

CLINICAL REVIEW

**Radioactive iodine (¹³¹I) therapy for thyrotoxicosis at
Groote Schuur Hospital over a 6-year period**

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Summary

The case records of 262 patients who received ¹³¹I therapy during a 6-year period were analysed retrospectively. These included seventy-eight patients who received more than one therapeutic dose.

The major indication for ¹³¹I therapy was thyrotoxicosis occurring in patients aged 40 years and over. The racial incidence in this series is striking.

The effects on thyroid function of two low-dose schedules (4 mCi and 6 mCi) were compared. The major complication encountered was hypothyroidism. 4 mCi appears to be as effective as 6 mCi with the added advantage of producing less hypothyroidism.

RADIOACTIVE iodine is now an integral part of the therapy of thyrotoxicosis in selected cases. Since the earlier reports of the work of Balls *et al.* (1955), Beierwaltes & Johnson (1956) and Chapman & Maloof (1955), much data has accumulated concerning the indications for, dosage of and complications following ¹³¹I therapy.

Discrepancies between the many reports available concerning the various factors involved with ¹³¹I administration has prompted us to evaluate our experience at Groote Schuur Hospital over a 6-year period (January 1965-March 1971).

Subjects and methods

344 thyrotoxic patients received ¹³¹I during the period January 1965-March 1971. The case records of 262 patients were available for retrospective analysis as regards age, sex, race and indications for

therapy. All the patients were seen at the Thyroid Clinic. Assessment of thyroid status was determined by the usual clinical criteria, 6- and 24-hr standard radioactive (¹³¹I) neck uptake studies, tri-iodothyronine (T₃) suppression test of neck uptakes, protein-bound iodine (PBI), the *in vitro* resin tests (viz. charcoal and red cell uptake of tri-iodothyronine), and total serum thyroxine concentration.

Seventy-eight (29.8%) of the 262 patients received more than one dose of ¹³¹I and were further studied with regard to the dose schedule, ¹³¹I uptakes, duration of symptomatology and interval between administered doses.

Dose schedules

From the period January 1965 to the beginning of 1968, the dose administered was 6 millicuries (mCi), irrespective of gland size, nodularity, ¹³¹I uptakes and duration of symptoms; from 1968 this dose was reduced to 4 mCi. In special circumstances, e.g. cardiac disease, 10 mCi were given.

Results

The age distribution of the 262 patients is shown in Fig. 1. The bulk of the patients fell between the ages of 40 and 59. Of this group thirty-three (12.2%) were males and 229 (87.8%) were females.

Our study confirms the belief that thyrotoxicosis is rare in the African (Bantu) (Table 1).

The main indications for ¹³¹I therapy were (a) age alone; (b) clinically important cardiac disease (including thyrocardiac and rheumatic heart disease); (c) recurrence after surgery; (d) failure of medical treatment, i.e. antithyroid and/or beta-blocking agents administered for not less than 6 months; and (e) a miscellaneous group including, amongst

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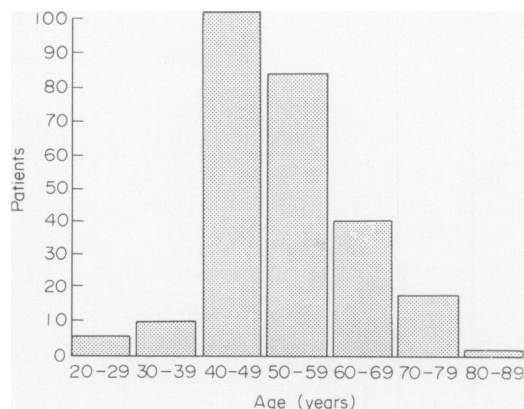


FIG. 1. Age distribution of 262 cases.

TABLE 1. Race distribution of the 262 patients

White	157	(59.9%)
Coloured	103	(39.3%)
African	2	(0.8%)
Total	262	

others, mental disease and malignancy (non-thyroid).

The number of patients falling into each subdivision is shown in Fig. 2.

The policy of the Thyroid Clinic has been to treat patients over 40 years of age with ^{131}I as the therapy of choice, provided there were no contraindications. For this reason, as seen in Fig. 2, in more than half the patients, age was the sole indication for ^{131}I . Although certain patients fulfilled more than one criterion only the major indication is tabulated in this figure.

