Papers and Originals

Clinical Trial of Different Doses of ^{131}I in Treatment of Thyrotoxicosis

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Radioactive iodine, principally ^{131}I , has been widely used for the treatment of thyrotoxicosis for over 15 years. This method has many advantages, particularly that it causes no discomfort to the patient, does not require admission to hospital, and a recurrence of thyrotoxicosis is rare. At first the main concern was that the irradiation might induce malignant disease, but the evidence to date suggests that the hazard is negligible, particularly if ^{131}I therapy is confined to the older age groups. The irradiation dose to the bone marrow is low, and the subsequent incidence of leukaemia is not significantly greater than that in the general population (Pochin, 1960, 1964; Green *et al.*, 1961). Thyroid neoplasms may follow irradiation of the thyroid in infancy and childhood, and cases have been reported after the use of ^{131}I for the treatment of thyrotoxicosis in children (Sheline *et al.*, 1962; Karlan *et al.*, 1964; Kogut *et al.*, 1965). Two cases of thyroid carcinoma have been reported after ^{131}I therapy of thyrotoxicosis in adults, but in both instances the carcinoma was probably present when the radioiodine was administered (Kilpatrick *et al.*, 1957; Staffurth, 1966).

Two definite disadvantages of ^{131}I therapy have emerged—namely, delay in controlling the hyperthyroidism and subsequently a rising incidence of hypothyroidism. These features have been stressed in several reports (Beling and Einhorn, 1961; Green and Wilson, 1964; Dunn and Chapman, 1964; Nofal *et al.*, 1966; Greig *et al.*, 1966). In some retrospective surveys of the results of ^{131}I therapy no relation could be established between the method of determining the dose of radioactive iodine and the subsequent development of hypothyroidism (Macgregor, 1963). However, examination of the results reported by Green and Wilson (1964), and of experiments on thyroid cell survival after irradiation (Al-Hindawi and Wilson, 1965), suggested that the increasing incidence of hypothyroidism with the passage of time was probably related to the dose. In these circumstances it was thought both justifiable and important to carry out a prospective clinical trial to clarify the effects of different doses of ^{131}I in the treatment of thyrotoxicosis. A preliminary report of this work has been published (Smith and Wilson, 1965).

Methods

Selection of Patients and Allocation in Trial.—The trial was begun on 1 June 1960. All patients referred for ^{131}I therapy of thyrotoxicosis were admitted unless they had previously received radioiodine therapy or surgical treatment or were suffering from severe cardiac complications of thyrotoxicosis. After the necessary assessments had been made they were allocated at random to the different treatment groups. Only a single dose of ^{131}I was given.

Calculation of Dose.—The method of calculating the amount of ^{131}I to be given was the same as that previously employed

in Sheffield (Blomfield *et al.*, 1959). Three different doses were used in the trials—the conventional one calculated to give about 7,000 rads to the thyroid, or twice or half this amount. Study of the factors involved has shown that these predictions are imprecise owing to fluctuations in uptake and persistence of ^{131}I in the thyroid and to errors in the assessment of the gland size. Differences between the uptake of the preliminary tracer dose and of the therapy dose and variability in the effective half-life of ^{131}I in the thyroid have been investigated previously (Blomfield *et al.*, 1959). The size of the gland throughout this trial was determined by palpation.

Estimation of Size of Thyroid.—In order to check on the reliability of the estimates of the weight of the thyroid gland, patients who were due to have a thyroidectomy were examined by the same doctors who were associated with the ^{131}I therapy. Before operation each doctor recorded independently his estimate of the weight, and then the mean was calculated. The excised portion was weighed, and an estimate was made by the surgeon of the amount of thyroid left in the body. The total weight of the gland was calculated, and this has been plotted against the estimate (Fig. 1). The correlation coefficient is +0.63 ($P < 0.001$).

FIG. 1.—Estimated mass of the thyroid gland in 107 patients plotted against the mass determined after operation.

Assessment of Progress.—The patients were seen at monthly intervals after the therapeutic dose of ^{131}I . If there was only a slow response to the radioiodine, so that troublesome features persisted, treatment with an antithyroid drug, usually carbimazole, was begun. The drug was given in a dose adequate to control the patient's symptoms, care being taken to avoid inducing hypothyroidism. The dose was gradually reduced, and finally stopped as soon as the treatment appeared unneces-

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sary. It was always stopped after two years in order to determine whether drug therapy was still required. If a relapse occurred a second course of drug therapy was given. No patient has been considered euthyroid after ^{131}I therapy until antithyroid drugs have been stopped for at least six months without recurrence of symptoms.

