THE DIAGNOSIS OF PRIMARY HYPOTHYROIDISM

A Critical Evaluation

of

The Clinical Features

and

Laboratory Aids to Diagnosis

by

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CONTENTS

PREFACE

"Myxoedema is perhaps the most frequently missed endocrine disorder"

Price's Textbook of Medicine (1956)

Such a statement as this initially excites surprise for the dull, apathetic, uncomprehending stare of the "myxoedematous facies" is so characteristic. On reflection, however, its truth is readily apparent since in most instances this typical clinical picture only evolves over several years. During this time the possibility that hypothyroidism is responsible for the patient's vague symptoms of ill-health has frequently not been considered.

This thesis is based on a study initiated in an attempt to clarify the difficulty that does exist in establishing the diagnosis of hypothyroidism at an early stage in the course of its development. It is mainly concerned with the "primary" or "idiopathic" form of hypothyroidism in the adult since it was considered that this presents the greatest diagnostic problem. When hypothyroidism is the result of such accidents as the destruction of the pituitary or over-treatment of thyrotoxicosis, the diagnosis is much more readily suspected.

The study has been presented in the sequence in which, it is suggested, the clinician usually approaches the problem of reaching a diagnosis in any patient. "The Clinical Evaluation" has been considered in Section I. A study was made of the clinical features of hypothyroidism both in patients in whom the diagnosis was obvious and in subjects where the condition was suspected but diagnostic difficulty encountered. In addition to demonstrating the diverse and often subtle ways in which the disorder may present, it permitted an evaluation to be made of the relative diagnostic importance of the different symptoms and signs that may occur. It seemed possible that this data would permit the extension of a study in which I had previously been priviledged to take part (Crooks et al, 1959). In this, it had been shown that the application of a statistical method of allocating numerical values to the clinical features of thyrotoxicosis provided greater accuracy in diagnosing this disease on clinical grounds. It will be shown that the application of this technique to hypothyroidism is also helpful in clinical practice.

In some patients, especially when the clinical picture is atypical or incomplete, the clinician frequently wishes to employ laboratory aids which will substantiate his clinical diagnosis. In Section II, therefore, "The Laboratory Confirmation" presents a review of the relative value of some of the procedures most commonly used to demonstrate thyroid hypofunction. A new method, the measurement of reaction time, has been introduced. It will be shown that this is a simple and rapid technique which provides considerable precision in demonstrating the presence of hypothyroidism.

The final proof of the accuracy of any diagnosis is the demonstration that the administration of appropriate therapy produces alleviation of symptoms and the disappearance of signs. This response is particularly important in the patient in whom the diagnosis remains in some doubt, even after full clinical assessment and investigation. In Section III, "The Therapeutic Trial" presents a study of the alterations in the clinical picture of hypothyroidism produced by the administration of thyroxine, and of the changes in the laboratory investigations which will support the clinical observations.

The term myxoedema is used properly to describe the state of hypothyroidism in which there is an abnormal infiltration of the skin and subcutaneous tissue with a muco-polysaccharide. However, this manifestation is not present in all cases of hypothyroidism and indeed is usually absent in early cases. Accordingly the term hypothyroidism is preferred to myxoedema and will not be used interchangeably.

For convenience in reading, the Tables and Figures referred to in the text have been bound separately in Volume II. They are followed by a list of the references to the literature quoted. Volume II also contains Appendices in which the results of the studies are tabulated in full.

The publications that have already appeared reporting part of the work included in this thesis, and those studies in which I have taken part and to which reference is made, are as follows:-

"Acroparaesthesia in Myxoedema" I.P.C. Murray and J.A. Simpson. Lancet (1958) i, 1360.

"The Reaction Time in Myxoedema" I.P.C. Murray. Lancet (1958) ii, 384.

"Radioactive Iodine Studies in the Diagnosis of Hashimoto's Thyroiditis" I.P.C. Murray and E. M. McGirr. Brit. med. J. (1960) 1, 838.

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

"Sleeping Pulse Rate in Thyrotoxicosis" J. Crooks and I.P.C. Murray. Scot. med. J. (1958) 3, 120.

"A Statistical Method applied to the Diagnosis of Thyrotoxicosis" J. Crooks, I.P.C. Murray and E.J. Wayne. Quart. J. Med. (1959) 28, 211.

