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TREATMENT OF THYROTOXICOSIS WITH RADIOACTIVE IODINE

REVIEW OF 140 CASES

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It is now thirteen years since Hertz and Roberts (1942) introduced radioactive iodine in the treatment of thyrotoxicosis, and in the succeeding years it has increasingly established itself in the therapy of this condition and has been widely used in the United States of America. We have previously recorded our experience in this country in a small series of cases (Blomfield *et al.*, 1951, 1953; Wayne *et al.*, 1952). Fraser and his colleagues (1954) have also described their results using a somewhat different technique. We have now treated more than 350 patients at Sheffield, and we present a detailed analysis of the results obtained in 140 cases followed up for at least one year. This period of time has been chosen because we found that the full effect of a single dose was obtained within one year. The same rather rigid technique has been used throughout with all the members of this group of patients, and we have aimed at producing a state of normal thyroid balance with a single therapeutic drink of the isotope. We put our results on record because we believe that they will be of interest and value to others who have used different methods to achieve control of the thyrotoxic state.

Selection of Cases

Most observers are now agreed on the main indications for isotope therapy in thyrotoxicosis. The only objection to its wider use is the possible late development of malignant changes in the gland itself. We discuss later the evidence for and against this eventuality. At present we accept the need for caution and we reserve radio-iodine therapy for those with an expectation of life less than that of the latent period for the development of carcinoma, about twenty years. In practice this means that we restrict treatment to the following groups of cases: (a) patients over 45 years of age; (b) those in whom associated disease reduces life expectancy to less than 20 years; (c) those who are

refractory or hypersensitive to antithyroid drugs and in whom thyroidectomy is either contraindicated or refused; (d) recurrence after thyroidectomy, since antithyroid drug therapy is unlikely to lead to sustained remission and a second operation is much more likely to be followed by further relapse or by some complication; (e) cases of heart disease associated with thyrotoxicosis, since expectation of life is low and operative mortality high.

The presence of a large goitre even with chronic pressure symptoms is not in itself a contraindication, as gland shrinkage invariably follows radio-iodine therapy. A toxic adenoma is not an absolute contraindication, and radio-iodine offers a valuable alternative if associated disease seriously militates against surgical treatment.

The only important contraindication is pregnancy. The risk of damage to the foetus as a whole is difficult to estimate but is probably not serious. The risk of the foetal thyroid taking up radio-iodine and receiving direct damage is real. Fortunately this does not occur until after the 14th week of gestation (Chapman *et al.*, 1948), by which time evidence of pregnancy is usually unequivocal.

Dosage and Technique

We have attempted in most cases to deliver to the gland a dose of between 6,000 to 8,000 rads.‡

The cases reported here all had preliminary tracer drinks of radioactive iodine, and from measurements following these we estimated the number of millicuries required to deliver the desired radiation dose. The actual dose delivered was estimated retrospectively from measurements made over seven days following the therapy drink.

The data used for both prediction and retrospective estimation of the dose in this series of cases were: (i) the peak percentage uptake of the isotope by the

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‡1 rad = 100 ergs per gramme of tissue.

gland (U) ; (ii) the total or effective half-life of the iodine in the gland (T) ; (iii) the mass of the thyroid (W). In the calculation of the rad dosage (D), the formula $D = \frac{164 \times T \times U \times M}{W}$ was used, where M is the number of millicuries in the drink administered.

Of these factors the most difficult to assess is the gland size. In the first twenty cases it was estimated by palpation, but later this was supplemented by physical measurements with a collimated Geiger counter. Measurements were made in two planes, and this enabled a diagram to be constructed of the distribution of activity in the neck so that the mass of the gland could be estimated (Blomfield *et al.*, 1953). The use of the Geiger counter in these measurements, however, required drinks of 100–200 μ c., which may have produced biological changes in the gland, since drinks totalling as little as 200 μ c. have been shown, especially in children, to have a biological effect (Werner *et al.*, 1952). By using a collimated scintillation counter it is now possible to reduce the drink required for estimation of the size of the gland to 50 μ c. An estimate of the biological half-life of the isotope was obtained at the same time.

Procedure

Preliminary radioactive iodine tracer study was usually arranged as an out-patient investigation, and from it the necessary estimates of gland size, peak uptake of radioactive iodine, and effective half-life of the isotope in the gland were obtained.

Thereafter the patient was admitted to hospital, was given a therapeutic drink, and remained in the wards for a further week, during which daily gland counts were carried out. If home conditions permitted she was discharged on the seventh day after therapy. Her subsequent course was supervised at the endocrine clinic, where she attended at monthly intervals for two months, and thereafter, as her progress warranted, at longer intervals.

