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TREATMENT OF THYROTOXICOSIS WITH RADIOACTIVE IODINE

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Radioactive iodine was first used in the treatment of thyrotoxicosis by Hertz and Roberts in 1942, and reports of its value have appeared from several American centres. Soley and Foreman (1949) have contributed a valuable review on the subject. More recently further series of American cases have been reported by Werner *et al.* (1949); Williams, Towery, *et al.* (1949); Feitelberg *et al.* (1950); Gordon and Albright (1950); Moe *et al.* (1950); Shipley *et al.* (1950); and McCullagh and Richards (1951).

Little experience has yet accumulated in this country regarding the therapeutic applications of the isotope. Paterson (1950) and Warrington (1950) have reported on its use in thyroid cancer.

This paper sets out the results of the treatment of the first 20 cases of thyrotoxicosis that have been treated in Sheffield with radioactive iodine (I^{131}) since January, 1949, and describes experience gained with the technique. The preliminary results in some of the cases have already been briefly communicated (Blomfield, 1950a). We have chosen to treat a relatively small number of cases, but have studied them in detail, with special attention to dosage and to the clinical progress after treatment.

Principles Involved in Treatment with Radioactive Iodine

Thyrotoxicosis and toxic adenomata are usually treated either by surgical excision of an arbitrary amount of the overactive gland or, alternatively, by the administration of suitable antithyroid agents, to prevent the synthesis of the thyroid hormone, the presence of which in excess quantities in the circulation is responsible for most of the symptoms of the disease.

Irradiation by x rays has been regarded by some people as a satisfactory form of treatment, but its chief disadvantage is that it is difficult to deliver an adequate dose to the gland without damaging the skin and causing severe mucosal reactions in the trachea and oesophagus. The biological effect on the tissues of the radiation from radioactive iodine is similar to that of x rays; because, however, iodine is in general specifically concentrated in

the thyroid gland, it is possible to deliver a very high local dose of radiation to functioning thyroid tissue with only a minimal effect on other organs in the body. The greater part of the therapeutic effect of radioactive iodine is provided by the beta radiation emitted by the isotope, and, as this does not travel further than 2.2 mm. in tissue, there is little effect on the organs beyond the capsule of the gland. Radioactive iodine is therefore a therapeutic weapon with which highly specific treatment can be given to one particular type of tissue—thyroid gland tissue that concentrates iodine.

Dosage

The problem of the selection of the correct number of millicuries of the isotope in the drink to be given to each patient is of fundamental importance and is dependent on several factors, reviewed by Williams, Jaffe, *et al.* (1949). Most groups of investigators aim at giving a drink containing about 100–200 μ c. per g. of estimated thyroid mass. We have in this series, so far as it was practicable and possible, made a careful attempt to administer a drink for each patient which would result in a predetermined dose in "equivalent roentgens" (e.r.) (being the total of beta and gamma-ray dosage) to the thyroid gland of between 8,000 and 10,000 e.r.

The roentgen dosage following a drink containing a specified number of millicuries is dependent on three variables, characteristic of the patient at the time of therapy, not all of which can be accurately predetermined. These are: (a) the fraction of the total active iodine administered taken up in the gland; (b) the rate of elimination of the iodine from the thyroid; and (c) the total mass of the gland. The first two of these can be determined by a preliminary tracer investigation, and this is done on all patients for whom therapeutic doses are contemplated. Up to the present we have been able to determine the mass of the gland only by manual palpation, and this can be no more than an intelligent guess. As explained later, it is possible that the mass of the gland may be more accurately assessed by a technique in which a highly collimated Geiger counter is used.

The formula we have used in calculating the dosage is

$$\text{Dose (D)} = (210 \pm 10) \times \frac{\text{T.U.M.}}{\text{W}} \text{ equivalent roentgens,}$$

where T is the total half-life—that is, the time taken for the actual measured radioactive content of the gland to fall to half its initial peak value (days)—U is the peak value of the percentage of the administered iodine taken up in the thyroid, W is the mass of the thyroid (grammes), and M is the number of millicuries of radioactive iodine in the drink. This dosage includes the contribution of both beta and gamma rays, the beta-ray dose being independent of the shape of the gland. The gamma-ray dosage is calculated for the centre of the two spheres of which the gland is assumed to be comprised. That is not strictly correct, as this dose is dependent not only on the mass of the gland but also on its shape. The dependence of the total dose on gland shape is, however, very slight, and for glands between 20 and 80 g. the variation is only a few per cent., the gamma-ray dose being only about 10% of the total. The numerical factor (210±10) is calculated from the average energy of the beta and gamma rays emitted. It is thus dependent on the decay scheme adopted in the measurement of the radioactive content of the drink. The above figure is calculated from the decay scheme and average beta-ray energy given by the Atomic Energy Research Establishment (1949, personal communication) and still used there, and the number of millicuries in any sample quoted by them is used. A check measurement is made with a counter to establish the constancy of these supplies. A later scheme suggested by Metzger and Deutsch (1948) would indicate, if true, that the dosage figures we have taken are 10% too low. All the roentgen doses quoted in this paper are, however, based on the formula given above.

We have more recently adopted the practice of measuring the amount of radioactive iodine by direct comparison with a standard radium source, using a gamma-ray ionization chamber. We have assumed a dosage rate at 1 cm. from 1 mg. of radium to be 8.35 r an hour and from 1 mc. of radioactive iodine to be 2.37 r an hour, as given by the Metzger-Deutsch disintegration scheme. A gamma-ray counter is calibrated from time to time from these measurements, and actual drinks to patients are measured on this, relative to a standard radium source. The dose is then calculated

in a similar way, but assuming an average beta-ray energy per disintegration of 199 kev as given by Gray (1949).

The mass of the gland, for the purpose of this series, has been assessed manually by one observer throughout (G.W.B.). After the therapeutic drink, observations are made on the patient to determine the uptake of the isotope by the gland, its biological half-life in the gland, and its urinary excretion. The actual dose delivered is then calculated retrospectively and compared with that predicted from the tracer investigations.