The results of some of these studies were also included by Professor E. J. Wayne in the second of his Lumleian Lectures, "Clinical and Metabolic Studies in Thyroid Disease" Brit. med. J. (1960) 1, 78.

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CHAPTER I

INTRODUCTION

Hypothyroidism results most commonly from a primary lesion in the thyroid gland resulting in a progressive loss of acinar tissue with accompanying impaired production of hormone. The clinical features can, therefore, be explained almost entirely from the knowledge of the actions of thyroid hormone. If, however, the function of the thyroid is diminished as the consequence of pituitary failure, as in Simmond's disease, the clinical picture of the remaining hypothyroidism will usually be different, since deficiencies of other hormones are also present. As thyroid hormone is essential for normal tissue metabolism, inadequate production will cause slowing of these processes throughout the body with characteristic changes in the mental and physical state. Usually the decrease in thyroid hormone occurs gradually. The changes develop slowly, but as the demands of different systems vary greatly, some symptoms and signs will appear at an earlier date than others. If the failure of hormone production is more abrupt, as for example following radioactive iodine therapy, the deprivation will affect all tissues more completely and the clinical pattern may consequently be different. In subsequent chapters these alterations in the clinical picture of hypothyroidism will be more closely examined.

In most conditions diagnostic difficulty usually arises when a clinical picture is incomplete, or when atypical features are present. 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 such variations seems to depend on the nature of the mental processes involved in making a diagnosis. In making 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, whether or not any single symptom or sign is present or not. Next, the physician must decide on the relative importance that he should attach to the clinical features of the case. At this point further differences in opinion arise because some clinicians regard certain features as of greater diagnostic significance than do others.

Such difficulties as these are accentuated in hypothyroid states because of the diversity of the signs and symptoms resulting from the generalised effect of lack of thyroid hormone. The clinical picture may, however, be dominated by the evidence of the deficiency on one particular organ or system. The condition may consequently present in many ways. These variations in presentation accentuate the difficulty in recognising the disorder that is produced by the insidious nature of its onset. The alteration in the individual's appearance may develop so gradually that it may pass unnoticed by the patient and her relatives, and often even by her own practitioner. Moreover, the accompanying mental changes tend to smother self-criticism and the patient may have very few complaints. Since, therefore, symptoms must frequently be elicited by specific questioning, it is even more important that the clinician is aware of the relative diagnostic significance of the clinical features.

Recognising these difficulties in making a clinical diagnosis of hypothyroidism, the clinical features of the condition have been reviewed. Special attention has been paid to the cases causing diagnostic difficulty and enquiry made into the reason for the difficulties and methods whereby these may be overcome.

CHAPTER 2

SYMPTOM AND SIGN ANALYSIS

The frequency with which characteristic symptoms and signs are to be found in hypothyroid patients has been analysed by several authors, for example Means and Richardson (1929) and Lerman (1948). Their figures, although of great interest, are not of great value to the clinician since they provide little information regarding the diagnostic significance of these features. This can only be obtained by comparing the incidence of such symptoms and signs as they occur not only in normal and frankly hypothyroid subjects, but also in those cases which have caused diagnostic difficulty. The following analysis is an attempt to provide this information.

Subjects

Throughout this study the patients have been divided into groups. Those in whom the diagnosis was obvious on clinical grounds have been called the "Definite" group. If, however, there had been difficulty in reaching a diagnosis by one or more hospital physician, patients were considered separately in a group termed "Doubtful". The final diagnosis was made only after investigation and prolonged observation, which included watching the response to specific therapy.

Fifty-five patients were unquestionably hypothyroid and have been called the "Definite Hypothyroid" group. They were matched by sex and age, in five year periods, with 55 normal subjects - the "Definite Euthyroid" group. None of these had attended practitioners with complaints of recent ill-health and in none was there any evidence of thyroid upset. All were continuing their normal occupations.

Difficulty in reaching a diagnosis has been found in 50 patients finally shown to be euthyroid and in 45 proved later to be hypothyroid. Accordingly these groups have been termed the "Doubtful Euthyroid" and "Doubtful Hypothyroid" groups respectively.

In all the hypothyroid subjects considered in this review the condition was either "idiopathic" or due to Hashimoto's thyroiditis. Similar studies were carried out in patients in whom hypothyroidism was secondary to pituitary insufficiency or followed treatment of thyrotoxicosis. The results will be considered separately.

