THYROTOXICOSIS

A clinical and experimental study of the disease

by

JAMES CROOKS.

M.B., Ch.B(Glasg.) M.R.C.P.(Lond.) M.R.C.P.(Edin.) F.R.F.P.S.(Glasg.)

From the

University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow.

PREFACE

The investigations which form the main part of this thesis were carried out between 1955 and 1958 in the University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow. They comprise observations on more than 800 subjects all of whom have been studied by me personally.

Some of the conclusions have already been published in the following communications.-

"The Red Cell Mass in Thyrotoxicosis and Myxoedema". Clinical Science (1957) 16, 309. (with F.P. Muldowney and E.J. Wayne).

"The Sleeping Pulse Rate in Thyrotoxicosis". Scottish Medical Journal (1958) 3, 120. (with I.P.C. Murray).

"The Basal Metabolic Rate in Thyrotoxicosis" Lancet (1958) i, 604. (with I.P.C. Murray and E.J. Wayne).

The following papers have been accepted for publication.-

"Statistical Methods Applied to the Diagnosis of Thyrotoxicosis". Quarterly Journal of Medicine (with I.P.C. Murray and E.J. Wayne).

"Studies of Body Composition in Normal and Pathological States Using Isotope Dilution Techniques". Proceedings of the 2nd World Conference on the Peaceful Uses of Atomic Energy. Geneva, 1958. (with M.M. Bluhm and E.J. Wayne).

The section which deals with the medical treatment of thyrotoxicosis has already been presented in abbreviated form to the British Pharmacological Society during their annual meeting in Glasgow in 1958.

The majority of the observations made in this thesis has been carried out by the author himself. He would like, however, to acknowledge the help he has received from his collaborators at both the clinical and technical levels. Dr. R. A. Robb, Mitchell Lecturer in Statistics, University of Glasgow, has given throughout the work invaluable advice on the statistical aspects.

Finally the author wishes to acknowledge the continued interest of Professor E. J. Wayne who first inspired him to take an interest in the field of thyroid disease and who provided the clinical and laboratory facilities which have made this thesis possible.

Whereas in the past clinicians relied on the empirical application of clinical impressions in the diagnosis and treatment of disease, latterly they have tended to place increasing emphasis on indices derived from laboratory procedures.

This tendency has developed notably in the assessment of thyroid gland function since many reliable laboratory aids have become available in recent years. The advent of these new diagnostic techniques, such as radioactive iodine studies, has decreased the value accorded to clinical evidence in the diagnosis of thyrotoxicosis. Further, no comparison of the diagnostic accuracy of clinical and laboratory procedures is to be found in the literature. Part I of this thesis describes an investigation designed to provide this comparison and for this purpose statistical techniques have been applied to clinical evidence in an attempt to increase the precision of clinical diagnosis.

The logical sequel to this investigation was an evaluation of the therapeutic measures available to the physician in the treatment of thyrotoxicosis. Part II of the thesis, which is concerned with this subject, again emphasises the correlation between clinical methods and laboratory procedures. The first section compares the effectiveness of the antithyroid drugs, potassium perchlorate, methyl thiouracil and carbimazole, while the second section comprises a study of different methods of

estimating dosage of radioactive iodine and an assessment of the results of this form of treatment.

The treatment of a thyrotoxic patient represents a dynamic metabolic experiment. Advantage has been taken of this fact to apply biochemical and radioisotopic techniques to a study of the changes in the total red cell mass and total exchangeable electrolytes produced by the disease. Part III of the thesis describes these investigations.

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PART I

THE DIAGNOSIS OF THYROTOXICOSIS

Physicians in general approach the diagnostic problem of suspected thyrotoxicosis by investigating four aspects of thyroid function and the methods by which a diagnosis can be reached are conveniently classified in the following way.-

(1) The effects of the thyroid hormone on target cells.

(a) Symptoms and signs (clinical diagnosis).

(b) Basal metabolic rate.

(c) Cardiac effects (e.g. sleeping pulse rate).

(d) Serum cholesterol.

(2) The amount of thyroid hormone released.

(a) Serum protein bound iodine.

(b) Serum protein bound radioactive iodine.

(3) The iodine requirements of the thyroid.

(a) The uptake of radioactive iodine by the thyroid.

(b) The clearance of radioactive iodine by the thyroid.

(c) Urinary excretion of radioactive iodine.

(4) Response to anti-thyroid drugs (therapeutic trial).

These different methods measure various aspects of thyroid function but although there is an extensive literature on each method there is a paucity of data which would allow a comparison of the diagnostic effectiveness of the various procedures. This is especially true when one attempts to compare the value of the clinical diagnosis with the other methods.

In this section of the work I will describe a method of clinical diagnosis which I believe increases the diagnostic

value of clinical evidence. I have compared the results of the clinical diagnosis with those given by radioactive iodine studies, basal metabolic rate estimations, sleeping pulse rate, and serum cholesterol levels. I have also used the data made available by this investigation to study the way in which these various parameters of thyroid function reflect the severity of the disease.

SECTION 1

The Background to the Present Study.

The clinical diagnosis.

The clinical picture called thyrotoxicosis was first described by the Bath physician, Caleb Parry, in 1786 but his account of the disease was not published until after his death (Parry, 1825). Robert Graves of Dublin, published three cases of the disorder in 1835 and first drew attention to the relation of the ocular complications to the disease. The most complete of the early clinical descriptions of the condition is acknowledged to be that of von Basedow (1840) and little has been added to this description up to the present day. Apart from identifying other clinical features of the disease he emphasised the diagnostic importance of the triad of exophthalmos, goitre, and palpitation.

Trousseau (1860) who labelled the condition Graves's Disease, regarded the syndrome as a neurosis analogous to hysteria. The suggestion, however, that the clinical features were due to excessive thyroid secretion was not made until 1884 by Rehn who performed the first sub-total thyroidectomy.

Plummer (1923) concluded that Graves's Disease or exophthalmic goitre was a different clinical entity to "adenomatous goitre with hyperthyroidism" basing his opinion on the varying therapeutic effect of iodine on the clinical features of the disease. Fraser (1926), however, did not subscribe to this opinion and concluded that these two conditions were different phases of the one disease (Fraser, 1931). He was

supported in this view by Marine (1927) and Harington (1933, 1935). Exophthalmic goitre, toxic nodular goitre, and toxic adenoma are now generally accepted to be variations of the same disease. I have accepted this view throughout the present study and have used the term thyrotoxicosis to describe the various combinations of symptoms and signs associated with excessive thyroid activity.

Radioactive iodine studies.

Following the initial studies of thyroid physiology using radioactive iodine by Hertz et al (1938), both he (1942) and Hamilton and Soley (1940) pursued these observations in disorders of thyroid function. They established the inverse relationship of thyroid uptake and urinary excretion of radioiodine. Since then various tests of thyroid function using radioactive iodine have been described and an extensive literature has resulted which has been reviewed by Werner et al. (1950) and Macgregor and Wayne (1957). These tests fall into four main groups -- the percentage of the dose of radioactive iodine taken up by the gland at a fixed time; the clearance rate of radioactive iodine by the gland; the amount of radioactivity excreted in the urine; and the measurement of protein bound radioactivity. The relative value of the different tests still remains a matter of controversy. McConahey et al. (1956) considered that a six-hour uptake was the best

routine radioactive iodine test. On the other hand, Pochin (1950) considered that the "neck to thigh" ratio, which correlates closely with thyroidal clearance of radioactive iodine, was more likely to be conclusive than measurements of urinary, plasma, or external body counting rates. Fraser (1953) favoured urinary radioactive iodine measurements to discriminate between hyperthyroid and euthyroid subjects. In a large series Goodwin et al. (1951) compared the relative diagnostic value of seven of these tests and concluded that the 48-hour protein bound radioactive iodine was the best single test. After further experience with this test, Wayne (1954) advocated its combination with the 4-hour uptake of radioactive iodine in order to improve the diagnostic accuracy. It is abundantly clear from the literature that these standard radioactive iodine tests have a high degree of diagnostic accuracy, that no one test is infallible, and that a clear comparison between them is made difficult by the varying selection of cases, and the impracticability of carrying out all the tests in one series. In the present series the radioactive iodine criteria chosen were the 4-hour uptake and the 48-hour protein bound radioactive iodine.

Basal metabolic rate.

Magnus-Levy (1895) first described the characteristic elevation of the basal metabolic rate associated with overactivity of the thyroid gland. Over many years, estimation of the basal metabolic rate has been a standard method of assessing

thyroid function and its value has been well established. The subject is well reviewed by Du Bois (1936) and Møller (1927). There are, however, three circumstances which decrease the reliability of the test and which are worthy of special consideration.

(a) Normal basal metabolic rates in thyrotoxicosis.

The possibility that a normal basal metabolic rate might be found in thyrotoxicosis was considered as early as 1916 by Du Bois. This association has been found by many workers including Means (1937), Bartel (1950) and Crooks, Murray and Wayne (1958) and accounts for the majority of the diagnostic errors given by estimation of the basal metabolic rate in the present investigation.

(b) Elevated basal metabolic rates in patients without thyroid disease.

The basal metabolic rate has been found to be elevated in leukaemia (Grafe, 1911), polycythaemia (Minot and Buckman, 1923), Hodgkin's Disease and lymphosarcoma (Du Bois, 1936). Elevated basal metabolic rates have also been recorded in diseases of endocrine glands other than the thyroid e.g. acromegaly (Boothby and Sandiford, 1922), and phaeochromocytoma (Howard and Barker, 1937). These conditions together with other causes of "extra-thyroidal hypermetabolism" do not in practice give rise to diagnostic difficulty since they are readily recognised and excluded.

(c) Reference standards.

The choice of a reference standard is an important factor

producing disagreement concerning the diagnostic accuracy of basal metabolic rate estimations. In an admirable review of this aspect of the subject Skanse (1949) points out that in various series the upper limits of normality have been +10%, +12%, +13%, +15%, and +20% of the mean standards laid down by Aub and Du Bois (1917). These standards are the usual ones used in clinical work but Robertson and Reid (1952) showed that they were inapplicable in this country, and provided alternative standards, which are not yet, however, widely applied. The advantages of the Robertson and Reid standards over those of Aub and Du Bois in the diagnosis of thyrotoxicosis have been confirmed by Crooks, Murray and Wayne (1958) and for this reason have been adopted in basal metabolic rate estimations throughout the present study.

Sleeping pulse rate.

In text-books dealing with thyroid disease numerous statements can be found concerning the value of the sleeping pulse rate in the diagnosis of hyperthyroidism. Rundle (1951) for example, states that thyrotoxic tachycardia is distinguishable from functional techycardia by the fact that it does not subside during sleep, or after a period of rest. Werner (1955) and McGavack (1951) agree with this statement. Spence (1953), on the other hand, believes that the pulse rate in hyperthyroidism may fall considerably during sleep, but that it still remains above the normal level. It should be noted that these writers

do not record a normal range for sleeping pulse rate which would allow it to be used in the diagnosis of hyperthyroidism. Many authors, referring to this diagnostic procedure, base their opinions on the observations of Boas (1932). Using a cardiotachometer Boas recorded the average minimal sleeping pulse rates in nine toxic cases, ten subjects with neurogenic sinus tachycardia, and 103 normal subjects. Although there was some reduction of the pulse rate during sleep in the toxic cases, it remained about 30 beats per minute above the average minimal rate for the normal subjects, and over 20 beats per minute above that of the patients with sinus tachycardia. His conclusion that the sleeping pulse rate was of diagnostic value in hyperthyroidism can be criticised on the grounds of the small number of abnormal subjects studied. Moreover, the use of a cardiotachometer converts a simple physical sign into a rather complex procedure and in addition the determination by any other means of an average minimal sleeping pulse rate is one of extreme difficulty. Accordingly, the normal values quoted by him cannot be used in routine clinical practice. Consequently before the diagnostic value of the sleeping pulse rate in thyrotoxicosis could be compared in the present study with other diagnostic procedures a normal range had to be established and a standard procedure adopted for making the measurements.

Serum cholesterol.

Following the description by Epstein and Lande (1922)

of serum cholesterol changes in hyperthyroidism many reports have appeared concerning the place of this investigation in the diagnosis of this disease. Mason et al. (1930), Hurxthal (1933a), and McElroy et al. (1938) observed that the serum cholesterol tends to be low in hyperthyroidism. On the other hand Luden (1918), Gardner and Gainsborough (1928), Levy (1931) and Brøchner-Mortensen and Møller (1940) found that the serum cholesterol was usually normal. Further, Peters and Man (1950) in a comparison of the diagnostic value of serum precipitable iodine and cholesterol stated that the latter was of no aid in detecting over-activity of the thyroid. This is opposed to the opinion of Hurxthal and Hunt (1935) who considered that the serum cholesterol estimations had a definite place in the diagnosis. The value of serum cholesterol estimations therefore in the diagnosis of thyrotoxicosis remains controversial.

SECTION 2

The Clinical Diagnosis of Thyrotoxicosis Based on a Clinical Diagnostic Index.

Most physicians would agree that while the diagnosis of thyrotoxicosis is often easy, there are many cases which give rise to uncertainty. This is especially so when the clinical picture is incomplete or when atypical features are present and in these circumstances even experienced clinicians may differ in their conclusions. Sometimes the same observer may alter his opinion on the same case on consecutive days. The reason for this state of affairs is not immediately obvious but it seems to depend on the nature of the mental processes involved in arriving at a diagnosis. In making his clinical assessment a physician must first obtain a reliable history and elicit accurately the appropriate physical signs. At this stage observer variation is encountered since there is rarely complete agreement even among a group of experienced clinicians. Next the physician must decide upon the relative importance he should attach to the diagnostically significant clinical features of the case. In so doing he falls back on his own experience or if he is more junior on that of his teachers. At this point further differences of opinion arise partly because some clinicians regard certain features as of greater diagnostic significance than do others and partly because anyone tends to be influenced by a fortuitous run of positive or negative findings occurring towards the end of the clinical examination.

It is because of these difficulties in making a diagnosis on clinical grounds alone that so many tests of thyroid function have been devised and are so widely used. This in its turn has had the unfortunate effect of making some clinicians feel that they must always have laboratory confirmation of their diagnoses even in the most obvious cases, or what is worse, of making them place too much significance on laboratory results which run counter to their clinical judgement. As Bauer (1956) has said "for these physicians the clinical evaluation lacks that one tangible asset, a figure reported in per cent elevation, per cent uptake or gamma per cent".

No comparisons have so far been reported between the initial diagnosis made by a clinician at his first interview with the patient and the results of laboratory tests. The present study was initially devised to make this comparison but by adopting a statistical procedure incorporating some of the principles of discriminant analysis (Rao, 1948; Zieve and Hill, 1955a) it was found possible to increase the accuracy of the initial clinical diagnosis and to study the effects of observer error. This was done by allocating a positive or negative score to each clinical feature, the values being based on an analysis of the relative frequency of symptoms and signs in the disease. In this way a total score, or clinical diagnostic index, can be obtained in each case. I shall produce

TABLE I

TABLE I

THYROTOXICOSIS - CLINICAL DIAGNOSTIC INDEX

Weighting Factors Allocated to the Symptoms and Signs of Thyrotoxicosis.

Symptoms of recent onset and/or increased severity	Present Score	Score
Dyspnoea on effort	+1	
Palpitations	+2	
Tiredness	+2	
Preference for heat (irrespective of duration)		-5
Preference for cold	+5	
Indifferent to temperature	0	
Excessive sweating	+3	
Nervousness	+2	
Appetite increased	+3	
Appetite decreased		-3
Weight increased		-3
Weight decreased	+3	

Signs	Present Score	Absent Score
Palpable thyroid	+3	-3
Bruit over thyroid	+2	-2
Exophthalmos	+2	
Lid retraction	+2	
Lid lag	+1	
Hyperkinetic movements	+4	-2
Fine finger tremor	+1	
HANDS		
Hot	+2	-2
Moist	+1	-1
CASUAL PULSE RATE		
Auricular fibrillation	+4	
Regular rates:		
Less than 80 per minute		-3
80 to 90 per minute	0	
More than 90 per minute	+3	

evidence that there is a wide difference between these scores in frankly thyrotoxic patients and in normal persons and that in practice they are helpful in distinguishing between toxic and non-toxic patients in cases presenting diagnostic difficulty. The index also provides a numerical estimate of the degree of severity of the disease which can be correlated with other indices of thyroid function.

The Development of the Clinical Diagnostic Index in Thyrotoxicosis

Study of definitely non-toxic and toxic subjects

Material. The group studied consisted of 182 cases of which 99 were unquestionably non-toxic and 83 unquestionably thyrotoxic. The non-toxic section of this group included not only normal subjects, mainly medical and nursing staff, but also patients with simple goitres, anxiety states and post-menopausal symptoms. This group is termed "definite" in the tables and discussion.

Method of clinical examination. In each subject the presence or absence of the clinical features, shown in Table I, was recorded. These signs and symptoms were chosen because they had previously been shown by a clinical survey to differ in their incidence in thyrotoxic patients and normal subjects (Wayne, 1954). A written questionnaire was not used to elicit symptoms and the method of history taking is described in Appendix I "Clinical Diagnostic Index -- Recommendations for Use". In order to reduce the effects of observer variation the procedure

TABLE II

TABLE II

Distribution of Clinical Diagnostic Indices in Cases of the Definite and Doubtful Groups

Diagnostic procedures	Ranges	DEFINITE GROUP Final diagnosis non-toxic	DEFINITE GROUP Final diagnosis toxic	DOUBTFUL GROUP Final diagnosis non-toxic	DOUBTFUL GROUP Final diagnosis toxic
Clinical	< +11	99(100%)	0(0.0%)	59(88.1%)	0(0.0%)
diagnostic	+11 to +19	0(0.0%)	0(0.0%)	7(10.4%)	6(11.8%)
index	> +19	0(0.0%)	83(100%)	1(1.5%)	45(88.2%)
Total cases		99	83	67	51

for the physical examination was rigid and the criteria to be fulfilled are described under the same heading.

The Clinical Index

The clinical features recorded in the cases which had given rise to no clinical diagnostic difficulty were weighted by allocating a score to each. The positive or negative values of these scores were initially allocated on the basis of the relative diagnostic significance of each symptom and sign as found by Wayne (1954), or in a few instances by Williams (1950). These scores were then modified so as to diminish the effects of observer variation. This was done by reducing in value the highest scores because, although attached to features of great diagnostic importance, differences between observers were found to give rise to considerable variation in the total score. The clinical diagnostic indices i.e. the total scores, were then calculated. These produced a good separation between non-toxic and toxic subjects, but the weighting factors for the individual clinical features were further modified to produce the widest possible separation between the two groups without reintroducing excessive observer variation effects. The final weighting factors arrived at are shown in Table I. The indices were then recalculated.

When the clinical diagnostic indices of the 99 non-toxic and 83 toxic subjects of the definite group were analysed (Table II, and Appendix II), the range of values was found to be from -16 to

FIGURE 1

The clinical diagnostic index applied to cases in the definite group.

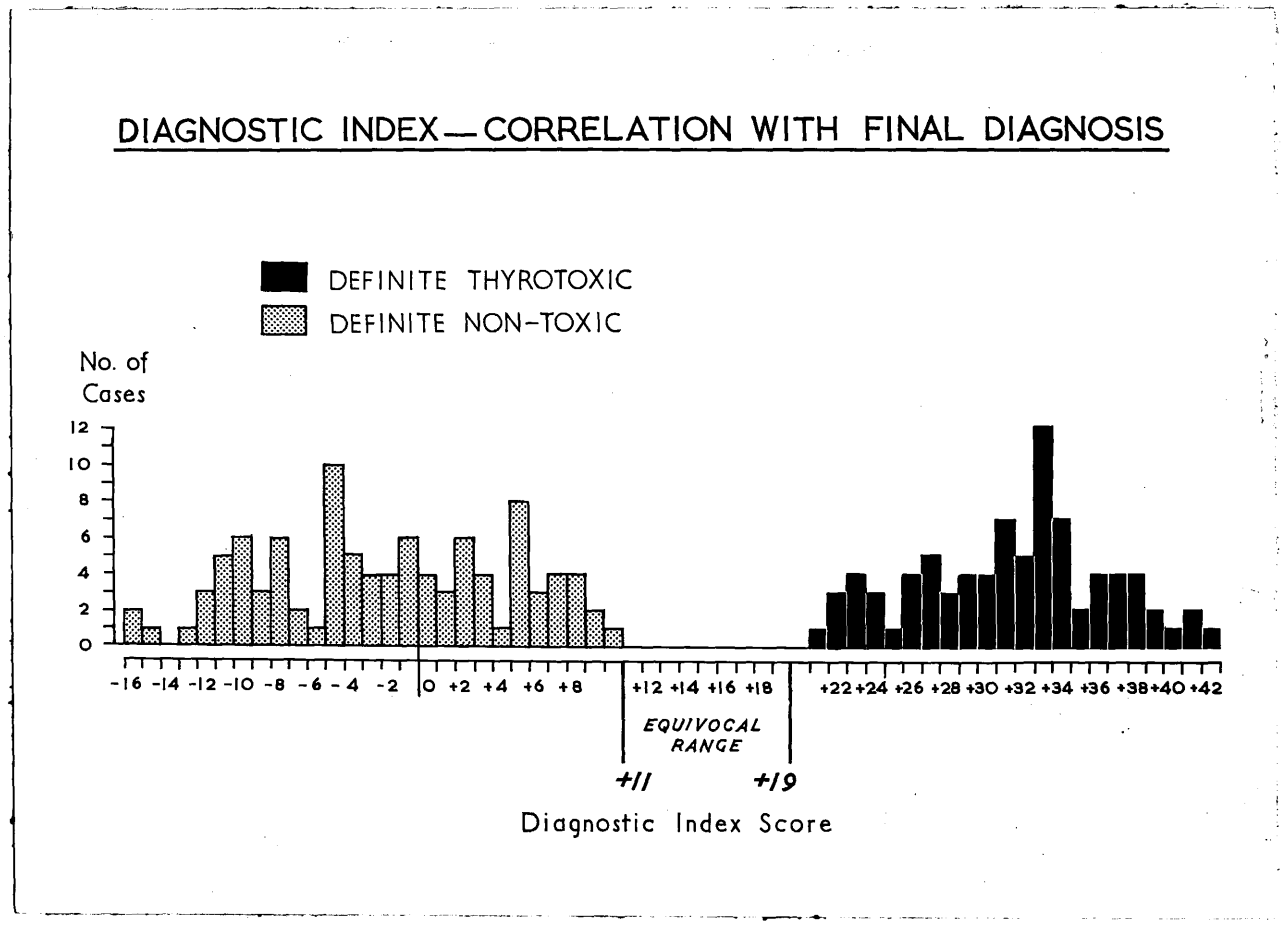

DIAGNOSTIC INDEX—CORRELATION WITH FINAL DIAGNOSIS
DEFINITE THYROTOXIC
DEFINITE NON-TOXIC
No. of Cases
12
10
8
6
4
2
0
-16 -14 -12 -10 -8 -6 -4 -2 0 +2 +4 +6 +8 +12 +14 +16 +18 +22 +24 +26 +28 +30 +32 +34 +36 +38 +40 +42
EQUIVOCAL RANGE
+11
+19
Diagnostic Index Score

FIGURE 1.

+10 for the former and from +21 to +42 for the latter. Figure 1 illustrates the distribution of these unequivocally non-toxic and toxic subjects and the division between them. Thus, an index of +10 or under indicated non-toxicity and indices of +20 or over indicated toxicity.

Statistical analysis of the results allowed the probabilities corresponding to the observed percentages, given in Table II, to be calculated.

Clinical diagnostic index	Definite non-toxic	Definite toxic
+10 and less	0.9738	0.0002
+20 and over	0.0005	0.9893

It will be seen that for values of the index below +11 and above +19 there is good agreement between the observed percentages of Table II and the above probabilities multiplied by 100. The agreement is due to the fact that "normal" distributions can be satisfactorily fitted to the definite non-toxic and toxic groups.

Study of subjects presenting clinical diagnostic difficulty

Material and methods. This group which is subsequently called "doubtful" consisted of 118 cases each of which had presented some diagnostic difficulty to one or more hospital physicians. All had been referred for radioactive iodine studies and the final diagnosis was made only after prolonged observation including the response to treatment. I am, however, confident of the final conclusions. At their first visit the presence

FIGURE 2

The clinical diagnostic index applied to cases in the doubtful group.

FIGURE 3

Distribution curves of clinical diagnostic indices in cases of the doubtful group.

DIAGNOSTIC INDEX—CORRELATION WITH FINAL DIAGNOSIS

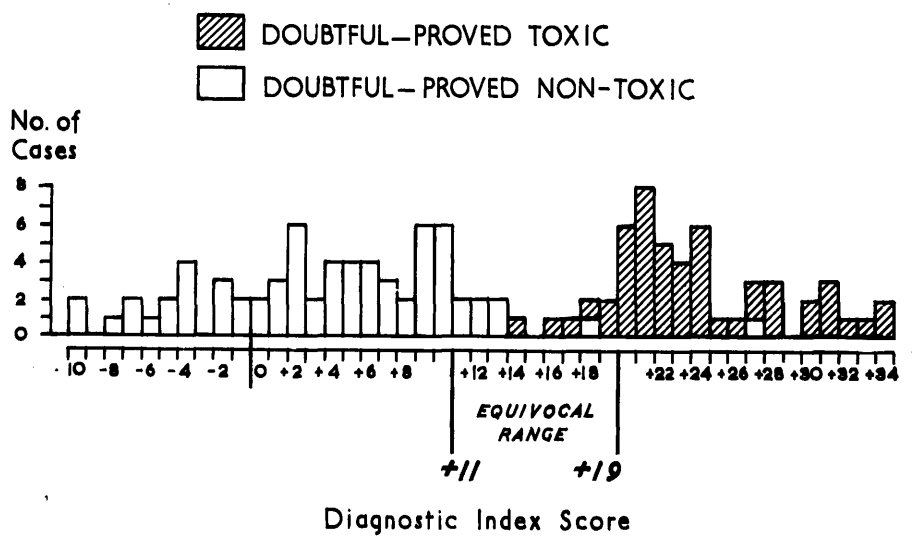
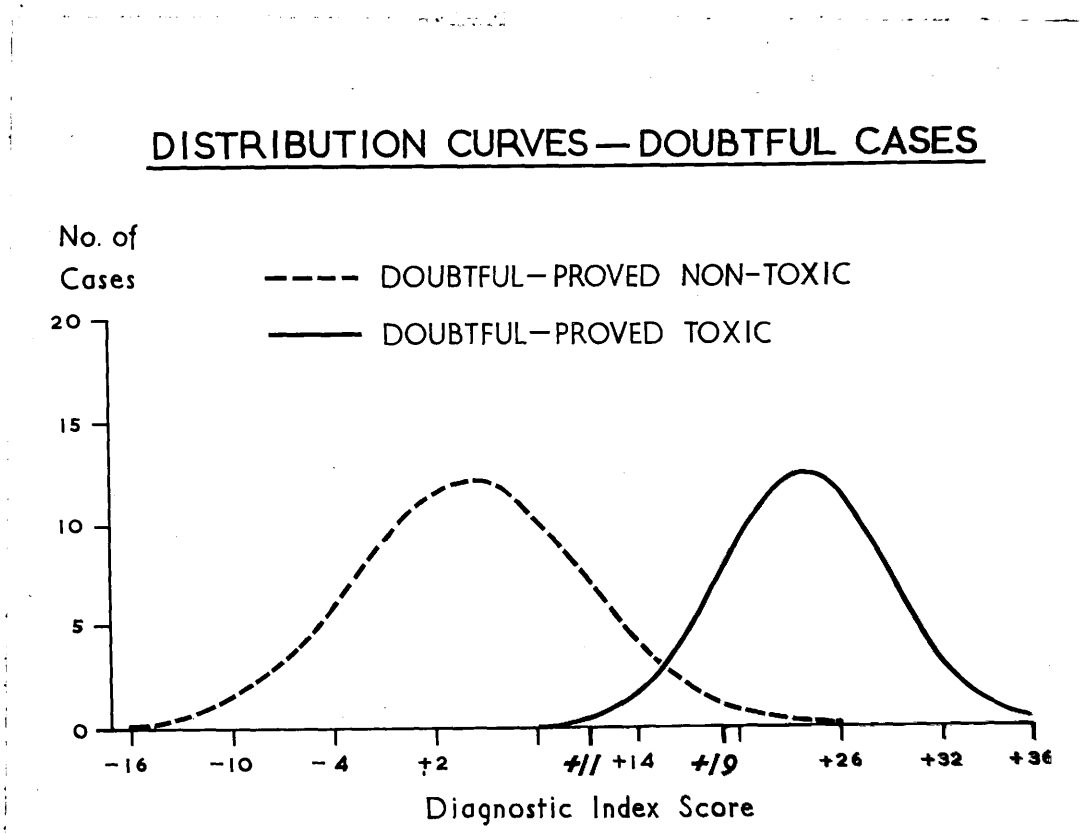


FIGURE 2.

FIGURE 3.


DISTRIBUTION CURVES — DOUBTFUL CASES
No. of Cases
DOUBTFUL — PROVED NON-TOXIC
DOUBTFUL — PROVED TOXIC
20
15
10
5
0
-16
-10
-4
+2
+11
+14
+19
+26
+32
+36
Diagnostic Index Score

or absence of the symptoms and signs listed in Table I were recorded using the criteria described in Appendix I. Clinical indices were calculated only when the final diagnosis was decided after full investigation and the results of therapy were known.

The clinical diagnostic index. Since the weighting factors allocated to the clinical features in the definite group had produced indices giving a wide separation between toxic and non-toxic cases, the same weightings were adopted in the analysis of the doubtful group.

The indices of the 118 subjects of this group are shown in Appendix III and their distribution in Table II and Figure 2. Thirteen cases had indices lying between + 11 and + 19. I have called this the equivocal range. One non-toxic subject had an index lying within the toxic range. A good division persisted, however, between cases finally shown to be non-toxic and those shown to be toxic, 88 per cent of each lying within the non-toxic and the toxic ranges respectively. The distribution curves for this group are shown in Figure 3.

Statistical analysis of the results allowed the probabilities corresponding to the observed percentages, given in Table II, to be calculated.

Clinical diagnostic index	Doubtful non-toxic	Doubtful toxic
+10 and less	0.8315	0.0035
+20 and over	0.0107	0.8051

For values of the index below + 11 there was reasonably

good agreement in the non-toxic group between the above probability multiplied by 100 and the observed percentage of Table II. As in the case of the definite group this was due to the fact that a "normal" distribution could be fitted to the doubtful non-toxic subjects. In the case of the doubtful toxic group, however, a "normal" distribution did not provide a good fit to the observed distribution and this may be partly or wholly due to the relatively small number (51) of patients in this group.

Observer variation studies.

Nine patients, not included in the present series, whose thyroid function was difficult to assess clinically were chosen for this study. Nine observers carried out an independent assessment of these patients using the scoring sheet shown in Table I. This group consisted of the author, three consultant physicians, two research fellows, one senior house officer, one house physician and one final year medical student. The medical student was given special training in the criteria and careful instructions on the use of the scoring sheet. The observers were thus chosen to include a wide variation of experience both in general medicine and in thyroid disorders. The results of these observer variation studies are shown in Table III. Analysis of variance of the indices in 63 observations carried out by observers 1 to 7 showed no significant difference ($f = 1.62$). Observers 8 (one research fellow) and 9 (the senior

TABLE III

TABLE III

Results of Observer Variation Studies Using the Clinical Diagnostic Index.

Observer \ Case	A	B	C	D	E	F	G	H	I	Mean values
1	+24	- 3	+14	+13	0	+10	+39	+35	+31	18.7
2	+29	+ 2	+15	+18	-1	+ 7	+37	+25	+21	17.0
3	+31	+ 1	+ 5	+19	-4	+ 1	+39	+34	+22	16.4
4	+20	+ 1	+ 4	+12	-8	+ 3	+39	+26	+25	13.6
5	+21	- 7	+ 7	+14	-6	+10	+33	+26	+30	14.2
6	+30	- 2	+17	+16	-2	0	+33	+32	+24	16.4
7	+29	- 3	+15	+ 6	-5	- 3	+36	+24	+26	13.9
8	+25	- 7	+11	0	-2	- 1	+25	+25	+29	11.7
9	+22	-11	+11	- 1	-5	- 5	+30	+26	+23	10.0

Observer \ Case	J	K	L	M	N	O	P	Q	R	Mean values
3	- 4	+22	+ 2	+31	+25	+17	+22	+32	+17	18.2
10	- 1	+16	- 5	+34	+22	+12	+22	+34	+13	16.3

house officer) both of whom were newcomers to the unit scored systematically lower.

A further nine patients were similarly assessed by myself and a newcomer to the department with a wide experience of thyroid disease gained at another centre. This physician was given only typewritten instructions on the use of the scoring sheet. The results are shown at the foot of Table III. There was no significant difference in analysis of variance of these scores ($f = 2.06$).

Comparison of the Clinical Impression with Laboratory Tests

SECTION 3

Comparison of the Clinical Diagnostic Index with Laboratory Tests.

TABLE IV

TABLE IV

Comparison of the Clinical Diagnostic Index with the 4-Hour Uptake of ^{131}I.

Diagnostic procedures	Ranges	DEFINITE GROUP Final diagnosis non-toxic	DEFINITE GROUP Final diagnosis toxic	DOUBTFUL GROUP Final diagnosis non-toxic	DOUBTFUL GROUP Final diagnosis toxic
Clinical	< +11	99(100%)	0(0.0%)	59(88.1%)	0(0.0%)
diagnostic	+11 to +19	0(0.0%)	0(0.0%)	7(10.4%)	6(11.8%)
index	> +19	0(0.0%)	83(100%)	1(1.5%)	45(88.2%)
Total cases		99	83	67	51
4-hour uptake ^{131}I	< 46%	34(87.3%)	1(1.9%)	56(89.0%)	3(6.4%)
	> 45%	5(12.7%)	52(98.1%)	7(11.0%)	44(93.6%)
Total cases		39	53	63	47

Radioactive Iodine Studies. Full studies were carried out in 91 of the cases presenting no clinical diagnostic difficulty (definite group) and in 110 of the subjects in which initial diagnostic difficulty had been found (doubtful group). These studies consisted of the estimation of the gland uptake of radioactive iodine and the protein-bound plasma radioactivity four and forty-eight hours respectively after the administration of 25 μc. of ^{131}I. The techniques used have been previously described by Ansell, Macgregor, Miller and Wayne (1953). The method of estimating protein-bound ^{131}I has, however, been simplified by the use of an ion exchange resin.

The results of measurements of the 4-hour uptake of radioactive iodine by the thyroid in 202 subjects are shown in Table IV and Appendices II and III. The upper limit of the normal range of the 4-hour uptake is taken as 45 per cent of the dose. In 87% of the non-toxic subjects included in the definite group in which the diagnosis was never in doubt, the uptake was within the normal limits. It was greater than this value in 98% of the toxic subjects of this group. In the doubtful group the diagnostic accuracy of the uptake was of the same order as that of the clinical index for the same group. Thus, 89% of non-toxic subjects (88% by the index) and 94% of toxic subjects (88% by the index) were correctly diagnosed by this test.

TABLE V

TABLE V

Comparison of the Clinical Diagnostic Index with the 48-Hour Plasma Protein Bound ^{131}I

Diagnostic procedures	Ranges	DEFINITE GROUP Final diagnosis non-toxic	DEFINITE GROUP Final diagnosis toxic	DOUBTFUL GROUP Final diagnosis non-toxic	DOUBTFUL GROUP Final diagnosis toxic
Clinical	< +11	99(100%)	0(0.0%)	59(88.1%)	0(0.0%)
diagnostic	+11 to +19	0(0.0%)	0(0.0%)	7(10.4%)	6(11.8%)
index	> +19	0(0.0%)	83(100%)	1(1.5%)	45(88.2%)
Total cases		99	83	67	51
48-hour plasma protein bound ^{131}I	< 0.4%	36(94.7%)	1(1.9%)	59(93.7%)	5(10.6%)
	> 0.39%	2(5.3 %)	52(98.1%)	4(6.3%)	42(89.4%)
Total cases		38	53	63	47

Estimations of the protein-bound radioactivity of the plasma at 48 hours were made in 201 subjects (Table V and Appendices II and III). In non-toxic cases 95% of the definite group and 94% of the doubtful group had values less than 0.4% of the dose per litre of plasma, which is considered to be the lower limit of the range indicating hyperthyroidism. In toxic subjects the protein-bound ^{131}I was above this level in 98% of the definite group and 89% of the group which had given diagnostic difficulty. Statistical analysis showed no significant difference between the proportion of correct diagnoses achieved by the index and radioactive iodine studies.

Basal metabolic rate. This was estimated in 108 subjects of the definite group and 80 subjects of the doubtful group. All basal metabolic rate estimations were carried out by one experienced technician using a Benedict-Roth apparatus. Patients were admitted to hospital and given 200 mg. of butobarbitone twelve hours before each test. The tests were carried out in duplicate on two successive days and the lowest of four estimations accepted, using the standards of Robertson and Reid (1952). Further details of the method are given by Crooks, Murray and Wayne (1958).

The results of the 188 basal metabolic rate estimations are shown in Table VI and Appendices II and III. In 98% of the non-toxic subjects of the definite group, the basal

TABLE VI

TABLE VI

Comparison of the Clinical Diagnostic Index with the Basal Metabolic Rate (Robertson and Reid)

Diagnostic procedures	Ranges	DEFINITE GROUP Final diagnosis non-toxic	DEFINITE GROUP Final diagnosis toxic	DOUBTFUL GROUP Final diagnosis non-toxic	DOUBTFUL GROUP Final diagnosis toxic
Clinical	< +11	99(100%)	0(0.0%)	59(88.1%)	0(0.0%)
diagnostic	+11 to+19	0(0.0%)	0(0.0%)	7(10.4%)	6(11.8%)
index	> +19	0(0.0%)	83(100%)	1(1.5%)	45(88.2%)
Total cases		99	83	67	51
Basal metabolic rate	< +16%	40(97.6%)	2(2.9%)	34(87.4%)	11(26.9%)
	> +15%	1(2.4%)	65(97.1%)	5(12.6%)	30(73.1%)
Total cases		41	67	39	41

metabolic rates were within the normal range of the Robertson and Reid standards. The basal metabolic rate was raised in 97% of toxic subjects of this group. Basal metabolic rates within the normal range were found in 87% of the cases presenting diagnostic difficulty and finally shown to be non-toxic, while only 73% of the toxic subjects of this group had elevated values. Statistical analysis showed no difference between the proportion of correct diagnoses achieved by the index and estimations of the basal metabolic rate.

Sleeping pulse rate. Sleeping pulse rates were obtained in 110 subjects of the definite group and 80 subjects of the doubtful group. Since no satisfactory ranges of abnormality and normality had been previously established sleeping pulse rates were also obtained in a further 56 patients (27 toxic, 29 non-toxic) in all of whom the diagnoses were unequivocal. These additional subjects have been added to the definite group in the analysis of results (Table VII). Sleeping pulse rates were obtained as follows.-

Nurses were instructed to count the radial pulse for one minute after they were satisfied that the patient was asleep. The sleeping pulse rates of patients admitted to hospital for full investigation of their thyroid function were taken as the means of the three lowest figures recorded.

TABLE VII

TABLE VII

Comparison of the Clinical Diagnostic Index with the Sleeping Pulse Rate

Diagnostic procedures	Ranges	DEFINITE GROUP Final diagnosis non-toxic	DEFINITE GROUP Final diagnosis toxic	DOUBTFUL GROUP Final diagnosis non-toxic	DOUBTFUL GROUP Final diagnosis toxic
Clinical	< +11	99(100%)	0(0.0%)	59(88.1%)	0(0.0%)
diagnostic	+11 to +19	0(0.0%)	0(0.0%)	7(10.4%)	6(11.8%)
index	> +19	0(0.0%)	83(100%)	1(1.5%)	45(88.2%)
Total cases		99	83	67	51
Sleeping pulse rate	< 81	67(97.1%)	35(36.1%)	38(97.5%)	29(70.7%)
	> 80	2(2.9%)	62(63.9%)	1(2.5%)	12(29.3%)
Total cases		69	97	39	41

During their stay in the ward they had received, on at least two occasions, 200 mg. of butobarbitone 12 hours preceding basal metabolic rate estimations. In the case of patients admitted solely for the purpose of obtaining basal metabolic rate estimations on two successive mornings, the lower of two sleeping pulse rates was accepted.

The values obtained for the sleeping pulse rate in the 246 subjects are shown in Table VII while the individual values for the patients of the definite and doubtful groups can be found in Appendices II and III. In the 108 non-toxic cases it was found that 97% of both the definite and doubtful groups had sleeping pulse rates of 80 or less. Of the 138 toxic cases, however, only 64% of the definite group and 29% of the doubtful group had sleeping pulse rates higher than 80. If the upper limit of the normal sleeping pulse rate is taken as 80 then the proportion of correct diagnoses given by this method in the doubtful group is significantly lower than that achieved by the clinical diagnostic index.

