BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 10 1959

TREATMENT OF THYROTOXICOSIS WITH ^{131}I

A REVIEW OF 500 CASES

BY

G. W. BLOMFIELD, M.B., F.R.C.S., F.F.R., M.R.C.O.G. H. ECKERT, M.B., Ch.B.

MONICA FISHER, B.Sc. H. MILLER, M.A., Ph.D., F.Inst.P.

D. S. MUNRO, M.D., M.R.C.P. AND G. M. WILSON, M.D., F.R.C.P.

Department of Pharmacology and Therapeutics, University of Sheffield, and Sheffield National Centre for Radiotherapy

The treatment of thyrotoxicosis with ^{131}I is now a well-established procedure. In the sixteen years since Hertz and Roberts (1942) and Hamilton and Lawrence (1942) introduced therapy with radioactive iodine, the use of this technique has spread enormously, and ^{131}I is certainly the radioactive isotope most extensively used in clinical practice. As a result, much published work has accumulated on the subject. As early as 1953 Seed and Jaffé analysed 1,720 cases from the collective results of all papers published up to April, 1952. These came from many centres in North America and Europe, and included many criteria for the selection of cases and different methods of treatment. The reports which have appeared vary from the study of small groups of patients treated by detailed techniques (Bauer and Blahd, 1957) to reports on the results obtained from the use of simple methods involving the minimum of equipment and measurement (Macgregor, 1957).

The techniques used in an endeavour to obtain satisfactory results differ greatly. Fraser *et al.* (1954) have combined a single-dose method with antithyroid drug and thyroxine premedication. On the other hand, Williams *et al.* (1949) have chosen to give small and repeated doses of the isotope. In spite of this wide variation there is little evidence that there is much difference in the final outcome. It is clear that some of the factors influencing the response of the thyroid to ^{131}I therapy are still little understood and remain uncontrolled. The difficulties and uncertainties with this form of treatment have been reviewed by Pochin (1958).

The present report describes the results obtained in 500 thyrotoxic patients treated with ^{131}I in Sheffield. It is thus an expansion of the two previous reports from this centre, in which the results in 20 and 140 patients were recorded (Blomfield *et al.*, 1951, 1955). The much larger number of patients in the present review permits a fuller statistical analysis of some of the factors influencing the final result.

Selection of Patients

The criteria for the choice of patients for ^{131}I therapy have remained constant throughout the period of study. The following groups have been considered suitable. (1) Patients over 45 years of age. (2) Younger patients in whom there is associated disease, particularly cardio-vascular complications, probably reducing the life expectancy to less than 20 years. (3) Patients who have relapsed following thyroidectomy. (4) Patients who have not remained euthyroid following a course of treatment with antithyroid drugs or have shown toxic reactions to these drugs and who are considered unsuitable for or have refused partial thyroidectomy.

Pregnancy is a complete contraindication for this form of treatment. The presence of tracheal deviation or compression associated with thyroid enlargement is not now regarded as a contraindication to ^{131}I therapy. Cases with this complication are described below.

Methods of Treatment

Dose of ^{131}I

The intention has been to deliver a dose to the thyroid in the region of 7,000 rads in the average uncomplicated case of thyrotoxicosis. A slightly greater dose has been chosen for patients with severe hyperthyroidism, nodular glands, or disabling cardiac complications. It has been thought advisable to give slightly smaller doses in the treatment of post-operative recurrences and milder cases with small smooth glands. However, in practice, accurate prediction of the dose is difficult and great accuracy cannot be achieved in delivering the prescribed dose.

The calculation of the number of millicuries of ^{131}I to be given to the patient to provide the intended rad dose to the thyroid depends on the size of the gland and the proportion of the dose taken up by and retained in the gland. The following formula, described in the earlier report (Blomfield *et al.*, 1955), has been used:

$$\text{Expected rads/mc.} = \frac{820 \times \text{48-hour \% uptake in preliminary tracer study}}{\text{Estimated gland weight in g.}}$$

In all cases a preliminary tracer test with ^{131}I was carried out shortly before ^{131}I therapy, and the uptake at 48 hours was measured as a forecast of the anticipated uptake of the therapy dose.

In estimating the gland weight, which is an obvious source of error, we have relied principally on palpation by several experienced observers, and the mean estimate of mass has been taken for the purpose of treatment. An attempt has been made to measure the size of the thyroid by counting antero-posteriorly and laterally

with a heavily collimated instrument (Blomfield *et al.*, 1953). In 21 experiments estimates of the size of various containers resembling in shape the thyroid gland and placed in a model neck were made with a scintillation counter. The volume of the active material was known accurately. In the small models up to 50 ml. the method gave an overestimate by as much as 50% or more. Above 50 ml. the scintillation method was accurate within the range of ±25%.

The actual irradiation dose received by the thyroid gland has been estimated retrospectively by daily measurements of the ^{131}I content of the thyroid gland over the ensuing eight days.

The following formula has been employed:

$$\text{Dose in rads} = \frac{164 \times T \times U \times M}{W}$$

where T is the effective half-life of the isotope in the thyroid, U the estimated peak percentage uptake of the therapy dose, M the dose in millicuries, and W the estimated thyroid mass in grammes.

Follow-up of Treated Cases.—The patients were seen at the thyroid clinic monthly for two months after therapy and thereafter at increasing intervals, provided satisfactory progress was made. The final assessment was made on clinical grounds, but in all cases of doubt confirmation was sought from further ^{131}I tracer tests and measurements of basal metabolic rate and serum cholesterol.

Repetition of ^{131}I Therapy.—A further therapeutic dose of ^{131}I was not given until at least three months had elapsed after the first dose. So long as any improvement was occurring a repetition of treatment was not considered. Persistent hyperthyroidism which remained stationary or became more severe after that interval indicated the need for further treatment with ^{131}I. The second dose was calculated on the same general principles as the first, but as some improvement had almost invariably taken place a slightly lower dose in the region of 5,000 to 7,000 rads was usually planned on a second or later occasion.

Results

The results of the treatment of thyrotoxicosis with ^{131}I in 500 patients since January, 1949, are shown in Table I. There are 398 women and 102 men, giving a female : male ratio of almost 4:1. The mean age of the group is 50.9 years, the distribution being shown in Fig. 1. The last patient first reported for treatment in February, 1957, and the results are based on a review completed in March, 1958. At that time in the whole group 80% had become euthyroid and 12% permanently hypothyroid; 2% were still hyperthyroid in varying degree, 4% had died before final assessment was possible, and 2% could not be traced.

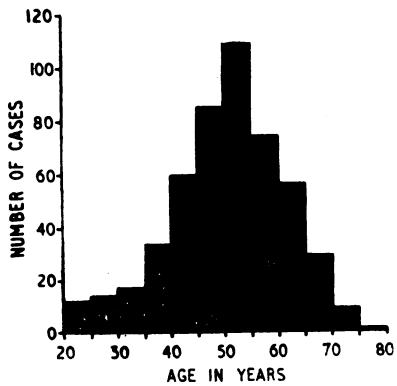


FIG. 1.—Age distribution of the 500 treated cases at the time of the first treatment.

The patients have been grouped on the basis of the clinical features presented by the thyroid gland. All post-operative recurrences of thyrotoxicosis have been considered separately, even though nodularity or diffuse enlargement developed after the operation. The remainder have been divided into three groups—namely, those showing no abnormality, those showing diffuse enlargement, and those with nodularity. No attempt has been made to place the solitary nodule or adenoma in a special category, as often this clinical finding is not confirmed by later pathological examination, which reveals many smaller nodules impalpable in life (Mortensen *et al.*, 1955). In all patients with thyroid enlargement, whether diffuse or nodular, definite shrinkage occurred after treatment. This ensured a good cosmetic result in all patients even though gross enlargement was present initially (Fig. 2). Improvement in exophthalmos and lid retraction was also the rule in the overwhelming majority of cases.

Euthyroid Patients

The proportion becoming euthyroid after a single dose is similar in all clinical groups and is in the narrow range 57–60%. In this group without palpable abnormality in the thyroid fewer required a second treatment and more became hypothyroid.

