Treatment of Thyrotoxicosis With Iodine-125.

A Clinical and Laboratory Study.

By

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Summary

This study is primarily a clinical assessment of a new radioisotope of iodine (iodine-125) for the treatment of thyrotoxicosis. I was attracted to this project by my close association with Dr. W.R. Greig who pioneered this approach.

The thesis consists of three sections, A, B and C. The first Chapter of Section A is concerned with the currently used treatments for thyrotoxicosis (Graves' disease), special attention being given to iodine-131. There is no excuse for the proportion of the Chapter which deals with the poor results, side effects and complications of the therapies, and again prominence is given to iodine-131 in particular the problem of post therapy hypothyroidism. Included in this Chapter is a personally analysed combined radiotherapeutic trial using iodine-131 and carbimazole.

The rationale for the use of iodine-125 is detailed in Section A Chapter II. The rich spectrum of low energy short range electrons emitted from iodine-125 preferentially irradiates the hormone producing region at the apex of the follicular cells without killing the cells. It is theoretically possible using iodine-125 to produce rapid control of the disease without causing post-treatment hypothyroidism. Animal experiments carried out by other investigators confirming this hypothesis are described.

Section B consists of three Chapters which deal with the clinical trials of iodine-125 in patients. In Chapter I the excellent results of large therapy doses justified this approach and encouraged extension of the trials using smaller but empirical doses. The method of calculating the rad dose at different levels of the follicular cell is described.

The main clinical trial, the treatment of 265 thyrotoxic patients with different dose schedules of iodine-125, is detailed in Chapter II. The outcome is related to the sex and age of the patients, the total dose prescribed, the thyroid size before therapy, the dose of iodine-125 prescribed per gram of thyroid and the length of follow up. Clinical trials of iodine-125 in three centres are discussed and the overall pattern of results integrated.

Complications which have arisen after iodine-125 treatment are included in Chapter III as are prospective investigations into potential hazards.

Two Chapters in Section C deal with the radiobiological differences in the thyrotoxic thyroid after treatment with iodine-125 compared with iodine-131. In the first Chapter, routine radioiodine tests, an intravenous perchlorate discharge test, radiochromatograms of serum and combined use of serum thyroxine, T3 resin and T.S.H. assay are utilised. In the second mathematical techniques are employed.

Preliminary results of certain aspects of the therapeutic use of iodine-125 have been published

Lancet (1970) 2: 840

New England Journal Medicine (1971) 285: 1099

Further Advances in Thyroid Research (1971)
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but the results in this thesis update all those in previous communications.

Reference is also made to other articles involved with (a) the general treatment of thyrotoxicosis, Scottish Medical Journal (1971) 16: 519, (b) thyroid carcinoma occurring after iodine-131 treatment, Journal Clinical Endocrinology (1971) 33: 287, (c) the combined use of carbimazole and iodine-131, Scottish Medical Journal (1972) 17: 57

and (d) the intravenous perchlorate discharge test, Journal Clinical Endocrinology (1972), 33: 148.

Communications about the therapeutic use of iodine-125 have been personally presented to the following learned Societies:

Scottish Society for Experimental Medicine (Aberdeen 1970)

The Thyroid Club (London 1971)

The Fourth Meeting of the European Thyroid Association (Berne 1971)

Acknowledgements

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Section A

Rationale for the use of Iodine-125 as an alternative to the currently used treatments, especially Iodine-131, in thyrotoxicosis.

Chapter I

Review of treatments of Thyrotoxicosis.

Introduction

In this chapter the treatment of an adult patient with the intriguing clinical problem of Graves' disease is considered in detail. Managements of hyperthyroidism due to a non endocrine tumour secreting T.S.H. or T.S.H. like material (Odell et al 1963, Odell 1968), factitial thyrotoxicosis (Rose et al 1969), thyrotoxicosis due to an ovarian tumour secreting thyroxine (Kempers et al 1970, Hershman and Higgins 1971) or a thyrotopin producing pituitary chromophobe adenoma (Hamilton et al 1970, Editorial 1971) are not included.

The natural course of untreated Graves' disease is described first to allow a comparison with the outcome following various methods of treatment. Radioactive iodine-131 therapy constitutes the major portion of the chapter and this is followed by a short discussion of other therapeutic approaches.

Natural Course Of Untreated Thyrotoxicosis

Because of the high morbidity of untreated thyrotoxicosis there is very little up-to-date information about the natural course of the disease apart from one report by McLarty et al (1971a) who followed the fluctuating clinical progress in five untreated patients with mild symptoms. Wilson (1967) deduced from survey of the literature that between 15 and 25 per cent of patients died as a result of their disease and although these percentages may not be representative for the present time they serve to emphasize that untreated thyrotoxicosis is dangerous. A larger proportion of patients remained chronically unwell and in the remainder spontaneous remission occurred and a proportion of these euthyroid patients eventually became hypothyroid (Sattler 1908).

The aim of therapy is to restore the patient to normal thyroid function and health as rapidly as possible by the least costly method with the least side effects (Chapman 1971a). The logical approach should permanently remove the cause of the disease but despite a greater understanding of the pathogenesis (Kriss et al 1964, Adams 1965, Lipman et al 1967, Hetzel 1968, Ochi and De Groot 1968, Kriss 1970, Munro 1970, Burke 1971, Munro 1972) this still remains unknown and treatment is directed at reducing the level of circulating thyroid hormones to normal since the clinical manifestations are produced by chronic hyperthyroxinaemia. This can be achieved by permanent destruction of the thyroid by radioactive iodine or by surgery. Alternatively the enzymes involved in thyroid hormone synthesis can be inhibited by antithyroid drugs which have the merit of doing no permanent damage to the gland. The treatment of thyrotoxicosis has been discussed in detail by many investigators (Franklin 1955, Asper 1960, Chapman 1961, Cassidy 1962, Means et al 1963, Hershman 1966,

1967, Howard 1967, Wilson 1967, Trotter 1967, Ingbar and Woebar 1968, McGirr and Greig 1968, Havard 1969, Swerdloff 1970, Werner 1971, McDougall and Greig 1971 and McGirr 1972) and in this review attention is focussed on the disadvantages, side effects and complications of the three standard methods.

Radioactive Iodine Treatment (Iodine-131)

The thyroid cells do not differentiate between radioactive and natural iodine and therefore a source of radiation can be localised within the colloid of the gland, and the radiations emitted destroy the surrounding hyperfunctioning follicular cells without causing irradiation damage to contiguous structures. In January 1941 the first thyrotoxic patient was treated with radioactive iodine (iodine 130 half life 12.5 hours) and by the following year two groups of investigators reported their preliminary results with this radionuclide (Hertz and Roberts 1942, Hamilton and Lawrence 1942). Until that time surgical thyroidectomy had been the only definitive treatment; the operation usually being performed on inadequately controlled patients so it is not difficult to understand why radioactive iodine therapy rapidly gained in favour. The radionuclide originally used, iodine-130, has a short half life and was superceded by iodine-131 (half life 8 days) which by 1960 was being used to treat the majority of thyrotoxic patients.

Aim Of Radioactive Iodine-131 Therapy

The aim of iodine-131 therapy is to obtain a high cure rate as quickly as possible with one therapy dose. 60 per cent of patients respond to the first "drink" (59 per cent De Gowin et al 1959, 59 per cent Sheline and Miller 1959, 55 per cent Werner et al 1957, 59 per cent Blomfield et al 1959, 63 per cent Rubenfield et al 1959 and 65

per cent Cassidy and Astwood 1959) and approximately 2 out of 3 resistant patients respond satisfactorily to each subsequent therapy dose. At least 3 months are allowed to elapse between therapy drinks, but by delaying the prescription for as long as 6 months Chapman (1971a) has demonstrated that a further 15 per cent of patients become euthyroid without further radioiodine.

With conventional doses of iodine-131 about 50 per cent of patients remain thyrotoxic for 3 months after therapy and many of them are not rendered euthyroid for a considerable time after this. A small group of patients do not respond even to repeated conventional doses and may require several drinks and eventually massive amounts. Automatic referral for surgery should not be considered since control of the disease will inevitably occur with iodine-131 alone (Silver 1968).

Early Complications And Side Effects Of Iodine-131 Therapy

1. Radiation Thyroiditis:

   A few days after therapy slight discomfort may occur over the thyroid but even mild analgesic treatment is seldom required (Einhorn et al 1967). The discomfort is occasionally referred to the teeth and gums (Chapman 1971a). The gland may be tender on palpation and localised swelling occur (Volpé et al 1960 and 1961). A more intense reaction with severe thyroidal pain and fever occasionally follows the use of cancericidal doses of iodine-131 (Hoschl et al 1965) and permanent hypothyroidism is the usual sequel of radiation thyroiditis (Schwartz 1970).

2. Exacerbation of Hyperthyroidism: Thyroid Crisis:

   Exacerbation of thyrotoxicosis is not uncommon but frank thyroid crisis following iodine-131 has been infrequently documented (Nelson et al 1952, Lamberg et al 1959, Rubenfield et

al 1959, Nofal et al 1966, Viherkoski et al 1970, Shafer and Nuttall 1971, Roizen and Becker 1971) and in some series no cases have been reported (Cassidy and Astwood 1959). Patients with cardiac disease independant of or secondary to thyrotoxicosis are ideally treated with radioactive iodine but in these high risk patients a slight worsening of the disease can precipitate a cardiovascular death without thyroid crisis and they should be treated with antithyroid drugs for a few weeks prior to the radioiodine.

A death occurring shortly after a therapeutic dose of radioiodine does not necessarily mean that the radioiodine has been the cause of death or that it has been precipitated by thyroid crisis (Sheline and Miller, 1959, Volpé et al 1961).

3. Radiation Sialitis:

Therapeutic doses of radioactive iodine especially cancer-ocidal doses can cause swelling and pain in the submaxillary and parotid glands (Rigler and Scanlon 1955, Goolden et al 1957, Chapman 1971a). The parotid is most frequently affected because of its high saliva to serum concentration of iodine (Bustad 1972). A fall in salivary amylase follows radioiodine treatment (Schneyer 1953) but like the sialitis it is transient and subsides without treatment.

Late Complications And Side Effects Of ^{131}I Therapy

1. Neoplastic Changes.

(a) Thyroid

All radiation is potentially carcinogenic. Epidemiological surveys have shown that external radiation to the neck undoubtedly increases the incidence of carcinoma of the thyroid in children (Duffy and Fitzgerald 1950, Wilson et al 1958). The series of

thyroid cancers in children reported by Winship and Rosvoll (1961) forcibly bore out this finding. Pincus et al (1967) estimated that the incidence of thyroid nodules occurring in children who had been treated in infancy with x - rays for thymic enlargement was 30 per cent; the risk of developing a thyroid cancer was just over one tenth of this figure. Using data from three sources Hempelmann (1968) has shown that a linear relationship exists between the incidence of thyroid nodules and the estimated cumulative radiation dose to the thyroid. An association between external radiation and thyroid neoplasia has also been shown to exist in adults (Goolden 1958, Willis 1959 and Wilson et al 1970).

Clinical surveillance of the atomic bomb victims of Hiroshima and Nagasaki (Hollingsworth et al 1963, Socolow et al 1963) has produced further epidemiological evidence that radiation to the thyroid is associated with an increased incidence of thyroid carcinoma. A similar finding is reported by Conard et al (1966, 1970) in the Marshallese people who were accidently exposed to radioactive fallout on the Rongelap Islands. In the 67 islanders involved, 3 cases of thyroid carcinoma and 16 cases of benign thyroid nodules have become apparent. These people have been exposed to estimated doses of 160 Rads from several isotopes of iodine (^{131}I, ^{132}I, ^{133}I and ^{135}I) as well as 175 Rad from gamma radiation. Children with small thyroid glands may have received up to 1,400 Rads from the radionuclides of iodine.

There has, however, been controversy as to whether treatment of hyperthyroidism with radioiodine causes a similar increase in the incidence of thyroid carcinoma. Experimental work in rats (Goldberg and Chaikoff 1952, Doniach 1956) has indicated that iodine-131 will produce thyroid tumours in these animals especially in a hyperplastic gland. In humans to date there are ten documented cases of thyroid

TABLE A1

Information about 10 patients who developed thyroid carcinoma after iodine-131 therapy

	Author		Age of Patient When Treated With Iodine-131	Sex	Dose (mCi)	Age at Diagnosis Of Tumour	Type of Thyroid Tumour	Comment
1.	Kilpatrick et al	(1957)	60	F	Not Stated	60	Papillary with metastases	Probably unrelated to therapy
2.	Sheline et al	(1959)	9	F	5.4	17	Low Grade Follicular	Histology
3.	Karlan et al	(1964)	11	F	1.25 2.0	13	Papillary Carcinoma Capsular Invasion	Histology, also x-rays from cardiac catheterisation
4.	Staffurth	(1966)	64	F	13.5	70	No Histology	Clinical assessment only
5.	Burke et al	(1967)	26	F	4.7	36	Follicular with metastases	Histology
6.	Baker	(1969)	52	F	9.0 7.0	64	Anaplastic	Histology
7.	Barnard and Parsons	(1969)	68	F	5.0	69	Probably Medullary	Histology - probably not related
8.	Stamler et al	(1970)	25	F	3.4	35	Follicular with metastases	Histology
9.	Lima et al	(1970)	32	F	5.0 4.0	36	Follicular	Histology
10.	McDougall et al	(1971)	60	F	12.5	72	Follicular with metastatic lymph node deposit	Histology

carcinoma (Table A1) (Kilpatrick et al 1957, Sheline et al 1959, Karlan et al 1964, Staffurth 1966, Burke et al 1967, Baker 1969, Barnard and Parsons 1969, Stamler et al 1970, Lima et al 1970 and McDougall et al 1971). The United States environmental protection agency have information of 16 cases of thyroid tumours following iodine-131, this number includes those listed above (Tompkins 1971).

Many hundreds of thousands of patients have been treated with radioiodine most commonly iodine-131. The low incidence of thyroid tumours is thus very striking in view of the reported incidence of thyroid neoplasia in surgically treated thyrotoxic patients which varies from 0.15 per cent (Sokal 1954) to 2.5 per cent (Olen and Klinck 1966). It is possible that iodine-131 may offer partial protection either by inhibiting the follicular cells from becoming malignant (Chapman 1971b) or by destroying latent neoplasms. Although most centres in the United States treat all thyrotoxic patients aged 20 or above with radioiodine, in the U.K. it has remained the policy to restrict this form of therapy to patients aged 40 years or more unless there are exceptional mitigating circumstances.

(b) Leukaemia

There is evidence from several sources that radiation increases the incidence of leukaemia. A higher frequency is found in the survivors of the atomic holocausts in Japan (Brill et al 1962) in patients with ankylosing spondylitis treated by X irradiation (Court Brown and Doll 1957) and in babies born to mothers who have had diagnostic radiology during their confinement (Stewart 1961). Green et al (1961) have calculated that 1 mCi of iodine-131 subjects the blood and marrow to 1.7 Rads and thus the blood forming organs in the "average" thyrotoxic patient treated with iodine-131 receives between 10 and 20 Rads.

Because of the possibility that iodine-131 might be leukaemogenic the United States Cooperative Therapy Follow-up Study has carefully investigated this relationship and have recently published their preliminary findings (Saenger et al 1968). In this study 18,379 patients treated with radioiodine were reviewed for 119,000 patient years. 17 patients developed leukaemia. 16 in a surgically treated group of 10,731 patients who were reviewed for 114,000 patient years were also found to have leukaemia. There was no statistical difference between the two groups. However, when corrections were made for sex and age the incidence of leukaemia in these patients irrespective of the mode of treatment (radioiodine or surgery) was 50 per cent greater than expected in the general population. Although there has been criticism of their conclusions, Saenger et al (1968, 1971) did not attribute this difference to the therapies and they found no evidence to support the contention that iodine-131 induces leukaemia. Their conclusions, therefore, support earlier studies (Pochin 1960, Werner et al 1961 and McCormack and Sheline 1963).

(c) Chromosomal Abnormalities

Chromosomal aberrations have been demonstrated in patients who have received iodine-131 (Boyd et al 1961, Cantolino et al 1966 and Nofal and Beierwaltes 1964). Many of these reports relate to patients who have received large doses for thyroid cancer and it is difficult to know the relevance of the relatively gross abnormalities produced, since they do not appear to be a prodromal phase of leukaemia (Vide infra, Section B Chapter III). Subtle chromosomal alterations produced by small doses of iodine-131 may be more relevant than the devastating effects of large doses (Macintyre and Dobyns 1962).

TABLE A2

Hypocalcaemia Following Iodine-131 Therapy (After Freeman et al 1969)

	Author		Age	Sex	Reason For Treatment	Total Dose ^{131}I(mCi)	Delay Before Onset of Hypocalcaemia
1.	Tighe	(1952)	14	M	Thyrotoxicosis	4	74 days
2.	Boulet et al	(1952)	25	F	Thyrotoxicosis	5	12 days
3.	Klotz et al	(1953)	36	F	Thyrotoxicosis	6	3 months
4.	Langerhorn and Vincent	(1957)	49	F	Thyrotoxicosis	10	3½ months
5.	Gilbert-Dreyfus et al	(1958)	48	M	Thyrotoxicosis	8 and 8	2 years
6.	Townsend	(1961)	52	M	Incapacitating Angina	30	4 months
7.	Eipe et al	(1968)	58	M	Thyrotoxicosis	15.7	7 months
8.	Freeman et al	(1969)	58	F	Thyrotoxicosis	3.5	5 days

2. Extrathyroidal Tissue Damage

In humans radioiodine therapy produces no detectable injury to the recurrent laryngeal nerves, trachea or larynx (Silver 1968) and tracheal compression has actually been relieved (Blomfield et al 1959). Nevertheless, tracheal constriction has been found in the offspring of ewes fed iodine-131; the foetal thyroids were probably exposed to more than 30,000 rads and the constriction may have been due to failure of the cartilage to develop or to contraction of fibrous tissue in the irradiated gland (Bustad et al 1957).

The maximum range of β rays emitted by iodine-131 is 2000 microns in tissues and it is unlikely that parathyroid damage results except when all the parathyroids are intrathyroidal. No cases of hypoparathyroidism have been noted after large doses of iodine-131 for thyroid carcinoma but surprisingly there are reports of hypoparathyroidism in thyrotoxic patients who have received radioiodine therapy, Table A2 (Tighe 1952, Boulet et al 1952, Klotz et al 1953, Langerhorn and Vincent 1957, Gilbert-Dreyfus et al 1958, Townsend 1961, Eipe et al 1968 and Freeman et al 1969). The doses of radioiodine administered to each of these patients were not excessive and none was hypothyroid at the time they became hypocalcaemic. When stressed with E.D.T.A. (Better et al 1969) a proportion of patients fail to maintain serum calcium in the normal range. Parathyroid function in iodine-125 treated patients is discussed below (Section B Chapter III).

Hypocalcaemia, thyroiditis and thyroid crisis have occurred simultaneously in one patient (Freeman et al 1969).

3. Fertility

Libido and fertility are decreased in active thyrotoxicosis

TABLE A3

Foetal Thyroid Damage after Iodine-131 Therapy for the Mother

Author		Iodine-131 Dose (mCi)	Weeks in Gestation	Effect on Foetus
1. Russell et al	(1957)	225.0	13	Hypothyroidism
2. Russell et al	(1957)	75.0	13	Athyroidism
3. Ray et al	(1959)	14.5	20	Hypothyroidism
4. Hamill et al	(1961)	77.0	12	Hypothyroidism
5. Fisher et al	(1963)	14.5	14 (approx)	Hypothyroidism
6. Pfannensteil et al	(1965)	99.0	10	Cretin

and treatment of the disease in females is often followed by unexpected pregnancies. Iodine-131 does not differ in this respect from surgery or antithyroid drugs (Volpé et al 1961). Menstrual disturbances have not been caused by the doses of radioiodine used to treat thyrotoxicosis, but very large doses used in the treatment of metastatic follicular carcinoma has produced amenorrhoea; irradiation from neighbouring functional metastases probably was the cause. 563 mCi of iodine-131 has produced no testicular atrophy (Kammer and Goodman 1969).

4. Effect on Infants Born to Patients Treated with Iodine-131

(a) Thyroid

The foetal thyroid retains and concentrates iodide after the first trimester (Chapman et al 1948) and pregnancy is considered by all therapists to be an absolute contra-indication to radio-iodine therapy. Unwittingly iodine-131 has been administered to pregnant patients but usually no untoward effects have been found in the babies (Volpé et al 1961, McGirr et al 1964 and Silver 1968) probably because the maternal thyroid by its avidity for iodine protects the infant. Foetal hypothyroidism has been found on six occasions, Table A3 (Russell et al 1957, Ray et al 1959, Hamill et al 1961, Fisher et al 1963 and Pfannensteil et al 1965).

(b) Genetic

If after a "drink" no female patient becomes pregnant and no male patient fathers a child there will be no increase in irradiation induced mutations. With the tendency to treat younger patients an increasing number of them do have children. To assess the genetic affects of irradiation the concept of the Doubling Dose is used. The Doubling Dose is the RAD dose which eventually causes a complete doubling of gene mutations; it has been estimated to lie between

TABLE A4

Congenital Malformations Following Iodine-131 Therapy in Patients from E.M. Chapman (1971a)

	Mother Given Iodine-131	Father Given Iodine-131
Normal	189	18
Congenital Heart Disease	2	1
Mongoloid (mother had mumps in first tremester)	1	
Club Foot	1	
Deaf	1	
Bilateral Hernia	1	
Mentally Retarded	3 (All in one family)	
XYY Karyotype	1	
Ureteral Stricture		1
TOTAL	199	20

15 and 30 Rads (Looney 1969). This concept is useful when considering populations but does not help in advising individual patients. There are also difficulties in making valid comparisons in the number of malformations found in children born to parents not treated with radioiodine since it may be impossible to exclude other stimuli which could be incriminated in producing mutations. The congenital abnormalities in infants of one group of iodine-131 treated patients are tabulated (Table A4). The number or type of abnormality does not differ from the general population in whom 4 to 5 per cent of all live births have congenital malformations (Chapman 1971a).

5. Hypothyroidism Following ^{131}I Therapy

(a) The Problem Revisited

Radioactive iodine destroys thyroid follicular cells and from its inception therapists expected and soon confirmed that some patients become hypothyroid because of excessive follicular cell destruction. In early reports the modal incidence of this iatrogenic complication was about 10 per cent (Soley et al 1949, Wayne et al 1952, Clarke and Rule 1955, Chapman and Maloof 1955, Beierwaltes and Johnson 1956, Werner et al 1957, Rubenfield et al 1959 and Sheline and Miller 1959). Some patients, having been unequivocally euthyroid for many years, subsequently became hypothyroid (Chapman and Maloof 1955).

Beling and Einhorn (1961) reported a progressive rise in the percentage of hypothyroid patients with the passage of time after iodine-131 therapy. Their finding was partially due to the methodology of expressing results. If the proportion of hypothyroid patients is calculated as a percentage of the total treatment group an artifically low result is obtained. A greater

but truer result is obtained if the percentage of patients who become subthyroid are calculated year by year. There is now universal confirmation of the cumulative incidence of post-treatment hypothyroidism (McGirr et al 1964, Green and Wilson 1964, Dunn and Chapman 1964, Editorial 1965, Greig et al 1966, Greig 1966, Nofal et al 1966, Editorial 1967, Smith and Wilson 1967b, Editorial 1968a, 1968b, Hagen 1968, Bronsky et al 1969, Tubiana 1971).

The main problem of hypothyroidism is diagnosis (Becker and Hurley 1971). Provided the patient at risk can be kept under medical supervision, however, the condition is seldom missed; reviews are best arranged with the aid of a computerised recall system (Philp et al 1968). Treatment with thyroxine is simple, cheap and efficient if regularly ingested. In many patients the thyroid failure is of insidious onset (Kaipainen et al 1970) and they are singularly complacent and uncomplaining about their health. One organ or system may be disproportionately involved by the subthyroidism resulting in referral of the patient to a cardiologist, neurologist or rheumatologist (Bland and Frymoyer 1970) who does not suspect the diagnosis (Editorial 1970b, 1970c). A diagnostic delay is serious since severe thyroid failure can cause ventricular fibrillation (Macauley and Shepherd 1971), coma (Royce 1971) and death (Plested and Pollock 1967a, 1967b).

A 70 per cent incidence of hypothyroidism may be encountered 10 years after iodine-131 therapy (Nofal et al 1966, Blahd and Hays 1972) and even then there is no evidence that the annual accrual rate is levelling off. There is no simple method of predicting which patient will be affected at any specific time and therefore all iodine-131 treated patients must be kept under periodic medical review either for life or until they have been stabilised on thyroxine replacement therapy. Routine life-long

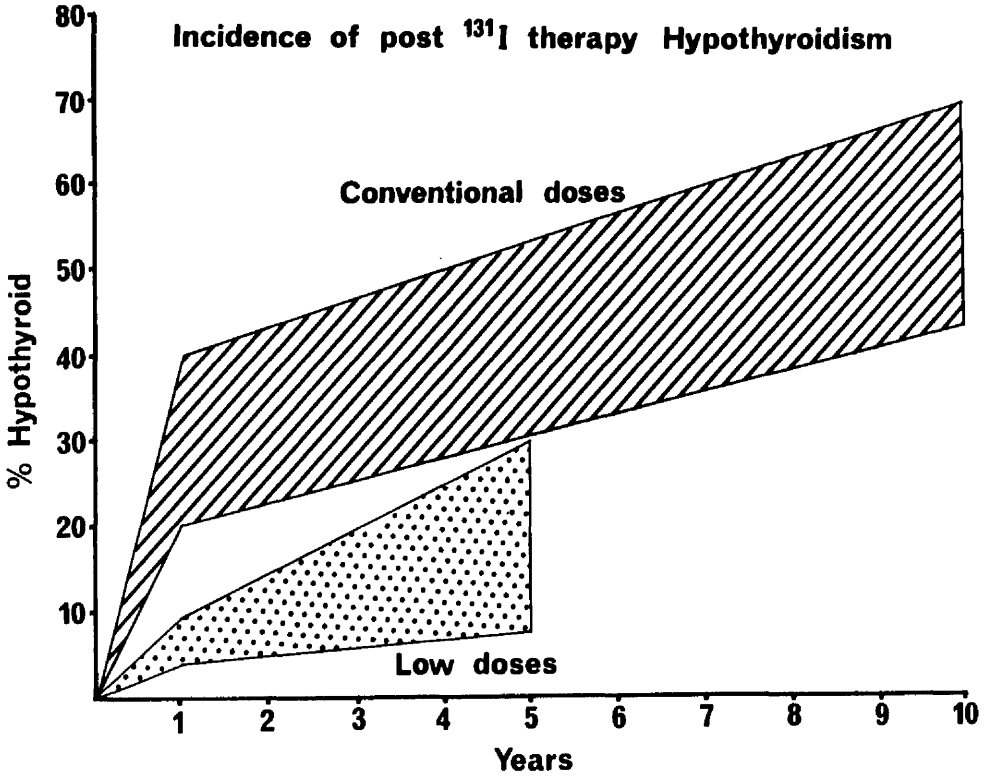
prescription of thyroxine for all radioiodine treated patients has been advocated by Selby (1965) and Esselstyn and Crile (1971). If this policy is adopted "guaranteed" control with large therapy doses is justifiable (Hamburger and Paul 1968) though certainly not ideal (Editorial 1968b).

(b) The Cause of Hypothyroidism

Untreated thyrotoxicosis may pass through the euthyroid state into hypothyroidism but this does not account for the alarming frequency of post iodine-131 hypothyroidism. Animal experiments have been carried out to obtain insight about the aetiological factors. The cell nucleus has been shown to be exquisitely radiosensitive and iodine-131 radiation of a thyroid follicular cell severe enough to reduce hormone production inevitably interferes with the cell's divisional integrity (Greig 1965, Philp 1966, Dobyns and Didtschenko 1961 and Dobyns et al 1967). The return of normal thyroid function following iodine-131 therapy points to subthyroidism at some time in the future since as each follicular cell dies, either naturally or as a result of radioiodine therapy it fails to divide and is not replaced. This topic is discussed in more detail in Section A, Chapter II.

There are other factors which have been incriminated in causing post therapy hypothyroidism. Firstly irradiation damage to the thyroid vasculature (Curran et al 1958, Stanbury and De Groot 1964), but this is usually not severe enough to reduce the blood supply to such a degree that the cells die prematurely. Secondly irradiation induced autoimmune thyroiditis (Blagg 1960, Einhorn et al 1965, 1970) is an attractive theory but although there is a transient rise in thyroid antibodies in the serum of some patients treated with iodine-131, the eventual outcome cannot be closely correlated

FIGURE A 1



The proportion of patients who become hypothyroid with the passage of time after iodine-131 therapy

Hatched area - after standard doses

Dotted area - after low (50 per cent standard) doses

with the antibody titres (Burke and Silverstein 1969). It is now thought that this hypothesis is also incorrect.

(c) Reduction of Frequency of Hypothyroidism

If hypothyroidism results from the irradiation damage of the follicular cell nuclei one obvious remedy is to administer smaller doses of radioiodine. The conventional therapy dose of iodine-131 administered is about 160 uCi per estimated gram of thyroid and this subjects the cell nuclei to between 7,000 and 10,000 Rads. Several groups of investigators have prescribed therapy doses of approximately 50 per cent of this (Tezcan et al 1967, Smith and Wilson 1967a, 1967b, Zellman et al 1968, Skillman et al 1969, Goolden and Fraser 1969 and Kaipainen et al 1970) and compared with "standard" therapy the hypothyroid frequency is reduced 1 year after therapy and even after follow up for 5 years remains lower when the low dose regime is used (Figure A1). There is a delay in symptomatic control, however, which requires the prescription of inorganic iodine (Hagen et al 1967), thiouracils (Smith and Wilson 1967a) or beta adrenergic blocking drugs (Hadden et al 1968, Franco et al 1970 and Lowe et al 1971). Lowe et al (1971) used a single dose of 2.5 mCi iodine-131 in each of their patients and even with this small dose there was a very disappointing incidence of hypothyroidism 2 years after therapy (19 per cent).

6. Delay in Control of Thyrotoxicosis After Iodine-131 Therapy

40 per cent of patients require retreatment when standard doses of iodine-131 are prescribed. The adoption of low dose regimes to overcome the problem of hypothyroidism necessitates the use of antithyroid drugs and often retreatment in over 60 per cent of patients. The disadvantages and side effects of antithyroid drugs are therefore added to those of radioiodine therapy. Pretreatment of patients

TABLE A5

Information about and outcome in patients treated with standard and low doses of iodine-131 prescribed after control with carbimazole (McDougall and Greig 1972).

	Standard Dose	Low Dose
Number of Patients	38 27 females: 11 males	36 32 females: 4 males
Mean age in years (range)	46.7 (38 - 68)	48.1 (40 - 61)
Mean gland mass in grams (range)	45.8 (30 - 90)	45.4 (25 - 75)
Mean percentage uptake of ^{131}I at 24 hours (range)	66.3 (25 - 100)	68.3 (29 - 100)
Mean dose of ^{131}I administered in mCi (range)	7.6 (4.5 - 20)	3.8 (2.0 - 12)
Mean dose of ^{131}I per gram of thyroid	167	83
Mean follow up time in months (range)	19.6 (7 - 29)	19.9 (8 - 27)
Therapeutic Outcome (Euthyroid	16 (42.1%)	16 (44.4%)
Therapeutic Outcome (Hyperthyroid	14 (36.8%)	17 (47.2%)
Therapeutic Outcome (Hypothyroid	8 (21.1%)	3 (8.4%)

with antithyroid drugs is one method of reducing the delayed symptomatic control. Recently a study has been undertaken (McDougall and Greig 1972) using standard and low doses of iodine-131 in 74 patients who had all been pretreated with carbimazole for 20 weeks. The average time to obtain control with carbimazole was 10.2 weeks despite the older age of the patients (38-68 years). This delay was similar to that experienced by Crooks and Wayne (1960). Following the course of carbimazole the patients were alternatively allotted to receive standard or low (50 per cent of standard) doses of iodine-131. After the dose of radioiodine all of the patients were treated with carbimazole for a further 20 weeks. Symptomatic control was assured during this 10 months of antithyroid drug therapy, thus giving the radioiodine therapy time to act.

Review of the patients after completion of the trial (follow up without antithyroid drugs 20 months) illustrated that in the standard dose group only 42.1 per cent remained euthyroid after 1 therapy dose. At that time 21.1 per cent had become hypothyroid and as many as 36.8 per cent had relapsed. In the low dose group 44.4 per cent were euthyroid, the percentage hypothyroid was reduced to 8.4 and 47.2 per cent remained thyrotoxic (Table A5). The results serve to illustrate the poor one dose response even with standard doses of iodine-131 given an optimum time to act.

Summary Of Iodine-131 Therapy

The simplicity, cheapness and convenience of radioiodine therapy are so attractive that it is difficult to envisage any form of therapy superceding it until the aetiology of thyrotoxicosis is clarified. The early side effects of therapy are rarely encountered in practice. Post-treatment thyroid cancer is found less commonly than it is in untreated thyrotoxic patients and leukaemia although found more commonly after iodine-131 therapy than in the general population is no more common than in surgically treated patients. Any genetic risks passed on to succeeding generations are small.