Serum cholesterol. The serum cholesterol was estimated by the method of Bloor (1916) in 119 subjects of the definite group and in 80 subjects of the doubtful group. Estimations were also carried out in an additional 53 cases (25 non-toxic, 28 toxic) with a diagnosis which was unequivocal. These cases were added to the definite group in the results (Table VIII) to provide more satisfactory ranges of abnormality and normality.

TABLE VIII

TABLE VIII

Comparison of the Clinical Diagnostic Index with the Serum Cholesterol Value

Diagnostic procedures	Ranges	DEFINITE GROUP Final diagnosis non-toxic	DEFINITE GROUP Final diagnosis toxic	DOUBTFUL GROUP Final diagnosis non-toxic	DOUBTFUL GROUP Final diagnosis toxic
Clinical	< +11	99(100%)	0(0.0%)	59(88.1%)	0(0.0%)
diagnostic	+11 to +19	0(0.0%)	0(0.0%)	7(10.4%)	6(11.8%)
index	> +19	0(0.0%)	83(100%)	1(1.5%)	45(88.2%)
Total cases		99	83	67	51
Serum	< 150	4(6.1%)	31(29.0%)	0(0.0%)	13(31.7%)
cholesterol	150 to 249	24(36.9%)	71(66.3%)	29(74.4%)	26(63.5%)
values (mgm.%)	> 249	37(57.0%)	5(4.7%)	10(25.6%)	2(4.8%)
Total cases		65	107	39	41

The results of the serum cholesterol estimations in the 252 subjects are shown in Table VIII and the individual levels for the patients of the definite and doubtful groups are shown in Appendices II and III. Of 104 non-toxic cases 94% of the definite group and 100% of the doubtful group had serum cholesterol values above 149 mg.%. On the other hand, of 148 toxic cases only 29% of the definite group and 32% of the doubtful group had values less than 150 mg.%. When the normal range for the serum cholesterol is taken as 150 to 250 mg.% then the diagnostic value of the procedure is significantly poorer than the clinical diagnostic index in discriminating between toxic and non-toxic subjects.

SECTION 4

Application of the Clinical Diagnostic Index.

TABLE IX

TABLE IX

Results of the Clinical Diagnostic Index in Different Hospitals

Hospital	Number of Cases	Agreement with Final Diagnosis
A	50	86%
B	74	84%
C	24	88%
D	23	83%
Total	171	85%

An aid to diagnosis in routine clinical practice

In order to obtain information on the diagnostic accuracy of the method in the hands of independent observers, score sheets, with written instructions for their use, were sent to three other hospitals (Table IX, Hospitals B, C, and D) in Scotland. At their routine clinics a total of 121 patients referred for assessment of thyroid function were selected at random and score sheets completed. The final diagnosis, usually based on a conventional clinical assessment, radioactive iodine studies and basal metabolic rate estimations was confirmed by therapeutic trial or observation. It can be seen from Table IX that the diagnostic accuracy obtained in this group of subjects was of the same order as that found in the doubtful group of the original series.

The practical application of the index was also assessed in a further series of 50 patients referred to the clinic by other physicians because diagnostic difficulty had been found. In the case of these subjects indices were obtained before any further clinical assessment was made or laboratory investigations carried out. The final diagnosis was reached after full investigations and follow up including therapeutic trials in some cases. The index gave the correct diagnosis in 43 (86%) of the 50 cases (Table IX, Hospital A).

Of the remaining 7 cases, all of whose indices lay within the equivocal range, 3 were finally shown to be toxic and 4 non-toxic.

The total number of correct diagnoses, 149 of 171 subjects (85%), in this additional investigation is comparable with the results obtained by the application of the method to the doubtful group of the original series. It is most important to note that of the 22 cases which were not correctly placed in toxic or non-toxic categories, the diagnosis was completely misleading in only 5 subjects (3%), since 17 fell within the equivocal range, thus indicating a suspension of judgement until further tests had been carried out.

The use of the index in selected cases to illustrate the technique of clinical diagnosis

A conventional clinical diagnosis involves the unconscious application of the principles underlying discriminant analysis (Rao, 1948; Zieve and Hill, 1955a) and examples of the use of the clinical diagnostic index from both the definite and doubtful groups of the original series are described below in order to illustrate some of the sources of diagnostic difficulty.

The toxic members of the definite group are of lesser interest and the correct diagnosis would have been

made with ease by conventional clinical methods. It is, however, worth while looking more closely at three groups of non-toxic subjects in each of which an inexperienced observer might have been confused by the presence of several symptoms usually associated with the thyrotoxic state.

Post-menopausal subjects. It has been suggested by Wayne (1954) that post-menopausal women show many of the symptoms of thyrotoxicosis, for example, dyspnoea, tiredness, excessive sweating, and that because of this such cases may cause diagnostic difficulty. He considered, however, that an experienced physician would be unlikely to misinterpret this clinical picture because of his skill in history-taking. When the index was applied to such patients they gained, as was expected, high symptom scores but these were nullified by their negative sign scores because of the absence of physical signs of high diagnostic significance. This is well shown in the following post-menopausal subject:

Case No. 49.

Female, aged 51 years (last menstrual period 16 months previously).

Symptoms

Dyspnoea on effort	(+ 1)	Preference for cold	(+ 5)
Palpitations	(+ 2)	Increased weight	(- 3)
Tiredness	(+ 2)		

Symptom score = + 7

Signs

Goitre absent	(- 3)	Hands cool	(- 2)
Bruit absent	(- 2)	Hands dry	(- 1)
Hyperkinesis absent	(- 2)	Casual pulse rate 84 per minute	(0)

Sign score = -10

Diagnostic index: - 3.

Radioactive iodine studies: 4-hour uptake 50%, 48-hour protein-bound radioactive iodine 0.12% per litre.

Basal metabolic rate: + 14%.

Sleeping pulse rate: 60 per minute.

Serum cholesterol: 222 mg.%.

Final diagnosis: Non-toxic, confirmed by observation.

It can be seen that in spite of the negative score for weight increase the patient still scored + 7 on symptoms. The negative values allocated to absent physical signs, however, more than compensated for this.

Normal young adult females with some features of thyrotoxicosis. These subjects were found among a group of nurses, fully employed, who made no spontaneous complaints. An example of this type of subject is shown below:

Case No. 85.

Female, aged 19 years.

Symptoms

Dyspnoea on effort	(+ 1)	Increased appetite	(+ 3)
Tiredness	(+ 2)	Increased weight	(- 3)
Excessive sweating	(+ 3)		

Symptom score = + 6

Signs

Goitre absent	(- 3)	Fine finger tremor	(+ 1)
Bruit absent	(- 2)	Hands hot	(+ 2)
Exophthalmos	(+ 2)	Hands moist	(+ 1)
Hyperkinesis absent	(- 2)	Casual pulse rate 86 per minute	(0)

Sign score = - 1

Diagnostic index: + 5.

The relatively high symptom score in this subject is not supplemented by a raised sign score and although she had several of the signs found in thyrotoxicosis, these were the least heavily weighted. She did express, for example, a preference for cold weather and admitted to nervousness, but these symptoms had been present for as long as she could remember and for this reason lost their diagnostic importance.

Anxiety states. This group of cases may cause diagnostic difficulty to the inexperienced clinician and accounts for a large proportion of the patients referred for radioactive iodine studies in whom the tests prove negative. This is especially the case if a goitre is also present. The absence of diagnostically important physical signs, however, compensates for the high symptom scores as in the following example:

Case No. 94.

Female, aged 33 years.

Symptoms

Dyspnoea on effort	(+ 1)	Preference for cold	(+ 5)
Palpitations	(+ 2)	Excessive sweating	(+ 3)
Tiredness	(+ 2)	Nervousness	(+ 2)

Symptom score = + 15

Signs

Goitre absent	(- 3)	Fine finger tremor	(+ 1)
Bruit absent	(-2)	Hands cool	(- 2)
Hyperkinesis absent	(- 2)	Hands moist	(+ 1)
		Casual pulse rate 88 per minute	(0)

Sign score = -7

Diagnostic index: + 8

Radioactive iodine studies: 4-hour uptake 36%, 48-hour protein-bound radioactive iodine 0.0% per litre.

Basal metabolic rate: + 13%.

Sleeping pulse rate: 64 per minute.

Serum cholesterol: 112 mg.%.

Final diagnosis: Non-toxic, confirmed by observation.

Subjects presenting initial diagnostic difficulty (the doubtful group), are of greater interest since they include the type of case which affords difficulty even to the experienced clinician. In order to find out why this difficulty arose an analysis was made of this group and the cases appeared to fall into the following categories:

Toxic subjects with many symptoms, but few signs. It is probable that these cases presented diagnostic difficulty chiefly because the positive signs appeared to be too few to allow a definite diagnosis to be made. The following patient complained of nearly all the more important symptoms of thyrotoxicosis, but few signs were present. The index, however, gave the correct diagnosis.

Case No. 258.

Female, aged 55 years.

Symptoms:

Dyspnoea on effort	(+ 1)	Excessive sweating	(+ 3)
Palpitations	(+ 2)	Nervousness	(+ 2)
Tiredness	(+ 2)	Weight decrease	(+ 3)
Preference for cold	(+ 5)		

Symptom score = + 18

Signs:

Goitre	(+ 3)	Fine finger tremor	(+ 1)
Bruit absent	(- 2)	Hands hot	(+ 2)
Lid retraction	(+ 2)	Hands moist	(+ 1)
Hyperkinesis absent	(- 2)	Casual pulse rate 70 per minute	(- 3)

Sign score = + 2

Diagnostic index: + 20.

Radioactive iodine studies: 4-hour uptake 69%, 48-hour protein-bound radioactive iodine 0.3% per litre.

Basal metabolic rate: + 14%.

Sleeping pulse rate: 64 per minute.

Serum cholesterol: 167 mg.%.

Final diagnosis: Toxic, confirmed by response to methyl thiouracil therapy.

Toxic subjects with few or atypical symptoms and many signs. Most physicians tend to regard positive physical signs as more reliable than positive symptoms and this group rarely gives rise to diagnostic difficulty unless the patient has symptoms which are regarded as highly unusual in a toxic patient. The following case, for example, is an exception to the rule that thyrotoxic patients are heat intolerant. The numerous positive signs more than compensated for this atypical feature and the index gave the correct diagnosis.

Case No. 267.

Male, aged 67 years

Symptoms

Preference for heat	(- 5)	Weight loss	(+ 3)
Nervousness	(+ 2)		

Symptom score = 0

Signs

Goitre	(+ 3)	Hyperkinesis	(+ 4)
Bruit present	(+ 2)	Fine finger tremor	(+ 1)
Exophthalmos	(+ 2)	Hands hot	(+ 2)
Lid retraction	(+ 2)	Hands moist	(+ 1)
Lid lag	(+ 1)	Casual pulse rate 100 per minute	(+ 3)

Sign score = + 21

Diagnostic index: + 21.

Radioactive iodine studies: 4-hour uptake 83%, 48-hour protein-bound radioactive iodine 4.25% per litre.

Basal metabolic rate: + 76%.

Sleeping pulse rate: 70 per minute.

Serum cholesterol: 105 mg.%.

Final diagnosis: Toxic, confirmed by response to methyl thiouracil therapy.

Toxic subjects with highly significant features missing.

In these case, despite a fairly complete clinical picture, there had been a reluctance to arrive at a definite clinical diagnosis because of the absence of one or more features classically found in thyrotoxicosis. In the following case there was no goitre.

Case No. 282.

Male, aged 63 years.

Symptoms

Dyspnoea on effort	(+ 1)	Excessive sweating	(+ 3)
Palpitations	(+ 2)	Weight decrease	(+ 3)
Preference for cold	(+ 5)		

Symptom score = + 14

Signs

Goitre absent	(- 3)	Hyperkinesis	(+ 4)
Bruit absent	(- 2)	Fine finger tremor	(+ 1)
Exophthalmos	(+ 2)	Hands hot	(+ 2)
Lid retraction	(+ 2)	Hands dry	(- 1)
Lid lag	(+ 1)	Auricular fibrillation.	(+ 4)

Sign score = + 10

Diagnostic index: + 24.

Radioactive iodine studies: 4-hour uptake 68%, 48-hour protein-bound radioactive iodine 1.1% per litre.

Basal metabolic rate: + 11%.

Serum cholesterol: 200 mg.%.

Final diagnosis: Toxic, confirmed by response to methyl thiouracil therapy.

It should be noted that this patient was a male and it is recognised that hyperthyroidism without a goitre may not infrequently occur in this sex. Indeed it is probable that the diagnostic accuracy of the index would be improved by omitting the negative score where a gland was not palpable in a male subject; this was not done since it would increase the complexity of the scoring system. The incidence of the disease in males is in any case low and they represent 18% of this series and 21% of a larger series reviewed by Skanse (1949).

Thyrocardiac subjects ("masked" hyperthyroidism). Thyrotoxicosis in patients with auricular fibrillation with or without cardiac failure who do not show the classical features of thyrotoxicosis are notoriously liable to have the true nature of their disease overlooked. Thus, Bortin, Silver, and Yohalem (1951) investigated 55 cases of auricular fibrillation in which the aetiology was not obvious and decided on the results of radioactive

TABLE X

TABLE X

The Final Diagnoses, Clinical Diagnostic Indices, and the Results of Laboratory Tests in Cases with Indices Lying in the Equivocal Range, and One Non-toxic Case Lying in the Toxic Range.

Case	Sex	Age	Final Diagnosis	Clinical Diagnostic Index: Symptom Score	Sign Score	Total Score	Radioactive iodine studies: 4hr. gland uptake (%dose)	Plasma prot.-bound activity at 48 hrs. (%dose/litre)	BMR %	SPR /min	Cholesterol mgm%
242	F	52	Non-toxic	+ 9	+ 2	+11	29.0	0.09	+ 8	74	230
243	F	20	Non-toxic	+12	- 1	+11	62.4	0.0	+ 3	72	235
245	F	49	Non-toxic	+10	+ 2	+12	45.0	0.09	+ 9	64	270
244	F	37	Non-toxic	+ 7	+ 5	+12	35.0	0.0	0	68	245
246	F	46	Non-toxic	+ 7	+ 6	+13	40.0	0.0	+ 3	72	309
247	F	72	Non-toxic	+12	+ 1	+13	17.3	0.0	- 4	78	256
250	F	45	Toxic	+ 2	+12	+14	84.9	0.63	+65	80	83
251	F	52	Toxic	+ 5	+11	+16	65.8	0.68	+ 4	64	242
252	F	51	Toxic	+ 7	+10	+17	50.5	0.44	+29	76	149
248	F	36	Non-toxic	+13	+ 5	+18	18.5	0.0	+ 7	64	170
253	F	47	Toxic	+16	+ 2	+18	62.3	0.29	+20	88	220
255	F	34	Toxic	+ 9	+10	+19	71.0	1.05	+28	87	149
254	M	50	Toxic	+14	+ 5	+19	65.0	0.90	+20	72	232
249	F	34	Non-toxic	+16	+11	+27	41.7	0.17	+ 6	72	195

iodine studies that 8 were examples of "masked" hyperthyroidism. In the present series of cases all of 13 patients with thyrotoxic auricular fibrillation were correctly placed by the index although one patient, seen subsequently, fell within the equivocal range. The index should be used with caution in patients with congestive cardiac failure since they usually score points (+ 6 or + 7) for dyspnoea, palpitations and either tachycardia or auricular fibrillation even if they are not thyrotoxic. Radioactive iodine studies or estimations of protein-bound iodine are of great diagnostic help in such cases.

Subjects with several atypical features and with indices in the equivocal range. The findings in 13 cases with diagnostic indices lying within the equivocal range and one non-toxic subject with an index in the toxic range are worth special consideration. Some details are given in Table X. Within this group the non-toxic cases would appear to lie at the lower limits and the toxic cases at the upper limits of the equivocal range. From the distribution curves of the non-toxic and toxic subjects of the doubtful group, however, it can be calculated that if a case has a score which falls within the equivocal range then the possibilities of toxicity or non-toxicity are equal (Figure 3). The reason why a toxic case may fall within this equivocal range

is almost always due to the absence of features of high diagnostic significance, as is illustrated by the following:

Case No. 252.

Female, aged 51 years.

Symptoms

Dyspnoea on effort	(+ 1)	Nervousness	(+ 2)
Palpitations	(+ 2)	Weight increase	(- 3)
Preference for cold	(+ 5)		

Symptom score = + 7

Signs

Goitre	(+ 3)	Hands hot	(+ 2)
Bruit absent	(- 2)	Hands dry	(- 1)
Hyperkinesis	(+ 4)	Casual pulse rate 105 per minute	(+ 3)
Fine finger tremor	(+ 1)		

Sign score = + 10

Diagnostic index: + 17.

Radioactive iodine studies: 4-hour uptake 50%, 48-hour protein-bound radioactive iodine 0.44% per litre.

Basal metabolic rate: + 29%.

Sleeping pulse rate: 76 per minute.

Serum cholesterol: 149 mg.%.

Final diagnosis: Toxic, confirmed by response to methyl thiouracil therapy. Conventional diagnostic methods would possibly have placed this patient correctly.

Non-toxic subjects falling within the equivocal range were usually patients with severe anxiety states. They had high symptom scores associated with one or two heavily weighted signs as for example the presence of goitre or tachycardia. Negative scores arising from the physical examination did not compensate for positive symptoms scores as is illustrated in the following case:

Case No. 245.

Female, aged 49 years.

Symptoms

Dyspnoea on effort	(+ 1)	Excessive sweating	(+ 3)
Tiredness	(+ 2)	Nervousness	(+ 2)
Preference for cold	(+ 5)	Appetite decrease	(- 3)

Symptom score = + 10

Signs

Goitre	(+ 3)	Fine finger tremor	(+ 1)
Bruit absent	(- 2)	Hands hot	(+ 2)
Lid lag	(+ 1)	Hands dry	(- 1)
Hyperkinesis absent	(- 2)	Casual pulse rate 90 per minute	(0)

Sign score = +2

Diagnostic index: +12.

Radioactive iodine studies: 4-hour uptake 45%, 48-hour protein-bound radioactive iodine 0.09% per litre.

Basal metabolic rate: + 9%.

Sleeping pulse rate: 64 per minute.

Serum cholesterol: 270 mg.%.

Final diagnosis: Non-toxic, confirmed by failure to respond to methyl thiouracil therapy.

Only two cases of this group, Nos. 243 and 253, were not correctly diagnosed by radioactive iodine tests. The basal metabolic rate estimations were diagnostically correct in all but one of this group (No. 251).

Non-toxic subjects following thyroidectomy, with indices in the toxic range. This group includes cases which are apt to be wrongly assessed both by the index and by conventional clinical methods. These patients who at some time in the past have suffered from thyrotoxicosis are well aware of the symptoms of the disorder. If, in addition, they have tachycardia, goitre or eye signs they tend to score heavily. Unfortunately, radioactive iodine studies often give misleading results in this group and the most reliable objective evidence is afforded by estimations of the basal metabolic rate or of protein-bound iodine. A therapeutic trial using an antithyroid drug is often the most effective way of arriving at a correct conclusion. The following case is an example:

Case No. 249.

Female, aged 34 years.

Symptoms

Dyspnoea on effort	(+ 1)	Preference for cold	(+ 5)
Palpitations	(+ 2)	Appetite increased	(+ 3)
Tiredness	(+ 2)	Weight decrease	(+ 3)

Symptom score = + 16.

Signs

Goitre	(+ 3)	Fine finger tremor	(+ 1)
Bruit present	(+ 2)	Hands hot	(+ 2)
Exophthalmos	(+ 2)	Hands dry	(- 1)
Lid lag	(+ 1)	Casual pulse rate 76 per minute	(- 3)
Hyperkinesis	(+ 4)		

Sign score = + 11

Diagnostic index: + 27.

Radioactive iodine studies: 4-hour uptake 42%, 48-hour protein-bound radioactive iodine 0.17% per litre.

Basal metabolic rate: + 6%.

Sleeping pulse rate: 72 per minute.

Serum cholesterol: 195 mg.%.

Final diagnosis: Non-toxic, confirmed by failure to respond to methyl thiouracil therapy.

SECTION 5

The Clinical Diagnostic Index as a Measure of Severity.

In toxic patients the index gives a quantitative measure of the severity of the disease as judged by the presence of symptoms and signs. It is of interest, therefore, to see the extent to which it correlates with laboratory findings.

When the values for basal metabolic rate estimations were plotted against the indices of 188 cases a signficant correlation ($r = 0.33$) was present in toxic subjects (Figure 4).

The values for the 4-hour uptake of radioactive iodine were plotted against the indices of 202 cases (Figure 5), and a significant correlation was found between them in the toxic subjects ($r = 0.36$).

A similar degree of correlation ($r = 0.36$) was found in toxic subjects between the index and the values for 48-hour protein-bound plasma radioactivity (Figure 6).

When the sleeping pulse rates (Figure 7) and serum cholesterol levels (Figure 8) were plotted aginst the diagnostic indices no significant correlation was found between them in either the toxic or non-toxic subjects.

FIGURE 4

The clinical diagnostic index used as a measure of severity and correlated with basal metabolic rate. The regression line of index on B.M.R. in toxic cases is shown.

FIGURE 5

The clinical diagnostic index uaed as a measure of severity and correlated with the 4-hour gland uptake of radioactive iodine. The regression line of index on 4-hour gland uptake of radioactive iodine in toxic cases is shown.

FIGURE 6

The clinical diagnostic index used as a measure of severity and correlated with the 48-hour plasma protein-bound radioactivity. The regression line of index on 48-hour plasma protein-bound radioactivity is shown.

FIGURE 7

The clinical diagnostic index used as a measure of severity and correlated with the sleeping pulse rate. The horizontal line indicates the upper limit of the normal range.

FIGURE 8

The clinical diagnostic index used as a measure of severity and correlated with the serum cholesterol. The horizontal lines indicate the diagnostic limits chosen.

FIGURE 4.

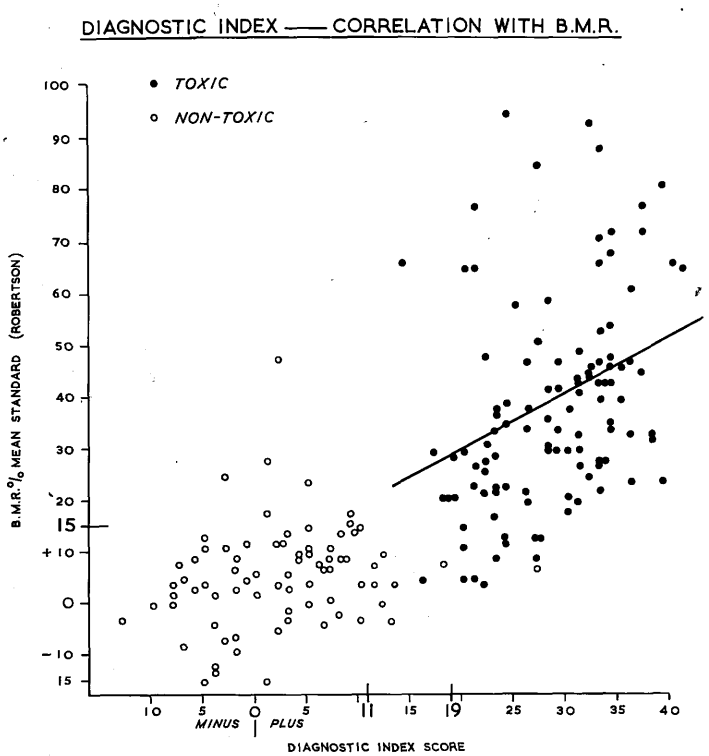

DIAGNOSTIC INDEX —— CORRELATION WITH B.M.R.
TOXIC
NON-TOXIC
B.M.R. % MEAN STANDARD (ROBERTSON)
100
90
80
70
60
50
40
30
20
15
+10
0
-10
15
10
5
0
5
11
15
19
25
30
35
40
MINUS
PLUS
DIAGNOSTIC INDEX SCORE

FIGURE 5.

DIAGNOSTIC INDEX —— CORRELATION WITH RADIO-IODINE STUDIES

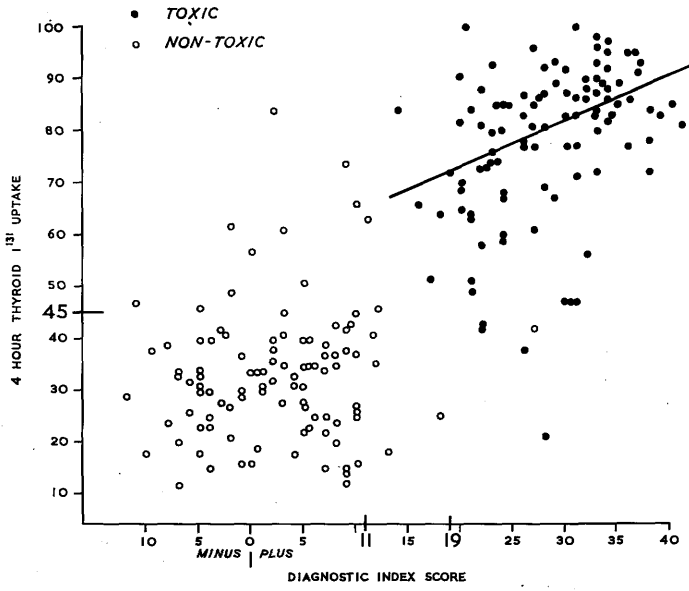


FIGURE 6.

DIAGNOSTIC INDEX —— CORRELATION WITH RADIO-IODINE STUDIES

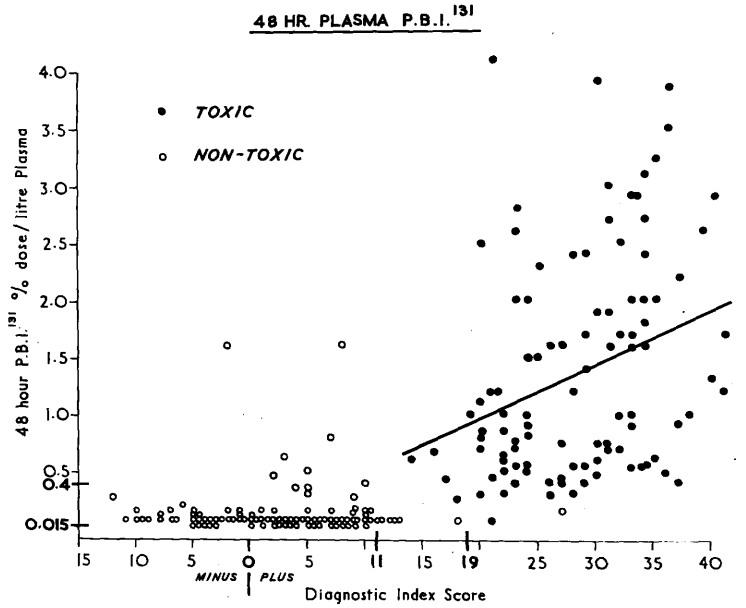


FIGURE 7.

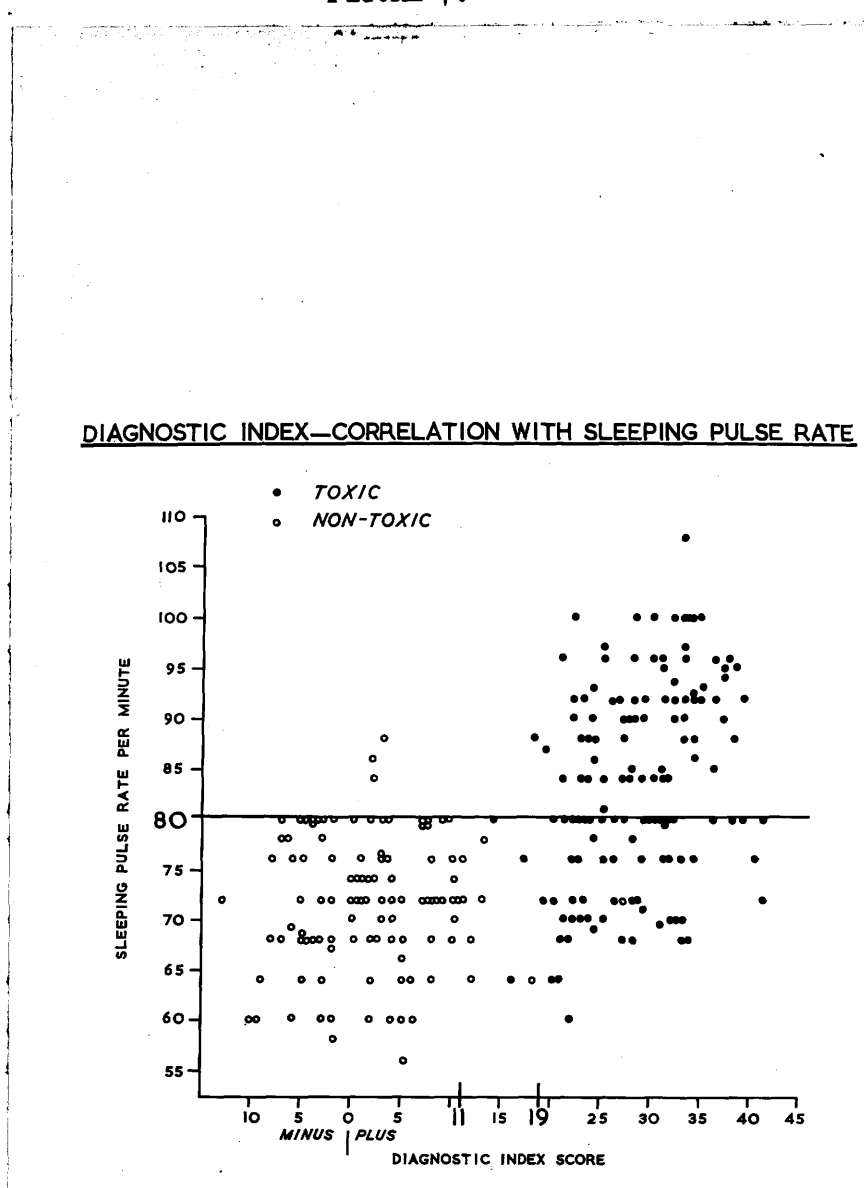
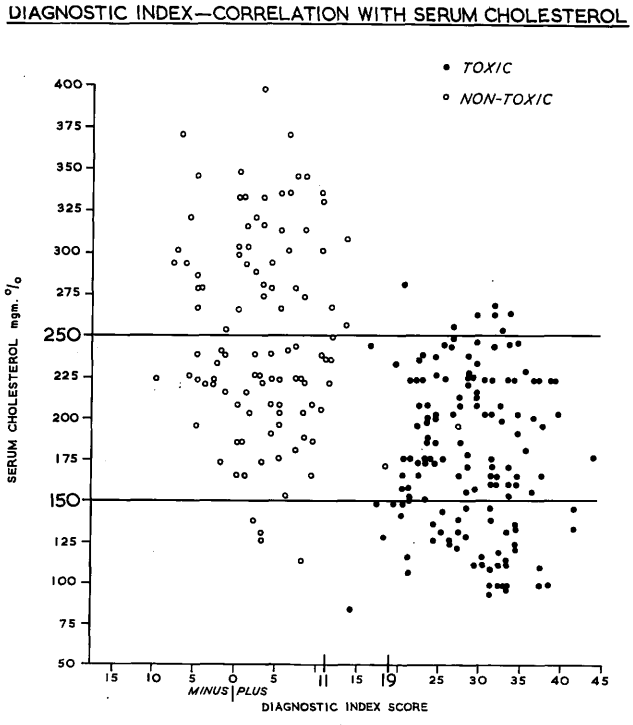

DIAGNOSTIC INDEX—CORRELATION WITH SLEEPING PULSE RATE
TOXIC
NON-TOXIC
SLEEPING PULSE RATE PER MINUTE
110
105
100
95
90
85
80
75
70
65
60
55
10
5
0
5
11
15
19
25
30
35
40
45
MINUS
PLUS
DIAGNOSTIC INDEX SCORE

FIGURE 8.


DIAGNOSTIC INDEX—CORRELATION WITH SERUM CHOLESTEROL
• TOXIC
○ NON-TOXIC
SERUM CHOLESTEROL mgm. %
400
375
350
325
300
275
250
225
200
175
150
125
100
75
50
15 10 5 0 5 11 15 19 25 30 35 40 45
MINUS | PLUS
DIAGNOSTIC INDEX SCORE

SECTION 6

Discussion.

The process of making a clinical diagnosis is complicated. It involves the sifting and evaluating of multiple symptoms and signs and results in the selection of the clinical syndrome which accounts best for the findings. The clinician attaches greater or less significance to the clinical features according to his past experience. He combines the findings into a formula, often subconsciously by applying the concepts of multiple correlation in a non-quantitative manner and in this way arrives at a diagnosis (Zieve and Hill, 1955a). The clinical diagnostic index applies this principle at a conscious level. Previously this concept has been used mainly in the evaluation of laboratory investigations. For example, Zieve and Hill (1955b) after studying 11 liver function tests found that four could be combined to produce a "cirrhosis abnormality score" which discriminated well between normal and cirrhotic subjects. Oyama and Tatsuoka (1956) used a similar technique to assess the prognosis of patients with pulmonary tuberculosis. Using thirteen characteristics they constructed an equation from which a score could be calculated for each patient. This score discriminated with 75% accuracy between those who eventually relapsed and those who remained well. In the field of thyroid disease, Schultz and Zieve (1956) have attempted with some success to predict a remission

of thyrotoxicosis following a single dose of radioactive iodine, from a score obtainedby allocating weighted values at intervals after therapy to the clinical state, the thyroid uptake of ^{131}I, the basal metabolic rate and the serum cholesterol.

In order to apply the technique to clinical diagnosis it is first necessary to carry out a symptom analysis in patients suffering from a particular disease and also in control subjects. The diagnostic significance of each feature can then be determined. A symptom analysis of thyrotoxicosis carried out by Wayne (1954) provided this necessary information and was used in the provisional allocation of values indicating the diagnostic importance of the various symptoms and signs. In this analysis it was apparent that the features most helpful in reaching a diagnosis were increased appetite, weight loss, preference for cold weather, hot sweating hands, persistent tachycardia and hyperkinesis. It can be seen from Table I that these are the features which have been given the highest positive scores. Additional features such as a bruit over the gland and excessive sweating have also been weighted heavily since Williams (1950) has shown them also to be of high diagnostic significance. When clinical diagnosis is taught or practised, emphasis tends to be placed on the presence of certain symptoms

and signs, but in many instances the absence of these features may be of equal importance. For example, the absence of peripheral vasodilatation favours the diagnosis of non-toxicity to the same extent that its presence favours toxicity. In order, therefore, to make the greatest possible use of the clinical evidence equivalent negative values were allocated to some of the features which carried the highest positive scores. This is illustrated by the weightings given to a palpable gland and a bruit over the gland. Thus a goitre (+ 3) with a bruit (+ 2) scores + 5 , while a goitre (+ 3) without a bruit (- 2) scores + 1. The values placed on the presence or absence of hyperkinesis, + 4 and - 2 respectively (originally + 5 and - 5) are examples of the modifications of the initial scores carried out to minimise the effect of observer variation since it was soon appreciated that hyperkinesis, although of considerable diagnostic significance may be difficult to recognise by those to whom the criteria have not been demonstrated. The justification, however, for the retention of its heavy weighting is the frequent presence of the sign in those atypical cases which show few other positive features. The decrease in the weighting of other highly significant diagnostic features was designed to make it impossible for a single observation of any one feature, however diagnostically

important to alter a patient's total score so markedly as to move it from the toxic to the non-toxic range, or vice versa.

The value of diagnostic procedures, clinical, chemical and physical, depends to a large extent on their reproducibility and the greater the human element in a method the higher is the probability of variation when the observations are repeated.

History-taking is prone to error as Cochrane, Chapman and Oldham (1951) have shown, and it is difficult to diminish the effects of observer variation since they arise in the mind of the patient as well as in the interpretation the physician places on the patient's statements. The use of a written questionnaire was avoided since Glaser and Whittow (1954) have shown its unreliability. Ninety per cent of their normal subjects questioned by this procedure recorded at least one symptom initially, but when the questionnaire was repeated there was a significantly smaller number of positive responses. Wayne (1954) also noted a high incidence of positive responses in a normal control group in reply to set questions, but suggested that appropriate supplementary questions would reduce this effect. In the present series the history was taken by conventional methods, leading questions were avoided, and appropriate supplementary

questions were asked about each symptom.

Inconsistencies in the recording of physical signs have been demonstrated by Fletcher (1952) in a study in which eight observers, all members or fellows of a College of Physicians, independently elicited the physical signs found in the chest of each of twenty patients suffering from emphysema. With most signs only two-thirds agreement was obtained. He suggested, however, that agreement might be improved by laying down more rigid criteria for the presence or absence of physical signs. The improvement in agreement between observers when the criteria for physical signs can be clearly defined has been demonstrated by Schilling, Hughes and Dingwall-Fordyce (1955), who compared the accuracy of two observers in making the diagnosis of byssinosis. It was for this reason that rigid definitions of physical signs were laid down in the present series.

The results of the observer variation studies (Table III) show that in the case of observers 1 to 7 these precautions were successful. It is of interest that observer 7, the senior medical student, who had had careful and detailed instruction on history-taking and the criteria for physical signs, showed no statistically significant difference in mean total score from the more experienced observers. Observers 8 and 9, however, who had no special experience of thyroid disease and,

having only recently joined the unit, had received no special instruction, scored systematically lower. It might be objected that the close agreement between the total scores of observers 1 to 7 reflects their common experience and training. It was to test this objection that observer 10, whose special experience of thyroid disease had been gained in another department, was asked to obtain the total scores in nine patients within one week of his arrival in this department. In his case there was no significant difference between his mean total score and that obtained by me. In the recording of individual symptoms and signs there was usually some disagreement between observers which in eight out of ten was insufficient to alter significantly their mean total scores. These observer variation studies suggest that no statistically significant difference will be obtained by observers using the diagnostic index provided they have some experience of thyroid disease. It is also clear that with the ranges of normality and abnormality used in this study inexperienced observers tend to score low and may fail to reach a definite diagnosis in a number of mildly toxic cases. Most of these, however, will fall into the equivocal range, thus indicating the need for further investigation.

It is customary in assessing the accuracy of tests

of thyroid function to correlate them with the final diagnosis arrived at after prolonged observation. No attempt has been made to correlate the initial clinical diagnosis based on signs and symptoms alone with either the results of laboratory investigations or with the final diagnosis. It is generally accepted that tests involving the use of radioactive iodine are especially reliable although different observers favour different techniques. In the present study the uptake of the thyroid gland was measured four hours after a dose of radioactive iodine had been administered and the protein-bound plasma radioactivity forty-eight hours after the dose. These tests had a diagnostic accuracy in the present series of the same order as that described by Wayne (1954) and Macgregor and Wayne (1957). These radioactive iodine tests were carried out on nearly all the members of the doubtful group and it was possible therefore to correlate the results with both the initial diagnosis given by the clinical index and with the final diagnosis. Comparison of the radioactive iodine tests and the clinical index is rendered a little difficult because the former assign patients to either toxic or non-toxic groups whereas the clinical index may place some patients in an equivocal group. There was, however, no statistically significant difference

between the accuracy of the index and either of the radioactive iodine tests, even when the equivocal results given by the index were regarded as entirely incorrect (Tables IV and V). Basal metabolic rate estimations were obtained in eighty patients of the doubtful group and Table VI shows that about one quarter of the toxic subjects of this group had basal metabolic rates within the normal range. Even if all the equivocal indices are counted as incorrect, the basal metabolic rate has no statistically significant advantage in diagnostic accuracy over the index.

The clinical diagnostic index is of greater diagnostic value than either the sleeping pulse rate (Table VII) or the serum cholesterol level (Table VIII), particularly in cases presenting initial diagnostic difficulty. The study has incidentally shown that sleeping pulse rates of more than 80 per minute make the diagnosis of thyrotoxicosis highly probable, and this agrees with the findings of Addis (1922). This, however, only occurred in a minority (29%) of the doubtful group finally shown to be toxic. It would appear that the serum cholesterol, contrary to the opinion of Hurxthal and Hunt (1935) has also a very limited place in diagnosis. Like the sleeping pulse rate its value lies in the diagnosis of toxicity which is highly probable if the level is below 150 mg.%. This finding is similar to that of Man et al. (1940).

It should be pointed out that irrespective of the diagnostic procedures used, the final decisions were based on the response to therapy and it follows that for the purpose of the present investigation thyrotoxicosis is defined as a condition in which antithyroid therapy produces a remission of symptoms and signs. This definition has the great advantage that it supplies the essential information which a physician requires.

