

# Treatment of thyrotoxicosis with radioactive iodine: A report on 137 cases

## INTRODUCTION

ALTHOUGH RADIOIODINE has been used in the treatment of thyrotoxicosis for the past 27 years, its exact place in the management of thyrotoxicosis is still not clear. The effectiveness of radioactive iodine in treating thyrotoxicosis depends on its localisation and retention in functioning thyroid tissue which is then subjected to radiation by Beta and Gamma rays. The maximum range of the Beta Particle is 2.0 mm and since it contributes 90% of the total dose, there is no significant damage to the extrathyroidal structures, such as the recurrent laryngeal nerve or the trachea. Silver, after experience with 4,000 cases treated over 22 years, feels that every case can be controlled with radioiodine therapy; the difficulty is that although this is possible, it does not necessarily arise that every case should be so treated. One has to consider radioiodine together with surgery and drug therapy. The selection of patients, choice of dosage and dosage schedules, delay in controlling symptoms of toxicity, rising incidence of myxoedema and these are the chief points of discussion.

Goldberg and Chaikoff's work on rats with radioiodine had brought out the question of carcinogenesis. Goolden's report of carcinoma of thyroid in children following external radiation to the neck had further cast doubts on the safety of radioiodine with respect to the remote possibility of carcinogenesis. However, over 200,000 cases of thyrotoxicosis have been treated to-date and there appears to be no risk of carcinoma arising from the use of radioiodine.

Similarly, the risk of leukaemia has been brought forward but Pochin (1960) showed that there was no

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increase in the risk of leukaemia. Lawrence (1967) has recently confirmed this finding. Sterility and genetic hazards do not arise from radioiodine and there have been reports of normal pregnancy and normal babies following inadvertent use of radioactive iodine treatment in pregnancy (McGuirr 1964: 3 cases — Bloomfield 1959 — Werner 1957). In fact, the total body dose, and the dose to the gonads following a therapy dose of radioactive iodine are comparable to routine procedures in radiology such as a barium meal examination or flouroscopy (Weijer, Duggan and Scott 1960).

## METHODS AND MATERIALS

At the Department of Radiotherapy and Nuclear Medicine here, radioiodine therapy for thyrotoxicosis has been offered for the past ten years. As patients are referred by doctors all over the country, the follow-up was inadequate. This report is based on 137

cases who had good follow-up records and who were all reviewed recently. The selection was purely on this basis but one cannot ignore the possibility of a bias towards those who responded well — as those who did not respond may have defaulted. Before treatment was started, all patients had a standard clinical assessment carried out, the therapeutic index (T I) described by Crooks, Wayne and Robb (1960).

In every case, a tracer study with the 4 or 6-hour uptake, 24-hour retention, and the 48-hour PBI 131 was carried out. The size of the thyroid gland was assessed clinically and by means of a thyroid scintigram. Cases were classified as nodular or diffuse. Eye signs were present in 2/3 of the cases and this was noted; also the presence of cardiac signs and symptoms and, where indicated, an ECG was done. All cases were admitted for the treatment, and cardiac patients were hospitalised for a longer period. During the initial period, patients were seen once a month but once symptoms were controlled they were seen at longer periods. Uptake studies and the chemical PBI were done to assess thyroid status during follow-up although the clinical picture was often quite clear. Blood cholesterol was also done to help in detecting cases developing hypothyroidism.

**RESULTS**

**(1) Racial composition of cases studied.**

Sex	Malay	Chinese	Indians	Others
Male	9	14	3	4
Female	9	89	4	5
Total	18	103	7	9

It is clear that Chinese are the predominant group involved. There is also the 5-to-1 female predominance, 107 females to 30 males. In all female patients, a careful menstrual history is essential and the therapy dose should be given immediately after a period to avoid giving it inadvertently to a pregnant subject. Lactation should also be a contraindication in the female. Many of the patients in the series had normal pregnancies and normal babies following treatment with radioiodine and this is of course not contraindicated. It appears from the above figures that the female to male ratio is higher among Chinese.