Method

In each subject, the presence or absence of each clinical feature was recorded. Initially, the signs and symptoms chosen were those studied by Lerman (1948), others mentioned frequently in textbooks of thyroid disorders, or on the basis of personal experience. After a short trial period, it became obvious that in some of these the observer error was high and these were omitted. Others, for example paraesthesiae, were added in the light of the frequency with which complaints had been spontaneously mentioned by patients. A written questionaire was not used. Care was taken to avoid leading questions and supplementary questions were always asked. The method of history-taking is described in Appendix I. In order to reduce the effects of observer variation, the procedure for the physical examination was rigid and the criteria to be fulfilled are also described in Appendix I. The findings were noted on a special sheet, which was filed until the final diagnosis had been established. They were then transferred to a punch-card. On completion of the series these cards were analysed.

Results

The full details of the incidence with which the various features were found are shown in Appendix II. In view of the great difference in numbers of male and female subjects, it is difficult to compare them accurately. Nevertheless, there does appear to be little significant difference between the results in the two sexes, except for the changes in hair which were noted less frequently by men. The results for both have therefore been considered together. The comparison of the frequency of symptoms is shown in Table 1 and of the signs in Table 2.

When the "Definite Hypothyroid" group is examined, it can be seen that the symptoms generally considered to be most typical of hypothyroidism were present in most of the patients. The characteristics of these symptoms will be considered later. As might be expected, few of the control euthyroid subjects had similar symptoms, although the frequency with which apparently normal individuals complained of tiredness, dyspnoea, nervousness and depression is perhaps surprisingly high. Nevertheless, there is a significant difference between the incidence of each symptom as it occurs in both groups. Thus, for example, even "tiredness" retains some diagnostic significance since although it was present in 42% of euthyroid subjects, 98% of the obviously hypothyroid patients had this complaint.

When the two "Doubtful" groups are considered, however, it becomes clear that the isolated finding of many of these symptoms must be interpreted with caution. In those patients finally proved to be hypothyroid, the incidence of typical symptoms is still high although, not surprisingly, it is generally rather lower than in the "Definite Hypothyroid" group. In those, however, who had presented diagnostic difficulty but were found finally to be euthyroid - the "Doubtful Euthyroid" group - it is obvious that this difficulty had in part arisen because patients had had one or more of the "typical" symptoms. Thus many had complaints of cold intolerance, hair changes, hoarseness, or a sensation of facial "puffiness". Tiredness was in fact present in 88%. On the other hand, some symptoms, such as lethargy, were encountered much less frequently in these patients than in the "Doubtful Hypothyroid" group and therefore are obviously of considerable diagnostic importance.

The conclusions that may be drawn from examination of the incidence of signs (Table 2) form a similar pattern. Thus in the "Definite Hypothyroid" patients most of the accepted clinical features were encountered, although in varying frequency. Again in the "Doubtful Hypothyroid" group the incidence of each sign was rather lower. These features were uncommon in the control normal individuals, although a hoarse voice, cold dry skin, or dry hair, were found in a considerable number. The incidence of these features in the "Doubtful Euthyroid" group suggests that as isolated phenomena their diagnostic significance is over-estimated. In the latter group, it is also clear that the possibility of hypothyroidism had been often considered because of the impression of puffiness of the face or periorbital tissues. This sign therefore must also be interpreted with caution and together with the other features. It is particularly interesting to observe the incidence of sparseness of the eyebrows, which is frequently mentioned as a typical sign. Although it was noted in 84% of hypothyroid patients, it was also considered to be present in 70% of the "Doubtful Euthyroid" group and in 47% of normal individuals. Eighteen hypothyroid women were of pre-climacteric age. Menstruation was unchanged in 5, while menorrhagia had developed in 6, and oligomenorrhoea had developed in 3. In 4 women who had noted amenorrhoea, normal menstruation returned after thyroxine therapy.

Discussion

The value of any diagnostic procedure, clinical, chemical or physical, depends to a large extent on its reproducibility. The greater the human element in a method, the higher is the probability of variation when the observations are repeated or carried out by different observers. Such observer variation may arise in two ways. In the first place, there may be disagreement between observers whether or not a sign or symptom is present. History-taking is particularly prone to such mistakes, as Cochrane et al (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 emphasis the physician places on the patient's statements. The use of a written questionaire 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 questionaire 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. Nevertheless, despite these precautions, a large proportion of the healthy normal individuals did admit to the presence of such symptoms as tiredness (64%) and breathlessness (52%). It must be remembered that in all these patients the symptoms were elicited by these methods and were not spontaneously complained of. The importance of this difference will be apparent when considering the ways in which the hypothyroid cases presented.