TABLE I.—*Results of Treatment with ^{131}I. Minimum Follow-up, One Year*

Clinical Group	Total in Group	% of Total	Euthyroid			Hypothyroid			Died before Euthyroid, still Hyperthyroid or Untraced			Age (Mean ±S.E.) (years)	Mean of First Dose (mc. ±S.E.)	Mean Irradiation to Thyroid from First Dose (Kilorads ±S.E.)
			One Dose	Two or More Doses	Total	One Dose	Two or More Doses	Total	One Dose	Two or More Doses	Total			
Impalpable gland or no recorded abnormality	85	17·0	50	11	61	12	3	15	5	4	9	55·1 ±0·98	6·9 ±0·34	6·8 ±0·23
Percentage of group			(59)	(13)	(71·8)	(14)	(4)	(17·6)	(6)	(5)	(10·6)			
Diffuse enlargement	192	38·4	116	46	162	16	3	19	4	7	11	48·4 ±0·74	8·6 ±0·33	7·0 ±0·17
Percentage of group			(60)	(24)	(84·4)	(8)	(2)	(9·9)	(2)	(4)	(5·7)			
Nodular enlargement	162	32·4	93	34	127	14	2	16	11	8	19	54·6 ±0·76	9·2 ±0·36	7·3 ±0·17
Percentage of group			(57)	(21)	(78·4)	(9)	(1)	(9·9)	(7)	(5)	(11·7)			
Post-operative	61	12·2	36	13	49	7	3	10	1	1	2	43·2 ±1·30	7·2 ±0·57	6·4 ±0·30
Percentage of group			(59)	(21)	(80·3)	(11)	(5)	(16·4)	(2)	(2)	(3·3)			
Total	500	100	295	104	399	49	11	60	21	20	41	50·9 ±0·48	8·3 ±0·20	7·0 ±0·10
Percentage of group			(59)	(21)	(79·8)	(10)	(2)	(12·0)	(4)	(4)	(8·2)			

The rate of response to treatment is important (Fig. 3). Out of the 295 patients requiring only a single dose, 227 (77% of the total) became euthyroid within six months and a further 52 (18%) within 12 months. Nine, who eventually became euthyroid, were unplaced owing to erratic attendance for assessment. Of the 104 patients who required two or more doses, 77 required two doses, 20 three doses, 6 four doses, and 1 five doses. This last patient was particularly resistant to therapy, and she had previously been treated by partial thyroidectomy and methylthiouracil. The details are as follows.

Case 1: Gross Resistance to ^{131}I Therapy.—A girl, first seen at the age of 19, complained of progressive enlargement of the thyroid and of features typical of hyperthyroidism. Partial thyroidectomy was performed, with improvement. Within six months, however, her symptoms returned. Methylthiouracil therapy was begun, but, despite continuous treatment for a year, she failed to gain weight and remained hyperthyroid. At this time her pulse was 132 a minute, sleeping pulse 90/min.; B.M.R. +50%; the thyroid was grossly enlarged. *X*-ray examination of the thoracic inlet showed considerable tracheal narrowing; radioactive iodine uptake studies confirmed a marked degree of thyrotoxicosis (4-hour uptake 76%, 48-hour uptake 50%, 48-hour plasma 3.22% per litre, 48-hour protein-bound ^{131}I 2.67% per litre).

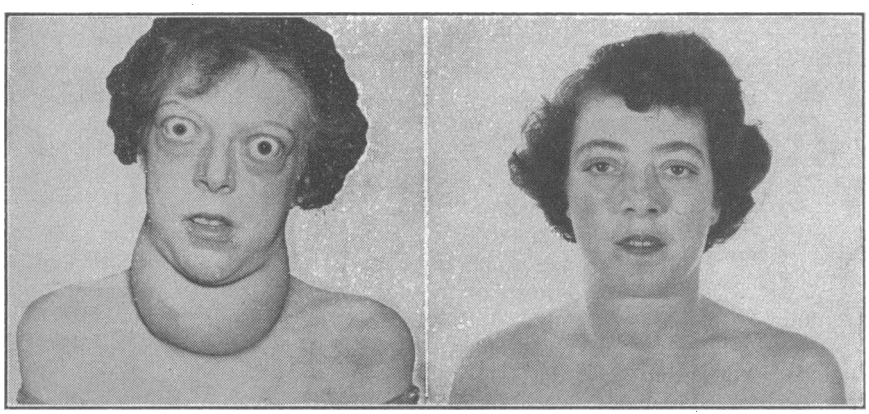


FIG. 2.—Clinical result of radio-iodine therapy. Left: Before treatment. Right: After treatment, showing shrinkage of gland and improvement of exophthalmos.

Although she was only 22 years of age at this time, it was decided to treat her with radioactive iodine in view of the severity of her condition and her resistance to other forms of treatment. She was given 11.2 mc. of ^{131}I, delivering 6,600 rads to the gland. She remained grossly hyperthyroid, and three months later a further 28.8 mc. (7,000 rads) was given. The improvement was only slight, and four months after this second dose another 18.0 mc. (4,000 rads) was given.

She then began to improve, but two further doses were required at eight months and 16 months after the third treatment (8.5 mc. (9,400 rads) and 4.2 mc. (6,200 rads) respectively). In all, she had received 70.7 mc. (33,200 rads) in five doses over a period of two years. When euthyroid, her gland, which was grossly enlarged before receiving ^{131}I, was no longer palpable and there was no evidence of tracheal compression.

Four years later she had a full-term normal delivery of a female child, who at the time of writing was 8 months old and entirely well.

Twenty-seven patients relapsed after an apparently successful first treatment. They had been considered euthyroid within six months of the administration of the therapy dose, but a few months later were again clearly hyperthyroid. Twenty-one became euthyroid after further doses and have remained so, two have become hypothyroid after a second dose, and four are still hyperthyroid, having recently been re-treated. None relapsed at a longer interval than one year after treatment.

Improvement may continue for many months after administration of a therapeutic dose of ^{131}I. The following case illustrates the importance of delaying re-treatment, even in patients with clinical and laboratory evidence of continuing hyperthyroidism, so long as there is any sign of improvement still occurring.

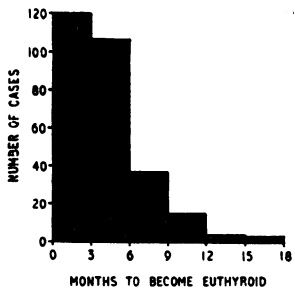


FIG. 3.—Time taken to become euthyroid following a single therapeutic dose of ^{131}I.

Case 2: Late Euthyroidism with a Single Dose.—A woman aged 65 had been treated for four years with intermittent courses of methylthiouracil with some improvement, but had never become completely euthyroid. Her main complaints were of swelling of the neck, loss of weight, and palpitations. On examination her pulse rate was 102/min., regular; her hands were hot and moist, with a fine tremor; the thyroid was enlarged (85 g.) and nodular; and a bruit was heard. There were no abnormal eye signs. She weighed 46.8 kg. (103 lb.) and the radioactive iodine tracer study was as follows: 4-hour uptake 55%, 48-hour uptake 57%, 48-hour plasma level 1.98% per litre, 48-hour P.B. ^{131}I 1.52% per litre. She was treated with ^{131}I (15.5 mc., 6,000 rads), but the response was slight.

Six months after therapy she weighed 46.4 kg. (102 lb.) and was still clinically thyrotoxic; pulse 120/min.; hands warm and moist, with a marked tremor; thyroid only just palpable. A repeat diagnostic tracer confirmed continuing hyperthyroidism (4-hour uptake 71.5%, 48-hour uptake 57.8%, 48-hour plasma 3.15% per litre, 48-hour P.B. ^{131}I 3.01% per litre).

She was requested to attend for further treatment, but failed to report and was not seen for a year. She attended again 18 months after therapy; her weight was then 52.7 kg. (116 lb.), pulse 100/min., and she was clinically mildly hyperthyroid. Repeat tracer study confirmed this (4-hour uptake 43.1%, 48-hour uptake 54.8%, plasma 1.34% per litre, P.B. ^{131}I 1.2% per litre). In view of her gain in weight it was decided to delay re-treatment, and on further review four months later her weight had risen to 55.9 kg. (123 lb.) and she was euthyroid; the pulse was 78 and regular, and she felt quite well. Six months later she had remained euthyroid.

The most valuable index to progress is a regular weight chart. If the weight is rising or steady the patient will often become euthyroid without further therapy. Although attention has been drawn to some cases in which the return to health was delayed it should be emphasized that in the majority this is achieved within four to six months. Furthermore, even in those not finally becoming euthyroid with one treatment some improvement always results and is noticeable within three or four weeks.

Hypothyroid Patients

The greatest incidence of hypothyroidism was seen in the group without palpable abnormality of the thyroid

gland. It was also above the average in the post-operative group. The patients with diffusely enlarged or nodular thyroids were apparently less liable to develop this complication ($P<0.05$). Hypothyroidism is usually manifest within six months of treatment (Fig. 4), but occasional cases have continued to appear. So far the longest interval has been 5½ years after therapy. In assessing results it is important to recognize this occasional late development of hypothyroidism. The following illustrative case is presented.

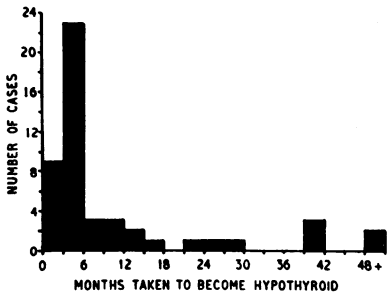


FIG. 4.—Time taken to become hypothyroid following a single therapeutic dose of ^{131}I.

Case 3: Late Myxoedema with a Small ^{131}I Dose. — A 23-year-old woman noticed prominence of her eyes and progressive enlargement of her neck; she complained of palpitations, excessive sweating, dyspnoea on exertion, nervousness, and irritability. On examination she had hot, moist skin; pulse rate 108/min. and regular; a diffusely enlarged thyroid; exophthalmos, lid retraction, and lid lag. She was treated with methylthiouracil for one year, but failed to improve, and partial thyroidectomy was carried out.

After the operation she remained well for six years, but at the age of 30 her symptoms recurred and she began to lose weight. On examination at this time she was obviously thyrotoxic and the thyroid was diffusely enlarged (estimated at 50 g.). Radio-iodine uptake study confirmed the diagnosis (uptake at 4 hours 65%, 48-hours 40.0%, 48-hour plasma activity 4.9% per litre, P.B. ^{131}I 3.8% per litre).