Table 2 details the relationship between three dosage levels and the thyroid status of the patient.

Thirty-one percent of the patients who received a single dose of 4 mCi ^{131}I were euthyroid within 1 year, whereas 36% were euthyroid in the same period after 6 mCi. It is noteworthy that with both these

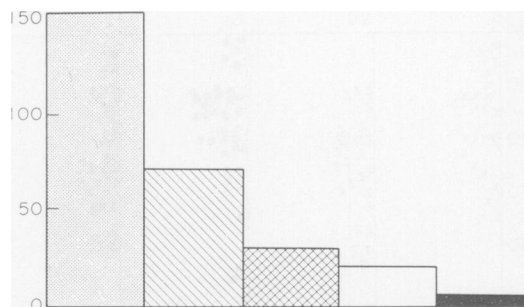


FIG. 2. Indications for ^{131}I therapy. Stippled column, age only; diagonally hatched column, cardiac disease; diagonally cross-hatched column, recurrence after surgery; open column, failure of medical treatment; closed column, miscellaneous.

dose schedules the percentage of patients who were adequately controlled within the first year was similar to the percentage requiring retreatment.

When 6 mCi were administered, 21% of patients were recorded as being hypothyroid at some stage during follow-up, as opposed to only 13% with 4 mCi. This hypothyroidism, as will be discussed later, may not necessarily be permanent.

It appears that more patients remained thyrotoxic after 4 mCi, but some of this group have received their ^{131}I only recently (Table 2, column 4).

Several patients have been referred from peripheral areas and their current thyroid status is unknown. Fifteen patients received an initial dose of greater than 6 mCi for various associated diseases, the most common being cardiac. The follow-up of this group is very poor as several of these patients have died. The ^{131}I uptakes of sixty-three of the seventy-eight (80.8%) patients who received more than one therapeutic dose are shown in Fig. 3. The range of uptakes in the two groups did not differ, so that comparisons are valid (Fig. 3).

Table 3 reflects the number of doses administered to the seventy-eight patients who needed retreatment. The majority required only two doses for control.

TABLE 2. Results of treatment of thyrotoxicosis with three dosage levels of ^{131}I

Dosage level (mCi)	No. of patients	Patients euthyroid (1 year after administration of a single dose of ^{131}I)	Patients hypothyroid (not necessarily permanent)	Patients still thyrotoxic	Unknown thyroid status	Patients retreated with ^{131}I
4	108 (100%)	34 (31%)	14 (13%)	12 (11%)	17 (16%)	31 (29%)
6	139 (100%)	50 (36%)	29 (21%)	3 (2%)	13 (9%)	44 (32%)
>6	15 (100%)	8 (53%)	—	—	4 (27%)	3 (20%)
Total	262 (100%)	92 (35%)	43 (16%)	15 (6%)	34 (13%)	78 (30%)

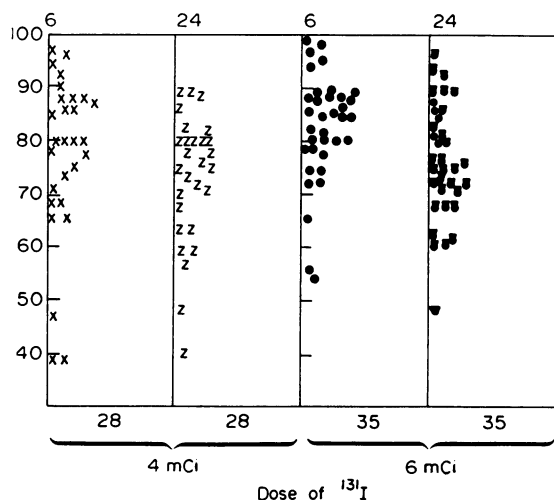


FIG. 3. 6- and 24-hr ^{131}I uptakes of the retreated group (percentage ^{131}I uptakes are represented on the ordinate).

TABLE 3.