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 20 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 et al (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.

Even if the actual observations by different clinicians are in agreement, however, differences in diagnosis may still arise through varying conclusions being drawn from them. This results from differences in interpretation of the clinical features and is probably the most important single cause for erroneous diagnoses. The importance placed on any symptom or sign by an individual is influenced by factors such as his experience and personal impressions. The true diagnostic significance of any feature can only be ascertained by careful study. In the first place it obviously depends on the frequency with which it occurs in patients suffering from the disorder. The relative incidence of signs and symptoms in proven hypothyroid patients was studied by Lerman (1948). A comparison between that series and the present study is to a certain extent difficult in view of probable differences in the degree of severity of the disorder of patients in the two groups.

In Table 3, however, the respective results are shown for some of the features studied in the two investigations. It may be noted that most of the symptoms and signs frequently found in the present study were also encountered most often by Lerman (1948). Possible differences in the criteria for recognition of the features must be remembered and may explain the slight differences in the results since the figures are in general lower for this series. It may be emphasised again that in this investigation all symptoms had to be of recent onset or of increasing severity before being recorded as present. Similar variations in the definition of the clinical features must be considered when studying reports by other authors of the incidence of symptoms and signs in hypothyroid states. Nevertheless, the results in 20 patients reviewed by Sheedy and Lienhard (1957) do show a similar pattern (Table 3), but it may be noted that apart from lethargy and weakness, the features were less commonly encountered. Their study and most others, however, are not strictly comparable with the present one or Lerman's (1948), since they are not based on a specially designed investigation where the presence or absence of specific features is elicited. Instead, the frequency with which selected symptoms and signs had been recorded in routine charts and case histories has been noted. It is likely that many symptoms might be ignored if not

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specially sought and this may in fact be the reason why the reported frequency of individual features is generally much lower. Thus in 151 hypothyroid patients studied in this way, Burnstein (1948) found fatigue present in only 44% and constipation in 40%. Apart from non-specific complaints, such as headache and backache, the incidence of all other symptoms was less than 20%. His results, however, like those of Sturgis (1922) and other workers, make quite clear the multiplicity of symptoms that may be encountered in hypothyroidism. It is all the more surprising therefore that these authors and Lerman (1948) did not also study the frequency with which the features might be found in euthyroid subjects.

The diagnostic value of any finding must depend on a comparison of its occurrence in normal and abnormal individuals. The results show that few of the typical symptoms and signs are present in healthy subjects with significant frequency. Some of the more non-specific features, however, were found sufficiently often to show that their presence in a patient suspected of hypothyroidism is of no diagnostic value. Joint pain, for example, was present in 29% of all hypothyroid cases and in 24% of the "normal" subjects. It is clear also that the finding of isolated signs, such as hoarseness or coldness of the skin, must be interpreted with caution.

A final evaluation of the diagnostic importance of the clinical features can only be obtained when the patients causing diagnostic difficulty are considered. As might be expected, the difficulty in establishing the diagnosis in those proved finally to be hypothyroid arose frequently because the clinical picture of "classical" hypothyroidism was incomplete. Although assessment of the duration of hypothyroidism is usually difficult since it depends so largely on the fortitude of the individual, the period of ill-health tended in general to be shorter in the "Doubtful Hypothyroid" group than in the "Definite" group. In many instances, therefore, it is likely that the "incomplete" clinical picture reflected the disorder at early stages in its development. The frequency with which symptoms and signs occur in such patients accordingly provides a guide to the sequence in which they appear. Thus, the comparison of this group with the "Doubtful Euthyroid" group provides the clearest evaluation as to which of the symptoms and signs can usually be taken to be of the greater value in establishing an early diagnosis.