Table I shows the general agreement between tracer and therapy measurements of gland uptake and total half-life. We rely on these tracer findings to calculate the number of millicuries required to produce a specific gland dose. The root mean square difference between the tracer and therapy results for the peak uptake is 10% of the therapy figure. The total half-life, however, shows somewhat greater divergence. Nevertheless, the values for the predicted and calculated gland dosage show reasonable agreement.

In some cases the therapy measurements gave a decay curve that was not even approximately exponential. Most of these could be divided into two roughly exponential portions with different half-lives, the dividing point being at about two days after ingestion. Where this is so, two values are given in Table I. From these two half-lives the dose can be calculated. If even this simplification is not possible the curve must be integrated graphically over the period of measurements. The total dose is then estimated, assuming that the gland content continues to decay with the half-life at the time when measurements ceased. This procedure is necessary, for instance, if one drink follows closely on another.

The greatest error in dosage prediction is likely to be introduced by estimations of gland size. Williams, Towery, *et al.* (1949) and Werner *et al.* (1949) found agreement with practice between estimated and actual gland size as found after operation, the error with the latter workers seldom exceeding 30%. We have not an extensive comparative series to check on clinical estimates of gland mass, but we believe our inaccuracies are not such as to affect seriously our estimations of the dose given.

An attempt to provide an independent and probably more accurate method of estimation of gland size has been made in a few cases by means of a detailed survey

TABLE I.—Comparison of Results Obtained from Measurements Following Tracer and Therapeutic Doses of I^{131}

Case No.	Peak Uptake % Drink		Total Half-life (Days)		Drink (mc.)	Estimated Mass of Thyroid (g.)	Dose (e.r.)	
	Tracer	Therapy	Tracer	Therapy			Predicted from Tracer	Calculated from Therapy
1	82	72	—	5-8	5.0	35	—	12,000
2	75	77	5.4	6.1	4.0	40	8,700	9,900
3	72	73	3.1	20	8.25	100	6,750	10,550
4	75	16	3.1	After 2 days 3.7	6.0	60	7,100	1,800
5	75	69	1.60	1.43	7.5	80	2,400	1,930
6	60	60	6.4	4.0	5.5	40	11,000	6,900
7	61	60	3.0	3.1	5.9	30	7,500	7,700
8	71	70	—	6.2	6.9	40	—	15,700
9	77	86	3.7	3.1	5.1	30	10,200	9,500
10	76	85	3.1	2.8 and 5.4	12.5	90	7,000	10,600
11	62	56	5.0	5.2	6.5	60	6,700	6,600
12	87	93	3.7	3.4 after 1 day	8.7	50	11,700	8,200
13	61	54	4.9	2.6 and 6-8	6.2	50	7,800	7,400
14	92	87	2.6	1.79 and 3.32	7.0	50	7,000	6,200
15	78	87	3.8	5.9	5.0	40	8,000	13,600
16	85	79	3.9	4.8	8.4	60	9,500	11,000
17	75	98	3.1	2.3 and 3.7	11.8	60	10,000	12,700
18	77	84	5.0	4.5	4.8	40	9,500	9,700
19	85	87	4.5	5.4	4.5	35	10,500	12,700
20	87	77	4	5.4	4.0	30	10,000	11,600

FIG. 1.—Distribution of radioactive iodine in the thyroid gland three days after ingestion of a therapeutic dose. The contours are lines along which the counting rate per minute in a collimated Geiger counter was constant.

using Geiger-counter measurements. The counting rate produced in a highly collimated gamma counter (Veall, 1950) is recorded when this is moved from point to point in a plane over the gland. This gives an estimate of the amount of active iodine within the field of the counter and, if the concentration of the iodine is uniform, a figure proportional to the thickness of the gland in that direction. The resulting diagram from Case 14 is shown in Fig. 1. The lines are drawn through points in the plane of equal counting rate and therefore probably of equal thickness of gland. Another diagram is drawn from measurements with the counter in a plane at right angles to the first. These show the general shape of the gland, but even an approximate estimation of the volume presents many difficulties owing to the unknown shape of the thyroid and the finite area covered by the counter for each measurement.

Work is still proceeding on this, and it is hoped to publish the results separately. So far it has not been possible to make such measurements on patients at the tracer stage with the present size of tracer drink (30 μ c.),

FIG. 2.—Autoradiograph of thyroid adenoma one year after treatment with radioactive iodine. The section is counterstained with Masson's light-green trichrome. It shows the fibrosis often associated with thyroid adenoma, but in this case attributable in part to previous radioactive iodine therapy. Note the rather patchy distribution of the isotopes, the highest concentration appearing in the more active follicles.

and volumes can therefore be estimated in this way only after therapy. While this is so, estimates of gland size made before treatment will remain somewhat arbitrary. We do not hesitate, however, to administer tracer drinks of 100 to 200 μ c. to patients for whom therapy is intended. Development of the use of scintillation counting may render even this size of dose unnecessary in the future (Allen *et al.*, 1951).

In the calculations of the dose delivered the further necessary assumption has to be made that the absorbed iodine is distributed uniformly throughout the gland. Measurements described above with a collimated counter show that in most cases of thyrotoxicosis the radioactive iodine is fairly uniformly distributed. Autoradiographic studies have, however, shown that the distribution is such that some cells will receive considerably more and some considerably less than the average amount of radiation. An autoradiograph (Fig. 2) was taken from a biopsy specimen of the gland of Case 3 twelve months after her second therapeutic dose of radioactive iodine and following a further tracer dose of the isotope. It demonstrates the patchy distribution of the isotope in the gland, and also the fibrosis which has occurred in the gland following the previous treatment. Up to the present we have no way of estimating the variation for any particular patient. It seems likely, however, that the areas which absorb most iodine, and therefore presumably those which are most actively producing thyroxine, are receiving doses considerably in excess of those stated.

Selection of Cases

Because of the unknown nature of the possible late effects of radiation from radioactive isotopes, we have restricted this form of treatment to patients in the older age groups. In certain circumstances, however, it may be the most suitable treatment whatever the patient's age. The following categories of patients have been treated: (1) Patients over 45 who were poor operative risks, and for whom it was felt that methyl thiouracil was unsatisfactory (Cases 11, 15, 16, 17, and 19). (2) Patients with recurrent thyrotoxicosis following partial thyroidectomy (Cases 5, 6, 7, 8, and 14). (3) Patients who have had reactions to methyl thiouracil necessitating withdrawal of the drug, where operation has been contraindicated (Cases 1, 2, and 4). (4) Patients who have relapsed on withdrawal of methyl thiouracil after at least one year's treatment, and in whom this form of treatment has been chosen in preference to surgery (Cases 3, 9, 10, 12, 13, 18, and 20). Full details of the cases treated are given in Table II.