Few forms of therapy are ultimately so uniformly successful since 100 per cent of thyrotoxic patients are eventually "cured" of their disease though an increasingly great number perhaps all eventually become hypothyroid. Smaller doses used to reduce the frequency of hypothyroidism slow the rate of control of the disease. It is conceptually impossible to believe that iodine-131 could ever be considered the ideal radionuclide for the treatment of thyrotoxicosis since prompt control of the disease and reduction of post-therapy hypothyroidism are mutually incompatible.

Surgical Treatment Of Thyrotoxicosis

Thyroidectomy was the only treatment for thyrotoxicosis till antithyroid drugs and radioiodine were introduced in the 1940's. The operation was reserved for severely ill patients and the risks were considerable until the introduction of inorganic iodine (Plummer 1923) to reduce the toxicity of the patient preoperatively. With experience in patient selection and preparation coupled with the improvement in surgical technique and anaesthesia thyroidectomy is a safe elective procedure.

The best candidates for partial thyroidectomy are patients under the age of 40 who fail to respond to two adequate courses of antithyroid drugs, patients with large goitres, (especially if nodular and causing pressure symptoms) and those with single toxic adenomas (McGirr and Greig 1968). Patients with thyrotoxic heart disease, impalpable thyroid glands and severe exophthalmos are best excluded (Riddell 1965) and the risks of a second partial thyroidectomy are so great that a reoperation should only be considered in exceptional circumstances (McLarty et al 1969).

It is surprising how many patients do become euthyroid after radical removal of an empirical volume of thyroid tissue. The results of operation vary considerably, this variance may partly reflect differences in surgical technique but usually depends on the length of follow up and whether surgeons or physicians review the patients. When surgeons report the experience the results usually show an uncomplicated cure rate of over 70 per cent with an overall low morbidity.

Post Operative Hypothyroidism

Representative figures for the incidence of post-operative hypo-

thyroidism vary from 5 per cent (Roy et al 1967) 6.5 per cent (McNeill and Thomson 1968) 9 per cent (Painter 1960) and 10 per cent (Colcock 1962) to 25 per cent (Olsen et al 1970), 28 per cent (Nofal et al 1966) 36 per cent (Hedley et al 1970) and 49 per cent (Michie et al 1972). Several but not all authors have found an increase in the incidence of hypothyroidism with the passage of time. The complication is most likely to develop in those with circulating thyroid antibodies (Buchanan et al 1962, Irvine and Stewart 1967) and with excessive lymphoid tissue in the resected thyroid (Greene 1950). The former group can be predicted preoperatively and should if possible be considered for alternative therapy unless there are pressing indications for operation. If operation is deemed essential, replacement therapy may be commenced in the early post operative period (Wilson 1967). The more recent reports of high and cumulative hypothyroid rates are disquieting and illustrate the necessity for vigilant supervision of the surgically treated thyrotoxic patient.

Post Operative Recurrence Of Thyrotoxicosis

The recurrence rates post operatively also vary widely, from 0.6 per cent (Painter 1960) to 12.2 per cent (McNeill and Thomson 1968) and are usually inversely related to the hypothyroid rate in any series. The results in the majority of reports are at the higher end of this spectrum.

Other Complications Of Thyroidectomy

Thyroidectomy necessitates a period of preoperative antithyroid drug therapy which may be prolonged, and a short stay in hospital usually between 5 and 10 days but longer if complications arise. The patient suffers a degree of pain. Operative mortality is extremely

low and in several series there have been no deaths. Wound infection, atelectasis, pneumonia and pulmonary embolus may arise as with any operative procedure (Gould et al 1965).

Post-operative thyroid crisis is extremely rare and should not occur if a careful preoperative policy is adhered to. The recurrent laryngeal nerve can be damaged during the operation and up to 30 per cent of patients notice an alteration in their voice (Painter 1960). Complete laryngeal nerve damage is irreversible but the incidence as judged by inspection of the vocal cords post operatively is, however, much lower. Riddell (1970) by meticulous identification of the nerves at operation followed by electrical stimulation to test each nerve's integrity has reduced the risk of this complication to 1.7 per cent in a total of 1,700 operations. Bilateral recurrent laryngeal nerve paralysis may necessitate tracheostomy or arytenoidectomy.

A rapidly enlarging wound haematoma may cause respiratory distress; in acute situations the wound has to be reopened and the blood evacuated, in less acutely ill patients needle aspiration of the haematoma will suffice.

Injury to the parathyroid glands or interference with their blood supply at the time of operation may lead to acute hypocalcaemia in 2 to 3 per cent of patients (Wade 1965). There is debate as to the incidence of chronic hypoparathyroidism following partial thyroidectomy (Editorial 1966). If E.D.T.A. infusion is used to artifically produce hypocalcaemia and test parathyroid reserve up to 25 per cent of patients may be deficient (Jones and Fourman 1963). The importance of this biochemical defect is uncertain since the patients are asymptomatic. Overall about 4 per cent of patients require prolonged replacement therapy with calcium and vitamin D (Wade 1965). An alternative cause of hypocalcaemia in post operative patients, who are in negative calcium

balance with calcium deficient bones (Michie et al 1971) is reversal of the deficit allowing the rapid transfer of calcium into the skeleton with the inevitable onset of hypocalcaemia.

An important post operative complication especially in the young female is an ugly keloid.

Surgery for thyrotoxicosis is not to be lightly embarked upon. Careful scrutiny of the results shows a not inconsiderable number of patients with chronic morbidity directly related to the procedure (Editorial 1970a). In a recent study (Hedley et al 1970) only 55 per cent of patients were unequivocally euthyroid.

Drug Therapy For Thyrotoxicosis

One important advantage of antithyroid drugs is that no permanent damage is done to the thyroid. The most satisfactory and best understood of the drugs used are the imidazoles and thiouracils. These drugs are equally effective when used in comparable doses (Wayne 1960) but even under optimum conditions there may be a mean delay of 9 weeks (Crooks and Wayne 1960) to 10 weeks (McDougall and Greig 1972) until the patient is euthyroid. After a full therapeutic course (18 months) on average about 50 per cent of the patients will suffer a relapse and those who remit would probably have done so spontaneously (Wilson 1967). There is no good way of predicting the outcome in a particular patient, although two clinical features, a short history of thyrotoxicosis prior to commencing therapy and shrinkage in the size of goitre during treatment are favourable they do not inevitably point to a successful outcome following drug therapy (Hershman 1967).

The triiodothyronine suppression test has been tried as an index of predictability, return of suppressibility during the course of antithyroid drugs has been accepted by some workers (Alexander et al 1966, 1967, 1970) to indicate that remission will occur on stopping

the drugs and likewise failure of suppression has been taken to indicate continuing disease and likely relapse. Recent studies have shown that individual cases do recur after suppression has returned to normal (Wils and Kloppenbog 1970a, 1970b) and the test has little value in practice (Lowry et al 1971). Using a variety of indices before and during therapy with the aid of computerised multidimensional analysis it may be possible to separate those who will remit from those who will not (McLarty et al 1971b) but this technique is at present only available for research purposes.

Because of the poor response following a standard course of drugs some investigators in the U.S.A. have prescribed antithyroid drugs over an indefinite period to control thyrotoxicosis (Hershman et al 1966). Conventional antithyroid drugs have an unfortunate habit of causing reactions and although these usually occur within a few weeks of commencing therapy (Howard 1967) they may occur once maintenance therapy has been established. The overall incidence of side effects is about 5 per cent (Greene and Morgan 1956) the most common being a maculopapular rash. Other side effects include fever, alopecia, lymph node enlargement, gastric upset and conjunctivitis. Agranuloytosis occurs in about 0.5 per cent of patients; aplastic anaemia (Burrell 1956) is exceptionally rare.

Inorganic iodine (Plummer 1923) is not routinely used because of its transient symptomatic control. Iodine may have a detrimental effect on patients with an organic binding defect (Braverman et al 1969, 1971) and it may precipitate thyrotoxicosis. It can cause an acneform skin rash and sialadenitis. Potassium perchlorate although tentatively claimed to be the antithyroid drug of choice just over a decade ago (Crooks and Wayne 1960) is now seldom used because several cases of fatal aplastic anaemia have been attributed to it (Editorial 1961, Hobson

1961, Johnson and Moore 1961, Krevans et al 1962.)

Amelioration of thyrotoxicosis may be produced by drugs which selectively interfere with the production or action of catecholamines. Reserpine (Canary et al 1957) is useful in thyroid crisis (Dillon et al 1970); guanethidine is as effective but is slow to act (Riddle and Schwartz 1970). The side effects of these drugs are, however, not tolerated with equanimity by most thyrotoxic patients. Propranolol attenuates the positive inatropic and chronotropic effect in the thyrotoxic patient (Wiener et al 1969, Levey 1971) and has been used in thyroid storm (Das and Kreiger 1969), in the preparation of patients for thyroid surgery (Vinik et al 1968) and in conjunction with radioiodine therapy (Franco et al 1970, Hadden et al 1968). These drugs do not influence the underlying disease process and their use alone often leaves the patient unwell.

Summary

Although each of the three currently used methods of treating thyrotoxicosis has its enthusiastic proponents none is ideal. The disadvantages of surgery include preoperative preparation, surgical morbidity and a very high incidence of postoperative hypothyroidism. Drug therapy even if protracted for up to two years has the disadvantage that less than 50 per cent of patients have a lasting remission. The rising incidence of hypothyroidism following iodine-131 therapy should not cause a resurgence of these approaches.

Section A

Chapter II

Choice of Iodine-125 as an Alternative to Iodine-131 in the Treatment of Thyrotoxicosis

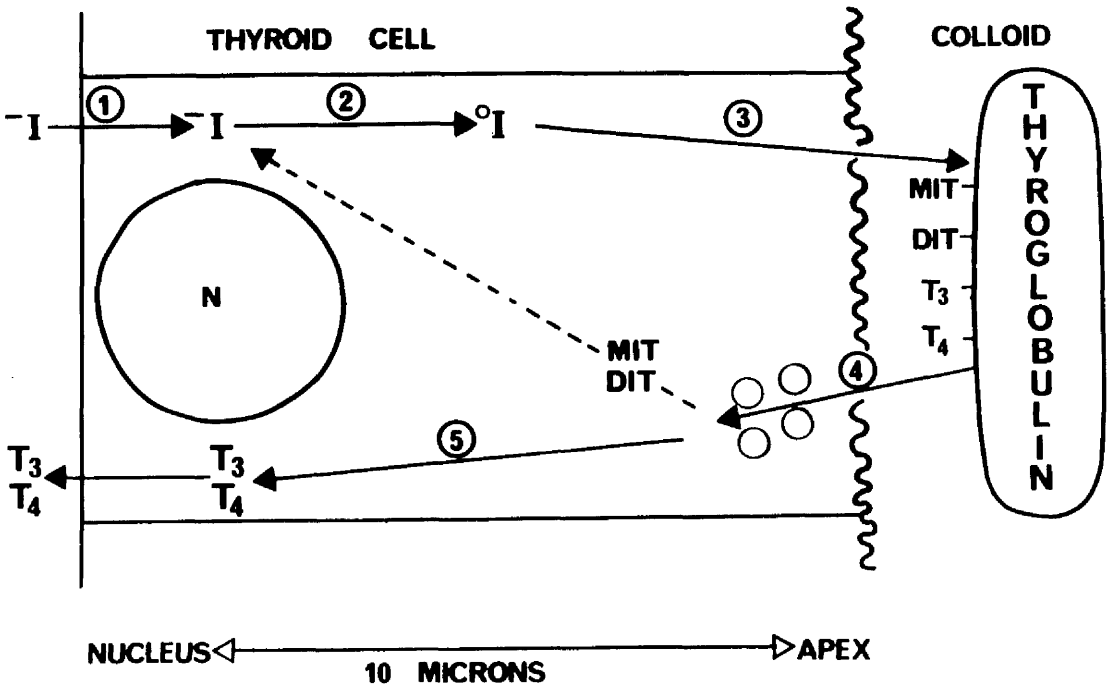
Section A

Chapter II

Introduction

Despite the slow rate of control and the cumulative incidence of hypothyroidism after radioiodine-131, the simplicity, inexpensiveness and eventual effectiveness are so advantageous that the concept of radioiodine therapy should be retained at least until the cause of Graves' disease is elucidated. In the previous chapter the likely cause of hypothyroidism, intense nuclear irradiation, was introduced and the ideal radionuclide should therefore not subject this part of the cell to high doses of radiation. After careful analysis of the pathological anatomy and pathophysiology of Graves' disease, Greig (1968) suggested that iodine-125 because of its unique spectrum of low energy electronic emissions might be of value in rapid and permanent control of this condition without causing thyroid failure. To illustrate the rationale of this hypothesis relevant details of the microanatomy and physiology of the thyroid are described and the pathogenesis of iodine-131 induced hypothyroidism reviewed in more detail. The decay of iodine-125 and its emissions are discussed and finally important radiobiological differences between iodine-125 and iodine-131 in the experimental animal are summarised.

FIGURE A 2



Diagrammatic representation of a thyrotoxic follicular cell. The steps in synthesis and probable site of thyroid hormone production are shown numerically.

(1) Trapping of inorganic iodide

(2) Oxidation of iodide to iodine

(3) Iodination of tyrosine at cell apex
Coupling of monoiodotyrosine (MIT) and diiodotyrosine to form triiodothyronine (T_3) and thyroxine (T_4)

(4) Pinocytosis of thyroglobulin

(5) Proteolysis with release of T_3 and T_4

Microscopic Anatomy of Thyroid Follicle and Follicular Cell

The follicle is the basic unit of the thyroid and the same general structure appertains to normal and thyrotoxic follicles (Heimann 1966). It is a rounded structure with a mean diameter of 300 microns (Rawson et al 1964) composed of a rim of follicular epithelium one cell in thickness surrounding a central core of colloid (Klinck 1964). Between twenty and forty follicles are closely grouped together to form lobules which are subunits of the thyroid lobes. The normal follicular cell is cuboidal in shape (Wissig 1960, 1964) its apex abuts on the colloid; the centrally placed nucleus lies about 2 to 3 microns from this junction (Lupulescu and Petrovici 1968).

In thyrotoxicosis the appearance of the follicular cells are altered (Doniach 1967, Heimann 1967). They become hypertrophied and are columnar in shape and undergo hyperplastic changes. The nucleus lies towards the base and the distance from the nucleus to the apical margin is increased to between 10 and 15 microns. The apical margin develops prominent microvilli. The colloid volume diminishes and increased follicular cell size coupled with cell multiplication produces infolding and projection of papillae into the colloid (Sommers 1968). The significance of these histological alterations will be discussed below in relation to the microdosimetry of iodine-125.

Physiology: Formation and Secretion of Thyroid Hormones

Synthesis and secretion of thyroid hormones (triiodothyronine and thyroxine) are the main functions of the collicle cell. The synthetic pathway (Figure A2) commences with trapping of circulating inorganic iodide. The trapping mechanism is probably a function of the base of the cell (De Groot 1965). Iodide is then oxidised to iodine and

attached to tyrosine, one of the constituent amino acids of colloidal thyroglobulin. Monoiodotyrosine (MIT) is formed when one atom of iodine is incorporated, and diiodotyrosine (DIT) if another iodine sub-unit is added. This very important step of iodination takes place at the apical surface of the follicle cell (Stein and Gross 1964, Nadler 1965a, 1965b, Sommers 1968) in close proximity to the microvilli which project into the colloid.

The iodotyrosines then couple to form the complete functional thyroid hormones, triiodothyronine (MIT plus DIT) and thyroxine (DIT plus DIT). This reaction probably takes place in the colloid and may be related to the steric structure of thyroglobulin allowing the constituent molecules to lie in close proximity with one another. Preformed hormones remain stored within the colloid and their release, which is accelerated in thyrotoxicosis, is brought about by intra-cellular enzymatic degradation of thyroglobulin. The sequence of events is that the cell is stimulated by long acting thyroid stimulator (T.S.H. in physiological circumstances) an activator of adenyl cyclase the enzyme responsible for the formation of cyclic A.M.P. (Deiss and Peake 1968). Cyclic A.M.P. may then stimulate pinocytosis of droplets of colloid. Intracellular lysosomes coalesce with the absorption droplet and cause proteotytic degradation of the thyroglobulin molecule releasing the active hormones (Fawcett et al 1969, Catt 1970).

Two of the most important steps in hormone synthesis and release iodination of tyrosine and pinocytosis of the colloid are functions of the apical cell margin.

Hypothyroidism After Iodine-131 Therapy for Thyrotoxicosis

Currently there is very substantial evidence that nuclear radiation damage is the cause of the progressive rise in hypothyroidism noted after iodine-131 therapy (Greig 1965). Iodine-131 (half life 8 days) emits β and γ rays. The average energy of the β rays is 187 Kev and these

emissions are absorbed over a path of 400 to 2000 microns. The δ rays have little therapeutic benefit since they are mostly unabsorbed by the thyroid (Doniach 1972). The radiation field of iodine-131 when stored in the colloid is relatively great in terms of follicle cell height (15 microns) or even follicle diameter (300 microns). Even allowing for differences in iodine uptake and turnover in individual follicles the majority of these units in diffusely enlarged thyrotoxic glands are subjected to uniform irradiation because of crossfire between adjacent follicles. The only exception to this is a narrow rim of peripheral follicles (Anspaugh 1965). Analogous to this is the fact that each part of the follicular cell, nucleus included, lies in this uniformly irradiated field.

Cell viability and ability to reproduce depend on the integrity of the nucleus. The metabolic functions of the thyroid cell have been shown to be considerably more resistant to radiation than the cell's reproductive capacity (Glucksmann 1954) even in thyrotoxicosis when hormone synthesis is less radioresistant. Normal secretory capacity may be possible in a cell which at the end of its normal life span will not reproduce itself (Skanse 1948, Maloof et al 1952, Dobyns et al 1953, Doniach 1958, Dobyns and Didtschenko 1961, Dobyns et al 1967, Doniach 1972). Progressively larger doses of radiation not only slow or halt cellular mitosis but may shorten the cells life span (Al Hindawi and Wilson 1965) or cause immediate cell death. "The comparative radiosensitivity of the nucleus is due to its content of unique macromolecules" (Doniach 1972). Lethal damage is followed by shrinkage of the thyroid and total replacement with fibrous tissue and hyaline material (Williams and Vickery 1965).

The aim of iodine-131 therapy is to cause a reduction in thyroid function. It is inconceivable that iodine-131 because of its lengthy irradiation path will ever preferentially diminish hormone synthetic

Table A 6

Radioisotopes Of Iodine

(After Myers 1966)

Mass Number	Mode of Decay (MeV)	Half Life
117	Electron capture, B^+	6.5 minutes
118	46% Electron capture 54% B^+	13.9 minutes
119	49% Electron capture 51% B^+	19.5 minutes
120	4.0 B^+	1.3 hours
121	Electron capture, 1.1 B^+	2.1 hours
121 m	Isometric transition	80 microseconds
122	Electron capture, 3.1 B^+	3.5 minutes
123	100% Electron capture	13.3 hours
124	Electron capture, 2.2 B^+	4.2 days
125	100% Electron capture	60.0 days
126	Electron capture, 0.57 B	13.3 days
126 m		2.6 hours
127	Non Radioactive	
128	2.12 B^-	25.0 minutes
129	0.15 B^-	16 x 10^6 years
130	1.02 B^-	12.5 hours
131	0.61 B^-	8.0 days
132	2.12 B^-	2.3 hours
133	1.30 B^-	21 hours
134	2.5 B^-	53 minutes
135	1.4 B^-	6.7 hours
136	5.6 B^-	83 seconds
137	B^- (n)	22 seconds
138	B^- (n)	5.9 seconds
139	B^- (n)	2.7 seconds

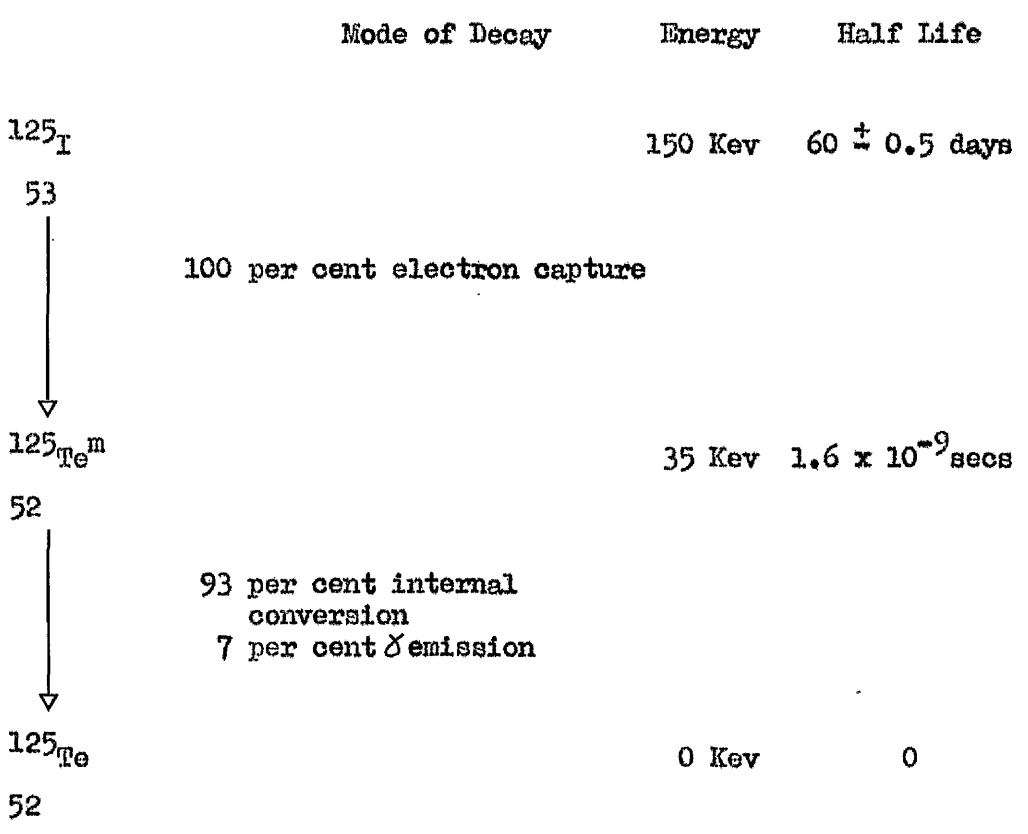
function. Any lessening in hypersecretion which results in the recovery of the patient inevitably indicates that the radiosensitive nuclei have been damaged; thyroid failure is predictable at some time in the future, the speed of onset of hypothyroidism being dictated by the amount of nuclear damage. Uniform cell death after very large therapy doses will cause early onset hypothyroidism whereas uniform cellular sterilisation without cell loss will cause late onset hypothyroidism. The rate of turnover of follicular cells although not known is minimal, most of the cells may not be replaced in a normal individual's life (Doniach 1971). Sheline (1969) found that less than 1 in 250 cells labelled with tritiated thymidine, suggesting that the remainder are in a resting phase and the delay in appearance of hypothyroidism in those patients with thyroid cell sterilisation is therefore related to the low rate of cell renewal. In the majority of iodine-131 treated patients a spectrum of cell death and cell sterilisation exists hence the variations in time of appearance of thyroid failure.

Theoretically, therefore, the aim of radioiodine therapy should not be uniform irradiation of the whole thyroid but selective damage of the hormone synthetic function. This is not possible with iodine-131 irrespective of dose manipulations. Iodine-125 has physical properties described in detail below which are almost ideal in preferentially irradiating the apex of the cell (the radioresistant functional part) and protecting the nucleus (the radiosensitive divisional region).

Discovery of Iodine-125

Iodine-125 discovered in 1946 by Reid and Keston is one of the 24 radionuclides of iodine (Table A6). A sample of tellurium had been bombarded with deuterons at the Massachusetts Institute of Technology and allowed to decay for six months. Originally it was thought that the long life radionuclide iodine-129 had been isolated but subsequent

FIGURE A 3


Mode of Decay
Energy
Half Life
$^{125}_{53}I$
150 Kev
60 ± 0.5 days
100 per cent electron capture
$^{125}_{52}Te^{m}$
35 Kev
1.6 x 10^{-9} secs
93 per cent internal conversion
7 per cent γ emission
$^{125}_{52}Te$
0 Kev
0

experiments proved that the radionuclide was iodine-125 (half life 60 $\pm$ 0.5 days).

Physical Decay of Iodine-125 (Figure A3)

The complex decay scheme of iodine-125 has been studied by several groups of investigators (Bergstrom 1951, Friedlander and Orr 1951, Bowe and Axel 1952, Myers and Vanderleeden 1960, Freige et al 1968, Ertl and Feinendegan 1969, Ertl et al 1970, Gillespie et al 1970 and Feige et al 1971). The data of Gillespie et al (1970) has been used in this thesis for the discussion below and for calculations of microdosimetry (Section B, Chapter I). Their results are in close agreement with those of other investigators.

The decay of iodine-125 occurs in two steps (1) transmutation to the metastable state of tellurium-125 by electron capture (half life 60 $\pm$ 0.5 days). (2) Tellurium $^{m}125$ decays to tellurium in the ground state either by the emission of γ radiation or by internal conversion (half life 1.6×10^{-9} secs).

(1) Electron Capture occurs predominantly from the K shell (82.2 per cent) the remaining transitions occur from the L_1 (14.4 per cent), L_{11} (0.4 per cent) and M shells (3.0 per cent) (Wapstra et al 1959). This process utilised 115 Kev of the total 150 Kev of iodine-125. Every captured electron converts a nuclear proton into a neutron and a neutrino; the emission of the neutrino imparts a nuclear recoil of 0.1 Kev.

(2a) γ Radiation: 7 per cent of the transition of metastable tellurium to the ground state occurs by the emission of γ radiation and by theoretical conversion coefficients calculated by Sliv and Bland (1961) and tabulated by Lederer et al (1967). Gillespie et al (1970) have shown that the radiation is highly converted, 78 per cent, 11 per cent, 1 per cent and 3 per cent in the K, L_1, L_{11} and M shells respectively.

Table A 7

Photon Emissions Of Iodine-125

Type of Emission	Energy KeV (E)	Abundance (Per 100 ^{125}I Decays) (A)	Mean Energy/Disintegration KeV ($A_1 \times E_{00}$)
Te γ rays	35.5	7	2.5
Te K_{B2}^{1} X rays	31.7	4.5	1.4
Te K_{B1}^{1} X rays	31.0	20.1	6.2
Te K_{A2} X rays	27.2	38.0	10.4
Te K_{A1} X rays	24.47	74.7	18.3
Te L X rays	3.7	8.3	3.1

Table A 8

Electron Emissions Of Iodine-125

Type	Energy KeV (E)	Abundance (Per 100 ^{125}I Decays) (A)	Mean Energy/Disintegration KeV ($^{A}_{100}K^{E}$)
Te M Conversion	34.5	4.0	1.4
Te L_2 Conversion	30.9	1.0	0.3
Te L_1 Conversion	30.5	10.0	3.1
Te L Conversion	3.7	78.0	2.9
Te KMM Auger	29.0	2.3	0.7
Te KIM Auger	26.3	6.0	1.6
Te KLL Auger	22.7	13.9	3.2
Te LMM Auger	3.0	115.4	5.0
Te MNN Auger	0.4	355.0	1.4
Te MNN Coster-Kronig	0.3	355.0	1.1
Te LLN Coster-Kronig	0.2	29.0	0.1

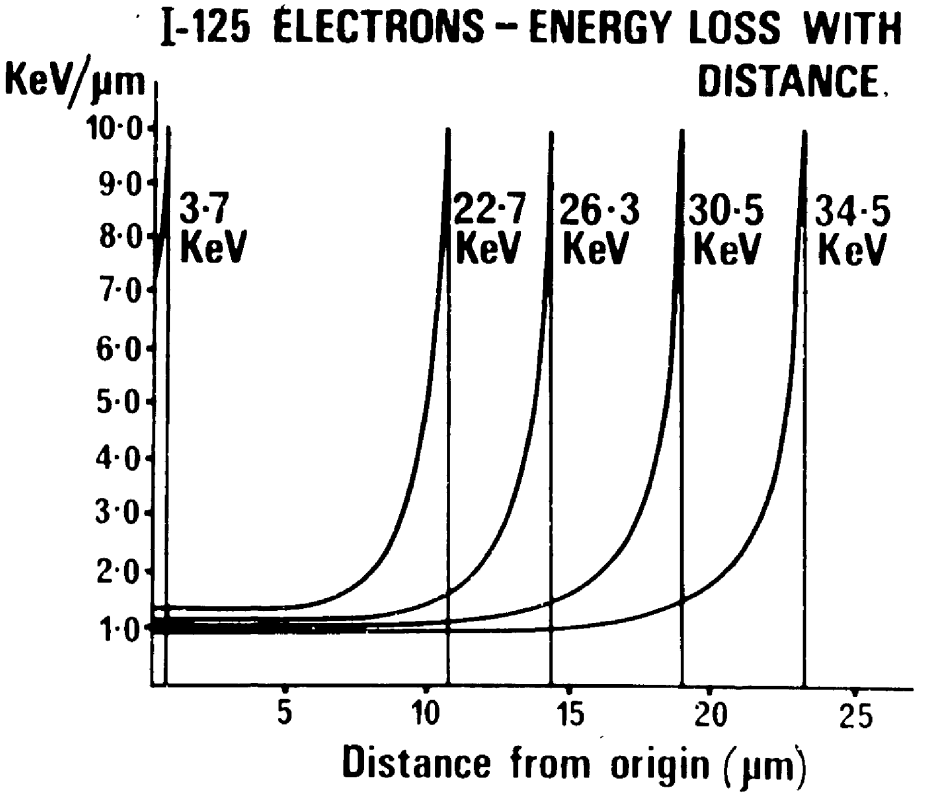
(2b) Internal Conversion: Energy imparted on the excited nucleus is transferred to the atomic shells causing the expulsion of electrons from their orbits. Each emitted electron has an energy equal to its original excitation energy minus the binding energy. Electrons may be emitted from K, L_1, L_{11} or M shells. 78 per cent of all electron emissions are from the inner shell and they have the greatest binding energies. The energy of these emitted electrons is only 3.7 Kev (35.5 - 31.8 Kev). 10 per cent are L_1 transitions with an energy of 30.5 Kev (35.5 - 5.0 Kev), 1 per cent are L_{11} conversion electrons with an energy of 30.9 Kev (35.5 - 4.6 Kev) and 4 per cent are M shell emissions of 34.5 Kev energy (35.5 - 1.0 Kev).

These processes create 193 electron holes, 100 from the original step of electron capture and 93 from the internal conversions. Outer shell electrons replace the gaps in the inner shells and because of the difference in binding energies an excess is created which is dissipated as soft x-rays. The transfer of energy to less tightly bound electrons in the outer orbits may also cause these electrons to be ejected as low energy Auger or Coster Kronig electrons. The photon emissions with their respective energies (E), abundance (A) and Kev are listed in Table A7. Table A8 gives the same information about the electronic emissions, which are mostly of very low energy. No β particles give rise to useless radiation and 95 per cent of them travel less than one micron.