The assessment of the result was made on clinical grounds. In all doubtful cases, however, the patient was readmitted to hospital for further detailed study. The sleeping pulse rate and the basal metabolic rate were determined, and radioactive iodine diagnostic tests were carried out, the latter being interpreted cautiously after radio-iodine therapy. Post-therapy hypothyroidism was similarly assessed on clinical grounds and further investigated by estimations of serum cholesterol and basal metabolic rate and by electrocardiography. Such cases were photographed and fully reviewed after six weeks' treatment with L-thyroxine sodium.

In those patients whose clinical condition was of such severity as to necessitate rapid control of the thyrotoxic

state we used one of the antithyroid drugs. A few days after discontinuing the drug we carried out our procedure as for previously untreated patients.

Results

In all, 140 cases were reviewed ; of these 106 were female and 34 male, giving a female: male ratio of 3:1. The average age of the treated cases was 48.9 years.

Table I shows the condition of the thyroid gland of the treated cases, from which it will be seen that the method has been applied to cases of thyrotoxicosis irrespective of the type of gland. The gland types were classified by palpation except in the post-operative group. The largest group had diffuse glandular enlargement (47%), with nodular enlargement next in frequency (20%). In 20 cases (14%) the gland was not enlarged, and in 17 (12%) the disease had recurred after previous thyroidectomy. In 6 cases (4%) a single toxic adenoma was thought to be present ; these cases were treated because of the coexistence of cardiac disease or because surgery was refused.

The clinical status of the patients at the time of assessment, and the number of treatments required to give the final clinical result, are shown in Table I. 118 (84%) cases are euthyroid, 87 of which (62% of the total number treated) were successfully cured with one drink. Two drinks were required in 25 (18%) cases, and in 6 (4%) three or more doses were required. It is our practice to allow four to six months to elapse between successive doses, since we have found that improvement may continue over this period of time. Nearly all patients are improved to some extent following a dose of radioactive iodine, so that this delay is relatively unimportant.

Of the 6 cases requiring three or more treatments, 5 required three and 1 required five. The last was a young woman who had a post-operative recurrence which was refractory to methyl thiouracil. She had a very large recurrent diffuse goitre and was extremely ill. She proved relatively resistant also to radioactive iodine and required five doses of the isotope over a period of two years, totalling 70.2 mc. and delivering an estimated 25,000 rads to the gland before she became euthyroid. One patient died from cerebral haemorrhage two days after receiving treatment, an incident which we do not relate in any way to radio-iodine administration. The average interval between treatment and the establishment of euthyroidism for single-dose cures was about 4.5 months, but since patients are not seen more frequently than once a month after therapy the actual time is somewhat less than this.

Four cases relapsed after apparently successful first treatments—two after eight months and one each after nine and ten months respectively. Two had nodular glands, in one the gland was not enlarged, and one was a recurrence after partial thyroidectomy. All have become euthyroid after a second treatment and have remained so.

Hypothyroidism.—Seventeen cases (12%) became hypothyroid following therapy (Table I)—15 after one drink and one each after two and three treatments. The average interval between therapy and established hypothyroidism for single treatments was eight months, with a range of three

TABLE I.—*Clinical Results of Radio-iodine Therapy. Minimum Follow-up, One Year*

Type of G and	No. of Cases	% of Total	Clinical Result								
			Euthyroid			Hypothyroid			Still Toxic		
			Total	One Treatment	2 or More Treatments	Total	One Treatment	2 or More Treatments	Total	One Treatment	2 or More Treatments
Diffuse	66	47	57	43	14	7	6	1	2	—	2
Nodular	28	20	25	16	9	1	1	—	1	1*	—
Not enlarged ..	20	14	15	12	3	4	4	—	1	—	1
Post-operative recurrence ..	17	12	13	9	4	4	3	1	—	—	—
Single adenoma ..	6	4	6	5	1	—	—	—	—	—	—
Not known	3	2	2	2	—	1	1	—	—	—	—
Total	140	99	118 (84%)	87 (62%)	31 (22%)	17 (12%)	15	2	4	1	3

One patient with a nodular goitre died of a cerebro-vascular accident two days after treatment and has been omitted from the results column of the table.

* Refused further therapy.

months to three years. We have not used the term "myxoedema" to describe these cases, because few of these patients showed the full syndrome. All degrees of hypothyroidism can occur, and the amount of thyroxine necessary to keep such patients in normal thyroid balance varies. Thus, of our 17 hypothyroid cases the daily dose of L-thyroxine sodium required to maintain normal thyroid balance is only 0.1 mg. in 9 patients, and only one requires 0.3 mg.

Inadequate Treatment.—At the time chosen for assessment four patients were still toxic (Table I), though all were improved. One declined further treatment because she felt so well, and the other three were subsequently re-treated and became euthyroid.

Factors Influencing Failure Rate

Information about many of the factors which could influence the final result has been obtained in the course of the study, and has been subjected to a variance analysis by one of us (J.C.J.). The analysis was restricted to the

results of the first or a single drink of the isotope, and the rad dose quoted is that estimated retrospectively after the therapy drink.