All except three patients (Cases 17, 18, and 19) are also included in the series of cases of thyrotoxicosis and toxic nodular goitre studied by Goodwin *et al.* (1951). All were fully investigated by the usual clinical and laboratory techniques, and fully studied with radioactive iodine as regards the thyroid gland uptake and the urinary excretion of the isotope, the thyroid clearance rate of plasma iodide, and the radioactivity present in the 48-hour protein-bound iodine fraction of the plasma. All cases were definitely thyrotoxic as judged by these tests of thyroid function, and all were graded clinically as regards the degree of toxicity present, the mildest cases being called Grade 1 and the most severe Grade 4 toxicity. We do not claim a high degree of accuracy for these figures, but they do represent the final average opinion of at least three observers, each of whom took into account every clinical aspect of the case.

TABLE II.—Details of Cases Treated with Radioactive Iodine

Case No.	Sex	Age	Diagnosis	Previous Treatment	Grade of Toxicity	Estimated Gland Size (g.)	B.M.R. (%)	24-hr. Gland ¹³¹ I Uptake (% Dose)	Thyroid Iodine Clearance Rate from Plasma (ml./min.)	48-hr. Protein Bound Plasma Activity (% dose/litre)	Date Treated	Dose		Follow-up Interval (Months)	Clinical Result	Weight Gain	
												mc. ¹³¹ I	Calculated e.r.			lb.	kg.
1	F	46	Thyrotoxicosis; hydronephrosis	P.T., D.X.R., I	4	35	24	82			12/1/49	5.0	12,000	21	Euthyroid	25	11.3
2	F	57	Thyrotoxicosis	T., P.T.	3	40	65	72			9/2/49	4.0	9,900	24	"	17	7.7
3	F	73	Toxic nodular goitre; auricular fibrillation	I., M.T.	2	100		67	330	2.45	4/3/49 21/6/49 22/6/50	4.5 13.7 14.2	6,000 8,500 10,550	7	Much improved	10	4.5
4	F	60	Thyrotoxicosis; malignant exophthalmos	M.T.	4	60	80	64	270	2.9	19.7/49 29.9/49	8.7 15.8	1,800 6,300	18	Euthyroid (receiving thyroxine for exophthalmos)	34	15.4
5	F	20	Thyrotoxicosis	Op., M.T.	4	80	30	55	220	3.4	27/10/49 31/5/50 5/6/50	7.5 13.3 10.4	1,930 11,600	8	Euthyroid	17	7.7
6	F	47	"	Op., M.T.	2	40	32	55	35	0.64	18/11/49	5.5	6,900	15	"	16	7.3
7	F	48	"	Op., M.T., D.X.R.	2	30	46	61	30	1.2	30/11/49	5.9	7,700	13	"	12	5.4
8	F	55	Thyrotoxicosis; auricular fibrillation	Op., M.T.	2	40	3	71			20/12/49	6.9	15,700	13	"	12	5.4
9	M	38	Thyrotoxicosis; suprarenal cortical insufficiency	M.T.	3	30	12	74	174	0.91	3/1/50	5.1	9,500	15	"	50	22.7
10	F	38	Thyrotoxicosis	M.T.	3	90	40	73	383	1.0	4/1/50 5/4/50	12.5 20.0	10,600 11,600	9	"	1	0.5
11	F	53	Toxic adenoma		1	60	17	62	65		1/2/50	6.5	6,600	11	"	16	7.3
12	F	42	Thyrotoxicosis	M.T.	4	50	40	79	226	1.6	22/3/50	8.7	8,200	7	"	19	8.6
13	M	54	"	M.T.	2	50	34	56	92	0.87	20/4/50	6.2	7,400	11	"	17	7.7
14	F	36	"	Op., M.T.	4	50	46	72	612	1.6	24/5/50	7.0	6,200	8	"	15	6.8
15	M	51	Thyrotoxicosis; auricular fibrillation		2	40	42	78	833	1.43	18/7/50	5.0	13,600	7	Improved	9	4.1
16	F	47	Thyrotoxicosis		2	60	29	76	1,780	1.24	15/8/50	8.4	11,000	7	Euthyroid	28	12.7
17	M	48	"		3	60	32	72	318	1.99	14/9/50	11.8	12,700	5	"	18	8.2
18	F	55	Toxic adenoma	M.T.	2	40	37	77	212	0.84	21/9/50	4.8	9,700	5	"	16	7.3
19	F	65	Thyrotoxicosis		3	35	48	84	154	0.42	27/9/50	4.5	12,700	4	Improved	25	11.3
20	F	60	"	M.T.	3	30	25	87	323	1.27	4/10/50	4.0	11,600	4	Much improved	11	5.0

D X R. = x-ray therapy. I. = Iodine therapy. Op. = Partial thyroidectomy. T., M.T., and P.T. = Thiouracil, methyl thiouracil, and propyl thiouracil.

Technique

All cases treated were studied as in-patients and all investigations were carried out in the medical wards and adjoining laboratories. When the patients had been fully assessed and the preliminary tracer investigations completed, they were transferred for their therapeutic dose of radioactive iodine to the radiotherapy wards of the infirmary. This was done to isolate patients receiving large doses of radioactive iodine from others receiving tracer doses. Measurement of gland activity in patients who had received therapeutic doses and the counting of plasma and urine samples were done in the same room. All glassware and other apparatus was marked and kept for use only for solutions of the same order of activity. Three sets were in use—one for handling drinks and liquids of high specific activity of the order of 100 μ c. per ml., a second set for urine and plasma samples from therapy patients, and another set for fluid samples obtained following the administration of small tracer doses.

It was found necessary to have a separate building for radioactive isotope work. This was a single storied

building consisting of three rooms. The handling-room and measurement-room were separated by an office which reduced any background radiation produced by samples in the former room.