Microscopic Inhomogeneity Of Radiations From Iodine-125

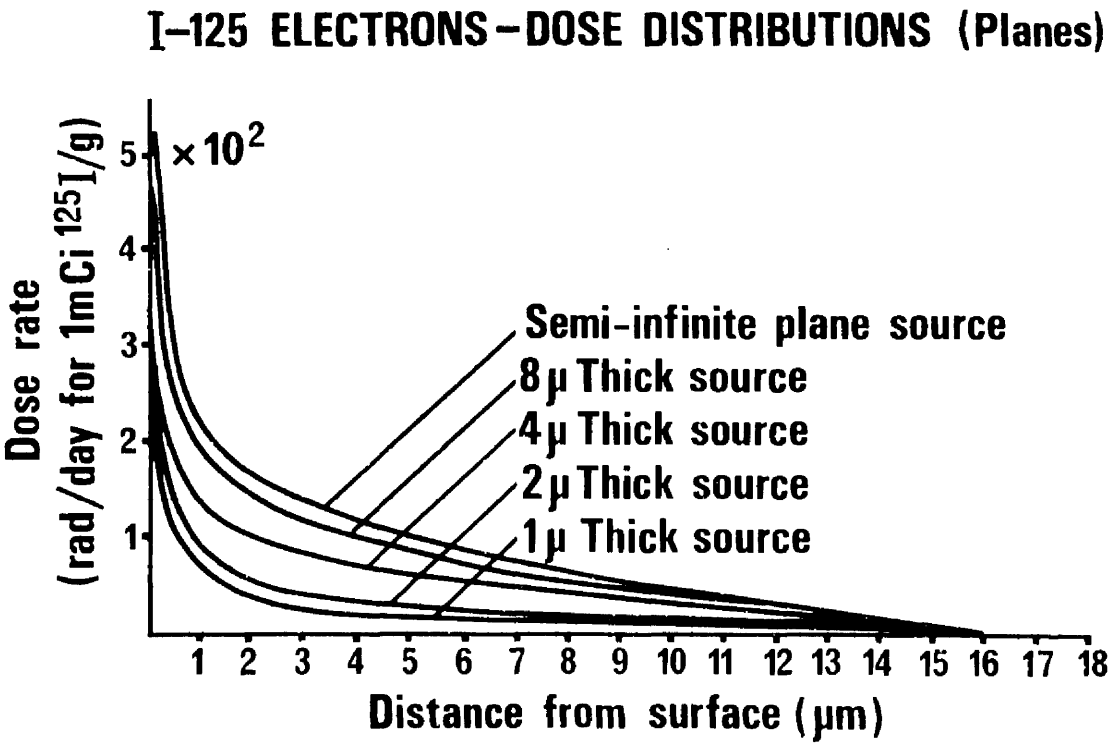
Although almost 70 per cent of the energy of iodine-125 is accounted for by the low energy X and γ rays only a small amount of this is absorbed within the thyroid. The reason for this is that the half-value thickness of the majority of the photons especially those in the range 24.5 Kev to 35.5 Kev is considerable and they pass through the thyroid without depositing energy (Table A9 from Greig 1970). The low energy Te L

FIGURE A 4



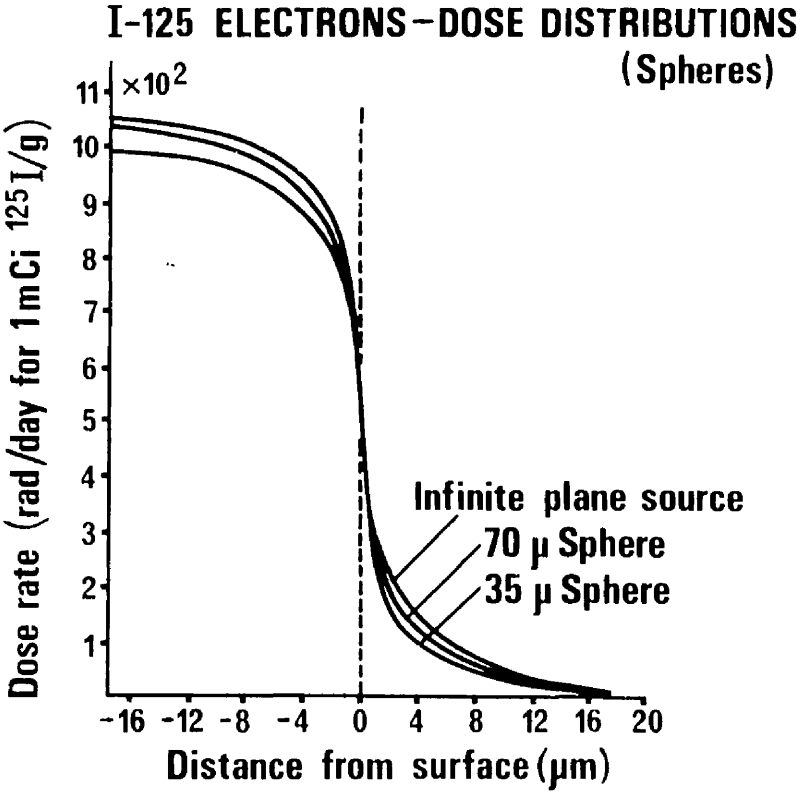
Range in tissues of the electronic emissions of different energies from a point source of iodine-125.

FIGURE A 5



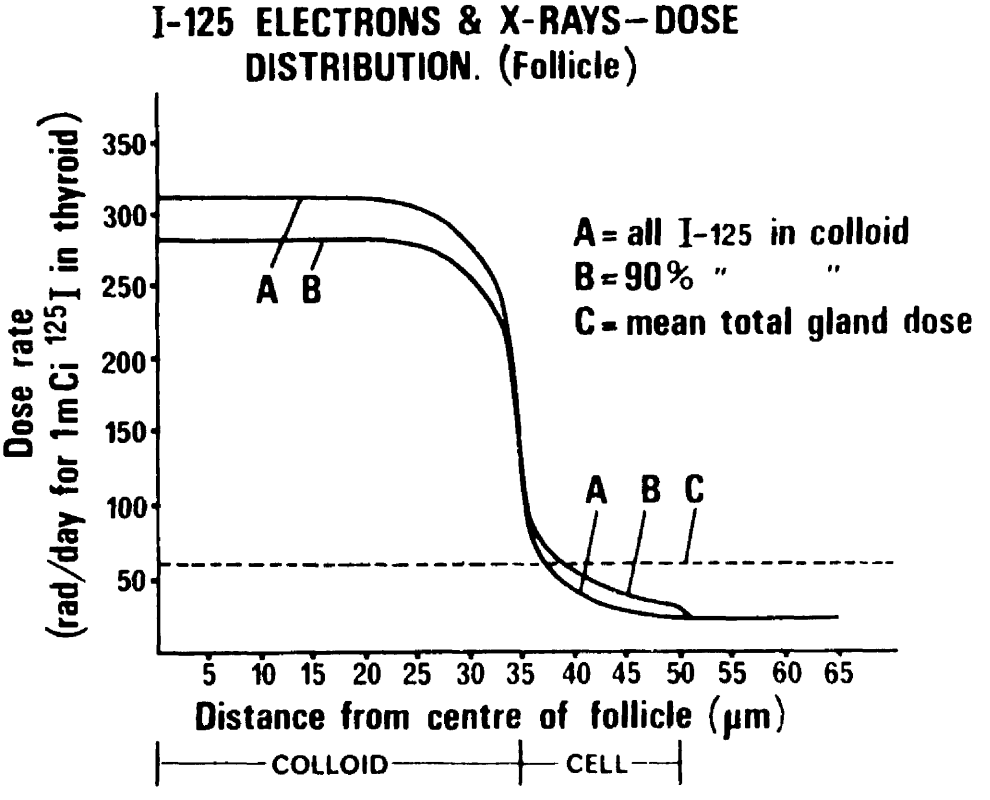
Decrease in the dose rates with distance from plane sources of iodine-125 of different thicknesses (1, 2, 4 and 8 microns and a semi-infinite source).

FIGURE A 6



Rapid fall-off in dose rate across the boundary of a sphere when all the iodine-125 is within the circumference of the sphere.

FIGURE A 7



Rapid fall in radiation dose from the colloid across the apex of the follicular cell towards the base of the cell

A. When 100 per cent of iodine-125 is in the colloid

B. When 90 per cent of iodine-125 is in the colloid and 10 per cent in the cell

C. Mean total gland dose

Table A 9

Approximate Range of Emissions of Iodine-125 in Tissues

(From Greig 1970)

Number per 100 Disintegrations	Approximates Range (Microns)
Photons	
23	100
112	30×10^3
24	50×10^3
7.3	70×10^3
Electrons	
376	0.02
78	0.30
156	0.40
15.4	12.00
8.8	15.00
12.0	22.00
3.7	26.00

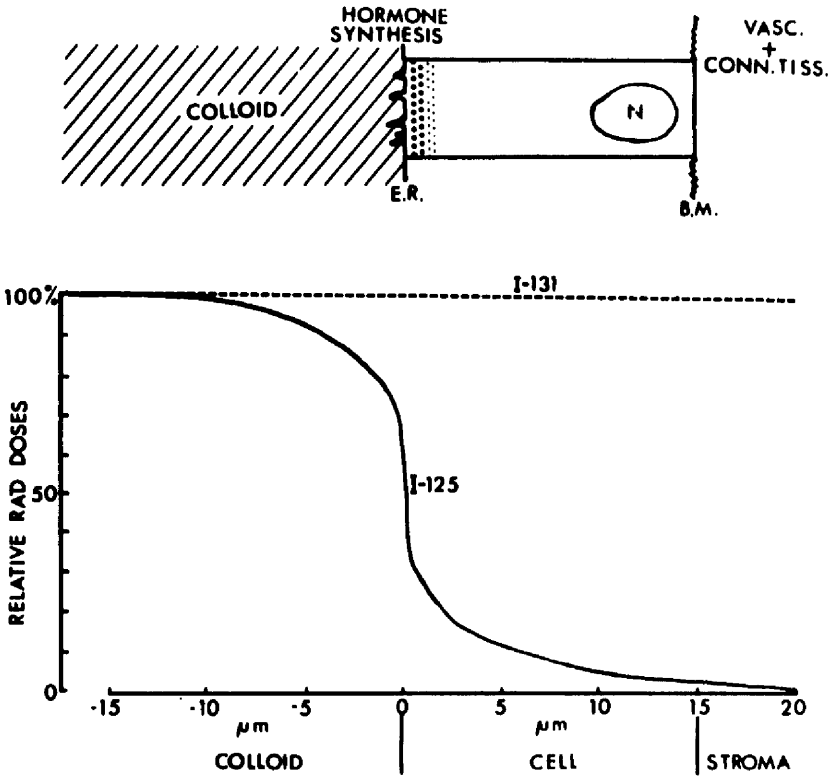
X rays (3.7 Kev) are almost all absorbed in the thyroid but in the rat these emissions and the γ rays are responsible for only about 15 per cent of the absorbed dose in the gland; in the larger human thyroid this may be increased to 20 or 25 per cent.

The majority of the energy deposited in the thyroid is therefore due to the low energy electronic emissions. Gillespie et al (1970) and Greig (1970) have calculated that from a point source of iodine-125 few electrons travel more than 15 microns and the maximum range is 26 microns (Figure A4). Table A9 lists the quantity and range of the emitted electrons in tissues. A similar pattern is true for iodine-125 radiations from plane sources of varying thicknesses; a rapid fall off in dose rate occurs in the first few microns from the source and this is most apparent when the source is only 1 micron thick (Figure A5).

From a spherical source of iodine-125 there is a dramatic fall off in dose rate across the sphere boundary (Figure A6), and alteration of the size of the sphere from 35 microns to 70 microns (chosen for similarity to proportions of colloid in rat follicles) does not greatly alter this. Factors which do affect the absorbed dose rate (rads per mCi per day) are differences in the size of the gland and changes in the relative proportions of the radionuclide within the colloid or the follicular cell (Figure A7). Iodine-125 has to cross the cell to be incorporated in the thyroglobulin and it re-enters the cell when resorption and proteolysis of colloid containing iodine-125 occurs. Even considering these factors the intracellular content of iodine-125 is not greater than 10 per cent and may be closer to zero (Nadler et al 1962, Wetzel et al 1965), thus 90 per cent or more of the radionuclide is in the colloid.

The total radiation dose from iodine-125 (electronic and photon) compared with iodine-131 on the thyroid is illustrated diagrammatically

FIGURE A 8



Diagramatic comparison of iodine-131 and iodine-125 radiation effects across a thyrotoxic follicular cell, showing dramatic drop in radiation dose across the cell from iodine-125 and uniform dose rate from iodine-131.

in Figure A8. The importance of this rapid fall off in radioactivity is discussed below in relation to the radiobiological effects in the experimental animal. Calculations of follicular cell rad doses in thyrotoxic patients treated with iodine-125 are based on the principles outlined above (Section B, Chapter I).

Production Of Iodine-125

There are several methods of producing iodine-125 (Myers and Vanderleeden 1960, Harper et al 1963). The method described below is used by the Radiochemical Centre (Amersham) who supply the therapy doses.

Enriched Xenon-124 is irradiated for one month at a flux between 1 to 2 x 10^{-14} neutrons per cm per cm^2. The material obtained contains equal amounts of iodine-125 and iodine-126 and it is left to decay for several months to allow iodine-126 with a short half life (12.8 days) to disappear. The eventual combination contains less than 1 per cent iodine-126 and this can be further reduced using a loop process circulating through charcoal.

Cost Of Iodine-125

At the present time the cost of iodine-125, £2.00 per mCi, is greater than had been envisaged (Myers 1965). There is, however, a greatly expanding market for iodine-125 for in vivo and in vitro diagnostic applications. If the therapeutic possibilities discussed below are substantiated this market will be considerably expanded. Iodine-131 costs £0.20 per mCi but its sales have reached a plateau. Continued expansion of sales of iodine-125 at the present rate will bring the relative costs of these radionuclides to £1.00 and £0.20 per mCi in 5 years time and £0.50 and £0.30 per mCi in a decade.

Non Therapeutic Uses of Iodine-125 Based On Physical Properties Of The Radionuclide

Myers (1965) reviewed over 90 published reports of the uses of iodine-125 which had been developed in the 4 years following its

"medical renaiscence". The half-life of 60 days provided a conveniently long shelf life to allow preparation and transport of doses anywhere in the world with no material loss of radioactivity. The emissions have an enormous potential for both in vivo and in vitro medical and biological investigations. Because of the low intensity of the photons, thinner crystals and less shielding are necessary and counting apparatus can be easily handled and inexpensive.

Thyroid scanning may very satisfactorily be done using the 27.2 Kev to 35.5 Kev photon emissions (Charkes 1964) and iodine-125 has been used for routine thyroid function tests (Ben Porath et al 1966) corrections, however, must be made for the size of the thyroid (Rollo 1971). The high γ to β ratio reduces the total body radiation dose which is important if this radionuclide is used for in vivo diagnosis in children (Riccabona 1965). Measurements of bone density are possible using iodine-125 as a source of soft x rays (Cameron 1964). The low energy conversion and Auger electronic emissions are ideal for high resolution autoradiographs (Andros and Wollman 1964, Noyan et al 1963, Stein and Gross 1964).

Summary of Emissions of Iodine-125: Relation to Theoretical Use in Treatment of Thyrotoxicosis

The abundance of low energy electrons from iodine-125 in theory suggest that if this radionuclide is used therapeutically, the functional segment of the follicular cell, the apex, should be subjected to a much higher dose rate than the nucleus. The dose rate across the cell does not fall to zero, however, because of the photon emissions, but the rad dose at the colloid cell interface is 3 or 4 times that at the nuclear level, 10 microns from the colloid (Gillespie et al 1970, Werner et al 1970). However, by incorporating a quality factor to convert the dose rates from rads to rems the membrane dose is increased to about 6 times the dose at the nucleus (Lewitus et al 1971). The reason for

this is that the quality factor is greater than one for the low energy electrons which travel 0.05 to 0.5 microns and hence preferentially irradiate the apical segment. Since these electrons do not travel as far as the nucleus the quality factor at that level remains one and the dose is the same in rads or rems.

To examine whether iodine-125 preferentially does reduce hormone synthetic function several groups of investigators, not all interested in its therapeutic application, have compared the effects of this radionuclide with iodine-131 in experimental animals.

Radiobiological Effects of Iodine-125 in Experimental Animal: Comparison With Iodine-131

A useful technique for assessing the degree of thyroid radiation damage is to measure the growth response of the gland to a goitrogenic stimulus (Doniach and Logothetopoulos 1955). Gross et al (1968) have compared the respective radiation effects of iodine-125 and iodine-131 utilising this technique. Iodine-131 in increasing doses progressively diminished the expected goitrogenic response probably because of intense nuclear irradiation. Iodine-125 in equivalent doses did not interfere with this response and indeed the total thyroid D.N.A. content was increased in animals treated with this radionuclide. Nevertheless rats treated with iodine-125 grew less well than those treated with iodine-131. This apparent paradox was attributed to an exagerrated destruction of thyroid hormone, especially iodothyronine, biosynthesis in the former animals. The pituitary glands from iodine-125 treated rats were significantly heavier than those of controls or of animals treated with iodine-131 suggesting that there was an increased secretion of pituitary thyrotropin in response to the reduced thyroxine production. The normal goitrogenic response illustrated that the follicular cells were still capable of responding to T.S.H. by producing D.N.A. and becoming hypertrophic. In a separate investigation Gross et al (1968) found two thyroid tumours in rats treated with

iodine-125.

Iodine-125, therefore, causes a relatively greater reduction in thyroxine synthesis than does iodine-131; thyroxine production is partly a function of the follicular cell apex. Iodine-131 on the other hand predominantly affects the response to thyrotropin and D.N.A. production both of which are regulated in the basal segment of the cell.

Greig et al (1970) have investigated the survival of rat thyroid cells after irradiation by iodine-131, iodine-125 and X rays respectively. Because of the extremely low rate of follicular cell proliferation in euthyroid rats an artificially increased rate was induced by methylthiouracil to facilitate the measurement of any differences. The Do values for x rays, iodine-131 and iodine-125 were 450 rads, 5,500 rads and 9,400 rads. The explanation for the difference in Do values for the two radionuclides was the inhomogeneous absorption of radiation across the follicular cells in the iodine-125 treated rats which significantly reduced the nuclear dose rate. The intense apical cytoplasmic dose did not, therefore, appear to be important in the maintenance of cell viability or reproduction. This thesis has been confirmed by the investigation of Munro (1970) who found no reduction in viability of Chinese hamster fibroblasts after intense α irradiation of the cytoplasm, nuclear radiation rapidly induced death of the cells. Red blood corpuscles are not killed unless subjected to very large doses of radiation (Schiffer et al 1966) probably because they are non nucleated.

An elegant series of experiments to compare the radiobiological effects of iodine-125 and iodine-131 in rats have been conducted by Vickery and Williams (1971) and they confirm that iodine-131 in increasing doses produces a progressive diminution of the expected response to a goitrogen. The effect of iodine-131 was increased if before the radionuclide was given the rats were fed an iodine deficient

diet to increase the thyroidal uptake of radioiodine-131. Iodine-125 did not diminish the goitrogenic response or produce the same degree of thyroid destruction in rats fed a normal diet and despite the increased radionuclide uptake after a period of reduced iodine intake there was surprisingly even less inhibition of goitrogenesis or cell destruction.

Iodine deficiency produces histological alterations in the follicular cell similar to those encountered in thyrotoxicosis. The nucleus lies basally in the follicle cell which becomes columnar in shape. It is, therefore, at a greater distance from the colloid and hence the iodine-125 irradiation source. The influence of this gap, probably about 10 microns, on the radiobiological effects of iodine-125 was dramatic. In the rats fed on a normal diet the ratio of destructive effectiveness of iodine-131 to iodine-125 was 18 to 1 (Vickery and Williams 1971). Calculations from iodine deficient animals gave a ratio of 60 to 1, iodine-125 produced even less cell destruction than it did in normal glands.

In animals treated with small doses of the radionuclides, nuclear aberrations typical of irradiation (Maloof et al 1952, Vickery 1964) were more common in the iodine-131 treated animals. Large doses of iodine-131 (300 uCi) cause severe and widespread damage and resulted in total fibrous replacement of the gland yet the same large doses of iodine-125 resulted were associated with "excellent preservation of structure".

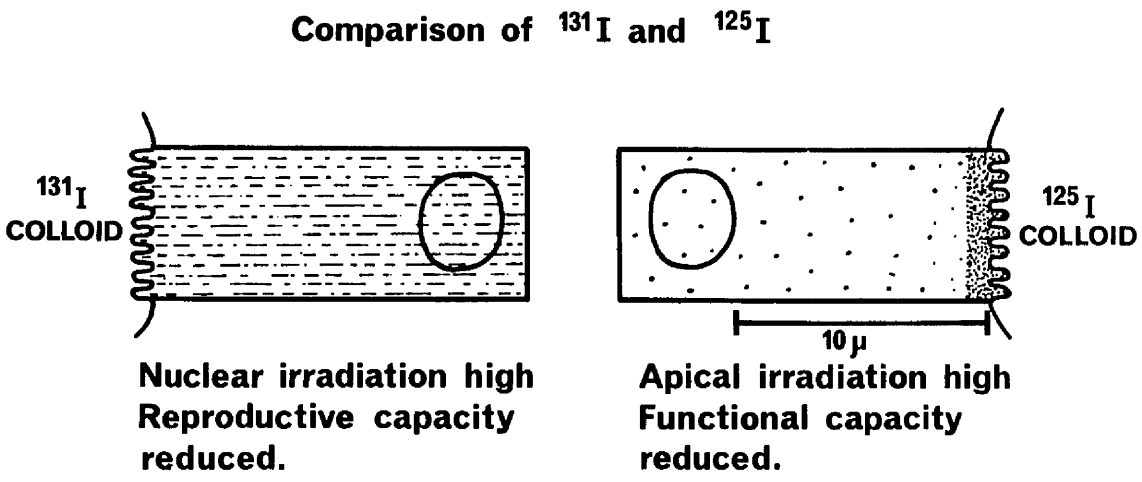
Jongejan and Van Putten (1972) have designed a trial of experiments to compare the radiation effects of different doses of iodine-131 and iodine-125 on functions located at the level of the apex, at the nucleus and at the base of rat and mice follicular cells. They selected (a) production of thyroid hormones (b) the maintenance of cellular structure and (c) the integrity of the iodide concentrating mechanism as representative functions of these respective levels. The degree of

inhibition of each of these processes has been measured in experimental animals treated with these radionuclides.

Iodine-131 was twenty times as effective as iodine-125 in reducing the level of circulating thyroxine, sixteen times as potent in producing nuclear damage and twenty times as effective in suppressing the iodide trapping mechanism. It is relevant that the relative cellular destructive effects of the radionuclides in the experiments of Jongejan and Van Putten were almost identical to the results obtained by Vickery and Williams (1971). The former authors believed because they were unable to demonstrate any gross variation in the radiation effects of iodine-125 across the length of the cell that iodine-125 has no extranuclear effect and they cited as additional evidence the work of Schiffer et al (1966) who have shown that radiation of the red blood corpuscle does not affect its function. Their conclusions are, however, open to discussion. Primarily there is no experimental evidence that the apical functional area of the follicular cell responds to radiation in the same way as the red blood corpuscle. Clinical evidence will be presented below to suggest that there is a difference in effect of iodine-125 and iodine-131 and that the action of iodine-125 is not solely a nuclear effect.

Lewitus and Shaham (1971) studied various parameters of thyroid function in rats treated with iodine-125. Even without the administration of a goitrogen the mass of the thyroid was found to increase from one week after administration of iodine-125 and this persisted for 3 months. These animals nevertheless had deficient hormone synthesis and pituitary T.S.H. was probably the stimulus for thyroid enlargement. Similar findings were described by Konecny (1969) who also confirmed that radiation changes in the thyroid were of much less degree in iodine-125 treated animals compared with iodine-131.

FIGURE A 9



Diagramatic comparison of the radiation effects of iodine-131 and iodine-125 in thyrotoxic follicular cells.

The uniformity of the results in these experiments confirm that in the thyroid of experimental animals the effects of iodine-125 are different from iodine-131. The former radionuclide caused marked reduction in hormone synthesis which was easily explained by the intense irradiation of the cell apex by low energy electrons (3.7 Kev and less). Although about 4 per cent of the electrons travel as far as the nucleus which also received photon irradiation the reduced nuclear dose allowed not only survival of the cell but the ability to hypertrophy and divide when stimulated by T.S.H.

Summary

The histological anatomy and physiological functions of the thyrotoxic follicular cell are outlined. The cell apex is important for hormone synthesis, the nucleus at the base of the cell is necessary for viability and reproduction. Hypothyroidism after iodine-131 therapy is due to intense nuclear irradiation.

The decay of iodine-125 is described in detail. The major emissions are very low energy electrons and when iodine-125 is stored in the colloid it causes intense irradiation of the apex (functional zone) and leaves the nucleus (reproductive zone) relatively unscathed (Figure A9). Radiobiological experiments in animals have shown that iodine-125 does in fact diminish cell function preferentially and cell divisional capacity is not impaired to the same extent.

Section B

Treatment Of Thyrotoxicosis With Iodine-125

Clinical Trials

Chapter I

Treatment Of Thyrotoxicosis With Iodine-125

Pilot Study and Dosimetry

Introduction

Iodine-131, because of the mutually unsolvable problems of the cumulative incidence of hypothyroidism and the slow rate of symptomatic control, is not the ideal radionuclide for the treatment of thyrotoxicosis (Section A, Chapter I). The physical decay of iodine-125 with its rich spectrum of low energy electrons raises the possibility that this radioisotope might partially overcome both of the deficiencies of iodine-131. The working hypothesis that iodine-125 does preferentially reduce thyroid cell function without causing cellular death or sterilisation has been confirmed by animal experiments (Section A, Chapter II). Limited trials in thyrotoxic patients were undertaken to assess whether radiobiological differences would be of clinical benefit as had been proposed by Greig (1968).

Pilot Study

Once permission to prescribe therapeutic doses of iodine-125 had been obtained from the Isotope Advisory Panel of the Medical Research Council, the first important factor to decide was the dose range which should be used in the preliminary studies. The low energy electronic emissions produce an intense irradiation of the colloid cell interface, but the rapid fall off in radiation across the cell when iodine-125 is used means that the nucleus is subjected to a considerably reduced rad dose compared with an equivalent dose of iodine-131. Therefore two possible approaches had to be considered. Firstly small doses of iodine-125 could be prescribed to produce an apical cytoplasmic dose similar to that delivered by standard amounts of iodine-131. This would greatly reduce nuclear exposure. The alternative method was to use amounts of iodine-125 which would expose the nuclei of the follicular cells to the same dose rate as iodine-131. The latter technique was adopted for the following reason. If small doses of iodine-125 had not produced a clinical improvement the planning of

Table B 1

Iodine-125 Control Of Thyrotoxicosis In Pilot Group Of 10 Patients

(From Greig et al 1969)

Patients	Gland Mass (G)	24 Hour Uptake Of Tracer Dose ^{131}I	Dose of Iodine-125 (mCi)	Weeks till Euthyroid	Eventual Outcome	Follow up in Months
1	60	73	57	6	Euthyroid	39
2	25	59	40	6	Hypothyroid	
3	40	53	40	6	Euthyroid	36
4	25	65	25	6	Hypothyroid	
5	25	61	25	7	Euthyroid	21
6	30	65	24	7	Euthyroid	33
7	50	70	56	8	Euthyroid	37
8	25	99	30	12	Hypothyroid	
9	25	74	25	20	Euthyroid	41
10	50	46	50	9	Euthyroid	38
Mean	35.5	66.5	38.2	8.5		

subsequent studies would have been difficult. With the large doses the nuclear irradiation should produce results at least as good as standard amounts of iodine-131 and if they were found to be ineffective further trials could confidently be abandoned altogether since the total body radiation burden of larger doses would be prohibitive.

Using iodine-131 a fairly predictable response can be expected with a dose of 10,000 rads, at least 50 per cent of the patients recovering in about 3 months. A decision was made to commence the trial with quantities of iodine-125 which would deposit this amount of radiation at 10 microns from the source (the distance of the nucleus from the colloid in the elongated thyrotoxic follicular cell). Since the nuclear dose is reduced by about 80 per cent with iodine-125 the original doses prescribed were the standard iodine-131 doses multiplied by a factor of 4.

Patients Studied

10 patients all over 60 years of age with confirmed thyrotoxicosis received large doses of iodine-125 (Table B1). The average dose prescribed was 38.2 mCi and two patients received more than 50 mCi. The mean time for recovery was 8.5 weeks (8 had normal thyroid status both clinically and biochemically by 10 weeks) and all 10 were euthyroid within 20 weeks (Greig et al 1969). The patients who received the largest doses, 56.0 mCi and 57.0 mCi, are still euthyroid after 37 and 39 months respectively. With iodine-131 a less satisfactory rate of control and recovery would have been expected and almost certainly at least 3 of the patients would have required retreatment.

The justification for the trials and for these dose schedules was, therefore, complete and the outstanding consistency of recovery suggested, though did not prove, that part of the effect of iodine-125 was indeed extranuclear. Hypothyroidism was predictable with these

nuclear dose rates and it rapidly occurred in 3 of the 10 patients. Iodine-125 was, therefore, known to produce rapid clinical control of thyrotoxicosis but it was then necessary using empirical dose schedules to prescribe successively smaller amounts and by careful clinical assessment decide which produced the best outcome. The pilot group received approximately 1,000 uCi per estimated gram of thyroid and this small group has grown by the accretion of 7 additional patients who have received more than 750 uCi per gram of thyroid. The trials were extended using progressively smaller doses per gram of thyroid (Greig et al 1971, McDougall et al 1970, McDougall et al 1971a, 1971b). There are now in addition to the group of 17 patients who have received the largest therapy doses, 6 other treatment groups who have been given 651 to 750 uCi, 551 to 650 uCi, 451 to 550 uCi, 351 to 450 uCi, 251 to 350 uCi and 151 to 250 uCi per gram of thyroid. Details of the patients in these groups are comprehensively discussed in Section B, Chapter II.

Calculation Of Rad Dose At Different Levels Of Thyroid Follicular Cell

The β particles emitted by iodine-131 travel distances which are considerably greater than the size of individual follicular cells or even thyroid follicles. With this radionuclide the irradiation of the whole gland is fairly uniform and the mean gland dose which is the figure used for therapy is an accurate indicator of the irradiation of all parts within the gland. With iodine-125 this is not the case. Photon emissions do irradiate the whole gland but their contribution is small. Because of the low energies of the electrons (especially those between 0.2 Kev and 3.7 Kev) there is no cross fire between follicles and the electron dose at any point in a follicle is due solely to the activity of that follicle. The majority of the electrons have ranges of less than 1 micron thus the dose at the nuclear level of the follicular cell is only a fraction of the dose at the colloid cell

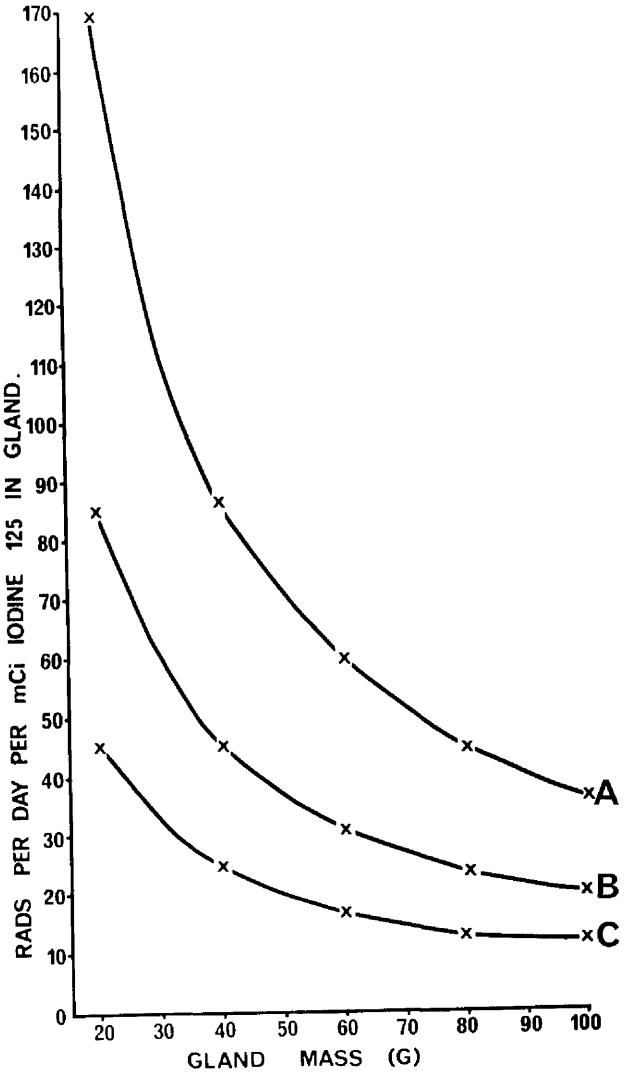
Table B 2

Dose Rate from 1 mCi Iodine-125 per day in Thyroids of Different Masses where 15 per cent of Gland is Colloid

Gland Mass (Gram)	90 per cent of Iodine-125 in Colloid			100 per cent of Iodine-125 in Colloid		
	Dose Rate Colloid-Cell Interface	Dose Rate 1 micron from Colloid	Dose Rate 10 micron from Colloid	Dose Rate Colloid-Cell Interface	Dose Rate 1 micron from Colloid	Dose Rate 10 micron from Colloid
20	170	86	46	176	73	33
25	138	71	39	136	62	28
30	114	60	33	112	52	24
35	98	51	29	100	44	21
40	87	45	25	90	39	19
45	78	41	22	82	35	17
50	72	37	20	74	32	16
55	66	34	19	68	30	15
60	60	32	17	62	27	14
65	55	29	16	57	25	13
70	51	27	15	53	24	12.5
75	48	25	14	50	22	11.5
80	45	24	13	47	21	11
100	36	20	12	38	17	9

interface even when the photon component is added to the important electronic component. Total thyroid rad dose is, therefore, meaningless with reference to iodine-125 therapy, and the important dose rates are at colloid cell interface and at the follicular cell nucleus (10 microns from colloid cell interface). Gillespie et al (1970) using models have calculated the rad dose from 1 mCi iodine-125 per day at these levels. There are certain factors which alter the dose rates, the first being the relative proportions of the radionuclide in the follicular cell and in the colloid. In general more than 90 per cent of stable iodine is in the colloid and 10 per cent in the cells (Nadler et al 1962) the same obtains for iodine-125. If 100 per cent of the iodine-125 is in the colloid the nuclear dose rate will be less than if 10 per cent of the radionuclide remains in the follicular cells. For calculations in this thesis it has been accepted that 10 per cent of the iodine-125 is in the cell and thus the nuclear rad dose quoted may be slightly exagerrated. The dose rate also varies depending on the gland size and on the fraction of the gland which is colloid. Rad calculations have been based on the clinical estimation of gland mass and in each patient the colloid fraction has been taken as 15 per cent. Using the general calculations of Gillespie et al (1970) which have been expanded to include glands weighing from 20 gram to 100 gram (Table B2) it is possible to construct graphs for the dose rate per mCi iodine-125 per day at different distances from the colloid in thyroid glands of different masses. Figure B1 shows the rad doses that one mCi would produce at the colloid cell interface and at one and 10 microns from the apical membrane assuming in each case that 90 per cent of the iodine-125 is in the colloid and 10 per cent in the follicular cell and that the colloid fraction is 15 per cent. Using the reading in rads per day per mCi iodine-125 from the desired graph it is possible to calculated the total rad dose at any level in the cell in any patient

FIGURE B 1



Dose rate (Rads) from 1 mCi iodine-125 per day in thyroid glands of masses from 20 grams to 100 grams

A. Dose rate at colloid cell interface
B. Dose rate at 1 micron from apical margin of cell
C. Dose rate at 10 microns from apical margin, the presumed site of the cell nucleus.

from the formula

$$\text{Rad Dose} = R \times \text{Administered Dose (mCi)} \times \frac{\text{Percentage Thyroid Uptake of Dose} \times Te}{100} \quad (1)$$

Where R = Reading from graph (as described)

Te = Effective half life of iodine-125 in thyroid

The factors in the calculation of (R) which are difficult if not impossible to estimate have been discussed. The administered dose is an exact measurement in this equation but the percentage uptake of iodine-125 into the thyroid is difficult to obtain. Iodine-125 emits photons in the 27 to 35 Kev range and although there is a high relative photon energy ratio which makes the nuclide suitable for counting (Riccabona 1965, Ben Porath et al 1966) absorption of radiation in glands of different sizes must be taken into account. Methods which have been designed to overcome this problem are rotating detectors (Gillespie and Fraser 1972) and application of the inverse square law principle (Rollo 1971) but because of the problem of exact measurement with iodine-125 the 24 hour uptake of the diagnostic tracer dose of iodine-131 was accepted to be representative of the uptake of the therapy dose. This may hold true for some patients but fluctuations in uptake over short periods of time are known to occur (Silver 1968, Childs and Holbrook 1969). The final measurement of this formula, the effective half life of the iodine-125, is subject to the great individual variation. For the basis of the calculations an effective half life of 15 days has been used. This result was obtained from the formula

$$\frac{1}{Te} = \frac{1}{T_B} \times \frac{1}{T_P} \quad (2)$$

Where T_B = Biological half life which is on average 20 days in a thyrotoxic patient (Rhodes and Wagner 1971)

T_P = Physical half life (60 days)

4 patients had serial whole body counts before and at intervals after iodine-125 therapy in an effort to calculate the effective half

Table B 3

Effective Half-Life of Iodine-125 by Direct Whole Body Counting and by Indirect Calculation using a Tracer Dose of Iodine-131

		Effective half-life Iodine-131 (days)	Biological half-life (days)	Effective half-life Iodine-125 (days)
By direct measurement				
Patient	1			20 (approximate)
	2			10 (approximate)
	3			7 (approximate)
	4			15 (approximate)
By indirect measurement				
Patient	1	6.8	42.4	25
	2	6.8	42.4	25
	3	7.3	73.9	33
	4	7.2	64.8	31
	5	7.3	73.9	33
From Werner et al 1971				
Shortest				6 (approximate)
Longest				27

life. Because of the difficulties in counting iodine-125 discussed above it was impossible to obtain a smooth curve of radioactive fall off with time. Invariably the whole body iodine-125 radioactive reading immediately after therapy was lower than the result 3 or 4 days later. The reason for this is that for the first estimation the radionuclide was in the gastrointestinal canal shielded by several centimetres of subcutaneous tissue whereas for the latter reading the vast majority of the material was concentrated superficially in the thyroid. Using this direct but inaccurate method the effective half life ranged from about 7 to 20 days. The same problem was encountered by Werner et al (1970) who found the range from 6 to 27 days. To overcome the counting difficulties 5 patients were given a 50 uCi tracer of iodine-131 simultaneously with the therapy dose of iodine-125. The 364 Kev photons from iodine-131 could then be accurately counted irrespective of the depth of the isotope in the body. Since both radionuclides were being handled simultaneously in the body it is fair to conclude that the biological half lives would be the same. Using this justifiable assumption the following series of steps were undertaken. The effective half life of iodine-131 in the patient was calculated by serial whole body measurements making standard corrections for the background radiation and fall in radioactivity in a phantom. Once this was obtained the biological half life was calculated from formula (2). With this result the effective half life of iodine-125 was obtained from the same equation but substituting the physical half life of 60 days. Table B3 shows the effective half life of iodine-125 in 4 patients by direct measurement and 5 patients by this indirect technique. The effective half lifes by the latter approach show a small variation (25 to 33 days). Recently the effective half life of iodine-125 in the thyroids of seven euthyroid radiation workers accidently exposed to iodine-125 vapour was calculated

Table B 4

Dose Rates at Nuclear Level of Follicular Cell and at Colloid Cell Interface in Patients, Depending on the Outcome of Therapy and on the Dose of Iodine-125 Prescribed per gram thyroid.