The results obtained in the present series suggested that the clinical index should be of practical value and this opinion was confirmed by the results obtained by other centres using the method in their routine clinical practice. It is of special importance to note (Table IX) that of the 121 patients assessed by the index at other hospitals only 15 were not correctly placed in toxic or non-toxic categories and of these 10 were placed in the equivocal group indicating the need for further investigation. In only five cases was the diagnosis completely incorrect. One of the centres also studied the results obtained by medical students who had not been specially trained in the use of the scoring sheets and confirmed the finding of the fallacies produced by inexperience. While the independent observers were satisfied that the method provided good discrimination between toxic and

non-toxic subjects, the opinion was expressed by one physician that his over-all clinical assessment would have produced a separation of the same order. Further observations would have to be made to confirm or refute this view but the index may well prove to be of most value to experienced clinicians who see cases of thyroid disease relatively infrequently.

The difficulty of obtaining a precise expression of clinical severity in thyrotoxicosis has complicated previous attempts to correlate its degree with objective measures of thyroid function. Goodwin, Macgregor, Miller and Wayne (1951), however, classified their cases on clinical impressions into four grades from mild and border-line to severe, and found a rough correlation between the 4-hour and 24-hour uptake of radioactive iodine and clinical severity. No such correlation was found in the case of the 48-hour protein-bound radioactive iodine. Fraser (1953) has stated that the correlation of the urinary excretion tests with clinical severity is poor. He suggested, however, (Fraser, Hobson, Arnott, and Emery, 1953) that one reason for this finding might be that when the "T" index is well above the normal range it increasingly underestimates the thyroid uptake of radioactive iodine. The clinical index is a measure of severity in so far as it indicates the number of target tissue effects.

The weightings alloted to individual features ensure moreover that emphasis is placed on those phenomena such as heat intolerance which are the more reliable indices of abnormality. It is thus possible to plot this measure of clinical severity against the results of radioactive iodine studies. It can be seen from Figures 5 and 6 that a significant correlation was found between the degree of severity as reflected by the indices and the values both for 4-hour uptake and 48-hour protein-bound radioactive iodine. It must be admitted, however, that if the weighting factors making up the clinical index had been modified so as to express the degree of abnormality of individual clinical features, for example, if different weightings had been given to different grades of tachycardia and loss of weight the correlation might have been better.

Both Means (1916) and Fraser (1953) agree that the basal metabolic rate is the best index of the severity of the disease. The clinical index correlates well with the basal metabolic rate (Figure 4). Foote, Mackenzie and Maclagan (1952) have shown that a significant correlation exists between the basal metabolic rate and the thigh-neck clearance of ^{131}I in thyrotoxicosis. It is, therefore, not surprising to find that the coefficients of correlation which exist between the index and the radioactive iodine criteria

used are comparable with that between the index and basal metabolic rates.

No such correlation, however, exists between the sleeping pulse rates and the diagnostic indices in the present series. These results agree with those of Sturgis and Tompkins (1920) who foundthat the basal pulse rate could not be taken as an absolute index of the activity of a given case of Graves's Disease, although they did find a close parallelism between the basal pulse rate and basal metabolism in successive observations on the same individual.

Hurxthal (1933 a, b) considered that the serum cholesterol reflected clinical severity and even suggested that in some cases its value in this respect exceeded that of the basal metabolic rate. He also considered that it bore a general reciprocal relationship to the basal metabolic rate but this finding was not confirmed by Man et al. (1940). The results of the present series do not show any correlation between clinical severity based on the diagnostic indices, and serum cholesterol levels.

The results in general confirm that the clinical index can be used as a measure of severity of the disease. They also raise the possibility of the existence of a continuous gradation of thyroid activity comparable to that found for blood-pressure levels by

Pickering (1955). It should be made clear, however, that when allocating numerical values to the features which contribute to the clinical index weightings were used which would separate sharply normality from abnormality and this would tend to obscure any continuous gradation of thyroid function which might lie between the obviously normal and abnormal. This problem is worth further study although it would involve changing the emphasis placed on the weighting factors. Estimations of non-radioactive protein-bound iodine might be the best index of thyroid function with which to correlate such a new index.

Conclusion

A clinical diagnostic index has been devised which has been found to be of value as a reliable and simple aid to diagnosis in day to day practice. When its application produces a score which falls into the equivocal range this indicates a case which is difficult to assess on clinical grounds alone and will require investigation by special tests. It has proved so reliable in routine practice that it has been possible to reduce the demands on the laboratory services. The clinical index enables one to see why certain cases of suspected thyrotoxicosis give rise to diagnostic difficulty and the analysis and classification of the responsible features should be of help to those who

have found themselves puzzled by a discrepancy between their clinical impressions and laboratory findings. The index makes it possible to minimise the effects of observer variation and also makes it easier to discover the reasons why differences in diagnosis occur. Lastly, it should be stressed that this technique is of more general application and might with advantage be applied to other diseases. Moreover, the application of the method to diagnostic problems throws much light on the technique of diagnosis and emphasises the value of precise clinical observation in modern medicine.

PART I

SUMMARY

1. Analysis of the frequency of symptoms and signs in thyrotoxic patients and normal individuals allowed the allocation of a numerical value to each clinical feature which varied with its diagnostic significance. The aggregate score in an individual case was termed the clinical diagnostic index and was derived in 99 unquestionably non-toxic and 83 unquestionably thyrotoxic subjects. The values attached to individual signs and symptoms were then modified to minimise the effects of observer variation and to produce the greatest possible separation between the two groups, so that all non-toxic subjects had indices of less than + 11 and all toxic subjects greater than + 19.

2. The method was then applied to 118 cases which had presented initial diagnostic difficulty using the weighting factors for clinical features established by the study of the definitely non-toxic and toxic cases. The clinical diagnostic indices produced good separation between cases finally shown to be non-toxic and those shown to be toxic. Fifty-nine of 67 non-toxic cases (88%) had scores less than + 11, 7 (10.5%) lay within the range + 11 to + 19 which is called the equivocal range, and 1 (1.5%) fell in the toxic range. Forty-five (88%) of the 51 toxic cases had scores greater than + 19 and the remaining 6 cases all fell within the

equivocal range.

3. Studies on observer variation showed no statistically significant difference between scores obtained independently by experienced observers.

4. The diagnostic accuracy of the method was not significantly different from that of radioactive iodine studies and basal metabolic rate estimations and was greater than that of sleeping pulse rates and serum cholesterol values.

5. The method has been applied in four different centres to 171 patients and the diagnostic accuracy (85%) was comparable with that of the original series of cases.

6. Examination of individual features making up the index often explains the mechanism by which a clinical diagnosis has been reached and makes it clear why, in certain cases, diagnostic difficulty has been found.

7. The scores can be used as indices of severity in toxic subjects and significant correlations existed between them and the 4-hour uptake of radioactive iodine, the 48-hour plasma protein-bound radioactivity and the basal metabolic rate. The indices did not correlate with either sleeping pulse rates or serum cholesterol levels.

PART II

THE MEDICAL TREATMENT OF THYROTOXICOSIS

At the present time the choice of medical treatment of thyrotoxicosis lies between one of the various antithyroid drugs and the use of radioactive iodine. In this part of the thesis it is proposed to describe work carried out to evaluate the effectiveness of various antithyroid drugs in current use and to describe the results of radioactive iodine therapy in a series of cases with particular reference to the technique of dose estimation and the effect of pre-treatment with antithyroid drugs.

SECTION 1

Antithyroid Drugs -- Introduction

Antithyroid drugs may be defined as chemical agents which interfere with the synthesis, release, or peripheral action of the thyroid hormone. A large number of chemically unrelated compounds are covered by this definition, but it is intended to deal only with those which have a place in the practical medical treatment of thyrotoxicosis. Such drugs can be divided into two categories.

(1) Drugs preventing the iodination of tyrosine.

(2) Drugs inhibiting the iodide trap of the thyroid.

Group (1) Drugs preventing the iodination of tyrosine.

The antithyroid drugs of particular importance in this group are the thiouracil and imadazole derivatives.

Mechanism of action. While the exact mechanism of action of these drugs is controversial, there is general agreement that they interfere with the iodination of the thyroid hormone precursors without affecting the ability of the gland to concentrate the iodide ion. The three current hypotheses given to explain this action are.-

(i) They may inhibit the enzyme system which oxidizes ionic to elemental iodine.

(ii) They may compete with iodide as a substrate for this oxidative enzyme.

(iii) Elemental iodine may be reduced to the iodide ion depriving the thyroid cell of iodine necessary for synthesis of the thyroid hormone.

Whatever the exact mechanism of action the effect of the drugs is to reduce the level of circulating thyroid hormone. This is accompanied by thyroid hyperplasia possibly due to increased production of thyrotropic hormone by the pituitary.

Group (2) Drugs inhibiting the iodide trap of the thyroid.

The anions which possess a significant goitrogenic action are, in order of decreasing activity, perchlorate, thiocyanate, and nitrate. Thiocyanate and nitrate have no therapeutic importance as antithyroid drugs because of their toxicity. Potassium perchlorate has, however, been used successfully in the treatment of thyrotoxicosis and much of the work to be described in the following sections consists of an evaluation of the place of perchlorate in the treatment of the disease.

Mechanism of action. The goitrogenic action of these anions can be overcome by the administration of iodide and this suggests that they interfere with the uptake of inorganic iodide by the thyroid (Franklin et al. 1944; Wyngaarden et al. 1952). Furthermore, inorganic iodide already trapped by the thyroid is discharged by the administration of the anions. The exact mechanism by which the anions act is unknown, but presumably if the circulating blood iodide level is high enough the block can be overcome.

The indications for using antithyroid drugs.

In recent years the indications for the use of these drugs in the treatment of thyrotoxicosis have become more clearly defined. Most authorities agree that young adults with small or moderately enlarged, diffuse goitres should be given a prolonged trial of antithyroid drugs. When the disease occurs during pregnancy or puberty this form of therapy allows more flexible control of thyroid function during a period when the metabolic demands on the thyroid are varying. Before partial thyroidectomy is carried out toxicity should be controlled by treatment with one of these drugs. In some thyrocardiac subjects where rapid control of toxicity is required a short course of an antithyroid drug can be given beginning ten days after radioactive iodine therapy. Finally, in patients where the diagnosis of thyrotoxicosis remains in doubt after full investigation, the patient's response to antithyroid drug therapy is of diagnostic value.

Historical

Thiourea, the parent compound of most of the antithyroid drugs of Group (1) which are used therapeutically, was shown to be goitrogenic by Griesbach et al. (1941) and Kennedy (1942). The latter also showed that a derivative of thiourea was responsible for the goitrogenic properties of Brassica seeds. Astwood (1943) further

confirmed the antithyroid activity of thiourea and its derivatives and in 1944 published the first clinical report of thiourea and thiouracil in the treatment of hyperthyroidism. The toxic effects of these drugs soon diminished the initial enthusiasm for antithyroid drug therapy, but this was revived by the introduction of 4-methyl thiouracil and 6-N-propyl thiouracil, which because of their greater potency were effective in smaller doses and had fewer side effects. Both drugs had extensive clinical trials and are still widely used. Stanley and Astwood (1949) then demonstrated that 1-methyl-2-mercaptoimidazole (methimazole, 'Mercazole', 'Tapazole') had greater antithyroid activity than any other known compound, while Bartels and Sjogren reported a successful clinical trial of the drug in 1951. Methimazole is widely used in the United States, but in this country 2-carbethoxythio-1-methyl-glyoxaline (carbimazole, 'Neomercazole') synthesized by Rimington and his associates (Lawson et al. 1951), is the more popular of the imidazole derivatives.

The history of drugs inhibiting the iodide trap of the thyroid began with the demonstration by Marine et al (1932) that acetonitrile and related compounds could produce thyroid hyperplasia and that the effect was antagonised by iodine. In 1952 Wyngaarden et al. studied

the antithyroid activity of various anions and concluded that the perchlorate ion was the most potent inhibitor of the iodide-trapping mechanism of the thyroid. This was followed in 1954 by successful clinical trials of potassium perchlorate in thyrotoxicosis (Godley and Stanbury, 1954; Morgans and Trotter, 1954).

SECTION 2

A Method of Comparing Antithyroid Drugs

The relative activity of antithyroid compounds can be assessed by a method described by Stanley and Astwood (1947) which depends upon their property of inhibiting the uptake of radioactive iodine. Their observations were carried out on normal human subjects and were thus more directly applicable to the clinical use of these drugs than those methods of assay which depend upon the goitrogenic action of the drugs in animals such as the immature rat (Astwood, Bissell and Hughes, 1945) or chick (VanderLaan and Bissell, 1946). It is, however, generally agreed that the order of antithyroid activity obtained by Stanley and Astwood is not necessarily applicable to cases of thyrotoxicosis. Moreover, it is valid only when applied to drugs which act at the same point on the chain of thyroid hormone synthesis and so cannot be used to compare the activity of a drug such as potassium perchlorate, which acts on the iodide trapping mechanism, with drugs such as the thiouracils and imidazoles which affect the conversion of iodide to organically bound iodine.

Ideally, drugs should be assayed on patients suffering from the disease for which they are to be used. The particular method by which their effect is produced then becomes unimportant. No satisfactory method of doing this in thyrotoxicosis has so far been described and

despite extensive clinical trials of various antithyroid compounds there is an absence of exact data by which the therapeutic efficiency of the various drugs can be compared. I have approached this problem in a new way. In Part I of this thesis I have been able to allocate figures indicating the relative diagnostic value of the various symptoms and signs of thyrotoxicosis by an analysis of their relative frequency in patients with the disease and in normal individuals. This procedure allowed me to derive, as previously described, a total score which I have called the clinical diagnostic index and I have shown that it has about the same degree of diagnostic accuracy as estimations of the basal metabolic rate or the results of radioactive iodine studies. By removing from the list of the diagnostic features of thyrotoxicosis those which are unaffected by treatment I have constructed a therapeutic index which gives a quantitative measure of the response to therapy. This section of the thesis describes the method and provides evidence as to its validity by applying it to a comparison of two antithyroid drugs, methyl thiouracil and potassium perchlorate.

Material and Methods.

Series 1. This series comprised 40 subjects who were definitely thyrotoxic. All were admitted to hospital and

TABLE I

TABLE I

THYROTOXICOSIS - THERAPEUTIC INDEX

Weighting Factors Allocated to the Symptoms and Signs of Thyrotoxicosis.

Symptoms	Score	Signs	Score
Dyspnoea on effort	+1	Hyperkinetic movements	+4
Palpitations	+2	Fine finger tremor	+1
Tiredness	+2	Hands:	
Preference for cold	+5	Hot	+2
Excessive sweating	+3	Moist	+1
Nervousness	+2	Resting Pulse Rate:	
Appetite increased	+3		
Weight decreased	+4	More than 85/minute	+3

the diagnoses were confirmed by radioactive iodine studies, including the 4-hour uptake of ^{131}I and the 48-hour plasma protein-bound radioactivity. Basal metabolic rate and serum cholesterol estimations were also carried out. All subjects had diffusely enlarged thyroid glands and were considered suitable for antithyroid drug therapy. They were allocated alternately to two groups, one to be given methyl thiouracil and the other potassium perchlorate. Methyl thiouracil was given in the doses used routinely in the Thyroid Clinic of the University Department of Medicine at Glasgow, namely 200 mg. three times a day for two weeks, followed by 100 mg. three times a day; potassium perchlorate was given in a dose of 200 mg. three times a day.

Before treatment began the patients were discharged from hospital and instructed to attend weekly. At the first out-patient attendance they were examined by a standard routine. Each subject was weighed in her clothes and asked to wear the same clothing on subsequent visits. She was then instructed to lie down on an examination couch and was left undisturbed for 10 minutes. The resting pulse rate was then counted for one minute. The presence or absence of the symptoms and signs shown in Table I was then recorded. The taking of the history and the physical examination were carried out in the

same way for each patient, the criteria for the identification of symptoms and signs being those laid down in Appendix 1 except for pulse rate where a resting pulse rate higher than 85 beats per minute was considered abnormal. Throughout the investigation all observations, with few exceptions, were made by one observer (the author) and I have shown in Part I of this thesis that my observations in observer variation studies involving the clinical features shown in Table I, did not differ significantly from those of 7 other experienced observers.

Numerical values were allocated to each clinical feature (Table I) on the basis of their diagnostic significance except in the case of appetite increase and weight loss. As I have previously described the combination of these two symptoms was of great diagnostic importance and for the purpose of diagnosis each was rated + 3 giving a value of + 6 if both were present. In the assessment of therapeutic response, however, the restoration of weight loss is of much greater significance than the return to normal appetite and for this reason the rating for the symptom of weight loss was increased to + 4 and that for appetite increase reduced to + 1. By adding the values obtained at the first out-patient attendance a total score which I term the therapeutic index was derived for each patient.

At the first out-patient visit treatment was started

with either methyl thiouracil or potassium perchlorate and patients receiving the latter drug were instructed not to eat fish or iodised salt, and to avoid medicines containing iodine.

At each subsequent weekly visit the procedure for ascertaining body weight, resting pulse rate, and the presence or absence of the clinical features of the disease, was repeated. When a symptom or sign disappeared completely its value was deducted from the therapeutic index of the previous week. In the case of weight increase one point was deducted from the initial index for each 4 pounds of weight gained. In this way a fresh therapeutic index was calculated weekly for each patient.

The week of full control or "cure" was defined as that week in which the therapeutic index first reached a value of 5 or less. If, however, the index fell below that value in either of the two subsequent weeks the week of "cure" was that with the lowest index. If in either of these two weeks it exceeded 5 it had to fall again in the way described above before the week of "cure" was reached. Indices of 5 or under were chosen to indicate full control because, irrespective of the other clinical findings, the combination of two or more clinical features of high diagnostic significance, and consequently

scoring highly would suggest the persistence of toxicity and result in a therapeutic index greater than 5. Moreover in patients who were considered to be satisfactorily controlled by antithyroid drugs therapeutic indices fluctuated within the range zero to 5 over long periods. For these reasons it was considered that an index remaining in this range for 3 successive weeks indicated that full control had been achieved.

In order to confirm that "cures" had been effected at the times of the lowest therapeutic indices, basal metabolic rate estimations were carried out at fortnightly intervals in all patients until the week of "cure" had been reached. This was done by admitting patients to hospital overnight and giving 200 mg. butobarbitone 12 hours before the test which was performed on the following morning. The procedure is described in greater detail by Crooks, Murray and Wayne, 1958. The serum cholesterol was also estimated each second week.

Following "cure" the patients were maintained in the euthyroid state with doses of the drugs ranging from 50 to 150 mg. daily for methyl thiouracil and 200 to 400 mg. daily for potassium perchlorate. After three months maintenance therapy the drugs were stopped.

Series 2. This study comprised 14 cases made up of two groups: 8 subjects of Series 1 who had been given

FIGURE 1

Times taken to effect "cure" by potassium perchlorate (600 mg. daily) and methyl thiouracil in patients of Series 1.

FIGURE 1.

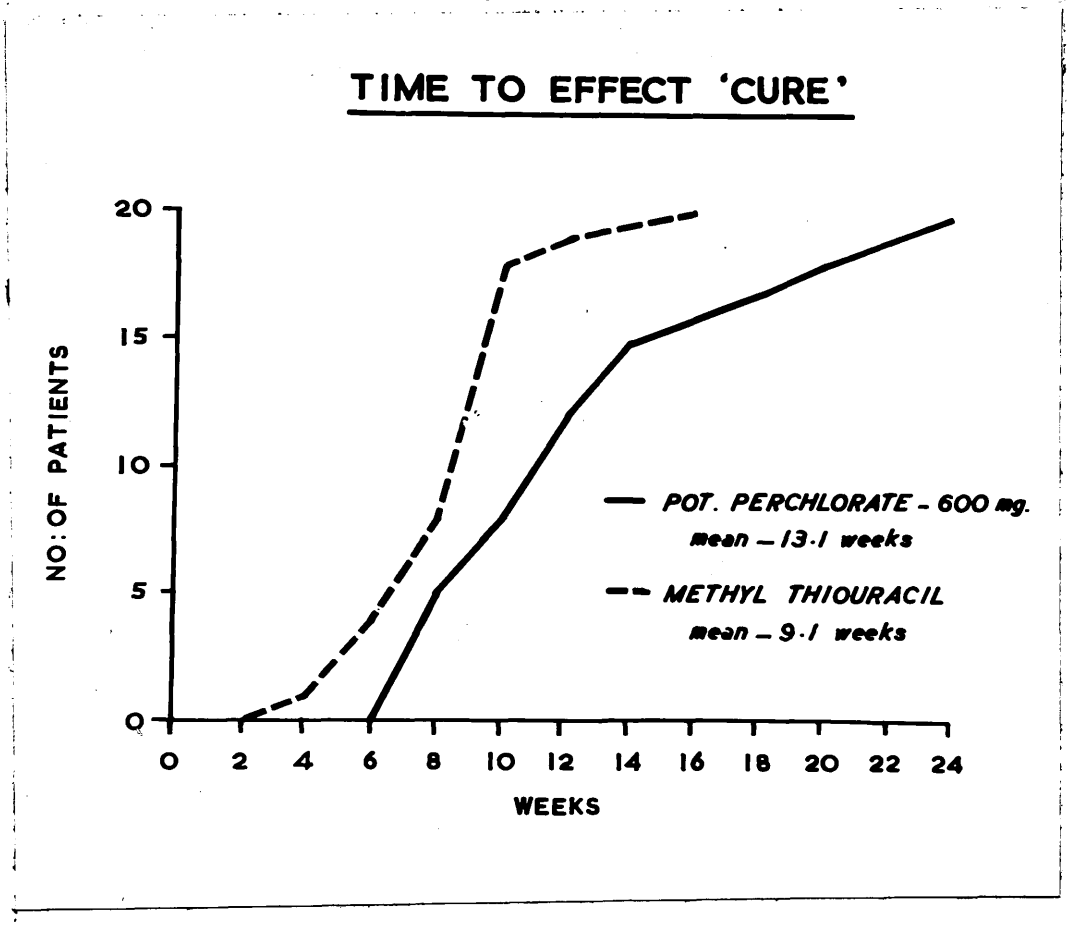

TIME TO EFFECT 'CURE'
NO: OF PATIENTS
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24
WEEKS
POT. PERCHLORATE - 600 mg.
mean - 13.1 weeks
METHYL THIOURACIL
mean - 9.1 weeks

TABLE II

2 – 4	1	–
5 – 6	–	–
7 – 9	4	5
10 – 10	10	2
11 – 12	1	4
13 – 14	–	3
15 – 15	1	–
16 – 18	–	2
19 – 20	–	1
21 – 23	–	1
24 – 24	–	1
	20	20

TABLE II

Distribution of Patients in Series 3 Receiving Methyl Thiouracil and Potassium Perchlorate (600 mg. Daily) Showing Time Taken to Effect "Cure".

Time to Effect "cure" (weeks)	Methyl Thiouracil	Pot. Perchlorate (600mg. daily)
3 - 4	1	-
5 - 6	3	-
7 - 8	4	5
9 - 10	10	3
11 - 12	1	4
13 - 14	-	3
15 - 16	1	-
17 - 18	-	2
19 - 20	-	1
21 - 22	-	1
23 - 24	-	1
Total	20	20
Mean time to "cure".	9.1 weeks	13.1 weeks

methyl thiouracil and who, because they relapsed following the cessation of therapy, were re-treated with potassium perchlorate; and 6 subjects who had been treated with potassium perchlorate and were re-treated with methyl thiouracil after relapse. The same dosage schemes for each drug were used in re-treatment as in the initial treatment and the follow-up procedure was identical.

Results

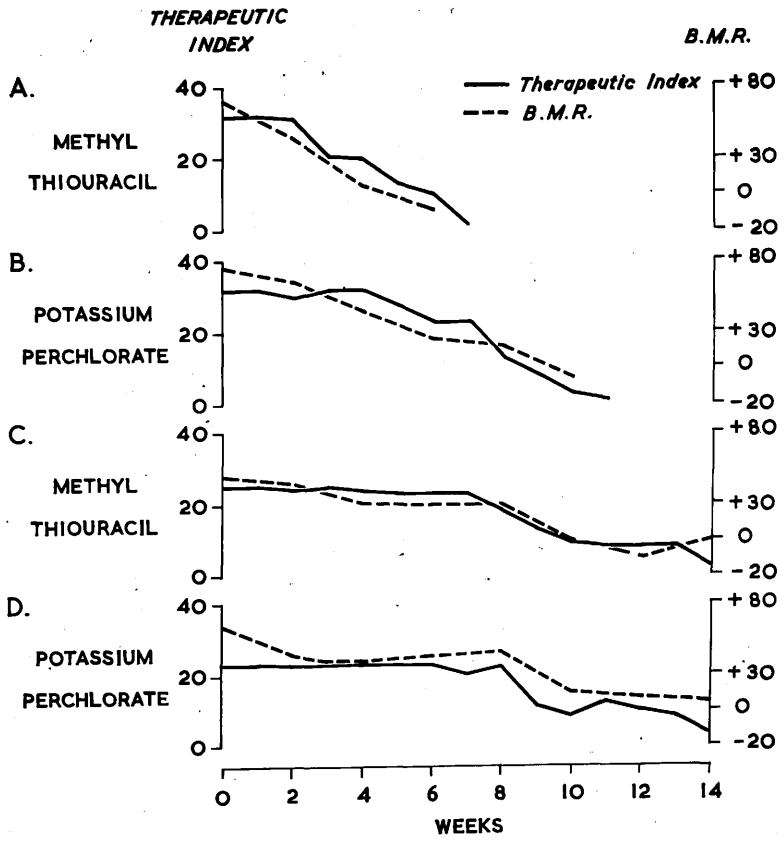
Series 1: Time of "Cure": The weekly therapeutic indices obtained in the patients of this series are detailed in Appendix IV (potassium perchlorate 600 mg. daily -- cases 1 to 20; methyl thiouracil -- cases 21 to 40). The times taken to effect "cure", i.e., to reach scores of 5 or less, are shown in Table II. The mean time to "cure" of the 20 patients on methyl thiouracil was 9.1 weeks and the comparable figure for the 20 patients on potassium perchlorate was 13.1 weeks. These values are significantly different ($p < 0.01$). Figure 1 illustrates the times taken to "cure" for both drugs and it can be seen that in the group of patients receiving potassium perchlorate the longest time taken to effect "cure" was 23 weeks compared with 16 weeks for methyl thiouracil. It also shows the larger number of cases receiving perchlorate who required long courses before "cure" was achieved.

FIGURE 2

Changes in therapeutic indices and basal metabolic rates during treatment with methyl thiouracil and potassium perchlorate (600 mg. daily). A and B show linear changes of the therapeutic indices with time. B and C show the delayed type of therapeutic response.

? C and D

FIGURE 2.


THERAPEUTIC INDEX
B.M.R.
Therapeutic Index
B.M.R.
A.
METHYL THIOURACIL
B.
POTASSIUM PERCHLORATE
C.
METHYL THIOURACIL
D.
POTASSIUM PERCHLORATE
40
20
0
+80
+30
0
-20
0 2 4 6 8 10 12 14
WEEKS

Variations of Therapeutic Index with Time: Typical examples of the changes in the index during therapy are shown in Figure 2A (methyl thiouracil) and Figure 2B (potassium perchlorate). The associated changes in the basal metabolic rate plotted on the same figures showed good agreement with the clinical method of assessment. In the case of both patients illustrated in those figures linear regressions of the therapeutic indices on time showed a significant fall in the values of the index with time. This relationship was found to hold in 17 of the 20 patients treated with methyl thiouracil. The remaining 3 patients were slow to respond to the drug and the changes in the therapeutic index and basal metabolic rate in this type of response are shown in Figure 2C. The indices of all three patients, however, reached values of 5 or less in subsequent weeks. Of the 20 patients treated with potassium perchlorate 16 showed significant falls in the regression coefficient of the therapeutic index with time. In one of the remaining 4 patients the values of the index suggested that the reason for the non-significant fall was the absence of data on three occasions on which she defaulted. The remaining 3 patients did not respond to treatment until 6 weeks or more had elapsed and an example of this type of response to perchlorate is shown in Figure 2 D.

TABLE III

TABLE III

Drug		BMR (%Robertson & Reid) Mean	S.D.	Serum Cholesterol (mg.%) Mean	S.D.
Methyl Thiouracil	Before therapy	+46.95		173	
	Time of "cure"	- 7.8	9.7	320	90.5
Potassium Perchlorate (600 mg. daily)	Before therapy	+35.7		171	
	Time of "cure"	- 2.2	12.2	248	61.9

Effect of Initial Values of the Therapeutic Index: A comparison between the initial values of the therapeutic indices and the times taken to effect "cure" showed that for the groups on either drug there was no significant correlation between these two variables. In other words, the time taken to effect a "cure" was uninfluenced by the initial values of the therapeutic index which is, of course, a measure of the severity of the disease.

Basal Metabolic Rate and Serum Cholesterol: All measurements of basal metabolic rate and serum cholesterol made in the patients of Series 1 are shown in Appendices V and VI respectively.

The mean values of basal metabolic rates in both groups before and after therapy are shown in Table III. Since the values of the basal metabolic rates were obtained at fortnightly intervals it was sometimes necessary to estimate the value of the basal metabolic rate corresponding to the therapeutic index when it had reached the week of "cure". These estimations were made by first finding the linear regression of the basal metabolic rate on time and then estimating it at any given time from this regression. At the beginning of treatment using methyl thiouracil the mean value for the 20 patients was + 46.95; at the conclusion when the patients had reached values of the

therapeutic index of 5 or less they had a mean value of - 7.8 with a standard deviation of 9.7. A normal group of individuals would be expected to have basal metabolic rates with a mean value of zero and standard deviation 7.5 approximately. Thus the 20 patients had attained the euthyroid state as measured by the basal metabolic rate since the mean value of - 7.8 is not significantly different from zero. At the beginning of treatment using potassium perchlorate the mean of the initial reading of basal metabolic rates for the 20 patients concerned was + 35.7; at the conclusion when the time of "cure" had been reached by the therapeutic indices, the mean value was - 2.2 with a standard deviation of 12.2. Thus, once again the estimations of basal metabolic rate confirmed that the patients were euthyroid at the time of "cure".

It was hoped that the estimation of serum cholesterol values at fortnightly intervals might yield confirmatory evidence of "cure". They were, however, found to be of little help. The mean values before and after therapy are given in Table III.

Series 2 -- Re-treatment: The therapeutic indices obtained at weekly intervals in the patients of this series are shown in Appendix VII. The times taken to effect "cure" in 8 subjects who initially received methyl thiouracil

TABLE IV

TABLE IV

Times Taken to Effect "Cure" in Patients who Relapsed After Treatment

Series 2

Case No.	Time to effect "cure" (weeks) Methyl Thiouracil Initial Therapy	Potassium Perchlorate Re-treatment	Difference (weeks)	Case No.	Time to effect "Cure" (weeks) Potassium Perchlorate Initial Therapy	Methyl Thiouracil Re-treatment	Difference (weeks)
21	9	12	- 3	7	18	10	+ 8
22	10	10	0	9	14	7	+ 7
23	9	22	-13	10	11	9	+ 2
24	11	9	+ 2	11	7	4	+ 3
25	15	22	- 7	13	13	14	- 1
26	10	12	- 2	14	9	4	+ 5
27	7	16	- 9	-	-	-	-
33	6	6	0	-	-	-	-
Mean time for "cure"	9.6	13.6	- 4.0		12.0	8.0	+ 4.0

and were given potassium perchlorate, following recurrence of the disease, are shown in Table IV. A t-test shows that the difference of 4 weeks is not significantly different from zero ($t = -2.18$, $0.05 < p < 0.10$). The smallness of the probability suggests that the difference is probably different from zero. It should be noted that the difference obtained, i.e. potassium perchlorate taking 4 weeks longer than methyl thiouracil for "cure" to be obtained, is similar to the difference found in Series 1. In 6 subjects who had received potassium perchlorate and who were given methyl thiouracil following recurrence of the disease, the times to "cure" are also shown in Table IV. A t-test shows that in this group of subjects the difference of 4 weeks is significantly different from zero ($t = -2.93$, $p < 0.05$). Again the slower rate of control by perchlorate is similar to that obtained between the two groups of 20 patients in Series 1.

From a comparison of the two cross-over tests it is apparent that the findings are the same irrespective of which drug has been given first. It is valid therefore to consider both cross-over tests together and to conclude that in this group of 14 subjects potassium perchlorate, in the doses used, took 4 weeks longer than methyl thiouracil to control the disease. This

confirms the results of Series 1 and provides evidence that the method of assessment is reproducible.

Discussion

Gaddum (1940) states, "Experiments on man are the only kind of experiment which can give certain evidence of therapeutic action on man". The truth of this statement is borne out by the work of Stanley and Astwood (1947) who found a poor correlation between their assays of antithyroid drugs in normal human subjects and the results obtained in the rat (McGinty and Bywater, 1945; Bywater, McGinty and Jenesil, 1945; and Astwood, Bissell and Hughes, 1945). There are many difficulties, however, in the way of assaying drugs in humans including individual variation of response, the small numbers as compared with animal experiments, the effect of suggestion, and the special difficulty of transferring results obtained in normal subjects to patients with disease. The various methods of carrying out drug assays in humans are admirably described by Gaddum (1954) who classifies the methods as direct assays, assays depending on measured responses, and those depending upon quantal (all or none) responses.

The method used by Stanley and Astwood to compare the antithyroid activity of various drugs is an example of the direct method of assay since they found the

minimum doses which would produce a definite inhibition of radioactive iodine uptake by the thyroid. By grading the degree of inhibition with various doses of the drugs these workers also incorporated the principles of assay by measured response and in this respect followed the design of the classical work on the antihistamines carried out by Bain (1949). Although this type of experiment gives reliable information about the relative activities of drugs in normal human subjects it is much more difficult to obtain comparable information in disease, yet this is the information which the practising physician requires. For example there appears to be a greater variation in the response to antithyroid drugs in patients with thyrotoxicosis than in normal subjects. This variation, which is generally accepted by clinicians, may be due to the varying amounts of stored hormone present in toxic glands before treatment, but irrespective of the reason it cannot be ignored when providing comparisons of antithyroid drugs intended to be of help in clinical practice.

The method of assay by measured response, like all methods in which responses to single doses of drugs are observed, has another disadvantage in that it fails to allow for the varying rates of accumulation of the drugs in the tissues. This is a particular disadvantage when comparing drugs with similar pharmacological

actions, such as the antithyroid drugs and can produce fallacies in the extrapolation of the results to clinical therapeutics.

The objection to applying the results of animal experiments to humans has been avoided in the present study by carrying out the assay procedure in patients with thyrotoxicosis and allowance has been made for the varying rates of drug accumulation by choosing the time taken to achieve "cure" as the response. Since "cure" is an all or none phenomenon the procedure used belongs to the group of assays by quantal responses. The difficulty in such assays lies in determining the end-point, in this case "cure". This decision is essentially a clinical one and is conventionally based on the individual interpretation of a number of observations. Such decisions can be criticised because of their subjective and interpretive basis and their scientific value has been questioned by a number of workers (Cochrane, Chapman, and Oldham, 1951). Due to the inherent variability in conventional clinical assessments of "cure" conflicting results may be obtained by different workers in comparing the effectiveness of drugs when this end-point is used. For example Bartels (1945) found that thiobarbital was 12 times more active in thyrotoxicosis than thiouracil

whereas Astwood (1945) found it to be only twice as active. The therapeutic index by expressing the response to therapy on a quantitative basis eliminates the necessity for reaching an opinion as to the time of "cure". Instead the end-point is reached when the indices become five or less. The advantages of expressing the therapeutic response of a disease on a quantitative basis have been pointed out by Schultze and Zieve, 1958. It allows much simpler statistical treatment and in the present study has enabled the high frequency of linear therapeutic responses with time to be identified. It has also made it possible to demonstrate that there was no relationship between the initial severity of the disease and the rate of therapeutic response.

The finding that the mean values of the basal metabolic rates in the two groups of Series 1 were not significantly different from zero when the decision as to "cure" was reached by this method supports its validity. The index was also applied in a cross-over test of the type widely used in the assay of insulin in rabbits. This has the great merit of using each individual as her own control. This procedure is of course only possible in those relatively rare instances in which it is legitimate to allow a patient to relapse before re-applying treatment. Fortunately,

this is accepted practice in the treatment of thyrotoxicosis with antithyroid drugs. The results obtained in the cross-over tests confirmed those found in Series 1 and provide further evidence of the validity and reproducibility of the method. They also suggest that the possible errors of alternate allocation of drugs to two groups (Gaddum, 1940) did not occur in Series 1. It was appreciated that observer variation effects might introduce fallacies in the type of assessment which has been described. Such variation has been minimised since the indices were derived by one observer, the author, who in addition has shown no statistically significant differences in observer variation studies carried out in a similar clinical assessment of thyrotoxic patients.

In the comparison of antithyroid drugs the question of dose is of great importance. The doses of methyl thiouracil and potassium perchlorate chosen were the standard ones in use at the time of the study. It is appreciated that it is generally desirable to use more than one dose of different drugs when comparing their relative potency and the method of comparison by therapeutic indices has been applied to potassium perchlorate at a higher dosage level and also to carbimazole in the investigation to be described in the next section of the thesis.

SECTION 2

Summary

1. A clinical method of comparing the therapeutic effectiveness of antithyroid drugs is described. The method is based on the allocation of numerical values to the reversible features of thyrotoxicosis, and the sum of these values for an individual case is termed the therapeutic index.

2. Therapeutic indices were obtained weekly in two groups of 20 cases, one group receiving methyl thiouracil and the other potassium perchlorate. The antithyroid activity of both drugs was assessed by the time taken to produce "cure" which was defined as a therapeutic index of 5 or under. "Cure" was confirmed by basal metabolic rate estimations.

3. The time taken to effect "cure" was uninfluenced by the initial severity of the disease and in 33 of 40 patients the rate of therapeutic response bore a linear relationship to time.

4. A cross-over test carried out on 14 patients who relapsed after the first course of treatment confirmed the validity of the method.

SECTION 3

A Comparison of Antithyroid Drugs, with Particular Reference to the Therapeutic Applications of Potassium Perchlorate.

The ideal antithyroid drug for the treatment of thyrotoxicosis should have a sufficiently potent antithyroid action to control the clinical features of the disease within a reasonable time, should be non-toxic in therapeutic doses, and should be inexpensive. The two antithyroid drugs most commonly used in this country, methyl thiouracil and carbimazole, fulfil the first requirement, carbimazole having a greater antithyroid action, weight for weight, than methyl thiouracil (Macgregor and Miller, 1953). Neither of these drugs qualifies as an ideal therapeutic agent in respect of non-toxicity since, in therapeutic doses both have caused serious side effects including agranulocytosis with a fatal outcome in some cases. Burrell et al. (1956) believe that fewer toxic effects are produced by carbimazole than by methyl thiouracil. In the case of both drugs the risks of toxic effects are less than the dangers of the untreated disease and for this reason they are acceptable therapeutic agents.

Potassium perchlorate was first shown to be an effective antithyroid drug in the treatment of thyrotoxicosis by Godley and Stanbury (1954) and later by Morgans and Trotter (1954), Beichart (1955), Buttaro and Brunori (1955), and Kleinsorg and Kruskemper (1957). It has a relatively simple molecule which would not be expected to produce

the serious side effects of the thiouracils and imidazoles, particularly on the haemopoetic system. The initial clinical use of this drug appeared to fulfil this expectation, and provided its low toxicity is confirmed it would be a better antithyroid drug in this respect than either methyl thiouracil or carbimazole. Morgans and Trotter (1954), however, had the impression that the average rate of response to perchlorate in the dose they used (400 mg. daily) was less than that produced by methyl thiouracil in a dose of 200 mg. daily and that even with larger doses of perchlorate occasional patients were not adequately controlled. Buttaro and Brunori (1955) who used doses of 600 mg. daily also considered that the drug had a slower action than the other antithyroid drugs. Although it is not always necessary or even desirable to treat thyrotoxicosis rapidly it is likely that in the doses used by these workers it was a less effective antithyroid drug than either methyl thiouracil or carbimazole. If, however, the dose of potassium perchlorate could be increased sufficiently to achieve control of the disease at a rate comparable with that produced by methyl thiouracil or carbimazole, without a coincident increase in toxicity, then it would be nearer the ideal antithyroid drug than either of the other two.

The investigation to be described has been carried

out to explore this possibility. I have used data obtained during the work described on the method of comparing the effectiveness of antithyroid drugs and in addition I have studied a further two groups of thyrotoxic patients who were treated with carbimazole and potassium perchlorate (1,000 mg. daily) respectively. I also took the opportunity to study certain other items of therapeutic interest, e.g.- the influence of variation in dietary iodide intake on the therapeutic action of perchlorate, the effect of potassium perchlorate and methyl thiouracil on the degree of exophthalmos, and the place of perchlorate in pre-operative preparation and in pregnancy complicated by thyrotoxicosis.

Material and Methods.