She was treated with ^{131}I, being given 7.8 mc., intended to deliver 6,000 rads to the gland. Retrospective estimation, however, revealed an actual dosage of only 2,500 rads due to an unduly short half-life of the isotope in the gland (1.4 days). The uptakes of the therapy dose agreed reasonably well with those of the tracer dose, being 62.5% at peak and 30% at 48 hours.

Despite the low radiation dosage received by the gland, she responded well, and eight months after treatment was considered euthyroid. Eighteen months after treatment she had a miscarriage, which may have been an early indication of a mild degree of hypothyroidism (King and Herring, 1939), although she was clinically euthyroid.

She was seen at regular intervals at the follow-up clinic, and three years after her radio-iodine therapy she complained of feeling cold and tired, of difficulty in remembering everyday events, and of a dry skin.

On examination her voice was gruff, the skin cold, dry, and scaly, the hair thin, and facies hypothyroid. Investigations showed: B.M.R. −23; serum cholesterol, 400 mg. per 100 ml.; E.C.G., low voltage with flattened T waves in all leads; 4-hour uptake of radio-iodine 4.0%, 48-hour uptake 4.7%.

She responded well to treatment with L-thyroxine sodium.

Hypothyroidism appearing within a few months of therapy may be transient. Several patients appear to pass through a hypothyroid phase in the period of two to three months after administration of ^{131}I and then recover spontaneously. The following patient illustrates this sequence of events.

Case 4: Temporary Myxoedema Following ^{131}I Therapy. —A man aged 57 complained of protrusion of the eyes for 10 months, associated with nervousness, excessive sweating, loss of weight, and palpitations. On examination his skin was warm and moist and there was a fine tremor of the outstretched hands. He had conspicuous exophthalmos and lid retraction. The thyroid gland was diffusely enlarged (estimated at 65 g.). He weighed 63.6 kg. (140 lb.).

A radioactive iodine diagnostic study was performed with the following results: uptake at 4 hours 83.5%, 48 hours 57.9%, 48-hour plasma activity 2.59% per litre, P.B. ^{131}I 2.34% per litre.

He was treated with 10 mc. of ^{131}I (6,000 rads) and improved rapidly, being euthyroid two months later—weight 74.1 kg. (163 lb.). In another month, however, he had developed a gruff voice, cold dry skin, and myxoedematous facies. He complained of feeling cold and of being slow in reaction and constipated. An E.C.G. showed low-voltage and flattened T waves in all leads; the serum cholesterol was 500 mg. per 100 ml. His weight had risen to 80 kg. (176 lb.).

Treatment was withheld and he slowly improved during the next six months, his E.C.G. reverting to normal and cholesterol falling to 320 mg. per 100 ml.

He has since been followed for another year, but has remained euthyroid, and his weight has stabilized at 75.9 kg. (167 lb.).

In view of the temporary nature of hypothyroidism in some patients, it is not our practice to institute treatment with thyroxine until observation has confirmed the permanent nature of the condition.

Factors Influencing the Response to ^{131}I Therapy

The intention is to restore health with a single therapeutic dose of ^{131}I, but in practice this has been achieved in only 59% of the patients. In the remaining 41% the reaction to the first dose has been either inadequate or excessive. Various factors that may influence the effect of a therapeutic dose of ^{131}I have been considered.

Age.—The response to the first therapeutic dose of ^{131}I in relation to the age of the patients has been studied. In the range between 20 and 80 years there is no evidence that there is any change in the sensitivity of the thyroid gland to irradiation.

Thyroid Gland Mass

The size of the thyroid is important in determining the dose of ^{131}I that is to be given. In the present work it has been estimated by palpation in all patients, and in 204 cases it has also been determined by scanning in two planes after a tracer dose. The palpation and scanning estimates differed by more than 20% in 80 patients, and in them the dose has been mainly based on the latter method. In the rest of the cases the palpation estimate only was available in deciding the therapy dose. An analysis of the response to the first treatment in relation to the estimated weight of the thyroid gland is shown in Table II. The percentage of patients still hyperthyroid after the first treatment rises with increasing gland mass and the proportion becoming hypothyroid falls. This relationship is statistically significant ($P<0.02$).

TABLE II.—*Relationship Between Clinical Result After First Treatment with ^{131}I and Estimated Gland Mass*

Gland Mass (g.)	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<40	145	96	66·2	18	12·4	31	21·4
41–60	188	108	57·4	20	10·6	60	32·0
61–80	80	44	55·0	7	8·7	29	36·3
81–100	48	30	62·5	3	6·2	15	31·3
101+	39	17	43·5	1	2·6	21	54·0
Total	500	295	59·0	49	9·8	156	31·2

It is difficult to check the accuracy of the estimates of thyroid gland size obtained by palpation, but the results obtained by this method have been compared with those recorded by the physical method in the same patients (Fig. 5). The latter shows a much wider range, and in comparison palpation has overestimated the size of the smaller glands and underestimated the size of

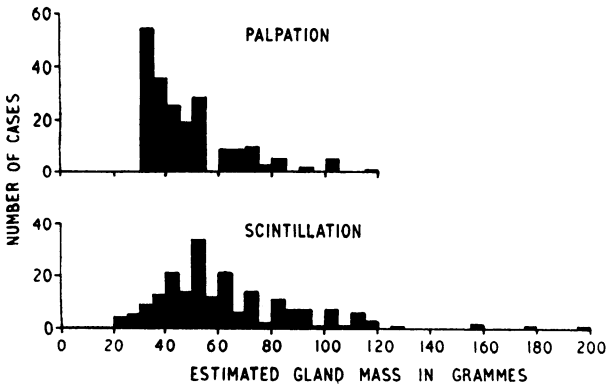


FIG. 5.—Comparison of the estimation of gland mass by palpation and by scintillation techniques.

the larger. In six patients dying within 10 weeks after the therapy dose the weight of the gland measured at necropsy is compared with the estimates made by palpation before treatment (Table III). If it is assumed

TABLE III.—*Comparison Between Palpation Estimates of Gland Mass and Necropsy Weights in Patients Dying Shortly After Therapy*

Patient	Necropsy Weight	Palpation Estimate	Interval Between Therapy and Death
G.B.	26 g.	50 g.	6 days
Z.D.	31 g.	40 g.	6 weeks
A.B.	40 g.	50 g.	10 ,,
O.H.	47 g.	40 g.	17 days
A.H.	130 g.	120 g.	4 ,,
I.G.	210 g.	115 g.	4 weeks

that the size of the gland does not change greatly within the relatively short period between therapy and death, it is again apparent in this series that on palpation the smaller glands have been overestimated in weight and the larger ones underestimated.

Thyroidal Uptake of ^{131}I

The therapy dose of ^{131}I is based on the uptake measured previously with a tracer dose of the isotope. The clinical result has been assessed in relation to this preliminary test (Table IV). In a small group the 48-hour uptake on the tracer test was low, below 40%, and in them the response to treatment was disappointing. The best results were seen in the group with an uptake in the 41–60% range, and there was a slight decline with the higher ranges of uptake.

In calculating the amount of ^{131}I required for treatment, the assumption is made that the uptakes of

TABLE IV.—*Relationship Between Clinical Result After First Treatment with ^{131}I and 48-hour Uptake of Tracer Dose*

*48-hour Uptake %	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<40	28	12	42·9	1	3·6	15	53·6
41–60	165	103	62·4	15	9·1	47	28·5
61–80	269	158	58·7	30	11·1	81	30·2
80+	31	17	54·8	2	6·4	12	38·8

* Not known in seven cases.

the tracer and subsequent therapy doses will be similar. However, there is often a considerable discrepancy between the two measurements. In Fig. 6 the distribution is shown of the differences in these uptakes expressed as a percentage of the tracer uptake at 48 hours. The therapy uptakes on the average are lower than the tracer, and the mean depression of −5.0% is significant ($P<0.001$). The two sets of measurements were made on different counter systems in different laboratories. Cross-checks did not reveal any consistent errors, though some minor fluctuations in sensitivity may occasionally have arisen. However, there are many wide variations in both directions, which cannot be accounted for by physical errors in estimating uptake. Nevertheless, these differences were not associated with definite changes in the clinical results of treatment. An

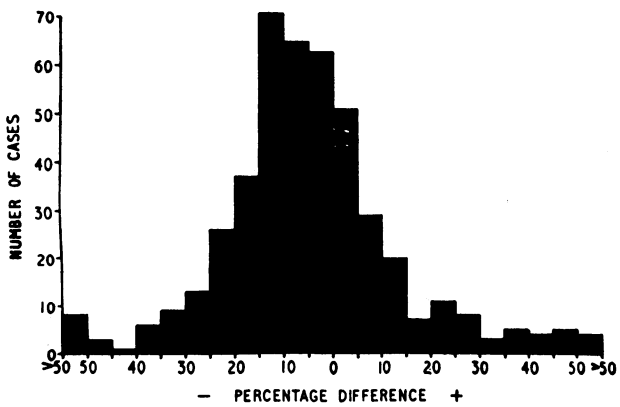


FIG. 6.—Distribution of difference between uptake of therapy dose at 48 hours and uptake of tracer dose at 48 hours as percentage of tracer uptake at 48 hours.

examination of 46 cases in which the discrepancy between the two tests lay outside the range ±12% did not show an increased incidence of hypothyroidism or of necessity for further treatment.