The failure rate (ratio of patients who remained toxic to the total number treated) can be correlated with the administered dose in rads, the mass of the gland, and the concentration of protein-bound radio-iodine in plasma 48 hours after the tracer dose (P.B.¹³¹I). Table II and the Figure demonstrate a definite relationship between dose and failure rate, although, using the chi-squared test, no significant difference in the results was obtained in the groups that received between 6,000 and 11,000 rads.

Figure showing relationship of rad dosage delivered to the thyroid gland to the clinical result, after the first drink of radioactive iodine to 140 patients.

Tables III and IV demonstrate the relationship of failure rate to gland mass and to P.B.¹³¹I. There was shown to be no correlation between rad dosage and either gland mass or P.B.¹³¹I, so in both instances results over the whole dose range are compared. Higher failure rates occurred with the larger glands and with higher blood concentrations, the results in both instances being significant on the chi-squared test at the 2% level.

No correlation was found between failure rate and age of patient, type of gland, or total half-life of ¹³¹I in the gland, this last finding being different from that of Schmidt and Nadelhaft (1953), who showed a higher failure rate in patients in whom the half-life was long.

TABLE II.—Relationship of Clinical Result to Rad Dosage

Dose (Kilorads)	Still Toxic	Euthyroid	Hypothyroid	Failure Rate: Still Toxic/Total
1-1.9 ..	2	0	0	1.0
2-2.9 ..	0	1	0	0.0
3-3.9 ..	2	0	0	0.67
4-4.9 ..	8	9	0	0.47
5-5.9 ..	8	9	2	0.42
6-6.9 ..	2	15	4	0.10
7-7.9 ..	3	13	4	0.15
8-8.9 ..	5	16	0	0.24
9-9.9 ..	4	10	0	0.29
10-10.9 ..	3	5	1	0.33
11-11.9 ..	0	5	0	0
12-12.9 ..	0	2	1	0
13-13.9 ..	0	1	2	0
14-14.9 ..	0	2	0	0
Total ..	37	87	15	0.27

TABLE III.—Relation of Clinical Result to Mass of Gland

Mass of Gland (g.)	Still Toxic	Euthyroid	Hypothyroid
30-49 ..	3	26	3
50-69 ..	7	30	9
70-89 ..	10	16	2
90-109 ..	6	9	1
>110 ..	11	6	0

TABLE IV.—Relationship of Clinical Result to 48-Hour P.B.¹³¹I

Plasma P.B. ¹³¹ I, % Dose Litre at 48 Hours	Failure	Euthyroid	Hypothyroid
<0.5 ..	2	10	2
0.5-0.99 ..	4	26	5
1.0-1.49 ..	8	24	6
1.5-1.99 ..	6	8	0
2.0-2.49 ..	4	3	1
2.5-2.99 ..	4	4	0
>3.0 ..	6	3	0
Not known ..	3	9	1
Total ..	37	87	15

From the practical point of view the fact emerges that the size of the gland and the 48-hour P.B.¹³¹I are important factors to be taken into account in prescribing the rad dosage. It is generally accepted that the failure rate is higher in nodular goitres than in diffuse goitres, or, in other words, nodular goitres should be given a higher radiation dose than would be judged necessary from a consideration of the size of the gland alone. Our results are consistent with this view. The relatively small number of cases studied and the wide range of rad dosage given make statistical evaluation inconclusive.

Other Effects of Therapy

Gland Shrinkage

Enlarged glands always become smaller and feel firmer after radioactive iodine therapy. The diffusely enlarged type usually returns to normal and nodular enlargement becomes less obvious. We have not observed early swelling of the gland after the drink, and we do not think there is any danger in using radio-iodine treatment in patients with compression of the trachea or with retrosternal glands.

Exophthalmos

Of the present series, 46 cases (33%) had exophthalmos of varying degree of severity, and in some it was the reason for their reference for radio-iodine therapy. It has improved considerably in many, and in no case in this series has it become worse.

In two subsequent cases, however, exophthalmos has progressed after otherwise successful treatment with the isotope. The first of these was a man who had light perception only in his right eye as a result of an accident at work six years previously. He presented with marked bilateral exophthalmic ophthalmoplegia and a severe degree of thyrotoxicosis with uncontrolled auricular fibrillation. Two months after a second therapeutic drink he developed a right hyphaemia with additional gross exophthalmos and chemosis. In view of the haemorrhage into the anterior chamber, blood studies were made; these showed normal bleeding, clotting, and prothrombin times, and red cell, white cell, and platelet counts were normal. A right enucleation was carried out. He is now in normal thyroid balance, and the degree of exophthalmos in his left eye has not altered since before therapy.

The second patient was a man with marked bilateral exophthalmos and thyrotoxicosis. Two months after otherwise successful radioactive iodine therapy the degree of exophthalmos increased, with the development of chemosis. The condition continued to progress in spite of every therapeutic measure, and decompression has been only partially successful. He still has gross exophthalmos, with considerable impairment of vision.

