THE CLINICAL APPLICATION OF RADIOACTIVE IODINE to the DIAGNOSIS AND TREATMENT of THYROID DISEASE, WITH ESPECIAL REFERENCE TO THYROTOXICOSIS

by

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INTRODUCTION

The work described in this thesis has been carried out in Sheffield as a member of a team of physicians, physicists, and radiotherapists who together have been developing and using techniques for the application of radioactive iodine to the diagnosis and treatment of thyroid disease, and for the elucidation of various problems connected with normal and abnormal thyroid physiology, and with the pharmacology of iodine.

This work has been carried out under the overall supervision of Prof. E. J. Wayne, Professor of Pharmacology and Therapeutics in the University of Sheffield. Mr. G. W. Blomfield, Medical Director of the Sheffield National Centre for Radiotherapy, has shared the responsibility for the therapeutic applications of the isotope.

The technical and physical aspects have been carried out by Dr. H. Miller, Chief Physicist, Sheffield National Centre for Radiotherapy, with the assistance of Mr. J. C. Jones, and co-operation with them has been exceedingly close at all stages of the study, and to them is due the credit for the development of some of the physical techniques that have been used to enable this study to be made.

I have been responsible, under the guidance of Prof. E. J. Wayne, for the selection of patients, and the clinical application and interpretation of the results of the use

of radioactive iodine, both in the diagnostic and in the therapeutic fields. In this work I initially was working in co-operation with Dr. J. F. Goodwin from May, 1948 to September 1949, and from June 1950, to June 1951, the clinical aspects were studied with the assistance of Dr. G. Ansell.

The selection, study, and assessment of all patients on whom the tests have been performed, and of all patients treated with the isotope, has been chiefly my responsibility, and the long term study of all patients treated, and of most patients investigated, has been by me at the Endocrine Clinic of Sheffield Royal Infirmary, which I conduct on behalf of Prof. E. J. Wayne.

At various times, communications and demonstrations of aspects of this work have been made to Sections of the Royal Society of Medicine, the British Institute of Radiology, the Medical Research Society, the British Pharmacological Society, and to the Oxford Isotope Techniques Conference held in July 1951, under the auspices of the Atomic Energy Research Establishment, Harwell.

Some of the work described in this thesis has been, or is being, published in the following papers, either by myself or jointly with the above mentioned collaborators:

(1). Macgregor, A.G.
Radioactive iodine in the diagnosis of thyrotoxicosis.
Brit. J. Radiol. 1950, 23,550.

(2). Macgregor, A.G.
The use of radioactive iodine in the diagnosis and

and treatment of thyroid disease..
North Wing (Journal of Sheffield University Medical School) 1950.3.19.

(3). Goodwin, J.F., Macgregor, A.G., Miller, H., and Wayne, E.J.
The use of radioactive iodine in the assessment of thyroid function.
Quart. J. Med. In press.

(4). Blomfield, G.W., Jones, J.C., Macgregor, A.G., Miller, H., and Wayne, E.J.
The treatment of thyrotoxicosis with radioactive iodine.
1. Brit. Med. J. 2,373,1951.
2. Symposium of Oxford Isotope Techniques Conference, 1951, H.M.Stationery Office. In press.

(5). Ansell, G., Macgregor, A.G., Miller, H., and Wayne, E.J.
The value of estimations of plasma radioactive iodine as an index of thyrotoxicosis.
Symposium of Oxford Isotope Techniques Conference, 1951. H.M.Stationery Office. In press.

I should like to take this opportunity to express my gratitude and indebtedness to Prof. E. J. Wayne for permitting me to carry out this work, and for his general guidance and advice during the conduct of the study.

I wish also to thank Dr. H. Miller for his kindness and close co-operation throughout this study of thyroid function in health and disease, for without the help of himself and of his technical assistants, the difficulties inherent in the application of radioactive isotopes to the clinical problems of thyroid disease would have been most formidable.

Finally, I wish to express thanks and appreciation to my wife for her long-suffering patience, understanding and help during the course of this work, and the writing of this thesis.

SECTION I

THE PHYSICAL BASIS OF ISOTOPE STUDIES

The chemical properties of an element depend upon the number of units of positive charge, or protons that are present in the nucleus of the atom. This number is the atomic number of the element, but the nucleus of each atom contains, as well as the protons, a certain number of neutrons. The atomic weight of an element is constituted by the sum of the neutrons and protons. Physical investigation of the elements has shown that some of them exist in forms of different weight, although possessing the same atomic number and identical chemical qualities, and such similar forms are termed isotopes. Some isotopes are stable, these being the common form of the element, but others are unstable, and these are termed radioactive as they emit radiation of various types, termed alpha, beta or gamma according to the physical characteristics of that radiation. There are few naturally occurring radioactive elements, such as radium, but radioactivity can be induced in most common elements by the bombardment methods of modern nuclear physics. Each radioactive isotope has its own physical characteristics, and can be readily distinguished by its own rate of radioactive decay and by the type of radiation produced. But whatever its physical characteristics, it behaves chemically in a fashion identical with the original element. A minute dose of such an isotope can therefore be administered to an animal or man, and its absorption and

subsequent metabolic fate followed by physical methods. It can, moreover, be safely assumed that the behaviour of the stable form of the element is the same as that of the atoms that have been "labelled" with the radioactive isotope. At the same time, the radioactivity of suitable isotopes is so short lived that the dose of radiation to the living tissues into which it is introduced is negligible.

Ordinary iodine, whose atomic number is 53 has an atomic weight of 127, but one of its isotopes has 4 additional neutrons in its nucleus, and has therefore an atomic weight of 131; this isotope is unstable and, accordingly, radioactive. This is the isotope I 131, now commonly used in studies of thyroid function, as it behaves chemically precisely as does iodine, I 127, itself. The disintegration of the isotope is due to the discharge of beta particles, or electrons, from the nucleus, which raises the positive charge on the nucleus to 54 protons, and the electrons surrounding the nucleus then rearrange themselves. The energy expended in the nuclear change is emitted as gamma radiation, a form of X-Rays. The beta radiation travels about 2.2 mm. only in tissue but it is used to measure the presence of the isotope in fluid samples - urine and blood, whereas the more penetrating gamma radiation is used to detect the isotope in the thyroid gland when a Geiger counter is placed above the patient's neck. After the isotope has disintegrated it no longer behaves as does iodine, as in the process of

disintegration, it acquires the additional proton on its nucleus and becomes, in fact, another element, xenon.

The instrument at present used to detect the presence of a given radioactive isotope is a Geiger Counter, a sensitive device that records the ionisation produced each time radiation from a decaying atom of the isotope strikes the counter. Special electronic scaling circuits are used to count the number of such disintegrations, a number proportional to the amount of the isotope present. Such Geiger counters vary in their sensitivity, and their collimation, according to their particular design and physical characteristics. Some are designed to count fluid samples, some to count radiations emitted from an isotope in a particular organ, and others are so designed that the area from which ionisations are counted is strictly limited so that the precise location of the isotope may be defined.

Soon after radioactive isotopes of iodine became available they were applied to the investigation of thyroid physiology, and subsequently have been widely used in the study and treatment of disease of the thyroid gland. The first investigations were made with I 128 by Hertz, Roberts, and Evans, (1938) but its short half life of only 25 minutes limited its use. Hamilton and Soley, (1939) used I 131, with a half life of eight days, and this has now become the standard agent used to study the pharmacological properties of iodine, the physiological role of the thyroid gland in human metabolism, and its behaviour when affected

by disease.

SECTION II

THE PHYSIOLOGICAL PRINCIPLES OF THE USE OF RADIOACTIVE IODINE

It is fortunate from the point of view of investigators with radioactive iodine that the thyroid gland is the most readily accessible and easily localised of all endocrine glands, for all observations upon it are correspondingly more easily performed than would be the case if it were situated as deeply as, for example, the suprarenal glands.

It has long been known that the gland is intimately concerned with the metabolism of iodine, and, although it weighs only about 0.05 per cent. of the total body weight, it contains over 20 per cent. of the iodine present in the whole body. (Best and Taylor, 1945). With radioactive iodine it has become possible to investigate the way in which the gland deals with any iodine presented to it by the circulation. The active principle of the thyroid hormone, thyroxine, contains iodine in its molecular structure. Much of the effort of the gland is directed towards introducing inorganic iodide, reaching it in the blood stream, into the benzene nucleus and thus producing thyroxine, which it then combines with a complex protein molecule to give thyroglobulin. The various steps of this process can be followed with the isotope and the speed with which they are accomplished, and the amount of the finished product, can be measured and used as an index to the grade of thyroid activity.

When radioactive iodine is administered, whether orally

or intravenously, a large part of the dose is collected by the thyroid gland, which has the capacity of concentrating inorganic iodine to 10,000 times the blood level of circulating iodine, (Hamilton, 1942). That partof the iodine which does not enter the thyroid gland is excreted by the kidneys at a rate which, in the absence of renal disease, is fairly constant, and which depends upon the concentration of circulating iodine. In some cases the radioactive iodine collected in the thyroid gland and excreted in the urine only accounts for 85 to 90 per cent of the total dose administered: the remainder is mainly distributed throughout other body tissues, some is excreted in the faeces, expired air, and sweat, (Kelsey, Haines, and Keating, 1949). There is, therefore, a constant state of competition between the thyroid gland and the kidneys to collect circulating iodine and any increase or decrease in thyroid activity is reflected in diminished or increased amounts excreted in the urine.

It is accordingly possible, by a study of the blood, urine, and thyroid gland content of radioactive iodine to study closely the fundamental processes that underly thyroid function, without the administration of quantities of iodine that might have a non-physiological, or a pharmacological action, upon the various phases of thyroid function.

Using the technique much information regarding thyroid physiology has been obtained, some of it new and much of it in confirmation of what had already been discovered by normal biochemical techniques.

The various steps in the cycle of iodine metabolism have been elucidated and the physiological aspects and inferences have been ably reviewed by Raben and Astwood (1949) and Rawson (1949) and more recently in this country Bryant, Corbett, Honour, and Pochin (1950) and Myant and Pochin (1950) have contributed new and fundamental information on the physiology of iodine and thyroxine metabolism.

These basic physiological studies provide an excellent example of the way in which radioactive isotopes can be used as a fundamental tool for medical research, and this is their most valuable role. This thesis is devoted to a discussion of the diagnostic and therapeutic applications of one particular isotope, applications made possible because of preliminary detailed physiological studies. It must never be forgotten that despite its very considerable value as a diagnostic and therapeutic agent, the most valuable role of radioactive iodine is as a tool enabling us to probe yet further into the physiology of the thyroid gland, and to investigate the precise abnormalities of function that exist in various pathological conditions of the gland. It is by such basic and fundamental studies with the isotope that that knowledge will be gained which will aid us to a closer understanding of the

mechanisms of disease, and thereby to a closer realisation of the means by which those diseases can be prevented or cured in their early stages.

SECTION III

THE DIAGNOSTIC APPLICATIONS OF RADIOACTIVE IODINE

(1). The Diagnosis of thyrotoxicosis

It was a natural sequel to the initial researches into thyroid physiology briefly described above, that attempts were made at an early stage to use the metabolism of radioactive iodine as a test of thyroid function in order to provide a clinically applicable diagnostic test. Hertz, Roberts, and Evans in 1938, using I 128 with a half life of only 25 minutes were able to observe fundamental differences in thyroid function in thyrotoxic, as compared with normal individuals. This isotope was not, however, suitable for clinical use because of its short half life, and only with the isotope I 131 becoming available did practical diagnostic tests of thyroid function become a real possibility.

Muchwork has been carried out in various centres in an attempt to evolve with radioactive iodine a reliable test of thyroid function, and workers have approached the problem in different ways. The rate and extent of uptake of radioactive iodine by the thyroid gland has been fully investigated by several groups of workers since Hamilton and Soley (1940) made the early observations on patients with various types of goitre. Keating, Wang, Luellen, Williams, Power, and McConahey, (1949) have assessed the value of such in vivo measurement of the quantity of radioactive iodine in the

thyroid gland. Werner, Quimby, and Schmidt (1949a) defined the range of uptake in normal individuals, and the deviations which occur in thyroid disease, and Werner, Hamilton, Leifer, and Goodwin (1950) reviewed their experiences of 1,400 estimations of thyroid gland uptake of radioactive iodine. They concluded that the thyroid gland uptake of the isotope after 24 hours was a suitable technique for diagnostic purposes and at the Presbyterian Hospital in New York this test is being substituted for the basal metabolic rate determination as the initial routine laboratory screening procedure in the diagnosis of thyroid disorder.

Studies of the urinary excretion of the isotope have also been widely used as an indirect index of thyroid function. Keating, Power, Berkson, and Haines (1947) and Skanse (1949) made very careful analyses of the results obtainable by this method, and some workers in this country, (Arnott, Emery, Fraser, and Hobson, 1949; Mason and Oliver, 1949) have felt that it provides a useful and accurate test for the diagnosis of thyrotoxicosis, especially if the urinary output during the 48 hours after administration of the isotope is subdivided into shorter periods. All workers agree, however, that the urinary excretion test alone does not differentiate clearly the normal from the abnormal in that important intermediate group of cases in which the diagnosis of thyrotoxicosis is clinically difficult and doubtful, that group, in fact, for which there is the most need for a reliable objective index

of thyroid function. McArthur, Rawson, Fluharty, and Means (1948) go so far as to state that a low urinary excretion of the isotope is a useful and valuable indication of thyrotoxicosis, but that intermediate degrees of excretion are of no diagnostic help.

In an attempt to obtain more useful and accurate guidance to the state of thyroid function, Keating, Wang, Luellen, Williams, Power, and McConahey, (1949) have developed the conception of an iodide accumulation rate of the thyroid gland, as distinct from the absolute amount of iodide absorbed by the gland. After 3 years experience of the radioactive tracer technique in 790 patients this group of workers at the Mayo Clinic (Keating, Haines, Power, and Williams, 1950) felt that measurement of radioactive iodine accumulation by any one of several means was a highly efficient diagnostic tool for separating more than 90% of cases of exophthalmic goitre from normals, but that it was less satisfactory with regard to the presence or absence of hyperthyroidism in cases of adenomatous goitre.

The same workers, and Myant, Pochin, and Goldie (1949) have also suggested a thyroid clearance rate of plasma iodide analogous to the more familiar renal clearance rate of urea. The rate at which iodide isbeing absorbed by the thyroid gland is deduced from the curve of thyroid uptake obtained by external counting by a Geiger counter over the gland, the

plasma concentration of radioactive iodine being determined simultaneously. Pochin (1950) has suggested that a simple clinical test that correlates closely with thyroid clearance of plasma iodine is the ratio of the counts obtained, one hour after the dose, over the thyroid gland to the counts obtainable at the same time over the thigh.

Foote and Maclagan (1951) have modified this latter test and have devised the "thigh-neck clearance", being the increase in neck counts per hour, divided by the maximum count obtained over the patient's thigh. They have claimed that this test is suitable for routine use as a diagnostic procedure.

Other studies of thyroid function have been carried out to determine whether or not uptake into the gland within the first few hours only is a valid diagnostic test. Miller, Dailey, Holmes, Alexander, and Sheline (1951) found that the initial rate of radioactive iodine uptake correlated well with the clinical evaluation of thyroid function, and Greer (1951) has demonstrated that uptakes at six and eight hours correlate quite satisfactorily with 24 hour uptakes.

The purpose of observations such as these is to determine the validity of tests which minimise the time for which the patient requires to be present for the test.

The "accumulation rate" of Keating and his associates, an accurate and sensitive index of thyroid function, has the disadvantage that it does require in vivo observations over

one or two days. Astwood and Stanley (1947) have devised a more empirical method of comparing the increase in thyroid radioactive iodine with time. They term this the accumulation gradient, and being a value obtained by plotting counting rate against the square root of time, they obtain a value in a few hours only. Keating, Haines, Power and Williams (1950) emphasise, however, that being an index expressed in arbitrary units dependent on many potentially variable factors, it is difficult for the values obtained for "accumulation gradient" in one laboratory to be compared with those observed elsewhere.

It has been shown by Vanderlaan and Vanderlaan (1947) that the administration of 1 - methyl 2 - mercaptoimidazole prevents the conversion of inorganic iodide to organic form and Stanley and Astwood (1948) have utilised this fact. They administer radioactive iodine within a few hours of a dose of 100 mg. of this drug and then measure gland uptake of the isotope. They claim that this measurement of thyroid iodide content, as contrasted with measurement of total iodine content, gives a very useful separation of hyperthyroid from enthyroid individuals.

Haigh and Reiss (1950) utilise a more complex test in which urinary output and initial gland uptake are combined to give a factor which is said to have diagnostic value, and Fryers (1951) has found that the product of the rate of accumulation at 4 hours with the absolute amount accumulated in the gland at that time gives a factor which discriminates

cleanly between thyrotoxic and normal individuals.

Once again, however, these tests require observations over at least a day, and any test which can be completed within a few hours is obviously preferable to a test which requires repeated or prolonged attendance.

All the tests mentioned so far have been measures of the capacity of the thyroid gland to concentrate iodide presented to it by the circulation, but this is only one aspect of thyroid function, and it does not measure at all the release of thyroid hormone from the gland - nor its utilisation by the body tissues. The effect of the latter aspect is the function chiefly measured by the basal metabolic rate estimation, and the former function is measured by the chemical techniques of protein-bound iodine estimations. This represents a standard method of assessing thyroid function, and Rapport and Curtis (1950) claim it to be the most reliable objective index of thyroid function. It has always been, however, a difficult, laborious, and impracticable biochemical procedure, and, as such, unsuitable for routine application. The newer and simpler technique of Barker, Humphrey, and Soley (1951) may make it an estimation of more general applicability, but the adaptation of the isotope technique to this facet of thyroid function has already been a valuable addition to the diagnostic armamentarium of the physician.

It is generally agreed that it is the presence of increased

amounts of circulating thyroid hormone which is responsible for the clinical manifestations of thyrotoxicosis, and any method of detecting such an increase should be a useful index of thyroid function. Furthermore, the work of Taurog and Chaikoff (1948) and Leblond and Gross (1949) in animals has shown fairly conclusively that circulating thyroid hormone is probably thyroxine itslef, and Rosenberg (1951) came to the same conclusion in man. Taurog and Chaikoff, (1947) using a butyl alcohol extraction method for separating out the thyroxine, diiodotyrosine, and inorganic iodine fractions of the total plasma activity due to circulating radioactive iodine came to the conclusion that about 90% of circulating iodine is in the form of thyroxine. Leblond and Sue (1941) have shown that the diiodotyrosine fraction of the protein-bound iodine is rapidly metabolised and broken down in plasma to form inorganic iodide, and therefore an estimation of the protein-bound iodine, separated from the non-protein bound fraction by precipitation with trichloracetic acid is essentially a measure of the thyroxine content of the plasma. The use of radioactive iodine enables circulating thyroxine in the blood to be easily "labelled" so that it becomes readily detectable and measurable. This estimation would be expected to give valuable diagnostic help, and it is, moreover, an estimation that can be made relatively simply.

McConaghey, K eating and Power (1949) have studied fully the behaviour of radioactive iodine in the blood and found,

as was to be expected, that higher levels of protein-bound radioactive iodine were present in thyrotoxic than in normal individuals, and similar findings were noted after 24 hours by Freedberg, Ureles, and Hertz (1949) and by Williams, Jaffe, and Bernstein (1949). Clark, Moe, and Adams (1949) and subsequently Sheline and Clark (1950), have utilised the speed of conversion of radioactive iodine into protein-bound form as a diagnostic test, and they found that thyrotoxic patients had more than 50% of the circulating plasma radioactive iodine in protein-bound form after 24 hours. This diagnostic test of thyroid function, using the isotope technique, has been found to correlate fairly well with chemical estimation of the protein-bound iodine (Sheline, Moore, Kappas, and Clark, 1951) and it is, of course, a very much more simply performed estimation.

Present investigation

It can be seen, therefore, from the diversity of tests that have been described, that although much work has been devoted to clarify the physiological behaviour of the thyroid gland and of thyroxine, there has been little agreement as to the most reliable and convenient way in which radioactive iodine may be used in the diagnosis of thyroid disease. There has always been a tendency for each group of workers to concentrate on the test which they have devised without making any especial effort to compare the tests with each other and so be in a position

to assess their relative merits and value.

Accordingly, the purpose of the studies undertaken in Sheffield has been to assess with a variety of different measures of thyroid function, a group of patients of all grades of thyroid activity. It was realised that only by such a composite study would it be possible to devise and select for routine diagnostic purposes a test which was at the same time a valuable and reliable screening test for the diagnosis of thyrotoxicosis while being also convenient for both patient and physician. The emphasis was, therefore, on the investigation of patients in whom there was a possibility of hyperthyroidism. The differentiation of normal from thyrotoxic gland function, is, moreover the aspect of thyroid physiology which most frequently gives rise to clinical difficulty.

Part "A" - Definition of Standards

This covered the period from April 1948 through June 1950, and during this period physical techniques were devised, perfected, and applied to the investigation of patients. The purpose of this study was to define the ranges of normality for a selected group of radioactive iodine tests of thyroid function, and to discover the deviations from normal that could be anticipated in association with hypothyroidism and hyperthyroid states.

From this study it was hoped that the most promising tests could be selected and applied to the investigation of a further group of patients.

Part "B" - General Application of Diagnostic Techniques.

This comprised the investigation of a further group of cases who were not all so fully investigated clinically and in whom an attempt was made to apply routinely certain of the tests of thyroid function which had been found in Study "A" to be the most reliable and helpful.

Part "A" - Definition of Standards

The group of patients studied contained patients of all grades of thyroid function, and it was decided, for the reasons already mentioned to carry out on each individual all those investigations which promised to be of diagnostic help, and initially a series of normal and thyrotoxic subjects was fully investigated. The severity of thyrotoxicosis was assessed using all the conventional clinical and laboratory methods that were available, and assigning to each patient a figure from one to four to indicate the degree of abnormality. Having thus obtained a standard for normal and thyrotoxic subjects the results were applied to a difficult intermediate group, the composition of which is discussed below.

All the patients studied comprised a total of 94 individuals of whom 16 were completely normal as regards thyroid function, and had no evidence of any other endocrine disturbance. Forty four patients were diagnosed as having primary thyrotoxicosis or toxic adenomata, the groups being composed of cases of all grades of toxicity, from mild,

borderline thyrotoxicosis, (Grade 1) to thyrotoxicosis of the most severe degree (Grade 4).

These gradings are essentially arbitrary in nature and no high degree of accuracy is claimed for these figures. They do, however, represent the final average opinion of at least three observers each of whom took into account every clinical aspect of the case. Cases in Grade 1 had least evidence of thyrotoxicosis, and some cases were only so classified after therapeutic trial with methyl thiouracil. The diagnosis was immediately obvious in cases in Grade 2, and the more severely affected patients were classified in Grades 3 and 4.

The "intermediate group" consisted of 30 patients in whom there was found no clinical evidence of toxicity after full and often prolonged study. Twenty five patients in this group presented features of past or present thyroid disorder, such as non-toxic goitres, simple adenomata, and patients with successfully treated or burnt out thyrotoxicosis. There were also five patients who presented clinically with symptoms which are often seen in thyrotoxicosis. They, however, had no thyroid enlargement and an anxiety state was eventually diagnosed in each case as, after further observation, features became apparent which were inconsistent with a definite diagnosis of thyrotoxicosis.

The patients included in the intermediate group are therefore those who usually present the most clinical difficulties with regard to diagnosis. There was moreover, the additional factor that in the Sheffield area there is a

high incidence of non-toxic goitre with slight enlargement of the thyroid gland, and, accordingly, the clinical difficulties are thereby slightly increased when there is the concurrence of symptoms that may or may not be due to true thyrotoxicosis.

Four cases of myxoedema were also included in this study.

During the course of the study, many cases of thyroid carcinoma were also studied, but rather less fully, and the results are not included here, but, in some cases, discussed later. The results in no way conflict, as regards thyroid function as a whole, with the general statements that will be made later.

METHOD OF INVESTIGATION

All patients were admitted to hospital for in-patient care and investigation. The history was taken and physical examination carried out by three observers independently and the final diagnosis and grading were discussed. All cases except the normal group were followed for long periods in the out patient department, and in toxic cases the results of therapy were taken into account. It must be emphasised that the final decision as to whether an individual was clinically thyrotoxic or not was only taken after the most thorough sifting of clinical evidence that could be devised. In no case were any of the observations using radioactive iodine taken into consideration in making

the final classification.

The collection of urine and blood specimens was very carefully supervised, as urinary samples especially tend to get mislaid if close watch is not kept on nursing staff.

Patients were fasting on the morning of test, and the tracer dose of 25 microcuries of radioactive iodine was administered orally and the container repeatedly washed out with water and subsequently monitored to ensure that all the dose was, in fact, taken. Patients were allowed to have lunch on the day of test, usually about 3 hours after the tracer dose had been given, while observations of the uptake of the isotope by the thyroid gland were being made. All urine specimens passed were collected, and subsequently aliquot samples of 10 ml. of each specimen were examined for their content of radioactive iodine.

At first estimations of blood activity were made on 0.5 ml. samples, but this was found to be unsatisfactory because separate estimations of the protein-bound concentration could not be made with the technique used. All estimations of plasma concentration included in this thesis were made on 20 ml. samples of blood withdrawn into a heparinised syringe. Samples of blood were usually taken at 1 hour, 3 hours, and 48 hours after ingestion of the radioactive iodine.

Figure 1. Method of application of shielded Geiger counter to measure gland content of radioactive iodine. (see text.)

COUNTING TECHNIQUE USED

The amount of the active material taken up in the gland was assessed by Dr. H. Miller, Chief Physicist to the Sheffield National Centre for Radiotherapy, by means of a calibrated gamma ray counter housed in a substantial lead shield. Lead diaphragms were introduced to produce a suitable collimation. The whole counter with the associated preamplifier unit was mounted on the arm of a modified mobile X-ray unit stand so that it could be conveniently adjusted with respect to the patient. (Figure 1).

For calibration of the counter, measurements were made using a solution of radioactive iodine in a small glass phial, and by using glass models of the thyroid gland filled with an active solution.

In order to reduce the effect of absorption in the tissues a filter was introduced in front of the counter. This consisted of 1 mm. thickness of lead supported on a thin brass plate. The filter reduced to a negligible amount the effect of the soft component of the gamma radiation of the radio-active iodine. It also had the effect of reducing to a small value the scattered radiation as measured by the counter.

The effective radiation centre of the gland in the patient was obtained from a plot of the reciprocal of the square root of the counting rate against distance. In the majority of cases this effective radiation centre was approximately 2 cms. below the skin over the thyroid isthmus.

In the build up curves in the gland, therefore, the calibration of the counter was deduced by measuring the concentrated source of radioactive iodine in its glass phial and this calibration was used after having deduced the effective radiating centre of the gland in question by the above method.

The effect of the 1 mm. of lead filtration in reducing the magnitude of the scattered radiation may be seen by comparing the method adopted by Myant, Honour, and Pochin, (1949). In their technique, using unfiltered radiation, the body tissues outside the immediate neighbourhood of the thyroid gland are screened from the counter but a large correction of the order of 21% for scattered radiation is necessary. In the Sheffield technique, devised by Dr. H. Miller, the filter used caused a reduction in the counting rate to a value of 60% of the unfiltered rate.

In plotting build up curves the usual practice was to count for a total of six minutes. This was divided into two periods of two minutes with the counter axis at a distance of 27 cms. from the skin over the isthmus, while between these counts one count was taken with a block of lead supported above the isthmus. The lead was 3.8 cms. thick and effectively cut out the radiation from the underlying gland leaving a background which fell slowly with time as the active material in the rest of the body was distributed and eliminated. The lead block was large enough in area

to eliminate radiation from the gland itself but it also cut out some radiation from the normal tissues of the neck. Since at peak take up, however, the blood concentration was generally less than 1% per litre of plasma, the amount of activity in the normal tissues of the neck underlying the lead block was certainly less than 0.5% of the ingested dose and was considered negligible. This was confirmed by the observed small counting rate over the thigh at a place where the cross section was roughly the same as the neck.

The actual counting rate for a dose of 20 μc and for a 50% uptake under the Sheffield conditions was approximately 350 counts per minute. The coefficient of variation (i.e. the standard deviation expressed as a percentage of the mean) for a particular point on the curve was therefore, generally less than 3%. It is believed that the figures of peak uptake are correct to within 5% which is sufficiently accurate for the purposes of this thesis.

Liquid samples were counted in the liquid counter devised by Veall, (1948). As a standard a thousand fold dilution of the stock solution was used. All liquids placed in the counter had a few milligrams per litre of sodium iodide introduced as carrier.

Urine concentrations over the first 24 hours were adequate to give a small statistical error in counts of 5 minutes and the error in estimating the total urine output

was influenced mainly by the adequacy of urine collection. If no sample was lost the estimates of urine output were expected to be correct to within 5%. No figures are quoted when a urine sample containing an appreciable activity was lost.

Blood samples were taken into heparanised bottles and spun and the plasma was introduced into the counter directly. A blood plasma concentration of 1% per litre gave with the usual tracer drink of 25 μc. about 25 cts. per min. Counts of at least 10 minutes were made on these samples. The background count was around 12 counts per min. The statistical error in these results is much greater than in the other measurements, but it is estimated by Dr. H. Miller that the coefficient of variation of the individual blood measurements is less than 10% except for concentrations less than 0.4% of the ingested dose per litre.

The estimation of the protein-bound iodine in the plasma was carried out by the technique used by Chaikoff, Taurog, and Reinhardt, (1947), as follows: 10 ml. of the plasma were precipitated with 30 ml. of 10% trichloracetic acid. This was centrifuged and the supernatant liquid poured off. The precipitate was then shaken with a further 30 ml. of trichloracetic acid and the whole cnetrifuged again. After a repetition of this last procedure the precipitate was dissolved in 2N NaOH. and its activity estimated. It was generally possible to dissolve the precipitated proteins

from 8 ml. of plasma in 10 ml of NaOH Counts on protein-bound speciments were normally carried out for at least 15 minutes and were subject to somewhat greater errors than on plasma specimens.

RADIATION HAZARD TO PATIENTS

The use of radioactive isotopes exposes both patients and workers with the isotopes to a certain amount of radiation, and it is important to consider whether or not any adverse effect is likely to follow their use.

It is essential that the dose of the isotope used for diagnostic tests be kept to a minimal level, but rather different considerations apply for such tests to those which are applicable to patients undergoing treatment with large doses of the isotope. The possible hazards of such therapy are considered in the Therapeutic section of this thesis.

It is recognised that in the use of doses of radio-active iodine of the order of 25 - 30 microcuries the dose of ionising radiation given to the thyroid gland itself is not negligible though the dose given to the rest of the body may be considered so. (Outside the thyroid this dose is everywhere less than 0.3 roentgen). If the uptake in the gland is 50% and the rate of biological elimination has a half life of 8 days the dose given to a gland of normal size is approximately 35 r following a tracer drink of 25 μc In Sheffield the doses given to the glands of the patients

have varied widely over a range of roughly 10 r to 100 r.

The International Recommendations on Radiological Protection recently issued by the International Commission of Radiological Protection (1951) state that the maximum permissible dose received by radiation workers exposed to external radiation should be 0.3 r/week, even when the irradiation is confined to a particular organ or tissue. It is not known how far doses in the tolerance region can be considered as cumulative, and whether it is legitimate for example, to consider a dose of 15 r in any one year on a limited volume of tissue as equivalent in radiation danger to 0.3 r per week over 50 weeks.

The International Commission on Radiological Protection does not make firm recommendations regarding the maximum permissible exposure to internal radiation. For occupational exposure a maximum permissible amount of radioactive iodine in the body is 0.3 microcuries as this would give a dose rate in the gland of 0.3 r per week.

In order to minimise the necessary dose, Dr. H. Miller in Sheffield has undertaken experimental work designed to give increased sensitivity to measurements of plasma protein-bound iodine samples. In the meanwhile, however, and with the equipment at present available, it was felt that tests on normal people should be made only once and the "Normal" group in this series is as small as could give reasonably representative figures.

It has been considered justifiable to use 30 microcuries in cases where there are reasonable grounds for suspecting thyroid disorder, but the tests have only rarely been repeated on a particular patient in less than 1 year except where radioactive iodine therapy has been intended to follow the investigation.

The practice of other workers has varied considerably as to the dose considered reasonable for diagnostic tests of this type, though some work has suggested that tracer drinks should not normally be greater than 10μc (Arnott, Emery, Fraser, and Hobson, 1949; Tait, Cook, and Worsnop, 1951). This would give a dose of about 15 r which, averaged over 1 year, is about the recognised maximum permissible dose for occupational exposure.