This comparison makes it evident that in the diagnosis of hypothyroidism the finding of positive clinical signs is of considerably more importance than the presence of symptoms. Many of the patients who were finally proved to be euthyroid did have symptoms suggestive of hypothyroidism. This, of course, explains why the condition was initially suspected, but at the same time makes it clear that many of the symptoms are in fact of much less diagnostic value than is generally accepted. This may be illustrated by studying the incidence of "cold intolerance", which would appear to be very significant, since it was present in 95% of all hypothyroid patients. Its importance is, however, considerably reduced by finding it in 64% of the "Doubtful Euthyroid" group. Similarly, such symptoms as tiredness and weight gain, only retain some significance since their frequency in hypothyroidism is so high. Others like breathlessness and depression can be seen to be of no diagnostic value at all. On the other hand, the results do show that the finding of such complaints as lethargy and recent constipation in a patient suspected of being hypothyroid strongly favours the diagnosis.

When the frequency with which abnormal signs were found in the two "Doubtful" groups is examined, it is clear that these form a pattern which is of considerable assistance in making a diagnosis. In nearly every instance there is a significant difference between the figures for the two groups. This difference does, however, vary considerably between the various signs. The degree of this variation reflects the relative diagnostic significance of the signs.

Conclusions

The true diagnostic value of any clinical feature may only be determined after careful consideration. Such factors as its liability to observer error and the stage in the development of the condition at which it most often appears must be taken into account. It is essential to compare the frequency with which it is found both in abnormal subjects and in apparently healthy individuals. In addition, its incidence in patients who have caused diagnostic difficulty must be studied. Only then is it possible to evalute the significance which a clinician may place on the presence or absence of an individual symptom or sign.

Such an analysis of the clinical features that may be found in hypothyroidism has made it clear that many of these features are non-specific since they occur frequently in euthyroid subjects. On the other hand, there are many symptoms and signs very typical of the disorder and of considerable significance when encountered. Nevertheless, some of these are only often found when the condition is fully established and are therefore of less value to the clinician who seeks an early diagnosis.

It is apparent that the symptoms of most value are lethargy, tiredness, paraesthesiae, cold intolerance, decreased sweating, dryness of the hair and skin, deafness, constipation, decreased appetite and increased weight. Similarly, special attention should be paid to determining the presence or absence of hoarseness, slow movements, impaired cerebration, periorbital or supra-clavicular puffiness, dryness of the hair and dry, cold, coarse and yellowish skin.

CHAPTER 3

IATROGENIC HYPOTHYROIDISM
SYMPTOM AND SIGN ANALYSIS

Whatever treatment is employed in the treatment of thyrotoxicosis, some patients will be rendered hypothyroid. As in primary hypothyroidism, the clinical picture is often clear-cut. In lesser degrees, however, it may be overlooked particularly since it differs somewhat from that typical of the primary disorder. In this chapter some of the clinical problems of the condition are considered.

Subjects

This study was carried out in 53 patients who had become hypothyroid as the result of therapy for proven thyrotoxicosis. The condition was produced in 4 by anti-thyroid drugs and followed thyroidectomy in 14. The remaining 35 had received therapeutic doses of ^{131}I. In all casesthe hypothyroid state was clear-cut.

All the subjects who had received ^{131}I were reviewed at 4 to 6 weekly intervals after their dose. When hypothyroidism was suspected, observation was continued for at least a further 12 weeks, if possible, before instituting therapy. In some cases, however, the clinical state necessitated treatment earlier.

In 4 of the 35 patients all evidence of hypothyroidism disappeared spontaneously. There was partial improvement in a further 13 cases, but some signs and symptoms persisted and were relieved only after treatment was started. In the remaining 18 patients the hypothyroid state showed no tendency to remission or became more marked.

In these 53 patients an analysis was made of the frequency with which the symptoms and signs of hypothyroidism were encountered. The method and the criteria for the presence or absence of the various features were the same as those employed in the symptoms and sign analysis carried out in primary hypothyroidism and previously described, but, in addition, the incidence of another sign - "muscle tenseness" - was noted. This sign was elicited by compressing the muscles of the patient's forearm, maintained in a relaxed position, between the thumb and forefinger. The sensation of tenseness, or firmness, was compared with that obtained by similar examination of the examiner's own forearm. Record sheets were completed whenever any symptoms of signs suggestive of hypothyroidism were first observed and thereafter at each visit. The record used for the analysis was the one completed when the hypothyroid state was most marked.