Results in brackets where effective half life is 30 days.

Patients Studied	Approximate Rad Dose at Nucleus	Standard Error		Approximate Rad Dose at Colloid-Cell	Standard Error	
Euthyroid	4,255	161	(8,500)	14,790	693	(29,500)
Hypothyroid	5,872	491	(11,500)	20,626	1,741	(41,000)
Thyrotoxic	2,860	236	(5,500)	9,574	896	(19,000)
151-250 uCi per gram	1,973	70	(4,000)	6,845	323	(13,500)
251-350 uCi per gram	3,012	108	(6,000)	10,375	351	(20,500)
351-450 uCi per gram	3,775	106	(7,500)	13,312	362	(26,500)
451-550 uCi per gram	4,666	112	(9,500)	16,304	391	(32,500)
551-650 uCi per gram	5,585	195	(11,000)	19,850	686	(39,500)
651-750 uCi per gram	6,549	282	(13,000)	22,752	969	(45,500)
More than 750 uCi per gram	9,869	984	(20,000)	35,451	2,237	(71,000)

to be 41 ± 2 days (Bordell et al 1972).

From the above argument the result of 15 days may be used as a working average figure but in some patients the effective half life may be twice as long and if the effective half life is doubled the rad dose to the patient is doubled. Table B4 shows the mean results obtained by simple but tedious application of equation (1) in the calculation of the rad dose at the colloid cell interface and at the level of the nucleus in the follicular cells. For each patient the uptake of isotope, the dose prescribed, and the reading from the graph depending on gland size have been multiplied together and the total multiplied by 15. The average results and standard error have been calculated in all the patients who became euthyroid and hypothyroid or who remained thyrotoxic after iodine-125. The mean results in the 7 treatment groups are also shown. In brackets are the results if the mean effective half life is 30 days this gives the greatest possible mean rad dose which could occur. Although it is agreed that some patients would have this amount of radiation the smaller results are most certainly a more accurate guide to the whole group of patients. Details of the total group of iodine-125 treated patients will be given in Section B, Chapter II.

Summary

A pilot study with large doses of iodine-125 in the treatment of thyrotoxicosis was extremely successful and justified extension of the trials with smaller therapy doses.

Calculation of the rad dose to various levels of the thyrotoxic follicular cell involves the use of several assumptions which are hoped to be valid when large numbers of patients are involved.

Section B

Chapter II

Treatment Of Thyrotoxicosis With Iodine-125: Full Scale Clinical Trial

Introduction

The clinical outcome of 265 patients treated with iodine-125 at the Department of Nuclear Medicine of the Royal Infirmary, Glasgow, from the commencement of the pilot study on 26th July, 1968, up until the first of October, 1971, is described in detail. No patient treated within this group has been excluded. The length of follow up in patients treated after the first of October has been too short for assessment.

Selection of Patients for Iodine-125 Therapy

Since the rate of symptomatic response to iodine-125 was unknown, all of the patients treated at the start of the trial were reviewed frequently. There was, therefore, a tendency to select patients who lived within a radius of about 30 miles of the Royal Infirmary. All patients treated with iodine-125, irrespective of their source of referral, continued to attend clinics at the Department of Nuclear Medicine; a small porportion of the 70 patients who were referred from other centres were also supervised at their "parent" hospital.

For two reasons a definitive policy was adopted to treat patients with small diffuse thyroid glands. Firstly estimation of the gland size by palpation was simpler and secondly any nodules arising after therapy would be detected more easily. After considerably experience had been gained a small number of patients with multinodular (14) or single toxic nodules (2) were treated with iodine-125. Therapy was restricted, as far as possible, to those aged 40 year or older.

Pre-Therapy Diagnosis of Thyrotoxicosis

Patients referred for radioiodine therapy usually were already diagnosed as thyrotoxic with confirmatory laboratory evidence of the diagnosis. If the only documented data was biochemical (protein bound iodine-127) the percentage thyroidal uptake of a 5 uCi tracer dose of iodine-131 24 hours after administration was estimated to

provide additional information. This result was available in 262 of the 265 patients before treatment was prescribed, the average result was 64 per cent (normal range 20 per cent to 50 per cent). The protein bound iodine-127 was also estimated in 137 patients (51.2 per cent of the total group) the mean result was 12.9 ug per 100 mls. and the range 6.8 to 20.0 ug per 100 mls. (normal range 4.0 to 8.0 ug per 100 mls.).

Discussion With Patient

Before treatment was prescribed either Dr. W.R. Greig or I interviewed each of the patients. The severity of the disease in each individual was assessed and the beginning of an important rapport established. Time was taken to explain the nature of the therapy, its lack of side effects and the probable rate of recovery. The possible need for retreatment or occurrence of thyroid failure in the future were introduced to emphasize the importance of intermittent review after therapy. All patients still in the fertile age range were advised to take contraceptive precautions for one year from the time of treatment.

Administration of Therapy Dose

After calculation of the individual doses in the manner described before, the therapy doses were ordered from the Radiochemical Centre, Amersham. Therapy drinks were always prescribed on a Friday. Knowledgeable advice was sought about precautions to be adopted to safeguard radiation exposure and after detailed consideration it was deemed unnecessary to take special precautions about the disposal of radioactive excreta and most of the patients attended the Department of Nuclear Medicine for only a few minutes on an outpatient basis. Nevertheless strict attention was paid to the technique of administration care being taken to avoid contamination.

Review Arrangements After Therapy

Routine reviews of the patients were undertaken by only two physicians (Dr. W.R. Greig and myself). This was important not only in the assessment of the therapeutic response but also in the maintenance of each patient's morale especially at times when the rate of recovery did not meet his or her expectations. If any patient failed to keep a clinical appointment a new date was arranged for one week later.

The necessity for frequent reassessment has been discussed and almost every one of the first 50 patients returned at fortnightly intervals until euthyroid; with greater experience in the pattern of recovery the frequency of follow up visits was reduced. Patients were then reviewed routinely four weeks after the therapy dose and depending on the general condition of each individual the succeeding visits were planned accordingly. If there was no diminution in the thyrotoxic features reviews were planned more often so that any adjuvant therapy or retreatment could be introduced without delay. Patients who became euthyroid and remained so returned after progressively longer intervals, two, three, four and six months. When a clinical suspicion of sub-thyroidism arose a sample of venous blood was withdrawn for estimation of serum protein bound iodine-127 and or serum thyroxine and review arranged one or two weeks later. With the knowledge of the biochemical results a decision was reached whether or not to start life long replacement therapy. No attempt was made to wean patients off thyroxine once it had been started though two patients did stop it of their own accord. Even when hypothyroid, patients were well established on thyroxine therapy they have been reviewed at 6 monthly intervals.

Table B 5

Age Of Patients At Time Of Iodine-125 Therapy

Age in Years	Number of Patients	Per Cent of Total	Follow up and Standard Error months	
Less than 40	10	3.8	12.3	2.7
40 - 44	51	19.3	17.6	1.2
45 - 49	55	20.8	17.3	1.2
50 - 54	47	17.7	21.1	1.2
55 - 59	41	15.5	18.4	1.4
60 - 64	29	10.9	21.6	2.1
65 - 69	24	9.0	18.7	2.4
70 - 74	5	1.9	24.6	5.2
75 - 79	3	1.1		
Range 33 to 76	265	100.0		

Table B 6

Gland Size Before Iodine-125 Therapy

Gland Mass (G)	Number of Patients	Per Cent of Total
25	53	20.0
30	58	21.9
35	20	7.6
40	62	23.4
45	5	1.9
50	51	19.2
Greater than 50	13	4.9
Not Noted	3	1.1
	265	100.0

Patients Treated With Iodine-125

Sex and Age Distribution

227 (85.7 per cent) of the treatment group are female and 38 are male (14.3 per cent). The age distribution of the patients at the time of treatment is shown in Table B5. The age range from 33 to 76 years includes 10 patients (3.8 per cent) who were under 40 years, 9 of these patients were either 38 or 39 year old. Almost three quarters of the total group (73.3 per cent) were aged between 40 and 59 years and only three (1.1 per cent) were 75 years of age or older.

Thyroid Gland Mass Before Treatment

Estimation of the thyroid weights was made by palpation and expressed to the nearest 5 grams. Impalpable glands were empirically accepted as weighing 25 grams and this was the lower end of the weight range, 75 grams was the heaviest. 72.5 per cent of the glands were estimated to weigh 40 gram or less. Details of the number and percentage of patients with glands of different masses are shown in Table B6. No record of gland mass was made in 3 of the patients (1.1 per cent).

Dose of Iodine-125 (uCi) Administered Per Gram Thyroid

Each patient received a preselected dose of iodine-125 per estimated gram of thyroid. The total administered dose was calculated from the formula

$$\text{Administered Dose (mCi)} = \frac{\text{Desired uCi dose per gram} \times \text{Thyroid mass (gram)}}{1{,}000}$$

7 treatment groups received the following mean doses, 203.3 uCi per gram (range 151-250), 309.6 uCi per gram (range 251-350), 399.1 uCi per gram (range 351-450), 498.1 uCi per gram (range 451-550), 600.9 uCi per gram (range 551-660), 692.6 uCi per gram (range 651-750) and 995.3 uCi per gram (greater than 750). Most of the patients in each group received a "whole number" dose, 200 uCi, 300 uCi etc. per gram. The

Table B 7

Number and Percentage of Patients who Received Different Administered Doses of Iodine-125 Per Gram Thyroid

Dose Range (uCi/G)	Mean	Number of Patients	Percentage of Total
Less than 150		2	0.8
151 - 250	203.3	45	17.0
251 - 350	309.6	61	23.0
351 - 450	399.1	48	18.1
451 - 550	498.1	32	12.1
551 - 650	600.9	35	13.2
651 - 750	692.6	22	8.3
Greater than 750	995.3	17	6.4
Not Noted		3	1.1
		265	100.0

Table B 8

Initial Doses Of Iodine-125

Dose (mCi)	Number of Patients	Percentage of Total
5 or less	15	5.7
6 - 10	65	24.5
11 - 15	76	28.7
16 - 20	55	20.7
21 - 25	22	8.3
26 - 30	25	9.4
31 - 35	0	0
36 - 40	4	1.5
41 - 45	0	0
46 - 50	1	0.4
Greater than 50	2	0.8
	265	100.0

Table B 9

Total Results After Iodine-125 Therapy

Status	Number of Patients	Per Cent of Total
Euthyroid	179	67.5
Hypothyroid	42	15.9
Thyrotoxic	33	12.5
Equivocal	8	3.0
Not Followed	3	1.1
Total	265	100.0

Table B 10

Outcome Following Iodine-125 Relation to Sex of Patient

	Females		Males	
	Number	Percentage	Number	Percentage
Total	227	85.7	38	14.3
Euthyroid	149	64.8	30	79.0
Hypothyroid	39	17.2	3	7.9
Thyrotoxic	28	13.2	5	13.1
Equivocal	8	3.5		
Not Followed	3	1.3		
Mean Follow (months)	19.0		17.9	
Range	(2-41)		(3-36)	

number in each treatment group and the percentage of the total group are shown in Figure B7. 2 patients received less than 150 uCi per gram of thyroid and the dose per gram was not calculated in the 3 patients whose gland sizes were not estimated.

Initial Total Dose of Iodine-125

The initial therapy doses calculated from the formula above varied in amount from 5.0 to 57.0 mCi. The number and percentage of patients treated with doses within a 5 mCi range are tabulated (B8). The range from 11.0 to 15.0 mCi was the most frequently used and 80.0 per cent of the patients received 20.0 mCi or less for the first therapy drink.

Results

Outcome in Total Treatment Group

179 of the entire group of 265 patients are euthyroid (67.5 per cent), 42 (15.9 per cent) have become hypothyroid and 33 (12.5 per cent) remain thyrotoxic (Table B9). 8 female patients (3.0 per cent) are classified as "equivocal"since although they are clinically euthyroid this status is not substantiated by laboratory results. Despite unceasing requests to attend for review 3 female patients (1.1 per cent) did not do so.

Relation of Sex of Patient to Eventual Thyroid Status

Table B10 records the percentage of male and female patients in these 5 outcome categories. 64.8 per cent of the females are euthyroid compared with 79.0 per cent of the males, the incidence of hypothyroidism in males (7.9 per cent) is lower than in females (17.2 per cent). An almost identical proportion of male and female patients are still thyrotoxic. There is no statistical difference in the length of follow up, the average time for females is 19.0 $\pm$ 9.3 months (range 2 to 41 months) and for males 17.9 $\pm$ 8.3 months (range 3 to 36 months).

Table B 11

Patient Information Depending on Outcome after Iodine-125 Therapy

	Euthyroid	Hypothyroid	Thyrotoxic	Equivocal	Not Traced
Total	179	42	33	8	3
Female	149	39	28	8	3
Male	30	3	5	0	0
Mean Age (Years)	52.0	52.7	52.4	52.0	64.5
Mean Total Administered Dose (mCi)	16.9	20.9	10.7	13.6	15.3
Mean Dose per Gram Thyroid (uCi)	442.4	581.7	303.1	350.0	555.7
Average Length of Follow (Months)	19.7	21.2	10.2	14.8	0

Euthyroid Patients (Table B11)

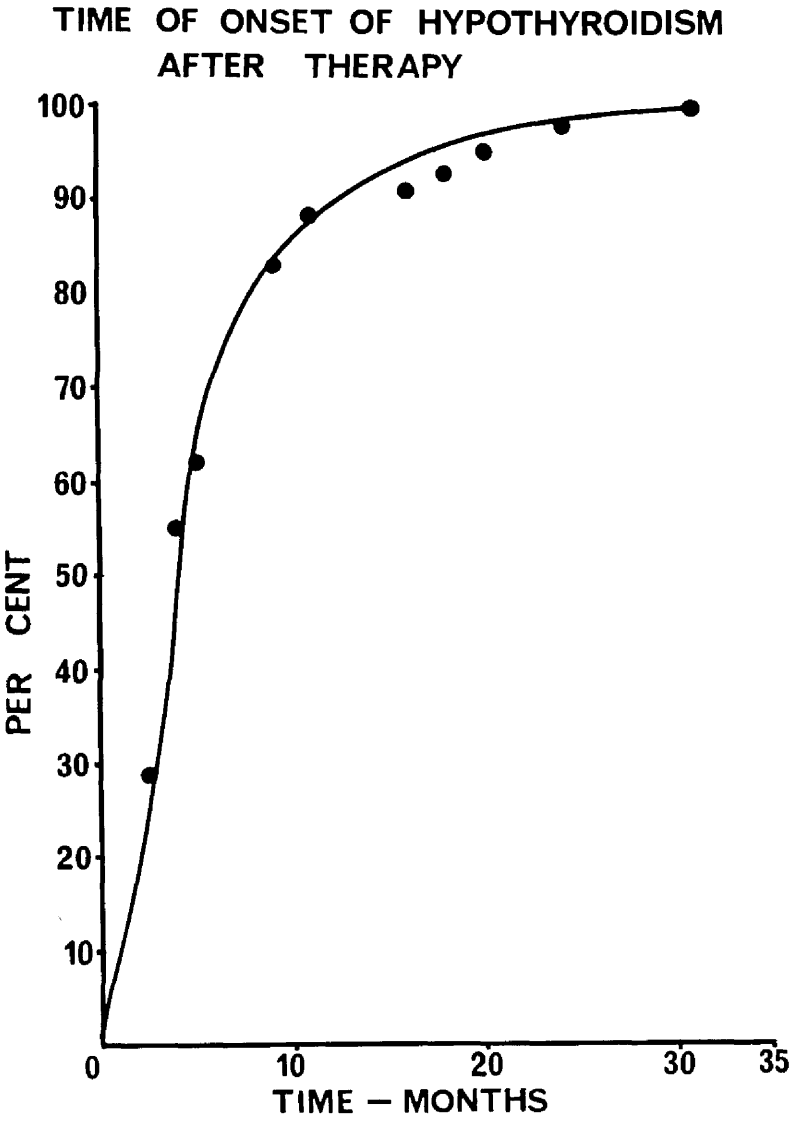
Of the 179 clinically euthyroid patients 149 are female (83.2 per cent) and 30 male (16.8 per cent). Their average age at the time of the initial therapy was 52.0 years (range 33.0 to 76.0 years) and an average dose of 442.2 ± 192.8 uCi iodine-125 was prescribed per gram of thyroid (range 200 to 1,120 uCi per gram) and the average first dose was 16.9 ± 9.43 (range 5.0 to 57.0 mCi). Retrospective calculations of the rad dose at the nuclear and apical levels of the follicular cells were 4,500 and 15,000 respectively (approximate). These patients have been under supervision for 19.7 ± 8.7 months (range 3 to 41 months).

Hypothyroid Patients (Table B11)

42 patients of average age 52.7 years (range 38 to 69) have become hypothyroid at varying intervals of time after iodine-125 therapy. 39 (92.9 per cent) are female and 3 (7.1 per cent) male. The mean administered dose per gram of thyroid was 581.7 ± 273.7 uCi (range 200 to 1,600 uCi per gram) and the mean initial therapy dose of 20.9 ± 8.23 mCi (range 6.0 to 40.0 mCi). These doses gave an average of approximately 6,000 rads to the follicular cell nuclei and 21,000 rads to the cell apices. The average length of follow up is 21.2 ± 8.5 months.

An average of 6.9 months (range 2 to 31 months) passed between the administration of the therapy dose and the onset of hypothyroidism. The cumulative percentage of patients who developed this complication and its time of onset are illustrated in Figure B2. 3 months after therapy 28.6 per cent were already hypothyroid, at 6 months this had risen to 66.7 per cent and by 1 year to 88.1 per cent. 11.9 per cent of the hypothyroid patients (1.9 per cent of the total group) developed thyroid insufficiency more than 1 year after treatment.

FIGURE B 2



Delay in onset of hypothyroidism in 42 patients expressed as a percentage of the total group against time in months.

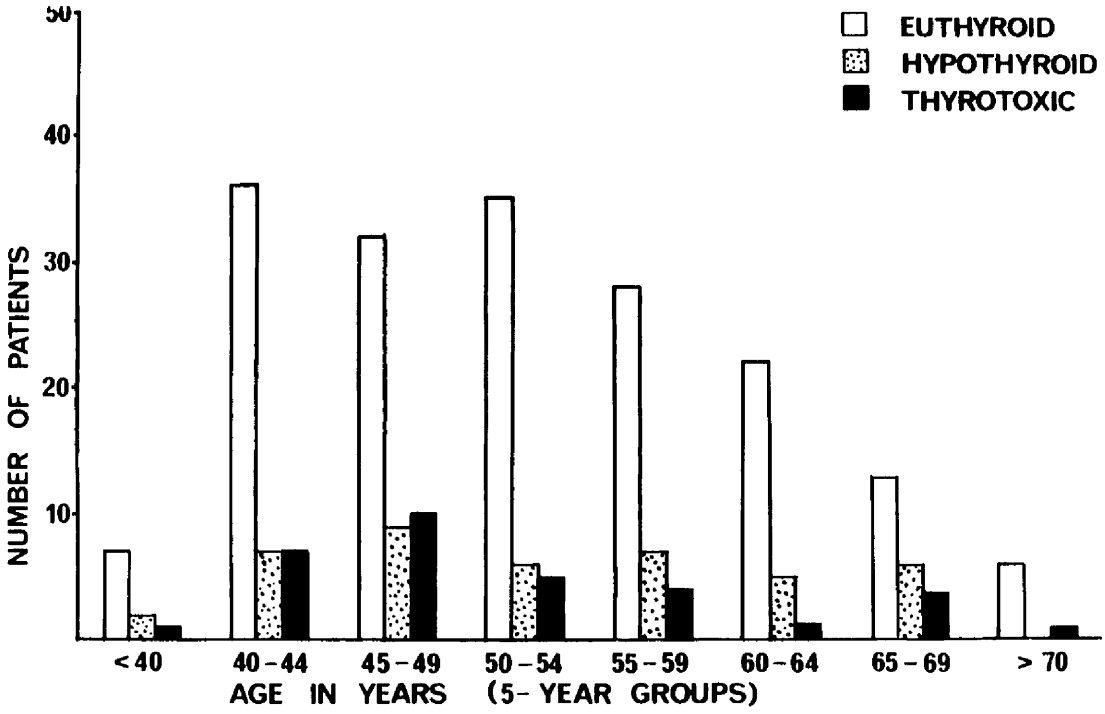
2 of the 42 patients were given iodine-125 since they had relapsed after surgical treatment of thyrotoxicosis. One patient although undubitably clinically thyrotoxic before treatment had completely normal results of thyroid function (protein bound iodine-127, 3.6 ug per 100 mls; 24 hour uptake of a tracer dose of iodine-131, 40 per cent and 48 hour protein bound iodine-131, 0.18 per cent dose per litre). A fourth patient had a well substantiated history of hypothyroidism treated with thyroxine for several years before she developed thyrotoxicosis. After iodine-125 therapy she promptly reverted to the hypothyroid state.

Thyrotoxic Patients (Table B11)

The 33 patients (12.5 per cent of total) who are still thyrotoxic after iodine-125 (84.8 per cent females, 15.2 per cent male) were 52.4 years of age at the time of therapy (range 40 to 75 years). The average dose prescribed per gram of thyroid was 303.1 $\pm$ 126.2 uCi and the initial mean dose 10.7 $\pm$ 4.4 mCi (range 5 to 20.0 mCi). The nuclear rad dose calculated in retrospect was about 3,000 rads and the apical dose about 10,000. Review has been undertaken for 10.2 $\pm$ 7.1 months on average (range 2 to 33 months), one patient followed for only 2 months died from a cerebrovascular accident (Section B, Chapter III), but she was still thyrotoxic at the time of her demise.

In these three main outcome groups euthyroid, hypothyroid and thyrotoxic the doses administered per gram were significantly different (euthyroid/hypothyroid, $P < 0.001$: euthyroid/thyrotoxic, $P < 0.001$). When the total doses prescribed were considered this level of significance was found between the thyrotoxic and euthyroid patients but the difference between hypothyroid and euthyroid patients was somewhat less ($0.05 > P > 0.025$). There was no difference in the length of time euthyroid and hypothyroid patients have been under surveillance but the shorter follow up of the thyrotoxic patients was highly significant

FIGURE B 3



Outcome after iodine-125 therapy (euthyroid, hypothyroid and thyrotoxic) depending on the age of the patient at the time of therapy.

Table B 12

Outcome Related to Age of Patient at Time of Iodine-125 Therapy

Age (Years)	Number	Euthyroid		Hypothyroid		Thyrotoxic		Not Traced		Equivocal		Follow up months
		number	per cent	number	per cent	number	per cent	number	per cent	number	per cent	
less than 40	10	7	(70%)	2	(20%)	1	(10%)					12.3
40 - 44	51	36	(72.5%)	7	(13.7%)	7	(13.7%)			1	(2.0%)	17.6
45 - 49	55	32	(58.2%)	9	(16.4%)	10	(18.2%)	1	(1.8%)	3	(5.5%)	17.3
50 - 54	47	35	(74.5%)	6	(12.8%)	5	(10.6%)			1	(2.1%)	21.1
55 - 59	41	28	(68.3%)	7	(17.1%)	4	(9.8%)			2	(4.9%)	18.4
60 - 64	29	22	(75.9%)	5	(17.2%)	1	(3.5%)			1	(3.5%)	21.6
65 - 69	24	13	(54.2%)	6	(25.0%)	4	(16.7%)	1	(4.2%)			18.7
70 - 74	5	5	(100%)									24.6
75 - 79	3	1	(33.33%)			1	(33.3%)	1	(33.3%)			
Total	265	179		42		33		3		8		

Table B 13

Outcome Following Iodine-125 Relation to Thyroid Gland Size

Gland Mass (G)	Number	Euthyroid		Hypothyroid		Thyrotoxic		Equivocal		Not Traced	
		number	per cent	number	per cent	number	per cent	number	per cent	number	per cent
25	53	33	(62.3%)	9	(17.0%)	8	(13.2%)	3	(5.7%)	1	(1.9%)
30	57	36	(63.2%)	11	(19.3%)	8	(14.0%)			2	(3.5%)
35	20	14	(70.0%)	4	(20.0%)	2	(10.0%)				
40	62	41	(66.1%)	9	(14.5%)	10		2			
45	5	4	(80.0%)					1	(20.0%)		
50	51	38	(74.5%)	9	(17.7%)	3	(5.9%)	1	(2.0%)		
greater than 50	13	10	(76.9%)			2	(15.4%)	1	(7.7%)		
Not Noted	4	3	(75.0%)			1	(25.0%)				
	265	179		42		33		8		3	

($P < 0.001$) when compared with both of the other groups.

Equivocal Patients

8 female patients all clinically well were originally classified euthyroid, however, in 3, serum thyroxine and T.S.H. levels suggested that they were in fact hypothyroid, the relevance of these findings will be discussed in Section C, Chapter I. In the remaining 5 patients the thyroxine levels were persistently elevated, though just above the upper limit of normal.

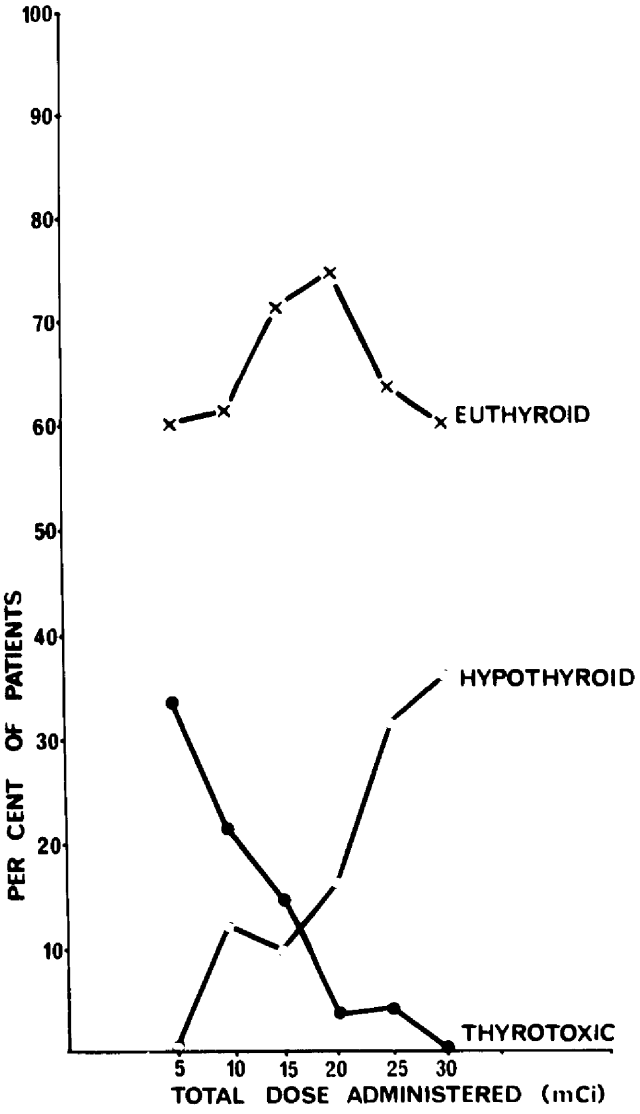
Outcome Related to Age of Patient at the Time of Treatment

Table B12 shows the number and percentage of patients who are euthyroid, hypothyroid and thyrotoxic after therapy depending on their age at the time of treatment. The smallest percentage of euthyroid patients are in the age groups 45 to 49 and 65 to 69, 58.2 per cent and 54.2 per cent respectively (Figure B3). In these groups a higher percentage of patients are still thyrotoxic (18.2 per cent and 16.7 per cent) but in the latter group 25.0 per cent are also hypothyroid.

Relation of Gland Size to Outcome

The status after radioiodine therapy is related to the estimated weight of the thyroid at the time of therapy (Table B13). 64.6 per cent with thyroid glands weighing 40 gram or less are euthyroid; 75.3 per cent of those with larger glands have a favourable outcome. The incidence of hypothyroidism in those patients with small thyroids is 17.2 per cent compared with 12.3 per cent in those with larger glands. Persistence of thyrotoxicosis after therapy is also more common in patients with thyroids weighing 40 gram or less, 14.1 per cent against 8.2 per cent. Nevertheless, if the small number of patients whose glands were estimated to weigh exactly 45 gram, and those with thyroids of more than 50 gram as well as those whose gland sizes were not assessed are excluded, the fairly uniform distribution of euthyroid,

FIGURE B 4



Percentage of patients euthyroid, hypothyroid and thyrotoxic after iodine-125 therapy related to the total initial dose prescribed.