Biological Half-life of ^{131}I in Thyroid

The rate of decrease of radioactivity in the thyroid gland is extremely variable, but despite these considerable differences it is not related closely to the clinical result (Table V). In this group of 420 cases the mean biological half-life was 13.0 days ± 0.25 (S.E.).

TABLE V.—*Relationship Between Clinical Result After First Treatment with ^{131}I and the Biological Half-life of the Therapy Dose in 420 Cases*

*Biological Half-life in Days	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
0–5	75	45	60·0	6	8·0	24	32·0
5·1–10	142	83	58·4	17	12·0	42	29·6
10·1–15	86	51	59·3	8	9·3	27	31·4
15·1–20	45	29	64·4	4	8·9	12	26·7
20·1–25	32	19	59·4	5	15·6	8	25·0
25·1+	40	22	55·0	3	7·5	15	37·5

* In 80 cases the activity in the gland following treatment did not fall away in an exponential fashion. No half-life was therefore calculated.

Irradiation Dose.—The relationship between the amount of ^{131}I in millicuries given to the patient and the clinical result is shown in Table VI. Judging by the percentage becoming euthyroid with one treatment, there is an apparent decrease in response with the larger amounts. These, however, were given to the patients with the bigger glands, and, as previously noted, their mass was probably underestimated.

TABLE VI.—*Relationship Between Clinical Result After First Treatment with ^{131}I and Dose in Millicuries*

*Dose in mc.	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<4	40	27	67·5	3	7·5	10	25·0
4·1–6	139	86	61·9	23	16·5	30	21·6
6·1–8	113	70	61·9	8	7·1	35	31·0
8·1–10	75	44	58·7	6	8·0	25	33·3
10·1–14	73	37	50·6	8	11·0	28	38·4
14·1+	59	30	50·8	1	1·7	28	47·5

* Record of dose in one patient not available.

TABLE VII.—*Relationship Between Clinical Result After First Treatment with ^{131}I and Irradiation to Thyroid in Kilorads*

*Dose to Thyroid in Kilorads	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<4·0	39	19	48·7	4	10·3	16	41·0
4·1–6·0	120	75	62·5	11	9·2	34	28·3
6·1–8·0	191	117	61·3	13	6·8	61	31·9
8·1–10·0	117	66	56·4	16	13·7	35	29·9
10·1+	32	18	56·2	5	15·6	9	28·2

* Record of dose in one patient not available.

The dose to the thyroid gland was calculated retrospectively in kilorads on the basis of the estimated gland mass, estimated peak uptake, and effective half-life, as previously described (Table VII). A small group received a dose to the thyroid of under 4 kilorads, and this was largely due to an unexpectedly short effective half-life in the gland. As might be anticipated, the number becoming euthyroid with this treatment was reduced. However, it should be noted that even at this level 10% became hypothyroid. At the other end of the scale there was a small group receiving over 10 kilorads. This high dose was usually due to a longer effective half-life and higher uptake than was anticipated. The percentage becoming hypothyroid was slightly above the average. Nevertheless, the percentage requiring a second treatment still remained high.

Protein-bound ^{131}I

In a previous review of the first 140 patients in this series a possible correlation between the level of P.B. ^{131}I measured 48 hours after a tracer dose and the clinical result after a therapeutic dose was noted. This relationship has now been examined in the whole series of 500 patients, but has not been confirmed (Table VIII).

TABLE VIII.—*Relationship Between Clinical Result After First Treatment with ^{131}I and 48-hour P.B. ^{131}I from Tracer Dose*

*48-hour P.B.^{131}I	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<0·5	35	19	54·2	5	14·3	11	31·4
0·5–0·99	134	91	67·9	14	10·4	29	21·6
1·0–1·49	145	84	57·9	17	11·7	44	30·3
1·5–1·99	64	33	51·5	6	9·4	25	39·1
2·0+	114	62	54·4	7	6·1	45	39·5

* Eight records not available owing to breakages in centrifuge.

Though there is a possible increase in persistent hyperthyroidism and a decrease in hypothyroidism with rising values of P.B. ^{131}I, this trend does not attain statistical significance.

Previous Treatment with Antithyroid Drugs

Thirty-nine patients had received methylthiouracil, propylthiouracil, or carbimazole within six months before the administration of the therapy dose, 16 of these having received the drug within a month of therapy. No iodide was given after stopping the treatment with antithyroid drugs, and the dose of ^{131}I was calculated in the same way as in the other cases. There was no definite evidence that the previous treatment influenced the response of the thyroid to irradiation. Twenty-one (54%) became euthyroid after a single dose of ^{131}I and six (15%) became hypothyroid. The numbers involved are small, and these results do not differ significantly from those recorded in the patients who had not received previous treatment with antithyroid drugs.

Factors Associated with Failure of First Dose of ^{131}I

The patients who developed hypothyroidism or required further treatment after the first administration of ^{131}I have been studied in relation to a combination of factors that may influence the actual dose to the thyroid gland. A greater dose than anticipated will be delivered to glands in which the therapy uptake exceeds the tracer uptake and in which the biological half-life is longer than usual. However, the majority of cases of hypothyroidism were not associated with these circumstances; conversely, persistent hypothyroidism was not more commonly associated with combined presence of a low uptake and a short biological half-life. Of all the factors that have been studied, the estimated gland mass has been the most important in relation to the clinical result.

Complications of Treatment

Exacerbation of Hyperthyroidism. — Although irradiation of the thyroid may lead to an increased release of iodinated compounds from the gland (Barker, 1955), transient exacerbation of thyrotoxic symptoms has been noted in only two patients. In none of the first 500 patients was any serious disturbance approaching a thyroid crisis observed, but subsequently we have seen one patient in whom a thyroid crisis occurred in the first week following 4.3 mc. of ^{131}I. In a few cases a transient aching in the neck has developed after therapy and persisted for a few days. This has never been severe and has caused only minimal discomfort. In the previous report (Blomfield *et al.*, 1955) two cases of urticaria and one of transient thrombocytopenia were noted, but no further cases have appeared.

Rheumatic Complaints.—Several patients have commented on transient rheumatic pains developing after treatment. These are commonly only mild and seldom require analgesics. A detailed analysis showed that 9% of patients attending at the follow-up clinics had complaints of this type. They probably do not represent a complication of treatment, as the incidence of rheumatic complaints in the general population is at about this level (Kellgren and Lawrence, 1956).

Associated Conditions

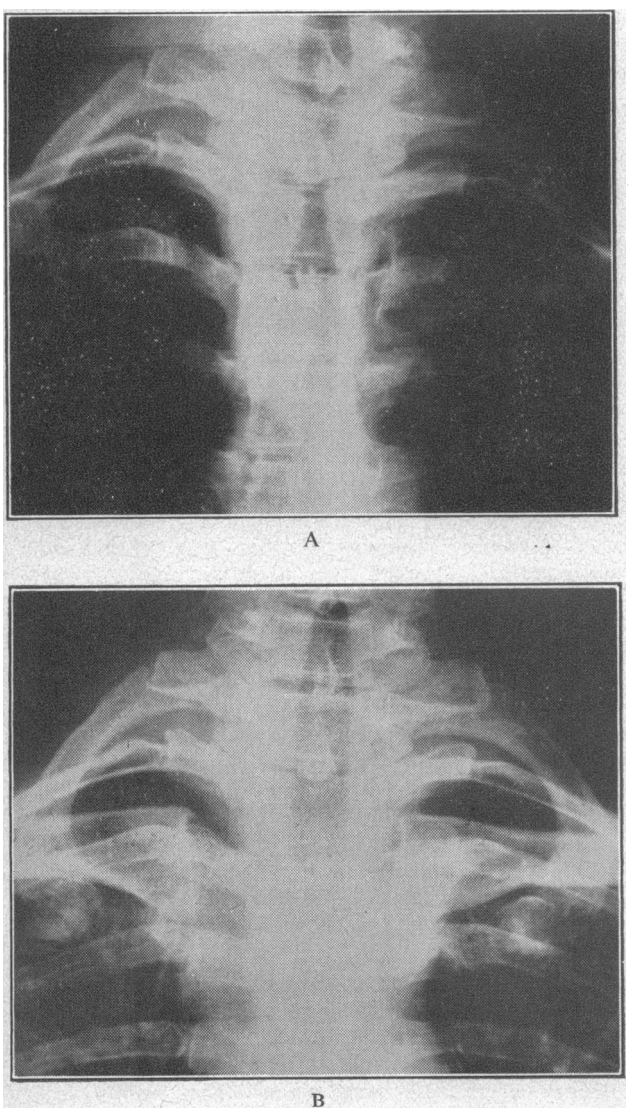
Tracheal Compression and Deviation.—In 78 patients there was definite radiological evidence of distortion of the trachea by an enlarged thyroid gland. The shrinkage of the gland after therapy was associated with a return of the tracheal anatomy to normal. Usually patients with severe tracheal compression have been treated surgically, but five with gross abnormalities in the trachea giving rise to symptoms have been treated with ^{131}I as they were extremely ill. The intention had been to refer them at a later stage for surgical relief of the tracheal distortion, but this was unnecessary, as contraction of the thyroid after radio-iodine therapy

entirely relieved the pressure on the trachea. The following two cases illustrate the relief of tracheal compression and tracheal distortion.