It has frequently been pointed out that radiation doses of the same order as those given in these tests are given routinely to limited regions of the body in many X-ray diagnostic techniques. This is especially true of the skin in normal screening procedures, (Martin, 1947 ; Braestrup 1942) The skin dose of radiation following an average barium meal examination is 45 r. The effects of such occasional exposures of this magnitude in normal diagnostic work of this kind have not so far been considered as of a serious nature. Although the lack of comment upon such exposures by diagnostic radiologists does not justify the procedure if there is an appreciable risk, it has at least

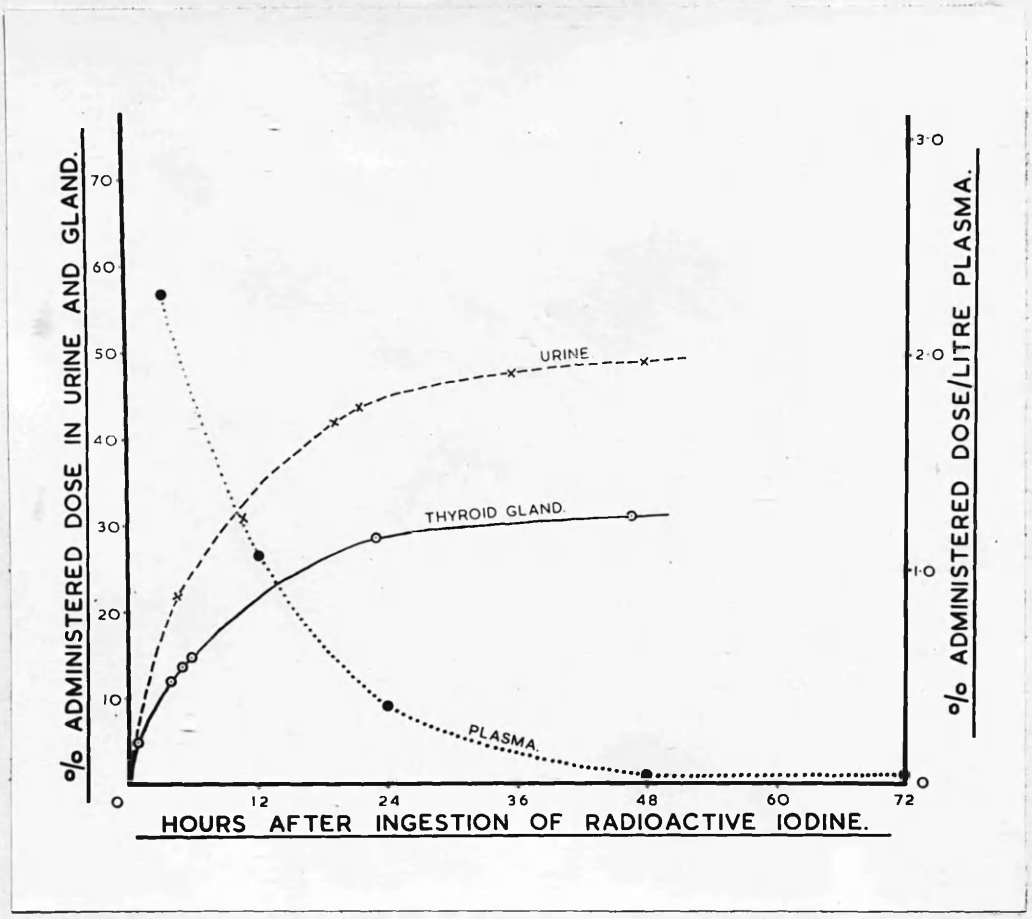

Figure 2. Curves showing the radioactivity present in the thyroid gland, urine, and plasma of a normal person after injection of radioactive iodine.

never been convincingly demonstrated that such exposures have ever been followed by any detrimental effects.

RESULTS

As has already been outlined under the section dealing with the physiological background of the use of radioactive isotopes, it was early found by other workers that the thyrotoxic gland had a very much greater avidity for iodine that the normal gland, and consequently the curve of gland activity when plotted against time was seen to vary very considerably between the different types of gland function. This alteration in the capacity of the gland to concentrate iodine has an effect on the curve of blood activity of radioactive iodine, and this latter curve is also affected because the thyrotoxic gland also turns out very appreciable quantities of thyroxine which, after the administration of the isotope, becomes radioactive and so readily detectable.

The curves in typical normal and typical thyrotoxic gland function are contrasted in Figures 2 and 3, and the blood curves are considered separately in Figure 4.

In normal gland function (Figure 2) the iodine is steadily concentrated by the thyroid gland, the balance being progressively excreted by the kidney. Myant, Pochin, and Goldie (1949) have shown clearly that the renal excretion rate of iodine is proportional to the plasma concentration of radioactive iodine, and furthermore, that

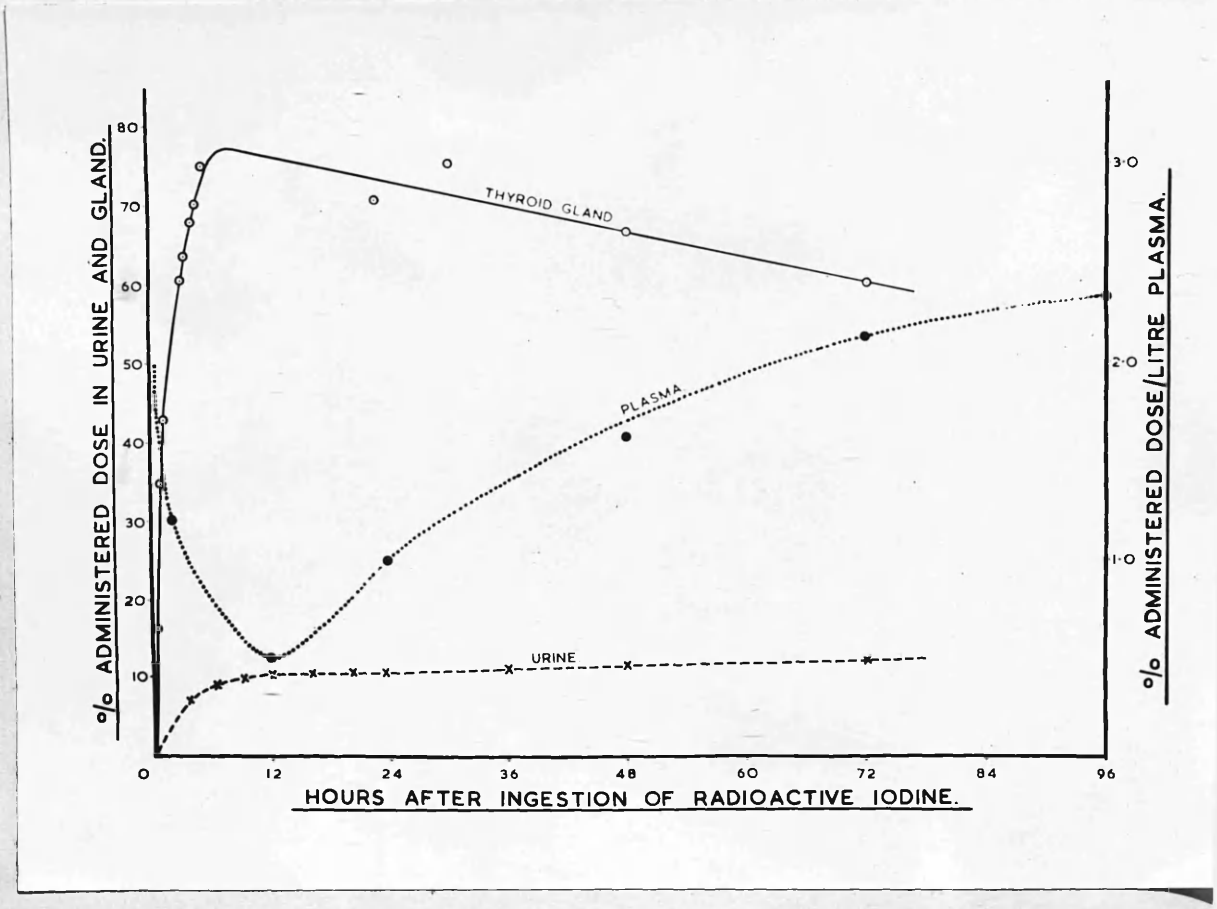

Figure 3. Curves showing the radioactivity present in the thyroid gland, urine, and plasma of a thyrotoxic patient after the injection of radioactive iodine.

the renal clearance rate for plasma radioiodide has the same value of about 30 ml. per minute both in normal and in thyrotoxic subjects. Any variation of thyroid clearance rate, is, therefore reflected in smaller or larger amounts of radioactive iodine being excreted in the urine. In the great majority of normal persons a greater amount of the isotope is excreted in the urine in the first day than is absorbed into the thyroid gland. As will be seen from the detailed results in Part "A" of this Section, most normal persons concentrate between 30% and 55% of the dose in the thyroid in the first 24 hours and excrete over 35% of it. Furthermore, the gland absorption is gradual, and not complete until at least 24 hours, and the curve may rise after that time.

In a thyrotoxic patient, on the other hand, there is a very much higher and more rapid gland uptake, usually exceeding 60%, and conversely a low urinary excretion. There is also, characteristically, a progressive fall in the thyroid activity after the peak point of the curve, a fall that is due to the release from the gland of the radioactive iodine that has become bound into thyroxine, and, as such, discharged into the circulation. In Figure 3, the corresponding blood curve is superimposed onto the other curves of gland and urine activity, and it can be seen that the secondary rise in plasma activity corresponds with the fall in gland activity.

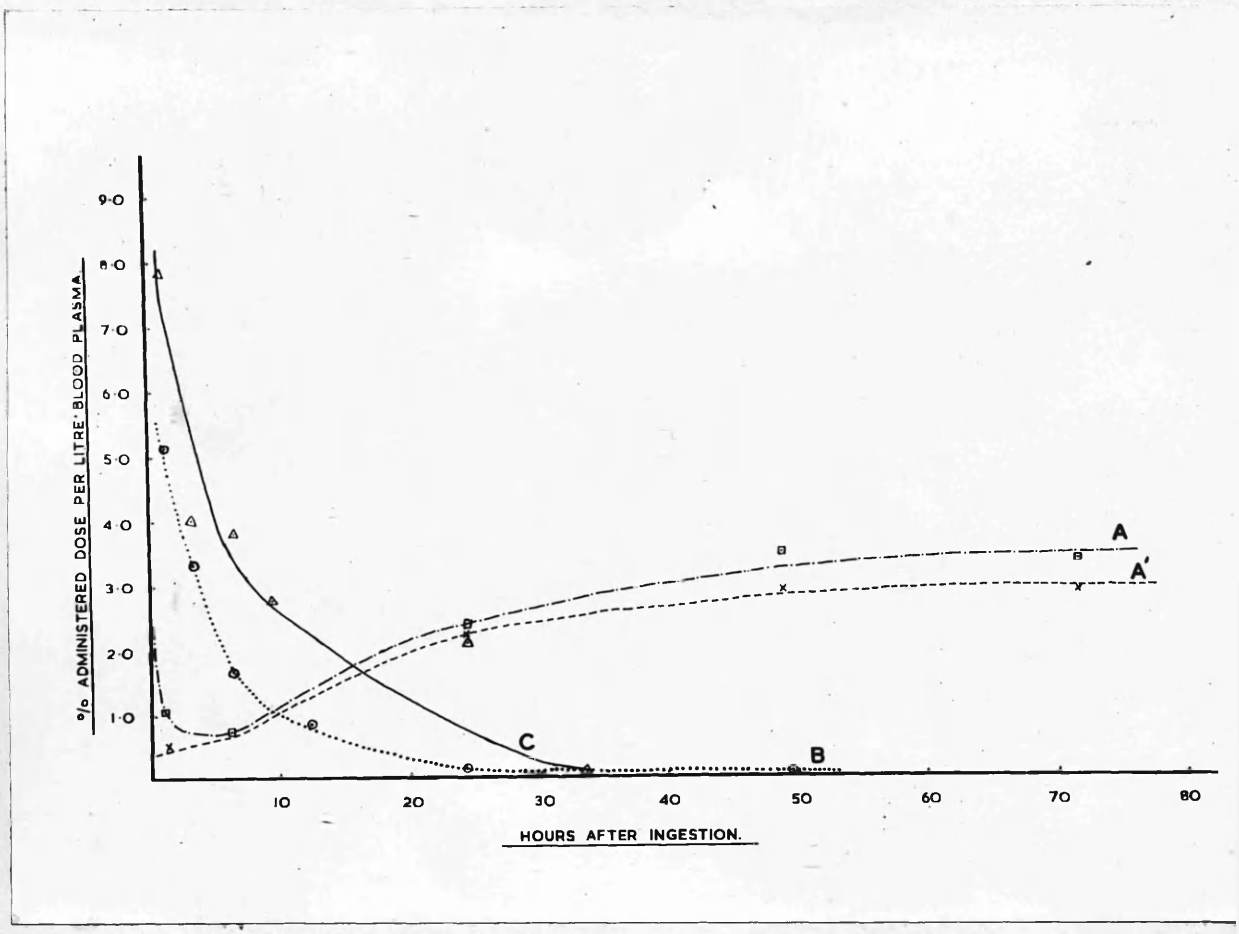

Figure 4. Curves showing plasma activity in selected typical cases after administration of radioactive iodine.

A. Total plasma activity, thyrotoxicosis.

A'. Plasma protein-bound activity, thyrotoxicosis.

B. Total plasma activity, normal individual.

C. Total plasma activity, myxoedema.

The typical curves of blood activity in myxoedema, normal, and thyrotoxic gland function are compared in Figure 4. After the initial rise in plasma concentration following upon absorption of the radioactive iodine, there is a fall of concentration, and this reflects the disappearance of radioactive iodine as iodide from the blood into the thyroid gland, urine and other sites of disposal. The rate of this disappearance of radioactive iodine from the blood reflects changes in thyroid function, being more rapid in thyrotoxicosis than in normal subjects, and conversely, less rapid in hypothyroidism.

Blood estimations during this phase are of definite diagnostic value, and the suggestion of Myant and Pochin (1949) that the isolated observation of plasma activity at 2 hours after administration of radioactive iodine is a valuable test is also based on utilising the fact that the disappearance of iodine from the blood is very rapid in thyrotoxicosis. They noted that the plasma activity in normal persons was at this time always more than, and in thyrotoxicosis less than 2%, of the administered dose per litre of plasma.

In toxic cases, therefore, a minimal level of plasma activity is reached at an early stage, corresponding to the earlier peak of thyroid absorption, whereas normal function is characterised by a more prolonged and gradual fall in activity.

Table I (cont.)

Ranges and means of results of tests of thyroid function in cases studied in Section I, Part A.

	B.M.R. %	Blood cholesterol mg. %	Gland uptake, %		Time to ½ peak (mins.)	24 hour urinary excretion, %	Thyroid iodide clearance rate ml./min.	48 hour plasma activity, % dose/litre	
			Peak	24 hrs.				Total	Protein-bound
Thyrotoxicosis (33)	-7 to +80	75-275	57-92	54-87	10-145	3-34	30-1780	0.24-5.5	0.13-3.4
	+34	192	78	71	66	13	346	1.56	1.15
Toxic adenoma (11)	0 to +43	140-380	56-76	55-76	20-140	1-34	36-330	0.25-3.07	0-2.45
	+21	220	64	63	96	19	100	1.48	1.17
Thyrotoxicosis + toxic adenoma (44)	----	---	74	69	74	14	297	1.53	1.15

Table I

Ranges and means of results of tests of thyroid function in cases studied in Section I, Part A.

	B.M.R. %	Blood cholesterol mg. %	Gland uptake %		Time to ½ peak (mins.)	24 hour urinary excretion, %	Thyroid iodide clearance rate ml./min.	48 hour plasma activity, % dose/litre	
			Peak	24 hrs.				Total	Protein-bound
Normal (16)	-16 to +13	210-300	21-54	19-53	126-480	20-59	10-46	0-0.64	0
	-2	244	38	37	293	46	24	0.12	0
Intermediate (30)	-27 to +36	140-385	24-69	23-68	108-410	24-61	10-71	0-1.16	0-0.4
	+3.5	248	48	47	215	41	36	0.19	0.05
Normal + Intermediate (46)	---	---	45	44	242	43	32	0.16	0.03
Myxoedema (4)	0 to -42	315-645	4-23	3-22	---	43-56	0.4-34	0.4-0.7	0
	-18	442	12	11		48	13	0.5	0

The next phase of the curve of radioactive iodine concentration in plasma is that which indicates the appearance in the blood of iodine in protein-bound form, probably chiefly as thyroxine. This phase starts much earlier in thyrotoxic individuals than in normal persons, and iodine in protein-found form can occasionally be detected in thyrotoxic individuals at a very early stage, within two or three hours and its continued discharge into the blood is shown by a marked secondary rise in the level of plasma activity. This rise is difficult to detect by present techniques in normal persons; in any case, it is of much less degree, and it is most unusual to find more than a negligible amount of radio-active iodine in protein-bound form present in a normal person before the third or fourth day. It was felt, therefore, that 48 hours would be the best time at which to measure plasma activity, both the total activity and that due to protein-bound iodine. Any activity then present should be due chiefly to protein-bound activity in toxic persons; in normal persons activity should be minimal because by that time the greater part of the administered dose should have been excreted in the urine or held in the thyroid gland from which the output of thyroxine has not yet begun.

The detailed data derived from the study of patients included in Part "A" are presented in Appendices I - V, with full particulars of the results of each test relating to every case. The results in Part "A" are summarised in

KEY TO HISTOGRAMS.

NORMAL, CASE 3. (16 CASES.)

INTERMEDIATE GROUP, CASE 36. (30 CASES.)

- NON TOXIC GOITRE.
- THYROTOXICOSIS IN REMISSION.
- ANXIETY STATE.

ALL CLINICALLY GRADED AS NON TOXIC.

THYROTOXICOSIS OR TOXIC ADENOMA, CASE 56. GRADE 3. (33 CASES OF THYROTOXICOSIS. 11 CASES OF TOXIC ADENOMA.)

GRADE.
1. MILD THYROTOXICOSIS.
2. DEFINITE TOXICITY.
3. MODERATE SEVERITY.
4. MOST SEVERE TOXICITY.

MYXOEDEMA, CASE 97. (4 CASES.)

Explanation of symbols used in Figures 5 - 12. Case numbers refer to numbers in Appendices I - V.

Table I. It was not always possible to carry out satisfactorily all investigations in every case, and when technical faults or inaccuracies in the collection or assessment of samples of blood or urine have made results unreliable they have been omitted.

The distribution of results of the investigations in all patients so tested is also presented in the form of histograms representing the results of patients' basal metabolic rate estimations (Fig.5); thyroid gland uptake of the radioactive iodine at the peak point of the collection of iodine by the gland (Fig.6); and at 24 hours after the dose was administered (Fig.7); the distribution of the times which elapsed until half the peak uptake was reached in each case (Fig.8); the urinary excretion of the isotope in bulked samples covering the first 24 hours (Fig.9); the thyroid clearance rates 2 hours after the dose was given, or at the time when the half peak uptake value was reached by the gland, whichever was the higher (Fig.10); the total plasma activity 48 hours after the dose, (Fig.11); and the plasma activity due to the protein-bound fraction of the 48 hour sample of plasma (Fig.12).

To assist recognition of individual cases so that reference can be made to the Appendices and to other Figures, the symbol representing each case bears the case number of the patient, and, additionally, symbols of thyrotoxic patients carry a figure representing the clinical grade of toxicity.

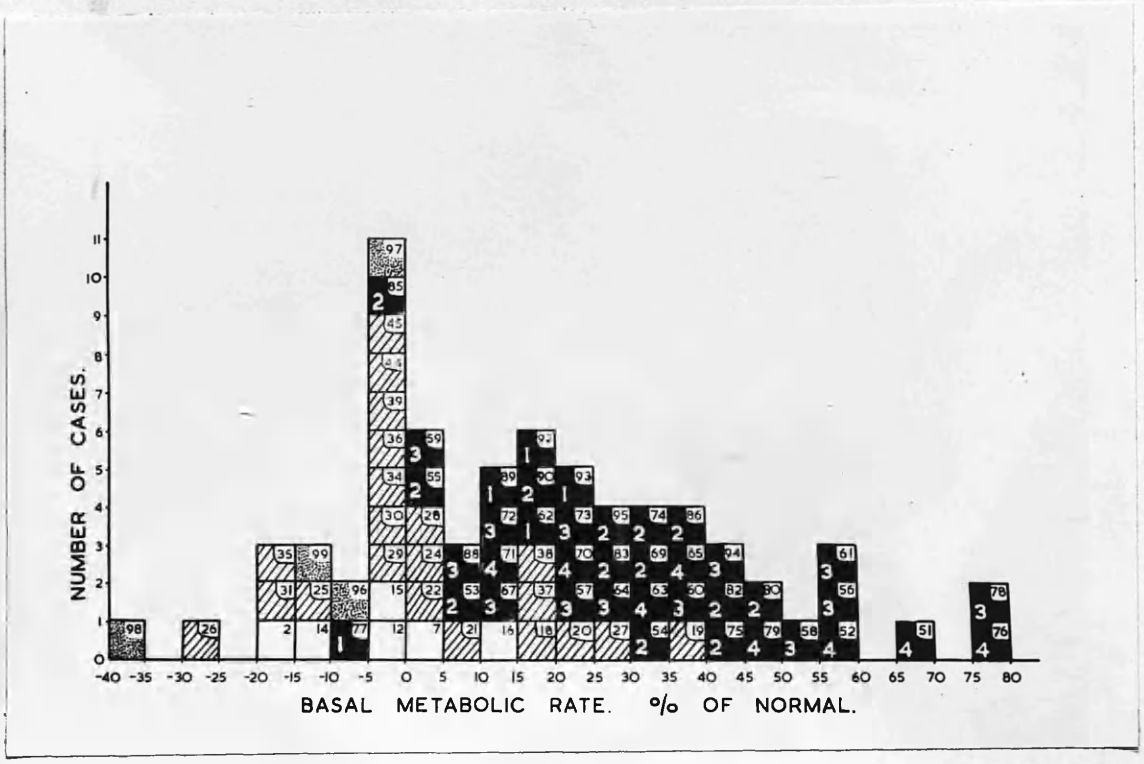

Figure 5. Distribution of results of basal metabolic rate estimations.

BASAL METABOLIC RATE

This estimation, (Fig.5.) was carried out by the Douglas bag method or with a spirometer and the figures quoted are the mean of two or more consistent results. The test was not carried out on all patients included in the normal group (Appendix 1), since we know that with our technique normal individuals may give readings lying between + 20 and - 20%. On this basis 13 thyrotoxic cases out of 39 on which the test was performed, or 33% of the total, had "normal" basal metabolic rates and included in that number are 5 of moderately severe or very severe degrees of toxicity (Cases 59, 67, 71, 72, and 88). In addition three cases of non-toxic goitre or anxiety state had basal metabolic rates in excess of 20%. These figures serve to confirm the generally accepted view that an estimation of the basal metabolic rate is of only doubtful value in differentiating between thyrotoxicosis and other conditions, when there is clinical doubt regarding the diagnosis. It is of interest that Keating, Haines, Power, and Williams, (1950) in their study of the value of radioactive iodine as a diagnostic aid found that, taking the Mayo Foundation standard deviation of the basal metabolic rate at any age as 6.9%, then 51% of their euthyroid patients had values outside the normal range, i.e. outside a range of 13 to -13% (± 20).

Bartels (1950), moreover, found the basal metabolic rate to be below 20% in 3% of a series of 1,000 thyrotoxic patients

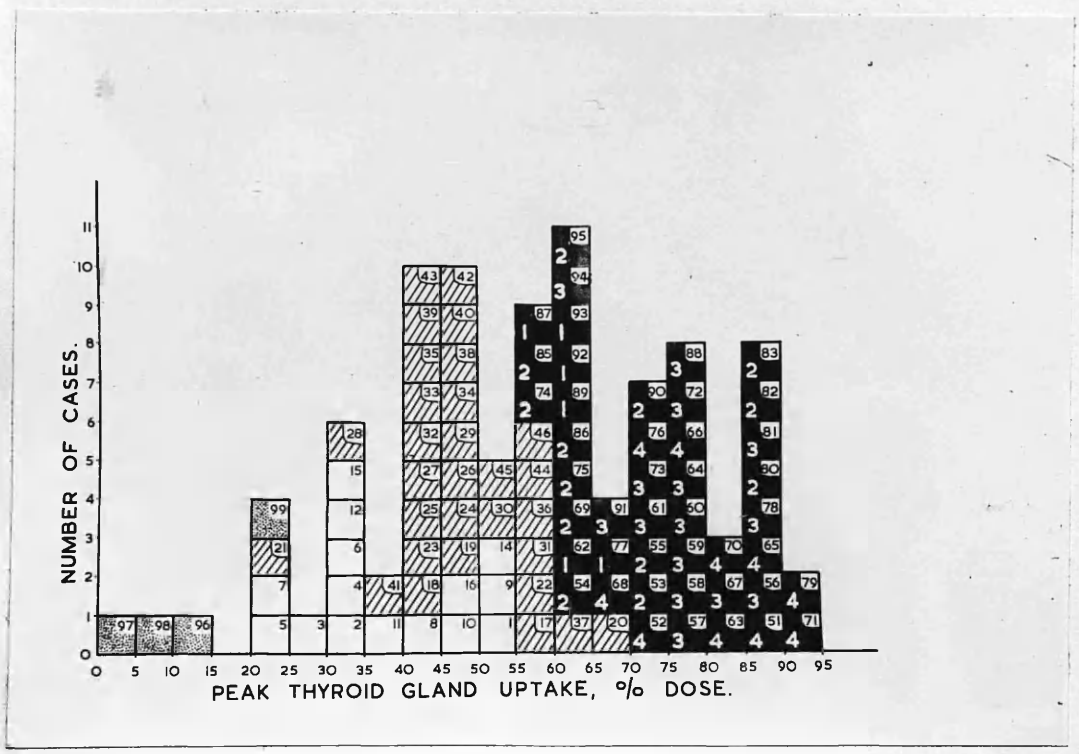

Figure 6. Distribution of estimations of peak thyroid gland uptake of radioactive iodine.

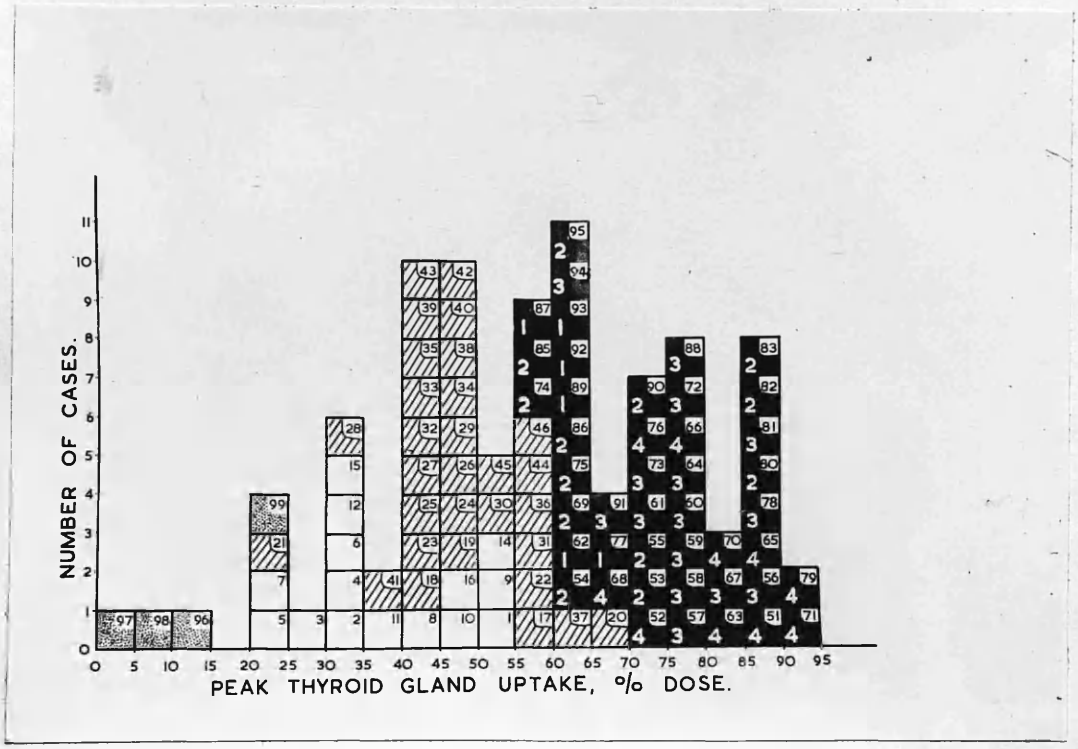

Figure 6. Distribution of estimations of peak thyroid gland uptake of radioactive iodine.

and in some cases a normal basal metabolic rate was found in the presence of severe thyrotoxicosis, a finding which was also noted in this series, (Cases 59, 67, 71, 72, and 88). Furthermore, a raised rate occurs in many conditions other than thyrotoxicosis, such as heart failure and pyrexia, and the presence of an apparently raised rate in some cases of anxiety state is not an uncommon finding.

This figure, therefore, suggests agreement with those who regard an estimation of the basal metabolism as of little help in doubtful cases rather than with Simpson (1948) who states that a normal basal metabolic rate is never found in thyrotoxicosis.

All the results of basal metabolic rate estimations are presented so that the value of this traditional investigation in cases of suspected thyrotoxicosis may be compared with the results of the more specific tests of thyroid function using radioactive iodine.

THYROID GLAND UPTAKE

The gland uptake of radioactive iodine at the peak value is shown in Appendices I - V and is charted in Figure 6. In the normal group the uptake was in the range of 21 to 54% of the administered dose with a mean of 38%. The intermediate group had a somewhat similar range, with a mean of 48% with the important exception that there were eight cases which had a peak uptake of over 55% (Cases 17, 20, 22, 31, 36, 37, 44, and 46). These eight cases overlap

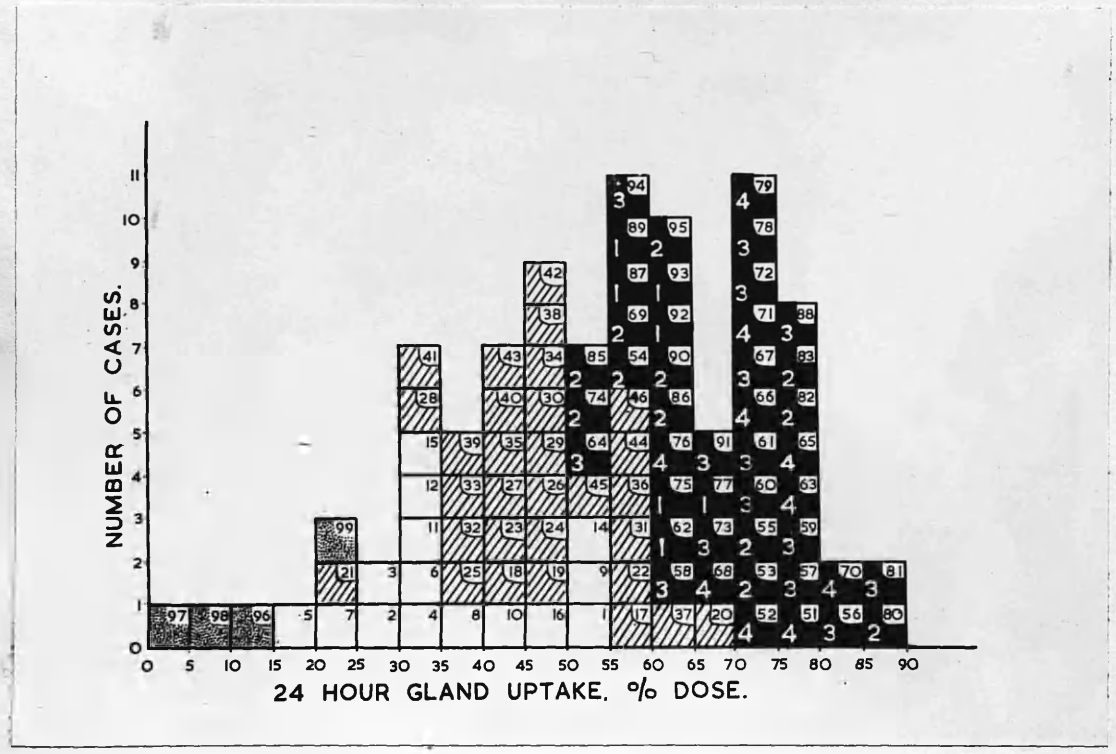

Figure 7. Distribution of estimations of thyroid gland uptake 24 hours after a dose of radioactive iodine.

with the toxic group of 44 patients, all of whom had peak uptakes of 56% or greater, the highest uptake in the series being 92% in two cases, (Cases 71 and 79) and the mean of the group 74%. All the toxic group had uptakes greater than any recorded in the normal group, and three of the four patients with myxoedema had the lowest uptakes recorded.

The uptake by the gland at 24 hours, (Fig.7) shows the same pattern of distribution as at the time of peak uptake, but even more overlap is apparent between the toxic and intermediate or normal categories. No less than twelve intermediate group or normal cases appear in the same overlap area in the figure as 21 toxic cases, but the greatest overlap occurs in the 50 - 60% range. In many toxic cases there is a drop in the 24 hour values as compared with the peak uptakes, and this fall in the amount of iodine retained in the gland is because of its conversion into thyroxine and transfer into the blood, a transfer known to correspond with a rise in the activity of plasma by that time. The fall in gland activity may be very considerable in some cases, as in Case 64 where a peak uptake of 75.5% had diminished to 55% by 24 hours, and in Cases 71 and 79 where the drop was in each case from 92% to 72%.

Gland uptake after 24 hours does not give as true an indication of the avidity of the gland for iodine as does the peak uptake, but it enables us to compare these values with those published by Werner, Quimby, and Schmidt, (1949a)

in one of the largest series so far reported. The Sheffield range for normal uptakes is 19 - 53% which compares with a range of 7 - 49% in the American workers' series of 57 normal controls. Whereas, however, only 6 (10%) of their cases had uptakes greater than 35%, there are 5 patients (35%) in the normal group in this series with uptakes of this order. We believe these differences to be significant and to be possibly connected with the known lack of iodine in the Derbyshire area (Murray, Ryle, Simpson and Wilson, 1948) It is recognised that thyroid glands with low iodine content from any cause have an increased avidity for iodine, and Leblond and Mann (1942) showed that continued dietary iodine deficiency led to increased thyroid iodine collection.

There is little overlap between the patients with thyrotoxicosis and the normal controls, in respect of their peak and 24 hour uptakes, but there are eight cases in the intermediate group with no evidence of toxicity who had either anxiety states or non-toxic goitres, and who had uptakes of 56% or greater and so overlapped with the toxic group. In the group studied by Werner and his associates no less than 40 out of 97 thyrotoxic patients had uptakes within the limits observed in their control subjects. If in their series 40% is taken as the upper limit of normal then only 4% of their normal cases fall in the toxic range, but 11% of their toxic cases then lie in the normal range.

Luellen, Keating, Williams, Berkson, Power, and McConahey

(1949) also noted that some euthyroid patients with nodular goitres may at times collect more radioactive iodine in their thyroids than other euthyroid subjects, and they concluded that adenomatous goitres, especially large ones, ought not to be regarded as entirely normal in function even in the absence of clinical hyperthyroidism. Werner, Quimby, and Schmidt (1949) and Myant, Pochin, and Goldie (1949) also mention cases of non-toxic goitre with uptakes of this order; the former workers have noted, in a series of patients investigated when in remission of hyperthyroidism as a result of various types of treatment, that the iodine uptake often continues at an elevated level, despite the regression of symptoms and the return of the basal metabolic rate to normal. Findings such as these, as well as similar observations, discussed later, made following effective therapeutic doses of radioactive iodine, show that unusually high uptakes of radioactive iodine by the thyroid gland may exist without there being overactivity of the gland as judged by other criteria.

The peak and 24 hour uptake of patients with toxic adenomata was, in general, lower than that of the group with diffuse thyrotoxicosis, the mean peak uptake of the adenomatous group being 64% as compared with a mean of 78% in the remaining toxic cases.