Table B 14

Outcome Following Iodine-125 Therapy Relation to Administered Dose

Dose (mCi)	Number	Euthyroid		Hypothyroid		Thyrotoxic		Not Traced		Equivocal	
		number	per cent	number	per cent	number	per cent	number	per cent	number	per cent
5 or less	15	9	(60.0%)	0		5	(33.3%)			1	(6.7%)
6 - 10	65	40	(61.5%)	8	(12.3%)	14	(21.5%)	1	(1.5%)	2	(3.1%)
11 - 15	76	54	(71.1%)	8	(10.5%)	11	(14.5%)			3	(4.6%)
16 - 20	55	41	(74.5%)	9	(16.4%)	2	(3.6%)	2	(3.6%)	1	(1.8%)
21 - 25	22	14	(63.6%)	7	(31.8%)	1	(4.6%)				
26 - 30	25	15	(60.0%)	9	(36.0%)					1	(4.0%)
31 - 35	0	0		0							
36 - 40	4	3	(75.0%)	1	(25.0%)						
41 - 45	0	0		0							
46 - 50	1	1		0							
Greater than 50	2	2		0							
	265	179		42		33		3		8	

Table B 15

Administered Dose of Iodine-125 Per Gram Thyroid

Patient Information of 7 Treatment Groups

Group	Average Dose uCi G	Range	Mean Administered Dose (mCi)	Sex		Mean Follow (± 1SD) (months)	One Dose		Two Doses		Three Doses		24 Hour Uptake of Iodine-131
				Female	Male		Number	per cent	Number	per cent	Number	per cent	
1	203.3	151-250	6.9 ± 2.6	41	4	10.4 ± 4.0	24	(53.3%)	15	(33.3%)	6	(13.3%)	64.6
2	309.6	251-350	11.7 ± 3.6	54	7	11.3 ± 6.8	42	(68.9%)	16	(26.2%)	3	(4.9%)	61.3
3	399.1	351-450	16.6 ± 4.0	43	5	24.6 ± 6.9	34	(70.8%)	11	(22.9%)	3	(6.3%)	63.5
4	498.1	451-550	19.6 ± 4.6	27	5	25.3 ± 6.8	24	(75.0%)	5	(15.6%)	2	(6.3%)	62.0
5	600.9	551-650	22.7 ± 6.8	30	5	22.7 ± 6.6	29	(82.9%)	3	(8.6%)	3	(8.6%)	62.9
6	692.6	651-750	24.5 ± 6.8	18	4	22.4 ± 8.3	18	(81.8%)	4	(18.2%)			64.1
7	995.3	greater than 750	32.2 ± 12.0	14	3	29.4 ± 9.0	15	(88.2%)	1	(5.9%)	1	(5.9%)	68.6

hypothyroid and thyrotoxic patients is apparent.

Outcome Related to Amount of Initial Therapy Dose

From Table B14 it can be seen that most of the patients who remained thyrotoxic after iodine-125 were treated with small doses and persistance of toxicity decreases as the size of the therapy dose increases. No patient who received an initial dose of more than 25.0 mCi is still thyrotoxic (Figure B14). The converse is not true for the hypothyroid patients; although there is a progressive rise in the proportion of patients who become subthyroid with larger therapy doses, this relationship only holds up to the dose range 26.0 mCi to 30.0 mCi. Only one of 7 patients who received more than 30.0 mCi has developed thyroid failure. The doses associated with the best results are the 11.0 to 15.0 mCi range (71.1 per cent euthyroid) and 16.0 to 20.0 mCi range (74.5 per cent euthyroid).

Outcome Related to Initial Administered Dose (uCi) per Gram of Thyroid

The 7 treatment groups who were given from 151 to 250 uCi up to the doses greater than 750 uCi per gram of thyroid have already been defined. The patient information and outcomes in the 7 groups are listed in Table B15 and B16. The mean dose prescribed per gram in each group is significantly different from every other group ($P < 0.001$).

Group 1 (151-250 uCi per gram)

45 patients, 41 female and 4 male, received a mean dose of 203.3 uCi per gram of thyroid, the mean initial dose per patient was 6.9 mCi. 57.8 are euthyroid, 8.9 per cent hypothyroid and 27.6 per cent remain thyrotoxic after a mean follow up period of 10.4 months. 4.4 per cent of the patients are not allotted to one of these outcome groups and 2.2 per cent have not been traced. The follicular cells have been subjected to approximately 2,000 and 7,000 rads at the nuclear and apical levels. 33.3 per cent and 13.3 per cent of patients have required second and third doses respectively reflecting the problem of

Table B 16

Outcome Following Iodine-125 Therapy

Relationship to Dose Administered Per Gram Thyroid

Group	Dose Per Gram uCi G (± SD)	Number	Euthyroid		Hypothyroid		Thyrotoxic		Equivocal		Not Traced	
			number	per cent	number	per cent	number	per cent	number	per cent	number	per cent
1	203.3 (± 10.8)	45	26	(57.8)	4	(8.9)	12	(26.7)	2	(4.4)	1	(2.2%)
2	309.6 (± 18.8)	61	41	(67.2)	3	(4.9)	15	(24.6)	2	(3.3)		
3	399.1 (± 19.5)	48	42	(87.5)	5	(10.4)	1	(2.1)				
4	498.1 (± 8.0)	32	21	(65.6)	7	(22.9)	2	(6.3)	2	(6.3)		
5	600.9 (± 8.0)	35	23	(65.7)	11	(31.4)			1	(2.9)		
6	692.6 (± 37.2)	22	14	(63.4)	7	(31.8)					1	(4.5)
7	995.3 (± 193.5)	17	10	(58.8)	5	(29.4)	1	(5.9)	1	(5.9)		

persistant thyrotoxicosis.

Group 2 (251-350 uCi per gram)

A mean dose of 309.6 uCi per gram of thyroid was administered to 61 patients of whom 54 are female. The initial average dose was 11.7 mCi. After 11.3 months of review 67.2 per cent are euthyroid but 24.6 per cent remain thyrotoxic. Only 4.9 per cent require substitution therapy with thyroxine. 26.2 per cent received a second therapy dose and 4.9 per cent required a third. The rad doses calculated in retrospect were about 3,000 to the nuclei and 10,000 to the hormone synthesising fraction of the follicular cells.

Group 3 (range 351-450 uCi per gram thyroid)

48 patients (43 females and 5 males) who received an average initial dose of 16.6 mCi have been under review for 24.6 months. 87.5 per cent are euthyroid, 10.4 per cent hypothyroid and 2.1 per cent thyrotoxic. 29.2 per cent of this group have required retreatment. The dose rates were approximately 4,000 and 13,000 rads.

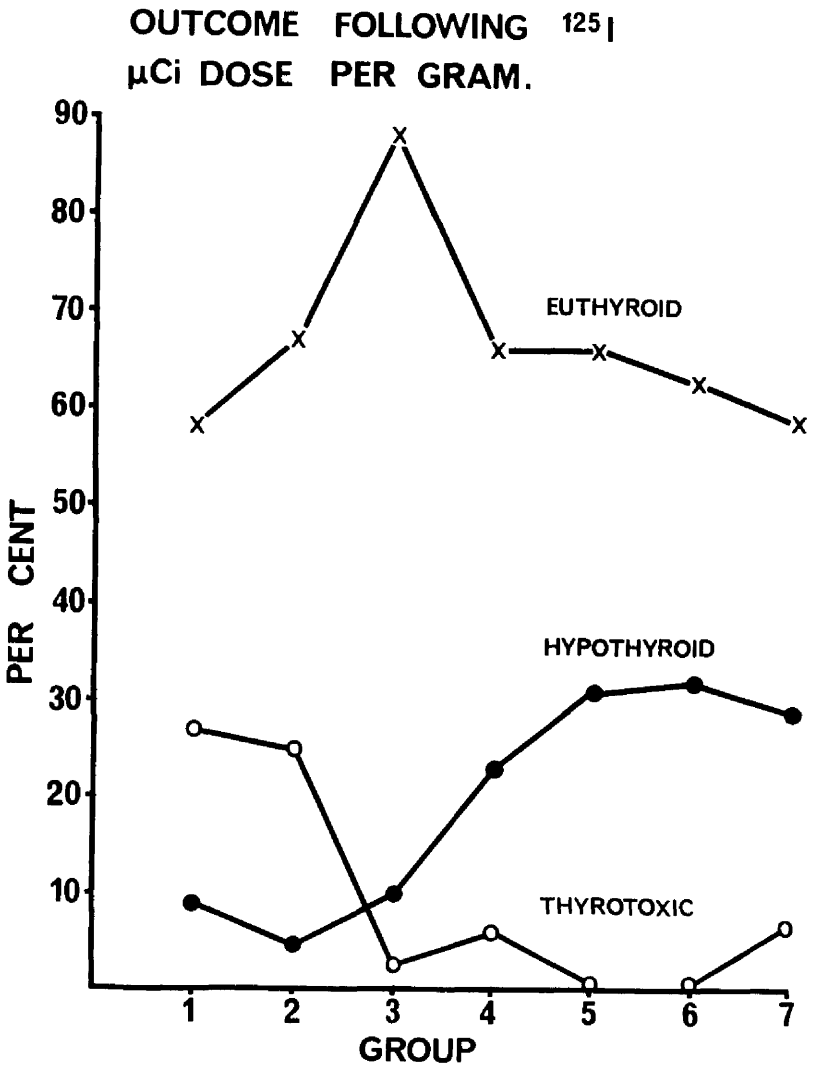
Group 4 (range 451-550 uCi per gram thyroid)

27 females and 5 males received an average dose of 19.6 mCi iodine-125. This dose was calculated to administer a nuclear dose of 5,000 rads and an apical dose of 16,000 rads. The follow up period is 25.3 months and after this time 65.6 per cent are euthyroid and 22.9 per cent hypothyroid. An equal proportion, 6.3 per cent are thyrotoxic and equivocal. One therapy dose was sufficient for the treatment of 75 per cent of the patients.

Group 5 (range 551-650 uCi per gram thyroid)

Of the 35 patients (30 females and 5 males) who received an average initial dose of 22.7 mCi and have been assessed over a period of 22.7 months, 65.7 per cent are euthyroid, 31.4 per cent hypothyroid and the remainder (2.9 per cent) equivocal. An equal proportion of the group 8.6 per cent required a second or third therapy dose. A nuclear rad

FIGURE B 5



Percentage of patients euthyroid, hypothyroid and thyrotoxic after iodine-125 therapy; relation to dose prescribed per gram of thyroid

Group 1	151 to 250 uCi
Group 2	251 to 350 uCi
Group 3	351 to 450 uCi
Group 4	451 to 550 uCi
Group 5	551 to 650 uCi
Group 6	651 to 750 uCi
Group 7	over 750 uCi

Table B 17

Number of Doses of Iodine-125 Administered

Number of Doses	Number of Patients	Percentage of Total
1	187	70.6
2	58	21.9
3	18	6.8
4	1	0.4
5	1	0.4
	265	100.1

Table B 18

Outcome Related to Number of Therapy Drinks of Iodine-125

		One Dose	Two Doses	Three Doses
Number of Patients		187	58	18
Males	(per cent)	27 (14.4%)	7 (12.1%)	3 (16.7%)
Females	(per cent)	160 (85.6%)	51 (82.9%)	15 (83.3%)
Mean Age	(Years)	52.2	52.6	52.6
Mean Dose	(mCi)	17.6	14.4	12.6
Dose Per Gram	(uCi)	474.5	373.1	383.3
Euthyroid	(per cent)	132 (71.1%)	36 (62.1%)	11 (61.1%)
Hypothyroid	(per cent)	37 (19.3%)	14 (6.9%)	1 (5.6%)
Thyrotoxic	(per cent)	11 (5.9%)	17 (29.3%)	3 (16.7%)
Equivocal	(per cent)	4 (2.1%)	1 (1.7%)	3 (16.7%)
Not Followed	(per cent)	3 (1.60%)		

dose of 5,500 rads and apical dose of 20,000 rads has been calculated.

Group 6 (range 651-750 uCi per gram thyroid)

In this group an average dose of 24.5 mCi has been given to 22 patients (18 females and 4 male). The nuclear radiation dose was approximately 6,500 rads and at the cell apex 23,000 rads. 63.4 per cent are euthyroid 22.4 months after therapy, 31.8 per cent hypothyroid and the remainder have not been traced. A second treatment dose has been required for 18.2 per cent.

Group 7 (greater than 750 uCi per gram thyroid)

An average dose of 32.2 mCi of iodine-125 has been administered to 17 patients (14 female and 3 male). The nuclear rad dose has been calculated to be approximately 10,000 rads and the dose to the colloid-cell margin about 35,000 rads. 58.8 per cent are euthyroid and 29.4 per cent hypothyroid29.4 months after therapy. 88.2 per cent of the group responded to the initial therapy dose.

Figure B5 illustrates graphically the percentage of patients who are euthyroid, hypothyroid or thyrotoxic in each of the 7 groups.

Number of Therapy Doses Prescribed

187 patients (70.6 per cent) have received 1 therapy dose, 58 patients (21.9 per cent) 2 doses and 18 patients (6.8 per cent) have required 3 doses. 1 patient (0.4 per cent) has received a fourth and 1 (0.4 per cent) a fifth dose (Table B17). Detailed information about these patients excluding the last 2 patients is shown in Table B18. There is no difference in age in those who have required 1 or more treatment dose and the sex distribution is also similar. The patients who responded to the first therapy dose received a larger initial amount (17.6 mCi) than those who have required two (14.4 mCi) or three doses (12.6 mCi). The dose per gram of thyroid shows a similar pattern.

Table B 19

Multiple Doses

Information about 58 Patients who had Two and 18 Patients Who required Three Therapy Doses of Iodine-125

	Two Doses	Three Doses
Number of Patients	58	18
Females	51	15
Males	7	3
Mean First Dose (mCi) and Range	14.4 (5-50)	12.6 (5-20)
Mean Second Dose (mCi) and Range	14.6 (4-30)	12.6 (5-60)
Mean Third Dose (mCi) and Range		17.2 (5-40)
Average Delay Between 1st and 2nd Drink (months) and Range	5.5 (2-16)	4.6 (2-7)
Average Delay Between 2nd and 3rd Drink (months) and Range		5.1 (1-10)

Table B 20

Patient Status Following Iodine-125 (Excluding Equivocal Patients and Those Not Traced)

Relationship to Length of Follow Up

Length of Follow Up (months)	Euthyroid		Hypothyroid		Thyrotoxic	
	number	per cent	number	per cent	number	per cent
3 - 6	12	(48%)			13	(52%)
7 - 12	35	(63.64%)	10	(18.18%)	10	(18.18%)
13 - 18	32	(69.56%)	7	(15.22%)	7	(15.22%)
19 - 24	41	(82.0%)	8	(16.0%)	1	(2.0%)
25 - 30	33	(75.01%)	10	(22.72%)	1	(2.27%)
31 - 36	22	(73.34%)	7	(23.33%)	1	(3.33%)
37 - 42	4	(100.0%)				
	179		42		33	

5.9 per cent of the patients treated with one dose are still thyrotoxic as are 29.3 per cent of those who have had two drinks and 16.7 per cent of the three dose groups. The number of patients who have become hypothyroid in the multiple dose groups are small but this may be a reflection of a shorter period of follow up since there was an average delay of 5.5 months between the prescription of first and second drinks and 4.6 months between second and third doses.

Table B19 lists the information about the doses prescribed on the second and third occasions. Of the 58 patients who received 2 doses, 49 had an identical second dose, 8 had a larger dose and 1 patient a smaller dose. All of the 18 patients who had 3 doses had the same amount on the second occasion but the third dose was tailored in an attempt to suit each individual and as a result 9 (50 per cent) received a larger and 3 (16.3 per cent) a smaller dose.

Outcome Related to Length of Follow Up

In Table B20 the outcome after iodine-125 has been related to the length of time (months) that patients have been under review. A patient who has become hypothyroid at 3 months but has been under review for 21 months is included in the 19 to 24 month group. The actual time of onset of thyroid failure after therapy has already been discussed. In those who have been under review less than 6 months, 48 per cent are euthyroid and 52 per cent remain thyrotoxic. The proportion who are thyrotoxic diminishes with the passage of time and only 3 are not controlled 18 months after the initial dose. From 7 to 36 months after treatment the percentage of hypothyroid patients remains fairly constant.

Adjuvant Antithyroid Drugs after Iodine-125 Therapy

31 patients (11.7 per cent of the total group) required additional drug therapy, 17 of them (54.8 per cent) received carbimazole and 11 (35.5 per cent) propranolol. These drugs were used in combination in two patients and one received potassium perchlorate because of previous

sensitivity to carbimazole (Table B21). Only after drug therapy had been discontinued for 2 months was any patient classified as euthyroid, this has happened in 14 of the patients treated with carbimazole and 8 of those who were taking propranolol. Those patients who are clinically completely normal but taking a small dose of antithyroid drug therapy are still classified as thyrotoxic. 71 per cent of the group who required drug therapy had received less than 450 uCi iodine-125 per gram of thyroid.

Outcome in Patients with Nodular Glands

14 patients (12 females and 2 males) had multinodular glands but after careful consideration they were treated with iodine-125. They were given a mean dose of 20.5 mCi or 463.5 uCi per gram of thyroid. 2 of these patients are hypothyroid and the remainder euthyroid after an average follow up of 24 months. (Table B22)

Discussion

Although patients were selected for iodine-125 therapy depending on a geographical basis and the anatomical type of thyroid they were overall representative of those referred to the Department of Nuclear Medicine for radioiodine therapy. Despite the importance of frequent review visits there was no bias towards the selection of females and the ratio of female to male 85.7 to 14.3 is similar to the overall ratio in iodine-131 treated patients at this Department 82.8 to 17.2 (McGirr et al 1964). Only 10 of the total iodine-125 treatment group were under the age of 40 years at the time of therapy and this is in keeping with the policy of reserving radioiodine therapy until this age is reached (McDougall et al 1971). The main indication for this arbitrary time limit has been concern about the genetic hazards of all radionuclides of iodine and the younger patients treated with iodine-125 have been advised to take contraceptive measures for at least 1 year. If no pregnancies arise there should be no increase in the burden of radionuclide induced mutations passed on to future generations.

There was no doubt about the degree of toxicity of all of the patients. The average 24 hour uptake of a tracer dose of iodine-131 was 64 per cent and the mean protein bound iodine-127, 12.5 ug per 100 mls. There was no significant difference in the uptakes of tracer doses in the 7 groups of patients treated with different doses of iodine-125 (range 61.3 to 68.6 per cent). Only one patient who has previously been discussed had normal thyroid function tests, she was clinically thyrotoxic and her thyroid may have been secreting inappropriately large amounts of triiodothyronine. Therefore, despite the selection of patients they did not have mild thyrotoxicosis.

The selection of patients with small diffuse glands was necessary to simplify estimation of thyroid mass. The difficulties and errors

in this estimation are well known but only two physicians, Dr. W.R. Greig and I were involved in this assessment. Early in the trial an attempt was made using finely calibrated rectilinear scans to convert the measurements of area, height and width of lobes into an index of mass using the formulae of Himanka and Larson (1955) and Myhill et al (1965). Because of differences in the results obtained the simple palpatory method has been used throughout. Impalpable glands were empirically gaged to weigh 25 gram (Meissner and Warren 1969) this, of course, might exagerrate the weight of some (Mochizuki et al 1963) yet in other patients it may be an underestimate. It is recognised that the mass of small glands is more often overestimated and the opposite is found in larger glands and a conscious effort was made to correct this. This will be discussed at greater length in the section dealing with the outcome in relation to gland size.

After similar lengths of follow up the final outcome in males (79 per cent euthyroid) has been superior to that in females (64.8 per cent euthyroid). There was no intention to prescribe different treatment schedules in males and throughout the 7 treatment groups (uCi per gram thyroid) the proportion of males and females is fairly constant. Less males became hypothyroid but surprisingly the proportion of males who received doses greater than 450 uCi per gram was slightly greater than in the lower dose schedules. This paradoxical combination of less hypothyroidism in patients who had received a slightly larger dose suggests that the males may be slightly more radioresistant. A similar conclusion does not hold true for iodine-131 therapy (Beling and Einhorn 1961, Blahd and Mays 1972). Most probably the small number of males treated (38) could account for this difference.

A greater increase in the incidence of hypothyroidism after iodine-131 therapy has been found in elderly patients (Green and Wilson 1964) and this has been attributed to the rising frequency of hypothyroidism which occurs spontaneously with aging. None of the 8 patients aged

70 years or more became hypothyroid after iodine-125 treatment yet they received as large an average dose as any other group. The lowest percentage of euthyroid patients were found in two groups of patients with age ranges of 45 to 49 years (58.2 per cent) and 65 to 69 years (54.2 per cent). An increased number of thyrotoxic patients in both of these groups partly accounted for the less satisfactory results but in the latter group 25 per cent (6 patients) have developed thyroid insufficiency. These 6 patients received large therapy doses and it cannot be concluded that their outcome was related to their age.

It is the general experience that iodine-131 is more often associated with hypothyroidism when the patient has a small gland, probably due to overestimation of the gland size and hence the therapy dose. Iodine-125 treated patients show a constant pattern of response through the 4 groups up to a gland mass of 40 grams (euthyroid 62.3 to 70.0 per cent, hypothyroid 14.5 to 20.0 per cent, thyrotoxic 10.0 to 16.1 per cent). Of the 5 patients whose thyroid glands were estimated to weigh exactly 45 gram, and the 13 patients with glands greater than 50 gram not one has become hypothyroid. A clinical underestimation of the gland size may have led to prescription of a smaller dose than intended but 16 of these 18 patients are euthyroid so if the dose prescription was too small it has certainly been enough to produce the desired effect. Because of the excellent results in these patients the outcome has been more favourable when the glands have been assessed to weigh more than 40 gram, 75.3 per cent are euthyroid compared with 64.6 per cent with smaller glands. Overall the degree of correlation between the clinical status after therapy and the gland size justifies the conclusion that up to 40 gramsclinical estimation of thyroid mass is quite accurate and dose prescriptions valid.

Relating the outcome following iodine-125 treatment to the initial total dose shows that no patient treated with 5.0 mCi has become

hypothyroid and that of all the patients who received doses up to 15 mCi the incidence is still only 10 per cent. Despite the low hypothyroid incidence the rate of control in the 5 mCi group has by stringent criteria been unsatisfactory since one third of the patients although improved are still clinically thyrotoxic. However, as the dose is increased control is more certain and in patients who have received 20.0 mCi or more it is virtually inevitable since only 1 out of 54 patients remains thyrotoxic. With doses of this size the problem of hypothyroidism is evident and is similar to the expected incidence 2 years after conventional doses of iodine-131 (about 30 per cent). These amounts of iodine-125 are three or more times the standard dose of iodine-131 yet calculation of the nuclear rad dose gives a similar result in both instances.

The most important index has been the clinical outcome in relation to the dose of iodine-125 prescribed per gram of thyroid. In the lowest dose group (200 uCi per gram) more than one half of the patients are euthyroid and 8.9 per cent have actually had sufficient thyroid destruction to make them hypothyroid. The proportion of hypothyroid patients has remained at about this level up to doses of 450 uCi per gram but yet through this dose range the number of persistently thyrotoxic patients decrease and hence the proportion of euthyroid patients is larger. For the best results at 24 months there appears to be a critical dose range of 350 to 450 uCi per gram thyroid, the group incorporates the highest number of euthyroid patients a very low failure rate and an acceptable number of hypothyroid patients. With smaller doses although the hypothyroid problem can be slightly reduced there is a slower rate of control; using larger doses hypothyroidism is a problem.

The nuclear rad dose in this best treatment group has been approximately 3,500 to 4,000 rads. If this had been subjected by

iodine-131 the majority of the patients would have required adjuvant drug therapy because of the slow rate of control (Smith and Wilson 1967). Second doses would also have been required in up to 60 per cent of the group. More than 70 per cent of the patients treated with iodine-125 responded satisfactorily to 1 therapeutic drink and only 12.5 per cent were given antithyroid drugs. From personal discussion with Smith (1972) the antithyroid drugs were prescribed to iodine-125 treated patients earlier than would have been the case with low dose iodine-131 treated patients. Overall, therefore, the difference in outcome proves that the two radionuclides are not working in the same way. The most likely explanation is that the intense irradiation of the important hormone synthesising segment has reduced thyroid hyperfunction and the low dose to the nuclei has prevented thyroid cell failure.

Additional evidence of the difference in action of these radionuclides is the average approximate rad dose (4,000 rads) to the follicular nuclei in the 179 patients who have become euthyroid. Such a low dose would not produce uniform success if delivered by iodine-131. The same applies in the patients who have become subthyroid. Thyroid failure has resulted from a mean nuclear dose of 6,000 rad and this would certainly not occur with iodine-131 2 years after therapy though it would at a later date. It is, therefore, possible that the intense irradiation of the cell membrane not only reduces function but if great enough will cause cell death.

In patients who have received different dose regimes of iodine-125 in excess of 550 uCi per gram thyroid the proportion of hypothyroid patients has remained constant around 30 per cent. This constant result has been obtained by a considerable variation in nuclear rad doses and it is suggested that the nuclear and apical doses may combine in producing sterilisation or death of the cells. With these larger doses the rate of control (average 8.5 weeks in the pilot group and 14

weeks for the first 50 patients) of the disease is considerably better than with iodine-131. Since both produce the same hypothyroid incidence which in the case of iodine-131 is due to nuclear damage the iodine-125 must also be reducing cellular secretory function. This difference is still apparent with the smaller therapy doses which have been calculated to deliver 2,000 rad to the nuclei. Recent trials with iodine-131 (1,750 rads) have necessitated prescription of anti-thyroid drugs to 80 per cent of patients for as long as 2 years (Smith 1972). Only 4 out of 45 patients in the lowest iodine-125 treatment group required additional antithyroid drugs and more than 50 per cent required only one therapy dose. When antithyroid drugs are used there is an impression that smaller doses are required, this has also been described by Lewitus et al (1971b).

Iodine-131 therapy for nodular glands is associated with a lower incidence of hypothyroidism and often the need to prescribe larger therapy doses to obtain the same results as in patients with diffuse glands (Silver 1968). It is, therefore, surprising that not one of the 14 patients with a nodular thyroid has remained thyrotoxic and the percentage hypothyroid (14.3 per cent) was similar to the total treatment group. It is difficult to explain this difference but the long half life of iodine-125 may be important. As overactive nodules have responded to treatment other relatively less active regions of the gland may take up sufficient radionuclide to be treated. This would be akin to giving small fractionated doses of iodine-131 over a prolonged period.

Hypothyroidism may follow iodine-125 treatment, when it occurs it usually does so soon after therapy, 88 per cent within the first 12 months. Because of the progressively smaller numbers of patients who have been under review for more than 2 and 3 years it has not been possible to calculate the progressive proportion of hypothyroid patients

by the method outlined by Beling and Einhorn (1961). But by simply showing the percentage hypothyroid in groups who have been under review for successive 6 month periods up to 42 months there has been a slight cumulative increase. None of the 4 patients who have attended longest have become subthyroid. The therapy doses prescribed to patients who became hypothyroid tended to be larger than those associated either with a favourable outcome or failure to control the disease (Table B11) and the nuclear and apical rad doses were also greater.

In view of the current tendency to favour antithyroid drugs and small doses of radioiodine it is conceivable that with low doses of iodine-125 (5 mCi or less) hypothyroidism could be completely avoided but adjuvant drugs might be essential. This is not the ideal solution and the aim throughout these clinical trials has been to find by empirical means the dose or doses which would produce the best clinical results without the need for other therapy.

Since the introduction of iodine-125 therapy (Greig et al 1969), 3 other groups of investigators have gained limited experience with this radionuclide. Werner and his colleagues (1970) have treated two series of thyrotoxic patients in different countries. 6 patients received treatment in New York and 7 in Amsterdam and although the mean dose for each group was the same (10.0 mCi) the initial clinical response was quite dissimilar. 5 of the patients in New York became hypothyroid whereas none of the Amsterdam group developed this complication. This paradoxical difference was tentatively explained on the basis that the two populations had iodide pools of different sizes. The New York patients were considered to be iodine replete whereas the Amsterdam patients were relatively iodine deficient (Wiener 1971, 1972). In the experimental animal iodine deficiency has two important effects in relation to the radiobiological action of radioiodine, in particular iodine-125. Firstly the follicular cell becomes elongated and secondly

the uptake of radionuclide is increased. Vickery and Williams (1971) have shown that the net result of these alterations considerably reduces the nuclear irradiation from a colloidal source of iodine-125. Although it is not known it is possible that iodine deficiency produces a further incremental increase in the length of the already elongated thyrotoxic cell. If this hypothesis is correct iodine deficiency should theoretically protect against hypothyroidism and an excessive iodine pool might increase the probability of subthyroidism following iodine-125. One method of proving or disproving this theory would be to measure the absolute iodine uptake and retrospectively compare the results in those patients who remained euthyroid with those who became hypothyroid.

Since their original communication (Werner et al 1970), however, it is relevant to note that 3 of the 5 patients who were hypothyroid have reverted to normal thyroid status (Werner and Johnson 1971). The resumption of normal thyroid function in 3 patients after a period of post iodine-125 hypothyroidism is of interest. It suggests that enhanced viability of the cells has been present leading to compensatory hypertrophy or hyperplasia resulting from increased pituitary T.S.H. secretion. Thus overall only 2 out of 13 patients remain hypothyroid (15.4 per cent). These investigators have also treated 18 patients with smaller doses of iodine-125 (50 per cent of original dose) and thyroid insufficiency has arisen in 1 patient (5.5 per cent).

I have not encountered any patient who once hypothyroid was able to discontinue thyroxine. No attempt was made to stop this treatment but two patients did so without medical advice. One rapidly became hypothyroid again and has restarted thyroxine, the other patient although well enough to continue at work is mildly hypothyroid with a low thyroxine and elevated serum T.S.H.

Lewitus (1969) prescribed even smaller doses of iodine-125 (2.75 mCi) in the first 4 patients he treated. Their rapid clinical improvement, all 4 were euthyroid by 14 weeks, was attributed to the intense radiation to the hormone synthesising apparatus and he believed that further clinical trials were justified. Thirty patients received doses ranging from 1 to 3.5 mCi (Lewitus et al 1970) and subjective improvement occurred in 95 per cent within 6 weeks and none of the patients became hypothyroid after a follow up period from 3 months to 1 year (one patient treated with this dose regime had a large thyroid, despite a nuclear dose of only 250 rads the outcome was reported as fair). An additional benefit of such low doses is the reduction in total body radiation to about 1 rad. With the extension of these low dose trials over a longer period of follow up Lewitus et al (1971a) found that the overall rate of control was unfavourable. They found that 20 per cent of patients who had been euthyroid both by clinical and laboratory indices relapsed. They considered that their original doses had been too low and because of this have advocated two alternative approaches. Firstly that the administered dose of iodine-125 be increased to the range of 4 mCi to 6 mCi or secondly that a combination of iodine-125 and iodine-131 be prescribed together. Using the first approach 10 patients were treated with an average dose of 5 mCi and 6 (60 per cent) responded satisfactorily (Lewitus et al 1971b). Following the latter suggestion they have treated 40 patients with a mixture of approximately 50 per cent iodine-125 and 50 per cent iodine-131 (mean doses 3.0 mCi and 3.8 mCi respectively). Of these patients 36 (90 per cent) are euthyroid, 1 (2.5 per cent) has failed to respond and 3 (7.5 per cent) have become hypothyroid. Despite the excellence of these results which also includes rapidity of control the criticism that iodine-131 has been employed must be levelled. Even with the doses of iodine-131 employed a cumulative incidence of hypothyroidism must be expected in the future. Proof of this is the 19 per cent

incidence found by Lowe et al (1971) 2 years after 2.5 mCi doses of iodine-131.

Siemsen (1971) in an unpublished report has prescribed therapeutic doses of iodine-125 based on the clinical experiences of Greig et al (1970) and McDougall et al (1970). 40 of 80 patients who received 100 uCi per gram thyroid responded poorly and he has abandoned this dose range. When the dose was increased to 200 uCi per gram three quarters of a group of 60 patients became euthyroid, 5 per cent hypothyroid and the remainder are still uncontrolled. There is no information about the length of follow up in these patients.

From the detailed results in this thesis and from information from other centres a pattern of response is emerging to different therapy doses of iodine-125 and despite various treatment schedules a consistency is noted. Small therapy doses 100 uCi per gram or total doses of 1 to 3.5 mCi do cause clinical improvement but a totally satisfactory outcome is obtained in only about 50 per cent of patients. The remainder either remain uncured or relapse after a partial remission. Hypothyroidism is virtually not encountered. Increasing the dose to 200 uCi to 300 uCi per gram (about 5 to 10 mCi) the rate of recovery is hastened and about 75 per cent of patients will become euthyroid without a significant incidence of hypothyroidism. No other investigators have prescribed larger treatment doses but by prescribing about 400 uCi per gram thyroid the speed and certainty of control of the disease are enhanced, however, about 10 per cent are hypothyroid after 2 years.