Pregnancy

As we have already pointed out, pregnancy is an absolute contraindication to the use of radioactive iodine. Two of our younger patients, however, unwittingly received treatment while pregnant. In one, conception had occurred some three weeks before the therapeutic dose, and in the other it followed about a week after a second (successful) treatment. In both cases pregnancy continued without upset and resulted in the full-term birth of healthy babies who have since developed normally.

Complications

In the previous presentation of our results with radioactive iodine (Blomfield *et al.*, 1951) one patient was reported who had a transient exacerbation of thyrotoxic symptoms following the therapeutic drink. No further episodes of this nature occurred in the present series, and indeed the method has been wholly free from any untoward immediate complication. A few patients complained of transient aching over the front of the neck for a few days after the therapeutic drink, but it was not severe enough to require the use of the mildest analgesics, and local tenderness could not be demonstrated in these or other cases.

Two patients developed urticaria a week after treatment, and in both it required continuous antihistamine therapy for many weeks before abating.

One patient developed transient thrombocytopenic purpura about 2½ months after treatment and about two weeks after becoming euthyroid. She had had a small dose of the isotope giving 5,700 rads to the thyroid gland, and her blood dose was only 5 rads. The condition cleared without therapy and she has remained in normal thyroid balance ever since (2½ years), with no further purpuric episodes. In view of the trivial blood dose and the fact that thrombocytopenic purpura is a well-known, if rare, complication of thyrotoxicosis (Caldwell and Meikle, 1953; Roberts, 1948; Evans and Perry, 1943), the grounds for indicting the isotope in this case seem to be slender. Blood counts have been carried out very frequently before and after isotope therapy for thyrotoxicosis, and in none has any significant alteration in the count taken place.

"*Rheumatic*" Complications.—Fifteen patients have complained of "rheumatic" symptoms—either articular or non-articular—after isotope therapy. The "rheumatic" lesions present in such cases are shown in Table V. Two

TABLE V.—"Rheumatic" Lesions Following ¹³¹I Therapy

Rheumatoid arthritis type	2
Osteoarthritis type	4
Non-articular rheumatism	7
Gout	1
Prolapsed intervertebral disk	1
	15 (11%)

patients developed a rheumatoid-like arthritis. In one of these it was an exacerbation of an old lesion and occurred four months after the drink of isotope. The pain responded well to aspirin, and the patient was eventually left with no residual disability. The other case had no previous history of arthritis, and developed fairly typical rheumatoid changes some two months after therapy. The condition ran a prolonged course, but is now (2½ years after radioactive iodine treatment) steadily improving, with increasing functional capacity. Four patients have had symptoms of osteoarthritic lesions with involvement of single large joints (hip and shoulder), and one of these with shoulder arthritis developed, in addition, some progression of a Dupuytren's contracture that had been present for years in the fingers of her left hand. The commonest complaint after therapy is of non-articular "rheumatism." This most frequently involves the neck and shoulder region. In no case has it been of more than average severity, and in all it has occurred about four to six weeks after therapy. Each case has recovered completely.

Discussion

The problem of the choice of suitable cases for radio-iodine therapy becomes more important as it becomes increasingly used. There is still, however, considerable difference of opinion about the best method of treatment of thyrotoxicosis. The disadvantages of the antithyroid drugs are the high rate of relapse after they are discontinued and the incidence of granulocytopenia or agranulocytosis, deficiencies from which not even the latest additions to the series are wholly free.

Surgery has been made extremely safe by the pre-operative use of antithyroid drugs, and in the best hands the mortality rate is less than 0.5%, although there is no doubt that where experience and specialized skill are not available it is considerably higher. The morbidity rate, however, remains significant, and tetany from parathyroid damage, section of the recurrent laryngeal nerve, wound sepsis, secondary haemorrhage, and adherent scars necessitating resection, as well as the pulmonary and other complications common to any surgical procedure, have all been recorded. It will be remembered, too, that bad operative risks are not usually subjected to surgery.

The obvious advantages of radio-iodine treatment are its immediate safety, and the certainty of being able to produce a remission with a minimum of discomfort to the patient, although this is achieved somewhat more slowly than by other therapeutic measures. Its disadvantages are the possible late development of carcinomatous changes in the gland and the somewhat high incidence of hypothyroidism. We shall therefore discuss these and the possible relationship of "rheumatism" to radio-iodine therapy in more detail before considering the best method of administering the isotope.