The equipment was not sufficiently collimated to decide whether or not the activity in the adenomata was

significantly higher than that in the surrounding thyroid tissue, a finding discussed by Means, (1949) with regard to the function of isolated thyroid adenomata. In five cases, however, (Cases 86, 87, 89, 92, and 95) it did appear that the greatest amount of activity present in the gland was concentrated in the palpable adenoma.

Two of the patients in the toxic group, Cases 74 and 75, with two of the lowest uptakes, 57% and 61% respectively, had previously had thyroidectomies, and the lesser amount of active thyroid tissue may be related to their smaller uptake of radioactive iodine, despite their undoubted toxicity.

It would appear, therefore, that where the volume or mass, of hyperfunctioning thyroid tissue is small, such as where there are nodular recurrencies after partial thyroidectomy, or where there is toxicity due to the presence of an adenoma, then the absolute amount absorbed by the gland as a whole is of less diagnostic value than in patients where the thyrotoxicosis is due to diffuse enlargement of the gland as in typical Graves disease. This accords well with the observation of Keating, Haines, Power, and Williams, (1950) that no matter by what technique radioactive iodine concentration in the thyroid gland is measured, there is a significant overlap with the euthyroid range, and that radioactive iodine tracer tests, as carried out by them were of limited value for indicating the presence or absence of hyperthyroidism

in cases of adenomatous goitre.

A further point of interest that emerged from the investigations was that a relationship appeared to exist between the severity of the thyrotoxicosis as assessed independently on clinical grounds, and the uptake of iodine by the gland. In the histograms of peak uptake (Fig.6) and 24 hour uptake (Fig.7) it can be seen that there is a tendency for cases of Grade 3 and 4 toxicity to fall among the upper values, and Grades 1 and 2 to fall among the lower values of the toxic group. If the "mean grade" of severity is estimated for each column of toxic cases in Fig. 2, there is a gradual rise of severity from a "mean grade" of 1.6 in the group with a peak uptake of 56% to 60%, through successive "mean grades" of 1.7, 2.6, 2.8, 3.1, 3.6, and 2.9 to a "mean grade" of 4 in the 91% to 95% column. A similar rough correlation exists with the 24 hour uptake figures.

TIME TO HALF PEAK UPTAKE

The rate of uptake of radioactive iodine by the thyroid gland is a measure of thyroid function which has been assessed in various ways by different groups of workers. A very simple measure of the rate at which the iodine is being removed from the blood by the thyroid is the time which elapses until half the maximum gland uptake has been ahhieved, (the time to the half peak value, Myant, Pochin, and Goldie, 1949) and observation of this value by serial

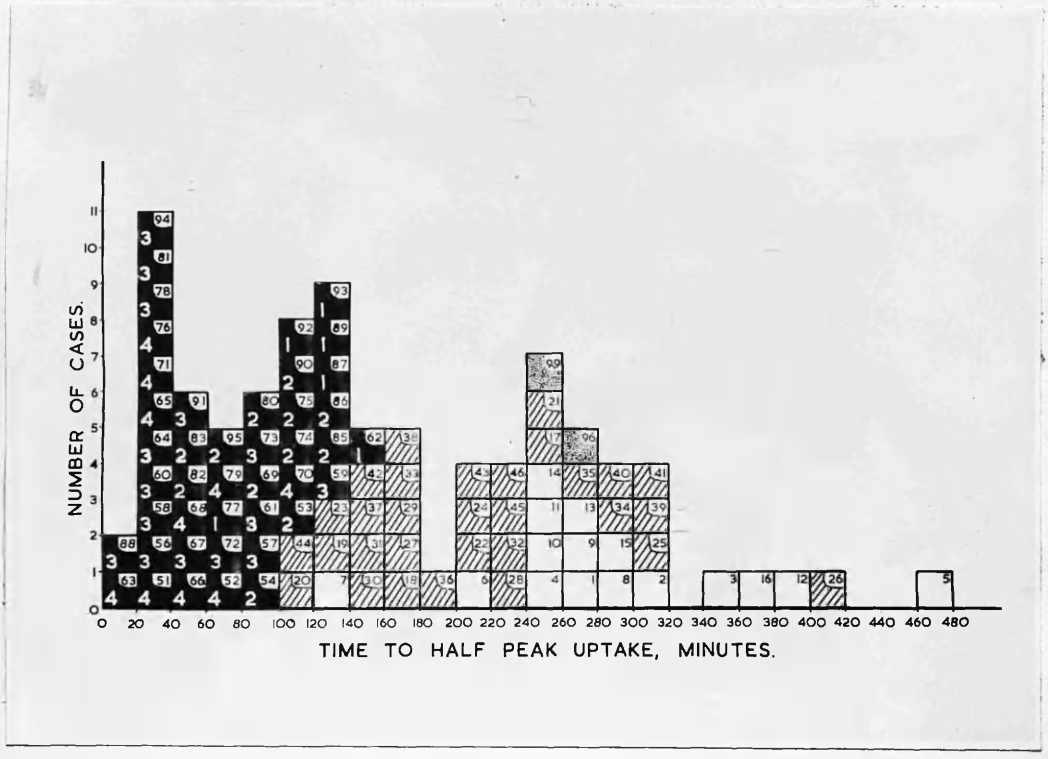

Figure 8. Distribution of estimations of "time-to-half-peak" gland uptake.

in vivo measurements of gland activity after administration of a tracer dose shows clearly that thyrotoxicosis is characterised by a very much more rapid "time-to-half-peak" than occurs in normal individuals. The values in this investigation are shown in Fig. 8. In this series all thyrotoxic patients had times which were over an hour shorter than 14 of the 15 normal controls. This index is a measure of the slope of the curve of uptake of radioactive iodine into the gland, and is affected by the rate of absorption of the oral dose of radioactive iodine, a variable which has induced some workers to use the intravenous route for administering their tracer doses (Pochin, 1950). The longest value, in the toxic group, Case 62, was in a patient who, through a misunderstanding received a light breakfast some two hours previously. Some of the other more prolonged values are undoubtedly related to variable rates of absorption from the bowel, quite apart from the rate at which the thyroid gland absorbed circulating iodide.

The mean time to half peak of the whole toxic group is 74 minutes, that of the intermediate group 215 minutes, and of the normals 293 minutes. Myant, Pochin, and Goldie (1949) quote values of 280 minutes for their control group and 54 minutes for their toxic group.

There is, however, a significant overlap between the groups, and a half-peak time between 100 and 150 minutes

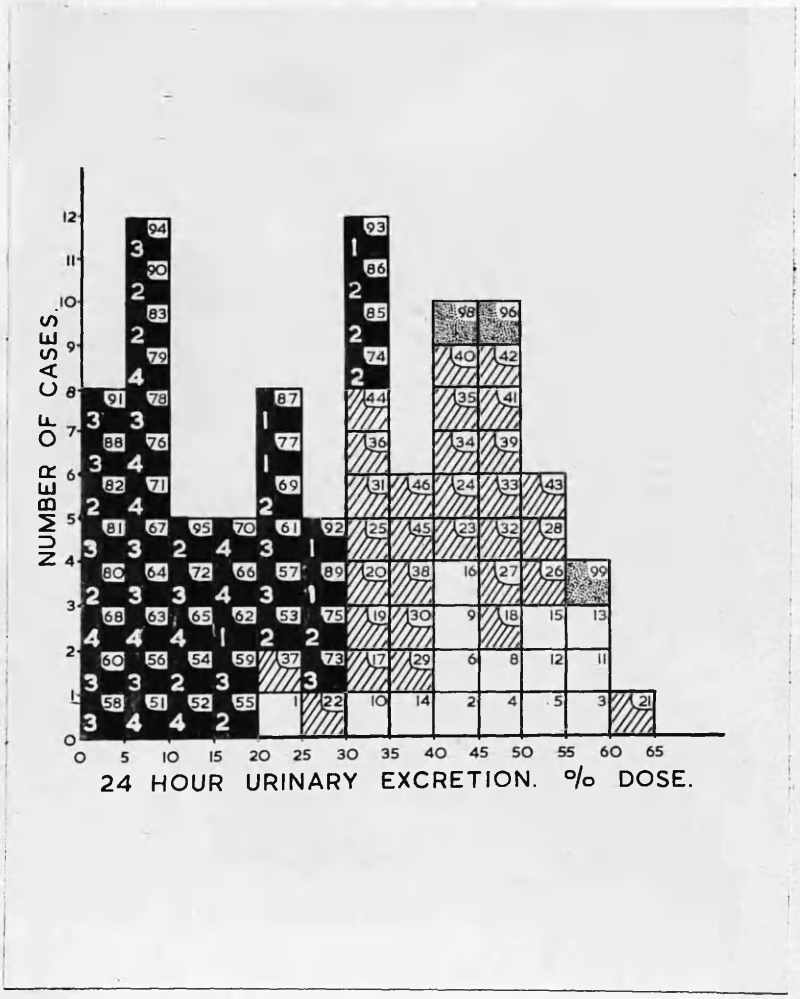

Figure 9. Distribution of estimations of 24 hour urinary excretion of radioactive iodine.

can occur in a normal, intermediate group, or toxic case. It will be noted that many of the cases in the intermediate group which occupy positions in the overlap zone are in a similar position in the gland uptake histograms.

The slow rise of gland uptake and the uncertainty regarding the time when maximum absorption is attained, makes it difficult to assess this value in myxoedema, but the times probably fall within the normal range.

24 HOUR URINARY EXCRETION

The values for the 24 hour urinary excretion of radioactive iodine show a distribution which is the reverse of that of gland uptakes, toxic cases excreting the least amounts, (Fig.9). There is a very considerable overlap when bulked 24 hour urine excretion figures are used, no less than 11 normal or non-toxic patients having urinary excretions within the same ranges as 14 patients with thyrotoxicosis, the overlap arising in the range of 20% and 35% of the administered dose. Marinelli, Quimby and Hine, (1948) found the test more useful if the excretion over the first 6 hours was neglected, and Mason and Oliver, (1949) and Arnott, Emery, Fraser, and Hobson, (1949) further subdivided the 48 hour period. In Sheffield, however, we restricted our observations to 24 hour samples and agree with these latter workers that it is not a practical prodedure to apply the mathematical analysis of Keating, Power, Berkson,

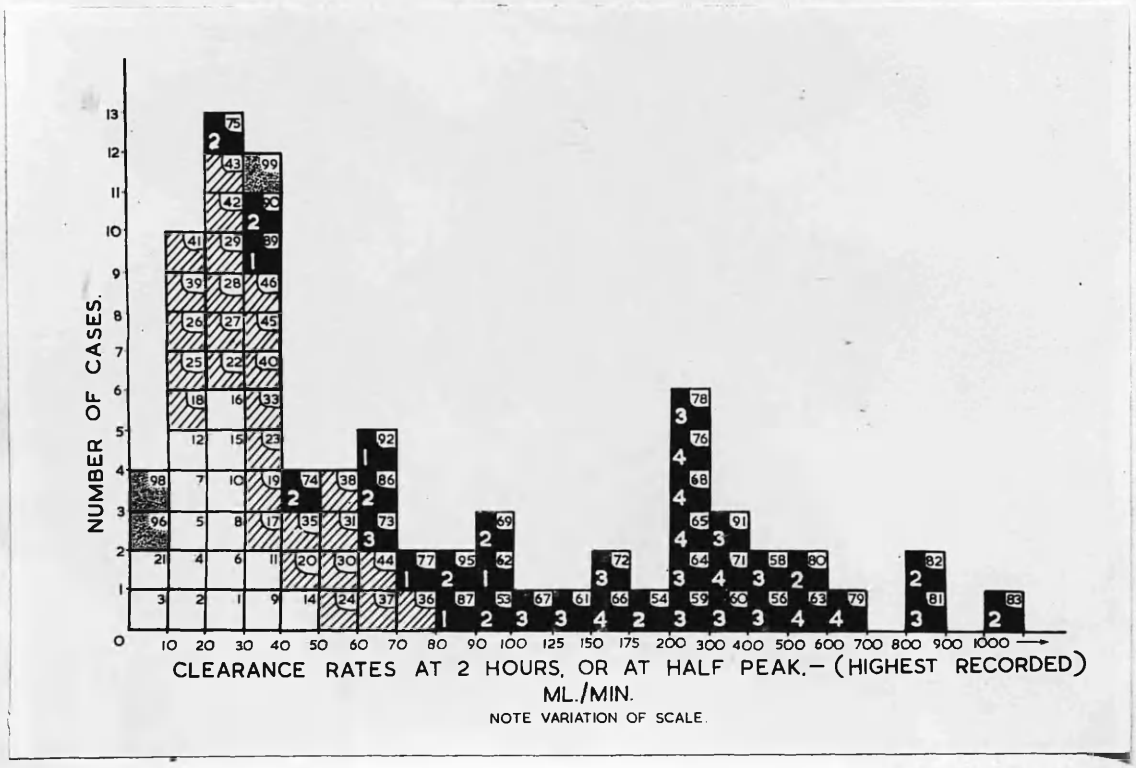

Figure 10. Distribution of estimations of thyroid clearance rates of plasma iodide.

and Haines, (1947) as a routine in all cases, because of the obvious unreliability of urine collection especially in the female, and because of the intrinsic inaccuracies of the method. Skanse, (1949) points out that the extent of overlap between thyrotoxic and euthyroid patients varies considerably in different studies and probably depends to a great extent upon the type of case studied. As with thyroid gland uptakes, some patients with non-toxic goitres may have urinary excretions of radioactive iodine which are intermediate between those found in normal controls and those which are typically thyrotoxic, and the test in some, such as those described by Fraser, (1949) may actually suggest frank thyrotoxicosis. Fraser points out that there is a trend towards a less abnormal urinary excretion as the diagnosis of thyrotoxicosis becomes less certain, and this trend is evident in Fig. 9.

THYROID CLEARANCE RATE

Another index of the rapidity of uptake of iodine by the thyroid gland is the plasma iodide clearance rate, a measure of the volume of plasma completely cleared of iodide by the thyroid in unit time. The clearance rates of the subjects in this investigation are charted in Figure 10, and show mean clearances of 24, 36, and 297 ml. per minute in the normal, intermediate, and toxic groups respectively. There is not, however, the clear cut separation between toxicity and normality described by

Myant, Pochin, and Goldie, (1949). The highest normal clearance rate was 46 ml./minute, but higher clearance rates were found in seven subjects in the intermediate group, with a reading of 71 ml./minute in Case 36, and clearances of the order of 20 - 80 ml./minute only in eight of the 31 thyrotoxic persons in whom the calculation was possible, all except one, Case 73, being patients with toxicity of Grades 1 and 2. The remaining thyrotoxic cases all had clearances in excess of 80 ml./minute, the value quoted by Pochin (1950) as being, in his experience, that below which Graves disease is not probable. Keating, Wang, Luellen, Williams, Power and McConahey, (1949) quote four cases of exophthalmic goitre with thyroid iodine clearance rates below 70 ml. per minute. The figures in this series would support these workers' findings that it is possible to detect comparatively low clearance rates in the presence of thyrotoxicosis, and the absence of such low readings in the series of Myant, Pochin, and Goldie (1949) is probably due to the absence of cases with only slight degrees of thyrotoxicosis. On the evidence of this series, there does not appear to be a clear cut separation between the thyrotoxic and the euthyroid individual, but a gradual gradation between the two. It can be seen that there is a tendency for the most severe cases to have the highest, and the mildest cases the lowest, thyroid clearance rates, with rates higher than normal

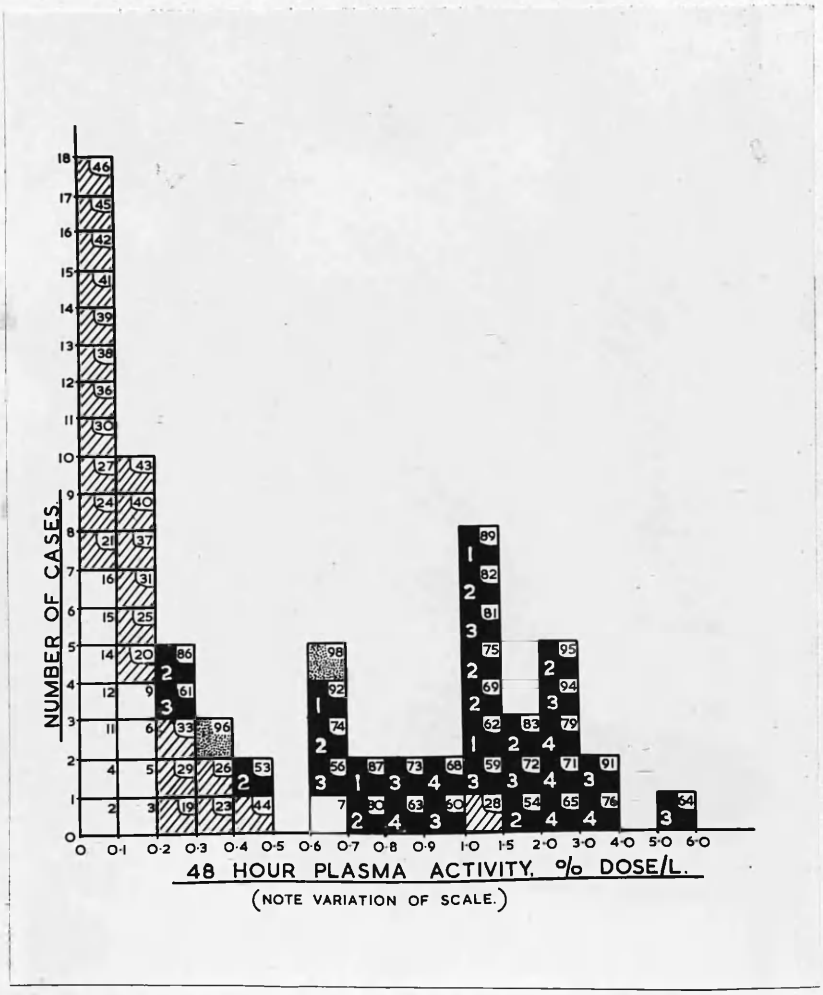

Figure 11. Distribution of estimations of total plasma activity 48 hours after a dose of radioactive iodine.

occurring in a selection of patients with anxiety state and non-toxic goitre.

It is possibly of significance that four of these eight cases had toxic adenomata rather than diffuse thyrotoxicosis, and patients with toxic adenomata usually have clearance rates very considerably lower than those found in diffuse thyrotoxicosis; this is undoubtedly because the probable higher clearance rate of the hyper-functioning adenoma is being masked by the relatively normal rate of the rest of the gland. Estimations of clearance rate have, therefore, a similar inability to indicate toxicity in this group as have the gland uptake figures, already discussed. They have, however, the advantage that they can be accurately calculated without knowledge of the actual dose given.

PLASMA ACTIVITY ESTIMATIONS

All the above results are in essence, indices of the capacity of the thyroid gland to concentrate iodide presented to it. Very soon after starting the work it was felt that a more physiological measure of thyroid function would be an index of the ability of the thyroid to convert iodide into thyroxine and discharge it into the circulation. It therefore became necessary to determine at what time the most valuable diagnostic information would be obtainable from an observation of plasma activity, both its total activity and that due to iodine in protein-bound form.

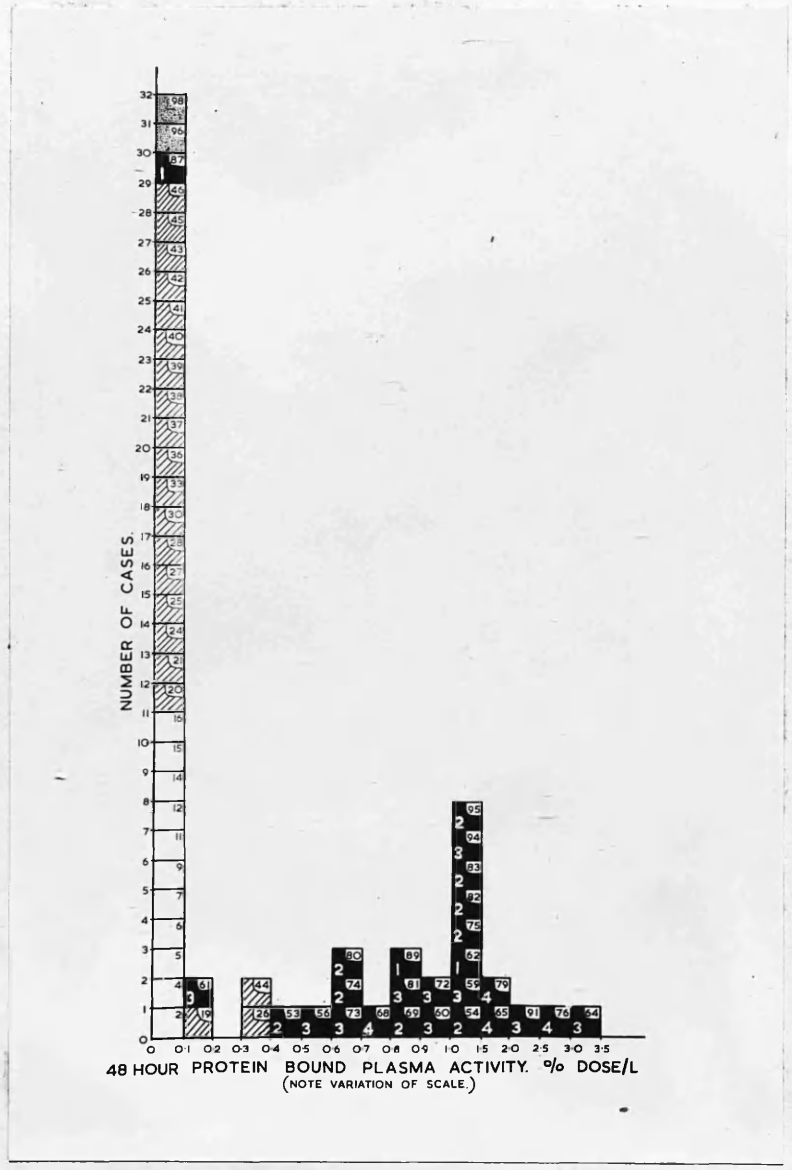

Figure 12. Distribution of estimations of protein-bound plasma activity 48 hours after a dose of radioactive iodine.

Preliminary work on a number of patients produced the data already discussed in connection with Figure 4 and, as mentioned there, subsequent observations were only made at the 48 hour time.

The results are shown in Figures 11 and 12. An estimation of the total activity alone provided a rough separation between the toxic individuals and those with normal or intermediate thyroid function. The cases in the overlap zone were chiefly those with low clearance rates and consequently more delayed absorption of circulating radioactive iodine by the gland. Nevertheless, there is almost a ten times difference between the mean of 0.16 per cent of the dose given per litre of plasma for the normal and intermediate groups (combined) and the mean of 1.53 per cent per litre for the toxic group. Values in excess of 0.7 per cent per litre were usually found in thyrotoxicosis, and seldom, if ever, in euthyroid persons, but lesser amounts than 0.7% per litre were not incompatible with a diagnosis of thyrotoxicosis.

When the protein-bound activity was measured, (Fig.12) a very sharp demarcation became apparent between the toxic group on the one hand, and the intermediate and normal groups on the other. In the absence of toxicity only two cases had a protein-bound activity in excess of 0.2% per litre, and 31 cases had values less than 0.1% per litre. Conversely, only two cases which had been definitely graded

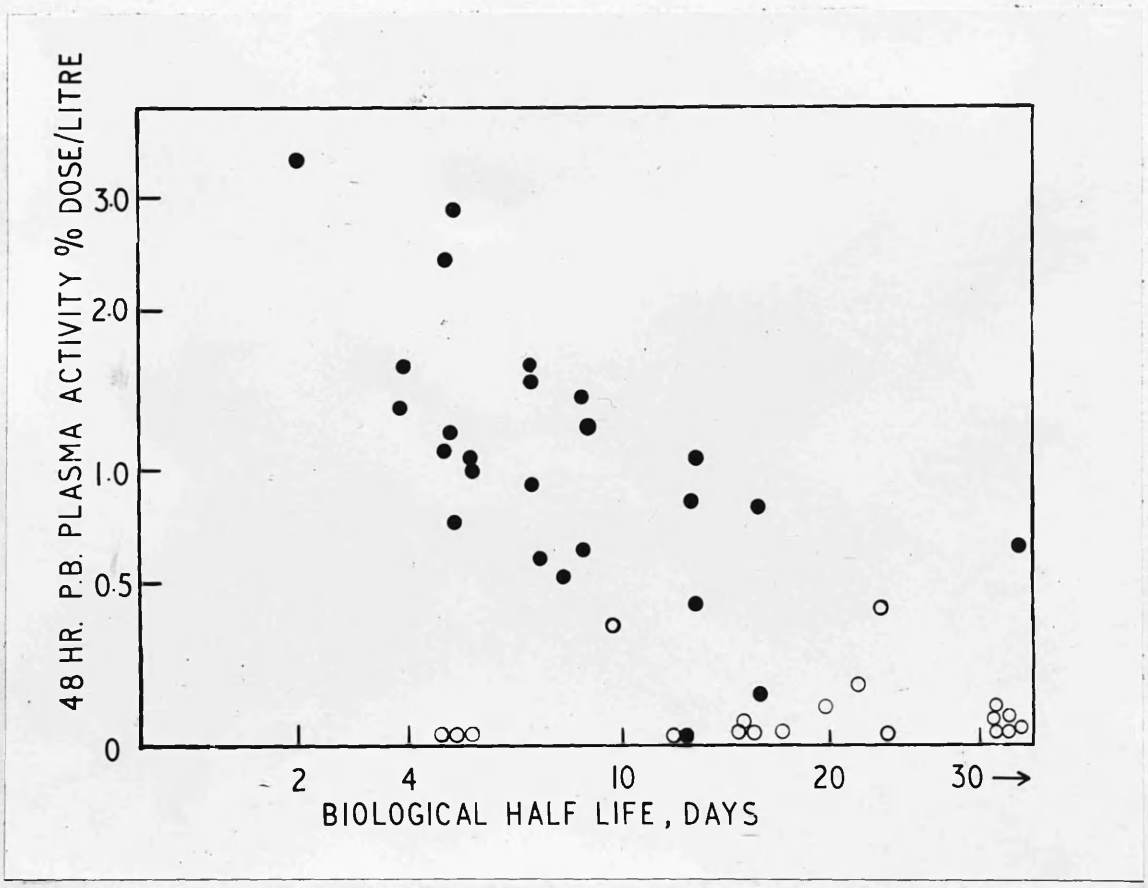

Figure 13. Relation between plasma protein-bound activity and the biological half life of the isotope in the thyroid gland.

In this figure, and in Figures 14 - 21, open circles indicate clinically non-toxic, and solid circles clinically thyrotoxic, patients.

as thyrotoxic had values less than 0.2% per litre, whereas all the remainder tested, (24 cases) had values in excess of 0.4% per litre. This test, therefore, was manifestly a useful diagnostic aid, and experience shows that if a greater amount than 0.4% of the dose per litre of plasma is present in the plasma at 48 hours in protein-bound form the patient should be regarded as a case of thyrotoxicosis; values below this are only occasionally found in the presence of thyroid overactivity.

The higher amounts of activity present in protein-bound form were found in those patients, (cases 64, 65, 76, and 79) with a rapid fall in the thyroid gland uptake after the peak value had been reached. This principle can be further emphasised by comparing the biological half life of the radioiodine in the thyroid gland with the 48 hour protein-bound plasma activity. In Figure 13 these values are charted for all the cases in Part "A" of this series where both are known, and it can be seen, with only a few exceptions that the higher values of protein-bound plasma activity are in those cases with the shorter biological half life. It is apparent, therefore, that as well as being an index of the amount of circulating thyroxine, 48 hour protein-bound plasma activity is also a measure of the rapidity of conversion of administered radioactive iodine into thyroxine and its discharge into the circulation.

While this work was in progress, several observers reported somewhat similar observations. They have usually, however, chosen to make their observations 24 hours after the dose, and their work has either centred upon a study of the rate at which radioactive iodine becomes protein-bound, or, alternatively, of the absolute amount present. Clark, Moe, and Adams, (1949) and Sheline and Clark, (1950) found that patients in whom at 24 hours more than 50% of the total plasma activity was due to protein-bound iodine were thyrotoxic. (The data presented here would confirm this finding for the 48 hour time.) They required, however, doses of at least 50 to 200 microcuries of radioactive iodine for their observations. Freedberg, Ureles, and Hertz, (1949) demonstrated that after 24 hours, protein-bound radioactive iodine reached higher levels in thyrotoxic patients than in normals, but found that, at that time, the total plasma activity did not sharply separate toxic from normal thyroid function. Williams, Jaffe, and Bernstein, (1949) also reported that in thyrotoxicosis the total and protein-bound radioactive iodine activity was above normal after 24 hours and they suggested, although they did not show, that a sharper separation might be achieved if longer intervals elapsed before the specimens were collected.

McConahey, Keating, and Power (1949) have noted that the levels of protein-bound radioactive iodine were higher in thyrotoxic than in euthyroid individuals. They also

noted that all the circulating radioactive iodine was protein-bound in thyrotoxic subjects after a period which averaged 48 hours, but that in normal individuals the average time required was about four days, a finding which re-emphasised the value of making plasma activity observations after 48 hours, a time chosen by us in Sheffield as the result of observations of plasma activity followed over a period of time, (Figure 4).

It should be emphasised that none of the above workers have carried out in the same individuals investigations both of thyroid uptake of radioactive iodine and estimations of plasma levels of protein-bound activity. It is only by such a comparative and comprehensive survey that the relative merit of the different tests can be assessed, and that the value of any particular test can be viewed in true perspective.

CONCLUSIONS DERIVED FROM PART "A"

After consideration of the facts demonstrated in the histograms which illustrate the results of Part "A", several conclusions can be drawn.

Firstly: An estimation of the basal metabolic rate alone does not appear to be of value in separating thyrotoxic from non-toxic individuals when the clinical decision regarding the diagnosis is difficult.

Secondly: The peak gland uptake of a tracer dose is a reasonably accurate measurement of the avidity of the gland for iodine, and that by it the great majority of thyrotoxic individuals can be separated from the non-toxic persons. In this respect it is far superior to the value obtained at 24 hours which so often, in thyrotoxic patients, may be very appreciably lower than the value of the peak point of the curve, because of the rapid turnover in the gland of the radioactive iodine, and ~~the~~ its discharge as thyroxine.

Thirdly: Measurements of 24 hours urinary excretion are equally valueless in diagnosing the clinically difficult cases. It can be seen from Figure 9 that all except 1 of the clinically less certain thyrotoxic cases, those of Grade 1 severity, had 24 hour urinary excretions in the overlap zone between 20% and 35%. This particular index did not, therefore, appear to have real clinical value.

Fourthly: Similarly, measurements of the time to half peak uptake value were not of great value in the doubtful cases, and, from the practical point of view, this index

requires as much work on the part of the observer for its recording as did the peak value itself, already shown to be more specific.

Fifthly: Thyroid iodide clearance rates can be seen to be of value in one particular fashion, that a high clearance rate, over 80 ml. per minute, appeared to indicate toxicity although lower rates did not exclude it. This value however, has the advantage that precise knowledge of the dose given is not necessary, as its calculation depends on its relation between the plasma concentration and the rate of gland uptake. Provided, therefore, that serial in vivo gland counts are taken on either side of the time at which the blood sample is obtained, then the index can be readily obtained.

Sixthly: Total plasma activity after 48 hours gives a reasonably good separation of the toxic from the non-toxic patients, above and below a value of about 0.6 - 0.7% per litre. Further, the 48 hour protein-bound plasma activity gives a surprisingly good separation, sharply differentiating the two types of cases in a way which closely corresponded to the very careful clinical assessment of the patients.

From the diagnostic viewpoint therefore, three tests stood out as being the most valuable.

(1). The Peak gland uptake.

(2). The thyroid iodide clearance rate.

(3). The 48 hour protein-bound plasma activity.

PART "B"

GENERAL APPLICATION OF DIAGNOSTIC TECHNIQUES

Scope of Investigation

This immediately succeeded Part "A", and its primary objective was to extend the studies already carried out, and to apply the selected tests routinely to further cases.

In practice, in about half the patients, as full investigations were performed as in Part "A", but for the purpose of analysis, all results have been presented with respect to the selected tests only.

The secondary objective of Part "B" was to determine whether any one test alone could be adopted as suitable for a single routine diagnostic test, divorced from the support afforded by the simultaneous performance of the other tests.

For this purpose it is of course highly desirable that any selected test must have several characteristics.

(1). It must be simple in the extreme.

(2). It must make minimal demands upon patients time and upon the time of physician and of technical staff.

(3). It must, if possible, be such that the minimum number of patients require to be more fully re-investigated later because of equivocal results in the original tests.

(4). Its requirements should be economical of hospital space, equipment, and facilities if it is to be suitable for general adoption in centres other than a well equipped teaching hospital.

(5). It must be readily applicable to outpatients.

With these considerations in mind, the peak uptake value obviously had several disadvantages, as frequent serial invivo gland counts are necessary to be able to define a peak value, and this was undesirable and impracticable for a routine test. On the other hand, thyroid iodide clearance rates can be measured accurately within a reasonable space of time after giving the dose, and, although, as with peak uptake values, in vivo counting techniques are required, with all the necessary equipment, the test is obviously readily applicable to out-patients.

The 48-hour protein bound plasma activity test, on the other hand, fulfils all the criteria necessary, and, on the face of it, appears to be ideal. Its reliability had, therefore, to be tested fully, and this was done by comparing it directly with the other indices and with the careful clinical assessments of the level of clinical thyroid function.