Results

The incidence with which the various features were encountered are shown in Appendix III. Although the numbers in each group are inadequate to allow accurate comparison, there appears to be little difference attributable either to sex or to the type of previous therapy. The results have, therefore, been considered together and the percentage frequency with which the symptoms and signs occurred are shown in Tables 4 and 5. When these are compared with the results obtained in all the patients with primary hypothyroidism, it can be seen that in most instances there is a close similarity between the incidence of symptoms and signs. Those features which were shown to be of greatest diagnostic importance previously, are also most often found in the present series. In this group, however, the complaint of "muscle weakness" occurred rather more often, 81% compared with 61% in the primary disorder. There is a significantly greater incidence of "muscle pain" (72% and 36% respectively). The physical sign termed "muscle tenseness" was found in 66% of these patients.

Discussion

The recognition of iatrogenic hypothyroidism is essentially clinical since, as will be shown later, the usual laboratory tests of thyroid function cannot be relied on with any certainty to provide confirmatory information. Appreciation of the clinical picture is therefore important. The clinician's task is, of course, easier in these particular patients since they are usually already under close observation. Thus, treatment with anti-thyroid drugs is the least frequently encountered cause of this form of thyroid insufficiency. Any symptoms suggestive of hypothyroidism are readily relieved by reduction of dosage. The incidence of hypothyroidism reported to follow thyroidectomy varies (Bartels, 1953), but the figure of 2.4% found in the series of 615 cases observed by Werner (1955) is fairly typical. The condition is, however, generally recognised as being much more frequently encountered after radioiodine treatment of thyrotoxicosis. The experience of most centres using this form of therapy is similar to that of Blomfield et al (1959). In their study of 500 cases followed for at least one year, the incidence of hypothyroidism was 12%. In view of the increasing use of radioiodine as the therapeutic agent of choice in thyrotoxic subjects over 40 years of age, iatrogenic hypothyroidism is likely to be encountered with increasing frequency. Even with increasing experience in the use of ^{131}I, it is unlikely that the proportion rendered hypothyroid will be significantly reduced since prediction of the correct dose depends on so many variable factors, some of which, such as the estimation of gland size, are liable to considerable inaccuracy. In the majority of cases, if hypothyroidism is to appear it will be apparent within the first 3 to 6 months after the therapeutic dose. Blomfield et al (1959), however, noted its late development in a number of cases, the longest interval being 5½ years after therapy. In the present series thyroid insufficiency had appeared within six months in all but 2 cases, in whom periods of 10 and 18 months elapsed before any evidence of hypothyroidism developed.

It is apparent from the symptom and sign analysis that in general the clinical picture of the hypothyroid state which follows therapeutic measures resembles that of primary hypothyroidism. Thus, those features which were shown to be of most significance previously are again most commonly found. Lethargy, for example, was a prominant feature in 85% of the cases of primary hypothyroidism and in 83% of those following anti-thyroid therapy. It must be remembered, of course, that in the latter some symptoms are more difficult to evaluate in view of their previous thyrotoxic state. There is obviously some difficulty in assessing the significance or degree of cold intolerance and decreased sweating in a subject who recently has complained of heat intolerance and excessive sweating. Similarly, increase in weight and decreased appetite are the changes to be expected in any patient whose hyperthyroid state has been successfully treated. It may be noted that a smaller proportion of the patients in the present study showed the typical cutaneous manifestations of hypothyroidism. Fewer also complained of deafness. These differences may be explained on the grounds that, when hypothyroidism follows therapeutic measures, patients are subjected relatively quickly to a change to underactivity of the thyroid. The symptoms, therefore, appear relatively rapidly and, since the patients are usually under medical supervision, the condition is recognised at an early stage. There is, therefore, less time for some of the chronic manifestations to develop. These features, of course, were found less often in the "Doubtful Hypothyroid" group with a relatively short duration than in those cases where the diagnosis was obvious. It might even be considered that in view of the rapid onset of "iatrogenic hypothyroidism" these features associated with more prolonged thyroid deficiency have been found surprisingly frequently. This analysis was, however, carried out in cases where there was little clinical doubt as to the diagnosis and that the record employed was that obtained when the condition was most obvious.