Series 1. This series comprised two groups of 20 thyrotoxic patients, one group being treated with methyl thiouracil and the other with potassium perchlorate (600 mg. daily) as described in the preceding section.

Series 3. This series consisted of 40 cases with unequivocal thyrotoxicosis. The basis of selection and the methods of confirming the diagnosis were as described previously for the subjects of Series 1. The patients were allocated alternately to two groups one to be given carbimazole and the other potassium perchlorate. Carbimazole was given in doses of 20 mg. three times a day for two

weeks followed by 10 mg. three times a day. This dosage scheme was chosen because it was the accepted equivalent of the dosage scheme for methyl thiouracil used in Series 1. In the case of potassium perchlorate the dose of 600 mg. daily used in Series 1 was increased to 1,000 mg. daily in five divided doses. The dietary iodide intake was not restricted in the patients of Series 3.

The method of comparing the effectiveness of the two drugs by changes in the therapeutic indices was identical to that previously described except that patients were seen at fortnightly intervals during treatment. Serial basal metabolic rate and serum cholesterol estimations were not carried out but "cure" was confirmed by estimation of the basal metabolic rate in each case.

Dietary intake and urinary excretion of iodide. In 8 patients of Series 1, all of whom had been treated with potassium perchlorate and advised to restrict their iodide intake, diet histories were obtained during the period of maintenance therapy. The histories were obtained by a dietitian who had no knowledge of the times taken to effect "cure" in the patients. From this data it was possible to estimate the approximate dietary iodide intake in each case.

The 20 patients of Series 1 advised to restrict their iodide intake because they were receiving potassium

perchlorate and the 20 patients of the same series treated with methyl thiouracil without restriction of iodide intake were asked to bring a sample of urine with them at each weekly visit, the sample being collected at 2 p.m. on the day of the visit. A qualitative test for the urinary iodide content of these samples was carried out in the following way.-

To a pair of test tubes were added 0.2 ml. and 1 ml. of the urine sample; standard tubes were also prepared with, instead, water and 0.1 ml. of a solution of iodide (0.5 mg. I per litre). To each tube the following was added: 5 ml. water, 1 ml. arsenious acid solution (0.075 N arsenious acid in 0.75 N H_2SO_4 and 0.5 per cent Na OH), and finally, in quick sequence along the tubes, 0.4 ml. ceric sulphate (0.1 N ceric ammonium sulphate in 3.5 N H_2SO_4). The result was read at half-an-hour. No fading of the yellow colour in either tube showed that no iodide was present and was recorded as (-); a relatively large amount of iodide produced complete fading in both tubes and was recorded as (++); all other results were recorded as (+).

This procedure is similar to that described by Fraser et al. (1953) except that these workers used aliquots of 24 hour samples of urine and consequently expressed their results in ranges of mg. of iodide per 24 hours.

FIGURE 3

Times taken to effect "cure" by carbimazole and potassium perchlorate (1,000 mg. daily) in the patients of Series 3.

FIGURE 3.

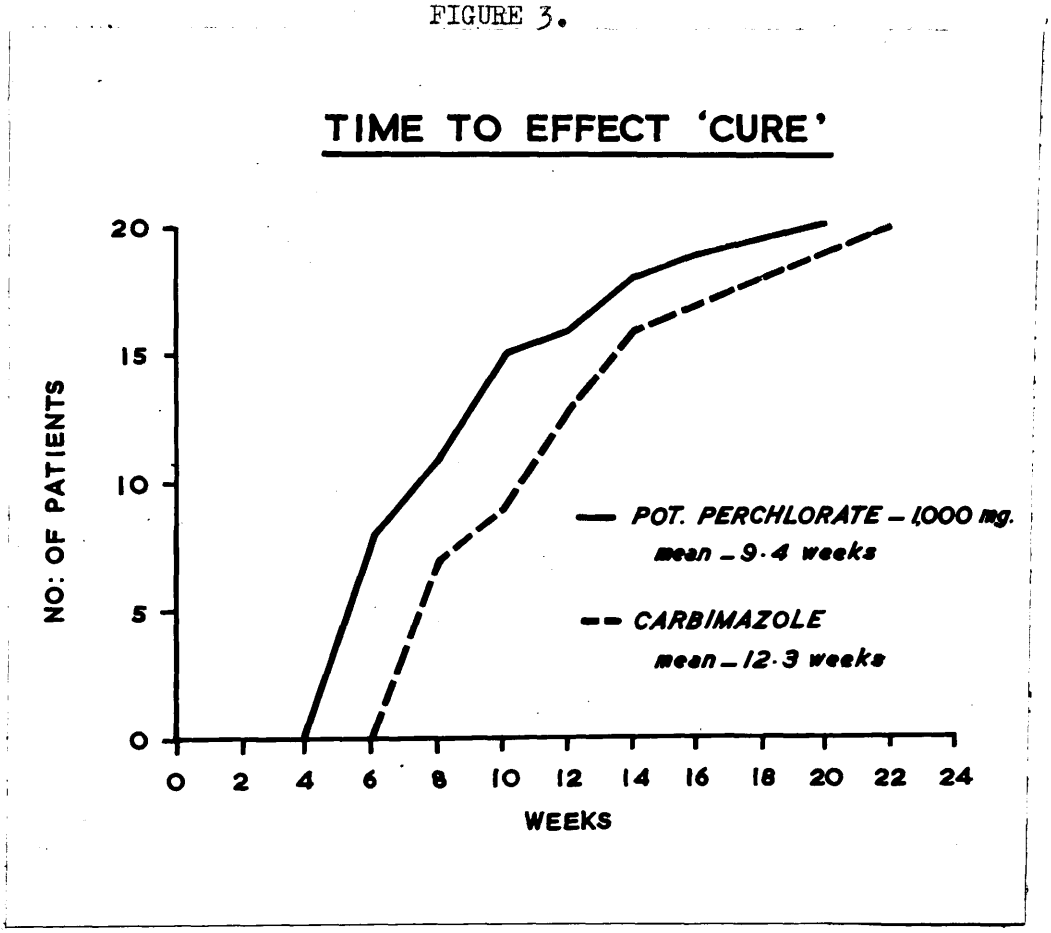

TIME TO EFFECT 'CURE'
NO: OF PATIENTS
20
15
10
5
0
0
2
4
6
8
10
12
14
16
18
20
22
24
WEEKS
POT. PERCHLORATE – 1,000 mg.
mean – 9·4 weeks
CARBIMAZOLE
mean – 12·3 weeks

TABLE V

Distribution of Patients in Series 4 Receiving Carbimazole and Potassium Perchlorate (1,000 mg. Daily) Showing Time Taken to Effect "Cure".

Time to Effect "cure" (weeks)	NUMBER OF PATIENTS	
	Carbimazole	Pot. Perchlorate (1000mg. daily)
3 - 4	-	-
5 - 6	-	8
7 - 8	7	3
9 - 10	2	4
11 - 12	4	1
13 - 14	3	2
15 - 16	-	1
17 - 18	2	-
19 - 20	-	1
21 - 22	2	-
Total	20	20
Mean time to "cure".	12.3 weeks	9.4 weeks

TABLE V

Distribution of Patients in Series 3 Receiving Carbimazole and Potassium Perchlorate (1,000 mg. Daily) Showing Time Taken to Effect "Cure".

Time to Effect "cure" (weeks)	NUMBER OF PATIENTS	
	Carbimazole	Pot. Perchlorate (1000mg. daily)
3 - 4	-	-
5 - 6	-	8
7 - 8	7	3
9 - 10	2	4
11 - 12	4	1
13 - 14	3	2
15 - 16	-	1
17 - 18	2	-
19 - 20	-	1
21 - 22	2	-
Total	20	20
Mean time to "cure".	12.3 weeks	9.4 weeks

Exophthalmometry. Twelve patients were chosen at random for this study from each of the two groups of Series 1, the one group receiving methyl thiouracil and the other potassium perchlorate. Weekly exophthalmometry readings were obtained using a Zeiss-Hertel exophthalmometer, without reference to the readings of the previous week, until the time of "cure" was reached. Thereafter readings were made at fortnightly intervals during the three-month period of maintenance therapy and for a further 6 weeks following the stopping of the drugs.

Results

Therapeutic indices. The weekly therapeutic indices obtained in the patients of Series 3 are detailed in Appendix VIII (carbimazole -- cases 41 to 60; potassium perchlorate, 1,000 mg. daily -- cases 61 to 80). The times taken to effect "cure" are shown in Table V and their cumulative distributions for both drugs are illustrated in Figure 3. The mean time to "cure" of the 20 patients on carbimazole was 12.3 weeks and the comparable figure for the 20 patients on perchlorate (1,000 mg. daily) was 9.4 weeks.

Table VI compares the mean times to effect "cure" of methyl thiouracil, carbimazole, and potassium perchlorate in doses of 600 and 1,000 mg. daily. For the purpose of statistical analysis the drugs have been represented

TABLE VI

TABLE VI

Mean Times to Effect "cure" for Methyl Thiouracil, Potassium Perchlorate, and Carbimazole.

	Drug	Time to effect "cure" (weeks)
A	Methyl Thiouracil	9.1
B	Potassium Perchlorate 600 mg. daily	13.1
C	Carbimazole	12.3
D	Potassium Perchlorate 1,000 mg. daily	9.4

by the letters A, B, C, and D as shown in the Table. An analysis of variance on the 80 patients studied shows that there are significant differences between the mean values for A, B, C, and D. In particular A is significantly different from B and C ($p < 0.05$); D is significantly different from B and C ($p < 0.05$); and there was no significant difference between A and D. A further analysis of variance was carried out on the 60 patients remaining after the exclusion of those who had been given methyl thiouracil. It was found that there was a significant difference between B and D ($p < 0.05$); a significant difference between C and D ($p < 0.05$; and no significant difference between B and C.

These results can be summarised as follows. In the doses used, methyl thiouracil and potassium perchlorate (1,000 mg. daily) were equally effective as measured by the time taken to effect "cure", while both were more effective than carbimazole or potassium perchlorate (600 mg. daily).

Dietary intake and urinary excretion of iodide. The approximate intake of dietary iodide in 8 patients of Series 1 receiving potassium perchlorate is shown in Table VII together with the times taken to effect "cure". From these results it can be seen that the iodide intake of subjects 11 and 1, who reached the time of "cure"

TABLE VII

TABLE VII

Daily Iodide Intake of 8 Patients Receiving Potassium Perchlorate

Subject No.	Time to effect "cure"	Iodine Intake mg./daily
11	7	94
1	8	122
10	11	56
5	12	65
9	14	120
7	18	99
4	18	124
8	21	120

TABLE VIII

TABLE VIII

Urinary Excretion of Iodide in Patients Receiving Potassium Perchlorate (600 mg. daily) and Methyl Thiouracil -- Series 1.

Drug	No. of Samples (-)	(+)	(++)	Total
Methyl Thiouracil	5	33	32	70
Potassium Perchlorate (600 mg. daily)				
"Cure" 1 - 12 weeks	15	26	9	50
"Cure" 13 - 23 weeks	16	28	6	50
Total	31	54	15	100

in 7 and 8 weeks respectively did not differ significantly from that of subjects 7, 4 and 8 who did not reach the time of "cure" until 18, 18 and 21 weeks respectively. This study therefore did not demonstrate any relationship between dietary iodide intake and the time of "cure".

Table VIII and Appendix IX show the iodide content of 70 urine samples obtained from 20 patients of Series 1 receiving methyl thiouracil and of 100 urine samples from 20 patients of the same series receiving potassium perchlorate. Significant differences were found between the two groups. In particular only 7.1% of the urine samples of the methyl thiouracil treated patients had no measurable iodide compared with 31% of the samples of perchlorate treated patients. Also 45.7% of the samples of the methyl thiouracil treated group had large amounts of urinary iodide compared with only 15% of the samples of the perchlorate treated group. It is probable that the advice given to the patients receiving perchlorate to restrict their iodide intake was responsible for this difference. When the iodide content of the urine samples of perchlorate treated patients reaching time of "cure" before 13 weeks were compared with those of patients on the same drug "cured" after that time (Table VIII) no significant difference was found. This finding like that of the dietary iodide study suggests that variations in the iodide

TABLE IX

TABLE IX

Exophthalmos -- Changes from Pre-Treatment Levels

Drug	Time of "cure" mm.	After 3 months Maintenance Therapy mm.	After Stopping Therapy mm.
Methyl Thiouracil (12 patients)	(mean) +1.92 Significantly different from 0 $p < 0.01$	(mean) +3.25 Significantly different from 0 $p < 0.01$	(mean) +1.62 Significantly Different from 0 $0.01 < p < 0.02$
Potassium Perchlorate (600 mg. daily) (12 patients)	(mean) +1.62 Significantly different from 0 $0.02 < p < 0.05$	(mean) +1.62 Significantly different from 0 $0.02 < p < 0.05$	(mean) +0.58 Not Significantly different from 0 $0.10 < p < 0.20$

intake of the patients receiving potassium perchlorate did not influence the time taken to effect "cure".

Exophthalmometry. All exophthalmometry measurements were expressed as the sum of the changes in the values for both eyes using the pre-treatment measurement as a base-line. The times chosen for comparison were the time of "cure", after three months maintenance therapy, and 6 weeks after the drugs were stopped. The data obtained for the 24 patients studied are shown in Appendix X and the mean values for the 2 groups of 12 patients receiving methyl thiouracil and potassium perchlorate (600 mg. daily) respectively are shown in Table IX.

In the case of both methyl thiouracil and potassium perchlorate there were significant increases in the degree of exophthalmos at both the time of "cure" and at the end of maintenance therapy compared with the pre-treatment levels. Six weeks after the drugs had been stopped this increase remained in the case of methyl thiouracil although the degree of exophthalmos had significantly diminished from the "end of therapy" levels (mean difference = + 1.62, significantly different from zero, $p < 0.01$). In the case of potassium perchlorate the "after therapy" value was not significantly different from the pre-treatment level but was significantly less than the mean value at the end of therapy (mean difference = + 1.04, significantly different from zero, $0.02 > p < 0.05$).

TABLE X

TABLE X

TOXIC EFFECTS

Toxic Effect	Methyl Thiouracil	Carbimazole	Potassium Perchlorate		
			600-1000mg.	1500 - 2000 mg.	Total
No. of cases	151	70	124	50	174
Skin Rashes	5	4	-	5	5
Nausea	-	1	2	2	4
Drug Fever	2	-	-	-	-
Agranulocytosis	2	2	-	1	1
Thrombocytopenia	1	-	-	-	-

Further statistical analysis carried out to compare the effects of the two drugs on the degree of exophthalmos showed no significant difference between them at any of the three times chosen for comparison.

In summary both drugs increased the degree of exophthalmos and this diminished after they had been stopped. Six weeks after the cessation of therapy the exophthalmos had returned to the pre-treatment level in the case of potassium perchlorate but remained significantly higher in the methyl thiouracil group.

Toxic effects. Since the three antithyroid drugs studied have a low frequency of toxic effects the incidence of such reactions in the patients of the present investigation are meaningless because of the small numbers. I have, however, obtained data on the toxicity of these drugs from a supplementary study carried out on all patients treated by me with antithyroid drugs in the University Department of Medicine, Glasgow between 1954 and 1958. The results are shown in Table X. It can be seen that 570 patients have been included who were given doses of potassium perchlorate exceeding 1,000 mg. daily and the vast majority of these received 2,000 mg. daily. The rate of control with the larger doses of perchlorate was not studied in detail but no obvious advantage was apparent although there may have been a slight increase.

In the case of methyl thiouracil and carbimazole the doses used were the same as those in the main investigation. It was found that there was no significant difference between the incidence of toxic effects for the three drugs when the two dosage schemes of potassium perchlorate were taken together. The toxic effects produced by potassium perchlorate, however, in doses of 1,000 mg. daily or under were significantly less frequent than with larger doses of perchlorate or with either methyl thiouracil or carbimazole.

Potassium perchlorate and Surgery. Seven patients chosen because they had small nodular glands were prepared by me for operation with potassium perchlorate alone and the surgeon who carried out the operation expressed the opinion that the glands were no more vascular than similar glands pre-treated with methyl thiouracil or carbimazole.

Potassium perchlorate and Pregnancy complicated by Thyrotoxicosis. Seven pregnant thyrotoxic subjects have been treated by me with potassium perchlorate. Control of the disease was good and the pregnancies were uneventful. Of the 7 babies 6 showed no evidence of thyroid disturbance while the seventh had a very small goitre which disappeared 6 weeks after birth.

Discussion

The results obtained in this investigation show that potassium perchlorate is an effective agent for controlling thyrotoxicosis and confirm the findings of Godley and Stanbury, (1954), Morgans and Trotter, (1954), and Kleinsorg and Krüskemper (1957).

Rate of control. Godley and Stanbury, found that the rate at which patients responded to treatment with potassium perchlorate varied widely but expressed the opinion that in general it compared favourably with the response rates to antithyroid drugs of the thiourea series. The dose they used was, with a few exceptions, 600 mg. daily but the number of patients was small and no control groups were studied. Morgans and Trotter on the other hand treated a much larger number of patients with perchlorate in doses of 400 mg. daily and came to the conclusion that the average rate of response was somewhat slower than was usually seen after treatment with methyl thiouracil 200 mg. daily. They also found that when patients on maintenance doses of methyl thiouracil were changed over to potassium perchlorate the average dose necessary for effective control was two to four times as great. The results obtained in Series 1 confirm their conclusion in the dose range

of perchlorate which they used. Buttaro and Brunori (1955) used the same dose of perchlorate as that used in Series 1 and also commented on "the slower action and less stable effects", compared with other antithyroid drugs. These workers comment on the frequency of cases which appear to be "resistant" to the drug and this was also found in the patients of Series 1 treated with 600 mg. daily of perchlorate. Indeed one quarter of the cases did not reach the time of "cure" until 17 to 24 weeks had elapsed. An example of this slow rate of response can be seen in Figure 2D and should be compared with the more rapid rate of control illustrated in Figure 2B. This variability of response rate is not however peculiar to perchlorate; slow responses occurred just as frequently with carbimazole and less frequently with methyl thiouracil. A comparison of Figures 2A and 2C illustrate this phenomenon in the case of methyl thiouracil. The explanation of these findings probably lies partly in variations in the amount of stored hormone which has to be utilised before the euthyroid state is reached, and also in the doses of the drugs being used. In any event the results of the present investigation indicate that an absence of clinical response after 6 weeks treatment with any of the drugs studied does not necessarily mean

that control will not be achieved ultimately.

That "resistance" to potassium perchlorate is in part a function of dosage and not a property of the drug is further suggested by the finding that when the dose was increased from 600 mg. daily to 1,000 mg. daily (Series 3) the rate of control became equal to that achieved by methyl thiouracil in the patients of Series 1 and more rapid than that of carbimazole (Series 3). This is also suggested by the findings of Smellie (1957) who treated 6 young children with relatively large doses of potassium perchlorate and found that the rate of response was no slower than that produced by propyl thiouracil. It is of interest that since the present investigation was completed Morgans and Trotter, 1957 in a letter to the Lancet confessed that their initial dosage scheme for perchlorate was too small and that they were now using larger therapeutic doses. Kleinsorg and Krüskemper (1957) also concluded that the speed of action of the drug is dependent upon the doses used from the results they obtained in a study of 47 patients given varying doses of perchlorate ranging from 800 mg. to 2,000 mg. daily. They also believe that in full doses it has a speed of action comparable with imidazole derivatives and point out that those who say that perchlorate has a slow action have all used small doses.

Macgregor and Miller (1953) using the technique of Stanley and Astwood (1947) found that the antithyroid effect of carbimazole was 50 times greater than that of methyl thiouracil. They emphasised, however, that considerable caution should be exercised in the transfer of potency trials of this type to clinical therapeutics. Both they and other observers have expressed the opinion that, weight for weight, carbimazole is 10 times more active clinically than methyl thiouracil although there are is no adequate data to support this view. The results of the present investigation suggest that this estimate is over-generous and carbimazole is only 7 to 8 times more active, weight for weight than methyl thiouracil.

Toxic effects. The results I have obtained demonstrate that the dose of potassium perchlorate can be increased sufficiently to make it comparable with the other antithyroid drugs in respect of rate of control. Since it is probable that this parameter of antithyroid activity is a function of both dose and the amount of stored thyroid hormone for each of the antithyroid drugs the choice of such a drug for clinical use will depend upon the incidence of toxic effects produced.

The findings in the present investigation that carbimazole is no different from methyl thiouracil in respect of toxicity is contrary to the conclusions of

Burrell et al. 1956 and Green and Morgan, 1956. The vast majority of the patients studied by these workers received doses of 20 to 30 mg. daily of carbimazole and their claim concerning the low toxicity of the drug may well be due to the low dosage schemes used. As in the case of the rate of control of thyrotoxicosis the incidence of the toxic effects of antithyroid drugs is likely to be a function of dose. This concept invalidates the numerous attempts made to evaluate the toxicity of the various antithyroid drugs by comparing series of patients in which different dosage schemes have been used. That this concept holds for potassium perchlorate is shown by the finding of the significant increase in the incidence of toxic effects when the dose was increased above 1,000 mg. daily.

The type of toxic effects produced by methyl thiouracil and carbimazole shown in Table X have all been previously reported by other workers. In the case of agranulocytosis the two cases produced by carbimazole can be added to the 10 already reported from the United States and Great Britain and this complication of treatment with this drug would not appear to be as rare as suggested by Burrell et al. 1956. Since potassium perchlorate has only been used as a therapeutic agent for a

relatively short time much less is known about its toxic effects. Godley and Stanbury (1954) reported one case of dyspepsia and one case in whom a duodenal ulcer perforated, in a series of 24 patients treated with perchlorate. Morgans and Trotter (1954) treated 108 cases with this drug and the only side effects observed were gastro-intestinal symptoms in two patients one of whom had a diaphragmatic hernia and the other a peptic ulcer. Kleinsorg and Krüskemper (1957) on the other hand found no gastro-intestinal upsets in their 47 patients. In the present study 3 of the 4 patients who complained of nausea continued taking the drug together with alkalis and the symptoms disappeared within one week in each case. The fourth patient refused to continue treatment and defaulted. The skin rashes which developed when a dose of 2,000 mg. daily was used were maculo-papular in nature and confined to the extremities except for one patient in whom the rash was generalised. In three of the 5 patients it was not necessary to stop treatment. Skin rashes produced by perchlorate have been previously reported by Kleinsorg and Krüskemper (1957) in 2 of 47 cases treated but in neither was it necessary to discontinue the drug. It is of interest that these workers were using large doses of the drug. They also reported a skin rash in one other case but this may

have been due to a barbiturate which had been given at the same time. When this patient was given perchlorate with prednisone, following operation, the skin rash did not return. Morgans and Trotter (1957), in a letter to the Lancet describing briefly their further experience with perchlorate using doses of 1,600 mg. daily also encountered, for the first time in their experience, skin rashes which occurred in two patients. Although no exanthems were produced in the present series with doses of perchlorate of 1,000 mg. daily or less Buttaro and Brunori (1955) reported a skin rash in one patient of 25 treated with doses of 600 mg. daily.

It is concluded, therefore, from the results of the present study and those of other workers that the skin rashes produced by perchlorate are relatively minor in nature and are more liable to be produced by doses larger than those which can effectively control thyrotoxicosis.

The case of agranulocytosis produced by perchlorate is of great importance since this complication has not been previously described. The patient, a young female, was an unequivocal case of thyrotoxicosis and was treated with perchlorate in doses of 500 mg. three times daily. During the third week of treatment she developed a sore throat and pyrexia with generalised muscle pain. Blood

examination revealed a polymorphonuclear leucocyte count of 750 per cmm. but the other blood findings were normal and the bone marrow histology showed no evidence of a maturation defect of the white cell series. After cessation of the drug, however, there was a rapid increase of the leucocyte count to normal levels. The patient had not been receiving any other drugs and the evidence points to perchlorate as the causative agent.

The fact that the rate of response to doses of 1,000 mg. daily of potassium perchlorate is comparable to that of the accepted therapeutic doses of the other antithyroid drugs and that this dosage scheme is associated with negligible side effects suggests that the use of larger doses of this drug should be avoided.

The effect of iodide intake on perchlorate therapy. Table VIII shows that the measures adopted to reduce the dietary iodide intake of the patients of Series 1 were successful. No correlation was found, however, between the degree of iodide deprivation, as measured by both the diet histories and urinary iodide values, and the time taken to effect "cure". Furthermore a significant increase in the rate of response to perchlorate was obtained by using a larger dose in the patients of Series 3 who continued to have their normal diet.

Perchlorate acts on the iodide-concentrating mechanism of the thyroid and would become ineffective if the blood-iodide levels were high enough to raise the concentration within the thyroid to the level normally attained by the gland's iodide-concentrating mechanism. Such a situation is unlikely to occur during therapy and the results obtained in this study suggest that the normal variations in dietary iodide intake do not influence the therapeutic response to the drug.

Changes in the degree of exophthalmos produced by potassium perchlorate and methyl thiouracil. Dobyns and Haines (1945) reviewed 11 cases in which patients with exophthalmic goitre were treated with thiouracil and followed carefully with exophthalmometric measurements. Seven of the 11 patients showed an increase in the prominence of the eyes ranging from 0.5 to 4.75 mm. On the other hand Beierwaltes (1948) studied 28 patients with thyrotoxicosis and without malignant exophthalmos who were treated with either thiouracil or propyl thiouracil. Weekly exophthalmometry readings for an average period of 4 months did not show a significant average increase in exophthalmos. He suggested that the difference in his findings from those of Dobyns and Haines might have been due to the inclusion by the latter of some cases of malignant exophthalmos. The present work confirms the findings of Dobyns and Haines and since I did not include any cases of malignant exophthalmos the explanation put

forward by Beierwaltes does not apply. Beierwaltes does not give any details of the dosage schemes he used nor of the rates of therapeutic response and it is possible that his failure to observe changes in the degree of exophthalmos might be explained by the difference between these two variables i.e. dose and rate of response, in his series and those of both the present series and that of Dobyns and Haines. Important confirmatory evidence of a true increase in the prominence of the eyes produced by antithyroid drugs is shown by the results I obtained after treatment had been stopped when a significant decrease in the "end of therapy" readings was found. The results also showed that the increase in exophthalmos during treatment with perchlorate was not as great as that with methyl thiouracil although the differences were not statistically significant. A significant difference was found, however, in the "after therapy" values for the two drugs, the perchlorate group reverting to the pre-treatment level while the methyl thiouracil group remained significantly above it. The dose of perchlorate given in this study was 600 mg. daily and the rate of response was slower than that produced by methyl thiouracil. This may account for the difference found in the effect of the two drugs on the degree of exophthalmos. The implication of this finding

is that the smaller dose of perchlorate should be given to patients with severe eye signs.

Potassium perchlorate and Surgery. Godley and Stanbury, 1954, treated 13 patients pre-operatively with potassium perchlorate and stated that it was the concensus of the operating surgeons that a few of the glands were more vascular than those of patients prepared with propyl thiouracil and iodine. Of two patients who received iodide in addition to perchlorate during the week before operation one escaped from control. For this reason Morgans and Trotter, 1954, did not use perchlorate for pre-operative preparation. On the other hand, Kleinsorg and Krüskemper (1957) carried out partial thyroidectomy in a small proportion of their cases and found that hyperaemia at operation was not great enough to give technical difficulties. The results I have obtained by the pre-operative use of perchlorate confirm their findings in respect of the absence of technical difficulties. Until satisfactory techniques for measuring the vascularity of the glands are evolved, however, for use in such studies no definite conclusions can be reached but for the present it would be reasonable to reserve the pre-operative use of perchlorate for patients

with small nodular glands.

Potassium perchlorate and Pregnancy complicated by Thyrotoxicosis. Goitre and hypothyroidism have been reported in the babies of mothers receiving antithyroid drugs of the thiouracil group during pregnancy (Eaton, 1945; Ball and Morrison, 1948) but this is an uncommon event. Astwood (1951) pointed out that if the dose of the antithyroid drug has been adjusted to ensure a normal output of hormone by the maternal thyroid it is unlikely that the function of the foetal thyroid would be significantly depressed. He reported 22 completed pregnancies in 19 patients, the 22 living children showing no evidence of thyroid disturbances. The use of potassium perchlorate in pregnant thyrotoxic patients has not yet been reported. As can be seen from the results 7 such patients have been satisfactorily treated with this drug and these findings suggest that potassium perchlorate is a satisfactory drug for use in pregnancy, complicated by thyrotoxicosis.

Conclusion

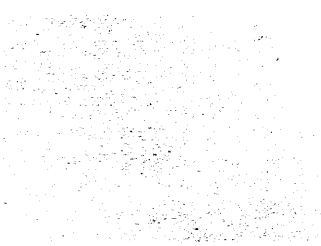
The studies described above in which I have compared potassium perchlorate, methyl thiouracil, and carbimazole in the treatment of thyrotoxicosis have led me to the conclusion that perchlorate is the antithyroid drug of choice in the medical treatment of

the disease. This conclusion is based on three points.-

(a) When perchlorate is administered in doses of 1,000 mg. daily the rate of therapeutic response is comparable with that produced by methyl thiouracil and exceeds that of carbimazole, the antithyroid drugs in current use in this country.

(b) At this dosage level the incidence of toxic effects is significantly less than with either methyl thiouracil or carbimazole in comparable therapeutic doses.

(c) Potassium perchlorate is the cheapest of the antithyroid drugs. Sufficient tablets to treat a patient at a dosage of 1,000 mg. daily for one month cost 5d. This is from a tenth to a three hundredth of the cost of equivalent doses of other antithyroid drugs in common use.



SECTION 3

Summary

1. The times taken to "cure" thyrotoxicosis have been compared in four groups of 20 patients treated with methyl thiouracil, potassium perchlorate (600 mg. daily), carbimazole, and potassium perchlorate (1,000 mg. daily). The mean time taken to effect "cure" for potassium perchlorate -- 1,000 mg. daily -- (9.4 weeks) was not significantly different from that of methyl thiouracil (9.1 weeks) and shorter than that for either carbimazole (12.3 weeks) or for potassium perchlorate -- 600 mg. daily -- (13.1 weeks).

2. The incidence of toxic effects with potassium perchlorate in doses of 1,000 mg. daily or under was less than with methyl thiouracil, carbimazole, or larger doses of perchlorate.

3. Variations in dietary iodide did not influence the times taken to effect "cure" by potassium perchlorate.

4. The mean degree of exophthalmos increased during treatment in two groups of 12 patients given methyl thiouracil and potassium perchlorate (600 mg. daily). The exophthalmos diminished when the drugs were stopped, returning to the pre-treatment level in the case of perchlorate and remaining significantly above it in the case of methyl thiouracil.

5. Experience in 7 cases prepared with potassium perchlorate for partial thyroidectomy suggested that this drug is a satisfactory antithyroid drug for pre-operative preparation in patients with small, nodular goitres.

6. Seven pregnant thyrotoxic patients have been successfully treated with potassium perchlorate. Six of the babies showed no evidence of disturbed thyroid function and the seventh had a small goitre which disappeared six weeks after birth.

7. It is concluded that potassium perchlorate is the drug of choice in the medical treatment of thyrotoxicosis.

PART II (ctd.).

SECTION 4

Radioactive Iodine Therapy in the Treatment of Thyrotoxicosis -- Introduction.

Radioactive iodine has been used in the treatment of thyrotoxicosis for two reasons. The first is the natural avidity of the thyroid for iodine in either its stable or radioactive forms. The second is that radioactive iodine decays within the thyroid by the emmission of high energy beta rays which penetrate only a few millimetres into the tissue and destroy it in the same way as X-rays produce tissue destruction. The radioactive isotope of iodine which is most suited for therapeutic use is ^{131}I because of its physical characteristics. It produces its irradiation effects primarily by the emission of beta particles and emits one half of its energy every eight days i.e., it has a half-life of eight days. ^{130}I which was the first radioisotope of iodine to be used therapeutically, has a half-life of only 12 hours.

Historical

Radioactive iodine treatment of thyrotoxicosis was introduced in the United States of America where, in 1941, a thyrotoxic patient was first given one millicurie of ^{130}I. By 1942 this dose had been increased by Hertz to 16 millicuries of ^{130}I and Hertz and Roberts (1946) described the results obtained in the first 29 patients treated between 1941 and 1943. These workers administered stable iodine following radioactive iodine treatment to prevent uncontrolled hyperthyroidism if the latter was

not effective. They found, however, that the thyroid function of the majority of the patients remained normal after the stable iodine was stopped. In this report they concluded that such treatment "is highly effective as a cure of the disease in about 80 per cent of cases". Since these patients had received stable iodine in addition to radioactive iodine it was difficult to discriminate between the effect of the radiation and that of the ordinary iodine but Chapman and Evans (1946) showed that radioactive iodine alone was effective in the treatment of thyrotoxicosis. They also reported that overtreatment produced myxoedema. In the same year ^{131}I became generally available in the United States and this isotope began to be used in many centres. Indeed 5 years later 130 centres were using ^{131}I in the treatment of the disease (United States Atomic Energy Commission, 1951). The effectiveness of ^{131}I therapy was rapidly confirmed by Soley and Miller (1948), and Werner et al. (1949), and in the first British report by Blomfield et al.(1951). Since then an extensive literature has grown on the subject and because of the early American experience the most complete reviews are to be found in the reports of American workers (Clark et al. 1952; Chapman and Maloof, 1955; and Werner et al. 1957).

The history of radioactive iodine therapy is one

of growing enthusiasm and there is no evidence in the 17 years of its use that the initial optimism was unjustified.

The advantages and disadvantages of radioactive iodine therapy. This form of treatment has many advantages among which may be listed simplicity of administration -- a drink of tasteless water through a straw --, its potential for treatment on an out-patient basis, its safety, and the ease with which re-treatment can be carried out if necessary. It has, however, certain disadvantages; its slowness in controlling the clinical features of the disease, the difficulties of dose estimation, its absolute contraindication in pregnancy, and the theoretical possibility of the treatment being carcinogenic. There is universal agreement that it is an effective way of treating thyrotoxicosis and it is only the doubts which remain concerning its possible carcinogenic effects which have prevented its use in the vast majority of cases of the disease. During the 17 years in which radioactive iodine therapy has been used, however, there has been no reported case of resulting thyroid cancer and this is also true of X-ray therapy for thyrotoxicosis which, though a disappointing form of treatment, has been widely used in the past. On the other hand carcinoma

of the thyroid has been produced in rats by ^{131}I (Goldberg and Chaikoff, 1951, 1952) and with ^{131}I and methyl thiouracil together (Doniach, 1953). In a further three years this type of treatment will have been in use for twenty years and provided that there is no increase in the incidence of thyroid carcinoma above that to be expected in the population at large, radioactive iodine may become even more extensively used than it is at present.

Indications for the use of radioactive iodine. The above considerations imply the selection of suitable cases for treatment with ^{131}I based on the principle that it should be reserved for those with an expectation of life less than that of the latent period for the development of carcinoma, i.e. about twenty years. Applying this principle Blomfield et al. (1955) advised the restriction of treatment to the following groups of cases.-

(a) patients over 45 years of age;
(b) those in whom associated disease reduces life expectancy to less than 20 years;
(c) those who are refractory or hypersensitive to antithyroid drugs and in whom thyroidectomy is either contraindicated or refused;
(d) recurrence after thyroidectomy, since antithyroid drug therapy is unlikely to lead to sustained remission and a second operation is much more likely to be followed by some post-operative complication;

(e) cases of heart disease associated with thyrotoxicosis since expectation of life is low and operative mortality high.

Most authorities agree with the above method of selection and it is on this basis that patients have been selected for radioactive iodine therapy in the investigations to be described in this section of the thesis.

SECTION 5

A Comparison of Various Methods of Dose Prescription in Radioactive Iodine Therapy.

The aim of radioactive iodine therapy in thyrotoxicosis is to produce the euthyroid state with as few treatments as possible. It is self-evident that in attempts to achieve this there will be an inverse relationship between the number of treatments necessary in any group of patients and the incidence of hypothyroidism due to overdosage. A few centres have evaded this difficulty by using multiple small doses (Werner et al. 1948; Williams et al. 1949; Gordon and Albright, 1950; McCullagh, 1951) but the inconvenience of this procedure to both patient and physician has not made it generally acceptable. Whereas the majority of workers aim at a high cure rate with one treatment there is considerable disagreement as to how this is to be achieved. Some centres for example select a dose which is thought to be effective in terms of ^{131}I concentration in the thyroid gland (Chapman and Maloof, 1955; Fraser et al. 1954) while others select their dose on the basis of the number of rads of radiation delivered to the gland (Blomfield et al. 1951, 1955; Freedberg et al. 1952). Macgregor (1957) on the other hand has criticised these methods because they are based on a number of assumptions which are not necessarily valid. He therefore adopted a simplified form of dose estimation by adjusting the dose in millicuries to that which

would produce a rapid clinical cure while avoiding, as far as possible, myxoedema. He admitted that in his method of dose estimation he was applying the experience he had gained while employing a precise and quantitative technique (Blomfield et al. 1955) for many years. The present investigation was carried out to ascertain if a physician (the author) who at the outset had no specialised experience in this field could prescribe doses of radioactive iodine by a method similar to that of Macgregor, although devised independently, and achieve results comparable to those of the latter and of Blomfield et al. (1955).

Before this investigation began a group of patients suitable for this form of treatment were treated by me with methyl thiouracil and became euthyroid before radioactive iodine therapy became available. Since there is much controversy and little published data on the effect of pre-treatment with antithyroid drugs on the response to radioactive iodine therapy I decided to answer this question by treating this group of patients with ^{131}I at random intervals during a period when newly diagnosed cases were being treated. In this way I have been able to compare the number of cures by one dose of ^{131}I in patients pre-treated with methyl thiouracil and in those who have had no previous treatment.

Material and Methods.

One hundred and fifty patients in whom the diagnosis of thyrotoxicosis had been confirmed by the clinical diagnostic index described in Part I of the thesis, and by radioactive iodine studies, were considered to be suitable for radioactive iodine therapy by the criteria laid down by Blomfield et al. (1955). The cases fell into the following categories.

Group 1 (28 cases).

The patients of this group had received treatment with methyl thiouracil for three months to one year before radioactive iodine therapy was given and were either euthyroid or only minimally thyrotoxic at this time. The drug was stopped 1 week before ^{131}I treatment. All cases of this group were treated with ^{131}I between January, 1954 and July, 1956. Originally there were 30 cases in this group but one patient died of a myocardial infarction 2 months after the second dose of radioactive iodine and 1 patient defaulted 2 months after treatment; both were excluded from the study.

Group 2 (45 cases).

The patients of this group were treated in the same period as those of Group 1 but had had no previous treatment with antithyroid drugs. One patient who became euthyroid with one dose of ^{131}I at 5 months, died a month later of broncho-pneumonia and has not

been included in the group.

Group 3 (21 cases).

This group had been previously treated with methyl thiouracil for periods similar to that of Group 1. The drug was also stopped one week before radioactive iodine therapy which was given between July, 1956 and August, 1957.

Group 4 (56 cases).

This group received radioactive iodine therapy during the same period as Group 3 but had had no previous treatment with antithyroid drugs. One patient in this group defaulted one month after the first treatment and has not been included in the study.

All cases, with the exception of a few at the beginning of the investigation, were given tracer doses of ^{131}I during the week before treatment and the 48-hour gland uptake of ^{131}I estimated. In the case of these patients who had been receiving methyl thiouracil the drug was stopped 48 hours before the tracer dose was administered.

In the first year of the investigation all patients were admitted to hospital both for the initial therapeutic dose of ^{131}I and for subsequent doses if necessary. After the first year, because of

the growing pressure on hospital beds, a large proportion of the cases were treated on an out-patient basis.

Method of dose estimation. The basic principle of dose estimation used was that small doses were prescribed for patients with small glands and large doses for patients with large glands. It was decided from a review of the results of other workers that patients with impalpable glands would be given doses of 4 - 5 millicuries (mc.), with minimal but definite diffuse enlargement of the gland -- 6 - 7 mc., and for patients with larger glands increasing doses up to 25 mc. Many other factors besides gland size influenced the dose prescribed; for example post-thyroidectomised patients were given 5 - 6 mc., unless the gland remnant was exceptionally large; larger doses were given to patients with nodular glands, with cardiac failure, with uncontrolled diabetes mellitus, or whenever the need for a rapid remission of symptoms outweighed the disadvantages of the possible production of myxoedema.

This method of dose prescription was used for the patients of Groups 1, 2 and 4. By July, 1956, however, it had become clear that only a small number of the patients of Group 1 were being cured with one

dose and from that time pre-treatment with methyl thiouracil was considered to be an indication for increasing by a factor of 25% the dose of radioactive iodine decided upon by the criteria already described. The doses of radioactive iodine given to the patients of Group 3 thus included this factor.