First of all, however, it became necessary to find an alternative test of the amount of iodide absorbed in the gland which gave as accurate an estimate of gland activity for iodide as the peak value. This meant a selection of a time at which the gland uptake for all cases could be assessed and at which time the content of the gland would bear some true relationship to that reached at the peak of the curve. Times after the peak are obviously unsuitable, for the reasons

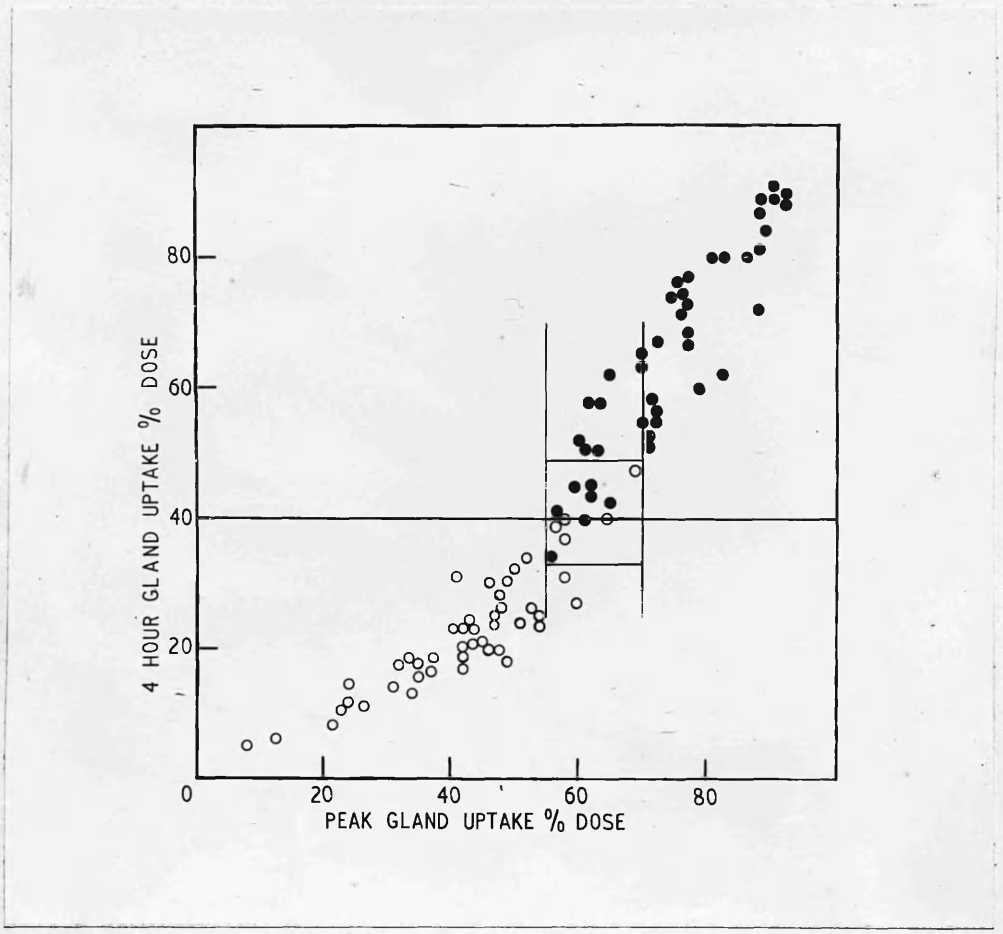

Figure 14. Relation of uptake of a tracer dose of radioactive iodine at 4 hours to the maximum uptake achieved.

discussed with regard to 24 hours uptakes.

The gland content 4 hours after an oral dose was, therefore, selected for the analyses of the results of these investigations, as it was a time manifestly suitable for use with outpatients, and which was sufficiently late after administration of an oral tracer dose to eliminate any variables of gland absorption.

Accordingly, the 4-hour uptake in all the cases in Part A was analysed and compared with the peak uptake. The results are described in Figure 14 where the open circles include both "normal" and intermediate group cases, all being, from the diagnostic point of view, "non-toxic". Solid circles indicate thyrotoxic cases.

It can be seen that the overlap zone between toxic and non-toxic gland function lies, with respect to peak uptake, between the vertical lines representing a range from 55% to 70% (as in Figure 6); within this range are some 16 thyrotoxic and some 7 or 8 non-toxic cases. On the other hand, the overlap zone for 4 hours gland uptakes, between the short horizontal pair of lines, includes only about half as many cases, the chief ones excluded being the thyrotoxic cases with low total peak gland uptakes. The reason for this is obviously that in thyrotoxic function iodide absorption is more rapid as well as being greater than normal, so that glands that possibly may not absorb a very high amount at the peak of the curve, absorb what they do concentrate very quickly, so that by only 4 hours after injection they have absorbed

almost as much, usually, as they are going to absorb in all. The result is, therefore, that their relatively high absorption after 4 hours more clearly differentiates them from non-toxic individuals than even the low peak uptake.

I t can be seen, therefore, that whereas 4 hour uptakes give essentially the same information as peak uptakes, they are preferable to it as being slightly more specific in their differentiation of the types of function, and they are, of course, very much more readily measured.

Accordingly, the results of the cases investigated in Part B were all analysed with respect to three indices,

(1) The 4 hour gland uptake, being an index of the absolute uptake and avidity of the thyroid for iodine.

(2) The thyroid iodide clearance rate about 1 hour after an oral tracer dose being an index of the rate of iodide absorption into the gland, in contrast to the amount absorbed.

(3) The 48-hour protein bound plasma activity, being an index of the capacity of the gland to synthesise thyroxine and discharge it into the blood.

For the purpose of the presentation of the results of this investigation, the results of all the cases observed in Part B (details in Appendix Vl and Vll) have been combined in Figures 15-20, with the results obtained from the patients in Part A. It is felt that thereby additional information can

be derived from the pooled results, information which allows us to compare carefully the three tests under review, and lets us balance their relative advantages and disadvantages.

In these figures the black symbols indicate thyrotoxic patients, of all grades of severity (see Figures 15-17), and the open circles indicate non-toxic patients, the "normal" and "intermediate" group cases in Part A being combined with all the non-toxic cases in the second series of investigations in Part B. From the non-toxic cases, those patients who at any stage raised in the mind of one or more observers the possibility that he or she might be thyrotoxic have been extracted and are represented in the figures as the "Doubtful" section of non-toxic patients. These cases were, however, all finally clinically classified as non-toxic despite the initial clinical impression. The "Definite" cases were those about whose normal thyroid function there was no doubt, and there was unanimous agreement clinically that they were not, in fact, thyrotoxic.

It can readily be appreciated that it is the differentiation of the "Doubtful, non-toxic" category from the "Grade 1, thyrotoxic" group which is the most difficult and important clinically, and any valuable routine test of thyroid function must be able to separate them fairly accurately.

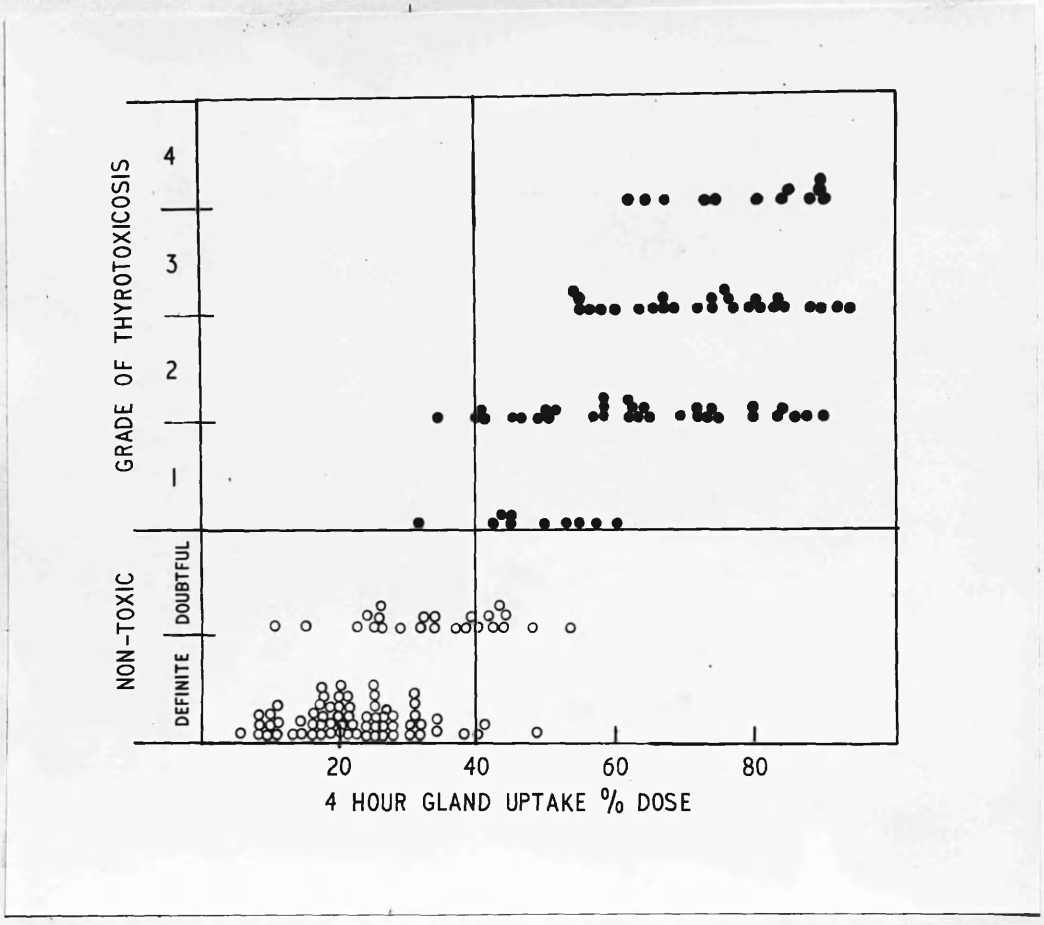

Figure 15. Relation of level of thyroid function to uptake of radioactive iodine after 4 hours.

The following remarks, therefore, apply to the interpretation of the data provided by the combined groups of cases, representing a total of 94 normal persons and patients classified as non-toxic, and 83 patients with one or other of 4 clinical grades of severity of thyrotoxicosis.

4-Hour Gland Uptake

The results of the analysis of the gland uptake figures after 4 hours are shown in Figure 15. It is again apparent, as occurred in the original group of cases, that there is roughly a gradual gradation in the result of this test that parallels the clinical gradation in severity throughout all cases.

Nevertheless, the 40% uptake level in 4 hour readings appears to separate fairly well the non-toxic from the thyrotoxic individuals, the latter almost invariably having a 4 hour uptake greater than this; the few exceptions were in cases of lesser degrees of severity. In nearly a dozen cases, however, uptakes of greater than 40% were encountered in non-toxic persons. These higher uptakes usually occurred in patients with a goitre, and were just in that group of people in whom the clinical differentiation was most difficult; some non-toxic nodular goitres had very high 4-hour gland uptakes, in particular cases 111, 134, 141 and 149.

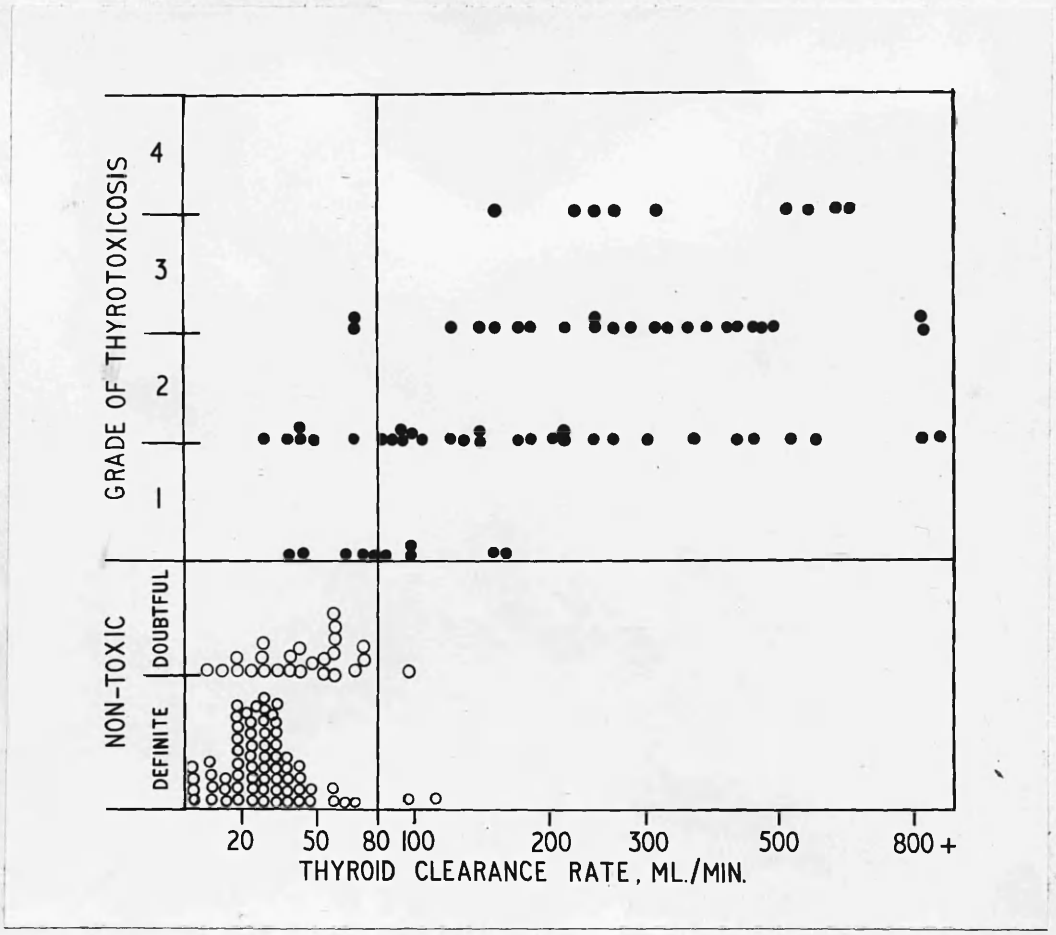

Figure 16. Relation of level of thyroid function to thyroid iodide clearance rate.

This pooled information might, therefore, be said to show that 4-hour uptake values only misdiagnose a thyrotoxic patient very rarely, but that some non-toxic patients react, with regard to this particular test of thyroid function, as though they were thyrotoxic.

Thyroid Clearance Rates

The results of the thyroid clearance rates are similarly presented in Figure 16. It was found, in agreement with Pochin (1950), that thyrotoxicosis is usually associated with clearance rates over 80 ml - per minute, but on the other hand, this large group of cases included an appreciable number, 17% of total thyrotoxic cases, with clearance rates between 30 and 80 ml. per minute, rates commonly encountered in non-toxic persons. Furthermore, only 38% of these cases with low clearance rates were of the mildest, Grade 1, severity, the remainder being quite definitely toxic and two cases were moderately severe. The extension of this study to the cases of Part B reveals 3 cases, Nos.101, 121 and 134, with rates over 90 ml. per minute, the level of thyroid function in two of them being indubitably normal.

Therefore, just as 4 hour uptakes chiefly misplaced non-toxic cases with high uptakes, this experience in the combined groups of cases suggested that the chief defect of clearance rates is that some toxic cases with low rates

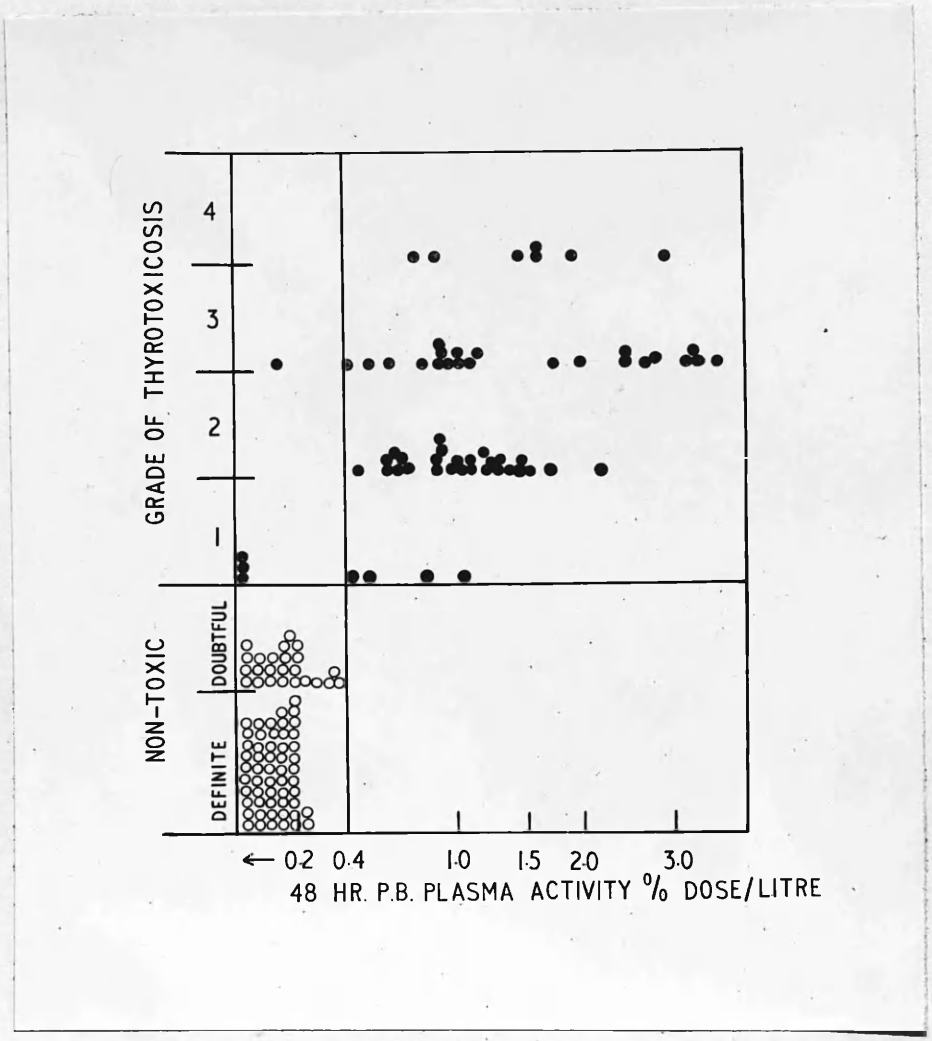

Figure 17. Relation of level of thyroid function to 48 hour protein-bound plasma activity.

(Scale not strictly logarithmic below 0.2%.)

behave with this test as if they were non-toxic.

48-hour Protein-Bound Plasma Activity

Figure 17 summarises the results in all cases of the estimates of protein-bound plasma activity. Even with the increase in the number of cases beyond those studied in Part A of this investigation, and represented in Figure 12, there still remains a very sharp demarcation between the two groups. All the thyrotoxic cases in which the test was performed except 4 (6%) had activities in excess of 0.4% per litre, and no non-toxic cases at all fell into this toxic range, giving an overall accuracy of 98% in the assignments of the case to the correct clinical category, taking a concentration of 0.4% per litre as the division between non-toxic and thyrotoxic gland function. It should be noted that three of the four toxic cases with low or negligible activities were only of Grade 1 severity, and the possibility of an error in clinical classification should always be borne in mind. Throughout this work the essential base line has had to be the eventual clinical classifications, but it is conceivable that in some cases the objective test may be the more accurate. After all, the eventual value of any objective test must be its ability to make diagnostic decisions easier, and so make it possible for the clinician to omit lengthy and time consuming clinical assessments.

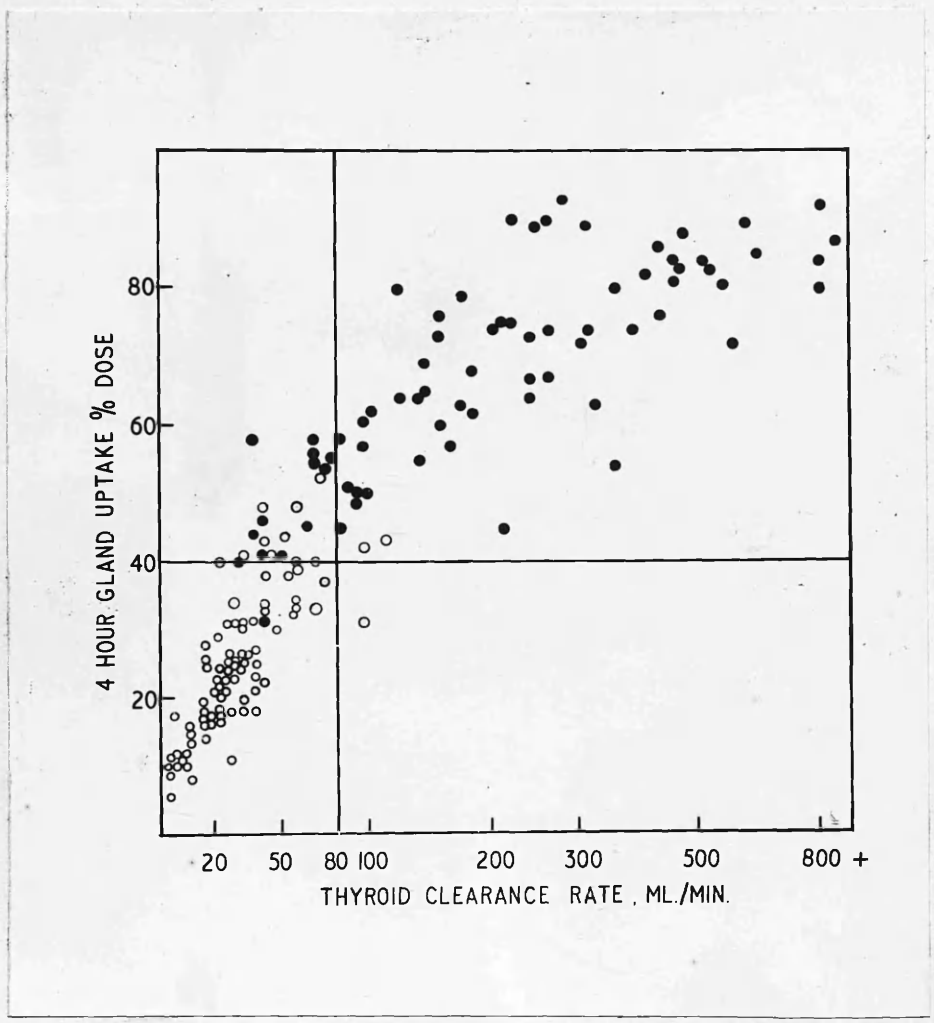

Figure 18. Relation of 4 hour gland uptake to thyroid iodide clearance rate.

Conclusions derived from Part B

It appeared therefore, that if these three tests 4-hour uptake, thyroid clearance rates, and 48 hour protein-bound plasma activities, were directly compared over a large number of cases, it could be concluded that:

(1) 4 hour uptakes gave an overall accuracy of diagnosis, in agreement with the baseline of clinical assessment of 93%;

(2) Thyroid clearance rates gave an overall accuracy of 91% and

(3) 48 hour protein-bound plasma activity estimations gave an accuracy of 98%.

Furthermore, it appeared that there was, as had been previously suspected, a gradation in the clinical severity of the cases which roughly corresponded to the gradation in the results of the tests that measured uptake of iodide into the gland, whether of absolute amount, or of rate of uptake. This can be well seen by study of Figures 15 and 16 and of Figure 18, where 4-hour uptake and thyroid clearance rates in all cases where both were observed, are related to each other. It can be seen that the vast majority of high uptakes were associated with high clearance rates, and that this association occurred in thyrotoxic patients. Conversely, low uptakes and rates were found together in most non-toxic patients. There was, however, a considerable overlap in as much as a number of non-toxic and thyrotoxic cases had high uptakes with low clearance rates, the high uptakes correctly placing the thyrotoxic cases,

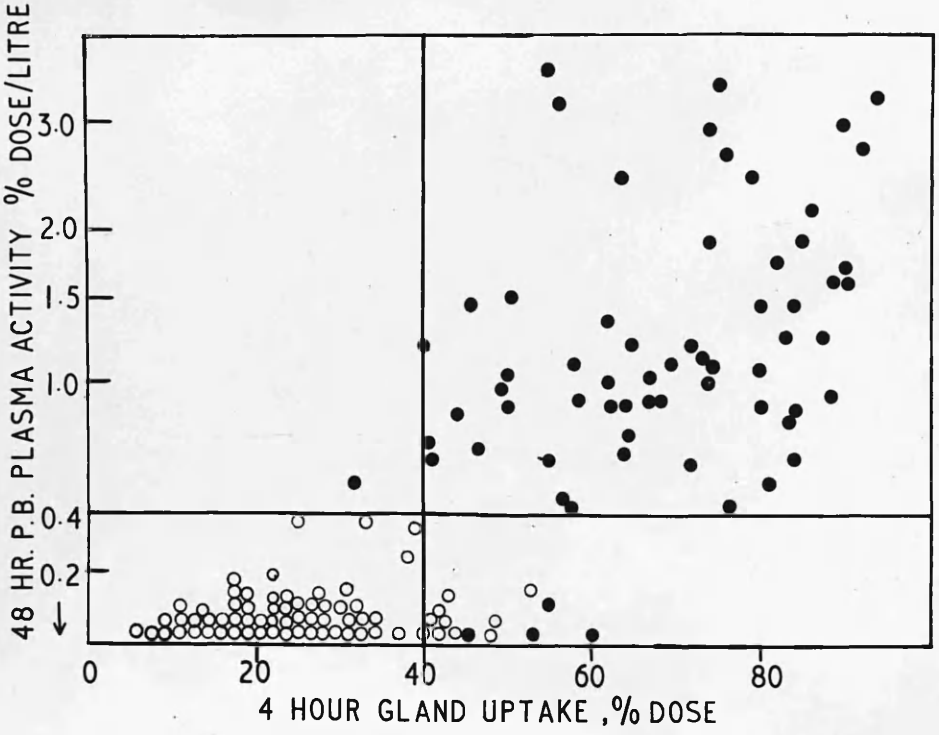

Figure 19. Relation of 4 hour gland uptake to 48 hour protein-bound plasma activity levels.

and the low clearance rates correctly placing the non-toxic cases. (Cases in top left hand corner of figure). Only 3 cases, two non-toxic and one toxic, had both tests at variance with that which was expected from their clinical category.

Therefore, the supportive value of carrying out two tests simultaneously became less if both tests were those measuring amount or rate of uptake, high uptakes associated with low clearance rates being a feature common to both thyrotoxic and non-toxic persons. There was manifestly some other factor which more closely related with clinical classification than either of these indices, and the experience in this study would suggest that this factor is adequately represented by a measure of the protein-bound plasma activity which is, as already mentioned, merely labelling the level of circulating thyroxine, and as such would be expected to be a more accurate diagnostic index.

This can be clearly seen if the 48-hour protein-bound plasma activity values are directly compared with each of the other two indices. In Figure 19 are plotted the 4-hour uptake figures against the 48 hour protein-bound plasma activity. It can be clearly seen that high uptake figures are usually associated with high levels of protein-bound activity, and conversely, but that in the case of the non-toxic cases with high uptakes, their low protein-bound activities accurately

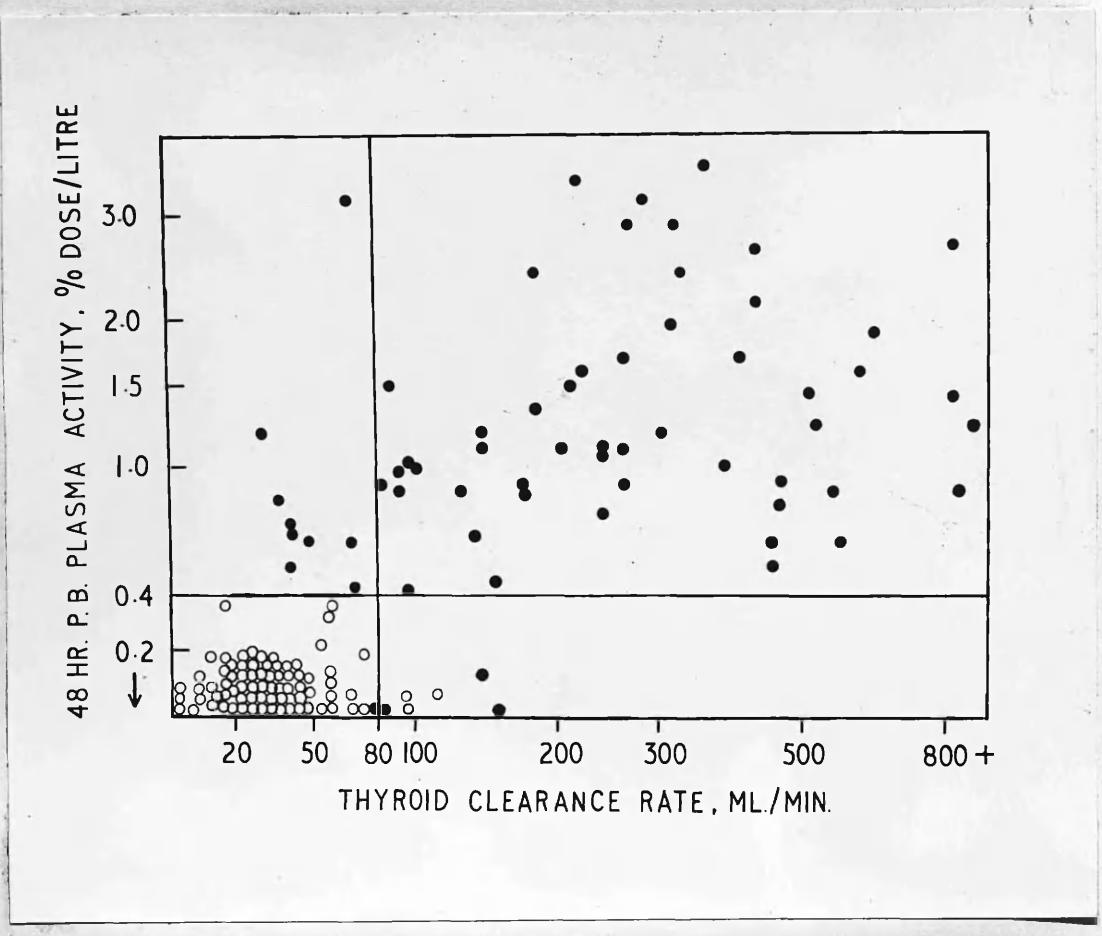

Figure 20. Relation of thyroid iodide clearance rates to 48 hour protein-bound plasma activity levels.

places them in the non-toxic category. Similarly, the cases with low and borderline uptake figures are shown, where toxic, to be accurately classified by their raised levels of protein-bound activity, the only exceptions being the four toxic cases with negligible activity in the plasma.

If this maneouvre is repeated with respect to the clearance values, Figure 20, it can be seen that high clearance rates are usually associated with plasma protein-bound activity levels well within the toxic range, except in the case of those non-toxic patients with high clearance rates. There are, in fact, shown to be non-toxic by their low protein-bound activity. More striking, however, is the way in which those cases considered to be toxic, but with low clearance rates, are shown to be toxic by their high plasma values. Once again the four thyrotoxic patients with low values are the anomalous cases. All four of these cases had 4-hour uptakes over 40%, two had clearance rates well outside the normal range, and two had clearance rates around 80 ml. per minute. It is possible that the latter two are wrongly classified clinically, and the former two are the only cases in the series where the 48-hour protein-bound plasma activity test has failed definitely to give a positive indication of existing thyrotoxicosis.

Reliance on this test alone, therefore, on the basis of the cases here represented, would give more consistently accurate and diagnostic information than any other test alone.

It would appear that no non-toxic cases would be suspect of being thyrotoxic, and only the exceptional thyrotoxic case would be misdiagnosed. It manifestly has very many advantages over any test involving the collection of urine, or any test where gland, or gland and thigh, counting is required, as such tests tend to be time consuming both to staff and patient, and to require an accurate geometrical set up of the equipment used.

The fact that the patient does not need to come into contact with any counting equipment, and that only two short visits are required, one to administer the oral dose of 25-30 micro-curies, and another for a few minutes 48 hours later for a vene-puncture, makes it an ideal and simple test for routine application as an in-patient or out-patient diagnostic technique. It is, in fact, therefore potentially applicable in a fashion which renders an objective test of thyroid function as easily performed as a Wasserman reaction, or any diagnostic investigation where all that is required from the patient is a sample of blood.

It was felt to be worthwhile, therefore, to test this latter statement by applying the method in practice, as an isolated diagnostic index in an attempt to provide an easy means whereby other clinicians could be afforded diagnostic assistance.

Accordingly, with the co-operation of a physician in Nottingham General Hospital, over 50 miles from Sheffield,

Table II

Results of Outpatient tests of 48 hour plasma activity estimations at Nottingham General Hospital.

No.	48 hr. activity Total	Protein bound %/litre	Diagnosis given	Clinical Impression at Nottingham
1	1.23	0.98	Toxic	"Mild thyrotoxicosis"
2	0.6	0.6	Probably toxic	"Probably toxic"
3	3.5	2.8	Very toxic	"Probably not toxic" (Exophthalmos, palpitations, sweating, nervousness)
4	1.7	1.3	Toxic	"Not now toxic, although was so in 1950"
5	0.62	0.56	Probably toxic	"Probably not toxic"
6	0.19	0.14	Non-toxic	"Anxiety state"
7	0.8	Not done	Possibly toxic	"Probably thyrotoxicosis"
8	1.62	1.0	Toxic	"Probably thyrotoxic"
9	0.1	0.1	Non-toxic	"Normal"

Dr. H. Miller and I arranged to despatch once per week, diagnostic doses of radioactive iodine which were administered to patients in Nottingham. Blood plasma samples withdrawn 48 hours later were returned to Sheffield for assay of their protein-bound plasma activity. The results are shown in Table II.

It can be seen that the predicted diagnosis made from the activites found in the samples agreed well with the clinical diagnosis made in Nottingham and forwarded subsequently to Sheffield with detailed case reports. It is felt that the cases where the results are inconsistent, represent probable errors in clinical assessment in Nottingham rather than misleading results of the radioactive iodine test. Later clinical evaluations in the light of this test will almost certainly be revised.

Discussion of Value of Tests using Radioactive Iodine in the Diagnosis of Thyrotoxicosis

The diagnosis of thyrotoxicosis can usually be made on the basis of history and physical examination alone. There are, however, many cases in which additional information is of great value and the problem of overactivity of the gland is always raised if the patient has a goitre and especially if there is in addition tachycardia. All patients who have had thyrotoxicosis in the past, and who have been treated, present difficulties in assessment. It is well known too, that many patients with an anxiety state may stimulate thyroid disease, in some respects.

The estimation of the blood cholesterol is acknowledged to be of little value in hyperthyroid states although it is of value in hypothyroidism, and Sheffield experience agrees with that of Peters and Man, (1950) and of Bartels, (1950). An estimation of the basal metabolic rate, on the other hand, can be of some value if done in hospital and in duplicate, but on balance the experience of Jaffe and Ottoman, (1950) who found only a 67% agreement when they correlated the clinical findings with estimations of basal metabolic rate, is fairly general and emphasises the frequent lack of value of the test where there is clinical doubt. (Cf. Figure 5).