Diagnosis of Hypothyroidism.—The patients were reviewed regularly at three- to six-monthly intervals after they had been judged euthyroid. The development of hypothyroidism was diagnosed on the basis of clinical symptoms and signs, and confirmed both by serum-protein-bound iodine determinations and by ^{131}I tracer studies. If hypothyroidism appeared within the first year after ^{131}I therapy the patient was observed for at least three months to ensure that this was not a temporary phenomenon. L-Thyroxine sodium was used as substitution therapy, and the dose and regularity of medication were checked at intervals not exceeding six months.

Results

Initial Pilot Trial

The patients were treated with either the conventional dose of 7,000 rads that had been employed in Sheffield up to 1960, or twice this amount, or half. However, when 78 patients had been followed for six months it was found that the incidence of hypothyroidism was 19% in the 26 patients given twice the conventional dose, 7.5% in those given the conventional dose, and 4% in the half-dose group. These conspicuous differences were confirmed in the subsequent follow-up (Fig. 2). Though the control of the thyrotoxicosis was also more rapid in the double-dose group it was thought unjustifiable to continue to allot patients at random to this group in view of the initial high incidence of hypothyroidism. Accordingly the definitive trial was continued, admitting patients only to the conventional dose and half-dose groups.

FIG. 2.—Incidence of hypothyroidism in the 78 patients admitted to the pilot trial. ●---● conventional dose; ●—● half dose; ○ double dose.

Comparability of Groups and Losses from the Definitive Trial

The groups receiving the conventional dose and the half dose are closely similar in respect of age and gland size, and the calculations designed to give 7,000 rads and 3,500 rads to the gland are reflected in the mean mCi doses of ^{131}I (Table I). There were 21 deaths during the course of the trial—13 in the conventional-dose group and eight in the half-dose group; none could be related directly to thyrotoxicosis or the method of treatment. Six patients were excluded, as a second dose of ^{131}I had to be given between a year and three years after the initial dose because of toxic reactions to antithyroid drugs or the development of cardiac complications; two of these patients were in the conventional-dose group and four in the half-dose group. Six patients were lost to close follow-up owing to irregular attendance or emigration from the country. Though they have been traced and it is known that they are alive, the records are inadequate, and they have been excluded from the analysis; two were in the conventional-dose group and four in the half-dose group. This left 276 patients in the conventional-dose group and 270 in the half-dose group, and the report is based on a study of their progress.

TABLE I.—Comparison of the Two Groups in the Trial

	Conventional Dose Mean $\pm$ s.d.	Half Dose Mean $\pm$ s.d.
Age in years	55.3 $\pm$ 9.0	53.1 $\pm$ 8.1
Gland size (g.)	35.7 $\pm$ 11.4	37.8 $\pm$ 24.7
Dose ^{131}I (mCi)	5.0 $\pm$ 2.0	2.8 $\pm$ 1.6
No. of patients	276	270

Progress after ^{131}I Therapy

Euthyroid Patients.—The proportion of patients becoming euthyroid in each group was calculated at intervals of six months over a period of five years (Table II). These patients either never required antithyroid drugs or remained euthyroid for at least six months after treatment with antithyroid drugs was stopped. During the first two years after the therapeutic dose of ^{131}I more patients became euthyroid after the conventional dose than after the half dose, but thereafter the results were similar up to four and a half years. At the end of the fifth year more in the half-dose group were euthyroid.

Persistent Hyperthyroidism and Drug Therapy.—The numbers of patients either showing mild hyperthyroidism not necessitating additional treatment or requiring drug therapy to control the hyperthyroidism at the various intervals after the ^{131}I therapy are given under the heading "hyperthyroid" in Table II. It should be emphasized that in fact these patients were not disabled by continuing thyrotoxicosis, as all except the mildest cases were receiving antithyroid drugs to control their symptoms. Nevertheless, ^{131}I therapy alone was not sufficient to cure the thyrotoxicosis after the time intervals shown. Throughout the period of study the half-dose group contained a higher percentage of patients falling into this category. A total of 291 patients required antithyroid drugs in addition to the ^{131}I

TABLE II.—Results of the Two Groups in the Trial

Years	Conventional Dose							Half Dose						
	No. of Patients	Euthyroid		Hyperthyroid		Hypothyroid		No. of Patients	Euthyroid		Hyperthyroid		Hypothyroid	
		No.	%	No.	%	No.	%		No.	%	No.	%	No.	%
1	271	107	39.5	148	54.6	16	5.9	268	64	23.9	196	73.1	8	2.9
1½	242	116	47.9	107	44.2	19	7.9	234	72	30.8	152	65.0	10	4.3
2	220	115	52.3	85	38.6	20	9.1	213	88	41.3	114	53.5	11	5.2
2½	198	104	52.5	68	34.3	26	13.1	184	93	50.5	81	44.0	10	5.4
3	178	106	59.6	47	26.4	25	14.0	165	90	54.5	66	40.0	9	5.5
3½	135	83	61.5	27	20.0	25	18.5	130	83	63.8	39	30.0	8	6.2
4	104	69	66.3	15	14.4	20	19.2	100	66	66.0	25	25.0	9	9.0
4½	81	56	69.1	7	8.6	18	22.2	86	51	59.3	27	31.4	8	9.3
5	61	42	68.8	4	6.6	15	24.6	50	36	72.0	10	20.0	4	8.0
	31	21	67.7	1	3.2	9	29.0	27	23	85.2	2	7.4	2	7.4

therapy to control the thyrotoxicosis: 118 received the conventional dose of ^{131}I (43% of this group) and 173 the half dose (64% of this group).