When each patient was being examined with a view to dose prescription the size of the gland was estimated in grammes, although the inaccuracies of this estimate were appreciated. This was done in order to obtain, after each patient had been treated, the dose which would have been given if the formula for dose prescription recommended by Blomfield et al. (1955) had been used. This formula is.-

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

These workers aimed to give 7,000 rads for diffusely enlarged glands, 5,000 - 7,000 rads for small post-operative recurrences, and 8,000 rads or more for large and multinodular glands.

Follow-up procedure. All patients were seen at monthly intervals at the Thyroid Clinic until they had either become euthyroid or required further treatment. The assessment of the euthyroid state was initially made on clinical grounds but was confirmed by basal metabolic rate estimation. The necessity for re-treatment was

$^{+}$One rad = 100 ergs per gramme of tissue.

considered at 3 - 4 months after the initial dose. Dose prescription in the case of re-treatment was based on the same principles as those for initial treatment. Doubtful cases were left for a further two months and if by that time the presence of toxicity was still in doubt they were re-admitted to hospital for further detailed study before a final decision was made. After patients became euthyroid they were seen at intervals of 2 - 6 months as the circumstances warranted.. Cases suspected of hypothyroidism on clinical grounds were further investigated by estimations of serum cholesterol and basal metabolic rate and also by electrocardiography. If the hypothyroidism was mild replacement therapy was not given because of the well-recognised occurence of transitory hypothyroidism. If the hypothyroidism persisted for 3 - 4 months or became more marked then l-thyroxine sodium was prescribed.

The minimum period of follow-up was one year and the maximum $3\frac{1}{2}$ years. Cure was considered to have taken place if the patient was euthyroid at 12 ÷ 18 months. Myxoedema was considered to have been a consequence of radioactive iodine therapy only if treatment with thyroxine was necessary.

Biological half-life of the therapeutic dose of ^{131}I.

The biological half-life of ^{131}I was measured in

TABLE XI

TABLE XI

Results of ^{131}I Therapy in 150 Cases

Type of Gland	No. of Cases	% of Total	EUTHYROID			MYXOEDEMA			Still toxic at 18 months
			Total	One dose	2 or more doses	Total	One dose	2 or more doses	
Diffuse (including not palpable)	90	60	84	57	27	4	3	1	2
Nodular	45	30	36	19	17	6	2	4	3
Post- thyroidectomy	15	10	14	9	5	0	0	0	1
Total	150	100	134 (89.5%)	85 (57%)	49 (32.5%)	10 (7%)	5 (3.5%)	5 (3.5%)	6 (3.5%)

13 patients of Group 1 and 16 patients of Group 2. This measurement was obtained as follows.-

An uncollimated scintillation counter with 1 inch of lead filtration was used in conjunction with an Ecko autoscaler. On the second day after the therapeutic dose of ^{131}I had been administered the counter was set up 12 inches above the isthmus of the thyroid gland and the radioactivity counted for 100 seconds. The neck was then shielded with 2 inches of lead and a background count made in order to obtain the net radioactivity from the gland in counts per 100 seconds. This procedure was repeated at intervals until the gland radioactivity had fallen by one half. After these values had been corrected for physical decay they were plotted against time using semi-logarithmic paper and the biological half-life recorded as the time taken for the radioactivity to fall to half of its original value.

Results

Present series. In all, 150 cases have been reviewed and of these 119 were female and 31 male, giving a female:male ratio of 4:1. The complete data in these cases is shown in Appendices XI, XII, XIII and XIV.

Table XI shows the distribution of the cases by gland types. The gland types were classified by palpation except in patients with post-operative recurrences. The

TABLE XII

TABLE XII

Clinical Results of Radioactive Iodine Therapy (Minimum Follow-up, One Year).

Series	Present	Macgregor (1957)	Blomfield et al (1955)
No. of Cases	150	150	140
Euthyroid with one dose	85(57%)	89(59%)	87(62%)
Myxoedema	10(7%)	13(9%)	17(12%)

largest group had either diffuse enlargement of the gland or an impalpable gland (60%), while there were 45 cases with nodular glands (30%), and 15 cases who had had previous partial thyroidectomy (10%). Table XI also shows that by 12 - 18 months 134 cases (89.5%) were euthyroid, of which 85 (57% of the total number treated) were successfully treated with one dose. Two or more doses were necessary to produce a cure in 49 cases (32.5%). Of these 49 cases 13 required 3 doses, and 10 required 4 doses. The treatment was considered to have failed in 6 cases (3.5%), 4 doses having been given to 3 of these cases, 5 doses to 2, and 6 doses to 1. Of these 6 failures 2 had diffusely enlarged glands, one being very large, 3 had nodular glands which were not unusually large, and 1 had a post-operative recurrence.

Ten cases (7%) developed myxoedema following treatment, 5 after one dose and five after 2 doses. All these cases returned to the euthyroid state following thyroid administration.

The mean number of doses used in the series was 1.86 doses.

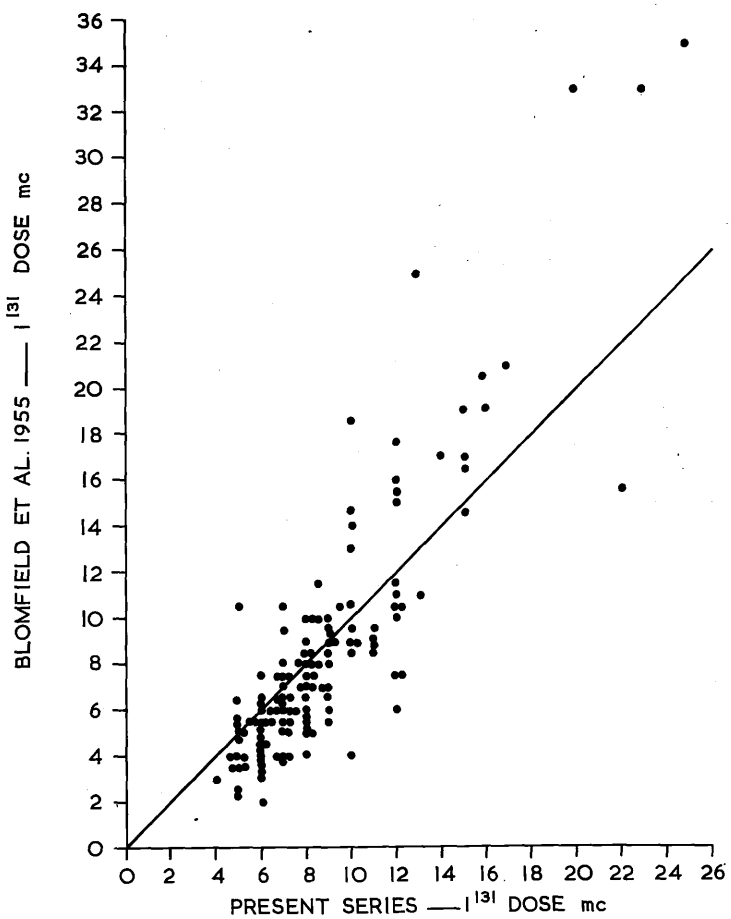
Comparison of one dose cure rates in the present series, with those of Macgregor (1957) and Blomfield et al. (1955).

This comparison is shown in Table XII. The one dose

FIGURE 4

Therapeutic doses of ^{131}I, prescribed in the present series, plotted against doses calculated from the formula of Blomfield et al. (1955). The oblique line has been drawn at 45^{o} to the ordinates.

FIGURE 4.


BLOMFIELD ET AL. 1955 — I^{131} DOSE mc
PRESENT SERIES — I^{131} DOSE mc
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36

cure rate of the present series, 57%, was not significantly different from the 59% of Macgregor (1957) who used a similar method of dose estimation, or from the 62% cured with one dose by Blomfield et al. (1955). The last group of workers aimed at delivering 6,000 to 8,000 rads to the gland and prescribed their doses by an elaborate method. Figure 4 is a scattergram in which the doses used in the present series have been plotted against the doses which would have been used if the method recommended by Blomfield et al. had been applied. It can be seen that in the lower dose range I have tended to give larger doses while in the higher dose range smaller doses have been given. This difference is not reflected in the one dose cure rates of the two series. The incidence of myxoedema produced by overdosage is not significantly different in the three series which have been compared in Table XII.

A separate analysis was made of the results obtained in the four groups of patients making up the present series.

Group 1.

The data for this group consisting of 28 patients pre-treated with methyl thiouracil is given in Appendix XI. Table XIII summarises the clinical results of radioactive iodine treatment. It can be seen that 19 cases have diffuse or impalpable glands (68%),

TABLE XIII

and

TABLE XIV

TABLE XIII

Results of ^{131}I Therapy in Cases of Group 1

Type of Gland	No. of Cases	% of Total	EUTHYROID Total	EUTHYROID One dose	EUTHYROID 2 or more doses	MYXOEDEMA Total	MYXOEDEMA One dose	MYXOEDEMA 2 or more doses	Still toxic at 18 months
Diffuse (including not palpable)	19	68	17	7	10	0	0	0	2
Nodular	6	21	4	0	4	2	1	1	0
Post-Thyroidectomy	3	11	3	1	2	0	0	0	0
Total	28	100	24 (86%)	8 (28.6%)	16 (57.4%)	2	1	1	2

TABLE XIV

Results of ^{131}I Therapy in Cases of Group 2

Diffuse (including not palpable)	28	62	27	25	2	1	1	0	0
Nodular	11	25	8	5	3	1	1	0	2
Post-Thyroidectomy	6	13	5	4	1	0	0	0	1
Total	45	100	40 (89%)	34 (75.5%)	6 (13.5%)	2	2	0	3

6 have nodular glands (21%), and 3 cases had post-operative recurrences (11%). Of the 28 patients in the group only 8 (28.6%) became euthyroid with one dose although cure was achieved by 18 months in 24 (86%). Two patients developed myxoedema and there were two failures. The mean number of doses given to this group was 2.35 doses.

Group 2.

This group of 45 patients had not been given methyl thiouracil before radioactive iodine therapy and the latter was given during the same period of time as that of Group 1. The data for this group is shown in Appendix XII. Table XIV summarises the results and shows that 11 of the cases (25%) had nodular glands and 6 (13%) had post-operative recurrences. The incidence of nodular and post-operative glands is therefore similar to that of group 1. The one dose cure rate, however, was 75.5% and the increase over the comparable figure for Group 1 (28.6%) was statistically significant. Two cases of this group developed myxoedema and there were three failures. The mean number of doses given was 1.5 doses.

Group 3.

This group of 21 patients, like those of Group 1, had received methyl thiouracil preceding radioactive iodine therapy. Because the unsatisfactory response

TABLE XV

and

TABLE XVI

TABLE XV

Results of ^{131}I Therapy in Cases of Group 3

Type of Gland	No. of Cases	% of Total	EUTHYROID Total	One dose	2 or more doses	MYXOEDEMA Total	One dose	2 or more doses	Still toxic at 18 months
Diffuse (including not palpable)	14	67	12	6	6	2	2	0	0
Nodular	7	33	7	4	3	0	0	0	0
Post-thyroidectomy	0	-	0	0	0	0	0	0	0
Total	21	100	19 (90.5%)	10 (47.5%)	9 (43%)	2	2	0	0

TABLE XVI

Results of ^{131}I Therapy in Cases of Group 4

Diffuse (including not palpable)	29	52	28	19	9	1	0	1	0
Nodular	21	37.5	17	10	7	3	0	3	1
Post-thyroidectomy	6	10.5	6	4	2	0	0	0	0
Total	56	100	51 (91.5%)	33 (59%)	18 (32.5%)	4	0	4	1

to treatment in many of the patients of Group 1 was already known the patients of Group 3 had their prescribed dose of radioactive iodine increased by 25%. The data for this group is shown in Appendix XIII and the results are summarised in Table XV. The incidence of nodular glands was 33% and 10 cases (47.5%) became euthyroid with one dose. Two cases became myxoedematous and there were no failures. The mean number of doses given was 1.9 doses.

Group 4.

This group comprised 56 untreated patients given radioactive iodine therapy during the same period as Group 3. The data is shown in Appendix XIV and the results summarised in Table XVI. The incidence of nodular glands was 37.5% and 6 patients (10.5%) had post-operative recurrences. Thirty-three patients (59%) became euthyroid with one dose and this one dose cure rate while higher was not significantly different from that of Group 3 (47.5%). Four patients of this group became myxoedematous and there was 1 failure. The mean number of doses given was 1.6 doses.

Biological half-life of the therapeutic doses of ^{131}I.

The biological half-lives of ^{131}I in the 29 patients studied are shown in Table XVII. The mean biological half-life in the 13 patients who had been pre-treated with methyl thiouracil was 11.0 days and this was

TABLE XVII

TABLE XVII

Biological Half-lives of Therapeutic Doses of ^{131}I

Cases pre-treated with Methyl Thiouracil (days)	Cases with no pre-treatment (days)
9.4	17.8
13.2	17.0
13.0	20.0
8.0	4.7
5.0	7.0
8.5	14.4
14.0	7.4
9.0	4.0
11.3	12.4
14.8	10.0
11.0	15.6
20.0	4.0
6.0	7.0
	23.0
	15.2
	12.4
Mean = 11.0	Mean = 12.0

not significantly different from the comparable value of 12.0 days in the case of the 16 patients who had received no pre-treatment with an antithyroid drug.

Discussion

The major difficulty in the use of radioactive iodine in the treatment of thyrotoxicosis is the determination of the dose. Most workers attempt to produce cure with one treatment. The prescription of the dose necessary to do this has been determined by many workers using principles which have been based on the assumptions that the gland volume and the biological properties of radioactive iodine can be accurately measured.

The inaccuracies which occur in estimations of gland size by palpation are generally admitted, even by those who incorporate this measurement in their dosage calculations, and estimations of gland size by this method have been shown to be inaccurate by as much as 40% (Soley et al. 1949). Attempts have been made to increase the accuracy of this estimate by comparing the clinical estimate with the true weight in glands removed at operation or autopsy. Another method advocated is the use of gland models at the time of palpation. These measures, while

increasing accuracy, still allow potentially large errors (Loevinger, 1953). The use of a collimated counter after the administration of a tracer dose of radioactive iodine can be used to measure gland volume (Allen et al. 1952; Bauer et al. 1952; Blomfield et al. 1955; and Bauer and Blahd, 1957). This technique does not wholly eliminate subjective bias and Kelly (1954) found large errors associated with techniques of this type. Franco and Quina (1956) have attempted to visualise the thyroid gland radiologically following oxygen insufflation of the neck and claim that the error of gland size estimate does not exceed 10%. This method, however, is time-consuming and potentially hazardous.

The three biological properties of radioactive iodine which influence dose estimation are the uptake of the radioisotope by the gland, its distribution in the gland, and the time it remains in the gland. The uptake of the therapeutic dose of radioactive iodine by the gland can be predicted with fair accuracy from the behaviour of a tracer dose (Keating et al. 1949; Freedberg, 1952). On the other hand the distribution of radioactive iodine in the gland is unpredictable (Fitzgerald and Foote, 1949; Kelsey et al, 1949), particularly in nodular glands (Le Blond et al. 1946). The third biological property of radioactive iodine

which influences dose estimation, the length of stay of a therapeutic dose in the gland, is also difficult to predict from the behaviour of a tracer dose as shown by Skanse, 1948; Miller and Sheline, 1951; Freedberg et al. 1952; and Blomfield et al. 1953).

The remaining factor which influences dose estimation is the sensitivity of the thyroid tissue to irradiation. As yet little is known of the variability of this factor owing to the difficulty of estimating the radiation dose which the gland actually receives. There is, however, evidence to suggest that considerable variation in gland radiosensitivity does occur (Myant and Pochin, 1955).

Owing to these uncertainties the amount of radioactive iodine necessary to give a critical radiation dosage cannot be determined with any degree of accuracy. It was for this reason that Macgregor (1957) adopted "by previous accepted standards a completely heretical technique". By his simple clinical scheme of dose prescription he achieved results comparable with those obtained by Blomfield et al. 1955 whose method involved precise and quantitative calculations. The results obtained in the present series confirm Macgregor's conclusions that complicated schemes of dose prescription have no therapeutic advantages. Indeed the results

obtained in the three series compared in Table XII are almost identical. Furthermore Bauer and Blahd (1957) using a similar method of dose prescription to that of Blomfield et al. obtained a one dose cure rate of 56.6% which is not significantly different from that of the present series.

In the early stages of the therapeutic applications of radioactive iodine it was obligatory to attempt to use precise methods of dose prescription until the effects of treatment were fully evaluated. The results of the present series and those of Macgregor (1957) suggest that this is no longer necessary and that radioactive iodine therapy can be administered by simple clinical techniques. Furthermore the suggestion by Macgregor that other physicians could achieve the same results as he did even if they had not previously had the advantage of experience with more meticulous methods, has been fully confirmed.

The adoption of a clinical method of dose prescription increases the responsibility of physicians prescribing such treatment to evaluate the various factors which influence their decision. For example, it can be seen from Figure 4 that doses prescribed in the present investigation tended to be larger in the lower dosage range than those which would have been prescribed if the method recommended by

Blomfield et al. (1955) had been used. On the other hand in the higher dosage range smaller doses were given using the clinical method. These findings emphasise one difference in the two types of dose prescription since a physician using the clinical method tends to be emotionally influenced by the dangers of myxoedema when large doses have to be given. Because very large doses are seldom necessary and because the percentage difference is less than with lower doses, the overall results are not appreciably affected.

Another factor which might influence dose prescription is previous treatment with an antithyroid drug. The results obtained in cases pre-treated with methyl thiouracil (Group 1) showed a significantly lower one dose cure rate than cases who had received no pre-treatment (Group 2). It can be seen from Tables XIII and XIV that this finding cannot be accounted for by variations in gland types between the two groups. Furthermore there was no significant difference between the average gland sizes of the two groups. It was considered possible that the biological half-life of the therapy dose might be shortened in the methyl thiouracil treated gland and in this way produce a decrease in the amount of irradiation. No significant difference was found, however, between the biological half-lives of therapeutic doses of ^{131}I in patients

who had received the drug compared with those of patients who had been given no pre-treatment (Table XVII). This finding is similar to that of Hamilton and Werner (1952). In addition consistency of dose prescription was ensured in the patients of Groups 1 and 2 by the fact that they were treated by the same physician (the author) during the same interval of time. It is possible that methyl thiouracil treatment might produce a more patchy distribution of the therapeutic dose of ^{131}I but there is no evidence available on this point, and indeed Fraser (1954) has used the drug to produce a more even distribution of ^{131}I within the gland. The other possibility which could account for the findings is that the methyl thiouracil treated gland is radio-resistant. This conclusion is supported by Werner (1955) who cites Rynearson, Williams et al. (1949) on the other hand studied a group of patients who had received radioactive iodine therapy following a course of propyl thiouracil and had the impression that these patients required smaller doses than untreated cases. His findings, however, were not subjected to statistical analysis.

The biological effects of irradiation are still improperly understood as are the factors which modify them. There is, however, evidence that thiourea

compounds can protect biological systems against the effects of irradiation. For instance Dale (1947) and Dale et al. (1949) demonstrated this protective effect of thiourea on certain enzymes and Limperos and Mosher (1950) showed the same phenomenon with nucleo-proteins in vitro and in vivo. The radio-protective action of thiourea compounds has also been shown in the case of bacteria (Forssberg, 1950), animal cells (Patt, 1952), and intact animals (Mole et al. 1950). Direct evidence of the modification of the irradiation effect of ^{131}I on thyroid cells, was obtained by Rugh, 1953 in work on the Japanese Fire Salamander. He found that thiouracil gave protection to thyroid cells for periods up to 7 months after the administration of the drug. One possible explanation of the protection given by thiourea compounds against irradiation may lie in their capacity as reducing agents since there is some evidence to suggest that diminished availability of intracellular oxygen is protective (Hollaender and Stapleton, 1953). It is of interest that other compounds containing sulphur or sulphydryl groups have a radio-protective action (Patt et al. 1952; Gray, 1954; Bacq, 1954; Rugh and Wang, 1953).

It was because of the poor therapeutic results obtained in the patients of Group 1 that I decided to

give larger doses of ^{131}I to patients who had previously received methyl thiouracil. This attempt to increase the one dose cure rate in such patients may be responsible for the fact that the results in Group 3 are not significantly different from those obtained in the patients of Group 4 who had received no pre-treatment. Possibly due to the small number of patients, however, no statistically significant difference could be shown between the one dose cure rates of Groups 1 and 3 although the respective percentages were 28.6 and 47.5. It is possible therefore that patients pre-treated with methyl thiouracil require more than a 25% increase of the dose of ^{131}I to completely overcome the effects of the antithyroid drug therapy. The necessity for increasing the dose of ^{131}I because of the effects of antithyroid drug therapy has been tentatively suggested by Hamilton and Werner (1952). They gave two groups of patients a two-weeks course of propyl thiouracil and 1-methyl-2-mercaptoididazole respectively, starting the drugs one week after ^{131}I therapy. When they compared the results with those obtained in a group who had had no antithyroid drugs they noted a tendency to increased resistance to the radiation effect of ^{131}I in the cases given antithyroid drugs with a diminution in the one dose cure rate. Their results

however, were only of border-line statistical significance.

The present investigation has clearly demonstrated that radioactive iodine therapy can be carried out successfully on a clinical basis and provided simple rules are observed this can be achieved with the maximum economy of both the patient's and physician's time. It is clear too that more extensive use of radioactive iodine in the treatment of thyrotoxicosis should not be limited because of the lack of experience of physicians in prescribing effective doses. The more general use of radioactive iodine therapy would further increase the responsibility of those centres with special facilities to evaluate fully the factors which influence dose prescription.

SECTION 5

Summary

1. One hundred and fifty cases of thyrotoxicosis have been treated with radioactive iodine using a simple clinical method of dose prescription. Twelve to 18 months after treatment had been started 134 (89.5%) of the cases were euthyroid, 10 cases (7%) had developed myxoedema, and 6 cases (3.5%) remained toxic.

2. Eighty-five cases (57%) were cured with one dose and this result was not significantly different from that obtained by Macgregor (1957), who used a similar method of dose prescription, or from that of Blomfield et al. (1955) who used a more complicated technique.

3. In 28 cases who had been receiving methyl thiouracil before radioactive iodine therapy the one dose cure rate of 28.6% was significantly less than the value of 75.5% obtained in 45 patients who had received no pre-treatment.

4. Twenty-one cases who had been receiving methyl thiouracil had their doses of radioactive iodine increased by 25% and the one dose cure rate obtained (47.5%) was not significantly different from that of 56 patients who had received no pre-treatment (59%).

5. Evidence is produced to show that the effect of methyl thiouracil on radioactive iodine therapy in the present study is not due to differences in gland type or size, or changes in the biological half-life

of the therapeutic dose. It is suggested that pre-treatment with the drug protects thyroid cells against the effects of irradiation and that this factor should be allowed for in the dose prescription of radioactive iodine.

6. Because radioactive iodine therapy can be carried out on a clinical basis its more extensive use should become possible.

PART III

METABOLIC STUDIES IN THYROTOXICOSIS

Increased thyroid activity influences the energy requirements of the body and has consequent secondary effects upon the metabolically active cell mass and the total body fat. The change in body composition produced by thyrotoxicosis is in the main due to a loss of both lean tissue and fat and a disturbance in the percentage contributions which each of these components makes to the total body weight. It is clear therefore that any metabolic studies in thyrotoxicosis using body weight as a reference standard will be difficult to interpret.

In recent years it has become possible to measure the metabolically active tissue mass or lean body mass by a number of techniques including the estimation of total body water. The derivation of lean body mass from total body water has as its basis the finding by Pace and Rathbun that there is a constant relationship between the two in guinea pigs and rats (Pace and Rathbun, 1945; Rathbun and Pace, 1945). These workers showed that in animals approximately three fourths of the total body water is associated with the metabolically active cell mass and there is no reason to doubt that the same relationship exists in man (Morales et al. 1945). This view is supported by the few published reports of direct analysis ofcadavers (Widdowson et al. 1951; Forbes and Lewis, 1956). Total body water can be measured in living human subjects

by using deuterium, tritium, or antipyrine dilution and from this measurement it is possible to derive fat-free weight or lean body mass.

By the elimination of the metabolically inert depot fat lean body mass should theoretically be a better reference standard than body weight for fundamental physiological values. This has been shown to be true by Miller and Blyth (1952-1953) in the case of oxygen consumption and by Muldowney (1957) for total red cell mass. These workers emphasised the fallacies which can be introduced by variation in the amount of depot fat in their subjects and recommended that this factor be taken into consideration in any metabolic studies. For this reason lean body mass has been chosen as the reference standard for the metabolic studies in thyrotoxicosis to be described in this part of the thesis.

It was decided to investigate the effects of the disease on the total red cell mass, and on the total exchangeable sodium, potassium, and chloride. In the case of total red cell mass a range of normal values based on lean body mass has been provided by Muldowney (1957), but normal ranges were not available for the exchangeable electrolytes. The investigation of the electrolytes in thyrotoxicosis had therefore to be preceded by a study of the relationship of total exchangeable sodium, potassium, and chloride with lean body mass in normal subjects. A range of normal values

for the exchangeable electrolytes based on lean body mass was thus provided. The section dealing with the exchangeable electrolytes in thyrotoxicosis contains an account of this necessary preliminary study.

SECTION 1

The Total Red Cell Mass in Thyrotoxicosis.

It has previously been shown by Muldowney (1957) that the relationship between total red cell mass and lean body mass is so close that if the latter is known then the former may be predicted with 95% confidence limits of ± 75 ml. He also showed that the relationship held for both sexes over a wide range of age and body weight and suggested that the correlation was based on the regulation of oxygen-carrying power or red cell mass by the oxygen requirements of the metabolically active lean body mass. He deduced that depot fat makes insignificant demands upon oxygen-carrying power and this view is supported by the fact that depot fat has a very low rate of oxygen utilisation (Krebs and Johnson, 1948). If the suggestion is valid that the relationship of lean body mass to red cell mass depends on basal oxygen consumption then in thyrotoxicosis where basal oxygen consumption is increased the total red cell mass might be expected to show a parallel increase. This relationship has been studied in the present investigation. Because cases of myxoedema have a diminished basal oxygen consumption and so might be expected to have a lower red cell mass than normal the opportunity was also taken to study the relationship in this condition. The observations to be described below confirm that the total red cell mass in thyrotoxicosis is increased relative to lean body mass and evidence will be presented that this increase is related to the changes in basal oxygen consumption of the tissues.

Methods. Seven thyrotoxic and 8 myxoedematous subjects were studied. In addition three thyrotoxic and three myxoedematous subjects were studied after treatment. The assessment of thyroid function in each case was made clinically and confirmed by special investigations, including estimations of basal metabolic rate and serum cholesterol, together with radioactive iodine criteria and response to therapy.

Antipyrine estimations were carried out by the method of Brodie et al. (1949). Antipyrine (2 g.) was administered slowly by intravenous injection from a calibrated syringe and blood samples were taken at $2\frac{1}{4}$, 3, $4\frac{1}{2}$ and 6 hours. Plasma water concentration of antipyrine was derived by multiplying the plasma concentration by 100/93 to correct for plasma proteins, which were assumed to average 7% of plasma volume. All estimations were carried out at room temperature, the extremes being 18 and 22°C. Lean body mass was derived from the total body water (antipyrine space) by means of the equation of Pace and Rathbun (1945).-

$$\text{Lean body mass} = \text{Total body water} \times \frac{100}{73}$$

Blood volume measurements were performed by means of the Evans blue (cellulose extraction) method (Bedwell et al. 1955). Extraction of Evans blue with this method has been constantly 96 - 100% with the majority of results falling in the range of 97 - 98%. Accordingly each estimation has

been corrected for an extraction rate of 97.5%. Ten ml. of 0.1% Evans blue were given intravenously to each subject from a calibrated syringe and samples were taken 15 and 30 minutes later.

Turbidity due to protein in the eluate of Evans blue was avoided by washing with teepol-saline until the filtrate was clear of turbidity on testing with 10% salicyl-sulphonic acid. (Muldowney, 1957).

Haematocrit figures were obtained with Wintrobe tubes spun at 3,000 r.p.m. for 55 minutes. A correction for trapped plasma was made according to the figures of Chaplin and Mollison (1952). The true venous haematocrit was then corrected by the factor 0.91 to calculate total body haematocrit (Chaplin et al. 1953). All subjects studied had mean cell haemoglobin concentrations within the normal range. Red cell mass was calculated from the Evans blue plasma volume as follows.-

$$\text{Red Cell Mass} = \frac{\text{Plasma volume X Total body haematocrit}}{(100 - \text{Total body haematocrit})}$$

Thiocyanate space estimations were carried out by the method of Bowler (1944). Sodium thiocyanate 1.2 g. was injected intravenously from a calibrated syringe at the same time as the antipyrine injection, and the $2\frac{1}{4}$ hour plasma sample was used for both thiocyanate and antipyrine estimations. Wedgewood et al. (1953-1954) have shown that the urinary excretion of thiocyanate during the first two hours after injection is less than 1% and accordingly no correction has

TABLE I.

The data.

Subject	Thyroid state	Age (yr.)	Height (cm.)	Body wt. (Kg.)	Anti-pyrine space (l.)	Lean body mass (Kg.)	Red cell mass (ml.)	Red cell mass percentage deviation from normal mean	B.M.R. percentage mean Robertson	Oxygen consumption (ml./min.)	Packed cell volume (per cent.)	Thiocyanate space (l.)
1	Toxic —untreated	35	159	56·36	29·7	40·65	1620	+ 8·8	+ 47	387	42·0	13·05
2	Toxic —untreated	35	164	54·1	28·25	38·7	1618	+14·5	+ 46	360	43·5	11·2
3	Toxic —untreated	24	240	44·5	24·6	33·7	1365	+ 8·3	+ 61	297	39·0	12·0
4	Toxic —untreated	55	160	67·4	33·2	45·4	1742	+ 6·0	+ 28	260	38·0	14·85
5	Myxœdema—untreated	63	160	61·8	28·1	38·5	1016	−29·2	− 21	142	38·0	13·6
6	Myxœdema—untreated	65	156	74·0	37·3	51·1	1442	−21·0	− 5	236	38·0	19·6
7	Myxœdema—untreated	64	157	74·5	33·5	45·9	1142	−31·0	− 36	140	36·0	15·3
8	Myxœdema—untreated	43	248	51·0	31·0	42·5	915	−41·0	− 26	150	35·0	—
9	Myxœdema—untreated	42	162	77·3	36·35	49·8	1458	−18·3	− 30	160	39·0	15·7
10	Toxic — untreated	28	175	60·0	38·3	52·75	2175	+ 15·4	+ 64	617	43·0	17·9
	Toxic — treated	28	175	82·4	50·25	68·8	2550	+ 5·8	− 6	262	50·2	17·7
11	Toxic — untreated	33	162	46·8	28·45	39·0	1505	+ 5·0	+ 27	280	37·5	10·85
	Toxic — treated	33	162	51·3	30·9	42·3	1468	− 4·5	− 7	180	37·0	13·2
12	Toxic — untreated	32	260	50·5	29·2	40·0	1655	+13	+ 47	300	44·0	13·02
	Toxic — treated	32	260	56·9	35·3	48·3	1730	− 0·5	− 2	207	45·0	16·4
13	Myxœdema— untreated	37	170	63·5	33·62	46·1	1181	−31·5	− 36	168	34·0	13·9
	Myxœdema— treated	37	170	55·0	33·42	45·8	1760	+ 6·0	+ 2	210	39·2	—
14	Myxœdema— untreated	47	152	62·7	29·3	40·1	1318	−11·0	− 5	196	39·0	13·45
	Myxœdema— treated	47	152	59·0	28·4	38·9	1535	+ 7·2	+ 19	226	41·2	14·1
15	Myxœdema— untreated	67	157	68·0	28·1	38·45	1198	−15·4	− 28	140	37·0	12·4
	Myxœdema— treated	67	157	64·6	25·6	35·0	1260	− 3·4	− 5	183	39·0	12·4

been made for this factor. The plasma concentration of thiocyanate was multiplied by the factor 100/93 to correct for plasma proteins, before calculating thiocyanate space. Fat-free body weight (including minerals) was derived from the equation as suggested by Keys and Brozek (1953) as follows.-

$$\text{Fat-free weight} = A + (0.563)(A - E)$$

Where A = antipyrine space and E = 0.7 (thiocyanate space). This value for fat-free body weight was compared with the value for lean body mass derived from the Pace-Rathbun equation.

In one additional case of myxoedema, red cell mass studies were carried out before and during the administration of 2,4-dinitrophenol (D.N.P.) which increases oxygen consumption without influencing thyroid function. The dose of D.N.P. was adjusted to maintain serum levels between 45 and 50 mg. per litre and these levels were maintained for ten days, the average daily dose being 200 mg. Somnolent metabolic rate estimations on this subject were carried out as described by Fraser and Nordin (1955) since difficulty was experienced in obtaining satisfactory basal metabolic rate determinations.

Results

The complete data are given in Table I, in which values for lean body mass were derived from the Pace-Rathbun equation. Comparison of the values for lean body mass derived from the Pace-Rathbun and Keys-Brozek formula in fourteen of the fifteen subjects showed that the latter provided a systematically higher estimate, the mean difference, however,

FIGURE 1

Red cell mass and lean body mass in thyrotoxicosis. The parallel lines represent the 95% confidence limits in 36 normal subjects.

FIGURE 2

Red cell mass and lean body mass in myxoedema. The parallel lines represent the 95% confidence limits in 36 normal subjects.

FIGURE 3

Red cell mass and basal oxygen consumption.

FIGURE 1.

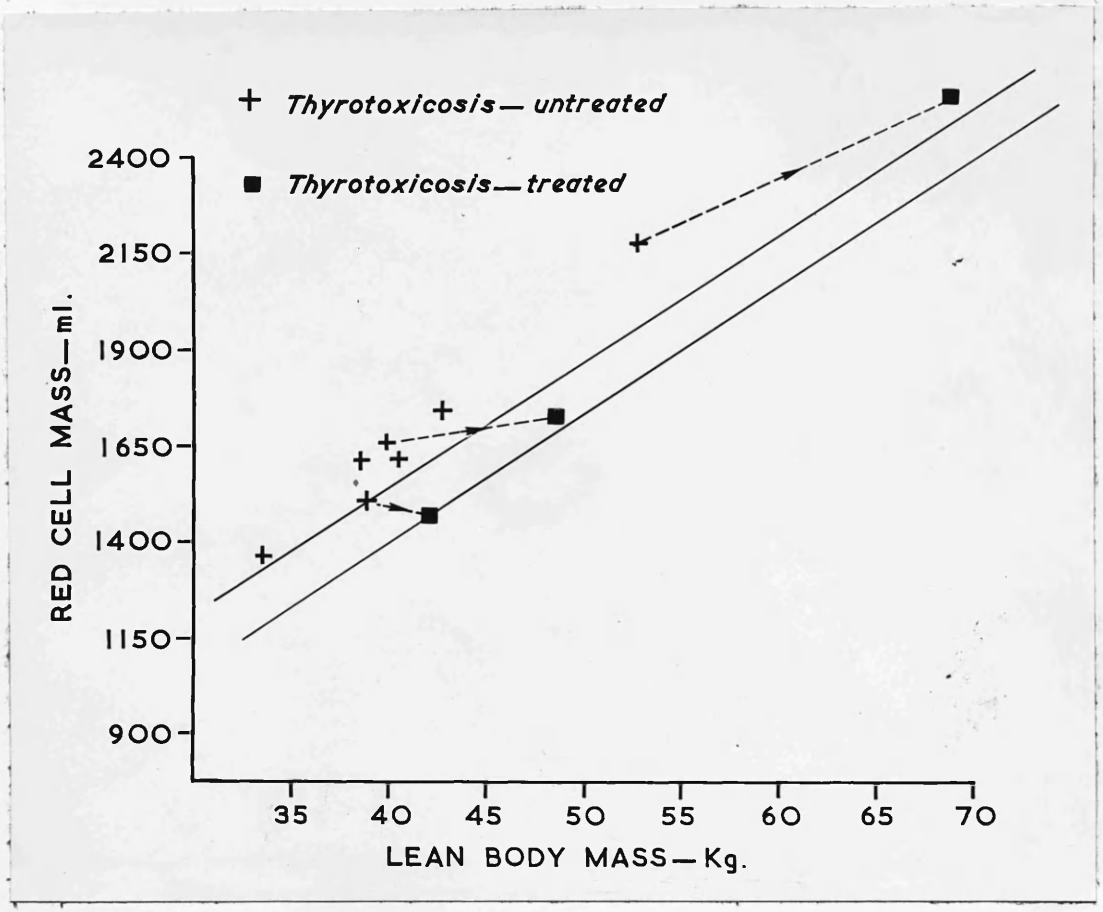

+ Thyrotoxicosis — untreated
■ Thyrotoxicosis — treated
2400
2150
1900
1650
1400
1150
900
RED CELL MASS — ml.
35
40
45
50
55
60
65
70
LEAN BODY MASS — Kg.

FIGURE 2.

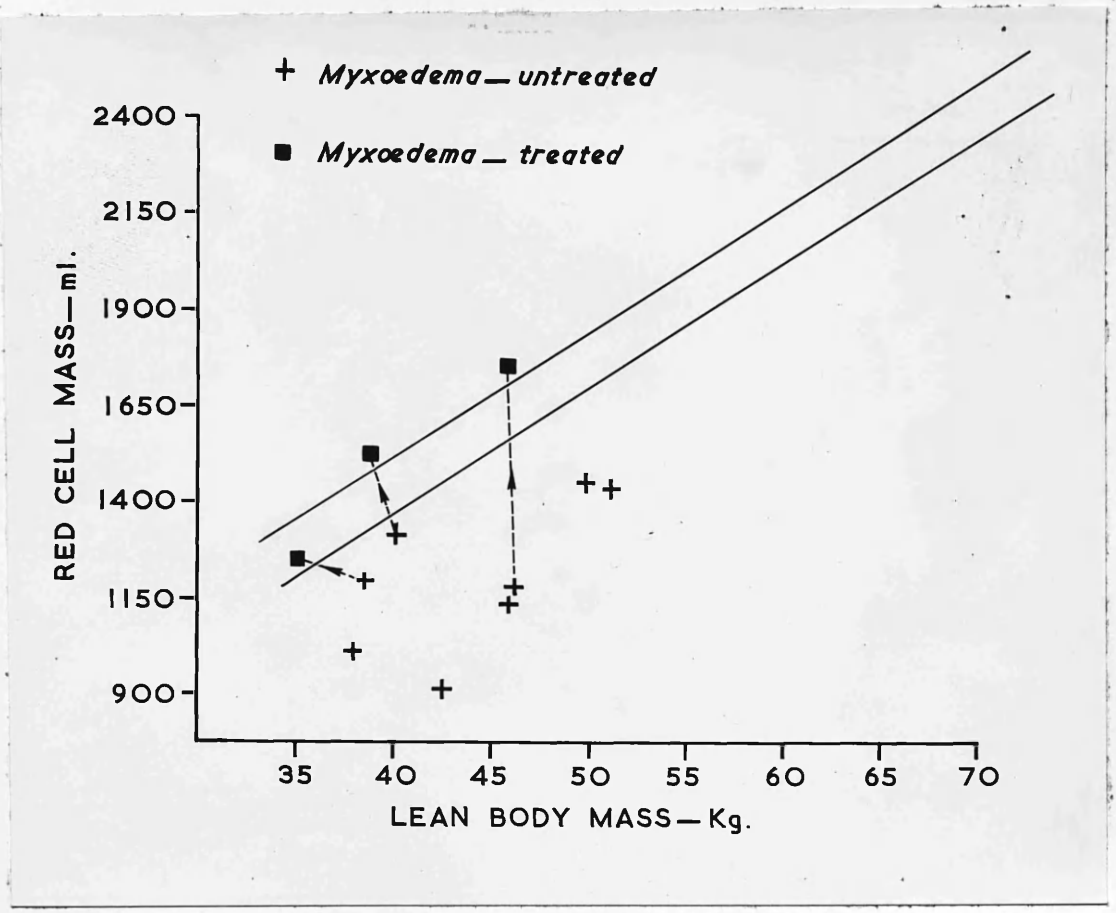
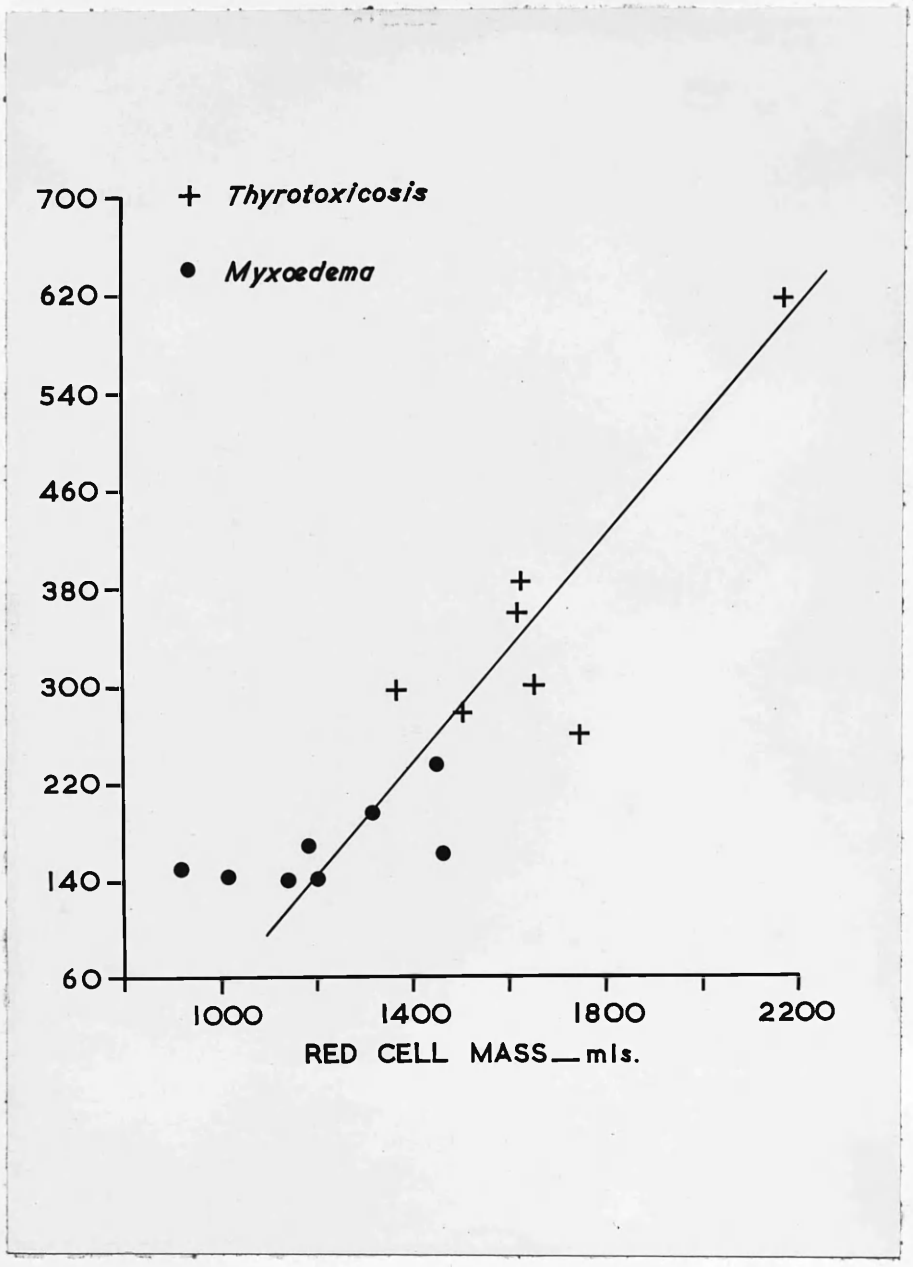

+ Myxoedema — untreated
■ Myxoedema — treated
2400
2150
1900
1650
1400
1150
900
RED CELL MASS — ml.
35
40
45
50
55
60
65
70
LEAN BODY MASS — Kg.