All active liquids were handled while wearing rubber gloves and long white coats. These, together with other outer clothing worn during the operations, were monitored periodically. Gloves were discarded as soon as they showed any contamination, and contaminated coats were put through a separate washing machine at the laundry.

The radioactive iodine was received in screw-top bottles. The volume of solution which was stated on the receipt note was usually between 1 and 2 ml. Water was run in from a burette until the volume was such that the removal of a convenient pipetteful either left or removed the required number of millicuries prescribed for the patient. The pipette was moved by remote control from behind a 1-in. (2.5-cm.) lead screen and operated by a syringe. Selection of a good well-lubricated syringe enabled fine control to be achieved with practice. If liquid counting was contemplated an

aliquot sample was removed and diluted for use as a standard. It was possible to avoid by this means all pouring of liquids, the remote control of which is rather complicated. The patient drank the liquid through a bent glass tube. We found that nearly all patients were able to do this without spilling, provided that they had previously been instructed in the technique by drinking water from the tube.

All urine from the patient was kept in cylindrical cans 12 in. (30 cm.) in diameter and 18 in. (45.5 cm.) deep. These were a convenient size for handling, and their simple geometric shape made possible the estimation of urinary volumes without further contamination of vessels. Faeces were not normally kept unless contaminated with urine, but were put down the sluice with repeated flushings. Urine was normally kept in any one container until the activity had decayed to below 1 mc. Carrier sodium iodide was added before it was put into the sluice emptying into the main hospital drain. Not more than 1 mc. was so discarded a week.

The patient undergoing therapy was kept isolated in a separate ward. Crockery, bed-pans, etc., were used only in that ward and were checked for contamination at the end of the treatment. Urine and blood were

There has been a diminution in the size of the thyroid gland in most cases, including Case 3, the only case of toxic nodular goitre with a very large gland. Small pseudo-adenomatous nodules associated with recurrences after thyroidectomy have practically disappeared.

We have noted that a favourable response is not usually apparent for at least four weeks, and if there is no improvement after eight weeks we have considered the initial dose to have been too small and a repeat dose has been given.

The results of investigations of thyroid function before and after treatment in six patients who have had repeated examinations are shown in Table III. It can be seen that gland uptake of the isotope was restored to what we regard as the normal range (below 55%) in five out of the six cases. Thyroid clearance rates were also all normal, but the activity present in the 48-hour protein-bound plasma fractions was still in excess of levels usually associated with non-toxic gland function (Goodwin *et al.*, 1951). The technique used for separation of the protein-bound fraction, that of Chaikoff, Taurog, and Reinhardt (1947), does not differentiate between the thyroxine and diiodotyrosine plasma fractions, and the recent work of Williams, Jaffe, and Bern-

TABLE III.—Comparative Results of Radioactive Iodine Tests of Thyroid Function Before and After Treatment

Case	Interval after Therapy (Months)	B.M.R. (%)		24-hr. Gland Uptake (% Dose)		24-hr. Urine Excretion (% Dose)		Thyroid Clearance Rate (ml./min.)		48-hr. Protein-Bound Plasma Activity (% Dose/litre)	
		Before	After	Before	After	Before	After	Before	After	Before	After
1	6	+24	-2	82	62	15	22	—	—	—	1.8
2	8	+65	-12	72	55	12	28	—	—	—	0.7
4	8	+80	-10	64	26	8	—	270	18	2.9	0.4
7	8	+46	—	61	34	28	—	30	22	1.2	1.2
9	11	+12	-28	74	20	10	49	174	22	0.9	0.4
12	4	+40	—	79	42	10	—	226	25	1.6	1.4

taken while wearing rubber gloves and gowns. All bed-linen and towels were checked for contamination after the patient had been discharged, and any article which showed appreciable activity was washed in a machine by itself.

After discharge from the hospital, which was usually about ten days after the treatment had been given, patients were normally seen at frequent intervals in the out-patient endocrine clinic until they became euthyroid, and thereafter they were seen at three-monthly intervals. All patients in this study are still under observation at progressively increasing time intervals. Certain selected patients have been readmitted for assessment or have had further tracer investigations carried out as out-patients (Table III).

Results

Eighteen cases have been followed for periods varying from 4 to 24 months (average, 10 months) after their last dose of radioactive iodine; 14 of these have received a single dose, three have had two doses, and one has had three doses. Sixteen of the 18 cases now have normal thyroid function, and two are greatly improved and almost normal. Two patients showed clinical evidence of transient hypothyroidism, but this became less evident later. In both cases the thyroid gland still retains the capacity to concentrate a normal amount of a tracer dose of radioactive iodine. Two other more recently treated cases have both gained weight and have considerable subjective improvement, but they are not yet normal.

stein (1949) and of Rall (1950) has shown that in some euthyroid and hypothyroid patients the diiodotyrosine fractions may be larger than had been previously appreciated. It is possible that in thyrotoxic patients after treatment there may be temporarily a relatively greater proportion of diiodotyrosine in the plasma fraction estimated by our technique, and separation of the plasma fractions by the butyl alcohol extraction method of Taurog and Chaikoff (1948) will enable this hypothesis to be tested. Alternatively, the phenomenon may be due to an alteration in the specific activity of the "labelled" plasma fraction after treatment.

Complications

In no case did we encounter any *local reaction* to the therapy, and there was no hoarseness, laryngitis, or salivary-gland reaction in any patient treated in this series.

Nor was there any general *systemic reaction*, although, in our experience, nausea and occasional sickness may occur after very large doses of 100 mc. or more used for treatment of malignant disease of the thyroid.

In no case in this series did we meet with the *temporary exacerbation* of thyrotoxicosis reported in a few cases by Williams, Towery, *et al.* (1949), but we have observed it in a further case more recently treated. In two of the cases of this series, Cases 10 (second dose) and 14, the degree of thyrotoxicosis was very considerable, and a course of methyl thiouracil was given for a period of four weeks before the administration of the therapeutic dose of radioactive iodine. In these two cases the

antithyroid drug was withdrawn at least a week before a further tracer dose of radioactive iodine, and it was found that the gland absorption had reverted to its previous level. The patients were, however, clinically much improved, and we feel that it may be a means of avoiding a transient exacerbation of thyrotoxicosis following the therapeutic dose. Recently we have given small doses of potassium iodide to severely thyrotoxic patients for a few days after their therapeutic drink, beginning not earlier than 24 hours after administration of the isotope. This has not appreciably affected the biological elimination of the radioactive iodine from the gland.