Number of patients	Number of doses (^{131}I)
55	2
20	3
1	4
0	5
1	6
1	7

The mean time interval between doses was 10.8 months, with the majority receiving the next dose after 6 months. Two patients each received a total of 46 mCi administered as six and seven doses respectively. Both patients had nodular thyromegaly and 6-hr uptakes in the region of 90%. It is interesting to note that one of these patients, followed subsequently for 3 years, has remained euthyroid; the other has received therapy too recently to assess.

Despite repeated doses, nine patients remained toxic for a period in excess of 3 years, controlled on antithyroid medication (Fig. 4).

Discussion

The efficacy and simplicity of radio-iodine administration with the incidental benefits of out-patient treatment, has made this the therapy of choice in a large number of clinical centres. However, the 30-year period during which it has been available is barely sufficient to evaluate its particular hazards.

In our series, the commonest indication for ^{131}I therapy was the age of presentation. In the selection of patients the policy of our clinic is to treat only those 40 years and over. This form of therapy was

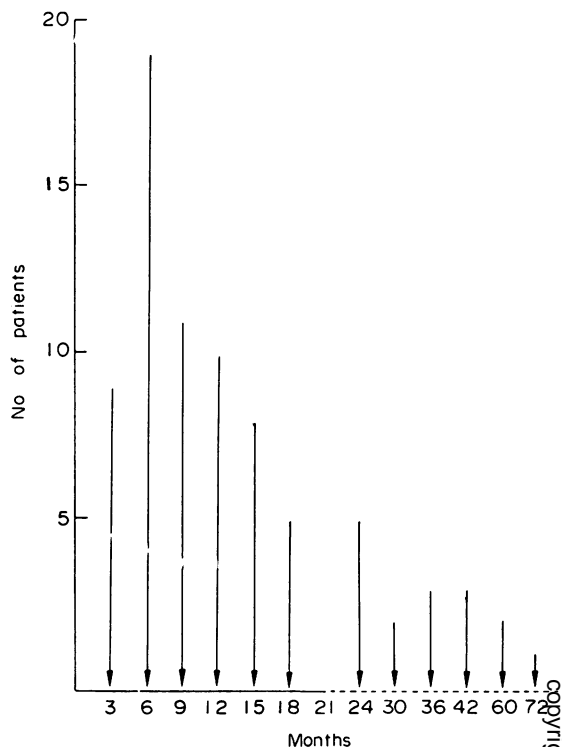


FIG. 4. Minimum symptomatic period of hyperthyroidism in patients requiring retreatment with ^{131}I (average period 15 months).

administered to patients below 40 years for the following reasons—poor operative risk, especially due to associated decompensated cardiac disease; recurrence of thyrotoxicosis following previous surgery; failure to respond to conventional medical treatment, i.e. carbimazole and beta-blocking agents; and an unrelated medical condition such as psychosis.

Until 10 years ago very few patients below the age of 40 were treated with radio-iodine. The fear of malignancy, viz. local in the thyroid gland or leukaemia, and genetic damage were the limiting factors, but this has not been substantiated. Hayek, Chapman & Crawford (1970) found neither carcinoma nor congenital abnormalities in the offspring of thirty patients treated between the ages of 8 and 18 years, after following them up for a mean period of 9.2 years. In fact, thyroidal cancer has only been reported in two cases out of a total of 177 young thyrotoxicos (Sheline *et al.*, 1962; Karlan, Pollock & Snyder, 1964). No case of leukaemia after ^{131}I treatment in children has been reported (Hayek *et al.*, 1970). Nevertheless, it is still advised that radio-iodine should not yet replace thyroidectomy or antithyroid medication in the young age group.

Recurrence of hyperthyroidism after subtotal thyroidectomy is best treated with radio-iodine. Besides the considerable technical risk of damage to the recurrent laryngeal nerves and parathyroid glands, the incidence of a further recurrence after a second operation (McLarty *et al.*, 1969; Hedley *et al.*, 1970), or after a full course of antithyroid medication (Solomon *et al.*, 1953) is high.

Twenty-seven of the thirty-six patients who developed recurrent thyrotoxicosis after thyroidectomy, previously reported from this unit (Baker & Pimstone, 1971) are included in the present series. This experience confirms that a second operation is rarely justified.