Rapport and Curtis, (1950) claim that the chemical estimation of the protein-bound iodine in the plasma is the best measure of thyroid function, and while this is probably the case, the technical difficulties involved in carrying out the determination accurately are much greater than in making observations with radioactive idoine, and this will remain the case until simpler methods, such as that of Barker, Humphrey and Soley (1951) are available.

Observations with radioactive iodine are not difficult to perform, once the basic equipment has been obtained, and where possible several types of test should be simultaneously carried out. If, however, it is desired to carry out routine observations on a large number of cases or to investigate them

as outpatients, it becomes necessary to select one, or at the most two, of the tests.

As assessment of the total amount of radioactive iodine that is absorbed by the thyroid gland, or excreted by the urine, indicates the inorganic iodide retaining capacity of the thyroid gland, a capacity which is known to be considerably influenced by previous administration of iodine or by the exhibition of drugs which have an effect on thyroid functions, such as thiocyanate, the thiouracil group, or resorcinol, (Bull and Fraser, 1950); furthermore, the capacity of the gland to retain the iodine may alter very considerably within a short time after cessation of administration of the drug. Nevertheless, iodide retaining capacity is a function of the thyroid gland which is very greatly increased in conditions where there is clinical evidence of increased thyroid activity. Measurements of the degree and rate of this uptake, therefore, provide an index of thyroid activity which, in the majority of cases, separates those persons with normal function from those with hyperthyroidism or with hypothyroidism. The degree of overlap, however, is such that the test is of less value in the difficult intermediate group of cases where there is a possibility of mild hyperthyroidism, or, alternatively, where the symptoms may be due to a non-toxic goitre with superimposed anxiety state.

Experience with observations of the uptake after a few hours only, however, appear to show that this is possibly of greater value than the observations of peak uptake, and 4-hour uptakes are certainly very much preferable to observation of the uptake after 24 hours, an index accepted by several clinical centres as suitable for routine adoption as a routine diagnostic screening test. (Werner, Hamilton, Leifer and Goodwin, 1950; Jaffe and Ottoman, 1950).

Recently, Miller, Dailey, Holmes, Alexander, and Sheline, (1951) have shown that the absolute uptake into the gland at any particular time between 2 and 7 hours after administration of the dose is of considerable diagnostic value; Kriss (1951) has demonstrated that the gland uptake one hour after an intravenous tracer dose is able to differentiate sharply between euthyroid and hyperthyroid individuals, and that it also is greatly superior to 24 hour uptakes in rapidity of execution, and improved diagnostic accuracy. Both these observations are in agreement with the findings of this series that gland contents at an early part of the uptake curve have considerable diagnostic utility.

Urine excretion of radioactive iodine is subject to the same objections as gland uptake, with, in addition, the added difficulties inherent in the collection of urine samples. It is moreover, very much less suitable as a diagnostic procedure applicable to outpatients, and the only merit is the relatively small dose of radioactive iodine necessary for its

performance. Skanse (1949) however, professes great faith in the diagnostic accuracy of the results obtained from analysis of 48 hour excretion samples of urine.

Arnott (1951) claims, moreover, that it is possible to devise a technique and organisation that permits of the application of the method of Arnott, Emery, Fraser and Hobson (1949), to routine outpatients in a General Hospital. The method involves the collection of urinary samples in divided time intervals over 48 hours, but equivocal and undiagnostic results are obtained in 10% of cases. Additionally, moreover, there is continual uncertainty regarding the accuracy of the urine collection, an accuracy which is necessary if the results are to be properly interpreted in the light of past experience. Experience in Sheffield, and in most American centres, is rather suggestive that the simplicity of urinary techniques is not repaid by sufficient diagnostic accuracy with the results obtained by them.

Of the figures which give evidence of the speed of uptake of iodine by the gland the best is probably the thyroid clearance rate, Myant, Pochin, and Goldie (1949), but Keating Wang, Luellen, Williams, Power, and McConahey, (1949), found that low clearances may occur in cases of undoubted thyrotoxicosis and the experience in the series here described is similar.

Pochin, (1950) has suggested a simple method of obtaining a measure of thyroid clearance rate by taking the ratio of counts obtainable over the thyroid to the counts over

the thigh one hour after a dose of radioactive iodine. This method, though simple, is less accurate than, and has the same defects as the measurement of clearance rates using the method which involves the taking of blood samples and the same criticism applies to that of Foote and Maclagan (1951) who measure thigh-neck clearance.

The methods so far discussed give figures which are related to the iodine concentrating and retaining capacity of the thyroid gland. The measurements next to be considered are related to the amount of circulating thyroxine and would appear, a priori, more likely to give figures which would correlate well with the deviations of the individual from normal thyroid function. This is found in fact to be the case. The total plasma activity correlates well and the protein bound activity agress very well with the clinical assessment of patients. The most striking difference between these results and those obtained by all the other methods of assessment with radioactive iodine is the way in which nearly all the normal and non-toxic group of patients fall in the normal range.

There is no doubt that measurement of the protein-bound activity of the plasma 48 hours after the administration of a dose of radioactive iodine is the figure which best separates the clinically toxic from the non-toxic group of individuals. This separation is essentially between those patients who require treatment and those who do not, as there must undoubtedly be a

complete "spectrum" of thyroid activity running from complete myxoedema to severe thyrotoxicosis.

The sensitivity of the test at present is not, however, such that measurements of the 48 hour protein-bound plasma activity can differentiate between patients in the normal and "intermediate" groups studied in Part A of this thesis. There is such a slight difference between the groups if mean uptake figures are compared in the two groups (Table II) and this is not reflected in the protein-bound activity estimations. It is likely that with improved counting technique it may be possible, with the same dosage used in this study, to demonstrate that there is in fact, a gradation of protein-bound plasma activity at 48 hours throughout the "intermediate" group. It is understandable that a patient who had had a previous thyroidectomy, and presented clinically with symptoms suggestive of thyrotoxicosis, should have some slight disturbance of thyroid function even if it is not of sufficient degree to constitute frank thyrotoxicosis. The results of the present study have shown that the presence of the clinical manifestations of thyrotoxicosis are in fact associated with protein-bound plasma activity at 48 hours usually in excess of 0.4% per litre, but, with improvements in counting technique it can be anticipated that it will become possible to separate out lesser degrees of abnormality of thyroid function.

Table III

Results, typical of many others, showing reproducibility of radioactive iodine tests of thyroid function.

Case No.	4 hr. gland uptake		48 hr. protein-bound plasma activity	
	FIRST TEST	SECOND TEST	FIRST	SECOND
	% dose		% dose/litre	
Toxic cases				
165	79	78	2.4	2.7
175	46	48	0.67	0.57
I.O.	79	79	0.9	1.2
A.C.	82	84	1.5	1.5
J.B.	57	68	1.2	1.2
Non-toxic cases				
36	37	36	negligible	negligible
125	18	21	negligible	negligible

Radioactive iodine tests of thyroid function are essentially reproducible in a given individual, provided that the test is carried out on successive occasions under the same conditions. We have not felt justified in repeating observations on individuals with demonstrable normal thyroid function, except in a few exceptional cases. Observations can, however, justifiably be repeated in thyrotoxic patients who may be subsequently going to receive therapeutic drinks of radioactive iodine, and experience with such patients shows that, with regard to 4 hour uptake figures and 48 hour plasma protein-bound activity levels especially, the results are closely reproducible, within the limits of biological variability and the statistical accuracy of the physical techniques used.

Typical repeat test results are shown in Table III, in a selection of 5 thyrotoxic and 2 non-toxic patients, the results being representative of many other similar observations that have usually been made in connection with studies of the pharmacological effect of drugs on thyroid function.

The few cases which gave anomalous and borderline results in the 48 hours plasma activity test must now be considered and the relevant information has been collected in Figure 21. Cases 87 and 180 showed results in all the tests which fell into the overlap zones, and it is possible that these patients clinically assessed as only grade 1, were, in fact, not suffering from thyrotoxicosis.

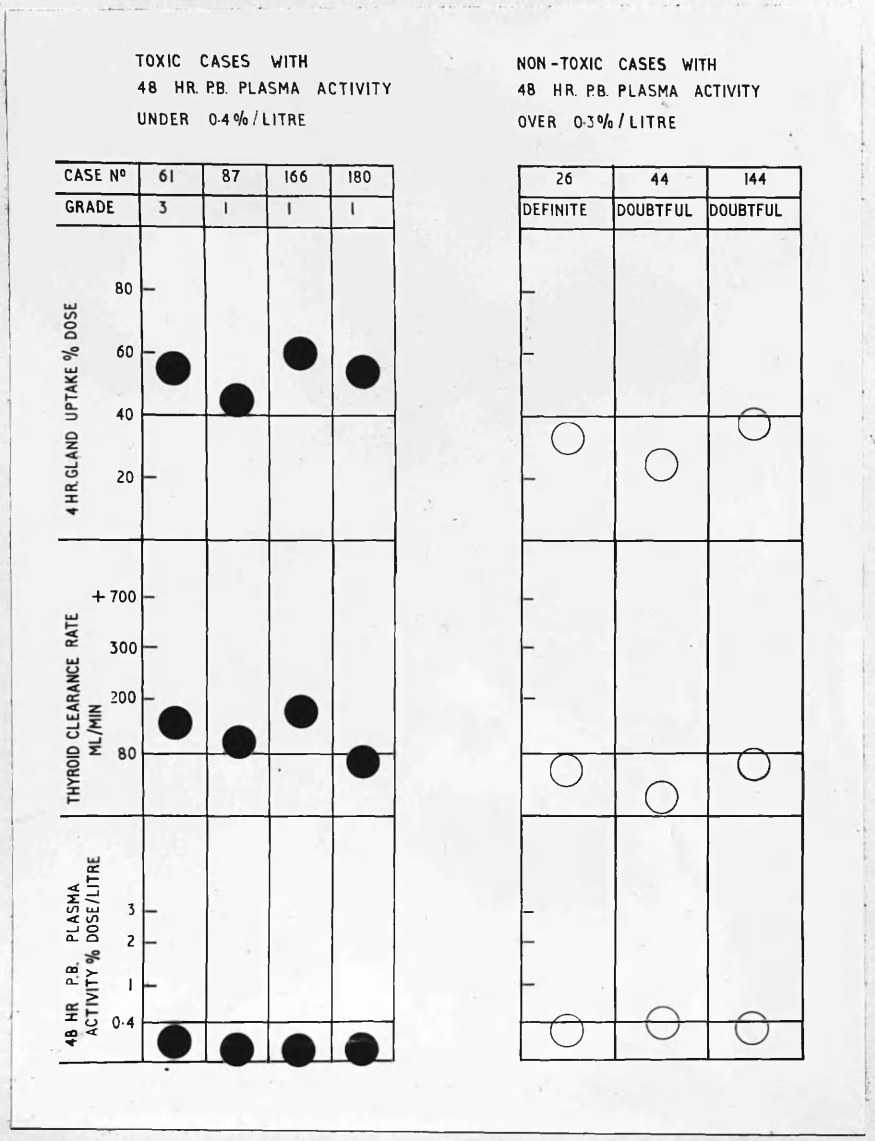

Figure 21. Distribution of results of tests of thyroid function in some anomalous and border line cases. (see text.)

Cases 61 and 166 fell into the toxic group both clinically (grade 3) and in respect of peak and 4 hour gland uptake and clearance rate. There may well have been an error in assay of protein-bound activity in these instances.

All three of the non-toxic cases with 48 hour protein-bound plasma activities of appreciable degree, but less than 0.4% per litre, had results in the other tests that were confirmatory of their non-toxic clinical states.

It is our experience that when a case was really difficult to classify clinically, we found subsequently that the iodine uptake figures and clearance rates were equally unhelpful. Nevertheless, the 48 hour protein-bound plasma activity estimation, being a functional index of circulating thyroid hormone, and quite separate from other indices measuring iodine uptake, would appear to assist in the further classification of these difficult cases, for in many such doubtful cases it is the only index that agrees with the ultimate clinical diagnosis, a diagnosis frequently only reached after many months.

In agreement with other workers, recent previous administration of iodine containing compounds, especially those used for diagnostic radiological procedures such as cholecystograms was found to depress iodine uptake figures considerably and render a radioactive iodine test invalid. All cases included in this series had not had any previous iodine administered. Nevertheless, in two cases not included in this series, clinical

frank toxicity was associated with elevated 48 hour plasma protein-bound activity values, whereas the gland uptake figures fell within the normal range. Both cases had had recent iodine administered to them, one in the form of a cholecystogram four weeks previously, and the other large doses of inorganic iodide within the previous three weeks. Keating, Haines, Power, and Williams, (1950) found that the depressant effect of iodine seldom lasted longer than two weeks, but that a cholecystogram might depress gland uptake of iodine for many months. The ingestion of thyroid extract also depresses iodine uptake very considerably (Skanse and Riggs, 1948).

Furthermore, the renal excretion rate of iodide is proportional to the plasma concentration of radioactive iodine, and the renal clearance rate has the same value in normal and in thyrotoxic subjects Myant, Pochin and Goldie (1949). In the presence of renal disease, however, when renal excretion of the isotope is delayed, it is possible to obtain abnormally high uptakes of radioactive iodine into the gland, thus possibly giving the impression of overactive thyroid function. In such circumstances there is no rise in the total or protein-bound plasma activity at 48 hours, and, by this criterion, toxicity would not be suggested.

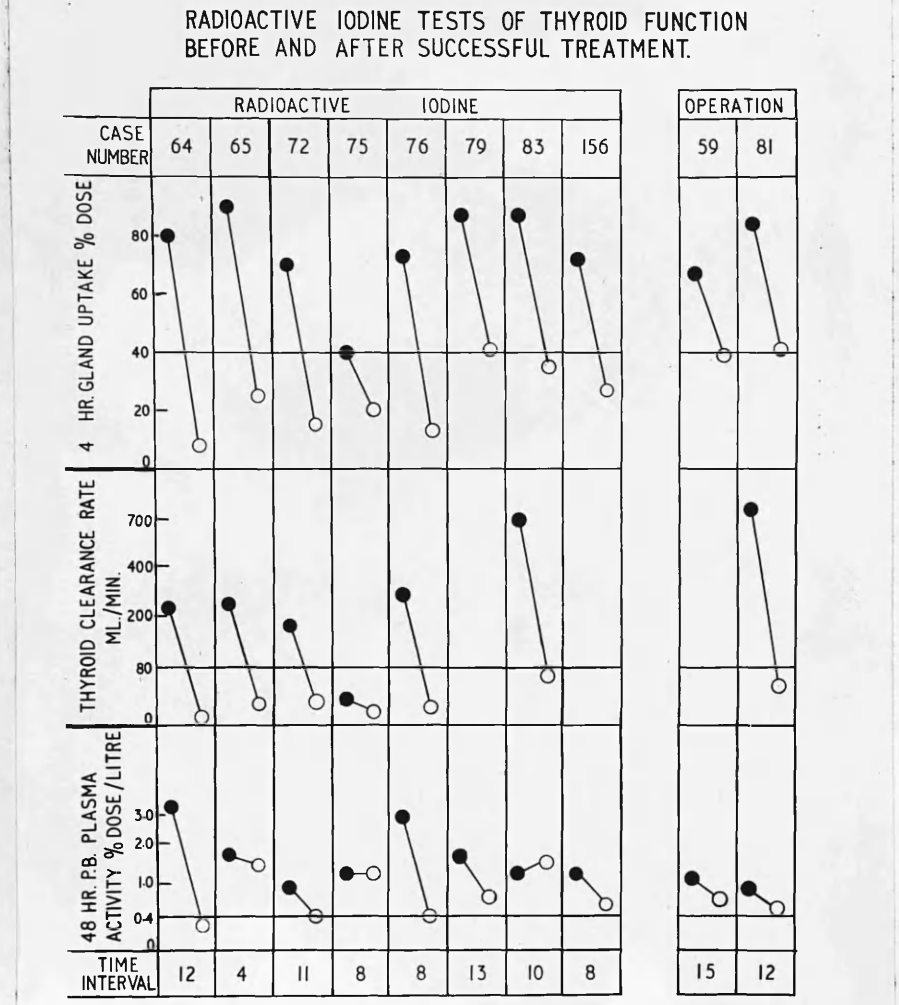

Figure 22. Results of radioactive iodine tests of thyroid function before and after successful treatment. In this figure solid circles represent the results when the patient was thyrotoxic, and open circles the results when euthyroid after treatment.

In most circumstances, therefore, this latter test would appear to be preferable to any other as a diagnostic index, but one inconsistency has been encountered which renders it less valuable in certain cases. The results of the various tests are shown in Figure 22 when they have been carried out in a group of patients before and after successful treatment with either radioactive iodine, or by partial thyroidectomy. Experience in this group of cases has shown that 4 hour uptake figures and clearance rates have more accurately reflected the restoration of clinically normal thyroid function than have the 48 hour protein-bound plasma figures. It can be seen that the initially elevated uptake figures and, with one exception, the clearance rates, all returned within or near the normal range, whereas although, there was usually a fall in the protein-bound plasma levels, it did not usually fall within the range, below 0.4% per litre, that is usually found to be associated with normal and non-toxic thyroid function in the untreated case. In such cases there appears to be a delay in the return of protein-bound plasma activity levels to the normal, following successful treatment, and clinical cure precedes the objective evidence of normal thyroid function as shown by this test. Rall (1950), has demonstrated that in some cases of thyroid disease a significant amount of activity may be present in the diiodotyrosine fraction of the protein-bound iodine in the plasma, and that with the lapse of longer time intervals

between the administration of the radioactive iodine and the withdrawing of the blood sample, the greater is the proportion of the radioactivity present in the thyroxine fraction of the plasma. It is conceivable that in these treated cases this may be a partial explanation of the anomalous cases, and this can only be tested by checking the fractionation of the samples by the method of Taurog and Chaikoff (1948). It is more probable, however, that the phenomenon is related to an alteration in the specific activity of the labelled thyroxine following treatment, only a small amount of functioning thyroid tissue being left, and it is being forced to synthesize thyroxine at a high rate. This hypothesis can only be tested by extensive parallel studies of radioactivity levels in plasma samples whose chemical protein-bound iodine content is being simultaneously estimated.

The findings, however, indicate that as a diagnostic index, 48-hour protein-bound plasma activity figures are less valuable if the patient has had previous treatment by operation or with radioactive iodine, but for how long this anomaly persists, there is as yet no indication.

Nevertheless, it is my considered opinion that if one single and easily performed test of thyroid function is required, then the estimation of the protein-bound plasma activity 48 hours after the administration of radioactive iodine gives the most valuable diagnostic information, and this test is suitable as a screening procedure on outpatients.

It should be realised, however, that no routine test of a single thyroid function is, by itself, adequate to establish the existence of abnormal thyroid activity, and radioactive iodine tests should be regarded as supplementary to other tests. Werner, Hamilton, Leifer, and Goodwin, (1950) claim that the combined use of gland uptake of radioactive iodine, basal metabolic rate determination, and chemical estimation of protein-bound iodine leads to 95% accuracy in the assessment of overall thyroid function. Similarly, with regard to the use of radioactive iodine, we have felt that if one is going to obtain and use the equipment necessary, it is worth while investigating every patient as fully as possible, so as to gain a composite picture of different aspects of thyroid function. From such a study the most accurate deductions can be drawn regarding the degree of over or underactivity of the gland.

The primary aim of this investigation was to define the best objective tests which would indicate the presence of thyrotoxicosis. There was not made, therefore, a detailed attempt to differentiate between the mechanism of primary thyrotoxicosis, and thyrotoxicosis secondary to previously existing adenomata or nodular goitres. The two groups are roughly separated in Appendix III and IV and the means of the results of the investigations in these two groups have been separately presented in Table I. The metabolism of radioactive iodine appears to be very similar in both groups, but we have

no evidence that it is identical.

Results of tests of thyroid function using radioactive iodine should always be regarded as supplementary and not replacing any of the other information available to the physician. The final decision must always be taken with all the information available from all sources, to be co-ordinated by the physician to the best of his ability and in the light of his experience.

There will always remain patients about whose thyroid function the clinician remains in doubt even after the fullest clinical and laboratory investigation. If their iodine metabolism is investigated by the isotope technique valuable additional information is obtained and it is felt that great reliance can be placed on these results. The accuracy of the final diagnosis with its therapeutic and prognostic implications is thereby greatly enhanced.

2. The Diagnosis of Thyrotoxicosis Factitia

The fact that, as has been shown above, true thyrotoxicosis is associated with an increased gland uptake of iodine renders possible the detection of thyrotoxicosis due to the ingestion, usually overtly, of thyroid extract. Such patients, some of whom have been described by Skanse and Riggs (1948) show the clinical features of thyrotoxicosis, an elevated basal metabolic rate, and, in contrast to true thyrotoxicosis, very low or negligible uptake of the isotope into the gland, the greater part of the tracer dose being excreted in the urine. This finding reflects the depression

of endogenous thyroxine production by the ingested extract.

3. The Diagnosis of Myxoedema

On the basis of the cases studied in Part A of the study of the techniques applicable to the diagnosis of thyrotoxicosis, it can be seen in Figures 6 and 7 that myxoedema is probably more accurately diagnosed by in vivo measurements of gland uptake than by 24 hour urinary excretion, clearance rates, or plasma activity levels. Nevertheless, from the practical point of view, as there is a delay in the excretion of the isotope, probably the most useful supportive test for the diagnosis of hypothyroidism is the raised urinary excretion of the isotope in the 24-48 hour period, as shown by Skanse (1949) and Arnott, Emery, Fraser and Hobson (1949).

Primary and secondary myxoedema can be differentiated by the radioactive iodine technique, as an initial low uptake of the isotope can be raised following the injection of thyrotopic hormone, if the myxoedema is secondary to a pituitary deficiency. This does not occur in primary myxoedema. (Stanley and Astwood, 1949); Reiss, Hemphill, Murphy, Halkerston and Badrick, 1949). I have no experience of the use of this particular application of radioactive iodine.

4. Diagnosis of Retrosternal Goitre

Not infrequently the presence of a retrosternal thyroid gland, or retrosternal extension from a normal thyroid gland, may be suspected as the cause of obstructive symptons of various degrees of severity. Occasionally also, thyrotoxicosis

may be found with little or absent glandular enlargement, and in some of these cases the overfunctioning gland may be situated retrosternally. Such cases can easily be demonstrated, as has been done by Ansell and Rotblat (1948), by the localisation with a collimated Geiger counter of the site where administered radioactive iodine is concentrated. By a similar technique it is possible to exclude, or confirm, an intrathoracic thyroid as the cause of an obscure mediastinal tumour detected either clinically or radiologically.

Our experience is that the technique is easily applicable, and when the necessary equipment is already available, it is very well worth while administering a tracer dose of the isotope to any patient in whom there is doubt regarding the nature of a radiological shadow in the thoracic inlet, or the cause of unexplained mediastinal obstruction. In no case, however, have we found an unsuspected goitre retrosternally, although clinical and radiological evidence of goitre has been confirmed on several occasions. In numerous instances the technique has been used to exclude functioning thyroid tissue as the cause of a suspected obstruction. It should always be remembered that the great majority of cancers of the thyroid do not concentrate iodine, and a negative result to a retrosternal "search" for concentrated radioactive iodine does not rule out the possibility of malignancy in an intrathoracic goitre, with replacement by tumour of all the normal thyroid tissue.

5. The Diagnosis of Benign Tumours of the Thyroid

The localisation of radioactive iodine in thyroid tissue makes it possible to determine whether or not a tumour in the thyroid is concentrating more, or less, iodine than the surrounding thyroid tissue. This can be done by directional counting with a Geiger counter so as to be able to find the relative concentration of the isotope in the tumour, as described by Dobyns, Skanse and Maloof (1948) who have shown that some tumours concentrate more, and some less iodine. Means (1949) has aptly described these as "hot" or "cold" modules respectively, and the solitary toxic thyroid adenoma in a typical "hot" nodule. A modification of this method with a less well collimated counter, was used to show that cases 87, 89 and 92 (in Part A of the Diagnosis of Thyrotoxicosis section of this thesis,) had concentrations of the isotope in the adenomas several times greater than the concentration of the isotope in the surrounding gland.

Conversely, nodules in the thyroid which show less activity may be benign, non-functioning, ademonata or they may be malignant growths. The demonstration by this technique of absence of iodine concentration at the site of an abnormal thyroid swelling may be taken as supportive evidence that the swelling is carcinomatous.

Alternatively, the technique of autoradiography may be used to demonstrate the relative concentration of iodine in tumours and Cope, Rawson and McArthur (1947) and Dobyns and

and Lennon (1948) have studied thyroid function by this technique. It, in principle, involves the radiation from the isotope being recorded on a photographic plate so that its presence can be detected in a histological preparation. In essence, the usual histological sections are mounted on plates or slides coated with photographic emulsion which are then developed and fixed after exposure for several days, and finally stained. The anatomical structures of the section are then seen with superimposed upon the section the blackening due to the radiation from the contained radioactive iodine.

The ability of carcinomatous tissue to concentrate radioactive iodine can be assessed in this way from biopsy specimens and the information used to guide treatment. (See Section on Treatment of Carcinoma of Thyroid).

6. Diagnosis of Carcinoma.

As just mentioned, the isotope can be used to detect increased or diminished iodine concentrating ability in a tumour and this can be of some value in the diagnosis of carcinoma of the thyroid.

Its real use, however, is made possible in those few cases, about 15 or 20% at most, of carcinomas that actually do concentrate iodine. Metastases of such growths may not infrequently be detected, if appreciably distant from the site of the thyroid, by the gamma rays emitted from them.

In this way functional boney, pulmonary, or glandular secondaries may be found. As will be described later, occasionally such a metastasis may be induced to concentrate iodine after removal of the primary growth and normal thryoid tissue, even although initially little iodine concentrating ability in the metastasis may be evident.

SECTION IV.

THERAPEUTIC APPLICATION OF RADIOACTIVE IODINE.

1. The Treatment of Thyrotoxicosis

Principles involved in the use of radioactive iodine

The treatment of thyrotoxicosis and toxic adenomata has traditionally been either by surgical excision of an arbitrary amount of the overactive gland, or alternatively, by the administration of suitable antithyroid agents, to prevent the synthesis of the thyroid hormone, the presence of which in excess quantities in the circulation is responsible for most of the symptoms of the disease.

Radiation by X-rays has been regarded as a satisfactory form of treatment by some people, but its chief disadvantage is that it is difficult to deliver an adequate dose to the gland without damaging the skin and causing severe mucosal reactions in the trachea and oesophagus. The biological effect on the tissues of the radiation from radioactive iodine is similar to that of X-rays; because, however, iodine is in general specifically concentrated in the thyroid gland, it is possible to deliver a very high local dose of radiation to functioning thyroid tissues with only a minimal effect on other organs in the body. The greater part of the therapeutic effect of radioactive iodine is provided by the beta radiation emitted by the isotope, and as this does not travel further than 2.2. millimetres in tissue, there is little effect on the organs beyond the capsule of the gland. Radioactive iodine is, therefore, a therapeutic weapon with which highly specific

treatment can be given to one particular type of tissue - thyroid gland tissue, that concentrates iodine.

Practical Application

Radioactive iodine was first used in the treatment of thyrotoxicosis by Hertz and Roberts in 1942, and reports of its use have appeared from several American centres. Soley and Foreman (1949) have contributed a valuable review on the subject. More recently further series of American cases have been reported by Werner, Quimby and Schmidt (1949(b); Williams, Towery, Jaffe, Rogers and Tagnon (1949); Feitelberg, Kaunitz, Silver, Simon, Wasserman, and Yohalem (1950); Gordon and Albright (1950), Moe, Adams, Rule, Moore, Kearns and Clark (1950); Shipley, Storaasli, Friedell and Potts (1950); and McCullagh and Richards (1951).

Because, however, radioactive iodine did not become available for general clinical use in this country until very much later than in the United States, no reports of its application in the treatment of thyrotoxicosis are yet available from this country, and the series described here represents the first group of patients in Europe treated with the isotope.

Selection of Cases

Opinion regarding the indications for radioactive iodine therapy has not yet crystallised and every group of workers in the field has come to its own conclusions regarding the policy to adopt. Chapman, Corner, Robinson and Evans (1948) found iodine concentrated in the human foetal thyroid about the fourteenth week of gestation and accordingly Chapman and Evans (1949) have stated that the only clear indication against the use of radioactive iodine for the treatment of thyrotoxicosis is in patients beyond the fourth month of pregnancy. Because, however, there is still not full knowledge regarding the late effects of internally administered radiation from radioactive isotopes, many groups are still restricting its use to certain categories of patients. Crile, McCullagh and Glasser (1949), have decided that it is the treatment of choice for those patients with thyrotoxicosis recurrent after operation, for those who are bad surgical risks and for elderly patients. Williams (1947) some years ago gave similar indications, and, in addition, included sensitivity to, refractoriness to, or lack of co-operation in the taking of antithyroid drugs such as the thiouracil group of compounds, and Werner, Goodwin, Quimby and Schmidt (1950) agree.

In general, current British opinion is to the effect that it is primarily indicated for recurrent thyrotoxicosis, (Trotter, 1950), and opinion regarding the other categories will form

Table IV

Summary of previous treatment given to cases of thyrotoxicosis treated with radioactive iodine.

		No. of Cases
Recurrent thyrotoxicosis after operation.		8
Patients who had had reactions to, or failed to maintain a remission following, the use of methyl thiouracil:		
where operation contraindicated,	6	
where operation refused,	3	
where operation not offered,	5	14
Patients given radioactive iodine as the treatment of election:		8
Total cases treated		30

as experience accumulates in this country.

The principle adopted in the selection of patients discussed in this series has been that radioactive iodine therapy has been suitable for patients in the older age groups, unless with large or unsightly goitres causing tracheal pressure or deviation, but that in certain circumstances it may be the most suitable form of therapy whatever the age of the patient.

The first patient was treated on 12th January, 1949, and up to 31st July, 1951, a total of 49 patients received radioactive iodine therapy for thyrotoxicosis and 30 of these have been observed following treatment for 3 months or longer; these cases only will be discussed and the results analysed.

Full details of all cases are given in Appendix VIII, and for the purpose of this section of the thesis, the cases are renumbered, with cross reference to their numbering in the diagnostic section.

The cases can conveniently be grouped into categories regarding their selection for treatment, and these are summarised in Table IV. It can be seen from this table and from Appendix VIII that there had been a failure of other methods of treatment in all cases except in the eight patients in whom it was the treatment of election. These 8 were all over 45 years of age except one male and one girl of 22. She had severe exphthalmos and was unsuitable for operation, and it was not felt justifiable to treat her with methyl

thiouracil as she lived a very long way from hospital and was unable to attend for frequent supervision of therapy.

The series consists of 24 women and 6 men, the average age of both sexes being 48, but the range of ages was 20 to 73 years. Twenty five of the patients were classified as having diffuse and five as having nodular goitres.

Technique Used

All cases treated were studied as in-patients and all investigations were carried out in the medical wards and adjoining laboratories. When the patients had been fully assessed, and preliminary tracer investigations completed, they were transferred for their therapeutic dose of radioactive iodine to the Radiotherapy Wards of the Infirmary. This was done to isolate patients receiving large doses of radioactive from others receiving tracer doses and in order to minimise the possibility of contamination of samples obtained from patients.

The solutions of radioactive iodine used, being of very much higher activity, 500 to 1000 times as much, as those used in tracer tests, were handled with especial care and precautions; dispensing of the required dose from the solution as received from Harwell was done by remote control methods.

The patients drank the radioactive iodine solution through a bent glass tube and all patients were rehearsed in this technique using water before being given the active solution.

All urine from patients undergoing therapy was stored in cylindrical cans whose simple geometric shape made possible the estimation of urinary volumes without further handling. Faeces were not normally kept unless contaminated with urine but were put down the sluice with repeated flushings. Urine was normally kept in any one container until the activity had decayed to below 1 millicurie. Carrier sodium iodide was added before it was put into the sluice emptying into the main hospital drain. Not more than one millicurie was so discarded per week.

The patient undergoing therapy was kept isolated in a separate ward. Crockery, bed pans, etc., were used only in that ward and were checked for contamination at the end of the treatment. Urine and blood were taken wearing rubber gloves and gowns. All bed linen and towels were checked for contamination after the patient had been discharged and any article which showed appreciable activity was washed in a machine by itself.

After discharge from hospital, usually about a week or ten days after the therapeutic drink, patients were seen one week later at the Outpatient Endocrine Clinic, and thereafter they were seen at two or three week intervals until they became clinically euthyroid. Thereafter they were seen at increasing intervals, and all are currently under observation.

Dosage

The problem of the selection of the correct number of millicuries in the drink of the isotope to be given to each patient is of fundamental importance and is dependent on several factors, reviewed by Williams, Jaffe, Towery, Rogers and Tagnon (1949). Most American groups have aimed at giving a drink containing about 100-200 µcs. per gram of estimated thyroid mass. It has been felt in Sheffield, however, that, insofar as it is practical and possible, a careful attempt should be made to predict and administer, a drink for each patient which will result in a dosage in "equivalent roentgens" (e.r) (being the total of beta and gamma ray dosage) to the thyroid gland of between 8000 to 10,000 er.

The roentgen dosage following a drink containing a specified numbe of millicuries is dependent on three variables, characteristic of the patient at the time of therapy, not all of which can be accurately predetermined. These are (a) the fraction of the total active iodine administered, taken up in the gland (b) the rate of elimination of the iodine from the thyroid and (c) the total mass of the gland. The first two of these can be determined by a preliminary tracer investigation and this must be done on all patients for whom therapeutic doses are contemplated. Until recently we have only been able to determine the mass of the gland by palpation, and this can be no more than an intelligent guess. In the series to be described palpation estimates have been

used in dosage assessments, but a technique has now been devised by Mr. J.C.Jones, Assistant Physicist at the Sheffield National Centre for Radiotherapy whereby it is possible to obtain a more accurate and objective estimate of gland size by the use of a collimated Geiger counter.

The formula that has been used in calculating dosage is:

Dose (D) = $(210 \pm 10) \times \frac{T.U.M.}{W}$ equivalent Roentgens, (e.r.) where

T is the total (not biological) half life, i.e. the time taken for the actual measured radioactive content of the gland to fall to half its initial peak value, (days)., U. is the peak value of the percentage of the administered iodine taken up by the thyroid; and W is the mass of the thyroid in grams, estimated clinically by palpation.