Transient hypothyroidism has occurred in two cases, Nos. 4 and 9. In Case 4, in which there was evidence of malignant exophthalmos, there was, before treatment, severe thyrotoxicosis with considerable wasting. Her first dose was considered to have been inadequate, and a few weeks after her second dose some degree of hypothyroidism developed without any deterioration in the eye signs, and treatment with thyroxine was instituted and has been maintained. On withdrawal of the drug there was little alteration in her clinical picture, and gland uptake of radioactive iodine was of the order of 26%; thyroxine treatment was, however, given in an attempt to improve her exophthalmos by inhibition of pituitary thyrotropic hormone, and her clinical condition is now excellent.

Case 9 was of special interest inasmuch as there was strong evidence of relative suprarenal cortical deficiency at the time when the patient was grossly thyrotoxic. After his therapeutic dose of radioactive iodine a very considerable gain in weight occurred, at one stage accompanied by evidence of hypothyroidism. Later, however, he was considered on clinical grounds to be in normal thyroid balance, and gland uptake of radioactive iodine was found to be 20% in the low normal range.

Arthritis.—One patient, Case 19, had a severe attack of gout affecting one hand, beginning about one week after her therapeutic dose. This attack was possibly unassociated with the administration of radioactive iodine, although it is known that a sudden metabolic disturbance, such as can be assumed to occur in the treatment of severe thyrotoxicosis with radioactive iodine, may sometimes fire off an attack in this condition. A further patient, Case 17, had an attack of arthritis, characterized by painful swelling of his wrist and finger joints and associated with limitation of movement and tenderness of the extensor tendons of his wrist, which occurred four months after his therapeutic dose. The condition, the precise aetiology of which is not known, was treated with high dosage of calcium aspirin, and gradually returned to normal with no residual disability. Case 16, who had evidence of old rheumatoid arthritis of her hands, stated that she had a slight increase in the usual amount of pain and stiffness of her fingers in the few weeks following treatment, but there was no objective alteration in her arthritic condition. The relationship of the manifestations of joint disease in these patients to their thyrotoxic condition, or to the treatment given, is not clear, but is under further study.

Congestive heart failure had been a recurrent feature in Case 3, and occurred once more a few months after her second dose of radioactive iodine, and again a year later, when she was once again thyrotoxic. She had a large nodular goitre, and we found, like Richards, Crile,

and McCullagh (1950) that the dosage requirement in such patients is very high; she received, in fact, the highest total dosage given.

No detrimental effect of therapy was noted on the *haemopoietic system*, nor on any other organs. Following upon very high dosage of radioactive iodine given to another case of metastatic thyroid carcinoma we have noted a fall in blood platelets and a transient fall in the leucocyte count (Blömfeld, 1950b), but we have not seen any similar effect in any case treated for thyrotoxicosis. Case 19 in fact had purpura with thrombocytopenia, there being only 90,000 platelets per c.mm. before treatment, a condition ascribed to her thyrotoxicosis. After her therapeutic dose of radioactive iodine her platelets steadily rose to a level of 330,000 per c.mm. six weeks later.

No alteration in *menstrual function* has occurred, nor have we noticed any alteration in the menses of a young patient, not in this series, successfully treated with several very large doses of radioactive iodine for recurrent thyroid carcinoma.

Discussion

In a disease such as thyrotoxicosis, for which there are already available satisfactory, efficient, and relatively safe methods of treatment, the acceptance of a new form of therapy must be shown to have considerable advantages before it can be universally adopted.

Medical treatment with one of the thiouracil derivatives is a suitable form of therapy for practically all cases of thyrotoxicosis, except those with pronounced tracheal compression or deviation or those in which supervision of medical treatment is difficult. Treatment with methyl thiouracil results in a permanent remission of the disease, after withdrawal of the drug, in only about two-thirds of patients, even when treated for over a year. This relapse rate is very much higher if treatment is discontinued before 12 months. Dunlop and Rolland (1950) found that of 72 patients treated for up to 12 months 50 relapsed, whereas of 54 treated for over 12 months only 18 relapsed. The great majority of relapses occur within four months of withdrawing treatment. The value of the drug is that with it patients may be tided over until natural remission occurs, as it does in about 50% of cases even if no effective treatment is given (Allbutt, 1897). Its use is associated with a mortality of not more than 0.5%, entirely due to agranulocytosis (Himsworth, 1948), but about 10% of patients have toxic reactions to the drug which Dunlop and Rolland (1950) found were sufficient to necessitate stopping treatment in 7%, and such patients can be effectively treated by operation. These findings correspond with those of Goodwin and Wilson (1951, personal communication) in a large series of cases studied in Sheffield.

Surgery is the treatment of choice for thyrotoxicosis, when the gland is very large or there are pressure effects, and the resultant cosmetic effect is usually good. It has the advantage that cure is more rapid, and more often permanent, than in cases treated solely with methyl thiouracil. The chief disadvantages of surgical treatment are that in this country, except in special clinics, the overall mortality rate is certainly considerably greater than 2% (Himsworth, 1948) and the majority of partial thyroidectomies are not carried out by specialists in the operation. There is in addition, moreover, an appreciable morbidity rate resulting from the operation

or complications therefrom, and the patient is left with a scar which, especially in young women, may be a disfigurement.

The great advantage of radioactive iodine is that there is no immediate risk of mortality or morbidity, and the treatment, from the patient's point of view, is completely devoid of unpleasantness and is supremely simple. There is remission of symptoms associated with shrinkage of the gland without any necessity either for prolonged hospital treatment and attendance or for a scar-producing operation. Repeated small doses of radioactive iodine, given without detailed study, will result eventually in full remission in practically all cases, and this is the practice in many American clinics where no specific attempt is made to measure accurately the dose given to each patient.