Carcinoma Hazard of Radioactive Iodine Therapy

Ionizing radiation is well known to have carcinogenic properties, and the use of radioactive iodine in the treatment of thyrotoxicosis raises the question of the degree of risk of subsequent neoplastic change in the thyroid to which the patient is exposed. The only suggestive evidence is from observations on animals. Thus, Goldberg and Chaikoff (1952) gave radio-iodine to rats and found that 7 out of 25 animals developed neoplastic changes in the gland. The doses of radiation, however, used by these investigators were enormous in comparison with those given for therapeutic purposes in man. The animals received 400 µc. of radio-iodine, which is comparable to a drink of 130 mc. to a human adult, and therefore about 14 times greater than the average single therapeutic dose. Doniach (1953), again using rats and giving doses of radio-iodine comparable to those used in the treatment of thyrotoxicosis in man, found no evidence of neoplastic change when radio-iodine was used alone, although he did note some increased simple adenoma formation. In his series, malignant change followed therapeutically comparable doses only when methyl thiouracil was given for long periods after the radio-iodine. This is in keeping with previous observations of carcinogenesis (Bielschowsky, 1944) that, while any one of two stimuli may alone be unable to produce thyroid carcinoma, their combined effect may do so. It is important to note that no experimental work in animals has demonstrated the development of carcinoma from the use of the isotope alone in doses comparable to those used therapeutically in man.

From our knowledge of carcinogenesis it probably takes about 20 years in man for a neoplasm to develop after exposure to ionizing radiations. Radioactive iodine has been employed in the therapy of thyrotoxicosis for 15 years, and so far no case of thyroid cancer has been reported following its use, though many thousands of cases have been treated by this method. One might have expected some cases already to have shown neoplastic changes if the risk of their development was significant, since skin cancer has been reported to have followed direct radiation after an interval of six years (Porter *et al.*, 1907).

It is known, further, that the type of radiation most likely to provoke carcinomatous change is small doses fractionated over a long period of time—so-called chronic radiation. The radiation from radioactive iodine is, however, of a more acute type, and is delivered in intense form over a short-lived period. It is thus, *a priori*, of the type least likely to result in neoplastic sequelae. The thyroid gland, moreover, appears to be relatively resistant to carcinoma, only about 0.4% (Tod, 1950) of all human cancer being of thyroid origin, and the Registrar-General's Statistical Review for 1952 shows that in that year 0.07% of all deaths, and 0.4% of total deaths from all neoplasms, were due to thyroid carcinoma. Furthermore, Quimby and Werner (1949) have shown that the risk of the development of thyroid cancer following conventional x-ray therapy for thyrotoxicosis, if it exists at all, is extremely low.

Finally, several careful studies of post-mortem thyroid histology have been carried out in cases which had received radio-iodine up to eight years before death, and no evidence of malignant change has been found, although some of these patients had received enormous doses of radiation with the object of producing myxoedema as a therapeutic measure for irreversible heart disease (Freedberg *et al.*, 1952; Dobyns *et al.*, 1953; Chapman *et al.*, 1954).

We feel, therefore, that the risk of neoplastic change in the thyroid following radio-iodine therapy is small, and we are impressed by the absence of any evidence that it is likely to occur in man following the use of radio-iodine alone in therapeutic doses. None the less, the final answer to the problem must await the passage of another decade and, in common with most workers in this field, we continue to limit the therapeutic use of radio-iodine to patients with a life expectation not exceeding 20 years with the exceptions stated in the introduction to this paper.

Post-Therapy Hypothyroidism

The rate of 12% post-therapy hypothyroidism in the present series is weighted by three patients out of our first seven cases who, from inexperience, were overtreated; in two of them repeat doses were given within an interval that we now know to be too short. If these first seven cases were excluded the overall incidence of post-therapy hypothyroidism would be reduced to 11% of 133 cases, a figure comparable to the one of 9% obtained in an analysis of the results of 1,720 cases taken from centres in U.S.A. and Europe, and reported by Seed and Jaffé (1953).

This incidence is higher than that following thyroidectomy, for which a mean rate of 5.4% of 6,442 cases emerges from a series of results from different centres cited by Bartels (1953). Post-operative myxoedema varied widely, however, in the different groups—from 2.9% (Grace and Weeks, 1941) to 21% (Crile and McCullagh, 1951). Crile (1949) has observed that the incidence of post-operative hypothyroidism is inversely proportional to recurrent thyrotoxicosis, and Bartels (1953) found it to be twice as high after second thyroidectomies.

It will be seen from Table VI that the average dose of radio-iodine which produced subsequent hypothyroidism was not greater than the average required to produce

our inability to measure radiation doses accurately must be borne in mind in assessing the significance of comparative figures.