FIGURE 3.


+ Thyrotoxicosis
● Myxœdema
700
620
540
460
380
300
220
140
60
1000
1400
1800
2200
RED CELL MASS — mls.

being only 1.3%.

The parallel lines in Figures 1 and 2 represent the 95% confidence limits relating lean body mass to red cell mass established by Muldowney (1957) in a series of normal subjects. The red cell mass of all subjects studied in the present series fell outside these limits, the thyrotoxic cases falling above (Figure 1) and the myxoedematous cases below the normal range (Figure 2). Thus, in terms of Kg. lean body mass, the thyrotoxic subjects had a larger red cell mass and the myxoedematous subjects a smaller red cell mass than normal.

It can also be seen from Figures 1 and 2 and from Table I that 3 thyrotoxic and 3 myxoedematous cases studied after treatment showed a reversion towards the normal range of red cell mass.

Figure 3 shows that the correlation between red cell mass and basal oxygen consumption in the thyrotoxic and myxoedematous cases is highly significant ($r = 0.88$).

In the case of the myxoedematous subject to whom dinitrophenol was given the total red cell mass before therapy was 998 ml. compared with a normal mean of 1725 ml. (based on a lean body mass estimate of 47.8 Kg.). Fifteen days after commencement of D.N.P., when the somnolent metabolic rate had risen from the pre-treatment level of - 38% to + 5%, the red cell mass had risen slightly to 1048 ml. After a further 6 days,

the red cell mass had risen to 1183 ml., representing an increase from - 42.2% to - 31.2% of the normal mean.

Discussion

The results show that in thyrotoxicosis there is an increase in the red cell mass relative to lean body mass. Furthermore the red cell mass - lean body mass relationship returned towards normal in the 3 thyrotoxic subjects studied after treatment. The mean cell haemoglobin concentrations did not vary following treatment and therefore the red cell mass changes reflect the changes in total circulating haemoglobin. The time taken to reach the euthyroid state varied from 6 to 12 weeks, but the picture after treatment was complicated by considerable increases in lean body mass. This was most marked in the case of subject No. 10 where lean body mass increased by 14 Kg. In this subject, although an absolute rise of 375 ml. of red cell mass occurred, the red cell mass per Kg. of lean body mass fell from + 15.4% to + 5.8% of the normal mean.

Gibson and Harris (1939) have shown that the blood volume tends to be increased in thyrotoxicosis but since they used total body weight as a standard of reference their results were not statistically significant. They were, however, able to show a decrease in the blood volume after treatment. The increase in total red cell mass found in thyrotoxicosis in the present series implies increased bone marrow activity and Axelrod and Berman (1951) have described

erythroid hyperplasia at the expense of fat in patients with the disease. Functioning cellular marrow may extend even into the long bones in the adult. The results also suggest that the moderate increase of faecal urobilin found in thyrotoxicosis (Werner, 1955) is probably due to an elevated total circulating haemoglobin undergoing breakdown at a normal rate rather than to an excessive rate of red cell destruction.

The relationship between lean body mass and red cell mass in the myxoedematous patients is in accord with that found in thyrotoxicosis. Thus, when thyroid activity was low the total red cell mass related to lean body mass was less than normal and returned towards normal with treatment. Gibson and Harris (1939) who studied blood volume in myxoedema showed a tendency to low values in this disease, but as in the case of thyrotoxicosis their results were not statistically significant presumably because of their use of body weight as a reference standard. They demonstrated, however, an increase in blood volume with treatment.

The validity of applying the Pace-Rathbun formula to derive lean body mass in thyrotoxicosis and myxoedema may be questioned on the grounds that in these conditions there may be a disturbance of the lean body mass - total body water relationship. Accordingly, the formula of Keys and Brozek (1953) for fat free weight incorporating a correction for changes

in extra-cellular fluid was also applied and these values compared with these obtained from the Pace-Rathbun equation. The estimate of lean body mass provided by the Keys and Brozek formula was systematically higher, the mean difference being 1.3%. This pattern corresponds exactly with that obtained in a group of normal subjects by Muldowney (1957). It is concluded, therefore, that the Pace-Rathbun formula for lean body mass in thyrotoxicosis and myxoedema requires no correction involving measurement of extra-cellular fluid.

The close relationship previously shown between red cell mass and lean body mass in normal subjects was regarded by Muldowney (1957) as a possible result of the correlation of each of these entities with basal oxygen consumption. He suggested that oxygen-carrying power, or red cell mass, may be regulated directly by basal oxygen demands. The results show that increase or decrease in basal oxygen consumption is accompanied by parallel changes in red cell mass. It is apparent, therefore, that the correlation between lean body mass and red cell mass in normal subjects no longer holds when basal oxygen requirements are abnormal. On the other hand, the relationship between red cell mass and basal oxygen consumption remains and this lends strong support to the view that this is the primary relationship on which the red cell mass - lean body mass correlation in normal subjects depends.

It may be argued, however, that the regulation of red cell mass is not achieved directly by changes in basal oxygen consumption, but by a coincident action of the thyroid hormone on the bone marrow. This has been discussed by Romford (1938) who suggested that the former explanation was the case but produced no evidence in support of this. It was, therefore, desirable to study the effect on red cell mass of an increase in basal oxygen consumption in the absence of any increase in circulating thyroid hormone. This was done by the administration of dinitrophenol to a myxoedematous subject, since this drug has been shown to stimulate oxygen consumption without affecting thyroid function (Castor and Beierwaltes, 1956). The absence of an effect on thyroid function was confirmed by the fact that the abnormally low uptake of ^{131}I by the gland before and during treatment was unchanged. In this case the red cell mass significantly increased in association with a rise in basal oxygen consumption and in the absence of increased production of thyroid hormone. This is further evidence that the bone marrow responds primarily to changes in basal oxygen demands.

The changes in red cell mass in thyrotoxicosis and myxoedema must be re-examined in the light of this concept. Thus, thyrotoxicosis is accompanied by a polycythaemia which may be regarded as a hypertrophy of oxygen-carrying tissue in response to increased metabolic demands. This

polycythaemia disappears with the decrease in basal oxygen consumption produced by antithyroid therapy. Conversely, the diminished oxygen requirements in myxoedema result in a shrinkage of red cell mass, thus producing an anaemia which may be regarded as physiological. This anaemia responds to thyroxine therapy and the response may be accounted for by the associated rise in basal oxygen consumption.

SECTION 1

Summary.

1. The relationship between total red cell mass and lean body mass has been studied in 7 thyrotoxic and 8 myxoedematous subjects.

2. There is a significant increase in total red cell mass in thyrotoxicosis and a significant decrease in myxoedema, and in both conditions treatment produced a return of the red cell mass - lean body mass relationship towards normal.

3. Red cell mass is closely related to basal oxygen consumption in both conditions.

4. Evidence is put forward that red cell mass is regulated by changes in basal oxygen consumption and not by a direct action of thyroid hormone on the bone marrow.

5. Thyrotoxicosis is thus accompanied by a polycythaemia which represents a physiological hypertrophy of red cell mass in response to increased oxygen demands, and myxoedema by an anaemia which represents a physiological re-adjustment in oxygen-carrying power.

SECTION 2

Total Exchangeable Sodium, Potassium, and Chloride in Thyrotoxicosis.

Physiologists have long appreciated that comparisons of the electrolyte content of various tissues are invalidated by variations in the proportion of lipid since the latter is poor in electrolytes (Hastings and Eichelberger, 1937). For this reason they expressed their measurements of electrolytes on the basis of fat-free weight rather than tissue weight. Thyrotoxicosis results in a variable loss of lean tissue and fat (Moore et al. 1952) and a study of the changes in the exchangeable electrolytes produced by the disease should take this factor into account. This cannot be satisfactorily achieved if body weight is used as the standard of reference. Notwithstanding the findings of physiologists clinical workers have continued to use body weight as a standard of reference for exchangeable electrolytes in both normal subjects (Ikkos et al. 1955; Corsa et al. 1950) and in thyrotoxicosis (Munro et al. 1958). Even the normal variation in the proportions of lean tissue and fat found in health may produce certain fallacies of interpretation. For example, Aikawa (1952) found that the exchangeable potassium (K_e) in females had a lower value per Kg. body weight than in males (Corsa et al. 1950). This finding, as will be demonstrated in the investigations to be described, is due to the greater fat content of females and the difference disappears when lean body mass in used as the reference standard.

Because of the varying fat component of normal subjects it was felt that the established mean values for exchangeable sodium (Na_e) (Miller and Wilson, 1953), exchangeable chloride (Cl_e) (Ikkos et al. 1955), and K_e (Aikawa, 1952; Corsa et al. 1950) would not be helpful in a study of the changes in these electrolytes produced by thyrotoxicosis. For this reason it was decided to substitute fat-free weight or lean body mass for body weight as the reference standard for the exchangeable electrolytes in a group of normal subjects as a preliminary to investigating the relationships between the three electrolytes and lean body mass in thyrotoxic subjects. In thyrotoxicosis there is an associated disturbance of bone metabolism (Aub et al. 1929). Since there is a special relationship between Na_e and Cl_e in bone the opportunity was also taken to study this relationship both in normal and in thyrotoxic subjects.

Subjects studied.

Na_e measurements were made in 21 normal males and 17 normal females. K_e was also measured in 21 males and 17 females, and Cl_e in 22 males and 19 females. In 24 of the normal subjects studied all three electrolytes were measured -- Na_e and K_e being measured simultaneously. The subjects covered a wide range of age and body weight as shown in Tables II and III.

All three electrolytes were measured in 20 subjects (19 females, 1 male) with unequivocal evidence of thyrotoxicosis -- Na_e and K_e being measured simultaneously. The diagnosis in each case was confirmed by measurement of the 4-hour uptake of ^{131}I and the 48-hour plasma protein-bound radioactivity. In all cases the basal metabolic rate was above the upper limit of the normal range (Robertson and Reid, 1952).

Methods.

Na_e was measured by the method of Miller and Wilson (1953), giving 30 μc. of Na^{24} orally and allowing an equilibration period of 24 hours. K_e measurements were performed by the method of Corsa and his colleagues (1950) 4 spot urine specimens being collected between 22 and 26 hours after injection of 150 μc. of ^{42}K (K Cl irradiated as $K_2 CO_3$) using a calibrated syringe. Simultaneous measurements of Na_e and K_e were made by the method of Munro et al. (1958). In this procedure 100 μc. of ^{42}K and 50 μc. of ^{24}Na were given intravenously from a calibrated syringe, and an equilibration period of 22 hours was allowed, after which a plasma sample was obtained followed by two spot urine specimens 1 and 2 hours later. Each spot urine was divided into two portions and potassium separated from sodium by precipitation of the former with sodium tetraphenylboron. Potassium and sodium concentrations in plasma and processed urine were estimated

by flame photometry. The measurements of Cl_e were carried out by the method of Bradley et al. (1956). Twenty/uc. of ^{82}Br (Na Br irradiated as NH_4 Br) were administered orally and an equilibration period of 22 - 26 hours was allowed. ^{82}Br was not given until at least 3 days after the administration of ^{24}Na and ^{42}K. This procedure ensured that ^{82}Br plasma counts required no correction for residual ^{24}Na. Plasma chloride concentration was estimated by the method of Van Slyke (1923).

To derive total exchangeable electrolyte the following equation was used.-

Total exchangeable electrolyte (mEq.) = Electrolyte space (litres) X plasma electrolyte (mEq./litre).

In the case of sodium, the electrolyte space and plasma concentration did not require correction by the Donnan Factor since this is cancelled by the correction for plasma proteins. In deriving the chloride space, however, it is necessary to correct for the Donnan equilibrium and for plasma proteins since they are additive for anions and a factor of 0.91 was therefore used. In the normal subjects where K_e had been measured by the method of Corsa et al. (1950) it was necessary to find a correction factor in order to make them comparable with the values given by the simultaneous Na_e and K_e technique. This correction was obtained by the following in vitro experiment.

A suitable quantity of ^{42}K was added to 1 litre of urine which was divided into 2 portions. Six aliquots of 1 portion were counted in an M.6 Geiger counter and the stable potassium concentration measured by flame photometry, this being the method of Corsa et al. (1950). Six aliquots of the remaining portion were processed as in the method of Munro et al. (1958). Consistent specific activities were obtained by each method, but the mean value given by the method of Corsa et al. was 6% higher than that given by the simultaneous method of obtaining Na_e and K_e. The data for K_e obtained by the former method was therefore corrected by this factor.

The radiation dose for a person of 70 Kg. weight did not exceed 0.07 rad due to 50 μc. of Na^{24}, 0.07 rad due to 100 μc. of K^{42}, and 0.05 rad due to 20 μc. of ^{82}Br, i.e. the radiation dose due to the combined technique lies considerably below the weekly tolerance dose of 0.3 rad.

Lean body mass was estimated from the Pace-Rathbun formula (Pace and Rathbun, 1945).-

$$\text{Lean body mass} = \text{Total body water} \times \frac{100}{73}$$

Total body water was measured by the antipyrine dilution technique of Soberman et al. (1949) the plasma concentration of antipyrine being corrected for plasma proteins. Antipyrine estimations were carried out by the method of Brodie et al. (1949). In a few normal subjects values of lean body mass

TABLE II

TABLE II -- NORMAL MALES

Case No.	Age	Ht. cms.	Body Wt. Kg.	Lean Body Mass Kg.	Na_e mEq.	K_e mEq.	Cl_e mEq.	Na Space / Cl Space
1	18	176	65.9	51.7	3070	3710	1970	1.192
2	33	165	63.6	51.7	2410	3140	1780	1.166
3	29	168	55.5	53.0	2360	2860	1800	1.096
4	36	175	97.4	61.6	3020	3520	2270	1.057
5	27	183	72.7	58.5	2910	3900	2000	1.083
6	22	177	65.4	48.6	2740	3210	1850	1.167
7	27	175	57.3	49.8	2760	2690	1950	1.086
8	35	184	83.0	66.0	3180	3020	2100	1.201
9	25	163	100.5	63.0	2790	3600	1880	1.240
10	21	174	69.0	51.5	3480	3280	2590	1.374
11	24	174	63.2	50.7	2840	3100	1710	1.324
12	18	175	79.5	67.0	3480	3580	2280	1.279
13	21	179	58.6	52.0	3080	3280	1790	1.320
14	28	182	71.8	61.1	2970	3740	2160	1.101
15	22	192	81.0	66.0	3320	-	-	-
16	24	179	92.0	57.0	2470	-	-	-
17	74	159	61.4	47.2	2590	-	-	-
18	31	182	80.0	60.5	3090	4130	-	-
19	67	165	57.3	52.5	2910	-	-	-
20	46	178	118.0	74.6	3530	-	-	-
21	65	165	55.5	44.7	2370	-	-	-
22	22	168	61.3	48.8	-	3140	1710	-
23	22	177	68.2	56.2	-	3240	2020	-
24	22	192	82.0	71.7	-	4500	3010	-
25	22	169	65.0	52.0	-	3080	1930	-
26	23	178	65.5	58.2	-	-	2190	-
27	25	183	87.2	72.6	-	-	2450	-
28	33	178	77.2	59.5	-	3600	-	-
29	43	165	61.0	57.5	-	-	1980	-

TABLE III

TABLE III

Case No.	Age	Ht. cms.	Body Wt. Kg.	Lean Body Mass Kg.	Na_e mEq.	K_e mEq.	Cl_e mEq.	Na Space / Cl Space
31	56	140	83.7	48.0	2600	1950	1580	1.260
32	31	159	65.0	41.5	2300	2480	1530	1.239
33	45	154	80.5	45.2	2490	2830	1730	1.159
34	51	161	84.3	46.0	2360	2580	1680	1.143
35	19	168	130.0	65.0	3510	3540	2210	1.295
36	68	154	89.1	58.0	2760	2730	1910	1.084
37	17	165	95.5	55.0	3500	3220	2270	1.223
38	21	157	49.4	34.5	2070	2470	1540	1.078
39	26	165	56.4	42.0	2040	2390	1650	0.972
40	57	151	104.0	62.5	3370	3530	2460	1.166
41	30	163	67.2	41.9	2200	-	-	-
42	71	142	72.2	46.5	2490	-	-	-
43	58	154	72.4	49.0	2290	-	-	-
44	34	160	59.5	40.7	2200	-	-	-
45	22	168	56.4	43.6	2530	-	-	-
46	21	165	65.0	47.7	2360	-	-	-
47	22	168	48.1	38.6	2090	-	-	-
48	55	157	82.7	48.5	-	-	1830	-
49	57	158	93.6	52.0	-	2540	1980	-
50	38	155	70.5	45.9	-	2220	-	-
51	81	152	44.5	33.3	-	1260	1250	-
52	55	156	66.0	45.3	-	-	1680	-
53	18	173	100.2	61.5	-	3080	2440	-
54	50	178	57.2	45.2	-	-	1730	-
55	51	151	50.0	36.7	-	1910	-	-
56	52	152	63.6	47.0	-	2160	1720	-
57	37	170	55.0	45.8	-	-	1830	-
58	66	163	54.0	42.1	-	1700	1370	-

TABLE IV

TABLE IV

Statistical Analysis -- Normal Subjects

Electrolytes and Reference Standards

Electrolyte y	Reference Standard x	Number of Males	Number of Females	All Subjects	r	95 per cent Confidence Limits mEq.	95 per cent Confidence Limits per cent of mean	Equation of Regression line
Na_e	B.W.	21	17	38	0.62	± 740	± 27	y-2750= 15.02(x-74.41)
Na_e	L.B.M.	21	17	38	0.82	± 560	± 20	y-2750= 40.72(x-52.48)
K_e	B.W.	21	17	38	0.45	±1250	± 41	y-3018=16.58(x-74.48)
K_e	L.B.M.	21	17	38	0.83	± 790	± 26	y-3018= 61.76(x-52.77)
Cl_e	B.W.	22	19	41	0.55	± 600	± 31	y-1942= 10.68(x-73.95)
Cl_e	L.B.M.	22	19	41	0.84	± 390	± 20	y-1942= 31.84(x-52.96)

B.W. = Body weight

L.B.M. = Lean body mass

were derived from measurements of red cell mass employing the correlation established by Muldowney (1957). The error in the derivation of lean body mass from red cell mass was estimated by taking half the difference between successive measurements of red cell mass and combining it with the 95% confidence limit of the correlation between red cell mass and lean body mass expressed as a percentage of the mean value of lean body mass. This error should not exceed $\pm$ 5%.

Results

Exchangeable electrolytes in normal subjects. The complete data obtained in the normal subjects are shown in Tables II and III, and the statistical analysis is given in Table IV. The reproducibility of the measurements of exchangeable electrolytes was tested by carrying out two successive estimations in a number of subjects. The standard deviations were $\pm$ 2.8% for Na_e (8 subjects), $\pm$ 3.5% for K_e (5 subjects) and $\pm$ 3.5% for Cl_e (5 subjects).

The relationship between Na_e and body weight is shown in Figure 4. The coefficient of correlation was 0.62 and the 95% confidence limits $\pm$ 27%. It was found that the majority of the points representing males lay above the regression line while the converse was true of the females. When Na_e was correlated with lean body mass, however, in the same subjects (Figure 5), both the correlation coefficient ($r = 0.82$) and the 95% confidence limits ($\pm$ 20%) were improved.

FIGURE 4

The correlation of total exchangeable sodium with total body weight in normal subjects showing the regression line and its 95% confidence limits.

FIGURE 5

The correlation of total exchangeable sodium with lean body mass in normal subjects showing the regression line and its 95% confidence limits.

FIGURE 6

The correlation of total exchangeable potassium with total body weight in normal subjects showing the regression line and its 95% confidence limits.

FIGURE 7

The correlation of total exchangeable potassium with lean body mass in normal subjects showing the regression line and its 95% confidence limits. The interrupted line is the regression line derived from the data of Ikkos et al. (1956).

FIGURE 8

The correlation of total exchangeable chloride with total body weight in normal subjects showing the regression line and its 95% confidence limits.

FIGURE 9

The correlation of total exchangeable chloride with lean body mass in normal subjects showing the regression line and its 95% confidence limits.

FIGURE 4.

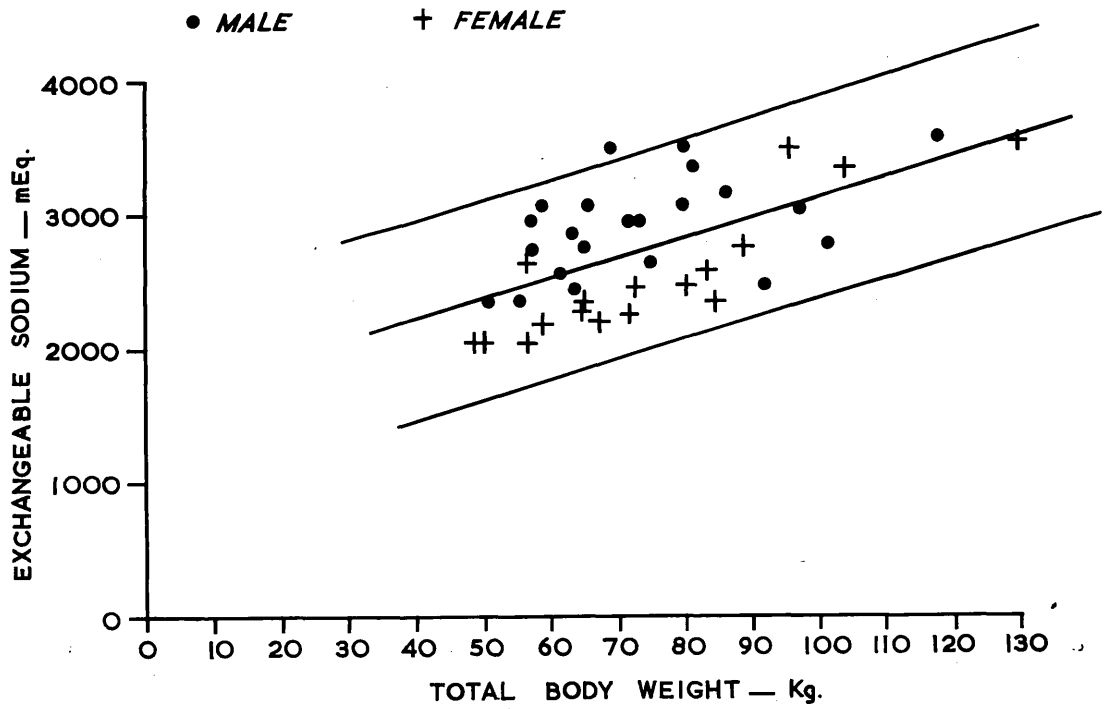


FIGURE 5.

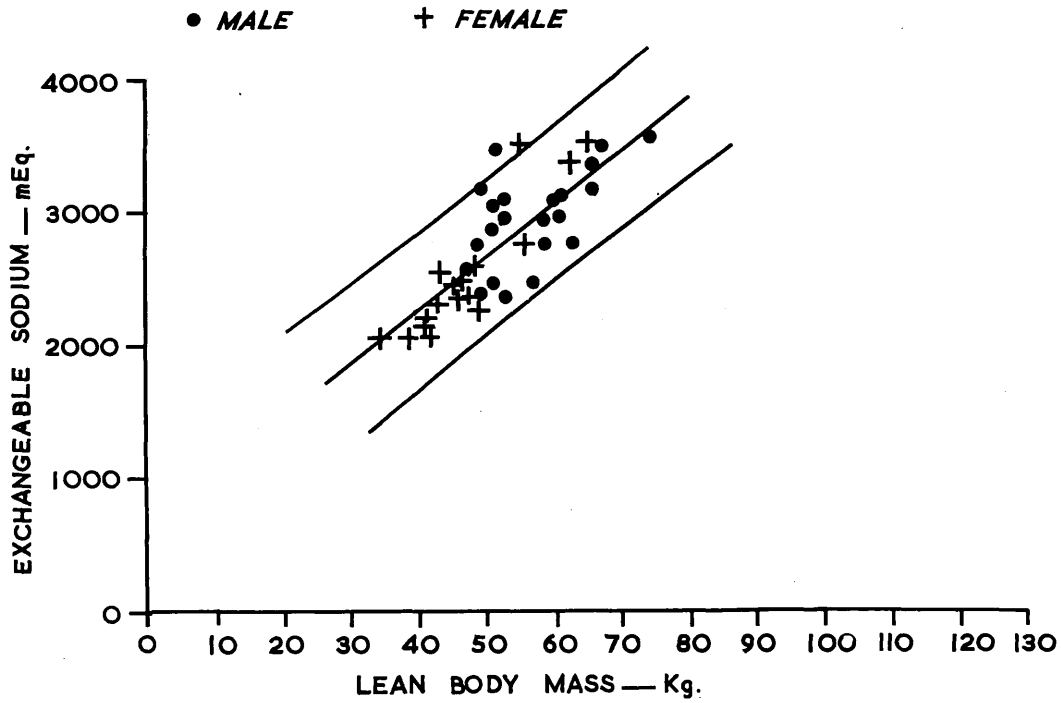


FIGURE 6.

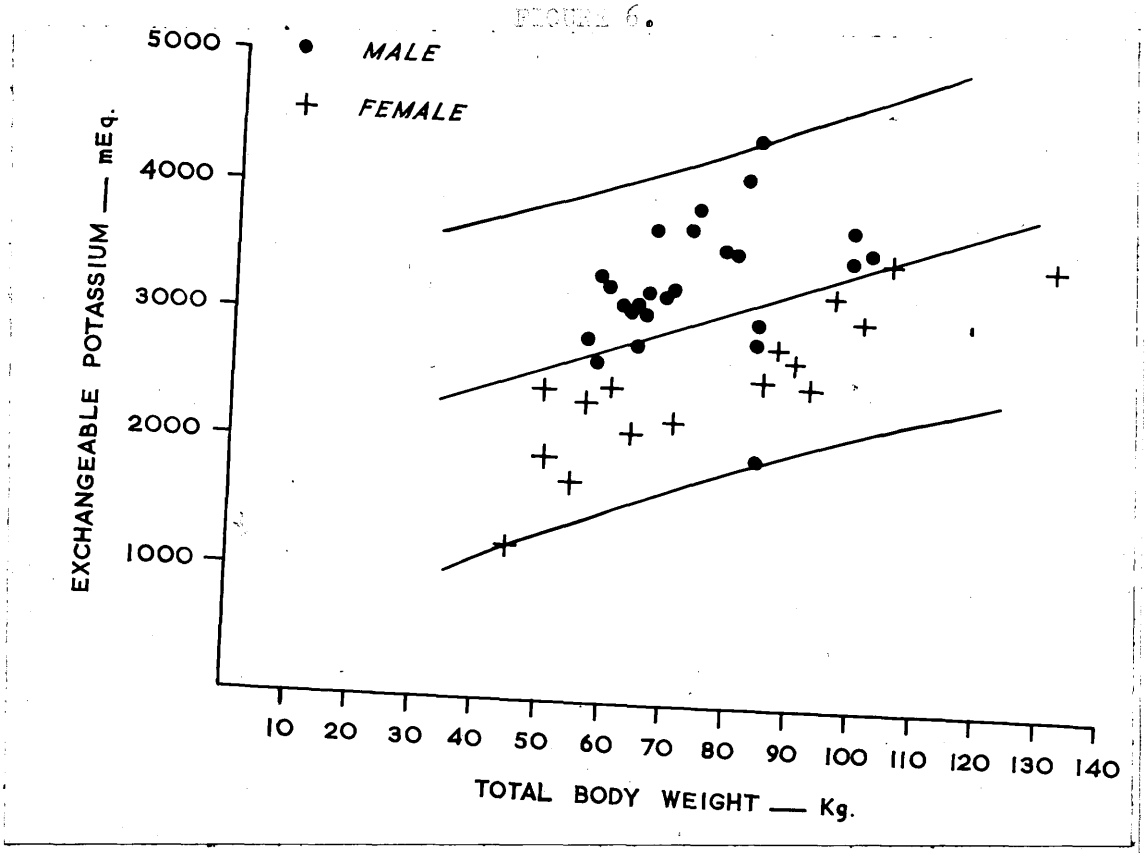


FIGURE 7.

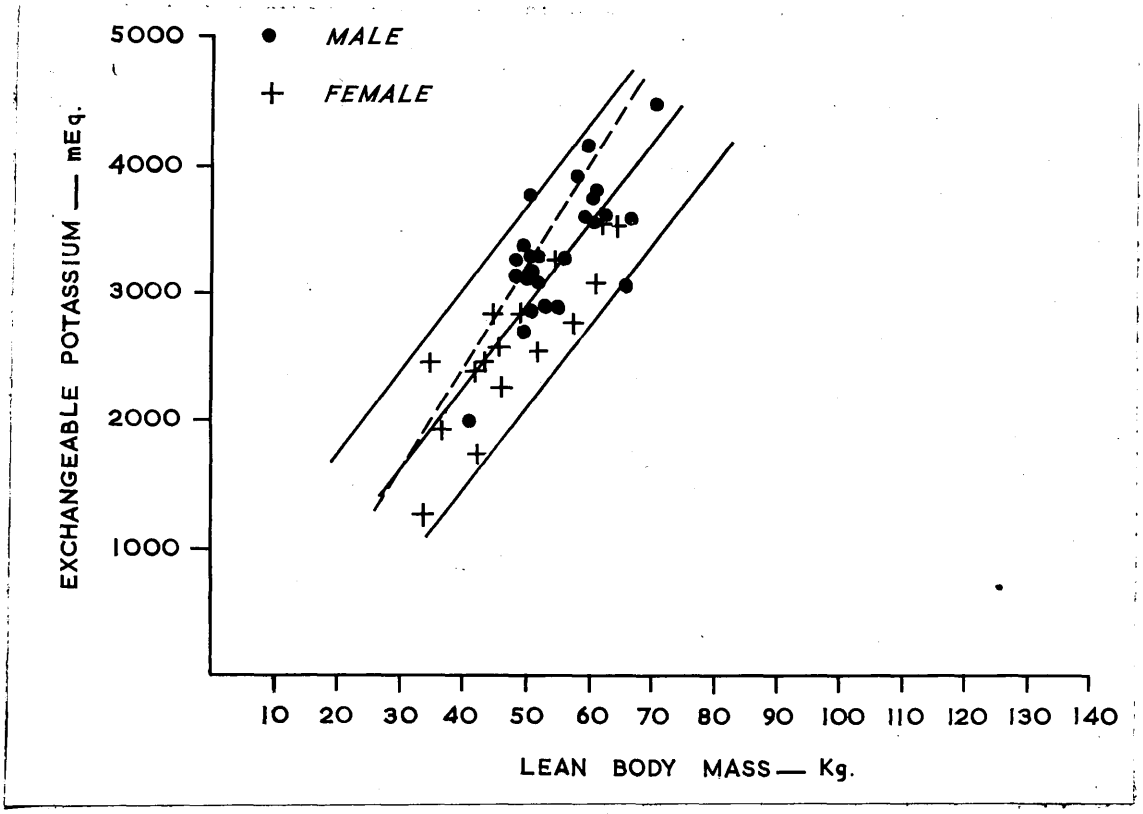


FIGURE 8.

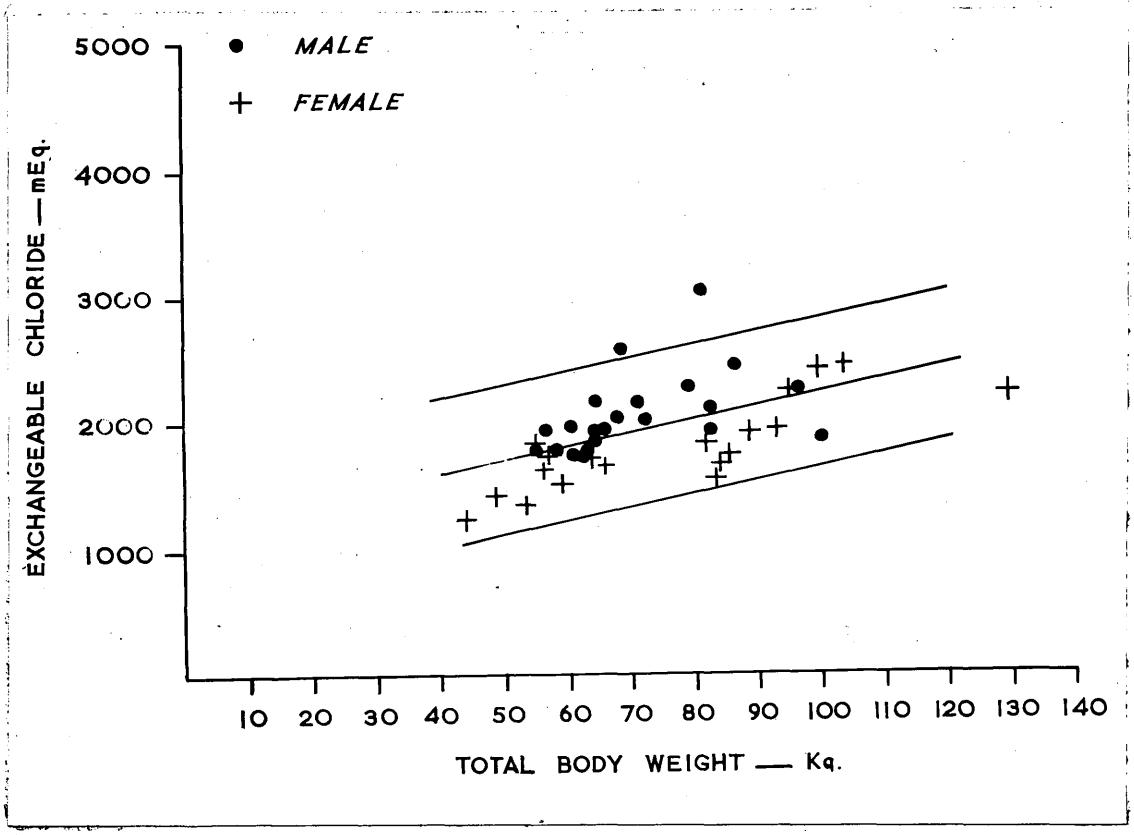
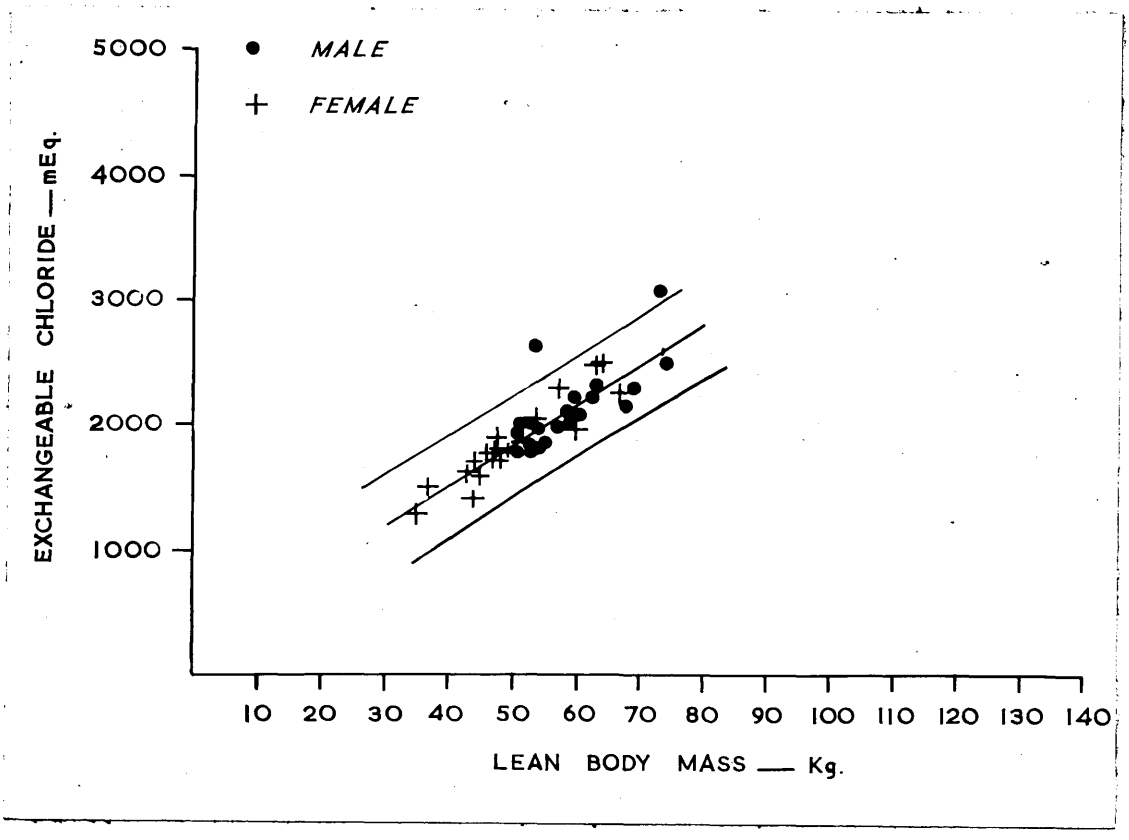


FIGURE 9.



The points for both males and females were also more uniformly distributed about the regression line. When K_e was correlated with body weight a very wide range of normal values was found (Figure 6). Once again most of the males lay above the regression line and the females below. When lean body mass, on the other hand, was used as the reference standard, the normal range narrowed and the male and female values were distributed on either side of the regression line (Figure 7). The effect of using lean body mass instead of body weight as a reference standard for Cl_e was similar to that observed in the case of Na_e and K_e (Figures 8 and 9).

In 14 males and 10 females the correlation between Na_e and Cl_e was highly significant ($r = 0.88$) and the 95% confidence limits ($\pm$ 17%) were narrower than those for Na_e when either body weight or lean body mass was used as a reference standard. Because of the primarily extracellular location of both these ions, this finding was not unexpected. Of greater interest, however, was the observation that in this group of subjects the Na_e could not be wholly accounted for by that present in the extracellular fluid, as represented by the chloride space, since the mean ratio of the sodium space to the chloride space, 1.179, was significantly greater than unity ($p < 0.01$, standard deviation of the mean = 0.024).