We, like other workers, have shown that it is possible to secure remission of the disease in a high percentage of cases, and that there is no accompanying morbidity and no mortality. Such advantages as these must be balanced against any possible adverse effect that may result from the radiation administered. The only reason that prevents its more general use, even if the necessary equipment were generally available, is doubt regarding the late effects of internally administered radiation from radioactive isotopes.

The chief arguments against its more general application centre upon the possibility that malignant changes may be induced in the thyroid gland many years later. It is, however, significant that the type of radiation known to be associated with the later development of malignant change is chronic radiation of low intensity, and not the brief and much more intense radiation provided by radioactive iodine (Werner *et al.*, 1949). Moreover, malignant change has not been noticed in the gland following external irradiation by x rays. Quimby and Werner (1949) reported an inquiry into the late effects on cases treated by x-ray therapy for thyrotoxicosis. Inquiries were made regarding the sequelae in such cases from 70 radiologists and 31 thyroid specialists. Although malignant disease arose in some cases in which the skin had been over-irradiated and in some cases in the trachea and the oesophagus, there was no evidence of malignancy arising in the gland as a result of ionizing radiation. Their conclusion was that this complication (malignant change in the gland), if it exists, must be very rare.

Although the beta-radiation of radioactive iodine is not strictly the same as the radiation of radium or deep x-ray therapy applied externally, there is no reason to suppose that it is fundamentally different in its effects, apart from the fact that such radiation is localized to the gland itself and is more intense in places where the concentration may be patchy. On a time-scale basis, however, the radiation from radioactive iodine would appear to be intermediate in its effect between a chronic radiation of low intensity and the brief but intense radiation of x rays.

Gorbman (1950) carried out some experimental work on mice, to which he gave very high dosages of radioactive iodine, and determined the dosage level, in microcuries per milligram of thyroid tissue, necessary to extirpate thyroid cells completely. He studied the histological features of the thyroid glands which had been given doses insufficient to kill all the cells, and in no case was neoplastic growth, or even metaplastic replacement, observed in mice studied up to one and a half

years after the administration of the radioactive iodine. He found, however, that the functional capacity of these surviving cells was impaired.

Doniach (1950) found that radioactive iodine significantly increased the formation of thyroid adenomas in rats as compared with controls not treated with radioactive iodine, in the following groups: those treated with radioactive iodine alone, those treated with methyl thiouracil, and those treated with methyl thiouracil and acetylaminofluorene. In addition, he found a thyroid cancer in the group of rats treated with radioactive iodine and methyl thiouracil, and one in the group treated with radioactive iodine, methyl thiouracil, and acetylaminofluorene. Doniach concludes from these findings that radioactive iodine acts indirectly as a stimulant of the production of pituitary thyrotropic hormone—increased production of which occurs after any treatment of thyrotoxicosis, whether by surgery, thiouracil, or radioactive iodine—and acts directly as a carcinogen. He states that the effects vary in the gland according to the state of the cells and the dose received.

This work must be interpreted with caution in view of the relatively small number of animals used, the high incidence of adenoma formation in the controls that did not receive radioactive iodine, and because increased adenoma formation, with occasionally apparently malignant changes, have been reported in rats by Griesbach, Kennedy, and Purves (1945), Purves and Griesbach (1946), and Gorbman (1947), following the long-continued administration of a goitrogenic drug such as thiouracil. Bielschowsky (1945) has shown that acetylaminofluorene enhances the effects of these agents. Furthermore Gorbman (1947) showed that on resumption of a normal diet the apparently malignant infiltrating thyroid tissue disappeared and the supposedly cancerous glands involuted.

Additionally, because of the minute size of the thyroid gland in rats and mice, experimental radiation effects are found in contiguous structures such as the trachea, which are within the range, 2.2 mm., of the beta-radiation of radioactive iodine. In man, however, the thickness of the gland capsule and the presence of surrounding connective tissue makes such effects improbable.

These findings chiefly serve to emphasize the difficulty inherent in the interpretation of histological findings relating to the thyroid gland. It is important to emphasize that there has not yet been produced any experimental or clinical evidence of the induction of carcinoma following the administration of radioactive iodine alone. It will be many years, of course, before such cases will appear, but, on balance, all evidence goes to show that the possibility of such appearances is most remote.

With regard to adverse effects of other types, the possibility of irreversible changes occurring, especially in the gonads, must be considered. Because of the high concentration of the isotope in the gland, there is little irradiation to other body organs, and Gorbman (1950) considers that ovarian sterilization by radioactive iodine need be considered as a potential hazard only when circumstances are such that thyroid iodine uptake is less than 10%. We have treated a young patient for malignant disease of the thyroid with up to 100 mc. of the isotope, and there has been no effect on her menses. The actual ovarian dose in the treatment of thyrotoxicosis is of the same order as the blood dose (Table IV), and a sterilizing dose is of the order of 250–400 r.

The possible genetic effect of such doses is analogous to the effects resulting from diagnostic radiological investigations for gynaecological conditions and pelvic mensuration.

The doses given to other parts of the body than the thyroid vary widely from patient to patient, depending on the blood concentration and rate of urinary excretion. The figures given in Table IV refer to the dose given to

TABLE IV.—*Plasma and Urine Doses After Treatment with I¹³¹*

Case No.	Dose per mc. (e.r.)		Estimated Dose Actually Given in Treatment (e.r.)	
	Plasma	Urine	Plasma	Urine
5	11.0	3.0	77	22
6	1.3	2.7	7	15
7	2.8	2.3	16	14
9	3.6	1.8	18	9
10	2.3	1.0	{ 29 46	{ 12 20

the blood plasma and to the urine. They were estimated by integrating the plasma concentration with time and are taken from the tracer measurements, and refer to beta dose only. The estimation from these figures of the actual dose delivered to body cells is a matter of considerable difficulty. A smooth surface bathed with these fluids would receive half the doses shown down to a depth of about 2 mm. Thus the dose received by the cells is not likely to be appreciably greater than the plasma dose, and in most cases will be very much less, unless there is appreciable concentration of iodine in any other part of the body. The dose to the bladder walls will be between 50% and 100% of the urine dose, depending on the involution of the bladder surface. The gamma-ray dosage is not likely to contribute more than about 20% of the beta-ray dose.