This dosage includes the contribution of both beta and gamma rays, the beta ray dose being independent of the shape of that gland, which does affect the gamma ray dose, but in any case the latter component is only some 10% of the total dose. The factor (210 ± 10) has been calculated from the average beta ray energy and that of the gamma rays emitted, using suitable data provided for the purpose by the Atomic Energy Research Establishment, Harwell.

Generally speaking, the tracer measurements of peak uptake and of half-life are fairly well reproduced by the therapeutic drink, and the predicted dose actually delivered to the gland. Table V shows, in the first 20 cases of this

Table V

Comparison of results obtained from measurements following tracer and therapeutic drinks of radioactive iodine.

Case No.	Peak uptake, %		Total ½ life (days)		Dose (e.r.) Predicted from	Calculated from
	Tracer	Therapy	Tracer	Therapy	Tracer	Therapy
1	82	72	-	5.8	-	12,000
2	75	77	5.4	6.1	8,700	9,900
3	72	73	3.1	20 after 2 days.	6,750	10,550
4	75	16	3.1	3.7	7,100	1,800
5	75	69	1.60	1.43	2,400	1,930
6	60	60	6.4	4.0	11,000	6,900
7	61	60	3.0	3.1	7,500	7,700
8	71	70	-	6.2	-	15,700
9	77	86	3.7	3.1	10,200	9,500
10	76	85	3.1	2.8 & 5.4	7,000	10,600
11	62	56	5.0	5.2	6,700	6,600
12	87	93	3.7	3.4 after 1 day	11,700	8,200
13	61	54	4.9	2.6 & 6.8	7,800	7,400
14	92	87	2.6	1.79 & 3.32	7,000	6,200
15	78	87	3.8	5.9	8,000	13,600
16	85	79	3.9	4.8	9,500	11,000
17	75	98	3.1	2.3 & 3.7	10,000	12,700
18	77	84	5.0	4.5	9,500	9,700
19	85	87	4.5	5.4	10,500	12,700
20	87	77	4	5.4	5,000	5,600

series, how these two factors varied on the two occasions. It can be seen that the total half life shows greater divergence in the therapeutic drink fromthat predicted for the tracer dose, than did the peak uptake. Doses calculated retrospectively from data derived from measurements following therapy are seen to correspond fairly well with the expected dose, and variations are chiefly due to variations in the total half life. This appears to be an unpredictable biological effect which must be taken into consideration when prescribing the dose for the patient. In case 5 the tracer total half life was only 1.6 days, and this meant that, to deliver an adequate roentgen dosage to the gland a high millicurie dosage was necessary. If following the therapy drink the isotope had had a longer total half life than expected, over-irradiation of the gland would have occurred. Accordingly, therefore, an intentionally small dose was prescribed, in her case, but in the event the total half life of the therapy drink was shorter than expected, and the dosage delivered therefore quite inadequate; a second drink was later given.

Nevertheless, despite occasional variances, dosage can be rendered more precise if preliminary note is made of the half life, as of the uptake, in the tracer investigation.

The greatest error in dosage prediction is likely to be introduced by estimations of gland size. Williams, Jaffe, Towery, Rogers and Tagnon (1949) and Werner, Quimby and Schmidt (1949), found close agreement with practice between estimated

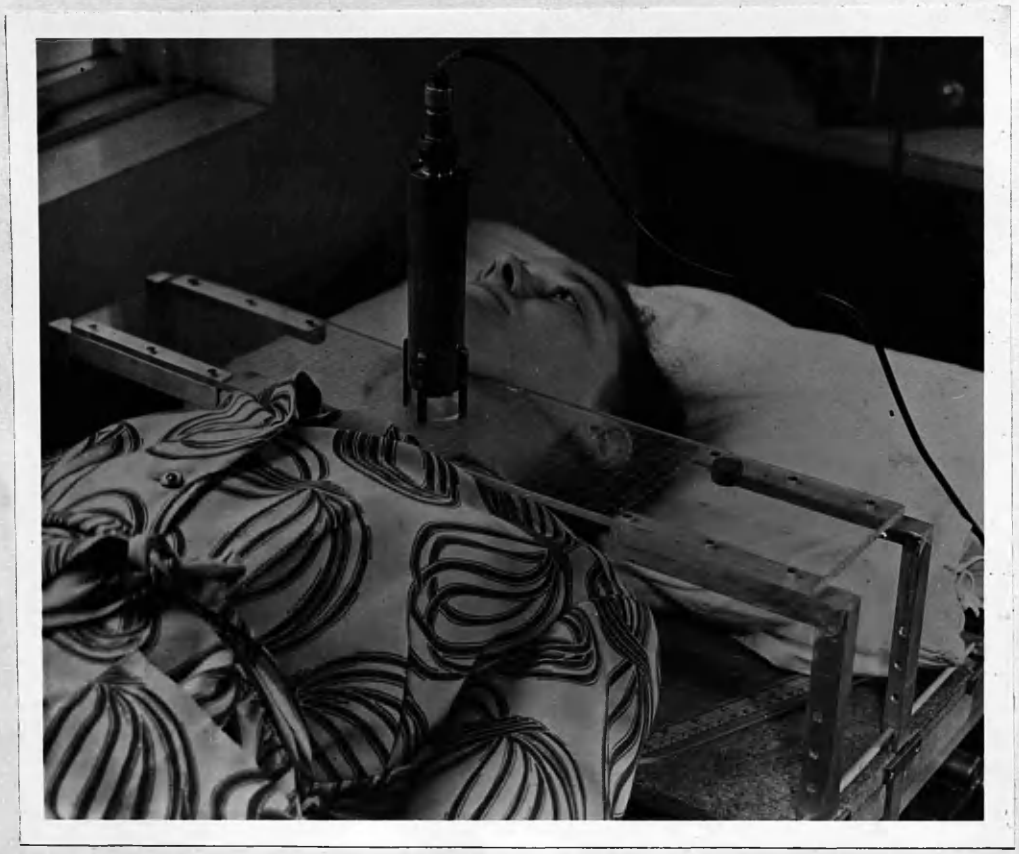

Figure 23. Equipment used to determine the distribution of radioactive iodine in the thyroid gland, using a collimated Geiger counter.

and actual gland size as found after operation, the error with the latter workers being 30%. I have not an extensive comparative series to check on clinical estimates of gland mass but it is felt that the inaccuracies of the method are not such as to affect seriously the estimations of the dose given.

In order to check this and to provide an independent and probably more accurate method of estimation, an attempt has been made recently by Mr. J.C.Jones in Sheffield to develop a technique of estimating the gland volume by means of Geiger counter measurements. The counting rate, produced in a highly collimated gamma counter (Veall, 1950) is recorded when this is moved from point to point in a plane over the gland. This gives an estimate of the amount of active iodine within the field of the counter and if the concentration of the iodine is uniform, a figure proportional to the thickness of the gland in that direction.

The counting rate is measured with the counter axis perpendicular to both the coronal plane and the saggital plane at centimetre intervals. The arrangement for the coronal plane is shown in Figure 23. A bridge consisting of a perspex sheet on which a co-ordinate system is ruled, is placed over and as near as possible to the neck of the patient who lies on her back with neck extended. The counter, which stands on three short legs, is moved from point to point in the plane.

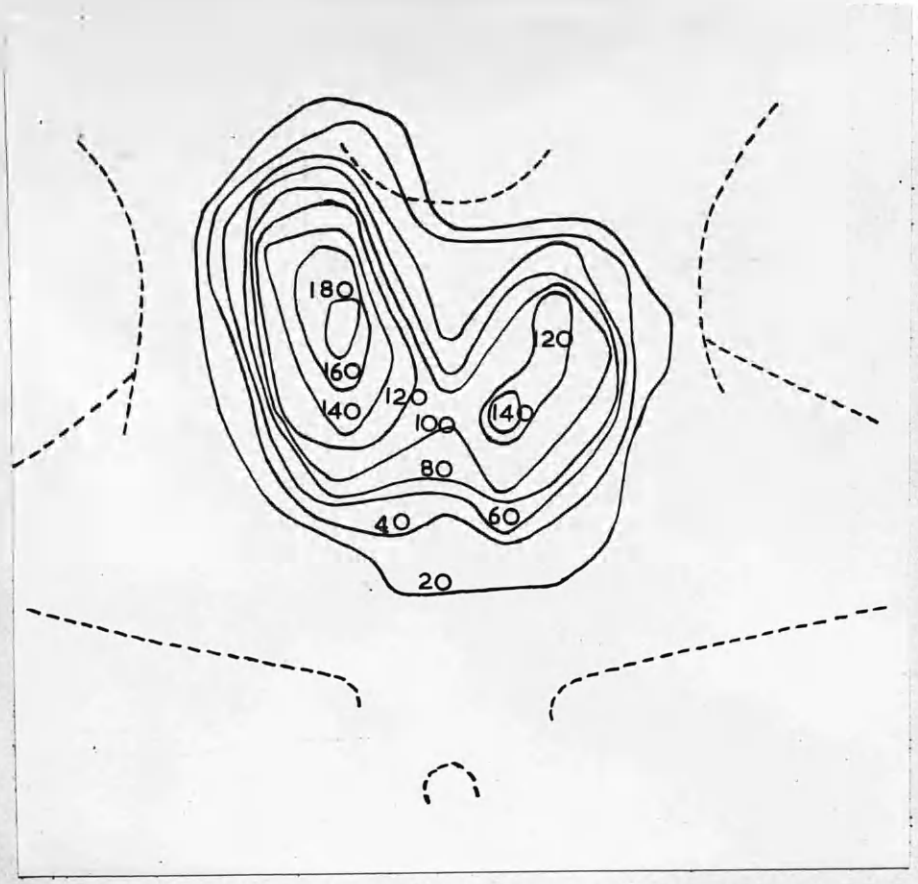

Figure 24. Distribution of radioactive iodine in the thyroid gland three days after ingestion of a therapeutic dose. The contours are lines along which the counting rate per minute in a collimated Geiger counter was constant.

For measurements with the counter axis perpendicular to the saggital plane the patient remains on her back and the counter is placed horizontally in a stand which can be raised by the insertion of wooden blocks and can be moved horizontally along a scale.

Diagrams are drawn showing lines of equal counting rate. A normally shaped thyroid produces diagrams similar to that shown in Figure 24. Anatomical features are noted on the co-ordinate system and transferred to the diagram as shown. Another diagram is drawn from the measurements made with the counter in the plane at right angles to the first. These diagrams show the general shape of the gland but even an approximate estimation of the volume presents many difficulties and involves highly complex mathematical and physical computations which are beyond the scope of this thesis to discuss.

The technique has been carefully calibrated by measurements of the volume of models of known shape and volume when these models have been mounted in scattering material to simulate the effect of the tissues surrounding the thyroid. The resulting diagram obtained in the coronal plane for a glass model thyroid is shown in Figure 25. In association with the corresponding diagram in the sagittal plane an estimate of the model's volume was made of 51 ml., the true volume being 63 ml.

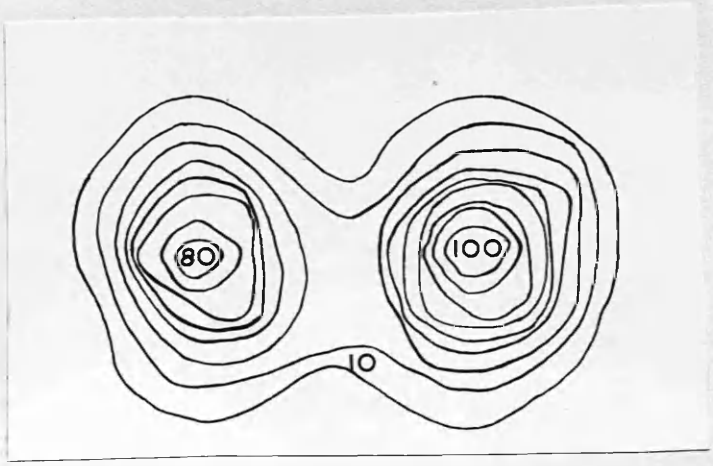

Figure 25. Diagram of lines of equal counting rate over a radioactive glass model thyroid. Estimated volume, 51 ml. True volume, 63 ml.

Sufficient be it to state that we believe that this technique, carefully and intelligently applied, will provide an accurate method of assessment of gland size, and thus define precisely the third variable factor, the knowledge of which is necessary for accurate dosage measurement.

Table VI shows the results of the application of this new technique in ten recent cases, not included in the series here reviewed. The first two columns represent the predicted and actual dosages delivered to the glands, assuming the accuracy of palpation estimates of gland volume. In the last column the calculated volume is used following the measurements made after the therapeutic drink, and differences between the last 2 columns are due to differences between the estimates of gland size as measured by palpation and by the new technique.

So far it has not been possible to make such measurements on patients at the tracer stage with the present size of tracer drink (30 µcs) and volumes can, therefore, be estimated in this way only after therapy, unless a larger tracer drink is given to assess gland size before the therapeutic drink. It is, of course, perfectly justifiable to administer to patients for whom therapy is intended tracer drinks of the order of 100 to 200 µcs. Development of the use of scintillation counting may render even this size of dose unnecessary in the future, as has recently been described by Allen, Libby and Cassen (1951).

Table VI

Comparison of,

Column A: Gland doses predicted from tracer measurements, using the gland volume as estimated by palpation.

Column B: Gland doses as measured following therapeutic drink, using gland volume as estimated by palpation.

Column C: Gland doses as measured following therapeutic drink, but using gland volume as calculated from plot of curves of equal counting rate.

No.	A.	B.	C.
1	8,000	8,600	4,300
2	10,800	13,500	13,500
3	7,900	7,500	7,500
4	8,700	8,300	8,300
5	9,000	5,600	4,700
6	8,000	7,300	4,800
7	11,000	11,800	8,500
8	6,200	6,200	5,600
9	8,500	11,300	10,200
10	8,000	7,300	4,900

In the calculations of the dose delivered, the further necessary assumption has to be made, that the absorbed iodine is distributed uniformly throughout the gland. Measurements described above with a collimated counter show that for most cases of thyrotoxicosis there is little or no gross heterogeneity. Autoradiographic studies have, however, shown heterogeneity larger than the range of the beta particles, so that some cells will receive considerably more, and some considerably less, than the average amount of radiation.

An autoradiograph, illustrated in Figure 26, was made from a biopsy specimen taken from the gland of Case 3 twelve months after her second therapeutic drink of radioactive iodine, and following a further tracer dose of the isotope. It illustrates well the patchy distribution of the isotope in the gland, and also the fibrosis which has occurred in the gland following the previous treatment. There is no way of estimating such a variation in the distribution of the isotope in any particular patient, but it seems likely, however, that the areas which absorb most iodine, and, therefore, presumably those which are most actively producing thyroxine, are receiving doses considerably in excess of the average dose throughout the gland.

Finally, the last unknown and completely unpredictable factor is the undoubted variation from patient to patient of the sensitivity of the thyroid gland to radiation. It seems unlikely that any particular dose, whether stated in millicuries,

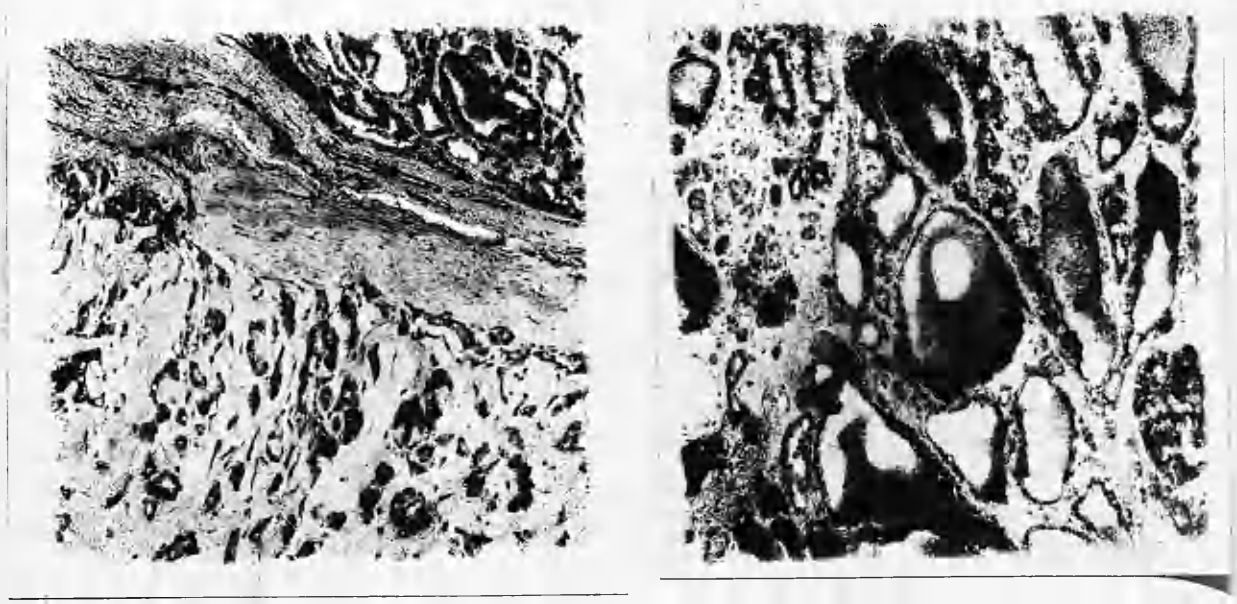

Figure 26. Autoradiographs of thyroid adenoma 1 year after treatment with radioactive iodine, and following a further tracer dose before biopsy. (Case 3.)

The section is counterstained with Masson's light green trichrome. It shows the fibrosis often associated with thyroid adenoma, but in this case attributable in part to previous radioactive iodine therapy. Note the rather patchy distribution of the isotope, the highest concentration appearing in the more active follicles.

or in equivalent roentgens to the gland, should prove exactly suitable for producing normal thyroid function in every patient without an occasional error in one direction or another. The optimum dosage can only be decided by trial and error, in the knowledge that underdosage is always preferable to overdosage, as failure to obtain a remission can always be remedied by the administration of a further dose.

It is known that the thyroid gland is not particularly sensitive to radiation, as it is extremely difficult, apart from the complicating factors that ensue, to induce hypothyroidim by X-ray therapy, and orthodox deep x-ray or radium therapy for hyperthyroidism was often carried out to the limits of skin or mucous membrane tolerance without success. In rats no histological changes, nor reduction in function, are produced by local X-ray doses up to as high as 5,000 r. (Bender, 1948). Results in animals are, however, difficult to interpret, but the consensus of opinion would appear to be that in man a dosage of about 8,000 to 10,000 er. is probably about the suitable level at which to aim in the treatment of thyrotoxicosis, and this has been the dose which in Sheffield we have attempted to deliver to the gland.

Results of Treatment

The clinical status at 31/7/51 of the patients in this group is shown in Table Vll. It can be seen that all patients who have been observed for more than ten months

Table VII

Present clinical status of cases treated with radioactive iodine, related to duration of observation following the last dose of the isotope.

Period of observation (months)	Euthyroid (no. of cases)	Hypothyroid (no. of cases)	Improved (but not euthyroid) (no. of cases)
3 - 10	7	-	8
11 - 24	14	1	-
3 - 24	21	1	8

are cured of hyperthyroidism, one patient only being hypothyroid. Of the patients observed for a shorter period, all have improved, some very considerably and seven of them also are euthyroid, but the remainder require a further dose to complete treatment and render them completely normal clinically. Treatment cannot be regarded as being yet completed in those cases, for the eventual restoration of normal thyroid function can be anticipated in all cases treated, and this has been the experience also of Feitelberg, Kaunitz, Silver, Simon, Wasserman, and Yohalem (1950), although in some cases multiple doses of the isotope may be required.

The relationship of the patients clinical status to the number of doses administered is shown in Table VIII. The only patient who has received 3 doses is Case 3 who had, and still has, a large nodular goitre and she illustrates the fact, as shown by Richard, Crile and McCullagh (1950), that very much larger doses are required for toxic nodular goitre than for thyrotoxicosis with diffuse gland enlargement. The fact that 18 out of the 30 patients were cured with only a single dose is taken as evidence of the value of careful preliminary measurements for dosage assessment.

With regard to the gains in weight following treatment, the patients who improved, but were not rendered completely normal, gained an average of 10 lbs, whereas the group that

became euthyroid gained an average of 19 lbs. The single hypothyroid patient gained two stone (28 lbs) but some members of the euthyroid group put on as much weight, and one patient (Case 9) gained over 47 pounds in weight with residual normal thyroid function. The change in the appearance of this patient is well seen in Figure 27. (p.102)

There was a diminution in the size of the thyroid gland in most cases, including Case 3, the case of toxic nodular goitre with a very large gland. Small pseudo-adenomatous nodules associated with recurrences after thyroidectomy practically disappeared. The diminution of the gland size, and improvement in the patient's facial appearance and demeanour, is evident in Figure 28.(p.104)

It was noted that clinical improvement with remission and disappearance of the clinical signs and symptons of the disease was not apparent for between 3 to 6 weeks, a time which corresponds with the experience of Hursh and Karr (1951). The time that elapses until the clinical response is evident depends to a certain extent on the pre-existing level of toxicity, but an early clinical improvement may herald eventual evidence of temporary or permanent hypothyroidism due to overtreatment. Using this isotope of iodine, I^{131}, it takes more than 20 days to have 90% of the radiation delivered, and this partly accounts for the delayed response. If there is no improvement within 8 weeks, the initial dose can be considered to have been inadequate and a further drink is

Figure 27 (a). Faces of patient (Case 9) before, (23.12.49), and after, (8.12.50) treatment with radioactive iodine.

indicated. This usually happens in those cases where the calculated initial roentgen dose to the gland is too low (Cases 4, 5 and 20) but knowledge of the delivered roentgen dosage is not a reliable guide to the clinical response. Figure 29 shows the effect of the initial dose in this series, the dose to the gland being calculated retrospectively from the actual uptake of the isotope into the gland, and its biological half-life, the volume of the gland being estimated clinically by palpation. (p.107).

It can be seen, as would be expected, that there is no relationship between the actual total number of millicuries of radioiodine in the drink, and the effectiveness of the dose.

All the 18 patients who became euthyroid after a single treatment, received more than 6,000 e.r., the average dose being 9,5000 e.r. Those patients in whom the response was inadequate usually received a dose well below this level, either because the uptake of the therapeutic dose was smaller, or its biological half-life shorter, than anticipated. The average dose in those who failed to respond sufficiently to the first dose was approximately 8,000 e.r. The patients who required more than one treatment to become euthyroid received a total average summated dose of 15,000 e.r.

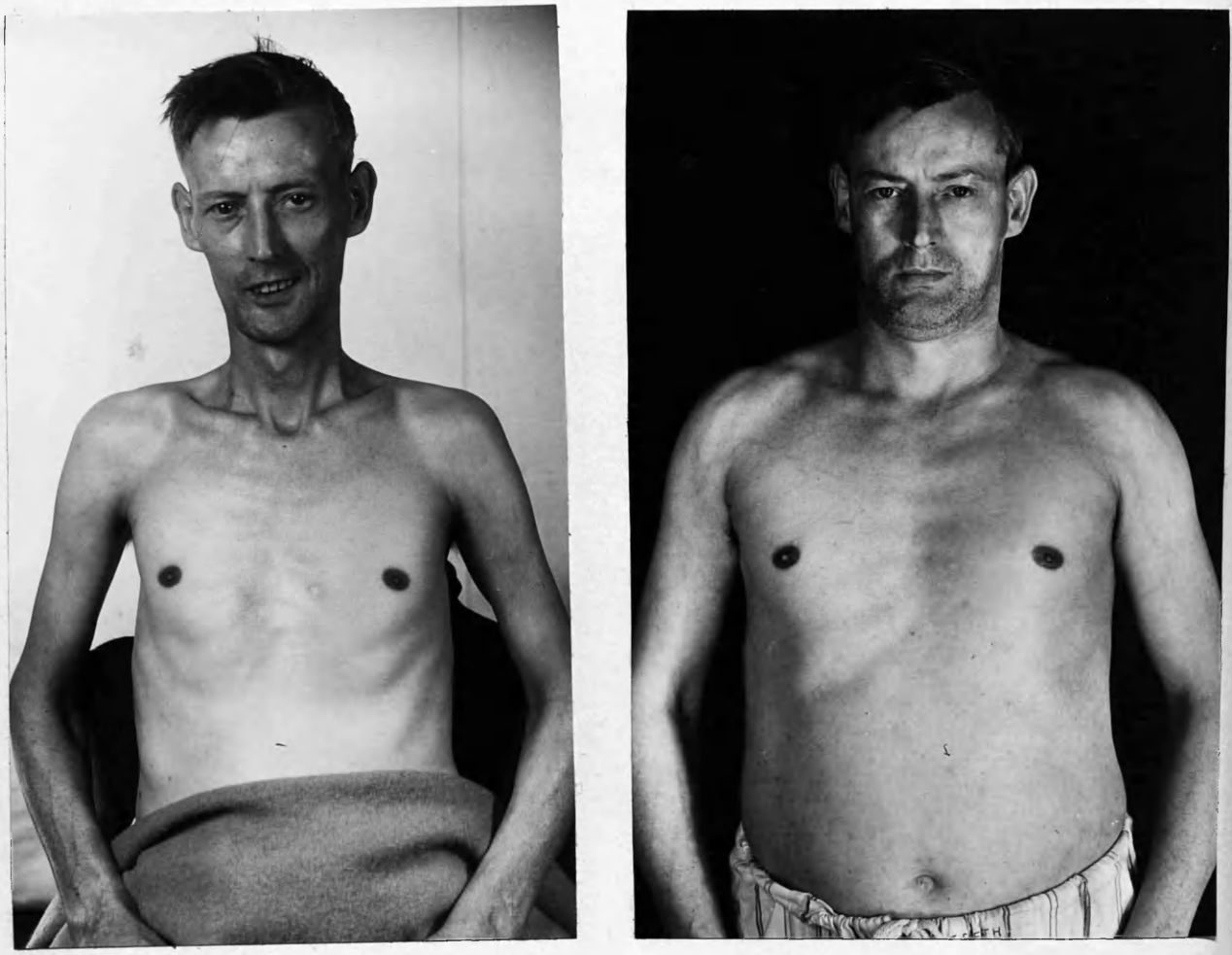

Figure 27 (b). Face and trunk of same patient, (Case 9) before and after treatment with radioactive iodine. Weight gain: 47 lbs. Residual normal thyroid function. (see text.)

A number of the patients successfully treated have had repeat tests of their thyroid function carried out with radioactive iodine, and these results have already been presented and discussed in Figure 22, in Section III, Part B.

Complications

In no case was there any local reaction to the therapy, and there was no hoarseness, laryngitis nor salivary gland reaction in any patient treated in this series, although a few had transient tenderness of the gland for a few days about a fortnight after treatment. Nor was there any general systemic reaction, although nausea and occasional sickness may occur following very large doses of 100 millicuries or more used for treatment of malignant disease of the thyroid.

In no case in this series was there any temporary exacerbation of thyrotoxicosis reported in a few cases by Williams, Towery, Jaffe, Rogers and Tagnon (1949) and mentioned by other groups. It has, however, been observed in one of the cases more recently treated, but responded satisfactorily to routine medical measures including the administration of inorganic iodide. In 3 of the cases of this series, Cases 10 (second dose) 14 and 29, the degree of thyrotoxicosis was very considerable, and a course of methyl thiouracil was given for a period of 4 weeks prior to the administration of the therapeutic dose of radioactive iodine. In these cases the

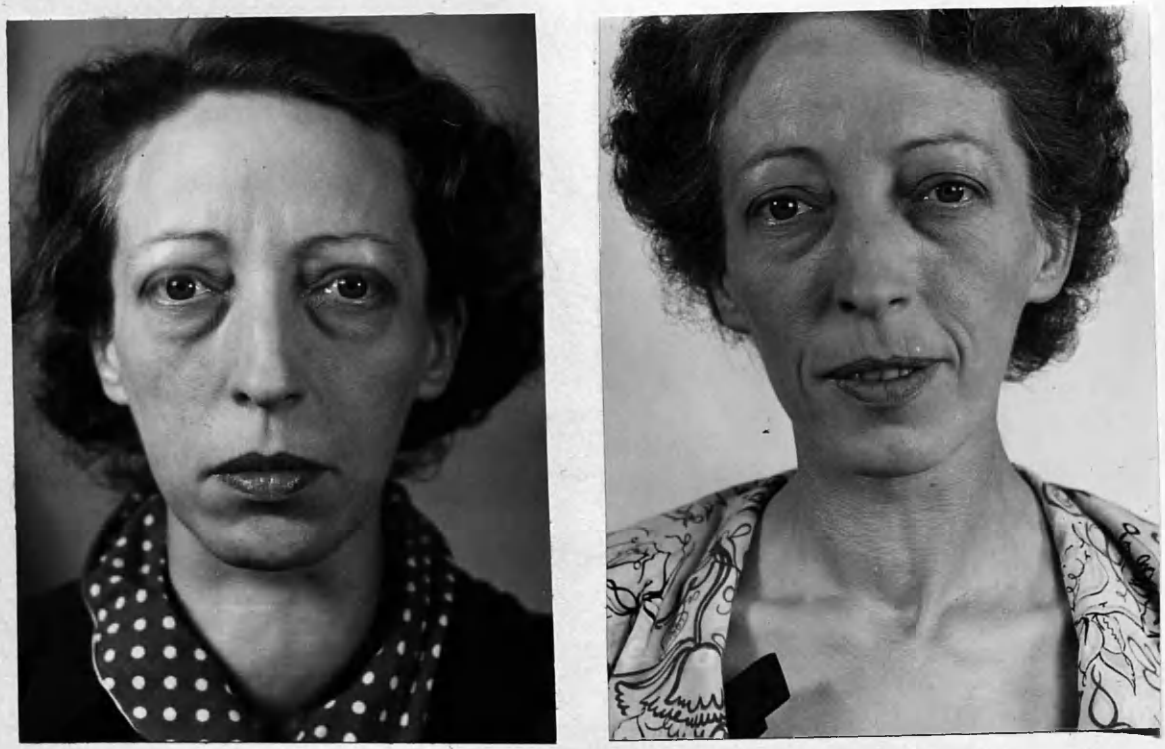

Figure 28 (a). Full face view of Case 10 before, (5.1.50), and after, (21.7.51) treatment with radioactive iodine.

Note disappearance of "stare" and anxious expression, and diminution in gland size. c.f. Fig. 28 (b).

antithyroid drug was withdrawn at least a week before a further tracer dose of radioactive iodine, and it was found that gland absorption had reverted to its previous level, as shown also by Chapman and Evans (1949). The patients were, however, very greatly clinically improved and it is felt that this procedure may reduce the risk of a transient exacerbation of thyrotoxicosis following the therapeutic dose.

Alternatively, it is possible and justifiable to administer small doses of potassium iodide, beginning not earlier than 24 hours after the therapeutic drink, to patients with severe toxicity. This gives the patient the benefit of the well known therapeutic action of iodides on thyrotoxicosis, whereas there is no appreciable effect on the discharge from the gland of the previously administered radioactive iodine, which by that time is practically 100% in protein-bound form. This is now a routine practice in Sheffield with the more severely ill patients.

Hypothyroidism was, unfortunately, induced in one patient, Case 5. She had severe recurrent thyrotoxicosis, and was insufficiently controlled by her first therapeutic drink. The second, however, resulted in slight overtreatment with the gradual onset of many symptons of hypothyroidism and with an associated rise in her blood cholesteral from 205 mg.% to 340 mg.% and she now receives maintenance doses of thyroxine.

Figure 28 (b). Full face view of Case 10 before treatment. Patient would not permit photograph to be taken with her chest bared unless her eyes were covered. Note size of gland in comparison to size after treatment. c.f. Fig. 28 (a).

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

Case 9 was of special interest inasmuch as there was strong evidence of relative suprarenal cortical deficiency at the time when the patient was grossly thyrotoxic. Following his therapeutic dose of radioactive iodine, a very considerable gain in weight occurred (Figure 27), which was at one stage accompanied by evidence of hypothyroidism. Later, however, he was considered on clinical grounds to be in normal thyroid balance, and gland uptake of radioactive iodine was fund to be 20%, in the low normal range.

Arthritis. One patient, Case 19, had a severe attack of gout affecting one hand, beginning about one week after her therapeutic dose. This attack was possibly unassociated

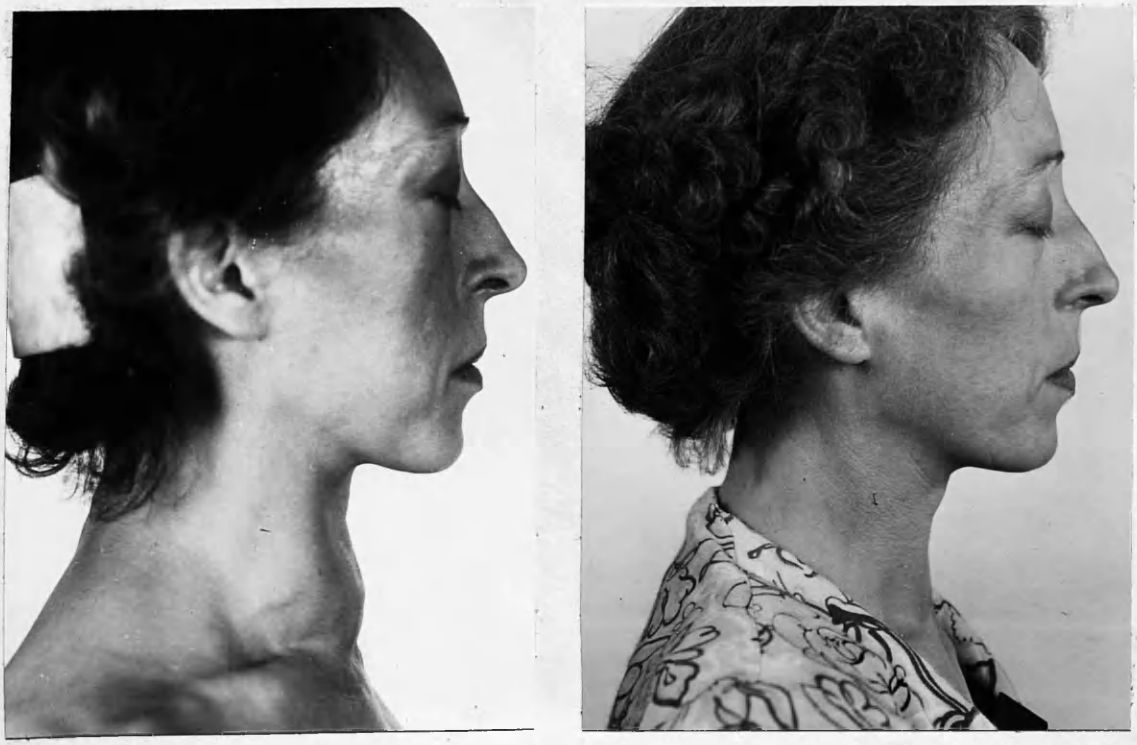

Figure 28 (c). Lateral view of face and neck of Case 10 before and after treatment. Note marked shrinkage of gland.