Case 5: Tracheal Compression.—A woman aged 23 complained of swelling of the neck of eight months' duration, associated with loss of weight, nervousness, irritability, excessive sweating, palpitations, and dyspnoea on exertion.

On examination she had warm, moist skin, with a marked tremor of the hands. The thyroid was diffusely enlarged, with a thrill palpable over it. There was conspicuous exophthalmos, lid retraction, and lag. She had early signs of congestive cardiac failure with slight ankle oedema and a raised jugular venous pressure. The B.M.R. estimation was +65% and *x*-ray examination of the thoracic inlet showed some tracheal narrowing.

Treatment was begun with carbimazole, 10 mg. three times daily, in an effort to improve her sufficiently for thyroidectomy. Two months later she was much improved, and, preparatory to surgery, the antithyroid drug was stopped and Lugol's iodine begun. However, her sleeping pulse rate remained high and she became rapidly more thyrotoxic, with a pulse rate of 150 and profuse sweating. She then developed stridor and the signs of a left lower lobe pneumonia. *X*-ray examination now showed the trachea to be narrowed and displaced anteriorly by an enlarged thyroid and confirmed left lower lobe consolidation.



A

B

FIG. 7.—Effect of radio-iodine therapy on tracheal compression. (A) Before therapy; (B) after therapy, showing restoration of the tracheal outline to normal.

On recovery from the pneumonia she was grossly thyrotoxic and her condition was regarded as too serious for operation to be considered. Treatment was instituted with carbimazole, 60 mg. daily, and L-thyroxine sodium, 0.2 mg. daily, in an attempt to prevent further enlargement of the gland. Despite this precaution, the gland size increased and the stridor became alarming. *X*-ray examination of the thoracic inlet showed the trachea to be considerably compressed just above the level of the clavicles (Fig. 7,A).

It was decided to treat her with radioactive iodine, and she was given 14 mc., which delivered 5,500 rads to a gland estimated as 200 g. in weight.

She improved following this, but four months later she was still hyperthyroid, and a further 20 mc. (5,500 rads) was given. She responded well to this second dose, but two and a half years later she required a final dose of 2.6 mc. (5,000 rads) to make her finally euthyroid.

At this time her gland was almost normal in size and her previously severe exophthalmos was considerably improved. A further *x*-ray examination showed the trachea to be midline with no visible compression (Fig. 7,B).

Case 6: Tracheal Compression and Deviation.—A 66-year-old woman complained of loss of weight, excessive sweating, palpitations, and swelling of the neck of six months' duration. She was treated with methylthiouracil and improved greatly, being considered euthyroid 12 months after starting with the drug, which was continued for another six months and then stopped.

She remained well for three years, when she again noticed loss of weight, excessive sweating, and palpitations. At the same time her goitre enlarged, causing a choking sensation, dyspnoea, and recurrent hoarseness.

On examination she was thin and hyperkinetic. There were no eye signs of thyrotoxicosis. Her hands were hot and moist, with a fine tremor. Pulse 90/min., regular; B.P. 190/90. The thyroid was firm and nodular, estimated at 100 g. There was a bruit over the larger left lobe. The trachea was deviated to the right. *X*-ray examination of the thoracic inlet confirmed marked tracheal deviation by an enlarged left lobe of thyroid (Fig. 8,A). A ^{131}I diagnostic tracer study was performed with the following results: 4-hour uptake 62%, 48-hour uptake 68%, plasma at 48 hours 0.22% per litre, 48-hour P.B. ^{131}I 0.18% per litre.

She was given 8.5 mc. of ^{131}I, delivering 7,400 rads to a 100-g. gland.

There was no increase in the tracheal compression symptoms, and she finally became euthyroid and asymptomatic four months after therapy. A follow-up *x*-ray examination of the thoracic inlet showed that the trachea had returned almost to the midline and was of normal configuration (Fig. 8,B).

Cardiac Abnormalities.—In 160 out of the 500 patients the thyrotoxicosis was complicated by the presence of cardiac complications. Congestive cardiac failure was present in 60 patients, and two-thirds of these, followed for periods of one to seven years after successful treatment of the thyrotoxicosis with ^{131}I, have remained free from further attacks of failure. Auricular fibrillation was observed in 90 patients before treatment and normal sinus rhythm was subsequently restored in 33. The nature and prognosis of the cardiac complications in these cases treated with ^{131}I are described in detail elsewhere (Sandler and Wilson, 1959).

Radioactivity in the Plasma and Pregnancy after ^{131}I Therapy

In thyrotoxic patients some of the administered ^{131}I is subsequently secreted as thyroid hormone. This results in a sustained high level of activity in the plasma and consequently in the irradiation of tissues distant

from the thyroid gland. The bone marrow and the gonads are of particular importance, the latter especially in the younger patients. The plasma dose was estimated for a group of 149 patients comprising women below the age of 45 and men below the age of 50. Plasma concentrations of ^{131}I were measured in all patients during the preliminary tracer test but in only a few after the therapy dose. However, on the occasions when both measurements were made, the proportion of the dose appearing in the plasma was approximately the same. The estimations were based mainly on the plasma activity at 48 hours in the tracer test, when the ^{131}I is largely protein-bound, but a small correction has been made for the dose received before the initial clearance of inorganic ^{131}I by the thyroid gland. The effective half-life of the activity in the plasma has been taken as seven days. The dose is almost entirely due to β-rays, but a small contribution (10%) from γ-rays is included.

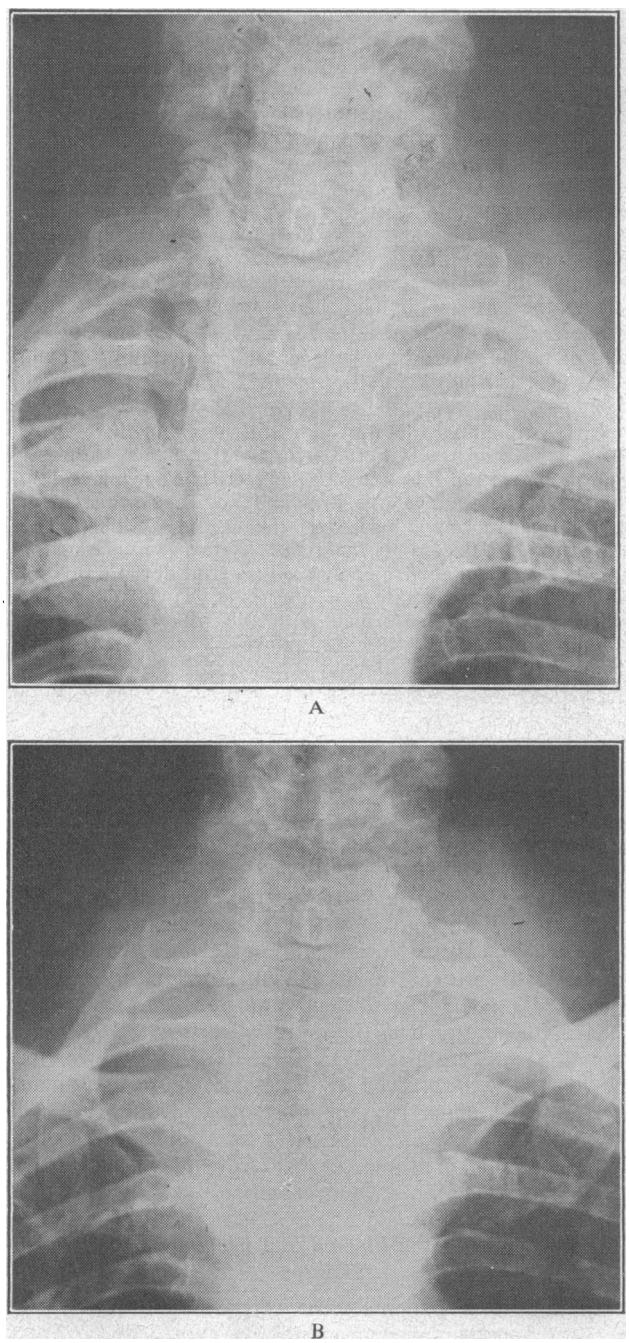


FIG. 8.—Effect of radio-iodine therapy on tracheal deviation. (A) Before treatment. (B) After treatment, showing almost complete return of the trachea to the midline.