**(2) Age groups.**

Age	20	20-29	30-39	40-49	50-59	60-69
No	0	1	22	64	38	12

The majority of patients treated have been in the

group between 40 and 49. Our youngest patient was 29 years old. There was a very big number over 50 years. It is recommended that the treatment should be reserved for patients over 40 years. Due to the shorter life expectancy and the earlier reproductive ages of local populations, this may be, in fact, lower for this country. In Silver's series, the youngest patient was four years old, with severe diabetes mellitus. One-third of his patients were less than 40 years old. Werner also had a similar number under 40 years. But very few authorities today treat patients less than 20 years. (De Gown 1959 and George Crile at the Mayo Clinic treat children with radioiodine). Hyperthyroidism in the aged, especially the thyrocardiac, is the prime indication for radioiodine therapy — where age is the chief factor.

**(3) Size and type of gland.**

Diffuse Thyroid	121
Multinodular	3
Solitary Nodule	12
Substernal Goitre	1

The majority of glands were diffuse. Some of the diffuse glands were quite large. There were 12 solitary nodules in the series. Of course, it is possible not all the solitary nodules were true Plummer's disease or autonomous nodules and some of them were really areas of increased activity in a diffuse gland. The nodular glands were common in the older patients. One substernal goitre in an elderly lady of 69 was treated with radioiodine with good results. The small diffuse gland is, of course, the ideal one for treating with radioiodine and in almost all, there was significant reduction in the size of the gland. Nodular glands are unsuitable for therapy with radioiodine because of the risk of malignancy (actually less than 5%), also because of difficulties in dose estimation.

The distribution of radioiodine is patchy in a nodular gland; certain areas are radiated more than others although these are, in fact, the active areas; further estimation of gland weight is difficult because of retrotracheal, retrooesophageal and retrosternal gland extensions. Although nodular cases are not easily controlled, the risk of hypothyroidism is lower and McCullagh (1954) and recently Hamburger (1967) have recommended treating these cases with single large doses of radioiodine. In the series here, all the 12 nodular cases responded well and there were no difficulties or complications.

**(4) Recurrence following surgery.**

Twelve patients had recurrent thyrotoxicosis following surgery and all of them were easily controlled with radioiodine. One case had two attempts at thyroidectomy. The average dose needed for these cases was 4 mCi and was less than the dosage needed for the rest. Gland size is often difficult to estimate clinically and although the scan helps, an arbitrary low dosage is preferable, as the risk of hypothyroidism is higher. Results of a second thyroidectomy in relapsed cases were poor (McLarty et al 1969 100% relapse rate after 2nd operation).

(5) Other indications for therapy include failure of medical treatment due to drug sensitivity, irregular patient, or relapse after medical treatment. This is the largest group (see Table 4). A recent study from Glasgow by McLarty showed that in cases of thyrotoxicosis which relapse after a course of drugs, 77% relapsed if a second course of drugs is given. In contrast, only two of 44 patients who had surgery relapsed. Radioiodine therapy is the other alternative and in this group the chief risk hypothyroidism.

Elective as first treatment		10
90 cases failed medical treatment	Drug sensitivity	11
	Relapse	69
	Irregular treatment	10
Refusal for surgery		
Recurred after surgery (2 after 2 attempts)		12
Co-existing diseases	Carcinoma (Cervix 4)	5
	Heart disease	2
	Diabetes	1
	PTB	1
	Hansons	1
	Other complications	3
Severe Exophthalmos		1

**Table 4 — Indications for treatment**

It is clear that many of the patients have had a course of antithyroid drugs before radioiodine. Crooks, Buchanan, Wayne and MacDonald (1960) found that Methyl Thiouracil given before radioiodine therapy reduced the number of patients who were cured with a single dose and also the average total dose needed is higher. Bloomfield and others (1959), with a smaller number of patients, did not notice any such difference. It is possible that more patients would have responded to a single dose if radioiodine had been used straightaway. At the same time, our low incidence of hypothyroidism may be

related to the pre-treatment with drugs that the majority had.