There are a few patients who despite receiving a small dose unexpectedly develop thyroid insufficiency because of the long physical half life of iodine-125 a small increase in the biological turnover of the isotope can considerably increase the radiation in these patients and this may be the reason. In others the thyroid cells may be exquisitely radiosensitive. There appears to date no way of

anticipating or preventing this complication but theoretically if an index of the amount thyroid cell destruction could be obtained most of the iodine-125 could be discharged from the thyroid and prevented from re-entering it by antithyroid drugs.

One unsettled question is whether the nuclear radiation in the hypothyroid patients has been small enough to allow cellular regeneration. Werner and Johnson (1971) have described this but it has not been seen in this study although substitution therapy was not routinely discontinued. The patients who are most liable to recover from hypothyroidism are those who received small therapy doses but in view of the possibility of unrestrained cell growth in response to elevated T.S.H. levels the policy of continuing the substitution therapy is justified. Analogous with this suggestion is the possibility that euthyroid patients may relapse if the follicular cells are capable of regeneration. Early relapse has been described by Lewitus et al (1971b) but in this series no patient has been unequivocally euthyroid, after iodine-125, then sufferred a relapse.

Summary

Iodine-125 is effective in the treatment of thyrotoxicosis. A very rapid certain cure is obtained with total doses of 20.0 mCi or individually calculated doses greater than 550 uCi per gram of thyroid. Despite a lower nuclear rad dose the problem of hypothyroidism equals that from standard iodine-131 therapy. Within the dose range 350 to 450 uCi per gram almost 90 per cent of patients are euthyroid 2 years after therapy. Doses of this magnitude or less cause very little thyroid failure.

Section B

Chapter III

Assessment of Real and Potential Side Effects Arising from Thyroidal and Extrathyroidal Radiations of Iodine-125

Introduction

The problems of delayed control and the cumulative incidence of hypothyroidism apart, side effects from iodine-131 treatment are relatively uncommon (Section A, Chapter I). It is, therefore, essential that iodine-125 is as benign in this respect; better therapeutic results cannot justifiably be obtained in the face of additional complications. The potential complications and problems which have arisen in iodine-125 treated patients are discussed under 6 headings; (1) immediate side effects of iodine-125 (2) thyroidal complications (3) effects of iodine-125 on haemopoietic tissues (4) extrathyroidal radiation effects (5) alteration in the course of infiltrative ophthalmopathy and (6) incidental complications. Within these sections are details of clinical problems as well as formal studies of morphological alterations in circulating lymphocytes and investigations of parathyroid function.

(1) Immediate Side Effects

A 64 year old female who had previously received 2 therapy doses of iodine-125 without ill effect was quite ill with vomiting several hours after a third therapy dose. Retrospective estimation of the thyroid uptake of iodine-125 as well as serum protein bound iodine-125 showed that she had absorbed at least 80 per cent of the dose. Prompt control of her disease confirmed this estimation. Most probably the symptoms were not directly related to the therapeutic drink since the patient had previously received two doses of similar amount with no ill effect. The remainder of the patients were singularly free of reactions.

Table B 23

Patients with Pain Over Thyroid Region After Iodine-125 Therapy

Dose Administered and Eventual Outcome

Patient	Age	Total Dose of Iodine-125	uCi per Gram Thyroid	Thyroiditis	Clinical Outcome
Female	65	30	1,200	Present	Hypothyroid
Female	51	20	400	Present	Euthyroid
Female	55	24	600	Present	Hypothyroid
Female	41	20	400	Absent	Euthyroid
Female	51	15	500	Absent	Euthyroid
Female	61	10	400	Absent	Euthyroid

Table B 24

Amounts of Iodine-125 Persisting in the Body of 4 Patients Treated 10, 12, 36 and 43 Months Beforehand

	Sex	Age (Years)	Dose Prescribed (mCi)	Amount in Body (uCi)	Time After Therapy (months)
1	F	53	7.5 + 7.5	0.6	10
2	F	60	5.0	0.01	12
3	F	47	20.0	1.1	36
4	F	68	57.0	0.8	43

(2) Thyroidal Complications

(a) Acute

No patient developed thyroid crisis and there was no apparent worsening of the disease following treatment with iodine-125. That thyroid crisis does occur after iodine-131 therapy has recently been proven forcibly, two elderly patients treated in our Department with iodine-131 within the last year succoumbed with intractable thyroid crisis despite the vigorous institution of antithyroid drugs, beta adrenergic blocking drugs and inorganic iodine. Three female patients who complained of pain in the thyroid shortly after treatment with iodine-125 did have objective evidence of radiation thyroiditis (Table B23). Two of them became hypothyroid at 3 and 8 months respectively after treatment. Three other female patients reported soreness in the throat on swallowing but there was no clinical suggestion of thyroiditis and in each case the outcome has been favourable. In the latter group of patients the symptom was probably not due to iodine-125, however, the prompt onset of thyroid failure in 2 of the 3 patients with thyroid tenderness tends to incriminate the therapy in the production of thyroiditis and subthyroidism. This sequence of events is known to occur with iodine-131 therapy (Schwartz 1970).

(b) Chronic

The important potential hazard of thyroid carcinoma arising in patients treated with iodine-125 is discussed in Section C, Chapter I. To date no patient who had a diffusely enlarged thyroid has developed thyroid nodules and none has required surgical exploration of the neck.

Van Middlesworth (1972) has drawn attention to a possible environmental hazard from patients treated with iodine-125. In experimental animals he and his co-workers (Van Middlesworth and

Murphy 1970, Grimm et al 1970) have convincingly demonstrated a slow turnover pool of iodine-125. The rats were fed a low iodine diet before the administration of iodine-125 and in this circumstance the biological half life of between 0.1 and 5.0 per cent of the dose exceeded that of the majority by up to 100 times. This persisting radionuclide could not be discharged with antithyroid drugs and they now believe that the slow turnover is caused by incorporation of a variable proportion of iodine-125 into psammoma bodies.

To assess the importance of this in iodine-125 treated patients, 4 unselected females who had received therapy doses, 10, 12, 36 and 43 months previously were investigated. Details of the age of the patients and the doses prescribed are shown in Table B24. Each patient had a whole body count for iodine-125 over a period of 1,000 seconds. Room background counts were made over the same length of time before and after each patient count. To obtain a quantitative result a known amount of iodine-125 was counted in a thyroid phantom passing under the body monitor at the same speed as the patients. By proportion the reading which a standard of 1 uCi of iodine-125 would produce was calculated and from the formula

$$\frac{\text{Patient count - average of room background counts}}{\text{counts produced by 1 uCi standard}}$$

the amount of iodine-125 (uCi) persisting in each patient obtained.

One patient has 1.1 uCi remaining in the body 36 months after a 20.0 mCi dose, the remainder had less than this (Table B24). The greatest proportion of the dose persisting was 0.006 per cent 36 months after a second therapy dose of 7.5 mCi. This proportion is more than would be anticipated if the effective half life was 15 days. Although the persistance of iodine-125 in the body has been demonstrated as long as 43 months after treatment the amounts present do not contribute to a significant environmental hazard.

(3) Effects of Iodine-125 on Haemopoietic Tissues

(a) In the Production of Persistent Chromosomal Aberrations in Circulating Lymphocytes

Introduction

During metabolism of a therapeutic dose of radioactive iodine the marrow and the peripheral blood are irradiated at three phases (Green et al 1961). For a short time (few days) following absorption from the gastrointestinal tract the radioiodine is in the circulation as iodide until it is trapped by the thyroid and stored in the colloid of the gland. In this iodide phase both marrow and peripheral blood are subject to irradiation. Thereafter blood passing through the thyroid is also subject to radiation but most of the exposure at this later phase arises from circulating hormone in the marrow and blood. This phase lasts up to 60 days if four effective half lives are considered to represent 94 per cent of the total irradiation exposure.

After 10 mCi of iodine-131 for thyrotoxicosis the blood receives approximately 17 to 23 rads (Green et al 1961) and the possible effect of this irradiation has been studied by examination for chromosome damage after culture of the circulating lymphocytes. Chromosomal aberrations have been detected regularly after standard therapeutic doses of iodine-131 for thyrotoxicosis and also after much larger doses given in the treatment of thyroid cancer (Boyd et al 1961, Macintyre and Dobyns 1962, Nofal and Beierwaltes 1964, and Cantolino et al 1966). There are certain potential hazards with iodine-125 therapy, in view of the long half life (60 days) and the unusual radiations emitted from this radionuclide; about 60 per cent of the dose from a point source of iodine-125 is electronic with paths less than a few microns, the remaining being "soft" x-rays or gamma rays (Gillespie et al 1970).

Table B 25

Chromosomal Aberrations in Patients Treated with Iodine-125 and in Controls

					Total Cells			Chromosome Aberrations		Chromatid Aberrations	
Number	Sex	Age	Dose mCi	Time After Iodine-125 (months)	Examined	With Chromosomal Aberrations	Stable	Fragments	Dicentrics and Rings	Breaks	Exchanged
1	F	62	15.0	7	100	11	8	5	3	5	1
2	F	51	15.0	4	100	6	10	18	3	1	0
3	F	52	30.0	2½	100	15	18	8	4	1	0
4	F	69	40.0	10	50	6	2	3	3	1	0
5	F	64	25.0	11	100	2	1	4	2	1	0
6	F	27	0	Control	100	0	0	0	0	1	0
7	F	44	0	Control	100	0	0	0	0	3	0
8	F	34	0	Control	100	0	0	0	0	1	0
9	F	38	0	Control	100	0	0	0	0	1	0

Chromosomal analysis of circulating lymphocytes from patients treated with iodine-125 have been undertaken to study the effects and to compare with previously documented iodine-131 induced aberrations.

Patients Studied and Procedures

Five female patients (average age 59.6 years, range 51-69 years) who had previously received iodine-125 therapy were taken at random; 10 mls. of venous blood was removed for the lymphocyte culture and chromosome examination. In Table B25 the age of each patient, the dose of iodine-125 and the latent period till the time of the study are listed. Venous blood from four females who had not received iodine-125 therapy was used for control information. None of the patients had been exposed to additional high levels of radiation although each had received diagnostic tracer doses of iodine-131 (5 uCi).

Culture of blood and chromosomal analysis was carried out by Dr. M.A. Ferguson-Smith. Whole blood cultures were made using 0.5 ml. of heparinised venous blood and 4.5 ml. of Ham's F.10 medium containing 10 per cent calf serum. The cultures were inoubated for 72 hours in the presence of phytohaemagglutinin and treated in the last 2½ hours with deacetylmethylcolchicine before being harvested by the routine air-dried technique. 100 cells were analysed by direct microscopy in every case except one (where only 50 cells were available for analysis). Chromosome and chromatid aberrations were scored, but the control and irradiated subjects were not identified by the cytogenetist until after the analysis was complete.

Results

Table B25 also gives details of the number and type of chromosome and chromatid abnormalities detected in cultured lymphocytes from each

of the five patients who had received iodine-125 as well as the control patients. The aberrations were most numerous in the patients treated with iodine-125 only 10 weeks before the study and least common in one patient who had therapy 11 months before. All of the iodine-125 treated patients had dicentric and ring formations which are extremely rare in normal people. These abnormalities are generally characteristic of radiation exposure and have been described after iodine-131 therapy too. It is of importance that no chromosome abnormalities were found in the lymphocytes of the unirradiated control subjects, the chromatid changes in this group were considered to be normal findings.

Discussion

This study shows unequivocally that iodine-125 in therapeutic doses causes a significant number of chromosome aberrations in the circulating peripheral lymphocytes of the type usually associated with radiation injuries; the evidence of damage persists for as long as 11 months after therapy. The alterations produced in the peripheral lymphocyte chromosomes are similar to those found after iodine-131 treatment (Boyd et al 1961, Macintyre and Dobyns 1962). They are also similar to those demonstrated after iodine-131 irradiation of the rat thyroid follicular cells. In this case the chromosome abnormalities being demonstrated after culture of the irradiated thyroid follicular cells (Speight et al 1968).

The majority of the electronic emissions from iodine-125 as described in Section A, Chapter II, are low energy electrons, over 95 per cent of which travel in fluid or tissue less than 1 micron. It seems unlikely, therefore, that these low energy electrons could cause lymphocyte damage in the marrow or in the circulating blood. Iodine-125, however, also emits x-rays and gamma rays (about 40 per cent of the dose) from a point source and both of these, particularly the

latter which has a tissue half life distance of up to 7 cms., might irradiate marrow and the blood cells uniformly. Gillespie et al (1970) have calculated that 10 mCi of iodine-125 might subject the blood to 4 rads and about 1 rad of this would be due to the x-rays or gamma rays. Even if all the emissions are considered iodine-125 gives less radiation to the blood than a therapeutically equivalent dose of iodine-131.

The main concern about blood and marrow radiation is that the cytogenetic aberrations might be associated with the later development of leukaemia. There is a large body of information intimately linking genetic alterations with the induction of cancer. Certainly external X irradiation both therapeutic (Court Brown and Doll 1957) and accidental (Norman et al 1964) cause an increase in leukaemia rates and in adults the data is suggestive of a dose-effect relationship. Although there are single case reports of leukaemia occurring in patients previously treated with iodine-131 neither Pochin (1960) nor Saenger et al (1968) found an increase in the incidence of leukaemia after surveyance of about 40,000 patients over 10 years or so. Certainly massive doses of iodine-131 (up to 200 mCi) given for the treatment of thyroid cancer are associated with a definite rise in the incidence of leukaemia (Pochin 1960). It appears, therefore, that the chromosome abnormalities noted in the peripheral lymphocytes of iodine-131 treated thyrotoxic patients are not associated with leukaemia but is this also to be true following iodine-125 therapy? Cells exposed to radiation sufficient to cause gross visible abnormalities are likely to be sterile and although they may live and function for a long time as most circulating lymphocytes appear to do, if this is the case the lymphocyte abnormalities of the type found after iodine-125 treatment may likewise carry no serious risk. More subtle but undetected alterations such as minor biochemical changes in D.N.A. perhaps even

involving single genes, might however be present too. For this reason the risk of leukaemia after iodine-125 cannot be dismissed until the length of follow up has been considerably increased.

(b) As a Possible Aetiological Factor in the Production of Thrombocytopenia.

One significant haematological problem did develop shortly after iodine-125 therapy. A 42 year old female was treated with 14.0 mCi (350 uCi per gram thyroid) on 24.9.71 and because of the severity of her disease propranolol 10 mg. four times per day was introduced at the same time. On 10.11.71 at a routine clinic visit she was noted to have several bruises which could not be attributed to trauma and Hess test was positive. Platelet count was 34,000 per mm and the patient was admitted to hospital for more detailed investigations.

Although the thrombocytopenia worsened haemoglobin and red cell absolute indices, white cell count and blood film were repeatedly normal. Sternal marrow aspirate was hypercellular and the megakaryocytes were normal both numerically and morphologically. The one positive diagnostic test homogeneous antinuclear factor at a dilution of 1 in 64 allowed the diagnosis of thrombocytopenia secondary to systemic lupus erythematosus to be made. Dramatic improvement of the thrombocytopenia followed the introduction of prednisolone 60 mg. per day and it has now been possible to discontinue the steroids completely with no evidence of haematological relapse to date.

There are three possible explanations for the occurrence of thrombocytopenia in this patient. The diagnosis which has been accepted is systemic lupus erythematosus and in retrospect the patient did have a history of joint pains and had mild arthritic changes in her hands consistent with this. The radiation dose to the marrow from 14.0 mCi iodine-125 would have been about 6 rads. Following

radiation platelets are less severely affected than granulocytes. With doses of radiation which cause 90 per cent mortality thrombocytopenia may be total but in this patient the level of radiation would not be expected to cause a severe fall in platelets (Cronkite et al 1969). None of the patients who received larger therapy doses in some instances three times as much had any bleeding problem though routine platelet counts were not done. Thrombocytopenia secondary to marrow radiation damage has been noted in Marshallese islanders but no haemorrhagic phenomena were encountered (Conard et al 1969). It is usually found in association with a diminished number of megakaryocytes or a totally hypocellular marrow, therefore, the histological findings in this patient do not substantiate the conclusion that iodine-125 caused the thrombocytopenia. The final possibility is that propranolol produced this haematological abnormality, so far this relationship has never been described, but as a precaution the drug was discontinued.

(4) Extrathyroidal Radiation Effects of Iodine-125

(a) On Parathyroid Function

Introduction

The energies of the β radiations of iodine-125 are completely deposited within the thyroid, however the photon radiations which account for about 20 to 25 per cent of the total dose travel several centimetres in tissues (Table A9). The dose to extrathyroidal tissues is mostly due to the χ and γ rays with energies greater than 4 Kev. For these emissions the effective mass absorption coefficient in soft tissues is 0.19 cm^2 per gram and from this value 1 mCi iodine-125 in a gland weighing 25 gram and a thyroidal uptake of 70 per cent the dose rate to adjacent tissues is 0.20 rad per hour (Greig 1970). The dose rate at 1 cm from the thyroid assuming the same gland mass and dose uptake is 0.05 rad per hour per mCi iodine-125. If the effective half

life of the radionuclide in the thyroid is 15 days the total doses per administered mCi iodine-125 are about 100 rads at the gland perimeter (parathyroid) and about 25 rads at a distance of one centimetre (larynx). Extrathyroidal tissues including the parathyroids are therefore irradiated and it is important to know whether iodine-125 therapy reduces the function of these glands. No patient treated with iodine-125 had clinical evidence of hypocalcaemia.

Calcium Homeostasis in Thyrotoxicosis Before and After Treatment

In thyrotoxicosis parathyroid function is suppressed. Evidence of this includes reduction in the excretion of urinary phosphorus (Harden et al 1963) and diminished phosphate clearance (Parsons and Anderson 1964). Suppression of parathyroid secretion probably results from excessive release of bone mineral which is known to occur in thyrotoxicosis. The reduced parathormone level helps maintain the serum calcium within the normal range in most patients though if calcium mobilisation is gross even this compensation may not prevent hypercalcaemia. In the face of persistent demineralisation of bone, heavy urinary and faecal losses of calcium occur resulting in a negative calcium balance (Baxter and Bondy 1966).

That calcium homeostatis may be altered after surgical treatment of thyrotoxicosis is widely accepted. Acute hypocalcaemia severe enough to cause tetany may occur and up to 28 per cent of the patients can be shown to have a reduced parathyroid reserve (Jones and Fouman 1963). The vehement protests of the surgeons that parathyroid damage during operation is not the cause of hypocalcaemia has recently gained acceptance and Michie et al (1971) believe that the rapid correction of the negative calcium balance may be a factor especially in the acute situation.

Table B 26

Details of 9 Patients Studied with E.D.T.A. Infusion as Test of Parathyroid Reserve

Number	Age (Years)	Dose Iodine-125 (mCi)	Delay Between Therapy and E.D.T.A. Test (months)	Thyroid Status
1	40	15.0	3	Euthyroid
2 *	54	5.0	3	Thyrotoxic
3	47	25.0	17	Euthyroid
4	64	20.0 x 3	13	Euthyroid
5	55	20.0	8	Euthyroid
6	47	7.0	8	Euthyroid
7	30	30.0	13	Euthyroid
8 *	54	5.0 + 10.0 + 10.0	12	Hypothyroid on Thyroxine
9	52	20.0 x 2	36	Euthyroid

Table B 27

Serum Calcium, Phosphate and Magnesium Levels in Iodine-125 Treated Patients Immediately Before and 24 Hours After E.D.T.A. Infusion

Patient	Calcium (Flame)			Calcium (E.D.T.A.)			Phosphate			Magnesium		
	Pre Infusion	Post Infusion	Ratio	Pre Infusion	Post Infusion	Ratio	Pre Infusion	Post Infusion	Ratio	Pre Infusion	Post Infusion	Ratio
1	10.4	10.0	94%	10.2	10.0	98%	2.6	3.0	115%	1.7	1.8	106%
2	9.1	9.0	99%	10.1	8.7	86%	3.5	3.8	109%	2.0	2.0	100%
3	8.9	8.3	93%	9.0	8.0	89%	2.8	2.9	104%	2.0	1.9	95%
4	9.4	9.2	97%	9.4	8.9	95%	2.5	3.2	128%	1.8	1.7	94%
5				9.6	9.6	100%	2.8	4.2	150%	1.7	1.7	100%
6	9.8	9.2	94%	9.6	8.7	91%	1.6	2.7	169%	2.0	2.1	105%
7	8.5	8.5	100%				2.2	2.0	91%	1.8	1.7	94%
8	9.2	8.7	95%	8.4	6.4	76%	4.6	3.3	72%	2.2	2.1	95%
9	8.7	8.4	97%	9.2	8.7	95%	3.8	3.2	84%	2.1	2.0	95%
Mean	9.25	8.91		9.44	8.63		2.93	3.14		1.92	1.89	
Standard Error	0.22	0.20		0.20	0.36		0.30	0.21		0.06	0.06	

There are few critically analysed reports of hypocalcaemia occurring in thyrotoxic patients treated with iodine-131 (Table A2). The doses prescribed were not excessive and the absence of this problem in patients subjected to large doses of iodine-131 for the treatment of thyroid cancer suggests that radiation damage has not been the sole cause of hypocalcaemia. Despite this if iodine-131 treated patients with normal resting serum calcium levels are subjected to artificial reduction of the calcium between 10 per cent (Adams and Chalmers 1965) and 23.5 per cent (Better et al 1969) have a diminished parathyroid reserve.

Patients Studied: Methods

An infusion of disodium hydrogen EDTA (70 mg. per Kg. in 200 ml. 5 per cent dextrose) was given to 8 patients who had previously received iodine-125 (details of the patients studied are summarised in Table B26). One patient was tested twice, once while thyrotoxic and then after she had developed hypothyroidism and was on replacement thyroxine. The infusion was given over 30 minutes and venous blood without constriction removed before and immediately after the infusion and at 2, 6, 12 and 24 hours post infusion.

Serum calcium was measured by E.D.T.A. titration in 8 of the 9 patients and by flame photometry in 8 of the 9 patients. Serum phosphate levels and serum magnesium were also measured in the 9 patients.

Results

Table B27 shows the results. The preinfusion calcium levels measured by flame photometry ranged from 8.5 to 10.4 mg per 100 ml. (mean 9.3 mg per 100 ml). 24 hours after E.D.T.A. infusion the range of results was 8.4 to 10.0 mg per 100 ml (mean 8.9 mg per 100 ml) ($P = 0.5$). No patient failed to restore the calcium level back to within 90 per cent of the basal level in 24 hours. Three patients

(one on two occasions) failed to reach 90 per cent of the pre-infusion result in 24 hours when the estimations were made by E.D.T.A. titration. The serum phosphate fluctuated considerably and 24 hours after infusion ranged from 72 per cent to 169 per cent of the basal results. Serum magnesium levels were very stable, the 24 hour post infusion value ranging from 94 per cent to 106 per cent of the basal readings (average pre and post infusion results 1.92 and 1.89 mg per 100 ml respectively).

Discussion

E.D.T.A. is a chelating agent which binds calcium; intravenous infusion of E.D.T.A. rapidly lowers the level of calcium in the plasma. In physiological circumstances the stimulus of hypocalcaemia increases parathormone secretion and within 24 hours the calcium level is restored to at least 90 per cent of the basal level (Jones and Fourman 1963). The dose of E.D.T.A. employed, 70 mg per Kg body weight, produced a satisfactory hypocalcaemic response many of the patients developed paraesthesiae in their hands and lips but in no instance did the test have to be reversed. Calcium for intravenous administration was always close to hand.

Using this stress none of the patients had deficient parathyroid reserve as defined above when the measurements were made using flame photometry. By E.D.T.A. titration 3 of the patients failed to raise the calcium to 90 per cent of the basal reading. Patient Number 2 was minimally thyrotoxic and her post infusion result of 8.7 mg per 100 ml was normal in this circumstance. She was reinvestigated (Number 8) at a time when she was hypothyroid but on thyroxine therapy and the response was less adequate suggesting that she probably had impaired parathyroid reserve. The other patient (Number 3) who just failed to reach the normal range (89 per cent) had a very severe hypocalcaemia

4.7 mg per 100 ml immediately after the E.D.T.A. infusion and the recovery was therefore fairly satisfactory. In the remainder of the patients the calcium results were normal.

Parathyroid reserve as stressed by E.D.T.A. infusion is, therefore, not impaired in patients previously treated with iodine-125. Serum parathormone levels were not measured. It has been suggested that parathyroid damage might be masked by a concomitant reduction in calcitonin because of irradiation of thyroid C cells. This suggestion is not tenable for two reasons. Calcitonin is now known to be produced in extrathyroidal sources and secondly the rise in calcium after E.D.T.A. points to some agent actually mobilising bone mineral, i.e. parathormone.

Similar studies in iodine-131 treated thyrotoxic patients using E.D.T.A. (Adams and Chalmers 1965) or molar phosphate (Better et al 1969) have demonstrated impaired parathyroid reserve. The γ radiation from a standard dose of iodine-131 produces about 400 to 500 rad which is probably less than the γ emissions from 10 to 15 mCi of iodine-125. It is possible, therefore, that the electronic radiations from iodine-131 which travel up to 2,000 microns may add to the γ radiation damage to the parathyroids, whereas the β rays from iodine-125 would not produce this summation effect.

The marked fluctuations in phosphate levels are difficult to explain but they do not correlate with the post infusion calcium levels. Patients 1, 4, 5 and 6 had 24 hour post infusion phosphate levels which were between 115 per cent and 169 per cent of the basal readings yet in each of them the calcium response was normal.

It is thought that in thyrotoxicosis the proportion of magnesium bound to protein is increased compared to euthyroid or hypothyroid patients. Overall the total level is not affected and the basal levels were normal in the patients studied. No statistical change in serum

magnesium levels was found after E.D.T.A. infusion.

(b) On Larynx

External radiation has been cited as an aetiological agent in laryngeal neoplasia (Goolden 1957). A 57 year old female complained of hoarseness 20 months after a 20 mCi. therapy dose of iodine-125. Investigation showed a polyp on her left vocal cord which has now been surgically treated. Histologically the polyp showed no evidence of malignancy. Although it would be wrong to exclude the iodine-125 therapy as being the cause of this lesion the most probable factor has been excessive cigarette smoking.

(5) Effect of Iodine-125 on the Course of Exophthalmos

Routine ophthalmometric measurements were not recorded in the majority of patients, the impression obtained, however, was that iodine-125 did not adversely affect the eyes. Two of the 265 patients did require definitive treatment for ophthalmic complications which progressed after the radioiodine therapy. A 46 year old male was treated with high doses of prednisolone for severe proptosis, the outcome was excellent. This patient is euthyroid 20 months after treatment. A lateral tarsorrhaphy was necessary in a 66 year old female who had become hypothyroid 3 months after a dose of 15.0 mCi. This incidence of ophthalmic complications is, therefore, well within the expected range (Werner 1971).

(6) Incidental Complications and Hazards

The spectrum of illness encountered did not appear increased in a group of 265 patients. Two females both aged 74 years at the time of therapy have died. One had a cerebro-vascular accident 2 months after the dose while she was still thyrotoxic, the other died because of an acute myocardial infarction. Both patients died in other hospitals

and no post mortem was carried out, the thyroid glands in particular were not examined.

A 58 year old patient suddenly became paraplegic 10 months after a 8.0 mCi drink. Investigation has proven that the underlying disease process was a bronchogenic carcinoma with vertebral metastases. Tuberculous endometritis, severe pulmonary embolus and a mild hemiparesis have occurred in each of three patients and a fourth patient attempted to commit suicide.

Van Middlesworth (1972) has also drawn attention to a potential hazard of iodine-125, namely prolonged environmental radioactive contamination from saliva of patients treated with this radionuclide. He has shown that one week after a 10 mCi therapy dose of iodine-131 that the patient might transfer 0.001 to 0.08 mCi of iodine-131 to a postage stamp. Because of the longer half life of iodine-125 he has suggested that contamination might persist for as long as one year. On careful scrutiny of his data the radiation levels have been quoted in millicuries rather than microcuries and hence are exagerrated by a factor of 1,000. Although the correct lower levels (0.001 to 0.08 uCi) cannot be completely disregarded they do not contribute to a significant environmental hazard.

Summary

Therapeutic doses of iodine-125 have not so far been associated with any major complications. Persistant chromosomal aberrations are found in circulating lymphocytes, but it is hoped that they will like those encountered in iodine-131 treated patients not be associated with any malignant alteration. Parathyroid function appears intact and environmental contamination not excessive.

Section C

Measurement of the Radiobiological Changes in the Thyrotoxic Thyroid due to Iodine-125

Chapter I

Functional Status of the Thyroid Following Iodine-125 Therapy

Introduction

Three different in vivo techniques and in vitro investigation of serum from iodine-125 treated patients have been used in an attempt to measure radiobiological changes in the thyrotoxic thyroid after therapy. Firstly routine radioiodine-131 tests (24 hour thyroidal uptake of a tracer dose of iodine-131, the 48 hour protein bound iodine-131 and butanol extractable iodine-131) are described. Secondly using a modified intravenous perchlorate discharge test patients were studied to assess whether a defect in organic binding of iodine could be demonstrated. To complement this in vivo test, sera from iodine-125 treated patients were examined electrophoretically and radiochromatographically for the presence of circulating iodoproteins labelled with iodine-125. Finally a study of serum thyroxine, T3 resin and serum thyrotropin (T.S.H.) levels related to the clinical assessment of each patient's thyroid status is described and the importance of elevated serum T.S.H. in this context discussed.

(a) Routine Iodine-131 Tests in Patients Treated with Iodine-125

Patients Studied

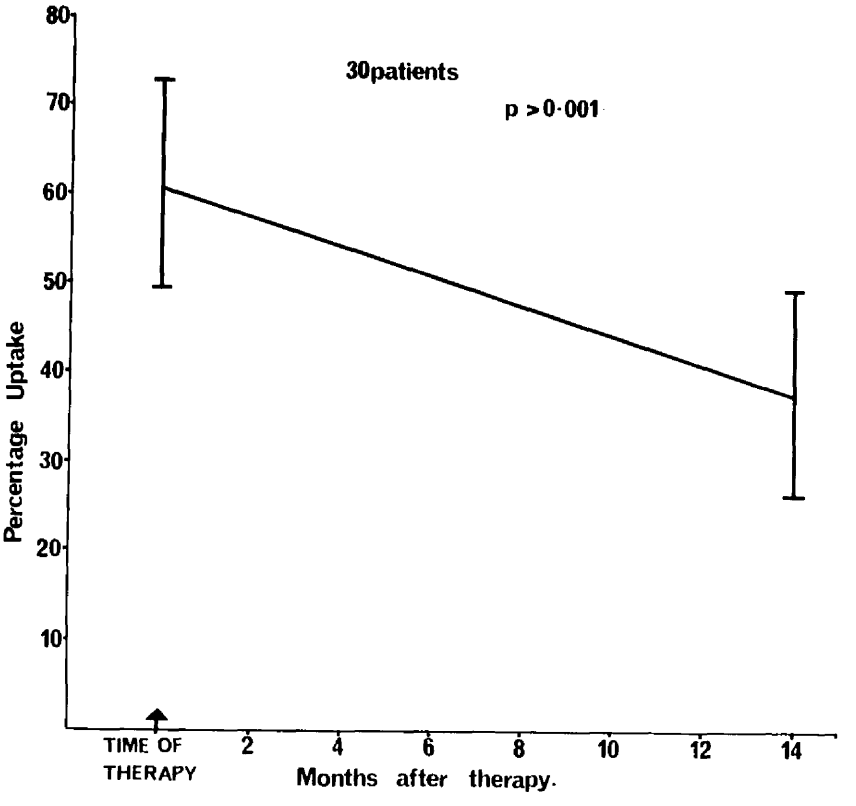
The functional ability of the thyroids of patients treated with iodine-125 was investigated using routine iodine-131 tests. Thirty unselected patients, 26 females and 4 males, each received a 5 uCi tracer dose of iodine-131 at an average time of 14 months after the therapy dose. The 24 hour thyroidal accumulation of iodine-131 was measured by directional counting and calculated as a percentage of the total dose. A venous sample of blood was withdrawn 48 hours after the administration of the tracer dose for measurement of the total plasma iodine-131 and the protein bound iodine-131. Butanol extractable iodine-131 was measured in 21 of the 30 blood samples.

The 24 hour uptake of iodine-131 before therapy had been estimated in all of these patients but the total protein bound radioactivity and protein bound iodine-131 levels were only available in 19 patients. The reason for this was that the other 11 patients had been referred to the Department of Nuclear Medicine with the diagnosis of thyrotoxicosis substantiated by biochemical investigations and the only confirmatory test carried out was the 24 hour uptake of iodine-131. These pre-therapy investigations were compared with the post therapy results.

Results

The total results are presented in Table C1. Before iodine-125 therapy the mean 24 hour tracer uptake was 60.9 $\pm$ 11.8 per cent (mean $\pm$ 1S.D.). After therapy this had fallen to 37.8 $\pm$ 11.6 per cent (Figure C1) and this difference was statistically different (P 0.01). The mean total plasma radioactivities before 0.78 per cent dose per litre and after therapy 0.84 per cent dose per litre were very similar

FIGURE C 1



Percentage uptake of tracer dose of iodine-131 ($\pm$ one standard deviation) in 30 patients before iodine-125 therapy and repeat uptake in the same patients at an average of 14 months after treatment.