Recurrence of Hyperthyroidism.—Particular attention was given to tracing patients who had been judged euthyroid to determine whether relapses occurred. None has taken place among the patients who became euthyroid after ^{131}I therapy alone. Among those who also received antithyroid drugs but were judged euthyroid six months after stopping this treatment 90 were followed for more than one year, and 45 of them for more than two years. There were only two recurrences of hyperthyroidism—one in the conventional-dose group and one in the half-dose group.

Hypothyroidism.—The incidence of hypothyroidism rose steadily in the group receiving the conventional dose of ^{131}I , but in the half-dose group notably fewer patients became hypothyroid, and the rise with the passage of time was conspicuously slower (Fig. 3). Patients becoming hypothyroid were treated with thyroxine. Among them there was no evidence of ill-health from failure to take the tablets regularly.

Fig. 3.—Incidence of hypothyroidism in the conventional-dose and half-dose ^{131}I therapy groups compared with that reported after partial thyroidectomy by Green and Wilson (1964). ●—● conventional dose; ●—○ half dose; ○—○ partial thyroidectomy.

Discussion

The trial shows clearly that halving the dose of ^{131}I decreases the incidence of hypothyroidism. After the conventional dose there was a steady increase in hypothyroidism, reaching 29% at five years, a figure similar to that reported in many other investigations where comparable doses of ^{131}I were employed (McGirr *et al.*, 1964; Crooks, 1965). When larger doses of ^{131}I were given the incidence of hypothyroidism was much greater, as in the series reported by Nofal *et al.* (1966). They gave a little over twice our conventional dose of ^{131}I , and after five years about 55% of their patients were hypothyroid. Their curve is similar to that obtained in the 26 patients in our pilot trial receiving the double dose (Fig. 2). On the other hand, the patients receiving half the conventional dose showed a much lower occurrence of hypothyroidism, about 8% at the end of five years. This only slightly exceeds the 5% seen in a previous series treated by partial thyroidectomy (Fig. 3). In determining the incidence of hypothyroidism a complete follow-up of all treated cases is essential. In our experience patients who fail to attend and are difficult to contact are often found to be myxoedematous when eventually traced, and indeed this is probably a factor in determining their unresponsiveness.

Hypothyroidism developing long after radioiodine therapy is probably due to the effect of irradiation on cell division. Animal experiments have shown clearly that the mechanisms involved in cell division are more radiosensitive than those controlling

biochemical function (Doniach, 1958; Greig, 1965; Philp, 1966). Irradiation impairs the synthesis of deoxyribonucleic acid (D.N.A.) in the thyroid and decreases the survival of thyroid cells (Al-Hindawi and Wilson, 1965). Studies of the histology and function of the human thyroid after ^{131}I therapy for thyrotoxicosis have shown bizarre nuclear changes and a decrease in the mass of active tissue (Dobyns *et al.*, 1953; Curran *et al.*, 1958; Eckert *et al.*, 1960). The effect of ^{131}I on thyroid-cell division and D.N.A. synthesis is long-lasting, and is closely related to the irradiation dose (Al-Hindawi and Wilson, 1965). These findings fit in closely with the observations in our clinical trial, and suggest that thyroid failure after ^{131}I therapy is due to gradual atrophy of the gland through failure of the cells to reproduce. The effect is less conspicuous with the smaller dose, but even here a slowly rising incidence is evident. A further reduction in the dose of ^{131}I would presumably lead to even less hypothyroidism but greater delay in securing control of the thyrotoxicosis without the aid of antithyroid drugs.

Thyroid neoplasms may be produced in rats by a low dose of ^{131}I followed by a course of antithyroid drugs (Doniach, 1958). It is probable that release of pituitary thyroid-stimulating hormone (T.S.H.) stimulated by the goitrogens is a factor in the induction of the carcinomas. The relevance of this work to the possible late development of human thyroidal cancer after a combination of irradiation and antithyroid drugs is unknown. However, it is a wise precaution to ensure that patients are not overtreated by antithyroid drugs, so that stimulation of the thyroid by T.S.H. is avoided.