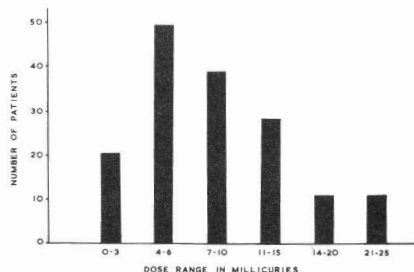
**(6) Dose calculations.**

A tracer study was carried out to determine the dose retained, the thyroid weight was estimated with the aid of the scintigram and clinical assessment and a dose calculated to deliver 7,000 rads to the thyroid was administered. In post-thyroidectomy cases, we had to use an arbitrary low dose.

Single dose	45
2 doses	27
3 doses	38
4 doses	16
more than 4 doses	11

**Table 5 — No. of Doses needed**

The majority of patients, 47, received an initial dose of from 4 – 6 millicuries and were controlled. There were no significant side effects. Most patients did not notice any changes during the first week. The earliest response was at the end of three weeks. There were quite a number who reported a sudden improvement at this time. Tenderness over the gland, cyctitis and parotitis were seen infrequently. Nearly all the cases had some improvement after the therapy. Many patients after the initial improvement relapsed.



**Fig 1: Total dosage needed**

As shown, only 1/3 of the patients were cured with a single dose. Rubenfield cured 88% with a single dose, Sheline & Miller cured 59% and Silver quotes a figure of 50%. It is clear that the size of the dose is a critical factor. Thus in Green & Wilson's study of full dose and 1/2 the dose, 43% were toxic after the full dose at one year, whereas 64% were still toxic at the end of one year after the 1/2 doze. Apart from the size of the dose, pre-treatment of patients with antithyroid drugs may necessitate more doses and total dosage — this was the case with many of our cases. However, as will be pointed out by the low

incidence of hypothyroidism, there may be other factors at work – racial, dietary, etc. The highest dose needed was 25 millicuries for a nodular gland.

#### (7) Control of symptoms.

At the end of one year, 16 of 37 patients had persistent toxicity; 21 were euthyroid. Our results confirm reports (Crooks 1963, Green & Wilson 1964) that there is a noteworthy morbidity with radioiodine in the form of persistent toxicity and long periods needed to control the toxicity. MacGregor also gives a figure of up to 40% with persistent symptoms albeit much improved following radioiodine after 6 – 12 months. The problem of management of the patient during this period depends on his condition, especially the cardiovascular situation. Use of antithyroid drugs has been tried but the difficulty in assessing the patient's improvement makes this inadvisable. Giving further doses of radioiodine to the patient who is gradually improving is likely to encourage hypothyroidism. Recently, we have put some of these patients on the Beta adrenergic blockers like Propranolol ("INDERAL") with good results. Most of these patients, having suffered from hyperthyroidism for many years, are prepared to wait, and are thankful for even the limited improvement at this stage.

#### (8) The Thyrocardiac.

Fifteen of the 137 patients had a trial fibrillation. This corresponds to the 10% incidence reported by Means, De Groot & Stanbury 1964. The majority of the 15 cases needed more than one dose to control the toxicity. In two recent cases, there was severe exacerbation of cardiac failure after about two weeks following the therapy dose of radioiodine. Three out of the 15 patients reverted to sinus rhythm spontaneously after the toxicity was controlled. The remaining cases were much improved though three of them needed to go on digoxin and diuretics for a prolonged period. Sandler and Wilson (1959) found 1/3 of their series reverted to sinus rhythm. Sandler and Wilson did not mention paroxysmal, a trial fibrillation, which is a very important feature in many of these cases.

The apparent reversion may really be a spontaneous case of sinus rhythm. Staffurth (1965) found 1/2 of the patients reverted to sinus rhythm following control of the toxicity with radioiodine. Compared to these figures, surgery gives a higher figure of reversion 75% but then patients who undergo surgery are usually younger and are not comparable.