Nevertheless, in one case (Case 5) the calculated plasma dose was quite considerable, and this was due to the fact that the patient had a very high degree of plasma radioactivity owing to rapid gland turnover and conversion of the radioactive iodine into thyroxine. Repeated blood counts on this patient, followed over many months, have not revealed any abnormality in any constituent, nor, with the exception already mentioned in one case, have we ever seen more than a transitory drop in the leucocyte and platelet count in patients treated with much more massive dosage of the isotope for thyroid cancer.

In thyrotoxicosis there is a release of radioactive thyroxine into the circulation. Courier *et al.* (1949) found some accumulation of radioactive thyroxine in the pituitary gland, and in one human case that came to necropsy after a large dose of radioactive iodine Chapman (1948) found 3% of the isotope in the pituitary. Gorbman (1950) noted, moreover, the development of non-invasive chromophobe adenomas of the anterior pituitary about eight months after thyroid-lethal doses of radioactive iodine in most of his treated mice. Goldberg and Chaikoff (1950) have shown that such changes cannot be produced in dogs nor in rats, and that feeding of thyroid extract to the irradiated mice prevents the development of the pituitary changes. It is probable, therefore, that they are a compensatory hypertrophy due to the production of complete hypothyroidism in the mice (Goldberg and Chaikoff, 1951). Similar changes have not been observed in man. Trunnell *et al.* (1950), in a study of the distribution of radioactive iodine in

human tissues, did not reveal a high concentration of radioactive iodine in the pituitary; nor did they find pituitary changes in patients having high doses of radioactive iodine.

We do not think, after careful consideration of all the available evidence, that the danger of late effects resulting from the radiation is great. Because of its possibility, however, we prefer, meanwhile, to reserve the treatment, in uncomplicated and previously untreated cases, for patients in the older age groups. Where, however, there are any factors which increase the risks of operation, or in any way unduly complicate treatment with methyl thiouracil, we prefer to balance the remote dangers of irradiation hazards against the risks and inconveniences involved in either of the more traditional forms of therapy. After such consideration we believe that the simplicity and efficiency of radioactive iodine therapy, especially from the patient's viewpoint, is such that any theoretical objections to its use can be discounted. This especially applies in the treatment of thyrotoxicosis recurrent after thyroidectomy, where antithyroid drugs are in any case less likely to obtain permanent remission and further operation is notoriously unsatisfactory. In such cases radioactive iodine therapy is the treatment of choice at all ages.

The above remarks refer chiefly to the use of radioactive iodine in the treatment of thyrotoxicosis with diffuse gland enlargement. In the case of toxic nodular goitre with large glands, surgery is probably the treatment of choice, unless, as in Case 3, other factors make the patient a bad surgical risk; in such circumstances a satisfactory remission in symptoms can be obtained with radioactive iodine, although larger doses of the isotope must be used (Richards, Crile, and McCullagh, 1950).

Furthermore, it must be appreciated that radioactive iodine is not suitable for the immediate treatment of patients who are critically ill, or who have such complications as thyrotoxic heart failure. For such cases conventional medical methods of treatment are necessary before the use of radioactive iodine can be considered.

There are other factors which still limit the more general application of this technique to the treatment of thyrotoxicosis. Expensive and elaborate equipment is necessary if administration of the isotope is to be on a scientific basis and not merely a matter of guesswork. The close collaboration of physicians, radiotherapists, and physicists is necessary, and such team-work is possible only in a few centres. Consequently, the treatment will be available only in certain places, and cannot be applied as a domiciliary method in outlying districts or in less well equipped hospitals.

The other factor which at present necessitates caution in the application of this form of treatment in this country is lack of knowledge regarding the precise dosage administered. As already pointed out, the calculated dosage is based on a formula involving the gland uptake of the isotope, its biological half-life in the gland, and the weight of the gland itself. If the treatment is to be rational and scientific, as close an estimate as possible should be made beforehand of the dose necessary for each patient. Half-life and uptake can be determined for each patient before treatment, and an estimate made of the size of the gland. Some American groups have tried to evolve short cuts to dosage assessment such as by gland size (Williams, Jaffe, *et al.*, 1949), level

of toxicity and gland size (Gordon and Albright, 1950), and so on, and Feitelberg *et al.* (1950) assume a biological half-life in their dosage assessment of six days, an assumption which study of Table I shows to be unwarranted.

Some American centres prefer to administer intentionally small doses, and give repeated drinks of the isotope, to avoid the possibility of hypothyroidism or myxoedema. The risk of the latter event is, however, probably less than the necessary prolongation of the period of hyperthyroidism which is implicit in the policy of the administration of repeated small doses. In circumstances where dosimetry cannot be precise, it is certainly preferable to give smaller doses, with the knowledge that failure to obtain a remission can always be remedied by administration of a further dose. When gland size can be accurately predetermined by development of the technique described earlier the last unknown factor in calculation of the dose will have been eliminated. We anticipate that then the necessity for further doses will be infrequent, with a corresponding saving in time off work and in hospital beds occupied.

Our experience with this small series of cases, and with subsequent cases treated, has convinced us of the many advantages of this form of therapy. It is our opinion that, with further experience and the development of new techniques, it will become a method of treatment for thyrotoxicosis suitable for many more cases than those for which it is now recommended and used with confidence.

Summary

Twenty selected cases of thyrotoxicosis have been treated with radioactive iodine, especial attention being paid to the dosage of radiation delivered to the thyroid gland.

It was possible to induce a satisfactory remission in every case, but some required several doses of the isotope. Larger doses were needed for toxic nodular goitre than for Graves's disease.

A technique is described by which the gland size may be accurately determined and precise dosage of radiation calculated.

The possibility of the induction of malignancy in the gland as a result of internal radiation is fully discussed. Such an eventuality is most improbable, and the immediate advantages of this form of treatment in many cases outweigh the remote risks of malignant change.

The simplicity, safety, efficiency, and lack of immediate complications of radioactive iodine therapy make it the treatment of choice for thyrotoxic patients in the older age groups. It is the most satisfactory treatment for all patients in whom thyrotoxicosis has recurred after operation.