Table C 1

Routine Radioiodine Tests of Thyroid Function Before and After Iodine-125 Therapy

	Pre Iodine-125 Therapy	Post Iodine-125 Total Group	Post Iodine-125 Thyrotoxic	Post Iodine-125 Euthyroid
24 Uptake of Iodine-131 (per cent of dose ± one standard deviation)	60.9 ± 11.8	37.8 ± 11.6	53.6 ± 6.2	34.4 ± 6.6
Total Plasma Iodine-131 per cent dose per litre	0.78 ± 0.47	0.84	1.05 ± 0.71	0.80 ± 0.6
Protein Bound Iodine-131 per cent dose per litre	0.73 ± 0.48	0.80	1.05 ± 0.71	0.75 ± 0.6

as were the total protein bound iodine-131 levels, 0.75 per cent dose per litre and 0.80 per cent dose per litre respectively. Of the thirty patients 5 were clinically thyrotoxic at the time of the post-therapy tests; comparing their results with the remainder of the patients (Table C1), both the 24 hour uptake (53.6 per cent) and protein bound iodine-131 (1.05 per cent dose per litre) were greater than those in the euthyroid patients (34.4 per cent and 0.75 per cent dose per litre). The uptakes were significantly different ($P < 0.01$).

The mean percentage butanol extractable iodine-131 was 91.1 $\pm$ 10.3 per cent. In 3 of the 21 patients (14.3 per cent) less than 85 per cent (60, 68 and 81 per cent respectively) of the radioactivity was extracted.

Discussion

Following destructive therapy of the thyroid either by surgery or by radioiodine-131, the interpretation of iodine-131 tracer studies may be difficult (Harden 1971). Soley et al (1949) noted an elevated uptake in a euthyroid patient who had received iodine-131. In Silver's series (1968), 46 out of 51 patients who were clinically euthyroid after iodine-131 had an elevated 48 hour protein bound iodine-131. 22 euthyroid patients had both a raised 24 hour tracer uptake and a high 48 hour protein bound iodine-131. The reason for the elevated uptake after definitive therapy is that only a small thyroidal pool of iodine remains (Jefferies et al 1956, Berson and Yalow 1954, Freedberge et al 1952) and the uptake of iodine-131 is exagerrated since the remaining segment of thyroid functions intensely to maintain normal serum thyroxine levels probably under the stimulus of raised circulating pituitary thyrotropin levels. There is evidence that the smallest intrathyroidal hormone pools are encountered in patients treated with radioiodine-131 though a similar situation may be encountered in other

thyroid diseases such as Hashimoto's thyroiditis (Eckert et al 1960, Buchanan et al 1965). The high values for the protein bound iodine-131 are also probably due to this same factor; the thyroid secreting hormone of high specific activity. One other possibility for the high protein bound iodine-131 is that a non active and non butanol extractable material is being produced by the thyroid though this is seldom found after iodine-131 therapy.

In the iodine-125 treated patients despite the significant fall in the 24 hour tracer uptake the 48 hour protein iodine-131 levels were elevated. Although the 24 hour uptake of iodine-131 and the protein bound iodine-131 were higher in the 5 patients who were still clinically thyrotoxic in the remainder of the patients each unequivocally euthyroid the protein bound-131 was in the "thyrotoxic range" in 20 (80 per cent). In fact, only 4 of the thirty post therapy patients had combined results in the conventional range for normality. The high uptake persisting after therapy is a more accurate guide to persisting toxicity after iodine-125 than elevated 48 hour protein bound iodine-131 levels. The butanol extractable iodine-131 was below 85 per cent in only 3 of the patients. It appears, therefore, that in the majority of the patients the high protein bound iodine-131 results were not due to the formation of abnormal iodinated proteins. Iodine-125 treated patients have a "small pool pattern" and in general produce active thyroid hormones. These results are in keeping with those in the next section (vide infra) which suggest that there is no block in iodination of thyroglobulin at the cell apex. They also confirm what is already known in iodine-131 treated patients that radioiodine tests alone may be misleading and that they should not be accepted as evidence of persistant toxicity and the need to retreat the patient.

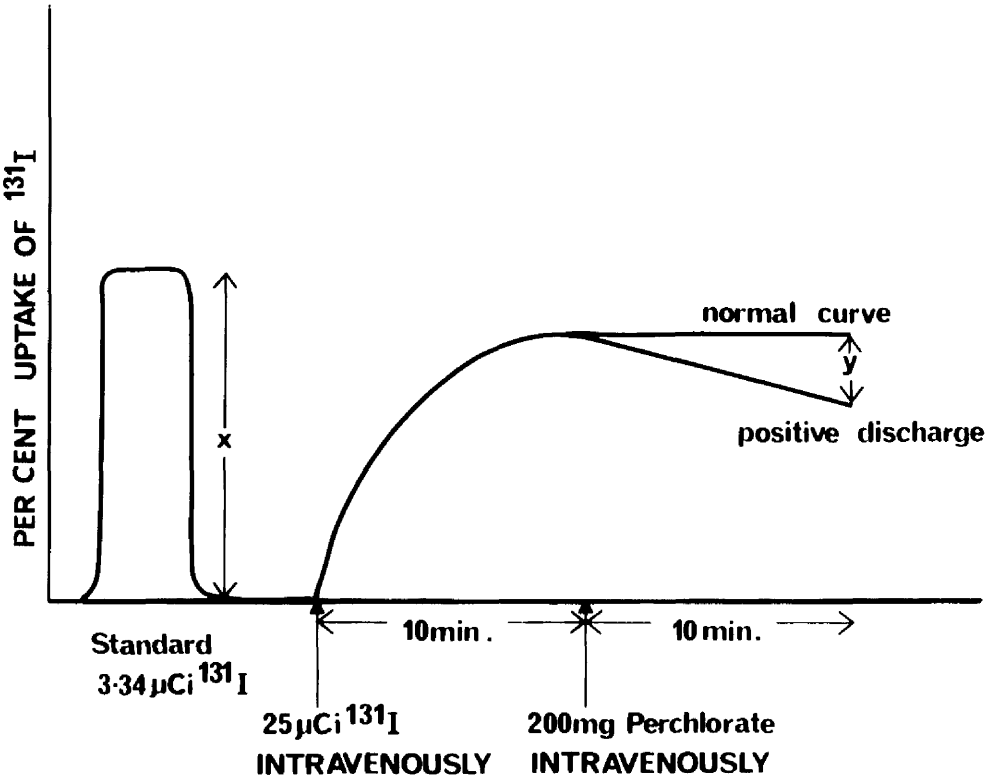
(b) Intrathyroidal Organic Binding of Iodine In Patients Treated with Iodine-125

Introduction

Iodide trapped by the follicular cell is rapidly bound to the tyrosyl radicals of mature colloidal thyroglobulin. The almost simultaneous occurrence of these steps mean that at any time in the normal gland there is either no free intrathyroidal iodine or only a minute amount. In certain circumstances the iodination step is inhibited leading to an accumulation of trapped iodine in the cell. Typically the thiouracil drugs interfere with organic binding (Silver 1968, Klopowitz and Solomon 1971) as do pharmacological doses of inorganic iodine (Wolff 1969). Patients with acquired thyroiditis (Hashimoto's) exhibit this block in hormone synthesis (Morgans and Trotter 1957) and it is also encountered as a hereditary disease in some patients with goitre and hypothyroidism (Ingbar and Woebar 1968) often associated with nerve deafness (Pendred's Syndrome).

Any build up of unbound intrathyroidal iodine can be demonstrated using perchlorate or thiocyanate. These drugs not only inhibit the mechanism responsible for the trapping of iodide but also discharge unbound iodine from the follicular cell. The "conventional" discharge test involves the administration of an oral tracer dose of iodine-131, the thyroidal content of the radionuclide is measured at intervals of 30 minutes using a directional counter. 2 hours after the tracer dose 500 mg. to 1,000 mg. potassium perchlorate is prescribed orally the directional counting is continued for a further 2 hours and any fall in thyroid radioactivity is accepted as an indication of discharge of free intrathyroidal iodine. Unfortunately this protocol has poor reproducibility, is non quantitative and is relatively insensitive, and these problems are reflected by different procedures used by various

FIGURE C 2



Diagramatic representation of tracing obtained in 20 minute intravenous perchlorate discharge test

x = number of units of uptake of known standard

y = number of units of positive discharge

Table C 2

Perchlorate Discharge - Patient Data

Number	Sex	Dose of Iodine-125 (mCi)	Time of Test after Iodine-125 Therapy
1	F	12.0	5 months
2	F	17.5	22 months
3	F	20.0	25 months
4	F	10.5	1 week
5	F	7.5	12 months
6	M	8.75	3 months
7	F	8.0	2 months *
8	F	5.0	12 months *
9	F	20.0	19 months
10	M	20.0	18 months *
11	F	13.5	7 months
12	F	12.5	7 months *
13	M	20.0	2 weeks
14	M	7.5	6 months
15	M	15.0	25 months
16	M	8.75	3.5 months
17	F	7.0	10 months
18	F	15.0	2 months *
19	F	7.0	3 months
20	F	15.0	5 months
21	F	12.0	2 months
22	F	15.0	6 months

* Time from latest therapy dose in patients who received more than 1 drink

groups of investigators (Floyd et al 1960, Baschieri et al 1963, Stewart and Murray 1966).

Iodine-125 irradiates the colloid-cell interface more intensely than the remainder of the cell. The apex of the follicular cell is recognised as the site of iodination of thyroglobulin (Stein and Gross 1964) and, therefore, an accurate test of organic binding in patients treated with iodine-125 is of paramount importance. Because of the disadvantages of the oral perchlorate discharge test a shorter but more sensitive and quantitative method (Gray et al 1972) has been employed to investigate the ability of the thyroids of 22 patients previously treated with iodine-125 to bind iodine.

Materials and Methods

Figure C2 outlines the basis of the test. Firstly, a standard dose of iodine-131 in a phantom was counted using a closely collimated directional counter 2" from the radiation source; the detector fed a continuous potentiometer recorder. The phantom was removed and the patient lay on a couch and the detector placed 2" above the neck over the region of the thyroid. 25 uCi iodine-131 (carrier free Sodium iodide-131, Radiochemical Centre, Amersham) was given intravenously through an indwelling catheter and the neck radioactivity recorded continuously for 10 minutes. 200 mg of sterile sodium perchlorate (specially prepared by the Pharmacy Department, Royal Infirmary, Glasgow) injected through the venous catheter and recording continued for a further 10 minutes.

Patients Studied

22 patients (16 females and 6 males) who had received iodine-125 therapy at varying intervals from 1 week to 25 months were asked to return for this investigation. In Table C2 the number of patients,

Table C 3

Percentage of Iodine-131 Discharged from Thyroids of Patients

Treated with Iodine-125 Using Intravenous Perchlorate

Number	Uptake of Iodine-131 Percentage of Standard Before Perchlorate	Uptake of Iodine-131 Percentage of Standard After Perchlorate	Percentage of Total D Discharged from Thyro
1	27.6	24.7	0.19
2	22.0	21.1	0.12
3	77.8	77.8	0
4	75.0	76.2	0
5	14.1	14.1	0
6	121.1	121.1	0
7	127.6	135.7	0
8	54.9	53.3	0.22
9	46.0	44.2	0.26
10	51.6	53.5	0
11	84.5	85.2	0
12	86.7	88.1	0
13	131.4	121.4	1.44
14	121.3	124.7	0
15	30.8	30.0	0.11
16	31.4	29.4	0.26
17	79.8	64.4	2.04
18	Test not completed		----
19	27.2	25.6	0
20	45.7	42.5	0.43
21	42.7	42.7	0
22	28.4	28.7	0
mean	63.2	62.1	
S.D.	37.6	38.2	

their sex, the dose of iodine-125 administered (mCi) and the time between the therapy dose and the perchlorate discharge test are shown.

Results

One of the patients (Number 18) could not tolerate the directional counter over her neck and in her case the test was discontinued. The results are shown in Table C3. The level of radioactivity 10 minutes after the intravenous iodine-131 has been expressed as a percentage of the radioactivity of the known standard and the percentage of radioactivity 10 minutes after the intravenous administration of sodium perchlorate listed in the adjacent column. The mean results before (63.2 ± 37.6 per cent) and after perchlorate (62.1 ± 38.2 per cent) are not statistically different.

A better and more meaningful method of expressing the results is from the formula

$$\frac{\frac{3.34}{x} \times Y}{25.0} \times 100$$

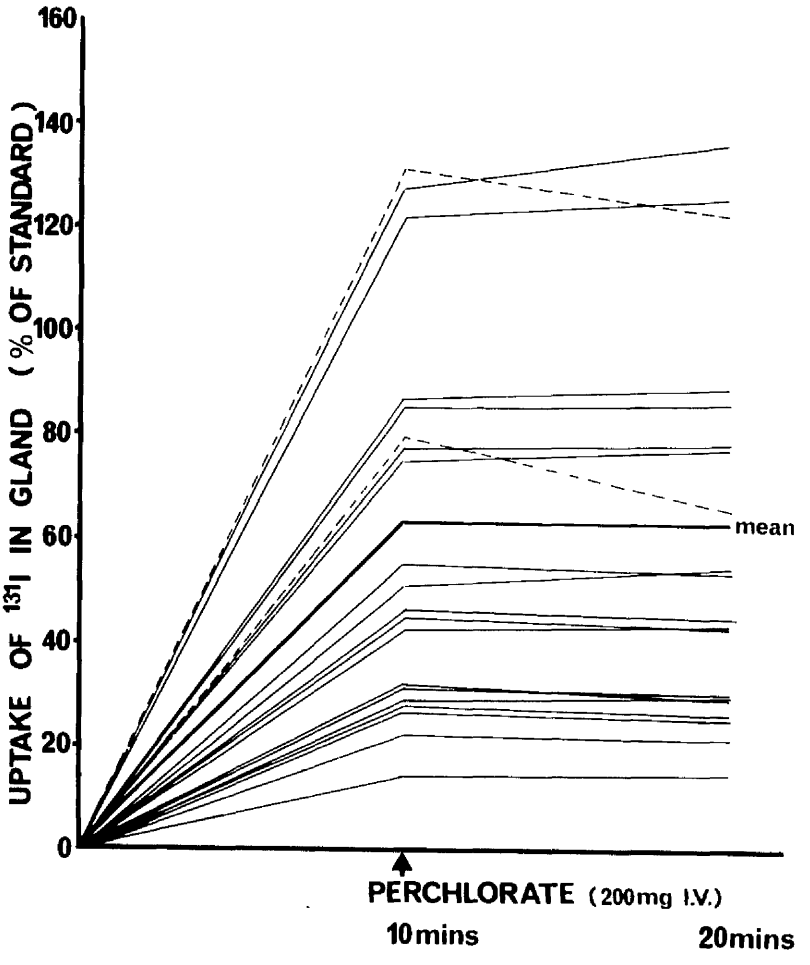
where 3.34 = standard dose of iodine-131 (uCi)
x = number of units for count of standard dose (Figure C2)
Y = number of units of discharge (Figure C2)
25.0 = amount of intravenous iodine-131

This expression calculates the actual percentage of the dose of iodine-131 which is discharged from the thyroid in the 10 minutes after the intravenous administration of 200 mg. sodium perchlorate. The results are shown in column 4. Only 2 patients, numbers 13 and 17, have a positive discharge (greater than 0.5 per cent of administered dose) hence an inhibition of iodination of thyroglobulin.

Discussion

The 20 minute intravenous perchlorate discharge test has been shown

FIGURE C 3



Results of 20 minute intravenous perchlorate discharge test in 21 patients who had received iodine-125 therapy. Solid lines show normal results in 19 patients, interrupted lines show 2 positive discharges. Mean result is illustrated by heavy continuous line.

to be exquisitely sensitive in detecting subtle degree of impairment of iodine binding (Gray 1972). In a large number of patients with no thyroid disorder and in patients with untreated thyrotoxicosis the fall in thyroidal radioactivity never exceeds 0.5 per cent of the administered dose (Gray et al 1972). Therefore only 2 of the 21 patients (9.5 per cent) exhibited a positive discharge (Figure C3).

Defects in intrathyroid organic binding of iodine have been detected in iodine-131 treated patients by Kirkland (1954) using oral sodium thiocyanate and by Kieffer et al (1965) with oral perchlorate. Patients treated with standard or low doses of iodine-131 are unduly sensitive to small doses of inorganic iodine (Hagen et al 1967, Braverman et al 1969) and often develop hypothyroidism soon after iodine administration. This usually indicates defective organic binding and undoubtedly the rapid onset of hypothyroidism is exagerrated by the diminished intrathyroidal stores of preformed hormones in thyrotoxicosis.

The remarkable feature of this study is that onlytwo of the patients showed a defect in organic binding, yet because of the physical properties of iodine-125 described previously (Section A, Chapter II) this radionuclide rather than iodine-131 should decrease iodine incorporation into thyroglobulin. The test itself has been shown to be successful in the diagnosis of minor degrees of deficient binding and indeed has been better than the oral test in this respect. The technique does not appear to be at fault. It is possible that the inhomogeneous irradiation of follicular cells by iodine-125 does not pertain to the "human model" although evidence that it does will be presented in Section C, Chapter II. The obvious explanation is that iodine-125 simply does not produce a defect in iodination in the majority of patients and the reduction in thyroidal activity is not due to impairment of this mechanism.

(c) "In Vivo" Labelled Radioactive Iodoproteins in the Circulation of Patients Treated with Iodine-125

(i) Thyroid Binding Proteins

Introduction

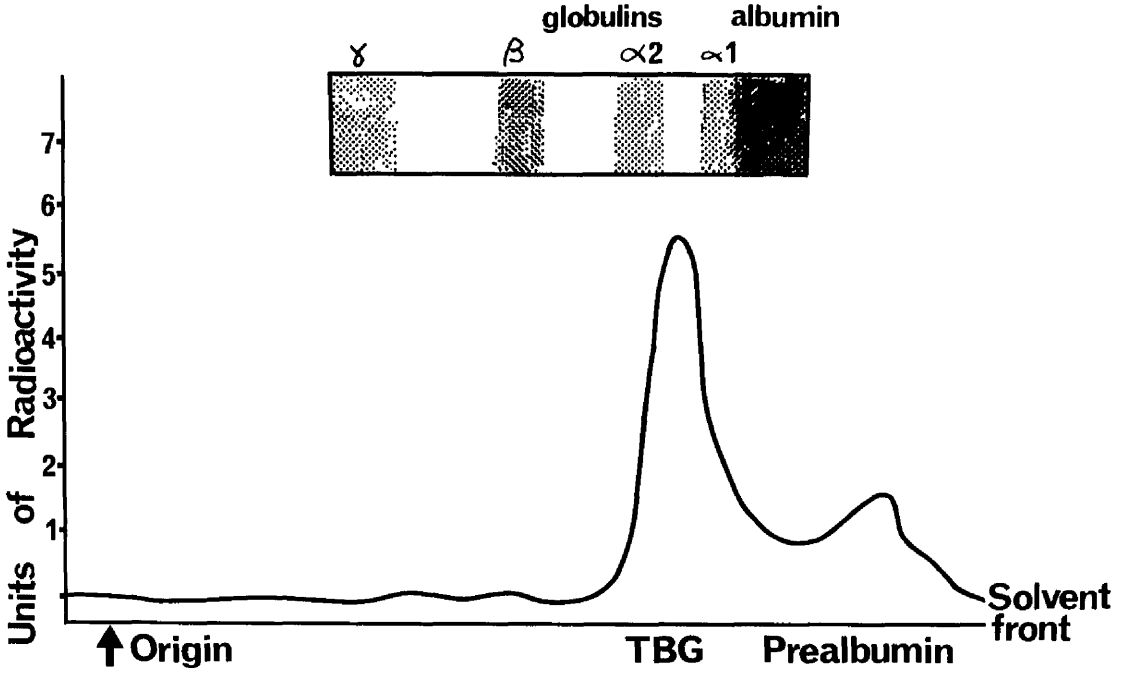
In physiological sates mature thyroid hormones (thyroxine and triiodothyronine) are transported in the circulation in loose combination with an interalpha globulin (T.B.G.), prealbumin (TBPA) and to a lesser extent albumin (T.B.S.A.) (Oppenheimer 1968, Oppenheimer and Surks 1971). Thyrotoxicosis does not qualitatively alter this general pattern (Inada and Sterling 1967). The binding proteins with the exception of albumin are present in such small amounts that they are not detected on stained electrophoretic strips, they can, however, be suitable "labelled" with radioiodinated thyroid hormones and detected by radiochromatographic scanning of the electrophoretic strips. A simple "in vivo" method of labelling these proteins or any abnormal protein carrying radioiodine is to give the patient a tracer or therapeutic dose of radioiodine and scan electrophoretic preparations for radioactivity.

There are reports of macroglobulins, probably thyroglobulin occurring in the circulation of patients treated with iodine-131 (Robbins et al 1952, Tata et al 1956) and also in rats given large doses of iodine-131 (Jovanovic et all969). Sera from patients treated with iodine-125 were studied for evidence of alterations in the binding of iodine-125 containing thyroid hormones and for the possible occurrence of abnormal circulating proteins such as thyroglobulins.

Patients Studied and Methods

The sera of 5 patients treated with iodine-125 and 2 patients treated with iodine-131 were studied. The age and sex of the patients, the dose of iodine-125 prescribed and the delay between therapy and the

FIGURE C 4



Protein Electrophoresis of serum from patient treated with iodine-125 (upper part) and radiochromatogram showing peak radioactivity in interalphaglobulin (TBG) and prealbumin (TGPA) bands (lower part).

Table C 4

Data about patients treated with Iodine-125.

In vitro studies of circulating iodoproteins.

Age	Sex	Dose Prescribed (mCi)	Nuclear Rad Dose (Approximately)	Eventual Outcome	Delay between therapy and study	
					Radiochromatogram	Electrophoresis
64	Male	25.0	9,000	Hypothyroid	6 weeks	---
65	Female	30.0	17,000	Hypothyroid	12 weeks	---
65	Female	57.0	10,000	Euthyroid	10 days 6 weeks	6 weeks
68	Female	40.0	8,000	Euthyroid	10 days 6 weeks	6 weeks
69	Female	40.0	13,000	Hypothyroid	10 days 6 weeks	6 weeks
62	Female	50.0	7,000	Euthyroid	6 weeks 9 weeks	9 weeks
64	Female	25.0	9,000	Hypothyroid	---	6 weeks

investigation are shown in Table C4. Also shown are the approximate apical and nuclear rad doses and the eventual therapeutic outcome. Sera from 3 of the iodine-125 group were studied by standard paper electrophoresis, one by cellulose acetate electrophoresis and one by both techniques. Only paper electrophoresis was used for investigation of the iodine-131 treated patients. The radioactivity of the "in vivo" labelled thyroid hormones was measured by radiochromatographic scanning (Packard).

Results

No difference was found in the radioscans between patients who received iodine-125 or iodine-131. Figure C4 diagrammatically shows the radiochromatogram scan and paper electrophoretic strip of the serum from one of the iodine-125 treated patients which is representative for all the specimens examined. The peaks of radioactive absorption corresponded with the interalphaglobulin and prealbumin bands and with one exception the peak was higher in the former. No radioactivity was detected in abnormal thyroglobulins.

Discussion

Electrophoresis is the basic method of identifying the proteins which bind thyroid hormones and the radioiodine incorporated into the hormones after therapy is a convenient marker for these binding proteins. In each serum sample studied the radioactive peak on both paper and starch gel electrophoretic strips corresponded with the normal thyroid binding globulin and prealbumin bands. There are reports of macroglobulins containing radioiodine being released into the circulation after widely differing doses of iodine-131 (Robbins et al 1952, Tata et al 1956). These macromolecules were almost certainly thyroglobulin and the hypothesis is that the irradiation damage disrupts the follicle

to such an extent that leakage of colloidal thyroglobulin occurs.

In the group of patients described this finding has not been confirmed. Considering the whole group of patients it is possible that the investigations may have been carried out at the wrong time interval after therapy for the detection of abnormal thyroglobulin. For the iodine-125 treated patients the delay of about 40 days corresponds to between 2 and 3 effective half-lives which should have been ideal for maximal damage. The one patient studied 63 days after therapy may have been investigated too late. Jovanovic et al (1969) found that large doses of iodine-131 in rats caused release of a 19S thyroglobulin but that this had disappeared from the circulation 11 days after therapy.

Abnormal proteins are only detected by the method described if they are carrying radioiodine and it is possible that thyroglobulin was released but had no radioiodine incorporated or that the material had been deiodinated in the circulation.

It is attractive to suggest that the inhomogeneous distribution of the follicle dose rate from iodine-125 might have caused intense irradiation of the cell apex yet left the overall structure of the follicle intact. Two of the 5 patients eventually became hypothyroid pointing to a nuclear dose rate of considerable effect and the mean dose 10 microns from the apex was approximately 10,000 rads the dose rate towards the base of the cell may have been even less allowing the basement membrane to remain intact. This might have been responsible for preventing release of these larger molecules.

(ii) Iodothyronines, Iodotyrosines and Free Radioactive Iodine

Introduction

Apart from a minor binding defect in 2 patients, the intravenous perchlorate discharge test failed to demonstrate an intrathyroid block

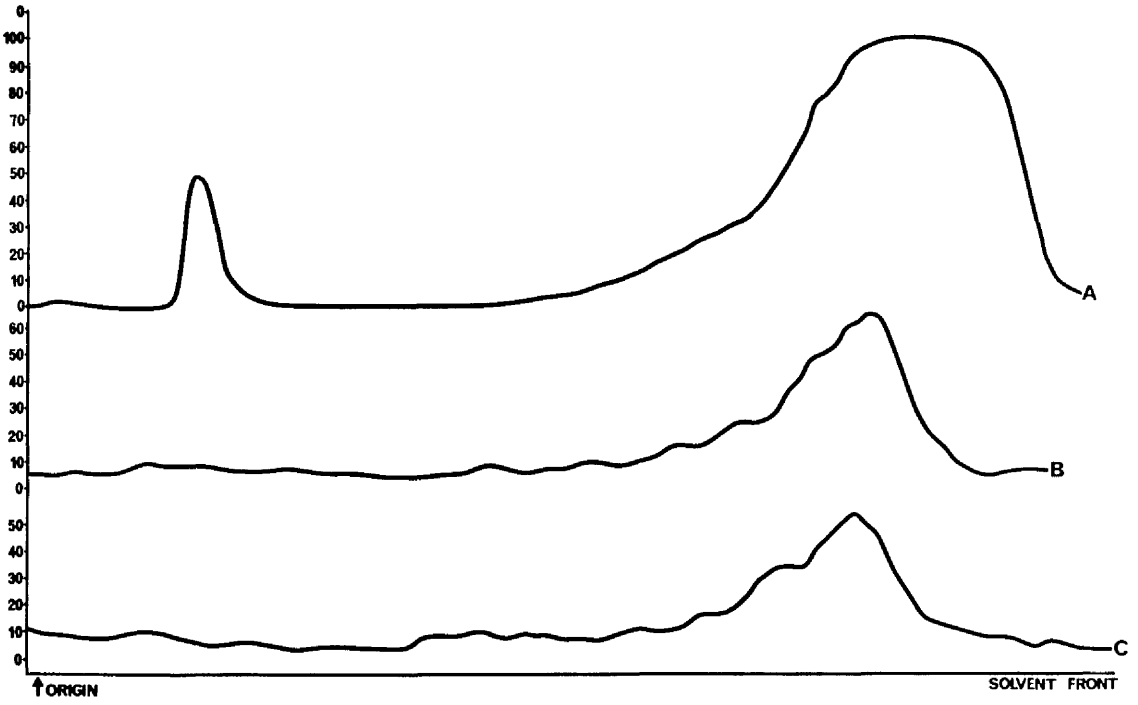
in the iodination of thyroglobulin. To complement the in vivo investigations, sera from patients who had been treated with iodine-125 at intervals from 10 days to 9 weeks previously were examined radiochromatographically to study the pattern of radioactive iodinated molecules, iodothyronines and iodotyrosines in the circulation.

Patients Studied and Methods

Serum from 6 randomly selected patients who had received radioiodine-125 treatment from 10 days to 63 days previously was used for the investigation. Serum from 3 of the patients was studied in two occasions at different time intervals after treatment. In Table C4 the age and sex of the patients, the dose of iodine-125 prescribed and the delay between therapy and the study are shown (4 of the patients were the same as in study i). For comparison, serum from two patients who had been treated with iodine-131 10 days beforehand was also studied. As a standard thyroxine labelled with iodine-131 was used.

5 mls. of test serum was extracted three times with butanol-thiosulphate and the pH of the extracts raised to 8 with concentrated ammonia. The combined extracts were evaporated to dryness under reduced pressure and the residue resuspended in three parts methanol to 1 part concentrated ammonia and centrifuged at 3,000 R.P.M. for 5 minutes. Chromatograms were set up with the resulting supernatant solution on butanol acetic acid. Two specimens from iodine-125 treated patients were also subjected to pancreatin digestion and run on butanol ammonia. The chromatograms were scanned for iodine-125 or iodine-131 depending on the therapeutic radionuclide the patient had received and scans compared with the iodine-131 thyroxine standard.

FIGURE C 5



Radiochromatogram of serum from iodine-125 treated patients

A. Iodine-131 thyroxine standard. Sharp peak free iodine-131 prolonged peak thyroxine.

B and C. Serum from patients showing radioactivity corresponding with thyroxine standard.

Results

The chromatograms from each of the iodine-125 treated patients were basically the same and two representative ones are shown diagramatically (b) and (c) in Figure C5 under the thyroxine standard (a). In the standard the first sharp peak is unbound iodine-131, the larger more protracted peak is thyroxine. In each of the chromatograms from iodine-125 treated patients the sole radioactive peak corresponds to thyroxine (iodothyronine) and no free iodine-125 or iodotyrosines were isolated. The findings were the same after pancreatin digestion and butanol-ammonia chromatography.

Discussion

Circulating iodine is mostly found incorporated in mature thyroid hormones, thyroxine and triiodothyronine (iodothyronines) (Oppenheimer and Surks 1971). There is some debate about the proportion of iodine in iodotyrosines in the circulation since some investigators believe that iodotyrosines are not found in the serum in physiological situations. Certainly these substances are found in the circulation of thyroiditis (Volpé et al 1965), they have been detected in almost 50 per cent of thyrotoxic patients (Farron et al 1959) and they occur in the circulation of rats subjected to prolonged feeding with iodine-125 (Radichevich and Werner 1967). The general belief is that they are normal constituents of the blood which are usually present in very small amounts (Rhodes 1968).

Patients treated with iodine-125 might be expected to have abnormal formation of thyroid hormones especially distortion of the process of iodination because of the intense apical radiation. Membrane destruction might be associated with leakage of free iodine-125 into the circulation. It is also possible that iodotyrosine coupling

might be defective due to the extremely high radiation doses within the colloid resulting in release of large quantities of iodotyrosines. There is no evidence to support these hypotheses since the only circulating material containing radioactive iodine corresponded exactly with the thyroxine standard. The absence of free iodine-125 in the circulations of the iodine-125 treated patients is of interest especially since a very small amount of free iodine was detected in iodine-131 patients.

The timing of the investigations was carefully selected. The mean effective half life of iodine-125 in the body is about 15 days and, therefore, post treatment sera at 10, 42 and 63 days gave a spectrum of times encompassing the probable maximum irradiation effect. In the iodine-131 treated patients the delay of 10 days was about twice the effective half-life which should correspond with the greatest damage.

The long half-life of iodine-125 and the recycling of iodine in the body are of theoretical importance. Patients treated with therapeutic amounts of iodine-125 can be thought of as "experimental animals" being fed iodine-125 over a prolonged period. Failure to demonstrate iodine-125 labelled iodotyrosines (in these patients as long as 63 days after treatment) is therefore significant; labelled iodothyronines were detectable at all times throughout the study. The normal results are in close agreement with the in vivo perchlorate discharge tests and suggest that if the extranuclear effect of iodine-125 is of therapeutic benefit it does not distort the synthesis of normal mature thyroid hormones. Because of the normal results the experiments were not expanded; it is very unlikely, however, that defective hormone production would be encountered at a later date.