The problem of the patient with persistent atrial

fibrillation following radioiodine therapy is that there are dangers like embolism and cardiac failure if the atrial fibrillation is untreated. In practice, most of the patients are quite well despite persistent fibrillation. A form of persistent heart disease may persist after successful treatment of thyrotoxicosis (Staffurth Gibberd et al 1965) post-thyrotoxicosis cardiomyopathy. Reversion in this situation may not help much. The possibility of this developing is a good reason why all cases of thyrotoxicosis with heart diseases should be promptly treated (Hudson 1959).

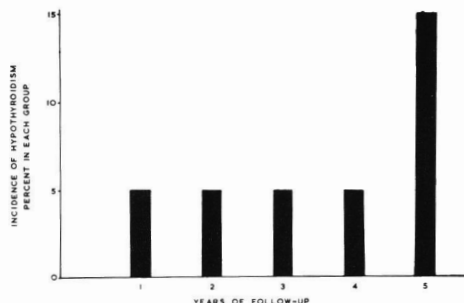


Fig 2: Percent of Hyperthyroid in each group

#### (9) Hypothyroidism.

The overall incidence of hypothyroidism at the end of five years was 14% in this group. There were no cases of hypothyroidism of 37 treated at the end of the first year. These figures are highly significant compared to results reported elsewhere. Beling and Einhorn had a 7% incidence of hypothyroidism at the end of one year and a rise of 3% per year to a figure of 30% at the end of seven years. Greigs, Crooks & MacGregor show that 25% became hypothyroid after a single dose of radioiodine. In Green & Wilson's study, a dose calculated to deliver 7,000 rads and not repeated led to a 29% incidence of hypothyroidism at the end of five years. The comparable figure for the 1/2 dose group is 5%.

It is clear that the low incidence of hypothyroidism in our group of patients cannot be explained purely in terms of low dosage. Although the amount of radioiodine dosage administered may be the same the radiation delivered to the thyroid gland is dependent on:-

1. Effective half-life of iodine in the body.
2. Weight of the thyroid gland.
3. Geometry of the thyroid gland.

It is possible that these may be different in our patients – for example, the effective half-life iodine may be shorter than the assumed six days due, for

example, to excess renal loss. The other factor, of course, is the radiation sensitivity of the thyroid. This may be more resistant to radiation in these patients. Lastly, many of our patients have been pre-treated with antithyroid drugs (Crooks et al 1960). It is interesting to note that in a recent study from Japan (Shizume 1968) an incidence of 8.4% at the end of ten years was recorded of hypothyroidism. The author feels that this low figure might be due to the high iodine content of the Japanese diet. It is possible that similar dietetic factors may be at play in this group, too, although racial factors may also be operating.

#### (10) Eye signs.

Two-thirds of our patients had eye signs. Only one patient had severe exophthalmos and radioiodine was given because of this. The eye signs in this case have regressed. No cases of exacerbation of eye signs have been observed in this group. As Hamilton et al point out, there would appear to be no special advantage from the eye point of view for radioiodine as compared to surgery or drugs. Recently, Koutras et al (1965) have shown in a controlled trial that the

choice of treatment in these cases may be radioiodine with L Thyroxine.

#### SUMMARY

1. 137 patients treated and followed up over the past five years with radioiodine for thyrotoxicosis have been studied.
2. The biggest group of patients was over 45 years.
3. Only 1/3 of patients were controlled with a single dose of radioiodine calculated to deliver 7,000 rads to the thyroid.
4. All the patients were ultimately rendered euthyroid.
5. An incidence of 14% of hypothyroidism at five years was noted.
6. The findings have been discussed with reference to literature on the subject.
7. Radioiodine therapy is an effective treatment for thyrotoxicosis. Local factors are important.
8. The low incidence of hypothyroidism and the smaller number of patients who could be controlled with a single dose was observed. In line with similar findings in Japan various racial, dietetic and other possibilities are explained.

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