The preponderance of thyrotoxicosis in females in our series (8 : 1) is in keeping with the usual incidence.

The difference encountered amongst the ethnic groups is extremely striking, the vast majority of our patients being white and coloured. African patients formed only 0.8% of our series (Table 1). The rarity of thyrotoxicosis among indigenous African populations has been well documented (Dancaster, 1970; Patel, 1962; Taylor, 1968). This phenomenon has been attributed to a possible immunological abnormality in these patients (Dancaster, 1970; Taylor, 1968), and this was confirmed by the work of McGill (1971).

Treatment of thyrotoxicosis with radio-iodine has been marred by the fact that hypothyroidism appears to be inevitable in a certain proportion of patients so treated. Attention has thus focussed on finding a dose that would exploit the advantages of this therapy while decreasing the risk of hypothyroidism. To this end low ^{131}I dosage has been recommended (Green & Wilson, 1964; Hagen, Ouellette & Chapman, 1961). However, the use of a low radiation dose has resulted in a higher proportion of patients who remained hyperthyroid after treatment (Smith & Wilson, 1967). Other therapeutic regimens have utilized the 24-hr ^{131}I uptake in calculating the dose requirement (Goolden & Fraser, 1969) to try and avoid hypothyroidism.

A low-energy isotope, ^{125}I , has been used in order to circumvent the difficulties encountered with ^{131}I . Theoretically post-irradiation hypothyroidism should be negligible, but experience with this isotope has not been encouraging (McDougal *et al.*, 1970).

Certain clinical situations, e.g. severe cardiac disease, require more prompt and decisive control of the hyperthyroidism. This is usually achieved by administration of large doses of ^{131}I (Hamburger *et al.*, 1964). In our series, fifteen cases had cardiac disease severe enough to warrant a dose in excess of 6 mCi (see Table 3).

Various workers (Seed & Jaffe, 1953; McGirr, Thompson & Murray, 1964; Sheline & Miller, 1959)

have shown that toxic autonomous nodular goitres and toxic multinodular goitres require a larger initial dose for adequate control. This was seen in our two patients with multinodular toxic goitres who had each received 46 mCi ^{131}I . Furthermore, the irregular distribution of radio-iodine in a toxic multinodular goitre may protect the patient against hypothyroidism when a single dose is given (Hamburger, Kadian & Rossin, 1967).

Gland size is used in several units as one of the indices of dose requirement, although it is well known that the determination of gland volume by palpation is subject to error and that the larger the gland the less accurate the estimate. A large thyroid gland appears to require larger doses of radio-iodine for restitution of euthyroidism. Goolden & Fraser (1969) have advocated a sliding scale in which the dose level was determined by gland size.

Prior to 1968, 6 mCi of ^{131}I was the standard dose administered to all our thyrotoxic patients requiring this form of therapy. Since then, 4 mCi has been employed irrespective of gland size and nodularity. Adequate documentation of gland characteristics was not always available and its relationship to the dose administered could thus not be meaningfully interpreted in this retrospective study.

Despite the various manoeuvres employed to achieve optimal results, these often fall short because the radiation sensitivity of the particular gland, and the recognized tendency of radio-iodine to have a patchy distribution within the gland cannot be assessed clinically (Hagen, 1968).

Complications

Table 4 lists the possible complications of radio-iodine therapy.

Initial reactions

Within 10 days a local, usually mild, reaction may set in with swelling and tenderness of the thyroid gland. In addition, exacerbation of thyrotoxic symptoms may occur. Two of our patients were noted to develop aggravation of their clinical state within this period, one with impending thyroid crisis (see Table 5).

Thyroid storm or crisis under these circumstances is thought to be due to liberation of preformed, stored thyroid hormone from a radiation-damaged gland. Treatment with beta-blocking agents, iodide and steroids may be necessary.