New light on this problem has been shed by the work of Greene (1953), who has studied the same problem following thyroidectomy. He has demonstrated a remarkably close correlation between post-operative myxoedema and the presence of lymphadenoid changes in the thyroid. Further, he has shown that, histologically, all grades of lymphadenoid change can exist, from single or scattered nodules to fully developed Hashimoto's disease, and that the incidence of post-operative hypothyroidism increases directly with the degree of lymphadenoid involvement, so that it is 100% in cases with fully developed Hashimoto's disease. Similar observations have been made by Bartels (1953). It is also a well-known surgical observation that the incidence of post-thyroidectomy hypothyroidism is not always referable to the amount of gland left behind, and, as Crile (1949) contends, it is the functional capacity of the remnant, and not its amount, that determines the state of post-operative thyroid balance. Clearly, the existence in the gland of progressive lymphadenoid changes will lead eventually to myxoedema in some cases, whether treated or not, and this end-stage will certainly be accelerated if a major part of the gland is excised surgically or destroyed by radiation. Greene (1953) stresses the fact that there is no clinical method of determining the existence of such changes in the gland before treatment, although he believes that they are more common in the older age group of thyrotoxic patients. We feel that these observations are especially applicable to our series because of the selection of the older age groups inherent in the use of the method. It would seem probable from Greene's work that a certain basic incidence of post-therapy hypothyroidism is inevitable with the treatment of thyrotoxicosis by any radical means, and that this incidence will increase with the age group of the patients treated.

Fraser *et al.* (1954), however, claim that preliminary treatment of patients with a drug of the thiouracil series combined with thyroxine makes the distribution and retention of radio-iodine in the thyroid gland more uniform. Only one of their 32 patients developed permanent myxoedema.

"Rheumatic" Sequelae

Of the "rheumatic" complications the non-articular variety almost invariably recovers promptly, and it is our impression that it occurs in association with a phase of transient post-therapy hypothyroidism. This does not apply to those cases which develop a rheumatoid-like picture. It seems most improbable that there is any direct relationship between the isotope *per se* and arthritic change. Numerous observers have reported a relationship between joint symptoms and thyroid function. The generally accepted opinion is that, while disturbed thyroid function has no aetiological significance in rheumatoid arthritis, pre-existing arthritis in thyrotoxicosis may be made either better or worse by treatment of the thyroid condition. The relevant literature is well summarized by Laine *et al.* (1954), who report in their own series of cases of thyrotoxicosis the aggravation or emergence of rheumatoid arthritis by thyroidectomy. Of our cases two patients developed rheumatoid arthritis after radio-iodine therapy, but in three others (one of the present series and two subsequently) who had rheumatoid arthritis of long standing no aggravation of joint symptoms occurred when they were euthyroid. Prévôt and Horst (1952) have also reported "fibrositic" lesions (10%) and rheumatoid arthritis (3%) after radio-iodine therapy; their cases of arthritis were victims of the disorder before isotope treatment. It seems probable that these "rheumatic" symptoms are in some way connected with alterations in thyroid function and may occur however this is induced.

Problems of Dosage

In our series of cases we have attempted to deliver to the gland a dose of between 6,000 and 8,000 rads in a single dose. We regard our single-treatment euthyroid

TABLE VI.—*Relationship of Clinical Result After a Single Treatment to the Size of the Millicurie Drink and to the Rad Dosage*

Clinical Result	Dose (Rads)		Drink (mc.)		Gland Size (g.)	
	Mean	Range	Mean	Range	Mean	Range
Euthyroid ..	8,000	2,800-14,300	9.6	2.4-22.4	62	30-175
Hypothyroid ..	7,950	3,800-13,700	9.2	5.2-15.9	55	30-90
Still toxic ..	5,700	3,500-10,500	12.2	4.0-31.6	90	35-270

normal thyroid function in other cases, and, indeed, several patients have become hypothyroid after doses which have been inadequate to make others euthyroid. The explanation of this phenomenon may lie in individual variations in the biological sensitivity of different glands to radiation, though

rate of 62% and our overall myxoedema rate (12%) as reasonably satisfactory. The chief difficulties which militate against precise dosage are the accurate assessment of gland size and the discrepancy between predicted and actual doses.

In spite of the use of scintillation counting techniques the errors in estimation of gland size must still be considerable, although we have not been able to check this in detail. The physical measurements, however, indicate the volume of the thyroid tissue actually taking up radio-iodine, and they are also of considerable value where the gland is in part retrosternal. Even so, it may be that this difficulty in accurately assessing gland size is one of the factors leading to overdosage and hypothyroidism. This point has recently been emphasized by Kelly (1954) in an analysis of the degree of error involved in "gland-size-estimating techniques," in which he found an average error of +49% in the method in use at the Veterans Hospital, Houston, Texas.

There is, in addition, a discrepancy between the predicted dose and that found retrospectively to have been delivered by the therapeutic drink (Blomfield *et al.*, 1953). In this series the mean ratio of the actual to the predicted dose was 0.98 ± 0.33 (S.D.). Part of this difference is due to the inaccuracy of physical measurement, but there remains a considerable biological factor. This mostly arises from changes in half-life between tracer and therapy drinks, although occasionally we find that the uptake of the therapy drink falls considerably short of that found following the tracer drink.