The mean plasma dose was 25 rads. The range was very wide, from 2 to 260 rads, the latter being the integrated dose to the patient with the highly resistant gland (Case 1). In most patients it was much less, but in a few of those receiving multiple treatments the dose was greatly in excess of the mean (Fig. 9). Although

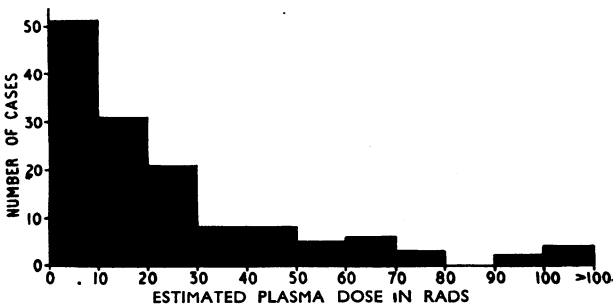


FIG. 9.—Estimated irradiation to the blood after ^{131}I therapy in women under the age of 45 and men under the age of 50.

the number of millicuries of ^{131}I given in second and later treatments is usually less than on the first occasion, the plasma specific activity is invariably higher; in consequence the plasma dose with repeat treatment is at least as great as with the first. The plasma dose and the gonad dose must clearly be associated, but the precise relationship in thyrotoxic patients is not known.

Pregnancy is an absolute contraindication to the administration of ^{131}I. However, one patient was inadvertently treated about three weeks after conception. Another conceived about one week after the administration of a therapeutic dose of ^{131}I. Both these pregnancies were mentioned in the previous report (Blomfield *et al.*, 1955), and the children have developed normally over the past five years.

Nine other patients have conceived at intervals sufficiently long after treatment to ensure that the foetus was not exposed to any radiation from ^{131}I, and eight live children have been born. One patient conceived after becoming hypothyroid, but was treated with thyroxine and gave birth to a normal child. Three miscarriages have occurred, all in the first trimester, but there was no evidence to suggest that they were in any way associated with the previous treatment. One of these was placed between two normal pregnancies, all three being post-therapy. The other pregnancies in our series were uneventful, and the children have shown entirely normal progress.

Deaths After ^{131}I Therapy

Thirty patients out of the 500 in the series had died at the time of completion of the review. The interval between the first therapeutic dose of ^{131}I and death ranged from four days to six and three-quarter years.

In 18 death was due to cardiovascular disease presenting as congestive cardiac failure, myocardial infarction, or cerebral thrombosis. In four the cause was a carcinoma, the primary sites being in the breast, ovary, rectum, and thyroid. The breast carcinoma was present before ^{131}I was given. The deaths from carcinomas of the ovary and rectum occurred 13 months and 2½ years after ^{131}I therapy respectively. The patient with carcinoma of the thyroid died nine months after

treatment; the carcinoma was almost certainly present when the ^{131}I therapy was given, and the details have been reported elsewhere (Kilpatrick *et al.*, 1957). In the remaining eight patients death was predominantly due to respiratory infections. Five died within a month of receiving treatment; in three, death was due to congestive cardiac failure, in one to myocardial infarction, and in one to hyperparathyroidism. There was no evidence in any of these cases that death was precipitated by the administration of ^{131}I.

Among the 500 cases treated before March, 1957, and reviewed a year later, there were no deaths associated with leukaemia, and no cases of leukaemia or aplastic anaemia have arisen in this group. However, one case has arisen in a patient treated at a later date. She was a woman of 50, who received 4.9 mc. of ^{131}I in April, 1957. She became hypothyroid in October, 1957, and was subsequently treated with thyroxine. She died with acute leukaemia in September, 1958.

Post-mortem examinations were carried out in 13 patients. The thyroid glands were specially studied (Curran *et al.*, 1958). The chief features observed in the glands of patients dying within seven weeks of treatment were cell necrosis, disruption of follicles, oedema of the stroma, vascular damage, and a patchy distribution of ^{131}I. In the glands examined at longer intervals after therapy, bizarre cell forms, pyknotic nuclei, stromal fibrosis, capillary telangiectasia, and a relative absence of colloid were particularly noticeable.

In one patient dying within four days of the administration of 13.5 mc. of ^{131}I, a detailed study of the distribution of radioactivity was made in various organs. The results are shown in Table IX. In this case the dose to the testis was approximately two and a half times as great as the blood dose calculated as described above.

TABLE IX.—*Radiation Dosage Received by Individual Organs Measured at Necropsy. Man aged 52. Therapy*—13.5 *mc. Four Days Before Death*

Organ	Dose in Rads	Organ	Dose in Rads
Thyroid	8,300	Blood	42
Testis	103	Pancreas	37
Spleen	56	Bladder	29
Liver	44	Kidney	22
Prostate	43	Stomach	16

Discussion

The advantages of ^{131}I treatment of thyrotoxicosis are readily seen. It is simple for the patient, effective, and devoid of any immediate serious complications. An ultimate permanent cure can be assured for all patients. The reaction to treatment is minimal and many can be treated on an out-patient basis. It is particularly suitable for those with cardiac complications. There are, however, some objections that can be raised to this form of treatment. They include a certain incidence of post-therapy hypothyroidism, delay in restoring euthyroidism in unduly resistant cases, the possible subsequent development of malignant disease, and undesirable genetic effects that might arise from exposure of the gonads to irradiation.

The problems of hypothyroidism and the necessity for repeated treatment in some cases are related to accurate assessment of the required dose. The incidence of hypothyroidism after partial thyroidectomy has varied from 2.9 to 13.9% (Bartels, 1953). The incidence reported after ^{131}I therapy also lies within this range, though on the average it is rather higher than commonly seen after surgical treatment. In the reported series of over 100 treated cases the incidence has varied from 2.5% (Gordon and Albright, 1950) to 17.2% (Clark and Rule, 1955). In the present state of knowledge accurate prediction of the correct dose cannot be ensured in all cases. The size of the thyroid is only one factor, but the results suggest that we have overestimated the mass of the smaller glands and thus tended to give too large doses at this end of the scale.

The minimum mass of the hyperactive thyroid has usually been regarded as 30 g., and our scale of estimates based on palpation has risen from this figure. However, in a series of 1,000 necropsies on euthyroid patients whose thyroids had been impalpable during life, Mortensen *et al.* (1955) noted that the largest number weighed between 15 and 35 g. Bauer and Blahd (1957) prepared scintigrams of 106 cases and report a range of gland sizes beginning at 15 g. The normal thyroid gland probably varies considerably in size in different parts of the world, and these American figures are not necessarily applicable to the Sheffield region. Nevertheless, the evidence obtained from our own scintillation studies and necropsy observations on hyperthyroid patients indicates that a lower figure for the impalpable thyroid would have been more appropriate. If this error had been avoided the incidence of hypothyroidism would have been slightly reduced but certainly not abolished. Accurate prediction in life of the mass of the thyroid is difficult, and a considerable error may be found in scintillation measurements when the estimates are compared with the actual weights of the glands (Kelly, 1954).

Attempts have been made to measure the size of the thyroid by radiography after injection of air into the neck (Franco and Quina, 1956), but it is doubtful if physicians would wish this procedure to be carried out routinely. Furthermore, the total mass of the thyroid does not necessarily reflect the dose that is required. The distribution of ^{131}I throughout the gland is irregular and there may be a considerable difference between the total weight of the thyroid and the mass of functioning tissue, particularly in the older patients with nodular glands. There are clearly many other factors apart from gland size which determine the dose received by the thyroid. In addition, there is a great individual and unexplained variability in sensitivity to irradiation. Some patients have become hypothyroid on exceptionally small doses. At the other extreme, some require repeated administration of large doses (Skillern *et al.*, 1951). The differences in sensitivity that we have observed are not closely related to gland size, uptake, or half-life of ^{131}I in the thyroid.

It is important to note that myxoedema occasionally appears a year or longer after ^{131}I therapy and that an initially satisfactory result does not invariably ensure continuing euthyroidism. The reported incidence of hypothyroidism will increase with the duration of follow-up after therapy. On the other hand, recrudescence of hyperthyroidism after the patient has been euthyroid for a few months following ^{131}I therapy is rare, whereas after surgery there is usually a small recurrence rate. These differences in the behaviour of the hyperactive thyroid following surgery or ^{131}I therapy are consistent with the histological changes observed in the gland after the two methods of treatment (Curran *et al.*, 1958).

Relation Between Irradiation and Cancer

Much attention has been directed in recent years to the relation between exposure to ionizing radiation and the subsequent development of malignant disease, and it is clearly important to review ^{131}I therapy in the light of this work. Initially, the possibility of inducing a thyroid carcinoma many years after treatment received most consideration. Experimentally, thyroid carcinomas have been produced in rats by the administration of ^{131}I alone (Goldberg and Chaikoff, 1952), but in order to obtain a high incidence of cancer the employment of both goitrogens and ^{131}I has usually been necessary (Doniach, 1958). Maloof *et al.* (1952), using ^{131}I alone, found only one adenoma in the thyroids of 500 rats given doses of from 1 to 300 μc. There are now several reports of human thyroid cancers following irradiation of the neck region in childhood (Duffy and Fitzgerald, 1950; Simpson *et al.*, 1955; Clark, 1955; Simpson and Hempelmann, 1957; Kilpatrick *et al.*, 1957; Wilson *et al.*, 1958). In these patients the latent period has often been under 10 years, and the association must now be regarded as well established.