TABLE V

TABLE V

Thyrotoxic Subjects

Case No.	Age	Height cms.	Body Weight Kg.	Lean Body Mass Kg.	Na_e mEq.	K_e mEq.	Cl_e mEq.	Na Space / Cl Space
1	44	166	70.2	43.2	2670	2580	1720	1.15
2	51	166	65.3	47.6	2900	2050	1920	1.17
3	41	164	50.8	41.2	2650	1910	1390	1.46
4	24	168	45.4	35.4	1880	1780	1580	0.97
5	48	147	45.7	30.8	1980	1500	1520	1.07
6	34	163	54.3	39.8	2550	1990	1590	1.20
7	49	150	55.9	36.1	2780	2500	1560	1.33
8	45	163	60.2	40.0	2430	2430	1890	0.99
9	54	163	47.2	39.8	2330	2500	1510	1.10
10	41	152	52.4	44.1	2940	2350	1520	1.38
11	37	168	47.3	43.3	2090	2800	1450	1.06
12	38	165	55.0	46.2	2790	2440	1940	0.97
13	19	150	38.2	25.9	1620	1720	1280	0.97
14	48	155	36.8	30.3	1810	1470	1440	0.96
15	45	157	59.3	39.6	2270	2590	1810	0.94
16	28	160	52.6	43.6	2840	2780	1950	1.13
17	66	169	57.0	41.0	2400	2060	1380	1.53
18	42	179	63.4	45.3	2550	3030	2030	1.08
19	40	174	46.4	37.1	2100	2340	1630	1.01
20	46	163	61.7	35.8	2400	2300	1590	1.23

Exchangeable electrolytes in thyrotoxicosis. The complete data obtained in the thyrotoxic subjects are shown in Table V. It was found that all but two of the values for Na_e (Figure 10) and all but 4 of those for Cl_e (Figure 11) lay above the regression line for the normal group.

In the case of K_e, however, there was a more even distribution of values about the regression line (Figure 12). The observed values of the exchangeable electrolytes were reduced to a common value of lean body mass in both thyrotoxic and normal subjects by using the regression line for each group. In the case of Na_e the difference between the mean values of the thyrotoxic and normal subjects was found to be statistically significant ($p < 0.05$). No statistically significant difference was found for K_e ($f = 5.87$, $p < 0.05$) and Cl_e ($f = 3.92$, $p < 0.05$).

The ratio of sodium space to chloride space was calculated in these subjects and found to be 1.135. This value is just within 2 S.D. of the mean value obtained in the normal group.

In 10 of the 20 subjects the measurements of exchangeable electrolytes and lean body mass were repeated as soon as the patients had become euthyroid. The changes in Na_e and Cl_e showed no consistent pattern but in all but one case K_e rose.

FIGURE 10

Total exchangeable sodium plotted against lean body mass in thyrotoxic subjects also showing the regression line and its 95% confidence limits for normal subjects.

FIGURE 11

Total exchangeable chloride plotted against lean body mass in thyrotoxic subjects also showing the regression line and its 95% confidence limits for normal subjects.

FIGURE 12

Total exchangeable potassium plotted against lean body mass in thyrotoxic subjects also showing the regression line and its 95% confidence limits for normal subjects.

FIGURE 10.

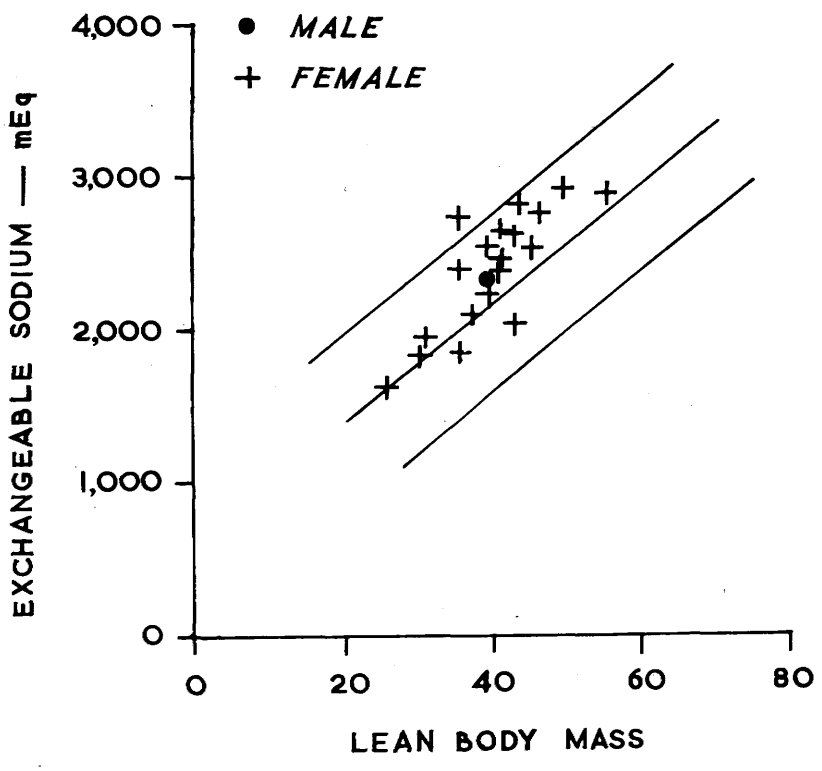

4,000
3,000
2,000
1,000
0
MALE
FEMALE
EXCHANGEABLE SODIUM — mEq
0
20
40
60
80
LEAN BODY MASS

FIGURE 11.

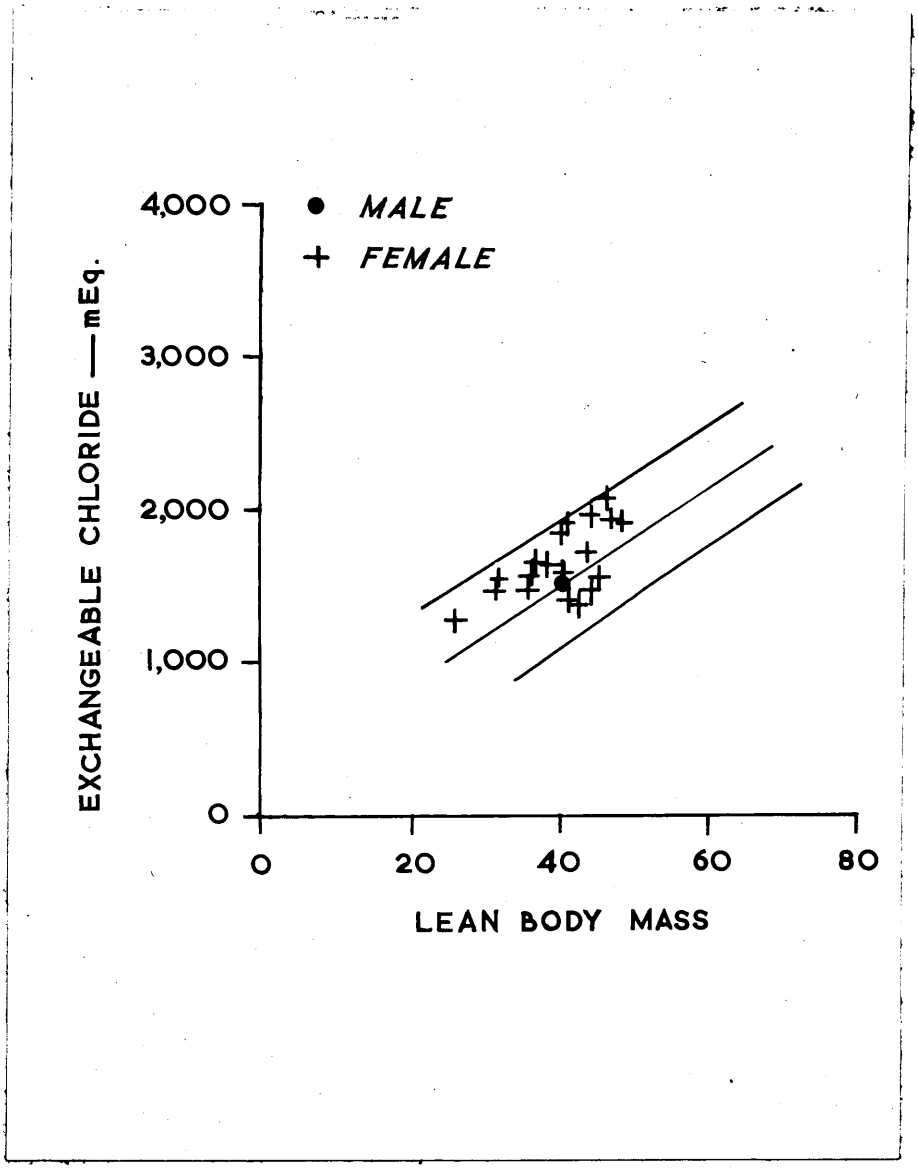
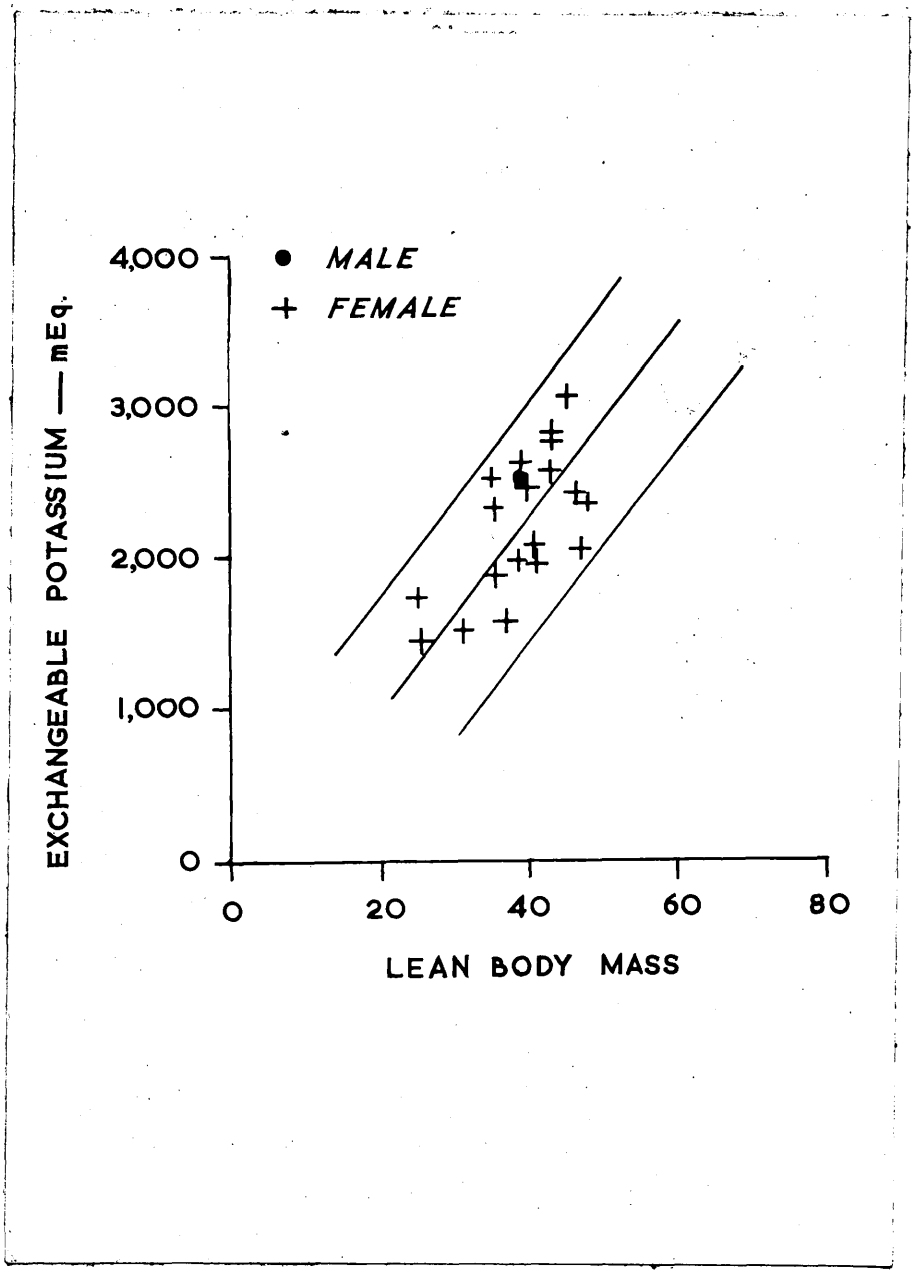

4,000
3,000
2,000
1,000
0
EXCHANGEABLE CHLORIDE — mEq.
MALE
FEMALE
0
20
40
60
80
LEAN BODY MASS

FIGURE 12.


4,000
3,000
2,000
1,000
0
MALE
FEMALE
EXCHANGEABLE POTASSIUM — mEq.
0
20
40
60
80
LEAN BODY MASS

Discussion

Exchangeable sodium. Miller and Wilson (1953), Forbes and Perley (1951), and Edelman et al. (1954) found no statistically significant difference in Na_e per Kg. body weight between males and females. The present series of normal subjects, however, shows a striking sex difference (Figure 4) which is accounted for by the inclusion of many obese females. Forbes and Lewis (1956) have shown by direct analysis that the sodium content of adipose tissue is low compared with that of the fat-free tissue. Hastings and Eichelberger (1957) also found that it was necessary to analyse fat-free muscle before consistent results could be obtained for the sodium content of different muscle samples. It might be expected, therefore, that Na_e per Kg. body weight would decrease as the proportion of depot fat increased. This effect is well illustrated by 2 of the normal subjects. One was a grossly obese female, with an Na_e of 27 mEq./Kg. body weight, this figure being lower than any of the published values for females. The other, a male subject, had an Na_e of 41 mEq./Kg. body weight. When expressed per Kg. lean body mass, the difference between those values was considerably reduced the values becoming 54 mEq./Kg. and 50 mEq./Kg. respectively. The findings, therefore, in conjunction with the evidence of direct tissue analysis, show that it is more accurate to predict Na_e from lean body mass than from body weight.

Munro et al.(1958) could not demonstrate any increase of Na_e in thyrotoxicosis before treatment because, in their own words, "the range of normal values is wide and in any condition in which weight has been altered it is of little value to compare the values as mEq. per Kg. of body weight with the range in health". By using lean body mass as a reference standard it has been possible to overcome this difficulty and the results of the present investigation show that there is in fact an increase in Na_e relative to lean body mass in this disease. This increase is probably due to the increase in plasma volume found in thyrotoxicosis by Gibson and Harris (1939). The increase in Na_e found in the present series is unlikely to be due to an associated increase in the Na_e of bone for reasons which will be discussed below. The fact that serum concentrations of sodium are normal in thyrotoxicosis (Werner, 1955) does not of course preclude an increase in total body content of the electrolyte.

Munro et al. (1958) also carried out serial measurements of Na_e in thyrotoxic patients undergoing treatment and found that the alterations did not follow any clear pattern. In the present investigation this finding was confirmed in 10 thyrotoxic patients in whom Na_e and lean body mass measurements were repeated as soon as they had

become euthyroid. This finding might be explained on the basis that treated thyrotoxic subjects do not return to metabolic normality when they reach the stage described by the clinician as the euthyroid state but remain in a condition of metabolic instability.

Excess exchangeable sodium of bone. The results show that the ratio of sodium space to chloride space in normal subjects is significantly greater than unity. This finding must be interpreted in the light of the available evidence on the distribution of sodium and chloride in body fluids and tissues (Figure 13). The sodium content of bone may be regarded as being divided into two parts, that contained in the extracellular fluid of bone, and that incorporated into the bone crystal itself (Robinson, 1952). The bone chloride, on the other hand, is confined to the extracellular fluid, where it is present along with sodium in the same ratio as in serum. Both ions in this compartment of bone are exchangeable. Bauer (1954) has shown by direct radioisotopic studies of rat bones that part of the sodium incorporated into the bone crystal is also rapidly exchangeable, and that it is in excess of the exchangeable chloride in bone. This excess of exchangeable sodium in bone is likely to lie at the surface of the bone crystal, where it would be in close contact with the extracellular fluid.

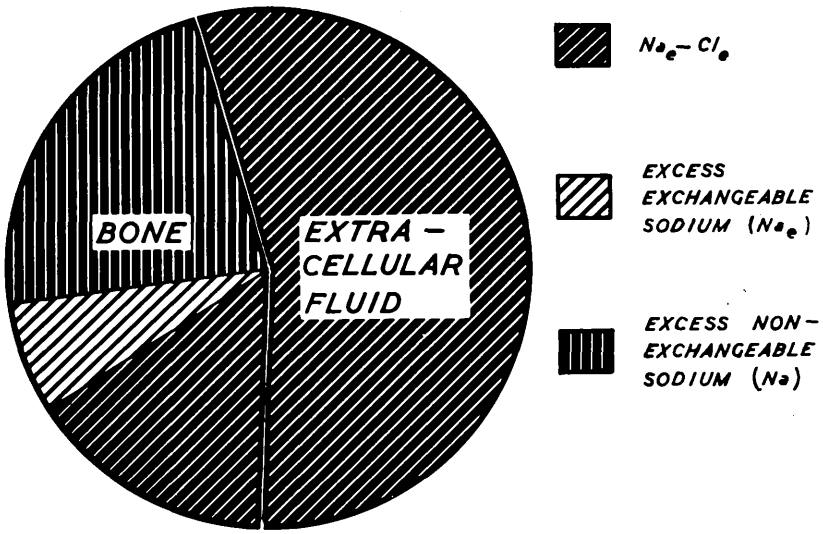
This finding that the ratio of sodium space to chloride space is significantly greater than unity therefore means

FIGURE 13

The distribution of sodium and chloride in bone and extracellular fluid.

FIGURE 13.

DISTRIBUTION OF SODIUM AND CHLORIDE



24 NORMAL SUBJECTS

$$\frac{\text{MEAN Na SPACE}}{\text{MEAN Cl SPACE}} = 1.179 \pm 0.024 \quad >1.0 \ (P<0.01)$$

that there is a pool of exchangeable sodium in excess of exchangeable chloride which is large enough to be detected by isotope dilution techniques. It seems probable from Bauer's work that the greater part of this excess is localised in bone although it is possible that a contribution is made by other tissue such as muscle (Harrison et al. 1936). Harrison (1937) has shown that the molar ratio of calcium to sodium in bone is the same in normal, rachitic and osteoporotic rats. It follows that disturbances in calcium metabolism might be associated with changes in the sodium of bone which might be demonstrable by an alteration in the ratio of sodium to chloride spaces.

Thyrotoxicosis is often associated with negative calcium balance and decalcification of bone (Aub et al. 1929). A close correlation has also been found between blood levels of protein-bound iodine and the ratio of calcium to creatinine in the urine (Crooks, Farrell, Macgregor and Nordin, unpublished data). The finding therefore that there is no significant change in the Na_e of bone, as reflected by the ratio of sodium space to chloride space suggests that either the relationship between calcium and sodium found by Harrison, does not hold in thyrotoxicosis or the ratio of sodium space to chloride space is not sensitive enough to detect small changes in the Na_e of bone. The fact that there is no significant difference in the ratio

of sodium space to chloride space between thyrotoxic and normal subjects also suggests that the increased Na_e in thyrotoxicosis is unlikely to be accounted for by an increase in bone sodium.

Exchangeable potassium. The correlation obtained between K_e and lean body mass is supported by experiments of other workers both in human subjects and in animals. Thus, Ikkos, Ljunggren, and Luft (1956) in Sweden as part of an investigation into the relation between extracellular and intracellular water in acromegaly, measured total body water and K_e in a control group of 33 normal subjects. From their data antipyrine space measurements were derived and, after correcting for the water content of plasma, lean body mass was estimated by means of the Pace-Rathbun formula. When this was done a regression line of K_e on lean body mass was obtained which has been included in Figure 7, the coefficient of the correlation being 0.92. This regression line lies within the 95% confidence limits of the present series, although a slight systematic difference is apparent. Carcass analysis in rats also provides direct evidence of a close correlation between total body potassium and lean body mass, (Cheek and West, 1955). The results obtained in the present series also provide a range of normal values much narrower than that given by body weight the 95% confidence limits being reduced from $\pm$53% of the mean to $\pm$ 25% of the mean as

well as eliminating the apparent sex difference due to the greater fat content of female subjects. They also allow a proper evaluation of the changes in K_e found in thyrotoxicosis, a disease in which, as previously pointed out, there are considerable changes in the proportions of lean tissue and fat.

The results obtained in the patients with thyrotoxicosis suggest that the diminution in potassium content in this disease shown by Danowski and Elkinton (1951) and Munro et al. (1958) can be wholly accounted for by a corresponding loss of lean tissue. In other words the change in body potassium is related directly to the diminution in cell mass. It is noteworthy that the mean value of the lean body mass in the thyrotoxic subjects of the present series was approximately 39 Kg. compared with a corresponding figure of 53 Kg. in the normal group. This finding accords well with the recognised negative nitrogen balance found in the condition.

Of 10 subjects in whom the measurements of K_e were repeated after treatment, the values increased in 9 and were associated with coincident increases in body weight. A similar finding was made by Munro et al. (1958) in 14 of 16 patients. This is confirmatory evidence of the close relationship between the changes in K_e and lean body mass found in the disease in view of the accepted

positive nitrogen balance and increase in lean tissue produced by treatment.

Exchangeable chloride. Weir (1940) has demonstrated that Cl_e is directly related to the lean carcass in dogs. This evidence suggests, therefore, that chloride is not present in depot fat. Forbes and Lewis (1956), however, have analysed two human cadavers and found an appreciable chloride content in adipose tissue. This appears to conflict with the results in the present normal series and with the data from animal studies quoted above. The discrepancy is, however, one of definition since the term depot fat, as used in the present study refers only to the lipid content of adipose tissue. Keys and Brozek (1953) estimate that lipids form 62%, water 31% and cell solids 7% of adipose tissue. These relative proportions of water and cell solids are similar to those obtained in muscle, and the non-lipid portion of adipose tissue is therefore included in the estimate of lean body mass derived from total body water. One would expect therefore that adipose tissue as a whole should contain a percentage of chloride in proportion to its non-lipid content. It is clear from the results obtained in the normal subjects of the present series that the relationship between Cl_e and lean body mass is closer than that between Cl_e and body weight and indeed the 95% confidence

limits of the former, $\pm$ 14% of the mean is narrower than those of Na_e or K_e.

Although ispection of Figure 11 suggests that there is an increase in Cl_e in thyrotoxicosis, which might be expected because of the increase in plasma volume found in the condition, the changes were not statistically significant. This may be due to the small number of cases studied. When measurements of Cl_e were repeated after treatment in 10 of the 20 subjects the same absence of any clear pattern was found as in the case of Na_e.

SECTION 2.

Summary

1. The correlations of total exchangeable sodium (Na_e), potassium (K_e) and chloride (Cl_e) with lean body mass is better than with body weight. In normal subjects it is the same for both males and females.

2. The ratio between sodium space and chloride space in normal subjects is significantly greater than unity and it is suggested that this is due to the excess of Na_e over Cl_e in bone.

3. In thyrotoxicosis Na_e increases relative to lean body mass whereas K_e remains unchanged. The relationship between sodium space and chloride space is undisturbed.

APPENDIX I

Clinical Diagnostic Index -- Recommendations for Use.

APPENDIX I

Clinical Diagnostic Index -- Recommendations for Use.

Symptoms

Questions requiring only positive or negative replies should be avoided and special care should be taken to ensure that the initial question about each symptom is not a leading one. Supplementary questions should always be asked and before a symptom is recorded as present these supplementary questions should confirm or clarify the initial answer. For example, in the case of temperature preference the patient should be asked first: "What type of weather do you prefer?" rather than "Do you prefer cold weather?". A suitable supplementary question would be "Do you feel comfortable or uncomfortable in a warm room?".

Only symptoms of recent onset or recently increased severity should be recorded with one exception. If preference for heat is present, irrespective of its duration, it should be regarded as significant since it is highly unusual in thyrotoxic patients. Where there is any doubt about the presence of a symptom it should not be recorded. The criteria for individual symptoms are as follows:

Dyspnoea on effort. The age of the patient should be taken into account. The symptom is only significant when it is of recent onset.

Palpitations are significant if they occur at rest or during moderate exercise. The age of the patient is relatively unimportant.

Tiredness refers to a feeling of unusual exhaustion after familiar physical effort and not to symptoms of psychogenic origin such as tiredness on first waking in the morning.

Temperature preference is of high diagnostic significance and the type of preference should be reached only after supplementary questions have been asked. Suitable ones elicit the presence of discomfort in a warm environment, the habit of sitting away from the fire and diminished use of hot water bottles.

Excessive sweating refers to both thermal and emotional sweating and the adjective "excessive" should be omitted from the initial question.

Nervousness. Questions should be asked about irritability, easy loss of temper, jumpiness and tenseness. The symptom is recorded only if these manifestations have shown a recent increase.

Appetite increase or decrease. The question "How is your appetite?" should be an enquiry as to whether it is regarded as less than normal, normal or excessive.

Weight increase or decrease should be definite, recent, progressive, and confirmed both by slackness or tightness of clothing, and by the opinion of friends or relatives. If the patient has kept records of weight an increase or decrease of 7 lbs. or more during a period of up to one year should be considered significant.

Signs

The following criteria must be fulfilled before a physical sign is recorded as present.

Palpable thyroid. The gland should be significantly enlarged and visible as well as palpable, except in the male, where any palpable thyroid tissue is considered abnormal.

Bruit over thyroid. The bruit should be high-pitched and systolic or to-and-fro, and to distinguish it from a venous hum it should be uninfluenced by rotation of the head or pressure on the neck veins.

Exophthalmos. Sclera should be seen between the lower lid and the iris of one or both eyes with the patient looking directly ahead.

Lid retraction. Sclera should be seen between the upper lid and the iris of one or both eyes with the patient looking directly ahead.

Lid lag. An area of sclera should increase or appear when the patient's eyes are fixed on the examiner's finger moving from above downwards. It should be noted that this criterion is more strict than that usually employed.

Hyperkinetic movements. The movements of removing and replacing clothing have to be unusually rapid and jerky, conveying an impression of over-reaction, wasted energy and clumsiness. It is the combination of rapidity and inaccuracy of movement which is significant.

Fine finger tremor. With the patient's eyes closed, the outstretched separated fingers should show a fine tremor.

Coarse tremor is ignored, but if doubt exists, the sign is recorded as present.

Warm, moist hands. The palms are compared with the hands of the examiner, taking into account the temperature of the environment and his normal vasomotor tone. They should be warmer than those of the examiner and a sensation of dampness should remain on his hands after withdrawal.

Casual pulse rate. This is counted for one minute at the end of the examination.

APPENDIX II

Definite Group

APPENDIX II

Definite Group - Non-toxic - 99 Cases

Case No.	Sex	Age	Diagnostic Index			4-hr. Uptake %	48-hr. P.B.I.^{131} %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
			Symptoms	Signs	Total						
1	M	23	-5	-11	-16	-	-	-	-	-	Normal subject
2	F	25	-3	-13	-16	-	-	-	-	-	" "
3	F	19	-5	-10	-15	-	-	-	-	-	" "
4	F	57	0	-13	-13	-	-	-4	72	-	Post-menopausal
5	F	37	-5	- 7	-12	28	0.29	-	-	-	Non-toxic goitre
6	F	20	-5	- 7	-12	-	-	-	-	-	Normal subject
7	F	20	-4	-8	-12	-	-	-	-	-	Normal subject
8	F	19	-5	- 6	-11	47.6	0.07	-1	60	222	Non-toxic goitre
9	M	28	0	-11	-11	-	-	-	-	-	Normal subject
10	F	19	+2	-13	-11	-	-	-	-	-	Normal subject
11	F	20	-5	- 6	-11	-	-	-	-	-	" "
12	F	20	0	-11	-11	-	-	-	-	-	" "
13	F	19	-3	- 7	-10	-	-	-	-	-	Non-toxic goitre
14	F	56	-1	-9	-10	-	-	-	-	-	Post-menopausal
15	M	27	0	-10	-10	-	-	-	-	-	Normal subject
16	M	29	0	-10	-10	-	-	-	-	-	" "
17	M	33	-5	- 5	-10	-	-	-	-	-	" "
18	F	19	-5	- 5	-10	-	-	-	-	-	" "
19	F	41	-1	- 8	- 9	-	-	-	-	-	Malig. exophthalmos
20	M	39	-5	- 4	- 9	-	-	-	-	-	Normal subject
21	M	21	-5	- 4	- 9	-	-	-	-	-	" "
22	F	44	-1	- 7	- 8	-	-	-	-	-	Anxiety state

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. Uptake %	48-hr. $P.B.I^{131}$ %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
23	F	44	-7	-1	-8	-	-	+1	68	-	Post-menopausal
24	M	68	0	-8	-8	-	-	-	-	-	Normal subject
25	M	53	-5	-3	-8	38	0	+3	76	292	" "
26	M	25	+2	-10	-8	-	-	-	-	-	" "
27	F	20	-5	-3	-8	-	-	-	-	-	" "
28	F	55	+3	-10	-7	33.2	0	-9	80	292	Post-menopausal
29	F	59	-1	-6	-7	19.0	-	-	-	-	" "
30	F	41	-2	-4	-6	31.2	0.34	+8	60	320	Non-toxic goitre
31	F	33	-3	-2	-5	39.4	0	-	-	240	" " " "
32	F	19	+1	-6	-5	29.5	0	+10	72	224	Anxiety state
33	M	44	+5	-10	-5	22.3	0	-17	68	284	" "
34	F	26	+2	-7	-5	33.6	0	+3	76	277	" "
35	F	66	+5	-10	-5	16.7	0.16	+12	68	344	Post-menopausal
36	M	34	+5	-10	-5	-	-	-	-	-	Normal subject
37	F	23	+5	-10	-5	-	-	-	-	-	" "
38	F	19	-5	0	-5	-	-	-	-	-	" "
39	F	19	-1	-4	-5	-	-	-	-	-	" "
40	F	20	-2	-3	-5	-	-	-	-	-	" "
41	F	32	0	-4	-4	29.0	0	-	-	-	Non-toxic goitre
42	F	55	+5	-9	-4	-	-	-	-	-	Post-menopausal
43	F	58	-4	0	-4	-	-	-	-	-	" "
44	M	37	0	-4	-4	-	-	-	-	-	Normal subject
45	F	22	0	-4	-4	-	-	-	-	-	" "
46	F	56	-2	-1	-3	27.8	0.03	+24	72	220	Non-toxic goitre
47	F	31	+1	-4	-3	41.8	0	-8	64	232	Goitre:Anx. state
48	F	21	+2	-5	-3	-	-	-	-	-	Anxiety state
49	F	51	+7	-10	-3	50.0	0.12	+14	60	222	Post-menopausal

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. I^{131} Uptake %	48-hr. I^{131} P.B.I %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
50	F	21	0	-2	-2	-	-	+8	76	237	Non-toxic goitre
51	F	30	-6	+4	-2	-	-	-	-	-	Anxiety state
52	F	47	+2	-4	-2	48.1	0.1	-7	67	240	Post-menopausal
53	F	26	+3	-5	-2	-	-	-	-	-	Normal subject
54	F	40	0	-1	-1	15.6	0.03	-	-	-	Non-toxic goitre
55	F	55	+6	-7	-1	29.2	0.12	-	-	-	Anxiety state
56	F	25	+3	-4	-1	36.6	0	-	-	-	" "
57	M	42	-1	0	-1	-	-	-	-	-	" "
58	F	20	+5	-6	-1	-	-	-	-	-	Normal subject
59	F	19	+2	-3	-1	-	-	-	-	-	" "
60	F	40	+2	-2	0	40.4	0.1	+1	80	208	Non-toxic goitre
61	F	27	+5	-5	0	33.9	0	+5	72	185	Anxiety state
62	F	19	0	0	0	-	-	-	-	-	Normal subject
63	F	21	+5	-5	0	-	-	-	-	-	" "
64	M	29	-1	+2	+1	29.2	0	+7	74	293	Anxiety state
65	F	25	+3	-2	+1	-	-	-	-	-	Normal subject
66	F	19	+6	-5	+1	-	-	-	-	-	" "
67	F	15	+1	+1	+2	-	-	-14	68	-	Anxiety state
68	F	42	+8	-6	+2	-	-	+11	74	287	Post-menopausal
69	F	21	-5	+7	+2	-	-	-	86	138	Normal subject
70	F	19	+3	-1	+2	-	-	-	-	-	" "
71	F	20	+8	-6	+2	-	-	-	-	-	" "
72	F	21	0	+2	+2	-	-	-	-	-	" "
73	F	21	+5	-2	+3	60.9	0	+2	72	130	Non-toxic goitre
74	F	44	+7	-4	+3	22.3	0	-10	76	280	" "

Case No.	Sex	Age	Diagnostic Index			4-hr. Uptake %	48-hr. P.B.I^{131} %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
			Symptoms	Signs	Total						
75	F	54	+4	-1	+3	23.8	0	+13	88	125	Post-menopausal
76	F	58	+7	-4	+3	34.6	0	-4	76	315	" "
77	F	20	+7	-3	+4	-	-	+9	70	277	Normal subject
78	F	44	+3	+2	+5	39.4	0.53	+14	60	335	Malig. exophthalmos
79	F	48	+5	0	+5	22.4	0	+10	56	202	Non-toxic goitre
80	F	19	0	+5	+5	34.3	0.09	-1	64	208	" "
81	F	29	+8	-3	+5	30.0	0	+9	68	175	Anxiety state
82	F	57	+2	+3	+5	-	-	-	-	-	" "
83	F	56	+5	0	+5	28.5	0.1	+3	66	265	Post-menopausal
84	F	48	+10	-5	+5	32.0	0.35	+10	-	314	" "
85	F	19	+6	-1	+5	-=	-	-	-	-	Normal subject
86	M	54	+9	-3	+6	-	-	-5	64	335	Anxiety state
87	F	21	+9	-3	+6	-	-	+6	-	240	Normal subject
88	F	20	+4	+2	+6	-	-	-	-	-	" "
89	F	42	+2	+5	+7	24.1	0.1	0	72	222	Anxiety state
90	F	26	+8	-1	+7	36.1	0	+8	80	277	Anxiety state
91	F	56	+5	+2	+7	-	-	+10	80	222	Post-menopausal
92	F	63	+8	-1	+7	-	-	-	-	-	" "
93	F	32	+13	-5	+8	41.9	1.52	+8	68	187	Malig. exophthalmos
94	F	33	+15	-7	+8	36.2	0	+13	64	112	Anxiety state
95	F	25	+6	+2	+8	-	-	-	-	-	" "
96	F	45	+12	-4	+8	23.0	0	-3	72	220	Post-menopausal
97	F	27	+7	+2	+9	42.2	0	+13	72	196	Anxiety state
98	F	19	+6	+3	+9	-	-	-	-	-	Normal subject
99	F	41	+5	+5	+10	65.1	0	+4	72	335	Non-toxic goitre

Definite Group - Toxic - 83 Cases

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. Uptake %	48-hr. $P.B.I.^{131}$ %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
100	F	35	+16	+5	+21	-	-	-	80	152	Diffuse goitre
101	M	54	+ 5	+17	+22	-	-	+30	92	172	" "
102	F	45	+11	+11	+22	57.8	1.03	+25	60	195	Nodular goitre
103	F	35	+7	+15	+22	-	-	+47	76	235	Diffuse goitre
104	M	70	+10	+13	+23	-	-	+33	84	208	Nodular goitre
105	F	38	+13	+10	+23	85.6	2.64	+8	88	151	Diffuse goitre
106	F	40	+13	+10	+23	92.6	0.55	+36	70	200	" "
107	F	35	+8	+15	+23	-	-	+21	80	198	" "
108	F	54	+14	+10	+24	-	0.5	-	-	163	" "
109	F	56	+13	+11	+24	58.3	1.55	-	-	164	Nodular goitre
110	F	44	+16	+8	+24	-	-	-	-	-	Diffuse goitre
111	F	41	+10	+15	+25	-	-	+57	81	143	" "
112	F	23	+11	+15	+26	77.7	1.7	+46	92	123	" "
113	F	35	+15	+11	+26	86.2	0.31	+21	80	255	Nodular goitre
114	M	33	+15	+11	+26	37.3	0.41	+37	76	203	Diffuse goitre
115	F	42	+16	+10	+26	82.7	1.71	+33	72	125	" "
116	F	54	+9	+18	+27	-	-	+50	84	167	Nodular goitre
117	F	38	+12	+15	+27	85.3	0.76	+12	84	209	Diffuse goitre
118	F	54	+12	+15	+27	76.2	0.47	+37	90	120	Nodular goitre
119	F	53	+11	+16	+27	-	-	-	-	-	Diffuse goitre
120	F	47	+17	+10	+27	96.6	1.64	+84	88	185	" "

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. Uptake %	48-hr. P.B.I^{131} %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
121	M	44	+12	+16	+28	-	-	+30	100	238	Diffuse goitre
122	F	28	+13	+15	+28	-	-	-	90	147	" "
123	M	52	+16	+12	+28	86.5	0.56	+58	78	209	" "
124	F	45	+11	+18	+29	92.8	1.49	+33	90	245	" "
125	F	34	+18	+11	+29	-	0.42	+29	80	213	" "
126	F	39	+12	+17	+29	82.5	1.7	+46	92	216	" "
127	M	69	+16	+13	+29	66.4	2.4	+41	80	262	Nodular goitre
128	F	46	+11	+19	+30	82.5	-	+17	84	203	Diffuse goitre
129	F	63	+15	+15	+30	46.0	0.76	+29	80	115	Nodular goitre
130	F	55	+10	+20	+30	76.6	1.9	-	-	222	" " (A.F.)
131	M	67	+10	+20	+30	85.5	3.92	-	96	117	Diffuse goitre
132	M	43	+21	+10	+31	82.1	1.6	+40	76	263	" "
133	F	43	+16	+15	+31	-	-	+48	84	167	" "
134	F	29	+15	+16	+31	-	-	+29	72	139	" "
135	F	48	+13	+18	+31	99.0	2.85	-	96	170	" "
136	F	50	+14	+17	+31	84.0	0.7	+42	-	145	Nodular goitre(A.F
137	F	24	+17	+14	+31	-	-	+43	76	175	Diffuse goitre
138	F	34	+16	+15	+31	-	-	-	85	203	" "
139	F	37	+18	+14	+32	-	-	-	93	98	Nodular goitre
140	F	47	+15	+17	+32	85.7	1.0	+43	70	111	" "
141	F	44	+18	+14	+32	87.9	1.7	+45	80	196	" "
142	F	34	+20	+12	+32	-	-	+92	90	253	Post-thyroidectomy
143	F	53	+12	+20	+32	89.0	2.59	+44	-	208	Nodular goitre(A.F

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. Uptake %	48-hr. P.B.I^{131} %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
144	F	45	+18	+15	+33	76.0	0.55	+39	68	112	Diffuse goitre
145	F	22	+21	+12	+33	86.0	1.79	+46	100	99	" "
146	F	42	+18	+15	+33	71.7	1.7	+21	88	160	Nodular goitre
147	F	37	+13	+20	+33	82.7	2.84	+65	70	97	Diffuse goitre
148	F	38	+18	+15	+33	94.7	1.64	+26	90	111	" "
149	F	46	+14	+19	+33	79.1	0.9	+52	96	130	" "
150	F	47	+15	+18	+33	-	-	+87	108	170	" "
151	M	50	+18	+15	+33	-	-	+27	76	245	Nodular goitre
152	F	39	+17	+16	+33	97.0	1.02	+26	100	263	" "
153	F	44	+21	+12	+33	93.7	2.96	+70	92	154	Diffuse goitre
154	F	55	+15	+18	+33	89.7	2.0	+42	-	222	Nodular goitre (A.F)
155	F	36	+12	+21	+33	72.9	-	+27	97	222	Diffuse goitre
156	F	27	+16	+18	+34	87.5	3.1	+33	92	203	" "
157	F	41	+18	+16	+34	95.6	0.58	+42	76	161	" "
158	F	30	+18	+16	+34	-	-	+47	100	245	" "
159	F	55	+18	+16	+34	-	-	+34	-	123	Nodular goitre (A.F)
160	F	45	+18	+16	+34	89.4	2.84	+45	88	-	Diffuse goitre
161	F	46	+18	+16	+34	96.5	2.06	+67	100	167	" "
162	F	47	+21	+13	+34	85.4	0.57	+71	-	120	" " (A.F)
163	F	24	+16	+19	+35	88.0	0.63	+45	93	231	" "
164	M	63	+21	+14	+35	85.2	2.0	+39	-	181	" " (A.F)
165	F	38	+18	+18	+36	76.5	3.7	+23	92	222	" "
166	F	53	+15	+21	+36	94.6	0.5	+46	85	156	Nodular goitre
167	F	32	+15	+21	+36	-	-	+60	80	222	Diffuse goitre
168	F	37	+15	+21	+36	86.5	3.82	+32	96	200	" "
169	M	70	+18	+19	+37	95.0	0.93	-	96	109	" "
170	F	28	+21	+16	+37	90.7	0.44	+76	94	98	" "

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. Uptake %	48-hr. P.B.I^{131} %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
171	F	37	+16	+21	+37	-	-	+44	90	196	Diffuse goitre
172	F	30	+18	+19	+37	92.5	2.2	+71	100	167	" "
173	F	33	+18	+20	+38	83.7	1.0	+32	95	98	" "
174	M	24	+21	+17	+38	-	-	-	-	-	" "
175	F	53	+20	+18	+38	71.0	1.6	-	80	222	" "
176	F	42	+21	+17	+38	-	-	+31	88	222	Nodular goitre
177	F	36	+21	+18	+39	82.6	2.6	+80	92	203	Diffuse goitre
178	F	34	+18	+21	+39	-	-	+23	80	128	" "
179	F	44	+21	+19	+40	85.0	2.94	+65	76	200	" "
180	M	34	+20	+21	+41	-	-	-	80	133	" "
181	M	39	+21	+20	+41	80.5	1.21	+64	72	145	Nodular goitre
182	F	52	+20	+22	+42	-	-	-	-	152	" " (A.F)

N.B. In all cases, except the normal subjects, where the results of radioactive iodine studies are not detailed the diagnoses were confirmed by the urinary excretion of radioactive iodine (T test).