(N.B. These photographs are typical of other similar records.)

with the administration of radioactive iodine, although it is known that a sudden metabolic disturbance, such as can be assumed to occur in the treatment of severe thyrotoxicosis with radioactive iodine, may sometimes fire off an attack in this condition. A further patient, Case 17, had an attack of arthritis, characterised by painful swelling of his wrist and finger joints and associated with limitation of movement and tenderness of the extensor tendons of his wrist, which occurred four months after his therapeutic dose. The condition, the precise etiology of which is not known, was treated with high dosage of calcium aspirin, and gradually returned to normal with no residual disability. Case 16, who had evidence of old rheumatoid arthritis of her hands, stated that she had a slight increase in the usual amount of pain and stiffness of her fingers in the few weeks following her treatment, but there was no objective alteration in her arthritic condition.

The relationship of the manifestations of joint disease in these patients to their thyrotoxic condition, or to the treatment given, is not clear, but is being at present further studied.

Congestive heart failure had been a recurrent feature in Case 3, and occurred once again a few months after her second dose of radioactive iodine, and again a year later, when she was once again thyrotoxic. She had a large nodular goitre and she received, as already mentioned, the highest

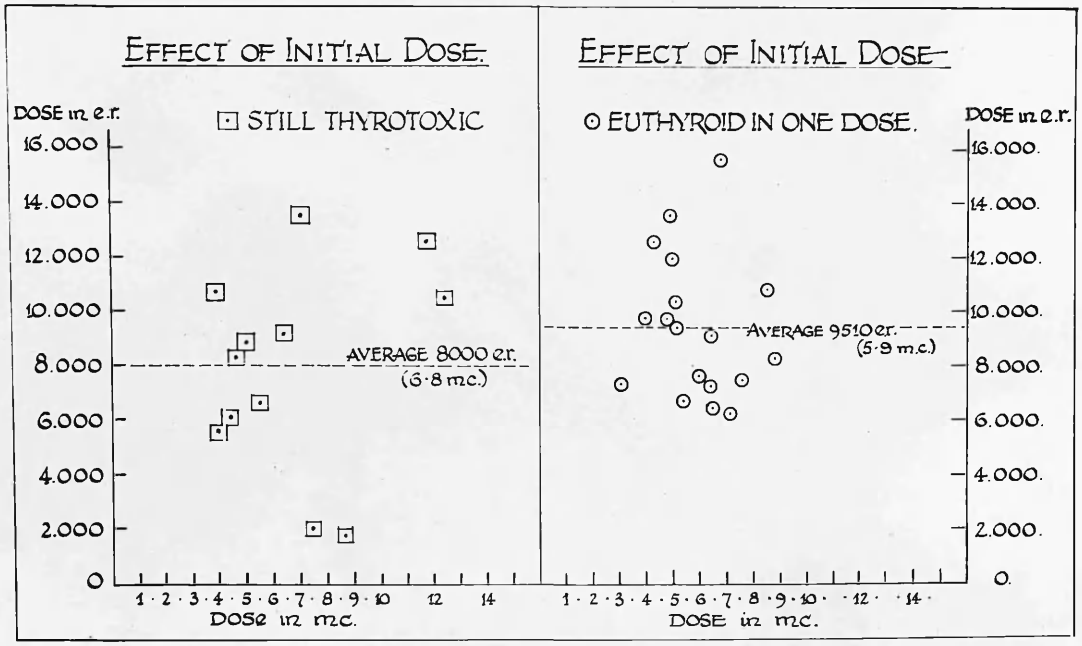

Figure 29. Distribution of doses received in those cases cured with a single therapeutic drink of radioactive iodine, and in those who subsequently required further treatment.

total dosage given. There has been no further recurrence of congestive failure since her third therapeutic drink.

No detrimental effect of therapy was noted on the haemopoietic system, nor on any other organs. Following upon very high dosage of radioactive iodine given to a further case of metastatic thyroid carcinoma, I have observed a fall in blood platelets and a transient fall in the leukocyte and lymphocyte count, but there has been no similar effect in any case treated for thyrotoxicosis. One patient, in fact, (Case 19) had purpura with thrombocytopenia, there being only 90,000 platelets per cu.mm. before treatment, a condition ascribed to her thyrotoxicosis. Following her therapeutic dose of radioactive iodine, her platelets steadily rose to a level of 330,000 per cu.mm. six weeks later.

No alteration in menstrual function has occurred, nor was there any alteration in the menses of a young patient successfully treated with several very large doses of radioactive iodine for recurrent thyroid carcinoma, as will be described later.

Discussion of role of radioactive iodine in the therapy of of Thyrotoxicosis.

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

Medical treatment with one of the thiouracil derivatives is a suitable form of therapy for practically all cases of thyrotoxicosis except those with pronounced tracheal compression or deviation, or in cases where supervision of medical treatment is difficult. Treatment with methyl thiouracil results in a permanent remission of the disease, after withdrawal of the drug, in only about two-thirds of patients, even when treated for over a year. This relapse rate is very much higher if treatment is discontinued before 12 months; Dunlop and Rolland (1950) found that of 72 patients treated for up to 12 months, 50 relapsed, whereas of 54 cases treated for over 12 months, only 18 subsequently relapsed. The great majority of relapses following methyl thiouracil therapy occur within 4 months of withdrawing treatment, and Trotter (1950) showed that relapse is very rare after 30 months from the end of treatment. Iversen (1951) in a considerable series has reported relapse or true recurrence of symptoms in 44% of cases treated.

The real value of the drug is that with it patients may be tided over until natural remission of the disease occurs, natural remission occurring in about 50% of cases even if no effective treatment is given (Albutt, 1897). Its use is associated with a very small mortality, less than 0.5%, and this is entirely due to agranulocytosis (Himsworth, 1948). The incidence of this complication is now very much

smaller than it was soon after the introduction of the drug, as at that time very much higher dosage schedules were used.

About 10% of cases have toxic reactions to the drug which Dunlop and Rolland (1950) found were sufficient to necessitate stopping treatment in 7%, but Iverson (1951) found he had to withdraw the drug in 14% of his patients because of adverse reactions. Such cases can usually be satisfactorily treated by operation. A major inconvenience of methylthiouracil therapy is undoubtedly the necessity for prolonged hospital attendance to control its use, and this has very definite psychological and physical disadvantages.

Thryotoxicosis should be treated surgically by choice where the gland is very large, or where there are pressure effects, and the resultant cosmetic effect is usually good. Surgery has the advantage that cure is more rapid, and more frequently permanent, than in cases treated solely with methyl thiouracil. The chief disadvantages of surgical treatment are that in this country, except in special clinics, the overall mortality rate is certainly considerably greater than 2% (Himsworth, 1948) and the majority of partial thyroidectomies are not carried out by specialists in the operation. There is moreover, an additional appreciable morbidity rate resulting from the operation or complications therefrom, and the patient is left with a scar which may be, especially in young women, a disfigurement.

The great advantage of radioactive iodine is that there is no immediate risk of mortality nor morbidity, and the treatment, from the patient's point of view, is completely devoid of unpleasantness, and supremely simple. There is remission of symptoms associated with shrinkage of the gland without any necessity for either prolonged hospital treatment and attendance or for a scar producing operation. Repeated small doses of radioactive iodine, given without detailed study, will result eventually in full remission in practically all cases, and this is the practice in many American clinics where no specific attempt is made to measure accurately the dose given to each patient. Such advantages as these must be balanced against any possible adverse effect that may result from the radioactive iodine administered. The chief arguments against its more general application centre upon the possibility that malignant changes may be induced in the thyroid gland many years later. It is, however, significant that the type of radiation known to be associated with the later development of malignant change is chronic radiation of low intensity, and not the brief and much more intense radiation provided by radioactive iodine (Werner, Quimby and Schmidt, 1949 (b)). Moreover, malignant change has not been noticed in the gland following external radition by X-rays and Quimby and Werner (1949) reported the results of an enquiry among radiotherapists and thyroid specialists of the late effects on cases treated by X-ray therapy for thyrotoxicosis.

Although malignant disease arose in some cases where the skin had been over-irradiated and in some cases in the trachea and the oesophagus, there was no evidence of malignancy arising in the gland as a result of ionising radiation. Their conclusion was that this complication (malignant change in the gland) if it exists, must be very rare. Although the beta radiation of radioactive iodine is not strictly the same as the radiation of radium and deep X-ray therapy applied externally there is no reason to suppose that it is fundamentally different in its effects, apart from the fact that such radiation is localised to the gland itself and is more intense in places where the concentration may be patchy. On a time scale basis, however, the radiation from radioactive iodine would appear to be intermediate in its effect between a chronic radiation of low intensity and the brief but intense radiation of X-rays.

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

capacity of these surviving cells was impaired.

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

This work must be interpreted with caution in view of the relatively small number of animals used, the high incidence of adenoma formation in the controls that did not receive radioactive iodine, and because increased adenoma formation, with occasionally apparently malignant changes, have been reported in rats by Griesbach, Kennedy, and Purves, (1945), Purves and Griesbach (1946) and Gorbman (1947), following the chronic administration of goitrogens such as thiouracil. Bielschowsky (1945) has shown that acetylaminofluorene enhances

the effects of these agents. Furthermore, Gorbman (1947) showed that the apparently malignant infiltrating thyroid tissue disappeared and the supposedly cancerous glands involuted, on resumption of a normal diet.

Additionally, because of the minute size of the thyroid gland in rats and mice, experimental radiation effects are found in contiguous structures such as the trachea, which are within the range, 2.2 mm., of the beta radiation of radioactive iodine. In man, however, the thickness of the gland capsule and the presence of surrounding connective tissue makes such effects improbable, and Soley and Foreman (1949) point out that if a direct comparison could be made between results in animals and in man, from 210 to 3,500 millicuries would be required to produce total thyroid destruction in an adult of 70 Kg. weight. This is very considerably more than is known to be required, and is approximately 20 to 200 times the usual maximum order of dosage used in the treatment of thyrotoxicosis. This safety factor, derived from animal experimentation, is far greater than is usual with most therapeutic agents.

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

Table IX

Summary of plasma and urine doses delivered following therapeutic drink of radioactive iodine for thyrotoxicosis.

Case No.	Dose per millicurie (e.r.)		Estimated dose actually given in treatment (e.r.)	
	Plasma	Urine	Plasma	Urine
5	11.0	3.0	77	22
6	1.3	2.7	7	15
7	2.8	2.3	16	14
9	3.6	1.8	18	9
10	2.3	1.0	(29 (46	(12 (20

balance, all evidence goes to show that the possibility of such appearances is most remote.

With regard to adverse effects of other types, the possibility of irreversible changes occurring, especially in the gonads, must be considered. Because of the high concentration of the isotope in the gland, there is little irradiation to other body organs, and Gorbman (1950) considers that ovarian sterilisation by radioactive iodine need only be considered as a potential hazard when circumstances are such that thyroid iodine uptake is less than 10%.

In cases of thyrotoxicosis, in contrast to cases of malignancy, a high proportion of the general radiation to organs other than the thyroid is due to the high level of circulating radioactive thyroxine, and in the treatment of thyrotoxicosis the actual ovarian dose is of the same order as the blood dose. The sterilising dose to the ovary is of the order of 250-400 r, and the possible genetic effects of such a dose are analogous to the effects resulting from diagnostic radiological investigations for gynaecological conditions and for pelvic mensuration.

Table IX lists a number of calculated blood plasma and urine doses which were estimated by integrating the plasma concentration with time. They were calculated from the tracer dose measurements of plasma radioactivity and refer to beta dose only, the gamma ray dose not being likely to contribute more than 20% of this dose. Myant (1951) has suggested that the circulating levels of radioactive thyroxine may be lower

following the therapeutic drink than following the tracer measurements in which case these calculated doses would be too high.

The dose received by the cells is not likely to be appreciably greater than the plasma dose, and in most cases will be very much less, unless there is appreciable concentration of iodine in any other part of the body. The dose to the bladder walls will be between one half and one times the urine dose depending on the involution of the bladder surface.

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

In thyrotoxicosis, there is a release of radioactive thyroxine into the circulation and Courrier, Horeau, Marois and Morel (1949) found some accumulation of radioactive thyroxine in the pituitary gland, and in one human case that came to autopsy after a large dose of radioactive iodine, Chapman (1948) found 3% of the isotope in the pituitary.

Gorbman (1950) noted, moreover, the development of non-invasive chromophobe adenomas of the anterior pituitary about 8 months after thyroid-lethal doses of radioactive iodine in most of his treated mice.

Goldberg and Chaikoff (1950) have shown that such changes cannot be produced in dogs nor in rats, and the same workers (1951) proved that feeding of thyroid extract to the irradiated mice prevents the development of the pituitary changes. It is probable, therefore, that they are a compensatory hypertrophy due to the production of complete hypothyroidism in the mice. Similar changes have not been observed in man. Trunnell, Duffy, Godwin, Peacock and Kirschner, and Hill (1950) in a study of the distribution of radioactive iodine, did not reveal a high concentration of radioactive iodine in the pituitary, nor did they find histological changes in the pituitary following high doses.

Kurland, Chamovitz, and Freedberg (1950) in a very similar study found no histological changes in any organ except the thyroid gland.

After careful consideration of all the available evidence, I feel that there is only very little chance of any late effects resulting from the radiation of radioactive iodine. Because of its possibility, however, it is probably wise meanwhile to reserve this form of treatment, in uncomplicated and previously untreated case, for patients in the older age groups. Where, however, there are any factors which increase the risks of operation,

or in any way unduly complicate treatment with methyl thiouracil the remote danger of irradiation hazards should be balanced against the risks and inconveniences involved in either of the more traditional forms of therapy. I believe that in such cases the simplicity and efficiency of radioactive iodine therapy, especially from the patient's viewpoint is such that any theoretical objections to its use can be discounted. This especially applies in the treatment of thyrotoxicosis after thyroidectomy, where antithyroid drugs are in any case less likely to obtain permanent remission, and further operation is notoriously unsatisfactory. For such cases radioactive iodine therapy is the treatment of choice at all ages.

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

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

radioactive iodine can be considered, although, in the case of patients with heart failure, subsequent radioactive therapy is to be greatly preferred to any therapeutic procedure.

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

The other factor which at present necessitates caution in the application of this form of treatment in this country is lack of knowledge regarding the precise dosage administered. As already pointed out, the calculated dosage is based on a formula involving the gland uptake of the isotope, biological half life in the gland , and the weight of the gland itself. If the treatment is to be rational and scientific, as close an estimate as possible should be made beforehand of the dose necessary for each patient. Half life and uptake can be, and should be, determined for each patient before treatment and as close an estimate as is possible made of the size of the gland.

Some American groups have tried to evolve short cuts to dosage assessment such as by gland size alone, (Williams, Jaffe, Towery, Rogers, and Tagnon, 1949); level of toxicity and gland size, (Gordon and Albright, 1950) Feitelberg and his co-workers (1950) assume a biological half life in their dosage assessment of 6 days, an assumption which study of Table V shows to be unwarranted.

Hursh and Karr (1951) summarise three techniques in use in the United States to assess dosage.

(1) Administration of a constant basic small dose to all patients, the treatment being repeated until remission is achieved.

(2) Administration of an oral dose calculated on the basis of a constant number of microcuries per gram of estimated thyroid gland weight. This custom neglects variabilities in gland absorption, half life, and errors in weight estimation.

(3) Administration of a constant number of microcuries taken up by the thyroid per gram of weight. This method is the best of the three, but it also omits measurement of half life, and again gland size estimation is by palpation.

These writers go so far as to reduce to the terms of a nomogram the calculation of the necessary oral dose in millicuries necessary to deliver a dose of 10,000 e.r. to a gland of estimated weight which has a known observed uptake of iodine, the biological half life being assumed to be 6 days.

When a few additional preliminary gland observations during the tracer dose study allow the biological, and hence the total, half life to be calculated ;

when by the technique described it is possible to obtain an objective estimation of gland size; and when the percentage uptake of the isotope is simply determined during the tracer investigations, it would appear to be unnecessary to make inaccurate assumptions in the assessment of dosage.

These devices, while simple, do not permit of the best possible use being made of the isotope, and the aim of treatment should be to cure the patient with a simgle dose.

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

Experience with this small series of cases, and with subsequent cases treated, has convinced those of us working in Sheffield of the many advantages of this form of

therapy. With further experience and the development of new techniques, it will become a method of treatment for thyrotoxicosis suitable for many more cases of this disease than those for whom it is now recommended and used with confidence.

2. The Treatment of Carcinoma of the Thyroid.

Radioactive iodine has not nearly such a well established place in the treatment of carcinoma as it has gained in the treatment of thyrotoxicosis. This is chiefly because such a small proportion of carcinomata of the thyroid exhibit the physical property of being able to concentrate iodine, this property being essential if the isotope is to be of any value in the treatment of the condition.

Frantz, Ball, Keston and Palmer (1944) were the first workers to demonstrate selective concentration of radioactive iodine in a thyroid carcinoma, and their first cases were all cases of " adenoma malignum". Subsequent work has shown that the only types of thyroid carcinoma which can concentrate iodine are some of those with a follicular structure, such as some varieties of adenocarcinoma. Undifferentiated carcinoma and papillary carcinoma do not concentrate the isotope. Where, however, the isotope can be concentrated in the primary or metastatic growth, it has some therapeutic value, and the progress of the growth can be arrested and life prolonged. In a recent review of the subject, Rawson and Trunnell (1951) with a very considerable experience, state that notwithstanding the fact that they have observed 'tumorcidal' effects of irradiation delivered by

radioactive iodine, they have not observed any cures of cancer of the thyroid in patients treated with the isotope.

A considerable literature has accumulated regarding this application of the isotope, and Paterson (1950) and Warrington (1950) have reported on its use in this country.

In addition to the fundamental work, chiefly with autoradiographic techniques, in elucidating the biological characteristics of thyroid carcinoma, most work has concentrated on methods by which tumor deposits can be induced to concentrate administered iodine when they have not initially shown this property, for thereby the field of application of the isotope can be broadened.

When the radioactive iodine is administered it is selectively concentrated by residual normal functioning thyroid cells, and, unless there are metastatic deposits in glands or bone distant from the primary growth, it is not easy to detect by in vivo counting the presence of any of the isotope in the malignant tissue. When, however, there is a bony metastasis in, say, the skull, collimated counting techniques can be applied to detect its presence. Where possible, a biopsy specimen should be taken following a tracer dose - which may be of a large order, - and the distribution of the radioactive iodine in the normal and cancerous tissues studied by autoradiography. By the combination of this technique with in vivo counting, the probability of the value of the isotope can be assessed for each case.

The primary treatment for any carcinoma should be the removal of the growth in the gland, and of as much of the normal gland as possible. An administered tracer dose subsequently cannot therefore be collected in the thyroid and is all excreted unless retained in metastatic deposits where it may be detected with a Geiger counter. It has been claimed by Seidlin, Rossman, Oshry, and Seigel (1949) that removal of the thyroid increases the output of thyrotropic hormone by the pituitary which may stimulate previously non-functional metastatic growth to concentrate iodine, and this does in fact appear to occur, although Paterson (1950) has not noted it in any of the cases studied in Manchester.

Rawson and Trunnell (1951) have found that following thyroidectomy the percentage pick-up of a dose of the isotope by a metastasis may increase tenfold, and in a case studied in Sheffield, (Blomfield,1950) we noted a slight increase in the uptake in a femoral metastasis, following thyroidectomy, from 5% to 8.5%, and in Case D.C., described later, uptake in glandular masses increased from an amount that was just appreciable to a total of 33% of the dose after ablation of the thyroid.

Thyrotropic hormone (T.S.H.) can also be administered to encourage increased uptake of the isotope, but Warrington (1950) has found it of little value, although Rawson and Trunnell (1951) have reported a fourfold increase in the uptake in metastases following its use. The same workers conclude that the most effective way of increasing primary and metastatic iodine uptake is to administer a thiouracil group

drug for long periods of time, and this, in their hands, has been the most useful measure used.

In the management of a case of thyroid carcinoma, the possibility of the use of radioactive iodine should be considered as a palliative, and possibly as a potentially durative measure, in any case with metastases provided that the primary growth can be effectively dealt with by surgery or by X ray therapy. The first step should be ablation of the thyroid by surgery or with large doses of radioactive iodine, and subsequently further doses administered, following the use of methyl thiouracil in large doses for some months. If evidence appears of any retention in the body of any of the dose of the isotope, this must be taken as evidence of residual iodine - concentrating tissue, which may be tumour tissue. Subsequent dosage should be as high as can be tolerated.

The problem of accompanying toxic effects following the large doses used, (perhaps over 100 millicuries) becomes real, whereas it is negligible in the treatment of thyrotoxicosis. There may be initial slight radiation sickness, and Rawson and Trunnell (1951) have had patients with severe or fatal leukopenia. In a patient in Sheffield a thrombocytopenia with purpura was a delayed, but temporary, result. These workers also noted amenorrhea occurring in a patient, and this is due to the very high blood dose that results. They adjust their dosage so that under average circumstances, a blood dose of under 100 e.r. is delivered.

It can be seen, therefore, that only exceptionally can radioactive iodine be used therapeutically for thyroid

carcinoma, but in the rare case where it is applicable, apparently satisfactory results can be obtained, at least temporarily, and, in this country Pochin (1950) has reported the considerable resolution of pulmonary metatases following the use of the isotope, where it had been shown that a high percentage of the dose was concentrated in the lungs.

Cases Studied.

During the past few years some 30 cases of thyroid carcinoma have been seen and investigated with radioactive iodine in cooperation with Mr. G. W. Blomfield, Medical Director of the Sheffield National Centre for Radiotherapy, and of these only 4 cases were found to concentrate iodine in the primary or metastatic tumour to the extent that made therapy practicable. In one case, an old lady of 60, reported by Blomfield (1950,) initial sclerosis was induced in a large femoral metastasis after thyroidectomy and the administration of a total of about 320 millicuries of radioactive iodine. Purpura with thrombocytopenia followed the last dose of the isotope, but was only temporary.

Two of the other cases are of considerable interest as the first, Miss D.C., illustrates the considerable potentialities of the technique in the rare occasions when it is applicable; the second Mrs.N.B., illustrates the use of the isotope in the elucidation of an unusual clinical picture, and it also shows how the isotope may fail in its purpose although at first it may appear to be of value.

Case Report 1. Miss D.C., Age 18.

This girl had good general health until 1945 when she first noted a hard painless swelling on the right side of her neck, to which she paid little attention. In August 1949 a further painless swelling was noted below the right ear and she consulted her doctor in October 1949. Biopsy showed the swelling to be due to lymphatic involvement with metastatic thyroid adenocarcinoma.

On admission to hospital she had no symptom referable to the swellings, and, apart from their presence, was healthy in every way. The left lobe of the thyroid was enlarged, and firm, but not fixed. There was a large fixed mass of glands at the apex of the right lobe of the thyroid, and a further mass of blands was palpable above the left clavicle.

Clinically she was otherwise normal, was in normal thyroid balance, and all haematological, biochemical, and radiological investigations were normal.

A tracer dose of 114 microcuries of radioactive iodine was given which demonstrated normal thyroid function. Search with a collimated counter showed rather less absorption in the left lobe of the thyroid, the glands above the left clavicle did not appear to concentrate iodine, but there was appreciably increased activity in the glands below the right ear, compared to the activity present at a similar site on the left.

Accordingly, following another tracer dose, an operation was performed on 13/2/50 in an attempt to eradicate

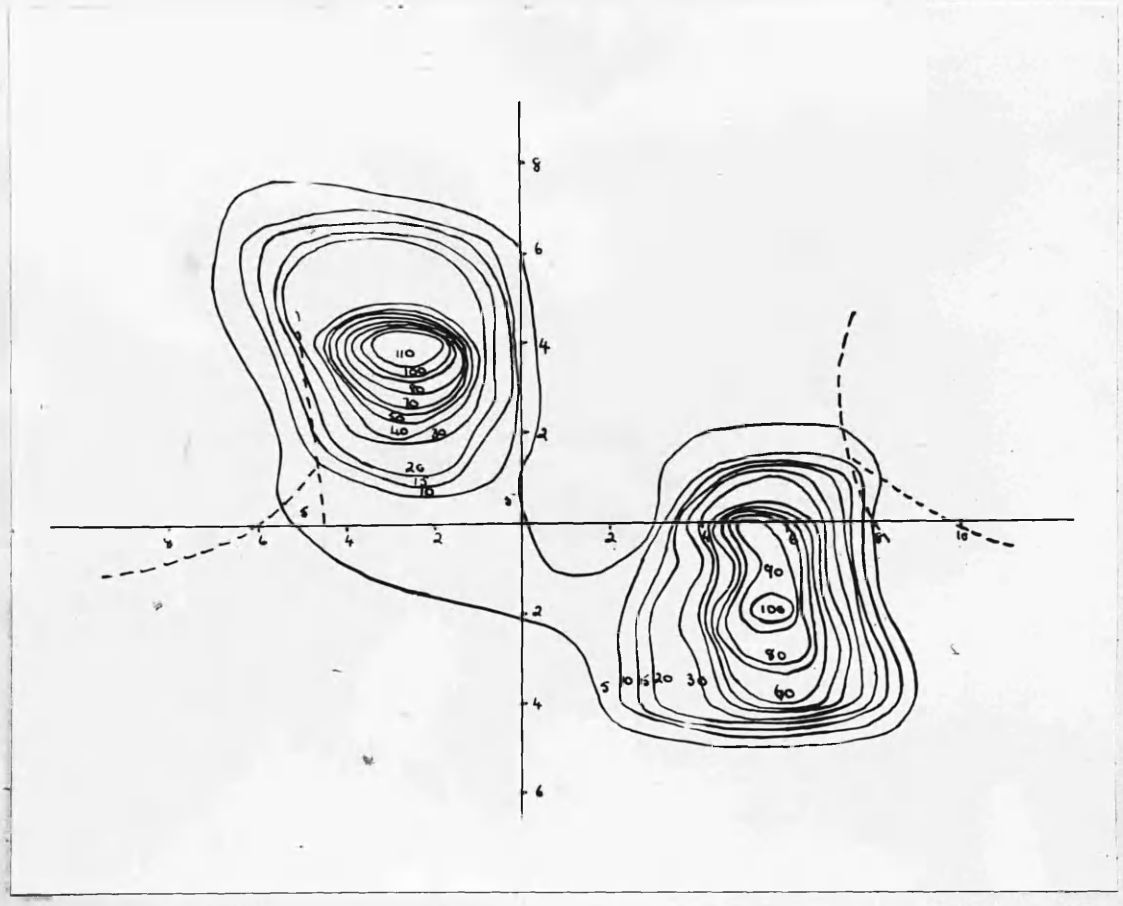

Figure 30. Diagram of lines of equal counting rate over functioning thyroid metastases, after previous ablation of the thyroid gland. Case, Miss D.C.

as much as possible of the primary and metastatic deposits. A left thyroidectomy was performed, but because of the infiltrating nature of the disease, the widespread glandular involvement that was demonstrated, and the involvement of the recurrent laryngeal nerve in glandular enlargement, the Surgeon was unable to remove the right lobe, nor resect the glands on the right side of the neck or above the left clavicle. Autoradiography of sections from the excised glands showed iodine concentration in the malignant tissue, and direct assay of the specimens showed a specific activity of up to 0.7 microcuries per gram of tissue.

On 4/3/50 a dose of 30 millicuries of radioactive iodine was given which was practically all concentrated in the right side of the neck, and delivered an estimated 36,000 e.r. to the residual thyroid tissue. Following this dose her condition remained excellent, her weight stationary, and there was no clinical evidence of myxoedema, and her blood cholesterol only rose from 215 mg.% to 260 mg.%

On 17/5/50 a larger tracer dose of 5 millicuries was given. There was no uptake at the normal site of the thyroid, 23% was taken up into the left supraclavicular glands, and 33% into the glands below the right ear, the 24 hour urine excretion being 40%. Figure 30 shows the distribution of the lines of equal counting rate over these two masses and demonstrates the absence of appreciable concentration over the thyroid area itself.

Accordingly, on the 14/6/50 a total of 67 millicuries was given to the patient which was concentrated entirely in the glandular masses, which were calculated to be 15 grams in weight above the clavicle, and 22 grams under the ear, and the delivered roentgen dosage following this therapeutic dose was 16,000 e.r. and 11,000 e.r. to the two masses respectively. Following this dose a detailed search with a collimated counter was made of the whole body and skeleton, but no appreciable take up elsewhere could be detected.

There were no clinical adverse effects consequent to this high dosage. The total blood dose was estimated to be only 14 e.r., as the blood concentration remained low, in contradistinction to the high concentrations reached in the treatment of thyrotoxic patients. (Figure 4 and Table IX). There was no demonstrable effect upon her haemopoietic system, and her menses were unaffected.

Her weight rose steadily from 9 stone to 10 st.10 lbs; clinical evidence of hypothyroidism developed and her blood cholesterol rose to 440 mg.%. Thyroxine therapy was instituted and maintained subsequently at 0.3mg.per day, and her blood cholesterol fell to 250 mg.%

There was a progressive diminution in size of the large glandular masses, and by 23/11/50 no abnormal glands could be palpated anywhere by any observer, and none have since recurred.

Her general clinical condition is excellent, she

is taking thyroxine in maintenance dosage, and her future management will entail repeated radioactive iodine tracer examinations to ensure that there is no retention of the isotope; any such retention could only be in malignant tissue, and further large doses would be expected to destroy any recurrence.

Conclusion: This case illustrates the way by which apparently gross carcinomatous infiltration in a suitable case can be radically and completely extirpated, with no systemic adverse reaction.

Case Report 2. Mrs. N.B. Aged 67.

This patient had good health until 1943 when partial thyroidectomy was performed for presumed thyrotoxicosis, but section of the specimen showed the presence of adenocarcinoma. In December 1945 nodular masses were apparent in the midline, to the right, and to the left, and there was fixation of the left vocal cord; biopsy revealed adenocarcinoma and X ray of chest showed no evidence of pulmonary metastatic spread.

She was given Deep X ray therapy in 1946 to a total of 3,000 r.deep dose and the masses resolved considerably to be replaced by induration. She remained well until November 1950 when she had a severe haemoptysis, and was found to have a fixed hard thyroid swelling, and chest X ray showed an upper mediastinal mass and multiple secondaries throughout both lung fields.

A tracer dose investigation showed uptake of

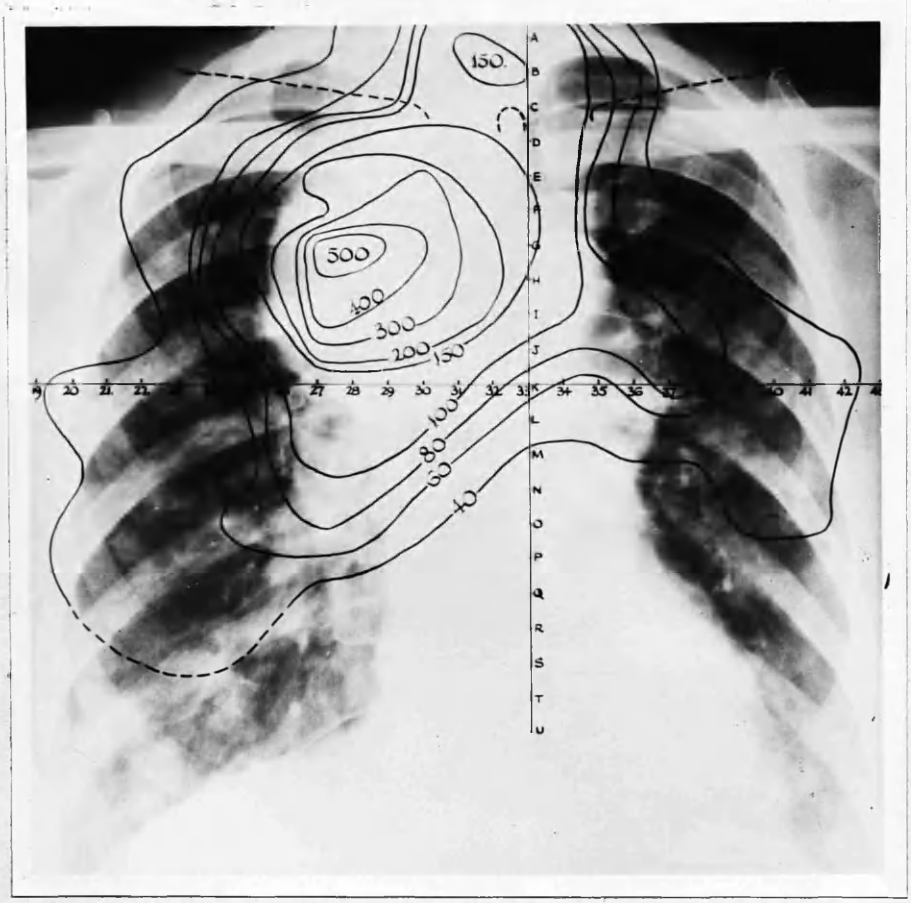

Figure 31. Radiograph of chest of Case Mrs. N.B. showing mediastinal secondary with metastatic deposits in lung fields. Superimposed on the X-ray are the lines of equal counting rate from radioactive iodine. Note the coincidence of the lines representing greater activity with the shadows of the metastases.

radioactive iodine in both the thyroid region (36%) and over the pulmonary and mediastinal masses (23%), urine excretion being 20%. The plot of the lines of equal counting rate showed a correspondence of areas of high activity with the observed radiological opacities, (Figure 31) which indicated significant iodine concentration in the secondaries. Accordingly a dose of 93 millicuries was given on 13/12/50 which delivered 30,000 e.r. to the thyroid and 9,000 e.r. to the secondaries.

No systemic reaction occurred and there was no further alteration in the secondaries, and a few months later, before a further dose had been given, the patient sustained a pathological fracture through the neck of her femur. Examination following a further tracer dose showed no concentration of the isotope at this site, and she is currently receiving further radioactive iodine therapy directed at her pulmonary lesions, which appear to have diminished slightly in size, and deep X ray therapy to her hip.