On the other hand, it is doubtful whether irradiation in adult life for the treatment of thyrotoxicosis predisposes to the development of a thyroid carcinoma (Quimby and Werner, 1949). In a survey of 100 patients with carcinoma of the thyroid, irradiation in adult life played no part in the pathogenesis of the disease (Kilpatrick *et al.*, 1957). Wilson *et al.* (1958) mention one patient, treated for thyrotoxicosis by *x*-ray therapy when she was 26 years old, who developed an anaplastic thyroid carcinoma 37 years later. Although many thousands of thyrotoxic patients have been treated with ^{131}I during the past 15 years no cases of carcinoma have yet been reported as a result of this therapy. If ^{131}I is carcinogenic in adults, the latent period is much longer than that observed following irradiation in childhood. The available evidence suggests that if ^{131}I therapy is restricted to adults the danger of the subsequent development of a carcinoma of the thyroid is remote.

Association with Leukaemia

The second possible radiation hazard is the subsequent development of leukaemia, and recent evidence suggests that this may possibly be more important than carcinoma of the thyroid. Leukaemia is a well-recognized consequence of irradiation (Medical Research Council, 1956), but it is still doubtful to what extent ^{131}I therapy may precipitate the development of this disease. Single cases of leukaemia have been described in patients treated for thyroid disorders by either external irradiation or large doses of ^{131}I (Delarue *et al.*, 1953; Seidlin *et al.*, 1954, 1955; Blom *et al.*, 1955; Rawson and Rall, 1955). Two cases of acute leukaemia have already been reported following the treatment of thyrotoxicosis with ^{131}I (Abbatt *et al.*, 1956; Pochin *et al.*, 1956), and we have now added a third. All three patients died within two years of a small dose, and the association may be fortuitous.

It seems probable that the dose to the bone marrow is of the same order as the blood dose. In adult patients developing leukaemia, after external irradiation employed in the treatment of ankylosing spondylitis, the dose to the spinal marrow in 2 out of 37 cases was 112 and 471 r (Court-Brown and Doll, 1957). In the remainder the dose varied between 500 and 2,000 r or more. These workers showed that under certain assumptions 30–50 r of irradiation with *x* rays to the whole marrow might be expected to double the incidence of leukaemia. The latent period for leukaemia after irradiation is usually about three to five years.

Genetic Effects

The effect of ionizing radiations on human genetics is at present ill understood, but they may increase the mutation rate, which "in a human population would have a relatively much greater effect upon the incidence of harmful than upon that of harmless or of advantageous hereditary traits" (Medical Research Council, 1956). This aspect is clearly of great importance in women who may later become pregnant and in men who are being treated with ^{131}I. The fraction of the dose received by the gonads after the administration of ^{131}I to euthyroid subjects is small, and in the studies of Kurland and Freedberg (1951) did not exceed 0.02% of the total amount given.

On the basis of this evidence it has been assumed by some that in thyrotoxic patients the exposure of the gonads will be less as a greater proportion of the dose is concentrated in the thyroid. However, after 24 hours P.B. ^{131}I is released from the gland in considerable quantity in thyrotoxic patients, and it is this fraction which is mainly responsible for the irradiation of the gonads. The measurement of the dose received by the testis in the thyrotoxic patient dying four days after the administration of ^{131}I, and the calculations made in other male patients and younger women, show that the gonads may receive an appreciable amount of irradiation. It is difficult to assess the significance of this exposure. The dose to the ovaries commonly given by *x* rays to induce an artificial menopause is approximately 400 r at a single occasion. However, there is no evidence to suggest that treatment with ^{131}I may lead to sterility, as the dose to the gonads is normally much below this level. The patient who received the largest plasma dose, 260 rads, became pregnant when euthyroid, and her child has developed normally. This dose was spread over five treatments during two years, however, and was therefore well below a sterilizing dose.

Apart from the possible direct effect on the patient, the contribution of ^{131}I therapy to the genetically significant irradiation exposure of the total population of the Sheffield region must be considered. About 270 cases of thyrotoxicosis are treated with ^{131}I in this region each year. The mean plasma dose to 149 younger cases (women under 45 and men under 50) was 25 rads. From the knowledge of the age and sex distribution of the treated patients under 50 years of age, the total genetically significant dose for our series of 500 cases was calculated. This was done by weighting the dose according to the risk of subsequent parenthood, as in the method used by Osborn and Smith (1956). The total genetically significant dose for these 500 cases was 1,526 rad-eg.* The annual genetically significant dose in the Sheffield region therefore due to this form of therapy might be expected to be approximately 824 rad-eg. In the 10 successful pregnancies occurring in our series the mean age of reproduction was 28.8 years $\pm$ 1.6 S.E. This suggests that the mean age of reproduction in these cases is not different from that of the general population.

*The rad equivalent genetic, or rad-eg, as used in this sense is radiation dose expressed in rads accumulated by the gonads of a person weighted according to the "risk of parenthood" taken from general population statistics.

The population of the region is 4.2×10^6 and the population of England and Wales is 44.9×10^6. Using the figures quoted by Osborn and Smith, the genetically significant natural background in the region would be about 0.28×10^6 rad-eg per year. The contribution of the ^{131}I therapy for thyrotoxicosis to the genetically significant dose is therefore approximately 0.3% of the natural background, as compared with the contribution made by diagnostic radiology estimated by Osborn and Smith as at least 22% of the natural background. Clearly, the contribution to any genetic hazard by the overall dose is small, provided that the basis of selection of patients for treatment remains unchanged.

Nodular Goitres

There has always been wide difference of opinion regarding the treatment of toxic nodular goitre. Patients with nodular enlargement constituted a large group in our series, but their response to ^{131}I therapy was just as satisfactory as that shown by the other groups. In treating patients with ^{131}I there is always the slight possibility that a carcinoma of the thyroid which is overlooked would have been revealed earlier by surgical operation. So far this has happened in only one of the 500 patients. Nodularity of the thyroid gland is extremely common in the older age groups (Schlesinger *et al.*, 1938). It is also important to appreciate that there is a conspicuous lack of correlation between the clinical assessment of thyroid nodularity and the pathological findings (Mortensen *et al.*, 1955). Furthermore, the majority of thyroid cancers probably do not arise in adenomatous goitres (Sloan, 1954). It is very doubtful whether nodularity of the thyrotoxic gland should be regarded as an indication for operation in the hope of discovering rather earlier a few cases of thyroid cancer. The basis for this opinion has been fully discussed elsewhere (Kilpatrick *et al.*, 1957).

Tracheal compression or deviation is often regarded as an indication for surgical treatment of thyrotoxicosis rather than for the administration of ^{131}I therapy. However, several patients in the present series with considerable tracheal abnormalities have responded well to treatment; the tracheal obstruction was not aggravated during the acute period after ^{131}I administration, and the compression and distortion were greatly relieved after a few months. Clearly ^{131}I therapy is not to be advocated for tracheal compression caused by calcified or fibrous glands or giving rise to symptoms for which urgent relief is required, but in suitable cases the final results are excellent.

Conclusion

From the point of view of the patient, ^{131}I is undoubtedly the most convenient form of treatment, as it involves no more than drinking a tasteless fluid, and admission to hospital is often not required. It does involve the availability of special equipment and the presence of specially trained personnel. The hesitation about its widespread adoption in all cases of thyrotoxicosis is largely based on the uncertainty regarding possible long-term undesirable effects. At the present time these are difficult to assess. If treatment is confined to adults the available evidence suggests that the danger of carcinoma of the thyroid developing is remote. ^{131}I therapy of thyrotoxicosis results in only a low exposure of the bone marrow to ionizing radiations, but in the present state of knowledge this cannot be dismissed as insignificant.

The latent period for the development of leukaemia following exposure to irradiation is considerably less than that commonly seen in carcinoma (Medical Research Council, 1956). It is clearly most important that this aspect should be kept under careful review. Genetic considerations do not apply to women over 45 years of age, but in males and younger women this must not be overlooked. These points confirm our previously expressed view that ^{131}I therapy should not be given to patients under 40 years of age unless other methods of treatment have failed or cannot safely be employed. For these older patients the accumulated evidence confirms that it is a most satisfactory form of treatment.

Summary

The results of the treatment of 500 thyrotoxic patients with ^{131}I during the period January, 1949, to February, 1957, were reviewed in March, 1958.

After the first treatment 59% became euthyroid and 10% hypothyroid. A further 21% became euthyroid after two or more treatments. The overall incidence of hypothyroidism was 12%.

Factors influencing the response to treatment have been investigated. The gland size was the most important, but this was difficult to determine accurately. The highest incidence of hypothyroidism occurred in the patients with small glands, the size of which was probably overestimated. The age of the patient and wide variations in uptake and half-life of ^{131}I in the thyroid did not have any consistent effect on the clinical result.

Patients with tracheal compression or distortion due to thyroid enlargement were treated. No symptoms due to tracheal compression occurred after therapy, and the subsequent shrinkage of the gland restored the tracheal abnormality towards normal.

The irradiation dose to the plasma has been calculated for the younger patients. The mean plasma dose was 25 rads, but this was greatly exceeded in a few of the patients receiving two or more treatments.

Several normal pregnancies have occurred following therapy. Thirty patients have died, and the causes of death have been investigated.

Though ^{131}I therapy is effective and safe, in the present state of knowledge it should be given to patients under 40 years of age only when other methods of treatment have failed or cannot be employed. For older patients it is the method of choice.

We should like to thank many past and present members of the two departments who, at various times, have taken part in this work, and the physicians and surgeons who kindly referred patients for treatment. We are grateful to Mr. S. B. Osborn for his advice on the calculation of genetic hazards.