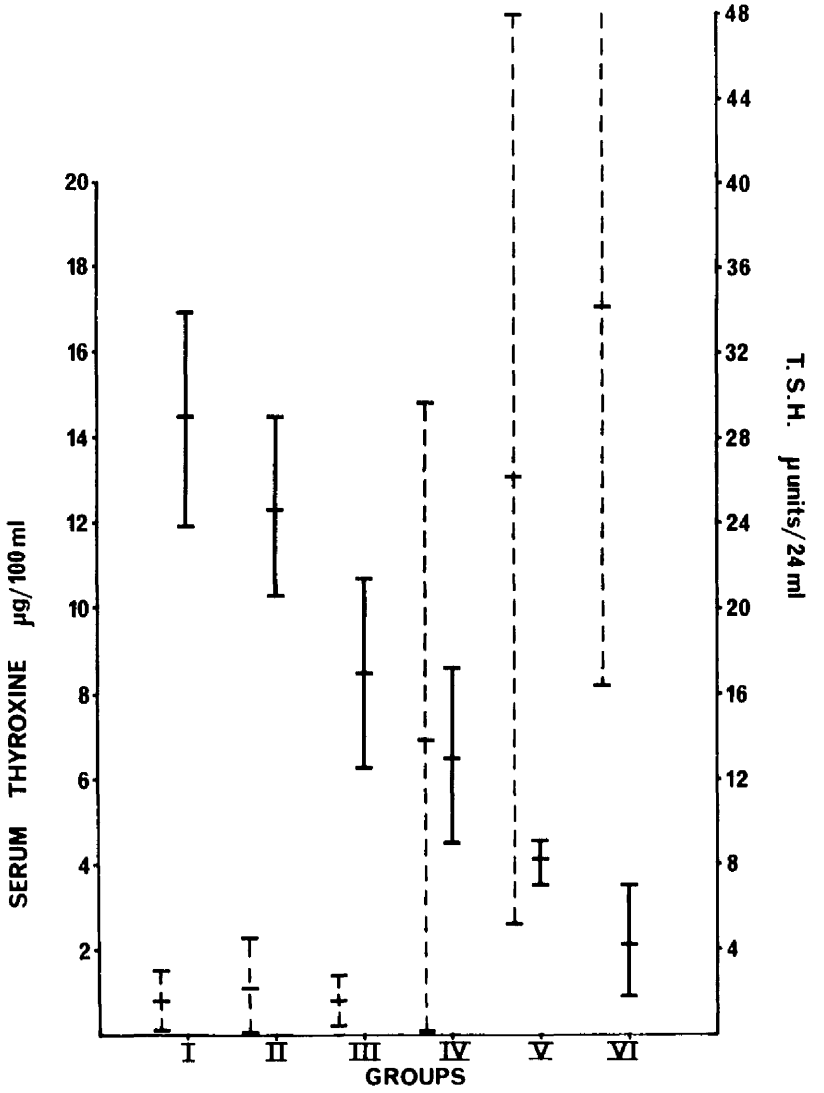
(d) Serum Thyroid Stimulating Hormone (T.S.H.) Levels in Patients Treated with Iodine-125

Introduction

Reliable, sensitive and specific radioimmunoassays of serum T.S.H. have been developed (Odell et al 1965, Utiger 1965, Raud and Odell 1969, Hall et al 1971, Hall 1972 and El Kabir 1972) and are available for clinical use. The main clinical importance of this estimation is diagnosis of hypothyroidism due to thyroid disease (Hershman and Pittman 1971, 1971b, Utiger 1971, Mayberry et al 1971) where an elevated level is a sine qua non. In euthyroid subjects the values are low but because of the insensitivity of current assays it has not been possible to separate euthyroid from thyrotoxic patients on the basis of serum T.S.H. levels alone. Theoretically thyrotoxicosis should completely suppress pituitary T.S.H. production. Normal levels of T.S.H. are also found in hypothyroid patients who are regularly ingesting a sufficient dose of thyroxine (Cotton et al 1971).

Radioimmunoassay of T.S.H. has exposed an interesting group of patients; they are classified as euthyroid on clinical grounds and have normal results for conventional biochemical tests of thyroid function yet they have elevated serum T.S.H. levels. They are best categorised as being subclinically hypothyroid (Editorial 1971a, Evered and Hall 1972). This condition may occur following surgical thyroidectomy (Hedley et al 1971) and iodine-131 therapy (Slingerland et al 1970). The importance of serum T.S.H. levels in patients treated with iodine-125 is apparent. Professor Reginald Hall of the Department of Medicine, University of Newcastle, very kindly agreed to undertake the radioimmunoassay of T.S.H. The technique was a double antibody assay as described by Hall et al (1971).

FIGURE C 6



Relation of serum thyroxine levels (mean ± one standard deviation) solid lines to serum thyrotropin levels (mean ± one standard deviation) interrupted lines in 6 groups of patients after iodine-125 therapy

Group	I	Thyrotoxic
Group	II	Hypothyroid on replacement thyroxine
Group	III	Euthyroid
Group	IV	Euthyroid with high TSH
Group	V	Misclassified
Group	VI	Hypothyroid

Table C 5

Thyrotropin Levels in Euthyroid, Hyperthyroid and Hypothyroid Patients

(After Hall et al 1971)

	Number	Mean	Range	Standard Deviation
Normal Controls	29	1.6	0.6 - 4.2	± 0.8
Hyperthyroid	18	1.0	0.5 - 1.7	± 0.4
Hypothyroid	19	177	6.5 - 588	± 152

Patients Studied

20 mls. venous blood was removed from each of 99 unselected patients who were attending the Department of Nuclear Medicine for routine clinical assessment at varying time intervals after iodine-125 therapy. The clinical status of each patient was determined. Serum thyroxine (Thyopac 4, Amersham) and T3 Resin uptake (Thyopac 3, Amersham) levels were estimated for each patient. Depending on the combined clinical and laboratory observations each patient was allotted to one of 5 groups: thyrotoxic, hypothyroid but on replacement thyroxine, euthyroid, wrongly classified as euthyroid and hypothyroid. A portion of each serum specimen was retained, given a coded number and frozen. 99 numbered serum samples without any clinical details apart from the therapy dose of iodine-125 and the date prescribed were dispatched to Newcastle where T.S.H. levels were measured. The serum T.S.H. levels were then studied in collaboration with the clinical and biochemical information.

Results

Table C5 is published by kind permission of Professor Hall and gives the expected T.S.H. levels in euthyroid, thyrotoxic and hypothyroid subjects. The normal ranges for serum thyroxine and T3 resin are also shown. Details of the results in iodine-125 treated patients are listed in Table C6 and shown graphically in Figure C6.

Results

Group I. Thyrotoxic Patients

24 of the 99 patients were clinically thyrotoxic and with one exception had raised levels of serum thyroxine 14.4 ug $\pm$ 2.5 ug per 100 mls (mean $\pm$ one standard deviation). The mean T3 resin level (108.9) was above normal (79 - 105) but 7 of the 24 patients had

Table C 6

Group	Number	Sex		Serum Thyroxine ug per 100 ml	T3 Resin Uptake	T.S.H. Uptake u Units per ml
		Female	Male	(Normal Range 4.6-11)	(Normal Range 79-104)	
I	24	20	4	14.42 ± 2.53	108.88 ± 10.95	1.62 ± 1.38 excluding 1 patient with high T.S.H. 1.31 ± 0.65
II	7	5	2	12.33 ± 2.09	102.42 ± 9.45	2.19 ± 2.30 excluding 1 patient with high T.S.H. 1.09 ± 0.71
III	39	35	4	8.42 ± 2.19	93.21 ± 9.78	1.65 ± 1.25
IIII	17	14	3	6.52 ± 2.08	86.71 ± 6.61	13.91 ± 14.94
V	3	3	0	4.03 ± 0.56	84.0 ± 8.19	26.60 ± 21.22
VI	9	9	0	2.14 ± 1.36	86.33 ± 10.09	34.46 ± 18.09

results which were within the normal range. Serum T.S.H. levels were low 1.6 ± 1.4 µU per ml but one patient had an abnormally high result (7.5 µU per ml).

Group II. Hypothyroid Patients Taking Thyroxine

7 patients who had been started on replacement thyroxine therapy had a mean serum thyroxine level of 12.3 ug per 100 ml. and their T3 resin results were at the upper limits of normality 102.4 ± 9.5. The average T.S.H. level was well within normal 2.2 µU per ml, one patient, however, did have a high T.S.H. level (7.7 µU per ml.).

The euthyroid patients were divided into 2 categories depending on the serum T.S.H. levels; Group III normal serum T.S.H.: Group IV elevated serum T.S.H. (an arbitrary level of above 5.0 uU per ml was accepted as an elevated result).

Group III.

39 patients all clinically euthyroid had normal serum thyroxine (8.4 ± 2.2 ug per 100 mls), T3 resin (93.2 ± 9.8) and serum T.S.H. (1.7 ± 1.3 µU per ml).

Group IV.

17 patients originally classified with Group III since they appeared euthyroid had normal serum thyroxine (6.5 ± 2.1 ug per 100 mls) and T3 resin (86.7 ± 6.6). In each of these patients, however, the serum T.S.H. level was above 5.0 µU per ml (13.9 ± 14.9 uU per ml). One patient in particular had a very high level (66.0 uU per ml).

Group V. Wrongly Classified as Euthyroid.

3 patients were clinically classified as being euthyroid but the serum thyroxine levels were reduced (4.0 ± 0.6 ug per 100 mls), T3 resin results in the low normal range (84.0 ± 8.2) and the T.S.H. levels elevated (26.6 ± 21.2 µU per ml).

Group VI. Hypothyroid

9 patients had biochemical evidence of hypothyroidism which was in keeping with the clinical assessment. In these patients the T.S.H. levels were the highest of the 6 groups (34.5 ± 18.1 uU per ml).

Discussion

In general the results obtained in Groups I, II, III and VI are as would be expected. The results in Groups IV and V provide interesting information that requires expansion. Before discussing these groups there were paradoxical results in two patients which also need clarification. One thyrotoxic patient (Group I) had anomalous results of interest in that the serum T.S.H. level was elevated (7.5 uU per ml) yet she was clinically thyrotoxic and had an elevated serum thyroxine (16.0 ug per 100 ml). It is unlikely that an error was made in the radioimmunoassay (Hall, personal comment). There may, however, have been a substance in the patient's circulation which cross reacted with T.S.H. yet did not have thyroid stimulating properties. It is equally possible that the cause of her thyrotoxicosis was, in fact, T.S.H. or T.S.H. like material. Rarely a chromophobe adenoma may secrete T.S.H. (Hamilton et al 1970) but more commonly the material is produced by an ovarian or trophoblastic neoplasm (Odell et al 1963, Hershmann and Higgins 1970). There has been no clinical evidence of either of these possibilities and although repeat serum T.S.H. levels are not yet to hand the serum thyroxine is persistently elevated.

The other patient (Group II) was on replacement thyroxine. She had normal biochemical tests but a raised T.S.H. level, a combination encountered when therapy is not regularly ingested.

The patients in Group IV fall into the category of subclinical hypothyroidism (Evered and Hall 1972). The importance of this

condition is still open to discussion. Bastenie et al (1967, 1971) suggest that there may be an associated preponderance of atherosclerotic vascular disease but to date there have been no prospective controlled trials of treated and untreated patients to confirm or refute this hypothesis. In the context of iodine-125 therapy this group is extremely important. If the theory of reduced nuclear irradiation is correct it might be expected that the presently elevated serum T.S.H. levels will in the course of time fall and the overall thyroid function remain virtually unaltered. This would be proof of cell regeneration and re-establishment of the normal physiological balance. However, if the cell nuclei have been permanently damaged or sterilised by the radiation a progressive rise in serum T.S.H. with a reciprocal diminution in thyroid function must be anticipated and the outcome similar to that following iodine-131.

Iodine-125 might have caused minimal nuclear damage because of the low intensity radiation, yet may not have sterilised the cells. In this situation a continued elevated T.S.H. stimulus might be dangerous since in the experimental animal this combination can result in neoplastic changes. Doniach (1971) believes that low doses of iodine-131 may leave areas of the thyroid capable of division and if toxicity persists or recurs there is a risk of induction of thyroid carcinoma. The same situation must apply in iodine-125 treated patients.

The 3 patients (Group V) who were wrongly classified are also of interest. On reappraisal without knowledge of the investigations they would still be classified as euthyroid. Nevertheless all the available biochemical and radioimmunoassay evidence points to the fact that they are subthyroid. Recent experimental evidence indicates that T.S.H. preferentially stimulates triiodothyronine secretion (Wahner and Gorman 1971). Triiodothyronine is not as potent as thyroxine in the inhibition

of T.S.H. secretion (Editorial 1971b, c) and theoretically it is possible that the raised serum T.S.H. in these patients is causing an inappropriately excessive secretion of triiodothyronine. This might be exagerrated by the preferential apical irradiation of the follicular cell although no block in iodination was demonstrated (supra). The patients, therefore, despite low serum thyroxine and high T.S.H. might possibly have normal thyroid balance. Serum has been retained for triiodothyronine assay but as yet the technique is not reliable and confirmation of this hypothesis is not available. However, the close inverse relationship of serum thyroxine and serum T.S.H. levels throughout the series does suggest that no other factors are involved.

Mayberry et al (1971) have shown that the T.S.H. levels in hypothyroid patients tend to be higher in younger patients; in this series there is no such correlation.

Section C

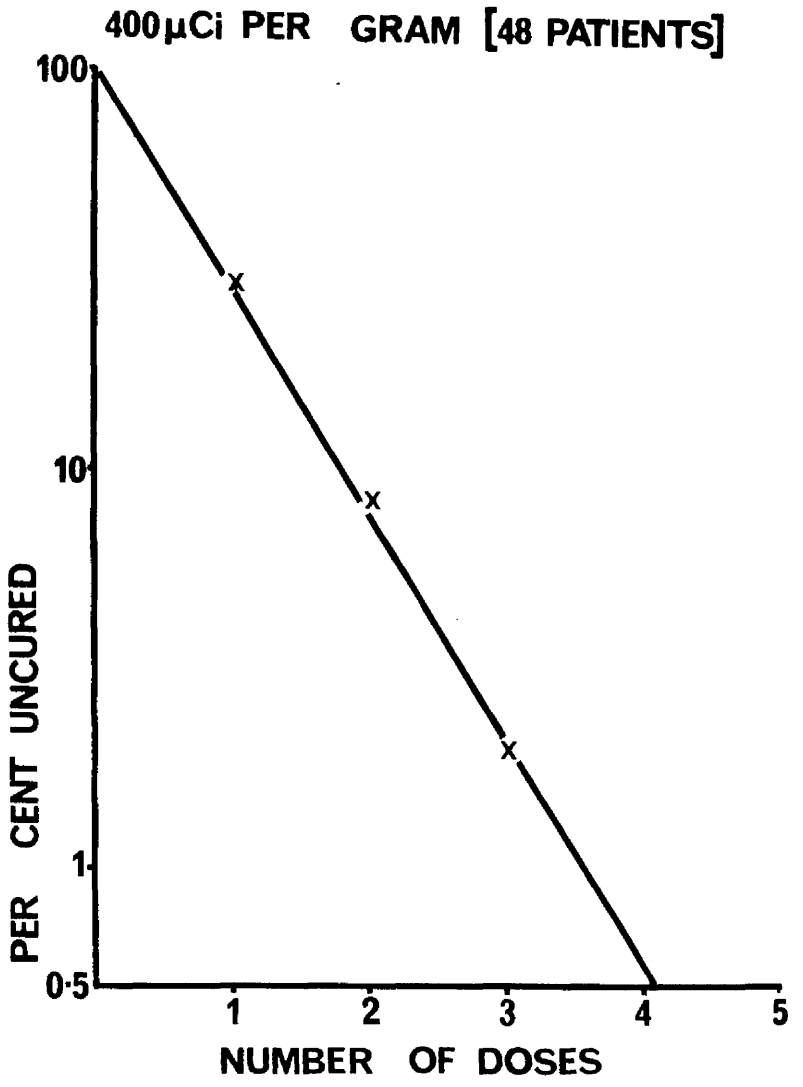
Chapter II

Is Iodine-125 Different From Iodine-131?

Introduction

Comparison of the therapeutic outcomes in different groups of patients treated with radioiodine is difficult. There are variable factors which have to be considered when this form of treatment is prescribed. These include the percentage of the therapy dose taken into the thyroid which may not closely mirror the uptake of a diagnostic tracer dose and once in the gland the distribution of the radionuclide is often uneven subjecting some areas to a much higher radiation dose than anticipated and other regions to a lower dose. The size of the gland, an important measurement for dose prescription, is difficult to assess accurately even with the use of precise scans and mathematical formulae to transform the area of the gland to a volume. Radiosensitivity of follicular cells does vary and is not simply a neat explanation for results which occurs unexpectedly. The outcome in apparently similar populations studied after similar radioiodine treatment schedules may, therefore, be quite divergent. Spencer (1971) has by the use of simple mathematical techniques made comparisons feasible.

Figure C 7



Percentage of uncured patients (logarithmic scale) after one, two and three therapy doses of iodine-125 who received from 351 to 450 uCi per gram of thyroid.

Table C 7

Response of Thyrotoxic Thyroid to Iodine-131

(From Spencer)

	Rate Constant	Number of Doses for 50% cure	Number of Doses per Patient
Silver (1968)	0.676	1.03	1.97
Maynard (1969)	0.936	0.74	1.61
Nofal et al (1966)	1.121	0.62	1.43

The percentage of uncured thyrotoxic patients are related to the number of therapy drinks that have been prescribed. A similar approach obtaining the same answer is illustrated in Figure C7 where the percentage of uncured patients have been plotted by logarithmic scale on the ordinate and the number of therapy doses prescribed poltted on the abscica. Using the results from the 400 uCi per gram of thyroid group (350-450 uCi) when zero therapy doses have been prescribed 100 per cent of the patients are thyrotoxic after 1 therapy drink, 30 per cent remain thyrotoxic, 8 per cent are not cured by the second drink and 2 per cent are still thyrotoxic after a third therapy dose. These points are joined and the exact slope of this line is obtained by the method of least squares to give the rate constant (λ).

The fraction of patients remaining thyrotoxic continues to be relatively constant from therapy dose to therapy dose. Because of this the number of uncured patients can be expressed in terms of an exponential equation

$$H = HoC^{-\lambda D}$$

Where H = the number of patients still thyrotoxic

Ho = the original number of thyrotoxic patients

D = the number of therapy doses

λ = rate constant

The rate constants in three iodine-131 treatment series (Silver 1968, Maynard 1969 and Nofal et al 1966) have been calculated by Spencer (1971) to be 0.676, 0.936 and 1.121 respectively (Table C7). The increase in the size of the rate constant is indicative of a steeper slope to the response line and hence a more rapid rate of control of the thyrotoxicosis. The therapy doses of iodine-131 prescribed by these investigators had been designed to introduce respectively into the gland 80 uCi, 100 uCi and 185 uCi per gram of

Table C 8

Response of Thyrotoxic Thyroid to Iodine-125

Group of Patients Studied	Number of Patients	Rate Constant	Number of Doses To Cure 50 per cent	Number of Doses per Patient
Total	256	0.845	0.82	1.36
Females	218	0.845	0.82	1.36
Males	38	0.852	0.81	1.34
151-250 uCi ^{125}I per G Thyroid	44	0.503	1.38	1.61
251-350 uCi ^{125}I per G Thyroid	61	0.596	1.12	1.36
351-450 uCi ^{125}I per G Thyroid	48	1.272	0.55	1.35
451-550 uCi ^{125}I per G Thyroid	31	1.199	0.58	1.29
More Than 550 uCi ^{125}I per G Thyroid	72	1.496	0.47	1.22

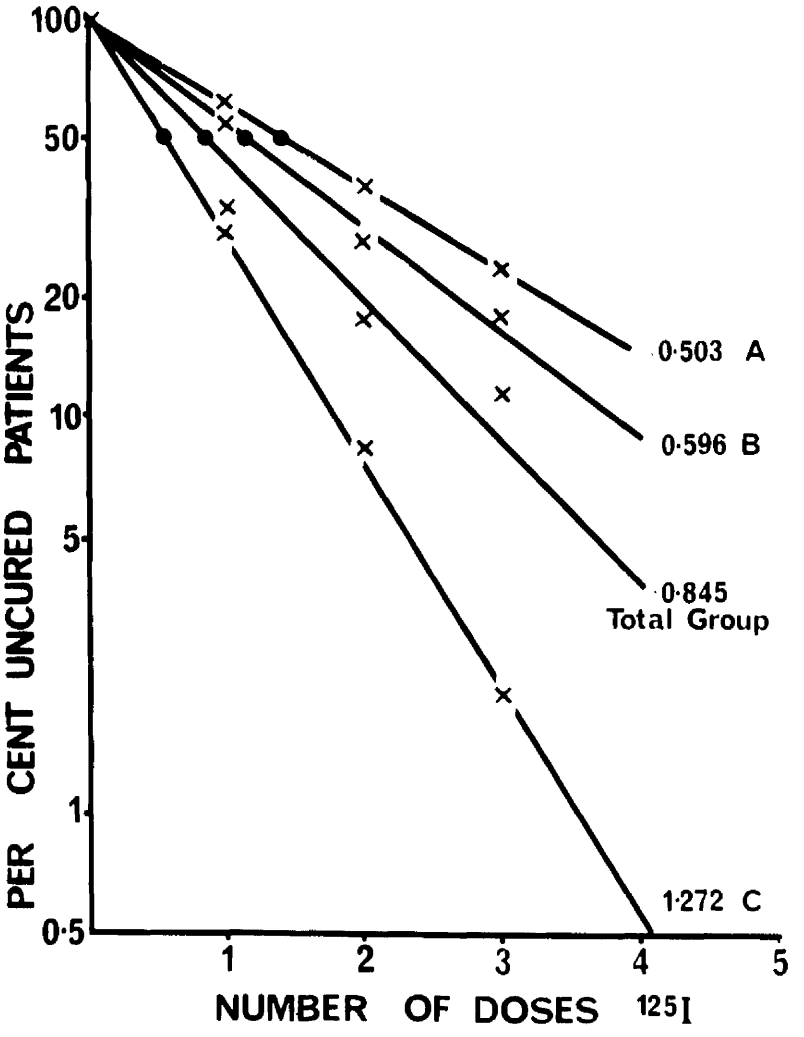
thyroid. The increase in the dose is, therefore, paralleled by an increase in rate constant.

The results obtained with iodine-125 treatment for thyrotoxicosis have been discussed in detail (Section B, Chapter II). Overall they appeared better than those achieved either with standard or low doses of iodine-131. The total treatment group, however, contains sub-groups of patients who received a variety of doses of iodine-125 and utilising the mathematical technique outlined above a rate constant has been obtained for the total group of patients, for males and females separately and for patients who received 151-250, 251-350, 351-450, 451-550 and more than 550 uCi iodine-125 per gram of thyroid. The last of these combines the results of the three treatment groups who were given 551-650, 651-750 and more than 750 uCi iodine-125 per gram of thyroid (groups 5, 6 and 7, Section B, Chapter II). These were taken together because of the small number of patients in each and because the outcome in the three groups was almost identical. 9 patients have been excluded, they are made up by three in whom the dose of iodine-125 per gram of thyroid was not known, three who received less than 150 uCi per gram and the three patients who failed to return for review. Using the rate constants a direct comparison with the results in the iodine-131 treated patients of Silver 1968, Maynard 1969 and Nofal et al 1966 has been undertaken.

Results

The rate constant of the total group 0.845 was similar to that in females 0.845 and males 0.852 (Table C8). The result was low (0.503) in patients who received the smallest dose of iodine-125 (151 to 250 uCi range) but as the dose increased the speed of control with one exception became more rapid and the rate constants greater (0.596, 1.272, 1.199 and 1.496). The group who received a mean dose

FIGURE C 8



Rate of control of thyrotoxicosis after iodine-125 therapy

A. Patients treated with 151 to 250 uCi per gram of thyroid

B. Patients treated with 251 to 350 uCi per gram of thyroid

C. Patients treated with 351 to 450 uCi per gram of thyroid

of 500 uCi per gram of thyroid was controlled slightly less rapidly than the group of 48 patients who received a mean dose of 400 uCi iodine-125 per gram thyroid.

Discussion

0.845 the rate constant for the total treatment group of iodine-125 treated patients is similar to the rate constant for the iodine-131 treated patients of Maynard (1969). His therapy doses were calculated to administer 100 uCi iodine-131 per estimated gram of thyroid. Since, as has been explained, the total group contains a spectrum of dose schedules the discussion will be focussed on the group treated with 351-450 uCi iodine-125 per gram of thyroid. The rate constant in this group 1.272 was greater than that calculated for the iodine-131 treated patients of Nofal et al (1966). An administered dose of 400 uCi iodine-125 per gram of thyroid is, therefore, superior to an intrathyroidal dose of 185 uCi iodine-131 per gram of thyroid. To obtain such a rapid rate of control with iodine-131 a considerable number of "cured" patients rapidly became hypothyroid and 2 years after therapy 46.6 per cent of these patients were thus affected (Nofal et al 1966). After a similar period of follow up in this iodine-125 treatment group only 10 per cent of the patients have become hypothyroid (Section B Chapter II). The excellent rate of control with an average dose of 400 uCi iodine-125 per gram of thyroid has been obtained with a reduction in thyroid insufficiency.

A second method of defining the rate of response to radioiodine is the concept of the number of doses per patient required to cure 50 per cent of the total group. This figure is the result of the abscisca of the graph corresponding to 50 per cent on the ordinate (Figure C8). An alternative method of obtaining the answer is from the formula

$$x = \frac{\text{Log}_{10}\ 100 - \text{Log}_{10}\ 50}{\lambda \text{Log}_{10}\ E}$$

Where x = number of doses to cure 50 per cent

λ = rate constant

In the patients treated by Silver (1968) 1.03 doses were required for each patient to cure 50 per cent of the group (Table C7) but with the larger doses prescribed by Nofal et al (1966) this was reduced to 0.62 doses per patient. In the iodine-125 treatment group who received 351-450 uCi per gram of thyroid only 0.55 doses were required per patient (Table C8).

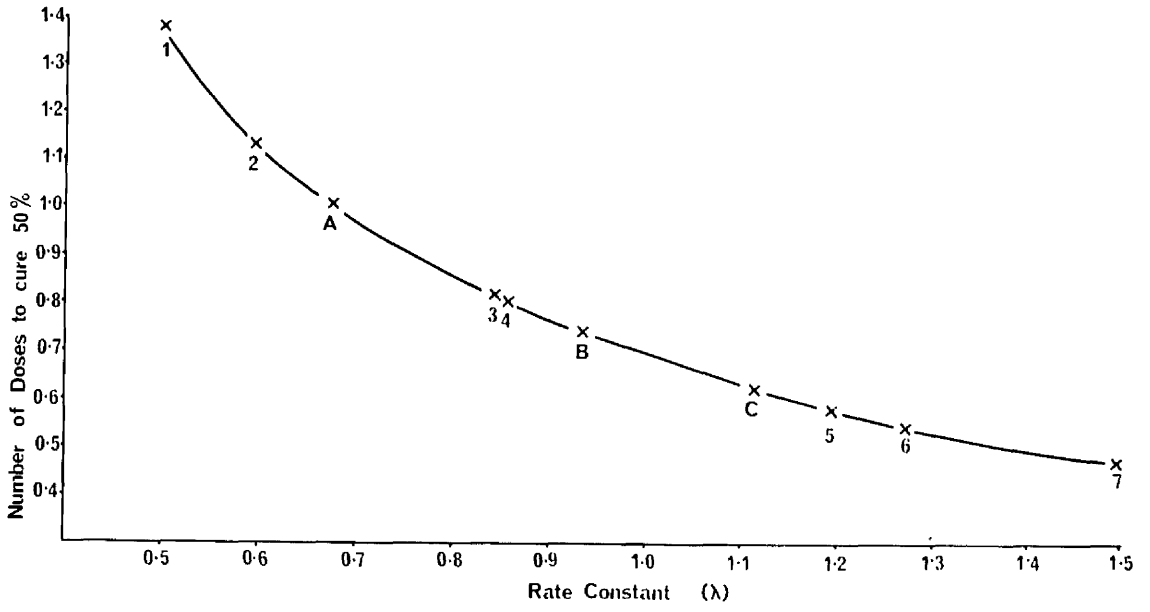
Further evidence of the difference between iodine-125 and iodine-131 is obtained by calculating the average number of doses prescribed for every patient in the treatment group. For example, if 100 patients received 1 drink, 100 patients 2 drinks and 100 required 3 drinks the number of doses per patient

$$= \frac{(100 \times 1) + (100 \times 2) + (100 \times 3)}{300} = \frac{2}{}$$

Silver (1968) prescribed 1.97 doses per patient but with a progressive increase in the prescribed amount this was reduced to 1.61 drinks by Maynard (1969) and 1.43 doses by Nofal et al (1966). These results are also tabulated in C7 and the corresponding results in iodine-125 treated patients in Table C8. 1.36 doses were prescribed per patient for the total group and in the best outcome group (351-450 uCi per gram) 1.35 doses per patient. Only 1.22 doses were required in patients given doses greater than 550 uCi per gram of thyroid.

The rapid rate of control in the 351-450 uCi group obtained with a low hypothyroid problem has required a small number of doses per patient and also a low number of doses for a 50 per cent cure. This superb combination of benefits cannot be obtained with iodine-131.

FIGURE C 9



Relation of rate constant (λ) to the number of doses of iodine-125 to cure 50 per cent of patients in each treatment group

1. Patients treated with 151 to 250 uCi per gram of thyroid
2. Patients treated with 251 to 350 uCi per gram of thyroid
3. Female patients treated with iodine-125
4. Male patients treated with iodine-125
5. Patients treated with 451 to 550 uCi per gram of thyroid
6. Patients treated with 351 to 450 uCi per gram of thyroid
7. Patients treated with more than 550 uCi per gram of thyroid

A. Results from Silver (1968): Iodine-131
B. Results from Maynard (1969): Iodine-131
C. Results from Nofal et al (1966): Iodine-131

One other factor of note is that with large doses of iodine-125 (more than 550 uCi per gram) the rate constant of 1.496 is outstanding. Only 1.22 doses are required per patient and rapid one dose cure is much more common than with large doses of iodine-131. The benefit of these large doses in the management of thyrotoxic patients with heart disease is obvious and although a definitive policy was reached not to undertake the treatment of euthyroid cardiac patients suffering from intractable angina or cardiac failure, iodine-125 in these large doses would appear to be more efficient than iodine-131 in reducing thyroid function.

The data from these calculations make it possible to compare doses of iodine-125 and iodine-131 which have approximately the same effect. The technique adopted has involved a combination of (a) the number of doses required to cure 50 per cent and (b) the rate constant. The rate constants of the iodine-125 treatment groups and the three iodine-131 reference series have been plotted against the number of doses in each of these which were required to cure 50 per cent of the group. This is shown graphically in Figure C9. An excellent relationship is shown to exist and the curve passes through all of the points, iodine-131 treated as well as iodine-125 treated.

Overall the outcome in all of the patients treated with iodine-125 is similar to that found in patients given an intrathyroidal dose of 100 uCi iodine-131 per gram. Administered doses of 400 uCi and 500 uCi of iodine-125 per gram of thyroid give results similar to but slightly better than an intrathyroidal dose of 185 uCi iodine-131. Accepting that the average thyroidal uptake of the therapeutic dose iodine-125 was 66 per cent of the prescribed dose approximately 264 to 330 uCi per gram of this radionuclide was introduced into the thyroid. The ratio of effectiveness of iodine-131 to iodine-125 at these dose levels is, therefore, about 1/1.5 - 2.0. At lower

dose ranges an administered dose of 300 uCi iodine-125 can be seen to be slightly less active than a thyroid dose of 80 uCi iodine-131. The ratio of effectiveness in this case is 1/2.5.

Summary

Using simple mathematical techniques iodine-125 has been shown to differ from iodine-131 in the following respects. Approximately double the dose of iodine-125 is required to produce the same therapeutic effect as iodine-131, but as the dose of radionuclide is decreased this ratio is increased to 2.5 to 1. Nevertheless for the same rate of control iodine-125 causes considerably less hypothyroidism after a similar period of follow up. Large therapy doses of iodine-125 almost inevitably produce a rapid single dose cure.

Final Conclusions and Possible Extensions of Investigations

Iodine-125 is successful in the control of thyrotoxicosis and in the dose range of 351 to 450 uCi per gram of thyroid is superior to iodine-131. Obviously no new therapeutic nuclide can be considered beneficial until it is shown to be as safe as the existing one. Iodine-131 has stood the test of time and the original fears of increased incidence of thyroid cancer and leukaemia following therapy have been partially discounted but this spectre still hangs over the use of iodine-125 therapy (Editorial 1971, 1972 a, b) and extension of the length of follow up is important from this point of view. With longer periods of surveillance any progressive rise in hypothyroidism will also be detected.

The exquisite simplicity of single dose radioiodine therapy is important but more intricate approaches using iodine-125 are probably justifiable in a limited number of patients. It is conceivable that hypothyroidism could be completely eliminated with the prescription of very small doses of iodine-125 (100 uCi or less per gram of thyroid). What remains to be answered is whether this size of dose would eventually control the disease in all of the patients treated, almost certainly drug therapy either conventional antithyroid drugs or beta adrenergic blockers or both would be required in a very large proportion if not all of the patients.

An alternative approach would be to prescribe a tailored dose to deposit, for example, 3,000 rads to the follicular cell nuclei. This would require accurate measurement of the effective half-life of iodine in each patient and also an accurate estimation of thyroid gland

mass and if possible the percentage of colloid in the gland.

There is another exciting but as yet theoretical method of tailoring the dose for each patient. If an accurate index of decreasing thyroid function existed and it was possible to judge when "normal" thyroid status reached after irradiation it would be theoretically possible to discharge the radionuclide from the thyroid using antithyroid drugs.

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