Current Procedure for Dosage Estimation

In order to determine the number of millicuries in the drink required to give the prescribed rad dose for cases treated after those recorded in this report, we have abandoned the use of detailed measurements of peak uptake and half-life at tracer level. For dosage prediction we now use the percentage of administered ^{131}I retained in the gland at 48 hours following the tracer drink. From the examination of the tracer and therapy measurements in our first 190 treatments we have derived a mean factor which relates the 48-hour percentage uptake to the total dose which the gland will receive for each millicurie of ^{131}I per g. of thyroid.* We now use this factor. With the method of prediction used in our first 190 treatments, the mean value of the ratio of actual to predicted dose was 0.98 ± 0.33 (S.D.). A retrospective application of our present formula for dose prediction showed that if this method had been used for these cases the mean value of the ratio would have been 0.96 ± 0.31 (S.D.). There is no statistical difference between these values. The method considerably reduces the amount of labour necessary, since the effective half-life need not be determined with the tracer dose.

For the retrospective assessment of the therapy dose actually given, we continue to measure peak uptake, and half life after the drink of the isotope.

Dosage Prescription

Our results indicate that for a given rad dose the failure rate is significantly higher for larger gland sizes and for high-protein-bound ^{131}I plasma concentration at 48 hours. We now aim to give 7,000 rads for diffusely enlarged glands, with 5,000 to 7,000 rads for smaller glands, particularly small post-operative recurrences. For large and multinodular glands we give 8,000 rads or more, and we may prescribe a higher dose for those with high protein-bound ^{131}I in their plasma after the tracer dose. We also tend to give rather more to elderly or severely toxic patients, or to those with severe cardiac involvement. The usual doses are smaller than those recommended by Fraser *et al.* (1954). This might be because the antithyroid drugs which these observers use before the radio-iodine is given may render the thyroid more resistant to the effects of ionizing radiation. Dale (1947) has shown that thiouracil increases radio resistance of enzymes in solution.

*This gives the formula:

$$\text{Expected dose in rads/mc.} = \frac{805 \times 48\text{-hour \% gland uptake}}{\text{gland mass (grammes)}}$$

Conclusions

Radio-iodine treatment of thyrotoxicosis has now fully emerged from the experimental stage, and the general trend of recent work suggests that a wider range of patients might legitimately be treated by this method. We do not believe that there is any adequate evidence of a significant risk of the late development of carcinomatous changes in the gland. No one can yet be certain about the statistical risks involved, and it is clearly this point which is important. Provided it is no greater than, say, 0.1%, isotope therapy will still be safer than any alternative form of treatment. In time this figure will be known with a greater degree of certainty, and our recommendations about the selection of suitable cases must therefore remain as stated in the introduction to this paper. On balance, however, we favour the view of those who hold that radio-iodine therapy will ultimately be shown to be free from risk and that it will probably become the standard treatment for thyrotoxicosis.

The chance of the development of myxoedema from radio-iodine therapy is on the average somewhat greater than from operation, but we believe that with improved techniques it will become less, although it is possible that any method which destroys a part of the thyroid gland must inevitably lead to the development of myxoedema in a proportion of cases. Rheumatic complications are transitory and not related specifically to radio-iodine treatment.

Although we used an elaborate method of dose prediction in this series our results have not been better than those reported by others whose dose prescription has been based on gland size alone or other empirical formulae. As a result we have already simplified our technique so that the gland size and 48-hour uptake are the only two factors required for dose prescription. While it is probably sufficient in many cases to prescribe a therapeutic drink based solely on gland type and size, it is felt that experience with ^{131}I therapy is as yet too short to allow a general adoption of empirical dose prescription, and that those centres with the necessary experience and equipment should continue their efforts to achieve more accurate dose prediction.

Summary

The results of radioactive iodine treatment of 140 cases of thyrotoxicosis followed for a minimum period of one year are recorded.

A technique aimed at delivering a single dose of 6,000 to 8,000 rads to the gland has been used.

62% of patients were made euthyroid with one therapeutic drink, and ultimately 84% were euthyroid, 12% showed evidence of hypothyroidism, and at the time of review 4% were still toxic.

Statistical evaluation of the results shows that for a given rad dosage the success of a first treatment was related to the mass of the gland and to the percentage of protein-bound radio-iodine in the blood 48 hours after the administration of a tracer dose.

It is concluded that at present there is no convincing evidence that radio-iodine treatment is likely to lead to the development of late malignant changes in the thyroid gland.

Some cases developed both articular and non-articular rheumatism, probably unrelated to isotope therapy.

The present criteria for the selection of cases and dosage assessment are discussed.