In patients over 40 years old with uncomplicated thyrotoxicosis ^{131}I therapy does not necessitate admission to hospital, operation is avoided, and there is no risk of damage to the parathyroids and laryngeal nerve. There is thus much in favour of developing a method of using ^{131}I which decreases the incidence of hypothyroidism and affords a prospect of the patients remaining euthyroid for many years. The lower dose of ^{131}I which was used in this trial—about 75 $\mu\text{Ci/g.}$ of thyroid, representing on average 3,500 rads—is not necessarily ideal. Even with this amount there is a slowly rising incidence of hypothyroidism, but it is also noteworthy that over the five-year period the recurrence rate was extremely low. It is certainly much lower than that encountered in the series of surgically treated patients with a similar incidence of hypothyroidism (Green and Wilson, 1964). This suggests that further trials with slightly smaller doses of ^{131}I are needed to define the optional amount to render the patient euthyroid, prevent recrudescence of hyperthyroidism, and limit the incidence of hypothyroidism to less than 1% per year. It must be accepted that a substantial proportion of patients treated in this way will require antithyroid drugs during the first two years after ^{131}I therapy. Rapid control of thyrotoxicosis by ^{131}I alone and a low subsequent incidence of hypothyroidism are mutually exclusive.

Summary

The chief disadvantage in the treatment of thyrotoxicosis with ^{131}I was a high incidence of hypothyroidism, which rose steadily with the passage of time. A preliminary trial suggested that the incidence was related to the dose.

A definitive trial was then carried out in which thyrotoxic patients were allotted at random to two treatment groups. The first group, containing 276 patients, received a conventional dose of ^{131}I , 140 $\mu\text{Ci/g.}$ of thyroid, delivering about 7,000 rads. The second group (270 patients) received half this amount. Only a single dose of ^{131}I was given. Thereafter if the thyrotoxicosis did not remit satisfactorily antithyroid drugs were given; this was required in 43% of the patients receiving the conventional dose and in 64% receiving the half dose. The antithyroid drugs were tailed off as the effect of ^{131}I became apparent. The patients were not regarded as euthyroid as a

result of ^{131}I unless they had been off the drugs for at least six months.

The initial control of hyperthyroidism by ^{131}I alone was slower in the half-dose group. After three years the results were similar, two-thirds being euthyroid in each group. Thereafter they were better in the half-dose group. There was one recurrence of thyrotoxicosis in the conventional-dose group and one in the half-dose group.

The incidence of hypothyroidism rose steadily in the conventional-dose group from 8% after one year to 29% after five years. In the half-dose group it was reduced to 4% and 7% at the corresponding intervals.

The advantages of treating thyrotoxicosis with a small dose of ^{131}I , followed when necessary by antithyroid drug therapy, are discussed. Further trials are required to determine the optimal dose of ^{131}I .

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Staphylococcal Sepsis in a New Surgical Ward

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The building of a new professorial block at Royal Prince Alfred Hospital (Loewenthal, 1962) has afforded the opportunity to study the effect of environmental factors on the incidence of surgical sepsis in patients undergoing a variety of general surgical operations. The new block was occupied at the end of December 1962, and the 1,337 patients admitted to its surgical ward up to the end of April 1965 form the subject of the present report.

Prior to this the patients of the professorial surgical unit were housed in an old open ward where there were high infection rates (Rountree, Harrington, Loewenthal, and Gye, 1960) and where there was widespread contamination of the air and bedding with *Staphylococcus aureus* (Rountree and Beard, 1962). Measures introduced into that ward in an attempt to reduce the infection rate included the sealing of all suitable wounds with plastic seals, the use of individual dressing-trays, the substitution of cotton for woollen blankets, and the institution of nasal prophylaxis with a cream containing neomycin and chlorhexidine (Rountree, Loewenthal, Tedder, and Gye, 1962). None of these measures was more than partially successful, and in 1962 14% of 326 operation wounds

were infected, the majority of these infections occurring in the ward.

Design of the Ward

The plan of the new ward was given by Loewenthal (1962). It is an adaptation of the Nuffield Ward and contains beds for 30 patients. Twenty-four beds are in six open bays containing four beds each; there are four single-bed rooms and one room with two beds. Each open bay has its own water-closet and wash-basin. There is an air-conditioned treatment-room in a central position in the ward.

Methods of Investigation

Swabs were taken from all surgical wounds which showed evidence of sepsis in the form of pus or discharge. Any other lesions, such as ulcers or pustules, present when the patient was admitted or which developed later were also swabbed. A nasal swab was taken from each patient on the day of admission or as soon as possible after this; thereafter each patient was swabbed once a week. At irregular intervals nasal swabs were taken from the nursing and medical staff.

From January 1963 to November 1964 environmental contamination was measured once a week. Settle plates were used rather than the slit sampler, since the architecture of the ward did not lend itself to the use of the slit sampler. These plates

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