References

Abbatt, J. D., Farran, H. E. A., and Greene, R. (1956). *Lancet*, **1**, 782.

Barker, S. B. (1955). In *The Thyroid*, Brookhaven Symposia in Biology, No. 7, pp. 74, 80. Upton, New York.

Bartels, E. C. (1953). *J. clin. Endocr.*, **13**, 95.

Bauer, F. K., and Blahd, W. H. (1957). *Arch. intern. Med.*, **99**, 194.

Blom, P. S., Querido, A., and Leeksma, C. H. W. (1955). *Brit. J. Radiol.*, **28**, 165.

Blomfield, G. W., Jones, J. C., Macgregor, A. G., Miller, H., and Wayne, E. J. (1951) *Brit. med. J.*, **2**, 373.

—— —— —— —— —— (1953). In *Radioisotope Techniques:* Proc Isotope Techniques Conference, Oxford, 1951, **1**, 23. H.M.S.O., London.

—— —— —— —— —— and Weetch, R. S. (1955). *Brit. med. J.*, **2**, 1223.

Clark, D. E. (1955). *J. Amer. med. Ass.*, **159**, 1007.
—— and Rule, J. H. (1955). Ibid., **159**, 995.
Court-Brown, W. M., and Doll, R. (1957). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 295. H.M.S.O., London.
Curran, R., Eckert, H., and Wilson, G. M. (1958). *J. Path. Bact.*, **76**, 541.
Delarue, J., Tubiana, M , and Dutreix, J. (1953). *Bull. Ass. franç. Cancer*, **40**, 263.
Doniach, I. (1958). *Brit. med. Bull.*, **14**, 181.
Duffy, B. J., jun., and Fitzgerald, P. J. (1950). *Cancer (N.Y.)*, **3**, 1018.
Franco, V. H., and Quina, M. G. (1956). *Brit. J. Radiol.*, **29**, 434.
Fraser, R., Abbatt, J. D., and Stewart, F. S. (1954). Ibid., **27**, 23.
Goldberg, R. C., and Chaikoff, I. L. (1952). *A.M.A. Arch. Path.*, **53**, 22.
Gordon, E. S., and Albright, E. C. (1950) *J. Amer. med. Ass.*, **143**, 1129.
Hamilton, J. G., and Lawrence, J. H. (1942). *J. clin. Invest.*, **21**, 624.
Hertz, S., and Roberts, A. (1942). Ibid., **21**, 624.
Kellgren, J. H., and Lawrence, J. S. (1956). *Ann. rheum. Dis.*, **15**, 1.
Kelly, F. J. (1954). *J. clin. Endocr.*, **14**, 326.
Kilpatrick, R., Blomfield, G. W., Neal, F. E., and Wilson, G. M. (1957). *Quart. J. Med.*, **26**, 209.
King, E. L., and Herring, J. S. (1939). *J. Amer. med. Ass.*, **113**, 1300.
Kurland, G. S., and Freedberg, A. S. (1951). *J. clin. Endocr.*, **11**, 843.
Macgregor, A. G. (1957). *Brit. med. J.*, **1**, 492.
Maloof, F., Dobyns, B. M., and Vickery, A. L. (1952). *Endocrinology*, **50**, 612.
Medical Research Council (1956). *Hazards to Man of Nuclear and Allied Radiations*. H.M.S.O., London.
Mortensen, J. D., Woolner, L. B., and Bennett, W. A. (1955). *J. clin. Endocr.*, **15**, 1270.
Osborn, S. B., and Smith E. E. (1956). *Lancet*, **1**, 949.
Pochin, E. E. (1958). In *Modern Trends in Endocrinology*, pp. 46–51, edited by H. Gardiner-Hill. Butterworth, London.
—— Myant, N. B., and Corbett, B. D. (1956). *Brit. J. Radiol.*, **29**, 31.
Quimby, E. H., and Werner, S. C. (1949). *J. Amer. med. Ass.*, **140**, 1046.
Rawson, R. W., and Rall, J. E. (1955). Cited by Pochin *et al.* (1956).
Sandler, G., and Wilson, G. M. (1959). *Quart. J. Med.* In press.
Schlesinger, M. J., Gargill, S. L., and Saxe, I. H. (1938). *J. Amer. med. Ass.*, **110**, 1638.
Seed, L., and Jaffé, B. (1953). *J. clin. Endocr.*, **13**, 107.
Seidlin, S. M., Siegel, E., Melamed, S., and Yalow, A. A. (1955). *Bull. N.Y. Acad. Med.*, **31**, 410.
—— Yalow, A. A., and Siegel, E. (1954). *Radiology*, **63**, 797.
Simpson, C. L., and Hempelmann, L. H. (1957). *Cancer (Philad.)*, **10**, 42.
—— —— and Fuller, L. M. (1955). *Radiology*, **64**, 840.
Skillern, P. G., McCullagh, E. P., and Hays, R. A. (1951). *Trans. Amer. Goiter Ass.*, p. 184.
Sloan, L. W. (1954). *J. clin. Endocr.*, **14**, 1309.
Williams, R. H., Jaffe, H., Towery, B. T., Rogers, W. F., and Tagnon, R. (1949). *Amer. J. Med.*, **7**, 718.
Wilson, G. M., Kilpatrick, R., Eckert, H., Curran, R., Jepson, R. P., Blomfield, G. W., and Miller, H. (1958). *Brit. med. J.*, **2**, 929.

Cerebral Palsy—Advances in Understanding and Care is published by the Association for the Aid of Crippled Children in New York (624 pages. Obtainable from Arthur F. Bird, 66, Chandos Place, London, W.C.2. Price 42s. 6d., plus postage 1s. 6d.). The author, Viola E. Cardwell, enlisted a team of expert advisers to help her in the preparation of the book, the primary objective of which "is to promote greater understanding, improved treatment, and more sympathetic guidance of the patient and his family who are faced with the multiplicity of the all but overwhelming problems engendered by cerebral palsy." The first part of the book is concerned with the medical aspects of cerebral palsy: aetiology, pathology, and diagnosis are all discussed in detail in the light of modern advances in neuroanatomy and neurophysiology. "The Individual with Cerebral Palsy and his Total Habilitation" is the heading of the second part, and here the author describes physical and psychological treatment and discusses the social and educational aspects of cerebral palsy so far as the individual is concerned. Finally, there is a section on community aspects of cerebral palsy, with chapters on research and prevention. This book gives a detailed account of how an advanced society is attempting by voluntary and municipal effort to meet the challenge which cerebral palsy presents to the medical and social services.

CANCER AND BRONCHITIS MORTALITY IN RELATION TO ATMOSPHERIC DEPOSIT AND SMOKE

BY

PERCY STOCKS,* C.M.G., M.D., F.R.C.P.
Colwyn Bay, North Wales

Residents in large towns of England and Wales have always been subject to higher death rates than country dwellers, and much attention has been given to this in the Registrar-General's reports during the last century. Subdivision into sex, region, and social class does little to explain the urban excess; in 1930–2, for example, the standardized mortality figures for men aged 35–64 in unskilled and semi-skilled occupations showed urban/rural ratios of 134/80 in the north and 105/73 in the south and east outside Greater London, and for their wives the corresponding ratios were 128/104 and 103/92 (Registrar-General, 1938).

Two diseases for which the urban excess is very pronounced are bronchitis and lung cancer, and this is so in some regions for gastric cancer, whereas cancers of the intestine and breast show little relation to urbanization in Britain. The death rates from bronchitis and lung cancer are higher than in any other country, as is also the amount of air pollution from domestic chimneys; and in countries where coal is little used for domestic heating the urban excess is much smaller. In view of these facts atmospheric pollution of the kind found in British towns has been under suspicion as a causative agent both for bronchitis and for lung cancer, and I have suggested that pollution of food by exposure to dirty air might be a cause of the higher incidence of gastric cancer in towns. This paper records an attempt to obtain more conclusive evidence on these points by relating standardized mortality from bronchitis and cancers of four sites, with measurements of atmospheric deposit and suspended matter (smoke), in the county boroughs of England and Wales and in the administrative areas of Lancashire and the West Riding of Yorkshire, where such measurements have been made. Throughout the paper "S.M.R." (standardized mortality ratio) means 100 times the actual deaths of residents in the area divided by the number which would have occurred if the death rates at each age had been the same as the rates for England and Wales as a whole.

Previous Work

Bronchitis.—In the period 1950–3 the S.M.R. for males increased with degree of urbanization from 60 in rural districts to 133 in the conurbations, and for females from 69 to 129 (Registrar-General, 1956). The crude death rate per 100,000 in 1954 was 63 in all towns of England and Wales and 42 in rural areas, compared with only 5 to 7 in Copenhagen and rural parts of Denmark (Christensen and Wood, 1958), whilst the smoke concentration in Copenhagen was similar to that in a small urban district of Anglesey (Campbell and Clemmesen, 1956). In 10 subdivisions of London the S.M.R. of females in 1955 was correlated with smoke ($r=0.71$), but how much of this was due to variables such as length of residence in London and social class distribution remained in doubt (Gore and Shaddick, 1958).

*In receipt of a grant from the Medical Research Council.