A.F. = Auricular fibrillation.

APPENDIX III

Doubtful Group

APPENDIX III

Doubtful Group - Non-toxic - 67 cases

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. I^{131} Uptake %	48-hr. P.B.I^{131} %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
183	F	25	-3	-7	-10	17.5	0.07	-	-	-	Anxiety state
184	F	37	-3	-7	-10	37.8	0.15	-	-	-	" " -goitre
185	F	35	-4	-4	-8	23.0	0.1	-1	68	300	" "
186	F	45	-3	-4	-7	32.0	0.16	+4	68	370	" " -goitre
187	M	24	0	-7	-7	11.8	0	-	-	-	" "
188	M	39	-1	-5	-6	25.5	0.2	+2	69	225	Non-toxic goitre
189	F	39	+2	-7	-5	46.0	0.11	-	-	-	Anxiety state-goitre
190	F	22	-3	-2	-5	30.0	0.05	-	-	-	Non-toxic goitre
191	F	34	+3	-7	-4	23.0	-	-15	68	264	" "
192	F	39	+7	-11	-4	39.6	0	-14	80	196	Anxiety state
193	F	25	+3	-7	-4	25.0	-	-5	80	277	Non-toxic goitre
194	M	45	+6	-10	-4	14.5	0.07	+1	68	222	Anxiety state
195	F	33	-5	+3	-2	26.6	0.17	+6	72	253	" " -goitre
196	F	67	+1	-3	-2	61.3	1.65	-10	68	215	" " -goitre
197	F	33	+5	-7	-2	20.4	0.03	+2	80	174	" "
198	F	52	+5	-6	-1	28.5	0.17	+4	68	167	" "
199	F	20	0	-1	-1	-	-	+11	70	185	Non-toxic goitre
200	F	30	+7	-7	0	33.0	0	-	-	-	Anxiety state
201	F	38	+1	-1	0	15.1	0	-	-	-	" "
202	F	32	-3	+4	+1	16.8	0.07	+27	72	165	" " - goitre

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. Uptake %	48-hr. ^{131}I P.B.I %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
203	F	36	+5	-4	+1	30.8	0	+17	74	202	Non-toxic goitre
204	F	31	+8	-7	+1	33.1	0.13	-18	76	215	Anxiety state -goitre
205	F	22	+7	-5	+2	37.0	0	-6	84	225	Anxiety state
206	F	33	-6	+8	+2	83.0	0.49	-	-	-	" " -goitre
207	F	27	-1	+3	+2	39.4	0	-	-	-	Non-toxic goitre
208	F	56	+5	-3	+2	-	0.52	+47	68	238	Anxiety state
209	F	33	+6	-4	+2	34.0	0.08	+3	60	225	" " -goitre
210	F	56	+4	-2	+2	35.1	0.1	+11	64	320	" "
211	F	67	+5	-2	+3	44.0	0.65	+5	70	396	Post-menopausal
212	F	44	+4	-1	+3	40.0	0.08	-2	76	220	Anxiety state
213	F	35	-3	+7	+4	32.9	0.37	+8	60	208	" " -goitre
214	M	56	+2	+2	+4	-	0	-	-	-	" "
215	F	50	-3	+7	+4	17.0	0	-	-	-	Malig. exophthalmos
216	F	46	-1	+5	+4	30.3	0	-9	68	238	Anxiety state
217	F	83	+5	0	+5	39.4	0.1	-	-	-	Anxiety state (A.F)
218	F	35	+8	-3	+5	34.2	0	-	-	-	" " -goitre
219	M	53	+9	-4	+5	26.6	0.13	-	-	-	" "
220	F	34	+3	+2	+5	50.7	0.31	+23	72	196	Non-toxic goitre
221	F	49	+9	-3	+6	-	-	+7	60	152	Anxiety state -goitre
222	F	58	+12	-6	+6	34.6	0.06	-	-	-	" "
223	M	31	0	+6	+6	29.4	0	-	-	-	Non-toxic goitre
224	F	46	+7	-1	+6	24.2	0.1	-	-	-	Anxiety state -goitre
225	F	35	+6	+1	+7	14.0	0	-	-	-	" " "
226	F	36	+2	+5	+7	30.7	0.18	+6	72	242	" " "
227	F	46	+8	-1	+7	36.7	0.16	-	-	-	" " "
228	F	43	+7	+1	+8	34.1	0.1	+8	76	200	" " "
229	F	39	+10	-2	+8	20.0	0	-	-	-	" " "

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. Uptake %	48-hr. P.B.I^{131} %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
230	F	22	+4	+5	+9	37.5	0.06	-	-	-	Anxiety state-goitre
231	M	42	+10	-1	+9	14.0	0.08	-	-	-	No goitre (A.F)
232	F	42	+9	0	+9	73.8	0.28	+17	80	167	Anxiety state-goitre
233	F	33	+15	-6	+9	15.3	0	-	-	-	" " "
234	F	33	+9	0	+9	37.8	0.2	-	-	-	" " "
235	F	34	+6	+3	+9	11.5	0.13	+12	80	207	" " "
236	F	43	+14	-4	+10	26.0	0.24	-	-	-	" " "
237	F	66	+12	-2	+10	45.8	0	+14	70	205	Non-toxic goitre
238	M	62	+11	-1	+10	26.7	0.14	-	-	-	Anxiety state-exophth.
239	F	72	+8	+2	+10	16.1	0	-	-	-	" " -goitre
240	F	62	+16	-6	+10	24.5	0.22	-	-	-	" "
241	F	34	+8	+2	+10	36.4	0.4	-4	72	205	Post-thyroidectomy
242	F	52	+9	+2	+11	29.0	0.09	+8	74	230	Anxiety state-goitre
243	F	20	+12	-1	+11	62.4	0	+3	72	235	" " "
244	F	37	+7	+5	+12	35.0	0	0	68	245	" " "
245	F	49	+10	+2	+12	45.0	0.09	+9	64	270	" "
246	F	46	+7	+6	+13	40.0	0	+3	72	309	" " "
247	F	72	+12	+1	+13	17.3	0	-4	78	256	" " "
248	F	36	+13	+5	+18	18.5	0	+7	64	170	" " "
249	F	34	+16	+11	+27	41.7	0.17	+6	72	195	Post thyroidectomy

APPENDIX III

Doubtful Group - Toxic - 51 cases

Case No.	Sex	Age	Diagnostic Index			4-hr. Uptake %	48-hr. P.B.I ^{131} %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
			Symptoms	Signs	Total						
250	F	45	+2	+12	+14	84.9	0.63	+65	80	83	Post thyroidectomy
251	F	52	+5	+11	+16	65.8	0.68	+4	64	242	Diffuse goitre
252	F	51	+7	+10	+17	50.5	0.44	+29	76	149	" "
253	F	47	+16	+2	+18	62.3	0.29	+20	88	220	Nodular goitre
254	M	50	+14	+5	+19	65.0	0.9	+20	72	232	Post ^{131}I therapy
255	F	34	+9	+10	+19	71.0	1.05	+28	87	149	Diffuse goitre
256	F	62	+12	+8	+20	64.5	0.7	+10	72	281	" "
257	F	56	+13	+7	+20	98.0	0.8	+4	64	158	Nodular goitre
258	F	55	+18	+2	+20	69.0	0.3	+14	64	167	Diffuse goitre
259	M	61	+10	+10	+20	90.7	2.53	+64	-	141	Nodular goitre (A.F)
260	F	20	+6	+14	+20	68.6	1.2	-	-	-	Diffuse goitre
261	F	25	+8	+12	+20	81.7	0.85	+29	80	175	" "
262	F	19	+9	+12	+21	-	-	-	-	-	" "
263	F	36	+15	+6	+21	99.0	1.2	-	-	-	No goitre
264	M	67	+14	+7	+21	-	-	+26	-	163	Diffuse goitre (A.F)
265	F	47	+10	+11	+21	62.4	1.29	+4	84	175	" "
266	F	51	+15	+6	+21	50.2	1.4	+64	68	150	Nodular goitre
267	M	67	0	+21	+21	83.0	4.25	+76	70	105	Diffuse goitre
268	F	36	+10	+11	+21	63.0	0.06	+22	68	222	Nodular goitre
269	F	70	+7	+14	+21	48.4	0.46	-	-	115	" " (A.F)
270	F	57	+15	+7	+22	80.3	0.86	+27	72	208	" "
271	M	52	+19	+3	+22	86.4	0.6	-	76	222	" "
272	M	41	+16	+6	+22	42.0	0.3	+21	80	167	Diffuse goitre

Case No.	Sex	Age	Diagnostic Index Symptoms	Signs	Total	4-hr. Uptake %	48-hr. ^{131}I B.P.I %	B.M.R. %	S.P.R. /min.	Chol. mg.%	Comments
273	F	31	+10	+12	+22	41.1	0.78	+3	80	222	Diffuse goitre
274	M	48	+19	+3	+22	73.0	0.5	-	-	-	Nodular goitre
275	F	72	+9	+14	+23	70.0	0.7	+15	92	238	" "
276	M	39	+13	+10	+23	79.5	2.1	+28	70	185	Post thyroidectomy
277	M	51	+11	+12	+23	75.1	2.7	+35	84	175	Diffuse goitre
278	F	56	+7	+16	+23	73.2	0.4	+22	72	-	" "
279	F	44	+17	+7	+24	84.3	0.56	+34	78	173	" "
280	F	35	+15	+9	+24	59.3	0.94	+22	68	137	Nodular goitre
281	F	49	+12	+12	+24	79.0	3.1	+38	86	203	" "
282	M	63	+14	+10	+24	67.6	1.1	+11	-	200	No goitre (A.F)
283	F	56	+11	+13	+24	84.8	0.84	-	-	-	Nodular goitre
284	F	26	+16	+8	+24	66.3	1.53	+12	70	185	Diffuse goitre
285	F	54	+18	+7	+25	78.0	2.4	-	-	-	Nodular goitre
286	F	57	+13	+13	+26	76.4	2.45	+19	92	249	Diffuse goitre
287	F	32	+15	+12	+27	80.4	0.56	+12	80	139	" "
288	F	41	+18	+9	+27	60.0	0.4	+8	68	130	" "
289	F	31	+21	+7	+28	68.0	2.46	+29	92	225	Post-thyroideotomy
290	F	37	+7	+21	+28	19.0	0.3	+41	72	170	Nodular goitre
291	F	49	+14	+14	+28	80.8	1.3	+34	68	179	" "
292	F	39	+12	+18	+30	91.9	0.6	+20	80	111	Diffuse goitre
293	F	43	+14	+16	+30	46.5	0.49	+37	100	-	" "
294	F	51	+16	+15	+31	46.6	0.77	+26	80	-	Nodular goitre
295	M	50	+15	+16	+31	76.2	3.0	+19	84	268	" "
296	F	50	+11	+20	+31	70.0	1.94	+32	80	242	No goitre
297	F	25	+15	+17	+32	56.0	0.7	-	70	119	Diffuse goitre
298	F	57	+21	+12	+33	-	-	+24	68	-	Nodular goitre
299	F	58	+18	+16	+34	81.5	2.49	-	92	133	" "
300	F	34	+19	+15	+34	-	-	+53	86	137	Diffuse goitre

N.B. In all cases where the results of radioactive iodine studies are not detailed the diagnoses were confirmed by the urinary excretion of radioactive iodine (T-test).

A.F. = Auricaulr fibrillation.

APPENDIX IV

Series 1 -- Therapeutic Indices

APPENDIX IV

THERAPEUTIC INDEX -- SERIES 1 -- POTASSIUM PERCHLORATE (600 mg. Daily)

Case No.	Week 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1	20	20	19	16	-	10	5	4	1															
2	21	17	-	13	14	13	7	11	10	4	5	2												
3	24	21	20	17	11	8	4	0																
4	20	20	19	20	20	19	20	20	20	11	13	13	14	16	10	9	9	9	3					
5	31	31	29	28	20	12	13	9	14	6	13	11	4											
6	20	18	18	18	16	16	12	8	2															
7	31	31	31	29	29	28	28	26	25	-	25	23	26	11	11	13	6	4	3					
8	24	21	19	21	9	10	-	-	13	8	10	15	15	17	15	10	10	9	10	10	9	2		
9	23	23	23	23	23	23	23	20	22	11	8	12	10	8	3									
10	32	32	30	32	32	28	23	23	13	9	3	1												
11	29	-	-	21	18	-	8	3																
12	31	30	27	27	-	14	12	-	7	5	5	-	6	5	4									
13	28	28	27	27	24	25	-	11	10	11	10	8	5	2										
14	31	31	25	17	14	-	-	6	3	2														
15	29	29	25	24	21	17	13	23	18	16	16	-	14	12	19	-	19	13	9	12	12	10	10	1
16	31	31	29	26	11	9	-	4	6	3														
17	21	21	15	9	8	9	8	8	6	5	7	2												
18	31	-	-	27	27	-	27	19	22	22	-	24	22	-	19	17	-	-	12	5	3			
19	25	22	18	16	12	5	6	9	0															
20	31	-	29	22	19	10	10	8	7	3														

APPENDIX IV

THERAPEUTIC INDEX -- SERIES 1 -- METHYL THIOURACIL

Case No. \ Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
21	28	28	25	25	24	23	18	20	3	0						
22	15	15	15	15	14	8	7	7	6	3						
23	28	18	-	15	18	7	10	10	7	2						
24	25	22	17	20	18	14	13	15	13	13	7	5				
25	25	25	25	25	24	23	23	23	18	13	10	8	8	9	3	0
26	24	24	21	19	10	8	7	6	5	5	2					
27	32	32	31	21	20	13	10	1								
28	20	20	20	-	20	20	20	10	9	7	1					
29	32	32	27	20	10	16	8	8	7	3						
30	31	-	-	22	19	17	23	21	8	5						
31	31	31	21	18	13	11	7	5	8	3						
32	18	12	12	12	11	6	2									
33	23	17	14	13	-	12	2									
34	31	18	14	12	4											
35	32	30	23	14	10	3										
36	22	18	15	-	-	11	10	2								
37	25	25	24	13	13	7	9	6	6	2						
38	20	20	12	9	13	13	3	6	4	1						
39	32	26	21	17	14	13	5	6	3							
40	23	13	8	9	7	6	3	2								

APPENDIX V

Series 1 -- Basal metabolic rates

APPENDIX V

POTASSIUM PERCHLORATE -- SERIES 1 -- BASAL METABOLIC RATE ESTIMATIONS

Case No.	Week 0	2	4	6	8	10	12	14	16	18	20	22
1	+75	+57	+ 8	+ 9	-	-	-	-	-	-	-	-
2	+27	+19	+18	+ 6	-14	- 3	- 6	-	-	-	-	-
3	+20	+22	+ 3	+14	-	-	-	-	-	-	-	-
4	+47	+50	+58	+36	+32	+35	+23	+36	+12	+ 9	-	-
5	+21	+18	+14	+ 7	+10	-	+ 4	-	-	-	-	-
6	+28	+ 5	- 8	+ 7	+ 2	-	-	-	-	-	-	-
7	+32	+39	+36	+ 5	0	-	- 7	- 9	- 7	-21	-	-
8	+ 8	+13	+10	-	+ 9	+ 2	-16	-18	-20	-15	-13	
9	+67	+45	+40	+44	+47	+16	-	+14	-	-	-	-
10	+76	+65	+45	+26	+19	- 3	-	-	-	-	-	-
11	+40	-	+16	+ 8	-	-	-	-	-	-	-	-
12	+60	+44	-	+30	+21	-	+16	+ 8	-	-	-	-
13	+46	+66	-	+18	+ 1	+20	-	+14	-	-	-	-
14	+26	+ 3	-	- 5	- 9	-	-	-	-	-	-	-
15	+33	+37	+32	+11	+18	-	- 6	-	+12	-10	+11	- 5
16	+17	0	- 8	-12	-17	-	--	-	-	-	-	-
17	+42	-	+39	+20	+11	+ 3	-	-	-	-	-	-
18	+20	-	+10	+31	0	+10	+25	+20	-	0	-	-
19	+13	+10	- 4	- 6	-12	-	-	-	-	-	-	-
20	+16	+13	+14	+ 8	- 1	-	-	-	-	-	-	-

APPENDIX V

METHYL THIOURACIL -- SERIES 1 -- BASAL METABOLIC RATE ESTIMATIONS

Case No.	Week 0	2	4	6	8	10	12	14
21	+22	+22	+35	+17	-14	-	-	-
22	+74	+20	+38	+20	+21	-17	+ 7	-
23	+45	-	+39	+22	+21	-14	-	-
24	+27	+19	+14	-12	-13	+10	-	-
25	+51	+47	+31	-	+31	+ 5	- 6	+ 6
26	+84	+47	+40	+34	+ 8	-14	-	-
27	+71	+46	+11	- 5	-	-	-	-
28	+36	+18	- 5	+12	-	-13	-	-
29	+54	+30	+12	+16	- 8	-	-	-
30	+23	+18	-14	-20	-14	-	-	-
31	+42	+20	+20	+10	+ 8	-	-	-
32	+71	+ 8	- 6	- 4	-	-	-	-
33	+17	+18	+ 2	-13	-	-	-	-
34	+41	+ 5	+ 8	-	-	-	-	-
35	+65	+28	+ 2	-	-	-	-	-
36	+47	+37	+18	+ 8	-	-	-	-
37	+46	+22	+ 8	- 1	- 8	-	-	-
38	+43	+44	+42	+15	- 2	-	-	-
39	+47	+37	+24	+17	+ 1	-	-	-
40	+53	+30	+17	+ 4	-	-	-	-

APPENDIX VI

Series 1 -- Serum cholesterol estimations

APPENDIX VI

POTASSIUM PERCHLORATE -- SERIES 1 -- SERUM CHOLESTEROL ESTIMATIONS

Case No.	Week 0	2	4	6	8	10	12	14	16	18	20	22
1	143	355	238	222	-	-	-	-	-	-	-	-
2	177	196	189	196	222	223	-	-	-	-	-	-
3	167	149	222	194	-	-	-	-	-	-	-	-
4	170	167	152	138	109	123	111	142	228	165	-	-
5	160	159	148	167	133	136	208	-	-	-	-	-
6	149	159	158	185	167	-	-	-	-	-	-	-
7	98	92	111	222	233	-	254	303	238	256	-	-
8	130	222	239	-	233	268	320	-	303	278	330	-
9	231	254	-	-	268	314	333	273	-	-	-	-
10	98	110	175	189	218	220	-	-	-	-	-	-
11	263	-	209	348	-	-	-	-	-	-	-	-
12	222	208	-	248	278	-	268	-	-	-	-	-
13	216	175	-	238	187	175	204	-	-	-	-	-
14	111	139	-	140	173	-	-	-	-	-	-	-
15	203	196	177	196	196	222	167	-	173	267	267	251
16	190	-	265	-	340	-	-	-	-	-	-	-
17	140	-	174	191	175	217	-	-	-	-	-	-
18	190	-	175	159	181	-	188	139	-	180	-	-
19	250	175	191	282	314	-	-	-	-	-	-	-
20	117	138	151	213	-	-	-	-	-	-	-	-

APPENDIX VI

METHYL THIOURACIL -- SERIES 1 -- SERUM CHOLESTEROL ESTIMATIONS

Case No. \ Week	0	2	4	6	8	10	12	14
21	128	245	172	249	333	-	-	-
22	213	231	370	397	347	278	315	-
23	156	-	208	245	257	196	-	-
24	222	242	228	274	303	292	-	-
25	130	214	222	208	228	264	245	304
26	123	158	-	438	440	461	-	-
27	99	109	163	463	-	-	-	-
28	200	208	333	347	370	-	-	-
29	208	-	333	450	346	-	-	-
30	222	-	279	272	314	-	-	-
31	161	196	208	222	213	-	-	-
32	151	238	347	439	-	-	-	-
33	203	387	-	370	-	-	-	-
34	167	203	282	-	-	-	-	-
35	200	256	347	-	-	-	-	-
36	235	256	-	257	-	-	-	-
37	160	206	303	277	334	-	-	-
38	222	287	256	225	248	-	-	-
39	123	141	153	151	154	-	-	-
40	139	203	152	165	-	-	-	-

APPENDIX VII

Series 2 -- Therapeutic Indices.

APPENDIX VII

THERAPEUTIC INDEX -- SERIES 2

RELAPSED AFTER POTASSIUM PERCHLORATE (600 mg. daily) -- TREATED WITH METHYL THIOURACIL

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Case No.																							
7	22	22	20	21	20	22	9	7	9	4	1												
10	29	26	24	18	15	11	13	10	7	2													
11	22	-	11	6	1																		
9	22	22	22	22	22	15	13	1															
13	26	25	26	26	19	25	25	16	16	11	11	14	12	9	3								
14	27	-	12	6	0																		

RELAPSED AFTER METHYL THIOURACIL -- TREATED WITH POTASSIUM PERCHLORATE (600 mg. daily)

21	17	17	10	-	6	5	4	7	3	6	2	2	1										
22	16	16	16	12	14	13	6	11	5	4	3												
23	24	24	24	24	21	20	18	13	12	15	12	13	12	14	8	9	10	8	6	7	7	5	1
24	22	21	21	19	19	16	8	8	9	0													
25	29	29	29	-	-	22	20	20	18	15	10	10	5	5	-	-	10	9	5	-	6	6	1
26	25	25	23	-	12	9	-	13	21	21	7	6	3										
27	28	28	24	22	25	25	25	26	27	20	19	19	19	11	11	10	4						
33	21	21	18	11	6	5	0																

APPENDIX VIII

Series 3 — Therapeutic Indices

APPENDIX VIII

THERAPEUTIC INDEX -- SERIES 3 -- CARBIMAZOLE

Week	0	2	4	6	8	10	12	14	16	18	20	22
Case No.												
41	32	27	21	12	5	3	2					
42	32	29	28	16	11	0						
43	19	14	6	7	1							
44	25	22	16	19	13	8	14	11	12	7	5	3
45	32	27	14	-	15	13	11	9	7	1		
46	28	24	16	5	5	0						
47	23	21	9	10	5	5	3					
48	27	22	18	11	10	5	6	1				
49	32	28	15	13	4	2	1					
50	22	15	15	13	14	14	14	11	7	5		
51	28	23	16	10	1							
52	20	16	16	12	9	6	0					
53	23	16	15	9	12	-	10	1				
54	18	17	14	3	0							
55	31	29	23	5	2							
56	27	20	10	9	9	6	7	2				
57	27	22	20	4	3							
58	30	27	27	27	26	18	10	17	17	4	5	3
59	26	24	-	6	1							
60	24	20	9	4	3							

APPENDIX VIII

THERAPEUTIC INDEX -- SERIES 3 -- POTASSIUM PERCHLORATE (1,000 mg. daily)

Case No. \ Week	0	2	4	6	8	10	12	14	16	18	20
61	29	17	17	7	1						
62	26	26	23	14	5	3					
63	21	18	6	0							
64	28	25	17	9	1						
65	21	6	4	0							
66	31	22	11	3							
67	18	13	8	3							
68	27	27	22	7	8	7	7	2			
69	17	17	14	0							
70	23	12	6	6	5	3					
71	27	23	22	25	25	18	12	2	1		
72	31	24	6	3							
73	24	24	19	5	5	2					
74	23	20	16	15	15	1					
75	25	23	21	14	13	5	4				
76	31	21	19	21	20	18	14	5			
77	28	19	18	4							
78	31	27	12	2							
79	28	27	26	12	2						
80	28	28	28	17	27	20	11	9	10	9	2

APPENDIX IX

Series 1 -- Urinary Iodide

APPENDIX IX

POTASSIUM PERCHLORATE -- URINARY IODIDE

Case No.	Time to "cure" (weeks)	Urinary Iodide			
		(-)	(+)	(++)	Total
1	8	2	1	-	3
2	11	-	4	1	5
3	7	-	3	2	5
4	18	1	7	3	11
5	12	2	3	1	6
6	6	3	-	1	4
7	18	-	6	1	7
8	21	4	3	1	8
9	14	-	3	3	6
10	11	-	4	1	5
11	7	-	2	-	2
12	14	2	2	-	4
13	13	5	1	-	6
14	9	3	-	-	3
15	23	4	3	-	7
16	9	1	2	-	3
17	11	-	3	-	3
18	20	1	3	1	5
19	8	1	2	-	3
20	9	2	2	-	4
	Total	31	54	15	100

APPENDIX IX

METHYL THIOURACIL -- URINARY IODIDE

Case No.	Time to "cure" (weeks)	Urinary Iodide			
		(-)	(+)	(++)	Total
21	9	2	1	1	4
22	12	-	1	5	6
23	11	-	3	1	4
24	11	-	3	2	5
25	15	-	4	2	6
26	11	-	2	3	5
27	7	-	2	2	4
28	10	-	-	4	4
29	9	-	2	1	3
30	9	-	2	1	3
31	9	-	2	2	4
32	6	1	1	1	3
33	6	1	1	-	2
34	4	1	-	1	2
35	5	-	-	-	2
36	7	-	2	-	2
37	9	-	2	1	3
38	9	-	3	-	3
39	8	-	1	2	3
40	7	-	-	2	2
	Total	5	33	32	70

APPENDIX X

Series 1 -- Exophthalmos

APPENDIX X

POTASSIUM PERCHLORATE — DEGREE OF EXOPHTHALMOS (mm)

Case No.	Euthyroid	End of 3 Months Maintenance Therapy	After Therapy
1	+4	+2.5	+3.5
2	+2	+2	0
3	+1	-0.5	-1
5	-2	-2	-2
6	+4	+4	+4
7	+4	+4	0
11	0	+2	-1
14	0	+3.5	+3
15	+2.5	+1	+0.5
16	+4	+4	+2
17	+1	+1	0
18	-1	-2	-2
Total	+19.5	+19.5	+7
Mean	+ 1.62	+ 1.62	+0.58

METHYL THIOURACIL -- DEGREE OF EXOPHTHALMOS (mm.

Case No.	Euthyroid	End of 3 Months Maintenance Therapy	After Therapy
21	+3	+3	+3
22	+1	+2	-0.5
23	+1	+1	0
24	+1	+3	+2
25	+4	+4	+2
26	+2	+3	+3
31	-2	+2	+0.5
32	0	+2	0
33	+3	+3	+2
36	+2	+8.5	+6.5
37	+4	+2.5	+0.5
40	+4	+5	+0.5
Total	+23	+39	+19.5
Mean	+1.92	+3.25	+1.62

APPENDIX XI

Results of Radioactive Iodine Therapy -- Group 1

APPENDIX XI

RESULTS OF RADIOACTIVE IODINE THERAPY -- GROUP 1 (28 cases)

Case No.	Sex	Age	Gland Type	Gland Size(G)	48-hr. Uptake ^{131}I %dose	Initial Therapy dose ^{131}I m/c.	Calculated dose (Blom-field et al) m/c.	No. of doses given	1 year after first dose	Remarks
1	F	55	D	50	-	8	-	1	Euthyroid	-
2	F	56	N	50	-	7	-	2	Minimally toxic	Euthyroid/18 months
3	F	70	D	50	-	7	-	1	Euthyroid	-
4	M	68	N	60	-	8	-	3	Minimally toxic	Euthyroid/18 months
5	F	42	D	75	-	8	-	2	" "	" " "
6	M	63	D	75	-	8	-	5	" "	Minimally toxic/18mths.
7	F	54	D	75	75	7	10.5	2	Euthyroid	-
8	F	23	P.T	35	75	6	4	1	Euthyroid	-
9	M	34	D	55	79	7	6	2	"	-
10	F	58	D	40	-	6	-	2	"	-
11	F	56	N	60	60	8	10	2	Mildly toxic	Myxoedema/18 months
12	F	55	D	55	70	7	7	3	Minimally toxic	Euthyroid/18 months
13	F	44	D	85	74	8	10	4	" "	" " "
14	M	60	D	50	45	7	7.5	1	Euthyroid	-
15	M	50	P.T	50	46	7	7.5	4	Minimally toxic	Euthyroid/18 months
16	F	48	P.T	50	66	5	5	3	Euthyroid	-
17	F	37	D	75	56	5	10.5	1	"	-
18	F	45	D	50	85	5	5.5	1	"	-
19	M	54	D	150	67	15	19	4	Minimally toxic	Euthyroid/18 months
20	M	51	D	25	60	5	4	2	Euthyroid	-
21	F	38	N	60	65	8	7	2	"	-
22	M	50	D	100	-	11	-	2	"	-
23	F	46	N	70	72	9	9.5	1	Myxoedema	-

RESULTS OF RADIOACTIVE IODINE THERAPY -- GROUP 1 (28 cases)

Case No.	Sex	Age	Gland Type	Gland Size(G)	48-hr. Uptake ^{131}I %dose	Initial Therapy dose ^{131}I m/c.	Calculated dose(Blom-field et al) m/c.	No. of doses given	1 year after first dose	Remarks
24	M	46	D	50	60	8	7	4	Minimally toxic	Euthyroid/18 months
25	F	55	D	25	74	5	3.5	1	Euthyroid	-
26	F	50	D	125	65	12	17.5	6	Minimally toxic	Minimally toxic/18 mth
27	F	43	D	50	75	7	6	1	Euthyroid	-
28	M	51	N	75	70	9	10	4	"	-

D = diffuse; N = nodular; P.T. = post-thyroidectomy.

APPENDIX XII

Results of Radioactive Iodine Therapy -- Group 2

APPENDIX XII

RESULTS OF RADIOACTIVE IODINE THERAPY -- GROUP 2 (45 cases)

Case No.	Sex	Age	Gland Type	Gland Size(G)	48-hr. Uptake ^{131}I %dose	Initial Therapy dose ^{131}I m/c.	Calculated dose(Blom-field et al) m/c.	No. of doses given	1 year after first dose	Remarks
29	F	55	N	50	-	7	-	3	Minimally toxic	Euthyroid/18 months
30	M	64	D	25	-	6	-	1	Euthyroid	-
31	F	50	D	75	-	7	-	1	"	-
32	F	52	D	100	-	9	-	1	"	-
33	F	51	N	50	67	7	8	1	"	-
34	F	46	P.T	35	53	5	5	1	"	-
35	F	45	D	50	79	7	5.5	1	"	-
36	F	49	D	60	71	7	7.5	1	"	-
37	F	45	N	100	60	10	18.5	3	Minimally toxic	Minimally toxic/18mths.
38	F	45	N	85	72	9	11.5	4	Mildly toxic	" " "
39	F	59	N	70	70	8	9	1	Euthyroid	-
40	F	44	P.T	45	67	5	4	1	"	-
41	F	41	D	50	64	8	8	1	"	-
42	F	56	D	50	62	7	6	1	"	-
43	F	45	D	60	70	6	7.5	1	"	-
44	F	50	D	45	61	5	6.5	1	"	-
45	F	31	P.T	30	72	4	3	2	"	-
46	F	25	D	45	72	6	5.5.	1	"	-
47	F	46	D	80	53	10	13	1	"	-
48	M	51	D	80	50	10	14	1	"	-
49	F	63	D	40	69	6	6.5	1	"	-
50	M	52	D	50	87	7	6	1	"	-
51	F	51	D	40	55	7	6.5	1	Myxoedema	-

RESULTS OF RADIOACTIVE IODINE THERAPY -- GROUP 2 (45 cases)

Case No.	Sex	Age	Gland Type	Gland Size(G)	48-hr. Uptake ^{131}I %dose	Initial Therapy dose ^{131}I m/c.	Calculated dose(Blom-field et al) m/c.	No. of doses given	1 year after first dose	Remarks
52	M	60	N	130	46	13	25	4	Minimally toxic	Euthyroid/18 months
53	M	61	D	40	60	6	6	1	Euthyroid	-
54	F	60	D	35	80	6	4.5	1	"	-
55	F	72	N	30	73	6	5.5	1	"	-
56	M	60	P.T	25	63	5	2.5	1	"	-
57	F	48	D	40	63	6	5.5	1	"	-
58	F	53	N	45	83	6	4.5	2	"	-
59	F	54	D	40	82	6	4.5	1	"	-
60	F	60	D	35	49	6	6	1	"	-
61	F	56	D	45	72	5	5.5	1	"	-
62	F	49	D	90	81	7	9.5	1	"	-
63	F	51	D	40	77	9	6	1	"	-
64	F	47	N	50	70	8	6.5	1	"	-
65	M	39	D	50	52	8	7	1	"	-
66	F	43	N	150	75	14	17	1	"	-
67	F	48	D	40	83	7	4	1	"	-
68	F	32	P.T	35	54	5	5	5	Mildly toxic	Mildly toxic/18 months
69	F	61	D	100	58	15	17	1	Euthyroid	-
70	F	58	N	40	70	7	5.5	1	Myxoedema	-
71	F	49	P.T	50	60	7	6.5	4	Euthyroid	-
72	F	56	D	40	48	9	8	1	"	-
73	F	59	N	50	92	8	5	2	"	-

D = diffuse; N = nodular; P.T. = post-thyroidectomy.

APPENDIX XIII

Results of Radioactive Iodine Therapy -- Group 3

APPENDIX XIII

RESULTS OF RADIOACTIVE IODINE THERAPY -- GROUP 3 (21 cases)

Case No.	Sex	Age	Gland Type	Gland Size(G)	48-hr. Uptake ^{131}I %dose	Initial Therapy dose ^{131}I m/c.	Calculated dose(Blomfield et al) m/c.	No. of doses given	1 year after first dose	Remarks
74	F	46	D	80	76	12	10.5	3	Euthyroid	-
75	F	57	D	90	63	12	15	4	Minimally toxic	Euthyroid/18 months
76	F	54	N	50	86	8	5	4	" "	" " "
77	F	48	N	90	84	11	9.5	1	Euthyroid	-
78	M	42	D	85	80	9	9	1	"	-
79	M	60	D	50	72	7	6	3	"	-
80	F	37	D	40	65	6	4.5	1	"	-
81	M	33	N	250	65	20	33	4	"	-
82	M	47	D	90	80	13	11	1	Myxoedema	-
83	F	43	N	100	84	12	10.5	1	Euthyroid	-
84	F	46	D	90	80	13	11	1	Myxoedema	-
85	F	68	N	40	97	10	4	1	Euthyroid	-
86	F	49	N	150	90	15	14.5	1	"	-
87	M	50	N	55	75	12	7.5	2	"	-
88	F	60	D	80	80	10	8.5	1	"	-
89	F	38	D	60	80	12	7.5	1	"	-
90	F	57	D	50	74	9	5.5	1	"	-
91	F	63	D	200	60	23	33	3	"	-
92	F	53	D	85	89	9	8.5	1	"	-
93	F	68	D	35	91	5	3.5	2	"	-
94	F	46	D	70	84	9	7	2	"	-

D = diffuse; N = nodular.

APPENDIX XIV

Results of Radioactive Iodine Therapy -- Group 4

APPENDIX XIV

RESULTS OF RADIOACTIVE IODINE THERAPY -- GROUP 4 (56 cases)

Case No.	Sex	Age	Gland Type	Gland Size(G)	48-hr. Uptake ^{131}I %dose	Initial Therapy dose ^{131}I m/c.	Calculated dose(Blom-field et al) m/c.	No. of doses given	1 year after first dose	Remarks
95	F	29	P.T	50	80	7	5.5	1	Euthyroid	-
96	F	60	D	120	72	15	16.5	3	Minimally toxic	Euthyroid/18 months
97	F	50	D	50	68	7	6.5	2	Euthyroid	-
98	F	57	D	45	51	10	9	2	Myxoedema	-
99	F	47	D	50	80	8	5.5	2	Euthyroid	-
100	F	46	N	60	68	9	9	1	"	-
101	F	73	N	80	66	8	10	1	"	-
102	F	60	N	35	-	8	-	2	Myxoedema	-
103	M	54	D	60	72	8	7.5	4	Mildly toxic	Euthyroid/18 months
104	F	59	N	70	47	10	14.5	1	Euthyroid	-
105	F	51	N	60	59	8	8.5	4	Mildly toxic	Minimally toxic/18mths.
106	F	47	N	70	84	9	7	1	Euthyroid	-
107	F	64	N	60	72	8	8	3	Mildly toxic	Euthyroid/18 months
108	F	47	N	180	51	25	35	2	Euthyroid	-
109	F	44	N	50	72	9	7	1	"	-
110	M	57	D	40	66	8	6	1	"	-
111	M	55	D	40	90	6	2	2	"	-
112	M	45	D	90	50	12	15.5	2	"	-
113	F	57	D	30	78	6	3.5	1	"	-
114	F	62	N	60	70	11	8.5	2	"	-
115	F	55	D	75	71	8	8	2	"	-
116	F	39	N	100	94	10	9	1	"	-
117	F	61	N	25	85	6	3	1	"	-
118	F	47	D	40	88	7	4	3	Minimally toxic	Euthyroid/18 months
119	M	60	D	60	60	8	8.5	2	" "	" /14 months

RESULTS OF RADIOACTIVE IODINE THERAPY -- GROUP 4 (56 cases)

Case No.	Sex	Age	Gland Type	Gland Size(G)	48-hr. Uptake ^{131}I %dose	Initial Therapy dose ^{131}I m/c.	Calculated dose(Blom-field et al) m/c.	No. of doses given	1 year after first dose	Remarks
120	F	59	D	50	80	6	5.5	1	Euthyroid	-
121	M	50	D	40	91	7	4	1	"	-
122	F	58	N	100	98	12	10	1	"	-
123	F	63	D	50	55	8	8	1	"	-
124	F	55	P.T	35	70	5	4	1	"	-
125	F	55	N	70	65	10	10.5	1	"	-
126	F	47	N	70	73	10	9.5	1	"	-
127	F	55	N	100	47	17	21	3	"	-
128	F	61	N	50	80	12	6	1	"	-
129	F	53	D	100	79	12	11	2	"	-
130	F	52	D	50	75	7	6	2	"	-
131	F	20	P.T	30	66	6	3.5	3	Minimally toxic	Euthyroid/13 months
132	F	37	P.T	25	70	5	2.5	2	Myxoedema	-
133	F	57	N	75	65	12	11.5	2	"	-
134	F	57	P.T	85	49	12	16	1	Euthyroid	-
135	M	68	D	55	51	9	9.5	1	"	-
136	F	62	N	60	65	11	9	1	"	-
137	F	47	D	50	59	8	7.5	1	"	-
138	F	44	D	40	88	5	3.5	1	"	-
139	F	51	D	130	69	16	19	2	"	-
140	M	44	N	35	96	6	3.5	1	"	-
141	F	53	D	45	95	7	4	1	"	-
142	F	52	D	80	94	9	6.5	1	"	-

RESULTS OF RADIOACTIVE IODINE THERAPY -- GROUP 4 (56 cases)

Case No.	Sex	Age	Gland Type	Gland Size(G)	48-hr. Uptake ^{131}I %dose	Initial Therapy dose ^{131}I m/c.	Calculated dose(Blom-field et al) m/c.	No. of doses given	1 year after first dose	Remarks
143	F	50	D	80	93	8	6	1	Euthyroid	-
144	F	64	D	30	88	6	3	1	"	-
145	F	50	D	30	56	6	4.5	2	"	-
146	F	62	N	50	86	8	5	1	"	-
147	M	47	D	50	86	7	5	1	"	-
148	F	68	D	50	85	7	5	1	"	-
149	F	48	D	50	75	8	5.5	1	"	-
150	F	55	P.T	100	81	11	9	1	"	-

D = diffuse; N = Nodular; P.T. = post-thyroidectomy.

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PART III

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