We are grateful to Dr. J. F. Goodwin for his assistance in the treatment of the first three cases in this series, and to those physicians who have referred cases suitable for treatment. We are indebted to Miss M. Foster, Miss D. Wemm, and Mr. E. Salvin for technical assistance. Mr. L. R. Reeves prepared the autoradiograph.

ADDENDUM

Since this paper was submitted for publication, 30 patients out of a total of 51 treated have been observed for three months or more after treatment. Of these 30, 21 are now euthyroid, 1 is hypothyroid, and 8 are improved but not yet normal. Eighteen of the 21 euthyroid patients were successfully treated with a single therapeutic drink delivering an average dose of 9,500 e.r. to the gland. The 8 improved but not yet normal cases are regarded as still under treatment and may require a further dose. All of the 15

patients observed for 10 months or longer are cured of their hyperthyroidism, as are 7 of the 15 observed for under 10 months.

REFERENCES

- Allbutt, T. C. (1897). *System of Medicine*, 4, 502. London.
 Allen, H. C., Libby, R. L., and Cassen, B. (1951). *J. clin. Endocrinol.*, 11, 492.
 Bielschowsky, F. (1945). *Brit. J. exp. Path.*, 26, 270.
 Blomfield, G. W. (1950a). *Brit. J. Radiol.*, 23, 566.
 — (1950b). *J. Fac. Radiol.*, 1, 255.
 Chaikoff, I. L., Taugo, A., and Reinhardt, W. O. (1947). *Endocrinology*, 40, 47.
 Chapman, E. M. (1948). Brookhaven Conference Report on Radioiodine, p. 59.
 Courrier, R., Horeau, A., Marois, M., and Morel, F. (1949). *C.R. Soc. Biol., Paris*, 143, 935.
 Doniach, I. (1950). *Brit. J. Cancer*, 4, 223.
 Dunlop, D. M., and Rolland, C. F. (1950). *Proc. roy. Soc. Med.*, 43, 937.
 Feitelberg, S., Kaunitz, P. S., Silver, S., Simon, N., Wasserman, L. R., and Yohalem, S. B. (1950). *Arch. intern. Med.*, 85, 471.
 Goldberg, R. C., and Chaikoff, I. L. (1950). *Endocrinology*, 46, 91.
 — (1951). *Ibid.*, 48, 1.
 Goodwin, J. F., Macgregor, A. G., Miller, H., and Wayne, E. J. (1951). *Quart. J. Med.* In press.
 Gorbman, A. (1947). *Cancer Res.*, 7, 746.
 — (1950). *J. clin. Endocrinol.*, 10, 1177.
 Gordon, E. S., and Albright, E. C. (1950). *J. Amer. med. Ass.*, 143, 1129.
 Gray, L. H. (1949). *Brit. J. Radiol.*, 22, 677.
 Griesbach, W. E., Kennedy, T. H., and Purves, H. D. (1945). *Brit. J. exp. Path.*, 26, 18.
 Hertz, S., and Roberts, A. (1942). *J. clin. Invest.*, 21, 624.
 Himsforth, H. P. (1948). *British Medical Journal*, 2, 61.
 McCullagh, E. P., and Richards, C. E. (1951). *Arch. intern. Med.*, 87, 4.
 Metzger, F., and Deutsch, M. (1948). *Phys. Rev.*, 74, 1640.
 Moe, R. H., Adams, E. E., Rule, J. H., Moore, M. C., Kearns, J. E., and Clark, D. E. (1950). *J. clin. Endocrinol.*, 10, 1022.
 Paterson, R. (1950). *Brit. J. Radiol.*, 23, 553.
 Purves, H. D., and Griesbach, W. E. (1946). *Brit. J. exp. Path.*, 27, 294.
 Quimby, E. H., and Werner, S. C. (1949). *J. Amer. med. Ass.*, 140, 1046.
 Rall, J. E. (1950). *J. clin. Endocrinol.*, 10, 996.
 Richards, C. E., Crile, G., and McCullagh, E. P. (1950). *Ibid.*, 10, 1077.
 Shipley, R. A., Storaasli, J. P., Friedell, H. L., and Potts, A. M. (1950). *Amer. J. Roentgenol.*, 64, 576.
 Soley, M. H., and Foreman, N. (1949). *J. clin. Invest.*, 28, 1367.
 Taugo, A., and Chaikoff, I. L. (1948). *J. biol. Chem.*, 176, 639.
 Trunnell, J. B., Duffy, B. J., Godwin, J. T., Peacock, W., Kirschner, L., and Hill, R. (1950). *J. clin. Endocrinol.*, 10, 1007.
 Veall, N. (1950). *Brit. J. Radiol.*, 23, 527.
 Warrington, H. C. (1950). *Ibid.*, 23, 556.
 Werner, S. C., Quimby, E. H., and Schmidt, C. (1949). *Amer. J. Med.*, 7, 731.
 Williams, R. H., Jaffe, H., and Bernstein, B. (1949). *J. clin. Invest.*, 28, 1222.
 — Towery, B. T., Rogers, W. F., and Tagnon, R. (1949). *Amer. J. Med.*, 7, 718.
 — Towery, B. T., Jaffe, H., Rogers, W. F., and Tagnon, R. (1949). *Ibid.*, 7, 702.

The social work of the Anglo-Iranian Oil Company began in 1909, and its amenities have always been shared by the local inhabitants of the island of Abadan (*Daily Telegraph* special article, August 1). The island has been so developed as to be able to support a population of about 140,000; the houses have proper drainage, and are served by metalled roads. The hospital is said to be one of the finest in the Middle East, and in one year alone 912,725 Persians were treated in its out-patient department; during that time 1,018 major, and 10,458 minor operations were performed. Since very few Persian doctors will consent to work in South Persia the company maintains its own staff of European doctors. But the company's main achievement lies in the success of its war against the principle diseases of the East, such as smallpox, malaria, typhus, and trachoma. In 1934 an elaborate system of canals was formed to prevent the spring rains from forming into stagnant pools, breeding grounds for malaria-carrying mosquitoes, and if any pools do appear they are sprayed with gas oil. Each year over 30,000 vaccinations are done, and smallpox has almost been eliminated.