Conclusion: This case illustrates the difficulty of the application of the isotope even to those cases where initial experience suggests it may be helpful. Some, but not all, of the metastases have iodine concentrating capacity, and X ray therapy is necessary as well in an attempt to cure the disease.

3. The Therapeutic Induction of Myxoedema.

A recognised treatment for both intractable cardiac failure and for severe angina pectoris has been the production of hypothyroidism either by total thyroidectomy (Blumgart,

Levine and Berlin,1931) or by the use of methyl thiouracil (Ben Asher,1947; Sharpey-Shafer,1946). Both these methods have their disadvantages, especially inasmuch as thyroidectomy is a serious operation to contemplate in a person whose clinical condition is so precarious that the operation is considered justifiable. Further, it is difficult and requires long and high dosage therapy to induce myxoedema with methyl thiouracil, and the advantages of the procedure are questionable, although some patients undoubtedly benefit by it. Firstbrook (1951) seriously questions its use for angina because of the resultant probable acceleration of the underlying atherosclerotic process.

The advent of radioactive iodine has provided a simple, safe, and effective means of intentionally ablating all thyroid tissue and a large number of cases have been treated in this fashion, especially by Freedberg, Blumgart, Kurland, and Chamovitz (1950).

Little experience of this use of radioactive iodine has been gained in this country, but three suitable cases have been treated in Sheffield, one with considerable benefit, and two with equivocal results.

Case Report 3. Mr.A.W. Aged 59.

This patient presented in March 1951 with a two-year history of typical angina pectoris, becoming very much worse in the previous two months, and on admission to hospital he had frequent angina at rest.

On examination he was slightly obese, and his blood

pressure was 160/100; clinical examination and ancillary investigations, with the exception of his electrocardiogram, were normal. This electrocardiogram showed minimal evidence ofcoronary insufficiency at rest, but on exercise over standard exercise tolerance test steps only 18 efforts could be made; this produced a severe attack of angina with gross electrocardiographic changes, there being marked S T segment depression in the standard and left precordial leads.

This condition was regarded as being very severe, and accordingly a dose of 23 millicuries of radioactive iodine was given on 6/4/51 delivering 20,000 e.r. to the gland. His clinical condition improved during the next six weeks in a most remarkable fashion, and clinical evidence of myxoedema was apparent by June 1951, by which time his blood cholesterol had risen from 264 mg% to 540mg%, and there were typical changes of hypothyroidism in his electrocardiogram. His exercise tolerance increased immeasurably, and by July there was no limit to the distance he could walk at a regular rate, unless the weather was unduly cold. His requirement for trinitroglycerin tablets dropped to zero from a high level, and he himself has been emphatic that his second state of fairly advanced myxoedema is to be greatly preferred to his previous painful, and miserable existence with angina decubitus. Conclusion: in certain selected cases the isotope can be used to induce myxoedema therapeutically with great ease and efficiency, and with considerable benefit to the patient.

Final Summarized Conclusions.

The work described in this Thesis has shown that in addition to fundamental information regarding the physiology, and the pathological physiology, of thyroid function, the advent of radioactive iodine has provided the means wherewith certain useful and valuable diagnostic and therapeutic techniques can be developed.

It has been shown that objective evidence of disturbed thyroid function is given by study of the amount and rate of uptake of the isotope, and of the amount that is converted into protein-bound form as thyroxine. Tests of this nature provide evidence of a correlation between clinical thyrotoxicosis and certain definite departures from the normal results of the tests. It has been shown that the uptake of the isotope into the gland after 4 hours is commonly under 40% in the presence of normal thyroid function, and in excess of that figure in thyrotoxicosis. Thyroid iodide clearance rates from plasma are commonly over 80 ml per minute in the presence of thyrotoxicosis, but lower rates can be encountered; and this test is less valuable in many instances as a diagnostic screening procedure.

It was concluded that on the basis of the series here reported an estimation of the protein-bound plasma activity after 48 hours provides the most consistently reliable diagnostic information, thyrotoxicosis being practically always associated with levels in excess of o.4 per cent of the dose per litre of plasma. Conversely, normal thyroid function was characterized

by levels below 0.4% per litre, and usually below 0.1% per litre. In a few cases studied after fairly recent successful treatment, persistent high levels of 48 hour protein bound plasma activity were encountered in the presence of clinically normal thyroid function.

Hypothyroidism was probably best diagnosed with radioactive iodine on the basis of a high urinary excretion after 2 days, and it has been shown that the isotope has a small but significant field of usefulness in the diagnosis of the site of aberrant functioning thyroid tissue and of carcinoma.

In the therapeutic field, very satisfactory results with no significant complications or disadvantages, have been achieved in the treatment of thyrotoxicosis, and it has been concluded that the risks of the use of the isotope are negligible compared to the value of utilising the efficiency, safety, and simplicity of the technique as a therapeutic procedure. Furthermore, it has been shown that with care, and with full preliminary study of all variable factors on which dosage depends, accurate estimates can be made of the size of the drink in millicuries to be given to the patient in the knowledge that such a drink will deliver the optimum roentgen dosage to the gland.

In rare selected and suitable cases radioactive iodine can produce dramatic results in the treatment of carcinoma of the thyroid, and it can also be usefully applied to induce myxoedema as a therapeutic measure for angina pectoris and for intractable congestive cardiac failure.

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Appendix I

Normal Cases. Part A

1. CLINICAL DETAILS

Case No.	Sex	Age	B.M.R. %	Blood chol. mg. %	Remarks
1	F	50	-	-	Sarcoidois
2	M	48	-16	-	Degenerative auricular fibrillation
3	F	44	-	-	Mitral stenosis Rheumatoid arthritis
4	M	37	-	-	Auricular fibrillation
5	M	33	-	-	Mitral stenosis
6	M	60	-	-	Ophthalmoplegia
7	F	64	4	240	Parkinsonism
8	F	25	-	-	Mitral stenosis
9	F	64	-	-	Pernicious anaemia
10	M	45	-	-	Mitral stenosis
11	M	34	-	210	Dermatitis herpetiformis
12	M	57	0	210	Dementia
13	F	37	-	-	Mitral stenosis
14	F	30	-11	255	Obesity
15	F	44	-1	250	Obesity
16	M	60	13	300	Ophthalmoplegia

Appendix I (cont.)

Normal Cases. Part A.

2. RESULTS OF RADIOACTIVE IODINE TESTS

Case No.	Gland uptake, % 4 hrs.	Peak	24 hr.	Time to ½ peak (mins.)	Biol. ½ life (days)	24 hr. urine %	Thyroid clearance rate ml./min.	48 hr. plasma activity Total % dose/litre	Protein bound
1	24	54	53	280	-	20.5	22	-	-
2	14	31	29	308	-	44.5	18	neg.	neg.
3	11	26	26	360	2.3	59.5	10	0.19	-
4	17.5	35	32	260	-	48.0	19	0.1	neg.
5	8	21.5	19	480	-	51.8	11	0.12	neg.
6	18	34	34	210	32	44.0	23	0.14	neg.
7	14.5	24	24	126	15.8	-	13	0.64	neg.
8	21	45	40	300	-	50.0	30	-	-
9	24	51	53	268	-	43.0	35	0.2	neg.
10	24	47	42	260	-	33.0	30	-	-
11	18.5	37.5	34	250	-	55.7	38	neg.	neg.
12	13	34	31	390	-	53.0	15	0.07	neg.
13	9.2	-	-	280	-	59.5	-	-	-
14	26	53	53	260	4.6	37.0	46	neg.	neg.
15	16	35	34	282	15.4	52.3	23	neg.	neg.
16	18	49	46	380	17.7	40.2	26	neg.	neg.

neg. = negligible activity.

Appendix II

Intermediate Group Cases. Part A

1. CLINICAL DETAILS

Case No.	Sex	Age	B.M.R. %	Blood chol. mg. %	Remarks
17	F	45	-	300	Thyroidectomy, 1947. Auricular fibrillation.
18	F	48	-	290	Thyroidectomy, 1942.
19	F	45	36	210	Large non-toxic goitre.
20	F	41	24	-	Non-toxic goitre and anxiety state.
21	F	37	10	210	Non-toxic goitre and anxiety state.
22	F	32	2	230	Small non-toxic goitre and anxiety state. (D)
23	F	39	18	200	Large non-toxic goitre. Treated by operation.
24	M	20	3	200	Small non-toxic goitre and anxiety state. (D)
25	F	61	-11	210	Non-toxic goitre. Anxiety state. Essential hypertension.
26	F	63	-27	320	Old thyrotoxicosis in remission. Essential hypertension. (D)
27	F	39	27	375	Anxiety state superimposed on old thyrotoxicosis.
28	F	58	2	240	Anxiety state.
29	F	47	-5	210	Anxiety state. (D)
30	F	27	0	200	Simple non-toxic adenoma.
31	F	32	-18	225	Anxiety state.

(D) = Case in "Doubtful non-toxic" category in Figures 15, 16, and 17.

Appendix II (cont.)

Intermediate Group Cases. Part A

2. RESULTS OF RADIOACTIVE IODINE TESTS

Case No.	Gland uptake, % 4 hrs.	Peak	24 hr.	Time to ½ peak (mins.)	Biol. ½ life (days)	24 hr. urine %	Thyroid clearance rate ml./min.	48 hr. plasma activity Total % dose/litre	Protein-bound
17	26.5	60	58	258	-	30.5	35	-	-
18	24.5	43	41	180	-	50	20	-	-
19	30	46	46	132	22	31.8	35	0.29	0.15
20	48.5	69	68	110	inf.	32.8	45	0.13	neg.
21	11	24	23.5	260	5	61	10	neg.	neg.
22	31.3	58	58	216	-	27	29	-	-
23	31	42.5	42	130	14	40.5	38	0.32	-
24	26	48	45.5	220	5.1	40.5	56	neg.	neg.
25	19	42	40	316	-	35	20	0.18	neg.
26	25	47	47	410	23.5	53.5	18	0.4	0.4
27	23	41.5	41.5	170	24	48.5	30	neg.	neg.
28	17.5	33	33	238	116	50.8	23.5	1.16	neg.
29	28.5	48	48	162	15.4	37	25	0.3	-
30	34	52	50	153	inf.	40	59	0.1	neg.
31	40	58	56	146	13	32	58	0.16	-

neg. = negligible activity.

Appendix II (cont.)

Intermediate Group Cases. Part A

1. CLINICAL DETAILS (continued)

Case No.	Sex	Age	B.M.R. %	Blood chol. mg. %	Remarks
32	F	47	-	-	Thyrotoxicosis in remission and anxiety state.
33	F	31	-	290	Non-toxic adenoma and anxiety state.
34	F	18	0	150	Small non-toxic goitre.
35	F	33	-18	270	Non-toxic goitre.
36	F	28	-3	320	Small non-toxic goitre and anxiety state. (D)
37	F	20	20	190	Non-toxic goitre and anxiety state. (D)
38	M	32	20	140	Invalided from R.A.F. 1942 with thyrotoxicosis. (D)
39	F	27	-3	183	Non-toxic goitre. Thyrotoxicosis ? diagnosed 1942.
40	F	37	-	270	Anxiety state.
41	F	55	-	-	Non-toxic goitre.
42	F	37	-	330	Anxiety state.
43	F	42	-	280	Simple non-toxic adenoma.
44	F	33	-3	320	Thyroidectomy 1946. Anxiety state. (D)
45	F	62	-3	-	Non-toxic goitre.
46	F	46	-	385	Thyrotoxicosis in remission. Anxiety state.

(D) = Case in "Doubtful non-toxic" category in Figures 15, 16, and 17.

Appendix II (cont.)

Intermediate Group Cases. Part A

2. RESULTS OF RADIOACTIVE IODINE TESTS (cont.)

Case No.	Gland uptake, % 4 hrs.	Peak	24 hr.	Time to ½ peak (mins.)	Biol. ½ life (days)	24 hr. urine %	Thyroid clearance rate ml./min.	48 hr. plasma activity Total % dose/litre	Protein-bound
32	20	42	38	240	-	47.5	-	-	-
33	23	42	38	180	-	48.9	39	0.26	neg.
34	20	47	46.5	300	-	41	-	-	-
35	20.5	43	43	280	40	41	45	-	-
36	37	58	57	186	12	33.1	71	neg.	neg.
37	40	64.5	64.5	146	70	24	69	0.18	neg.
38	32	50	50	171	19.6	38.4	56	0.1	0.09
39	17	42	36	310	-	48.4	17	neg.	neg.
40	20	46	44	286	-	40.8	31	0.19	neg.
41	16.5	37	35	310	-	49.6	18	neg.	neg.
42	31	49	49	145	-	48.8	30	0.1	neg.
43	23	43	43	212	-	52.3	21	0.2	neg.
44	39	56.5	56.5	108	9.5	32	60	0.44	0.35
45	25	54	54	226	30	37.8	31	neg.	neg.
46	27.5	55.5	55.5	238	14.8	40	39	neg.	neg.

neg. = negligible activity.

Appendix III

Diffuse thyrotoxicosis cases. Part A

1. CLINICAL DETAILS

Case No.	Sex	Age	Grade of toxicity	B.M.R. %	Blood chol. mg. %	Treatment	Remarks
51	F	34	4	66	150	M.T.	-
52	F	57	4	56	210	I^{131}	-
53	F	28	2	10	185	Op.	-
54	F	53	2	33	230	M.T.	Later got carcinoma thyroid.
55	F	55	2	3	250	I^{131}	Auricular fibrillation.
56	F	33	3	60	200	Op.	-
57	F	38	3	24	-	M.T.	-
58	F	58	3	53	190	I^{131}	Previous failure with M.T.
59	F	22	3	2	275	Op.	Failure with M.T.
60	F	39	3	40	155	I^{131}	Very large goitre.
61	M	34	3	59	160	M.T.	-
62	F	38	1	17	195	M.T.	-
63	F	24	4	32	200	Op.	-
64	F	20	3	26	205	I^{131}	Previous op. and M.T.
65	F	42	4	40	230	I^{131}	Previous M.T.
66	F	45	4	-	-	-	Died. Congestive cardiac failure.

M.T. = methyl thiouracil.
Op. = partial thyroidectomy.
I^{131} = radioactive iodine.

Appendix III (cont.)

Diffuse thyrotoxicosis cases. Part A

2. RESULTS OF RADIOACTIVE IODINE TESTS

Case No.	Gland uptake, % 4 hrs.	Peak	24 hr.	Time to ½ peak (mins.)	Biol. ½ life (days)	24 hr. urine %	Thyroid clearance rate ml./min.	48 hr. plasma activity Total % dose/litre	Protein-bound
51	88	88	75.5	28	3.8	8	-	-	-
52	67	72.5	72.5	68	33	12.5	-	-	-
53	57	70.5	70.5	106	13	22.5	100	0.42	0.41
54	62	65	58	90	3.9	11.9	184	2.0	1.35
55	51	-	71	-	-	20	-	-	-
56	81	88	82	24	8	5.6	458	0.68	0.52
57	60	79	77	90	23	24.3	-	-	-
58	77	77	65	30	6	5	-	-	-
59	67	77	77	125	13	16	245	1.04	1.06
60	74	76	73.5	24	5.4	4.2	383	0.98	1.0
61	55	72	72	96	16.1	20.8	140	0.24	0.13
62	50	63	62.5	145	5.3	20	97	1.26	1.05
63	80.5	82.5	76.5	10	10	5.5	560	0.87	-
64	75.5	75.5	55	37	2	8.6	220	5.5	3.4
65	90	90	79	24	7	10.3	226	2.2	1.6
66	73	76.5	71	42	15	15.5	153	-	-

Appendix III (cont.)

Diffuse thyrotoxicosis cases. Part A

1. CLINICAL DETAILS (cont.)

Case No.	Sex	Age	Grade of toxicity	B.M.R. %	Blood chol. mg. %	Treatment	Remarks
67	F	31	3	15	150	I^{131}	Also with thrombocytopenic purpura.
68	M	22	4	-	200	Op.	Large goitre.
69	M	54	2	34	220	I^{131}	-
70	F	46	4	24	170	I^{131}	Also with hydronephrosis.
71	F	28	4	14	220	M.T.	-
72	M	38	3	12	75	I^{131}	-
73	M	49	3	22	230	M.T.	-
74	F	47	2	32	200	I^{131}	Previous op.
75	F	47	2	43	130	I^{131}	Previous op.
76	F	60	4	80	195	I^{131}	Malignant exophthalmos.
77	F	45	1	-7	190	M.T.	-
78	F	33	3	80	175	M.T.	-
79	F	36	4	46	230	I^{131}	Previous op.
80	F	21	2	49	195	Op.	Failed with M.T.
81	F	34	3	-	200	Op.	-
82	M	51	2	42	220	I^{131}	-
83	F	47	2	29	112	I^{131}	-

M.T. = methyl thiouracil.
Op. = partial thyroidectomy.
I^{131} = radioactive iodine.

Appendix III (cont.)

Diffuse thyrotoxicosis cases. Part A

2. RESULTS OF RADIOACTIVE IODINE TESTS (cont.)

Case No.	Gland uptake, % 4 hrs.	Peak	24 hr.	Time to ½ peak (mins.)	Biol. ½ life (days)	24 hr. urine %	Thyroid clearance rate ml./min.	48 hr. plasma activity Total % dose/litre	Protein-bound % dose/litre
67	80	81	74	50	5.3	9	123	-	-
68	64.5	70	67.5	41	4.8	3.5	244	0.96	0.74
69	50	61	56	100	12.8	21.3	92	1.03	0.87
70	62	82.5	82.5	120	-	15.5	-	-	-
71	89.5	92	72	27	4.6	10	320	2.9	-
72	68	77	74	80	7	10.5	174	1.6	0.91
73	55	72	70	85	8.5	28	67	0.87	0.63
74	41	57	54.5	104	32	34.5	50	0.64	0.64
75	40	61	61	102	4.7	28.5	30	1.5	1.2
76	74	75	64	39	5	8.5	270	3.5	2.9
77	55	70	70	117	-	23	79	-	-
78	89.8	90	72.5	36	2.8	7	250	-	-
79	89.5	92	72	67	3.9	8.8	612	2.3	1.6
80	72	88	87	90	7.2	3.3	578	0.78	0.61
81	84.5	89	87	35	-	4.7	885	1.29	0.86
82	80	86	78	44	8.5	3.6	833	1.48	1.43
83	87.5	88	76	48	8.8	6	1780	1.77	1.24

Appendix IV

Toxic adenoma cases. Part A

1. CLINICAL DETAILS

Case No.	Sex	Age	Grade of toxicity	B.M.R. %	Blood chol. mg. %	Treatment	Remarks
85	F	55	2	0	195	Op.	Auricular fibrillation.
86	F	33	2	36	200	Op.	Large adenoma.
87	F	52	1	-	270	Op.	Increased concentration of I^{131} in nodule.
88	F	56	3	7	380	Op.	Large goitre.
89	F	42	1	13	275	Op.	Increased concentration of I^{131} in nodule.
90	F	65	2	18	200	Op.	-
91	F	73	3	-	140	I^{131}	Auricular fibrillation and congestive failure.
92	F	53	1	17	290	I^{131}	Increased concentration of I^{131} in nodule.
93	F	26	1	23	140	M.T.	-
94	F	56	3	43	165	Op.	-
95	F	58	2	30	165	M.T.	Auricular fibrillation and congestive failure.

M.T. = methyl thiouracil.
Op. = partial thyroidectomy.
I^{131} = radioactive iodine.

Appendix IV (cont.)

Toxic adenoma cases. Part A

2. RESULTS OF RADIOACTIVE IODINE TESTS

Case No.	Gland uptake, % 4 hrs.	Peak	24 hr.	Time to ½ peak (mins.)	Biol. ½ life (days)	24 hr. urine %	Thyroid clearance rate ml./min.	48 hr. plasma activity Total % dose/litre	Protein-bound % dose/litre
85	34.5	56	55	140	-	31.5	-	-	-
86	58.5	63.5	63	134	25	31	70	0.25	-
87	45	60	60	136	12	21	84	0.74	neg.
88	72	76	76	20	15	3.5	-	-	-
89	44	62	60	126	16	28	36	1.15	0.82
90	58.5	71.5	63.5	108	6	7.5	36	-	-
91	63.5	70	67.5	41	4.8	1.2	330	3.07	2.45
92	45	62	62	104	14	29	65	0.63	-
93	42.5	65	64.5	135	-	34	-	-	-
94	58	62	57	36	4.7	6	-	2.4	1.1
95	50.5	60.5	60.5	77	7	12	89	2.1	1.5

neg. = negligible activity.

Appendix V

Myxoedema. Part A

1. CLINICAL DETAILS

Case No.	Sex	Age	B.M.R. %	Blood chol. mg. %	Remarks
96	F	61	-8	390	Also a diabetic with peripheral vascular disease
97	F	59	0	315	-
98	M	62	-42	645	-
99	F	64	-15	420	Also with Raynaud's disease.

2. RESULTS OF RADIOACTIVE IODINE TESTS

Case No.	Gland uptake, % 4 hrs.	Peak	24 hr.	Time to ½ peak (mins.)	Biol. ½ life (days)	Urine excretion, % 24 hr.	48 hr.
96	6	12.5	12.5	280	11.9	46	62
97	-	4	3.5	-	-	-	-
98	5	8	6.3	-	-	43	45
99	10.5	23.4	22.5	260	7.0	56.5	63.3

	Thyroid clearance rate ml./min.	48 hr. plasma activity Total %/litre	Protein-bound
96	5	0.4	neg.
97	-	-	-
98	0.4	0.7	neg.
99	34	-	-

neg. = negligible activity.

Appendix VI

Non-toxic cases. Part B

CLINICAL DETAILS						RESULTS OF RADIOACTIVE IODINE TESTS		
Case No.	I.P./O.P.	Sex	Age	Diagnosis	B.M.R. %	4 hr. uptake %	Thyroid clearance rate	48 hr. P.B. activity %/litre
101	O.P.	F	34	N.T.G. A.S. (D)	-	42	96.8	neg.
102	O.P.	F	57	N.T.G.	-	9.5	4.1	neg.
103	O.P.	F	46	A.S.	-	-	27.6	neg.
104	O.P.	F	37	A.S.	-	11	4	0.16 (x)
105	O.P.	F	30	A.S. (D)	-	25.5	40	neg.
106	O.P.	M	65	T.T.	-	26	34.7	0.1
107	O.P.	F	29	A.S. (D)	-	-	33	neg.
108	O.P.	F	23	A.S.	-	30.5	46	neg.
109	I.P.	M	40	T.T.	-12	21	37	neg.
110	O.P.	M	33	N.T.G.	-	16	17	neg.
111	O.P.	F	20	A.S. (D)	-	-	27	0.2 (x)
112	I.P.	F	51	N.T.G. (D)	13	48	56.3	neg.
113	O.P.	F	49	N.T.G.	-	25	25.6	neg.
114	O.P.	F	38	N.T.G.	-	-	61.2	0.35 (x)
115	I.P.	F	61	N.D.T.	-	10	3.8	neg.
116	I.P.	F	27	A.S. (D)	10	43	42.3	0.15
117	O.P.	F	30	T.T.	-	5.5	2.8	neg.
118	O.P.	M	31	A.S. (D)	-	33.5	68.5	neg.

Appendix VI (cont.)

Non-toxic cases (cont.) Part B

CLINICAL DETAILS					RESULTS OF RADIOACTIVE IODINE TESTS			
Case No.	I.P. / O.P.	Sex	Age	Diagnosis	B.M.R. %	4 hr. uptake %	Thyroid clearance rate	48 hr. P.B. activity %/litre
119	O.P.	F	25	A.S. (D)	-	26	29.4	-
120	I.P.	F	38	N.T.G.	-	20.5	25.2	neg.
121	I.P.	F	37	N.T.G. A.S.	-	31	99.4	neg.
122	I.P.	F	39	N.D.T.	17	24.5	27	neg.
123	I.P.	M	46	N.D.T.	4	17.5	10.3	0.18
124	O.P.	F	36	N.D.T.	-	34	26.9	neg.
125	I.P.	F	27	N.D.T.	-	18	34.6	neg.
126	I.P.	F	69	N.T.G.	-	27	18	0.04
127	I.P.	F	56	N.D.T.	-	11.5	6	neg.
128	O.P.	F	28	A.S.	--	41	32.4	neg.
129	O.P.	F	42	N.T.G.	-	31.5	31.4	neg.
130	I.P.	F	59	A.S.	-2	32	40.7	neg.
131	I.P.	M	68	N.T.G.	-3	10	9.1	neg.
132	O.P.	F	54	A.S. (D)	-	24	27.6	neg.
133	O.P.	F	42	N.T.G.	-	24	23.6	neg.
134	O.P.	M	55	N.T.G.	-	43.5	113.5	0.1
135	I.P.	M	41	A.S. (D)	7	10.5	9.4	0.17 (x)
136	I.P.	M	59	N.D.T.	-	21.5	24.7	0.2

Appendix VI (cont.)

Non-toxic cases (cont.) Part B

CLINICAL DETAILS					RESULTS OF RADIOACTIVE IODINE TESTS			
Case No.	I.P./O.P.	Sex	Age	Diagnosis	B.M.R. %	4 hr. uptake %	Thyroid clearance rate	48 hr. P.B. activity %/litre
137	I.P.	F	56	N.D.T.	-	20	-	-
138	O.P.	F	41	N.T.G.	-	21	24	neg.
139	I.P.	F	64	N.D.T.	-	-	-	0.18
140	O.P.	F	63	A.S. (D)	-	18	17.6	0.07 (x)
141	O.P.	F	36	N.T.G. (D)	-	44	53.2	neg.
142	I.P.	F	58	N.D.T.	-10	38	44.2	0.16 (x)
143	I.P.	F	34	A.S. (D)	15	38	54.5	0.23
144	O.P.	F	56	N.T.G. (D)	-	41.5	48.3	0.1 (x)
145	O.P.	F	31	T.T. (D)	-	15	11	neg.
146	I.P.	M	52	N.D.T. (D)	-	22.5	45	neg.
147	O.P.	F	26	N.T.G. (D)	-	-	37.8	neg.
148	I.P.	F	51	A.S. (D)	21	33	55.8	0.37
149	I.P.	F	39	N.T.G. (D)	11	53.5	72	0.16
150	I.P.	F	40	N.T.G.	-	21.5	22.9	0.17

N.T.G. Non-toxic goitre, diffuse, colloid, or simple adenoma.
A.S. Anxiety state.
T.T. Thyrotoxicosis treated in the past and in remission.
N.D.T. No disease of thyroid present nor suspected.
I.P./O.P. In-patient investigation/Out-patient investigation.
P.B. Protein-bound.
(D) Case included in "Doubtful non-toxic" category in Figures 15-17.
(x) Signifies 48 hr. total activity in plasma.
neg. Negligible activity.

Appendix VII

Toxic cases. Part B

		CLINICAL DETAILS					RESULTS OF RADIOACTIVE IODINE TESTS		
Case No.	I.P. / O.P.	Sex	Age	Grade	B.M.R. %	Treatment	4 hr. uptake %	Thyroid clearance rate ml./min.	48 hr. P.B. activity %/litre
155	I.P.	M	51	3	44	Op.	54.5	352	3.6
156	I.P.	M	37	2	28	I^{131}	72	308	1.21
157	I.P.	F	37	3	15	I^{131}	82.5	411	1.74
158	I.P.	F	31	2	22	M.T.	65	144	1.2
159	I.P.	F	28	1	4	M.T.	60.5	100	0.4 (x)
160	I.P.	F	65	3	48	I^{131}	76.5	154	0.42
161	I.P.	F	67	2	47	I^{131}	40.5	42	0.7
162	I.P.	M	39	2	-	Nil	49	95	0.96
163	I.P.	F	39	3	61	M.T.	67	266	0.9
164	I.P.	F	55	2	37	I^{131}	75	212	-
165	I.P.	F	67	3	53	I^{131}	79	172	2.45
166	O.P.	F	56	1	-	Nil	58	153	neg.
167	O.P.	M	60	2	-	I^{131}	62.5	176	0.87
168	I.P.	F	67	2	-	I^{131}	69.5	147	1.1
169	I.P.	F	20	3	37	M.T.	83.5	464	0.8

Appendix VII (cont.)

Toxic cases (cont.) Part B

		CLINICAL DETAILS					RESULTS OF RADIOACTIVE IODINE TESTS		
Case No.	I.P. / O.P.	Sex	Age	Grade	B.M.R. %	Treatment	4 hr. uptake %	Thyroid clearance rate ml./min.	48 hr. P.B. activity %/litre
170	I.P.	M	48	3	32	I^{131}	74	318	1.99
171	O.P.	F	28	2	-	I^{131}	73	245	1.14
172	I.P.	F	54	2	28	I^{131}	45.5	211	1.46
173	I.P.	F	67	3	20	Op.	56	68	3.17
174	I.P.	F	22	2	-	I^{131}	84	453	0.62
175	I.P.	F	48	2	20	I^{131}	46.5	43	0.67
176	I.P.	F	31	2	22	I^{131}	58.5	83	0.9
177	O.P.	F	37	2	-	I^{131}	83	522	1.24
178	I.P.	F	22	3	50	I^{131}	76	430	2.67
179	I.P.	F	21	3	74	M.T.	88.5	473	0.93
180	I.P.	F	43	1	13	Op.	53	71	neg.
181	O.P.	M	41	1	-	M.T.	57.5	169	0.43
182	O.P.	F	35	2	-	M.T.	74	201	1.09
183	I.P.	F	21	3	-	I^{131}	92	864	2.71
184	I.P.	F	64	2	-	I^{131}	90	264	1.7

Appendix VII (cont.)

Toxic cases (cont.) Part B

	CLINICAL DETAILS						RESULTS OF RADIOACTIVE IODINE TESTS		
Case No.	I.P./O.P.	Sex	Age	Grade	B.M.R. %	Treatment	4 hr. uptake %	Thyroid clearance rate ml./min.	48 hr. P.B. activity %/litre
185	I.P.	F	51	2	40	I^{131}	80	361	1.25
186	I.P.	F	57	3	63	I^{131}	93.5	289	3.69
187	I.P.	F	26	4	70	M.T.	84	512	1.45
188	I.P.	F	24	4	50	I^{131}	85	636	1.97
189	O.P.	F	65	2	-	I^{131}	63.5	129	1.47
190	I.P.	F	48	2	27	I^{131}	62	101	1.1
191	I.P.	F	44	1	18	I^{131}	31.5	41	0.52
192	I.P.	F	12	2	15	M.T.	86	430	2.33
193	O.P.	F	55	2	-	I^{131}	64	138	0.8

P.B. Protein-bound.
I.P./O.P. In-patient investigation/Out-patient investigation.
Op. Partial thyroidectomy.
M.T. Methyl thiouracil.
I^{131} Radioactive iodine.
(x) 48 hr. total plasma activity.

Appendix VIII

Cases of thyrotoxicosis treated with radioactive iodine.

Case No.	Ref. No. in Appx. III, IV, VII	Reason for selection	Gland size (grams)	Date of treatment	Dose m.c.	Dose e.r.	Follow-up (months) (to 30.6.51)	Result	Weight gain (lbs.)
1	70	T.F.1	35	12.1.49	5	12,000	21	Eu.	25
2	52	T.F.2	40	9.2.49	4	9,900	24	Eu.	17
3	91	T.F.1	100 (N)	4.3.49 21.6.49 22.6.50	4.5 13.7 14.2	6,000 8,500 10,550	7	I	6
4	76	T.F.1	60	19.7.49 29.9.49	8.7 15.8	1,800 6,300	18	Eu.	34
5	64	R.T.	80	27.10.49 5.6.50	7.5 23.7	1,930 11,600	12	Hy.	28
6	74	R.T.	40	18.11.49	5.5	6,900	18	Eu.	16
7	75	R.T.	30	30.11.49	5.9	7,700	18	Eu.	15
8	55	R.T.	40	20.12.49	6.9	15,700	18	Eu.	4
9	72	T.F.1	30	3.1.50	5.1	9,500	18	Eu.	47
10	60	T.F.2	90	4.1.50 5.4.50	12.5 20	10,600 11,600	12	Eu.	4
11	92	T.E.	60 (N)	1.2.50	6.5	6,600	17	Eu.	13
12	65	T.F.2	50	22.3.50	8.7	8,200	12	Eu.	21
13	69	T.F.3	50	20.4.50	6.2	7,400	12	Eu.	14
14	79	R.T.	50	24.5.50	7	6,200	13	Eu.	17
15	82	T.E.	40	18.7.50	5	13,600	10	Eu.	13
16	83	T.E.	60	15.8.50	8.4	11,000	10	Eu.	43
17	170	T.E.	60	14.9.50	11.8	12,700	9	I	18

Appendix VIII (cont.)

Cases of thyrotoxicosis treated with radioactive iodine (cont.)

Case No.	Ref. No. in Appx. III, IV, VII	Reason for selection	Gland size (grams)	Date of treatment	Dose m.c.	Dose e.r.	Follow-up (months) (to 30.6.51)	Result	Weight gain (lbs.)
18	164	T.F.3	40 (N)	21.9.50	4.8	9,700	9	Eu.	27
19	160	T.E.	35	27.9.50	4.5	12,700	9	Eu.	33
20	58	T.F.3	60	4.10.50	4	5,600			
			40	8.5.51	5.5	8,770	2	Eu.	6
21	156	T.E.	50	2.11.50	6.4	9,100	8	Eu.	23
22	157	R.T.	50	30.11.50	4	10,800	7	I	14
23	167	T.F.3	30	19.12.50	5	8,800	6	I	6
24	161	T.F.3	40 (N)	25.1.51	7	13,500	5	I	14
25	176	T.F.1	30	31.1.51	3.1	7,330	4	Eu.	9
26	175	T.F.1	35	6.2.51	4.7	8,500	4	I	-2
27	165	R.T.	35	14.2.51	6.6	9,200	4	I	9
28	171	R.T.	33	5.4.51	5.5	6,700	3	I	6
29	168	T.E.	70 (N)	6.4.51	7.7	7,500	3	Eu.	19
30	174	T.E.	60	13.4.51	5.2	10,200	2	Eu.	6

R.T. Recurrent thyrotoxicosis following operation.
T.F.1 Relapse or reaction after methyl thiouracil, operation contraindicated.
2 do. , operation refused.
3 do. , operation not offered.
T.E. Treatment of election.
Eu. Euthyroid.
I Improved.
Hy. Hypothyroid.
(N) Nodular goitre. (Glands diffuse unless specified "N")