Prophylactic depletion of intrathyroidal hormone by antithyroid drugs has been advocated in patients with severe cardiac decompensation prior to ^{131}I therapy (Hamburger & Sukhamoy, 1968). We have not employed this form of 'pretreatment' routinely in our cardiac patients, but have maintained them on diuretics, digoxin and, in selected cases, the beta-

TABLE 4. Possible complications of radio-iodine therapy

(a) Initial reactions	Swelling of thyroid gland Aggravation of hyperthyroidism	
	Thyroid storm	CVS mental
(b) Late complications	Hypothyroidism	temporary permanent
	Nodulation of thyroid Induction of thyroid carcinoma Induction of leukaemia Genetic damage Disturbance in calcium metabolism	
	Hypoparathyroidism	temporary permanent
	Recurrence of hyperthyroidism	

Other rare toxic reactions include arthralgia, arthritis, thyroiditis, parotitis, myasthenia, and transient slight hair loss.

blocking agent practolol (Epstein & Pimstone, 1971). Thus, intensive antidiabetic-failure therapy has prevented deterioration of existing cardiac disease which may occur following radio-iodine. The addition of carbimazole 4 weeks after ^{131}I administration has controlled the hyperthyroidism until adequate radiation effect has occurred.

Late complications

The appearance of hypothyroidism in patients treated with radio-iodine is generally considered to be due to a number of factors, *viz.* radiation-induced thrombosis and obliteration of small blood vessels, initiation or aggravation of an auto-immune process (Stanbury & de Groot, 1964), or radiation damage to the replicative capacity of the thyroid cell (Greig, 1965).

Although hypothyroidism is usually permanent, that developing shortly after radio-iodine therapy is sometimes transient. Indices of thyroid function after this form of treatment usually show a close correlation with the clinical evaluation, but occasionally the standard tests may be misleading. It is well recorded that despite clinical euthyroidism, the PBI and serum thyroxine concentration may drop to hypothyroid levels soon after therapy (Chapman *et al.*, 1954). In this phase of temporary hypothyroidism substitution therapy should be withheld or used on a short-term basis for symptomatic cases until repeat tests are performed 3 months later. In our series the incidence of hypothyroidism includes both the temporary and permanent state. As expected this complications more common with 6 mCi.

Most patients become euthyroid within 6 months after receiving ^{131}I . At this stage thyroid status should be re-assessed. Those patients who are still mildly toxic may be tided over with antithyroid medication. Those severely toxic may require further radio-iodine therapy. In this manner it is hoped to reduce the incidence of hypothyroidism to a minimum. In the majority of our retreated patients 6 months had elapsed before administration of the next dose.

Nodulation of the thyroid as a late complication of radio-iodine therapy was found in 8% of 177 young thyrotoxic patients reported in the literature (Hayek *et al.*, 1970).

The possible carcinogenic and genetic hazards have been mentioned previously.

Although overt hypoparathyroidism is a very rare complication of ^{131}I therapy (Tighe, 1952; Eipe *et al.*, 1968; Orme & Conolly, 1971), Adams & Chalmers (1965) found that 10% of patients so treated were unable to restore serum calcium levels to normal following intravenous infusion of ethylene diaminetetracetic acid (EDTA). We have not

TABLE 5. ^{131}I -aggravation of thyrotoxic symptoms in two patients

Patient	Clinical features	Thyro-megaly	Dose of ^{131}I (mCi)	Time of onset post ^{131}I (days)	Features of reaction	Treatment	Result
J.H. 68 years	Apathetic	—	4	4	Withdrawn, hallucinated, psychotic	Lugol's iodine, propranolol, carbimazole	Improved ↓ Apathetic ↓ Normality
A.P. 55 years	Nervous, irritable, loss of weight, personality change, paranoid	Diffuse enlargement	6	4-5	Impending thyroid crisis, pyrexia 101°F, tachycardia 140/min, disorientated, increased confusion	Hydrocortisone, Lugol's iodine carbimazole	Thyroidectomy, uneventful postop. course

encountered clinical hypoparathyroidism nor have we investigated our patients for reduced parathyroid reserve.

Recurrence of hyperthyroidism once normal thyroid function has been maintained for 6 months, is extremely rare (Chapman & Maloof, 1955). We have not encountered this in our series.

We conclude from our experience of 262 patients treated for thyrotoxicosis with either 4 mCi or 6 mCi of ^{131}I , that 4 mCi is probably as effective as 6 mCi in achieving euthyroidism. The incidence of hypothyroidism appears to be less with the 4 mCi dose. A time period of 6 months is recommended before repeat administration.

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