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ANTIBODY RESPONSES AND CLINICAL REACTIONS WITH SALINE AND OIL ADJUVANT INFLUENZA VIRUS VACCINES

SECOND PROGRESS REPORT BY THE MEDICAL RESEARCH COUNCIL'S COMMITTEE* ON CLINICAL TRIALS OF INFLUENZA VACCINE

In the past few years a number of reports have appeared on the adjuvant effects obtained by adding various chemical substances to bacterial or virus vaccines. These materials produced an enhanced antibody response to the antigens used, but severe local reactions were at times encountered in man. A relatively stable water-in-oil emulsion prepared by using an emulsifier known as "arlacel" and a mineral oil ("bayol F") was introduced by Freund *et al.* (1948a, 1948b), and this was found by Salk and Laurent (1952) to be relatively free from undesirable side-effects. Salk *et al.* (1952) used an influenza virus vaccine to which arlacel and bayol F had been added, and confirmed the adjuvant effect which these materials produced in man. They found that the antibody response was enhanced in amount so that the titre of serum antibodies after use of one-tenth the normal amount of antigen in an adjuvant menstruum was greater than that produced by the full amount of antigen in a saline medium. The antibody response was also prolonged in duration, and twelve months after inoculation the level had fallen only slightly from the peak titre. Salk further stated (1953) that the breadth of antibody response was increased so that an injection of a single antigenic type of influenza virus A caused anti-

bodies to be formed against a related yet distinct antigenic type of virus A as well as against the homologous antigen.

These reports led the Medical Research Council's Committee on Clinical Trials of Influenza Vaccine to explore the use of oil adjuvant influenza vaccines in this country. It was decided first to compare the serological response to a single (monovalent) influenza A vaccine in saline to which aluminium phosphate had been added with that found when the vaccine was suspended as a water-in-oil emulsion. A supply of purified arlacel and of a mineral oil was obtained through the courtesy of Dr. Salk. The Liverpool strain of influenza virus A (A/Eng/1/51) was selected as suitable for use partly because this strain had been used with apparent success in earlier trials in Great Britain and partly because egg- and mouse-adapted lines or substrains were available.

Since the previous report of this Committee (1953) evidence has been obtained in the laboratory that mouse-adaptation of an influenza virus appears to confer an improved antigenicity upon the strain when the latter is compared with the same virus passaged only in eggs. This was first shown to be true by immunization experiments in mice (Isaacs and Sampaio, 1953), and later the serological response in man to a mouse-adapted virus (Liverpool, A/Eng/1/51) was compared with that exhibited to the egg-adapted line of the same strain. Table I shows the geometrical mean titre of serum anti-

TABLE I.—Geometric Mean Haemagglutination-inhibition Titres of Individuals Vaccinated with Saline Vaccines from Egg- and Mouse-adapted Lines of A/Eng/1/51 Virus and Tested with Homologous and Heterologous Viruses

Virus	Serum	Vaccine			
		A/Eng/1/51 Mouse-adapted		A/Eng/1/51 Egg Line	
		Antibody Titre	Ratio	Antibody Titre	Ratio
Homologous	{ Pre-inoculation Post-inoculation	9.5 107	11.2	17.8 89.0	5.0
Heterologous	{ Pre-inoculation Post-inoculation	17.8 100	5.6	10.0 47.9	4.8

Notes:—(i) Sera with titres < 10 were given an arbitrary score of 5.
(ii) The antigenic relationship between the egg line and the mouse-adapted A/Eng/1/51 virus was tested by haemagglutination-inhibition tests with ferret antisera. The titres were as follows:

Virus	Ferret Antisera	
	A/Eng/1/51 Egg Line	A/Eng/1/51 Mouse-adapted
A/Eng/1/51 egg line	5,120	3,840
A/Eng/1/51 mouse-adapted	7,680	10,240

bodies in 57 men before and after inoculation subcutaneously with an egg-virus vaccine suspended in saline and similar titres in a further 78 men receiving a mouse-adapted virus vaccine containing the same concentration of virus. The antibody response to the latter virus appeared to be superior to that produced by the egg virus, as determined by the haemagglutination-inhibition test.

These previously unpublished experiments reported to the Committee in 1953 suggested that a further trial comparing mouse- and egg-virus vaccines made from the same strain but to which oil adjuvants had been added would give useful additional information. It was therefore decided to use the mouse-adapted line of the Liverpool strain of virus A both in a saline and in an oily medium, and to use the egg strain in an oily medium only. This study was designed to test the antibody response to these three vaccines and to obtain information upon the local and general reactions consequent upon their inoculation.

*Members of the Committee: Professor C. H. Stuart-Harris (chairman), Dr C. H. Andrewes, Dr B. E. Andrews, Brigadier G. T. L. Archer, Dr W. H. Bradley, Brigadier A. E. Campbell, Surgeon Captain T. L. Cleave, Professor R. Cruickshank, Professor A. Bradford Hill, Dr F. Himmelfeit, Dr A. Isaacs, Dr F. O. MacCallum, Dr J. C. McDonald, Dr W. J. Martin, Dr J. J. O'Dwyer, Professor Wilson Smith, Dr I. N. Sutherland, Group Captain J. S. Wilson, Brigadier A. E. Richmond (Secretary).