is greater than that which follows thyroidectomy. Green and Wilson (1964) contrasted an incidence of 20% in their radioiodine treated patients with 5% after operation.

Thyroid antibody appears to have no influence on the development of post radioiodine hypothyroidism (Irvine and Stewart, 1967). Two of our patients with antithyroglobulin antibody titre of 1:250,000 and 1:400,000, have not become hypothyroid up to the period of present study.

The cellular reaction of the thyroid following radioiodine treatment and its relationship to the development of hypothyroidism has been discussed at length by Greig (1966). Many techniques have been described to lower the incidence of hypothyroidism after radioiodine: of promise is the use of smaller doses of radioiodine supplemented with antithyroid drug (Smith and Wilson, 1967) and the replacement of ^{131}I with ^{125}I (Greig *et al*, 1969).

We have found photomotography useful in the early detection of post-radioiodine hypothyroidism (Cheah and Tan, 1969).

Of the 61 cases with thyrotoxic heart disease, 45 (73·8%) had auricular fibrillation. Following radioiodine therapy, 19 cases (42·2%) reverted to sinus rhythm. All the 19 cases reverted within a year after therapy; 11 cases (57·9%) had cardiac failure before radioiodine therapy. Of the remaining 26 cases that continued to have auricular fibrillation, 16 (61·5%) had cardiac failure. In the series reported by Sandler and Wilson (1959), about one-third of the cases with auricular fibrillation reverted to normal rhythm after radioiodine therapy. Our findings do not support their view that cardiac failure is the most important factor that adversely influences reversion. Though myocardial infarction is said to be very uncommon in thyrotoxicosis, there are 3 cases in our series; one of them has been reported in detail elsewhere (Cheah, Lee and Chew, 1970).

Thyrotoxic ophthalmopathy (with exophthalmos) was present in 20 cases (14·8%). Most cases were mild; only one case had ophthalmoparesis. Exophthalmos is more common in European patients; thus Buchanan *et al* (1962) reported an incidence of 75%. Our findings support the findings of Koutras *et al* (1965) that after radiotherapy, most cases of exophthalmos became worse. They advocated the addition of thyroxine after radioiodine therapy.

SUMMARY AND CONCLUSION

A review of 135 cases (107 females; 28 males) of thyrotoxicosis treated with radioiodine was made. Most cases received only one dose; 12 cases received 2 doses and one had 3 doses. The average dosage received by a patient was 8·4 millicuries.

Forty-five (33·4%) were followed for less than a year while 10 cases (7·4%) were followed for more than 4 years. Seventy cases (51·8%) became euthyroid, 53 cases (39·3%) were still toxic and 12 cases (8·9%) became hypothyroid.

Sixty-one cases (45·2%) had heart disease; auricular fibrillation was present in 45 cases. After radioiodine treatment, 19 cases (42·2%) reverted to normal rhythm. Age, cardiac failure and thyroid status after treatment do not appear to influence reversion.

Ophthalmopathy (with exophthalmos) was present in 20 cases (14·8%). Most cases either remained unchanged or became worse after therapy.

The two major disadvantages of radioiodine therapy are persistence of toxicity and hypothyroidism. There was no case of leukaemia or thyroid carcinoma after radioiodine treatment.

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