It is clear from a perusal of the serial records that at an early stage in the development of their hypothyroid state many patients complained of a sensation of "puffiness". This soon was followed by a feeling of tenseness and tightness chiefly affecting the legs and arms, often constricting in nature. Frequently this was accompanied by muscle pain, precipitated usually either by walking or repetitive movements, and often of considerable severity. Some experienced pain in the muscles at rest and some had nocturnal cramps. This muscular pain is a curious phenomenon to which attention was drawn by Kocher (1883) in patients following thyroidectomy and by Blomfield et al (1951) in ^{131}I treated subjects, although the latter (Blomfield et al, 1959) have subsequently been less impressed by this symptom. The present study confirms its existence as a highly characteristic feature of "iatrogenic hypothyroidism". Pain of this nature, but usually much less troublesome, was present in 36% of the patients with primary hypothyroidism, but was encountered in 72% of the patients with undoubted hypothyroidism consequent on therapy. Similar aches in muscles of the arms and legs of less marked degree had been present at some time in many of the remaining 28%. They were also frequently experienced by those demonstrated to have mild transient hypothyroidism and who have not been included in the analysis. Many patients also complained of impaired strength, especially in their arms.

These symptoms of muscular discomfort and pain, therefore, are of the highest diagnostic significance. Any individual previously treated for thyrotoxicosis, who complains of such symptoms should be closely observed for the development of other features of hypothyroidism.

When these complaints are encountered, examination of the relaxed forearm or calf reveals a peculiar, but typical, firmness of the muscles. These often feel very hard, as if in maximal voluntary muscular contraction. It is difficult to provide strict criteria for this sign, which was noted in 66% of the patients in this study. Once the clinician is aware of the typical quality of the firmness, however, he will easily be able to detect its presence. It is readily distinguishably from the infiltration of the subcutaneous tissues by myxoedematous tissue found both in primary and "iatrogenic hypothyroidism". The appearance of these muscular disorders is clearly related to the rate of onset of thyroid insufficiency, but the mechanism of their production is unknown. Lambert and Sayre (1955) showed that electromyographic abnormalities in thyroidectomised rabbits was accompanied by vacuolation of the muscle fibres and hyaline degeneration. These changes were reversed by tri-iodothyronine administration. Similar abnormalities have been observed in some patients with primary hypothyroidism (Lambert, 1960) but no attempt was made to correlate their incidence with the severity of the disorder or its rate of onset.

A further important difference exists between primary and iatrogenic hypothyroidism. In the former, it is desirable to institute therapy at an early stage in its development in order to reduce the period of ill-health. The hypothyroid state produced by treatment of thyrotoxicosis, however, may in some instances be transient. Spontaneous recovery was observed in 4 patients in this study and has been noted in many other cases showing stigmata of hypothyroidism, but excluded from the analysis since in them the clinical picture was incomplete. Therapy in such patients greatly reduces the possibility of remission because of the suppression of the thyroid remnant. The individual may, therefore, be unnecessarily condemned to lifelong treatment. In this form of hypothyroidism, therefore, the recognition of the stigmata of the disorder should be an indication that the patient should be closely observed for a period of several weeks, if the condition is not unduly incapacitating, before deciding on the permanent nature of the thyroid insufficiency.

Conclusions

The clinical picture of the hypothyroid state that follows therapeutic measures resembles that of primary hypothyroidism in most respects. It does, however, show certain differences, probably related to the more rapid rate of onset of the thyroid insufficiency. Thus, the more chronic manifestations, such as the cutaneous changes, are less frequently encountered, while muscular changes, characterised by a sensation of tightness, weakness and often pain, are much more common. Whenever these symptoms are encountered in a patient who has received anti-thyroid therapy, a close watch should be kept for the development of other stigmata of hypothyroidism. Even when the clinical picture is unmistakeable, however, it is desirable to withhold therapy in order to observe whether the condition is transient.

CHAPTER 4

"PITUITARY HYPOTHYROIDISM"

The clinical picture of multi-glandular insufficiency resulting from pituitary failure will depend on the degree of destruction of the pituitary. Thyroid function will nearly always be impaired, but the extent to which this occurs varies considerably and the features of hypothyroidism are frequently masked by the accompanying deficiencies of other glands. In this chapter, therefore, the clinical picture of hypothyroidism resulting from pituitary failure has been reviewed.

Subjects

The diagnosis of hypopituitarism was established in 15 patients, 14 of whom were female. It was initially made on the basis of the clinical findings and confirmed by laboratory investigations. The response to treatment with thyroxine, adrenal steroids and sex hormones was also observed. The pituitary insufficiency resulted either from post-partum necrosis or from chromophobe adenomata.

Results

The results of an analysis of the incidence of the symptoms and signs associated with hypothyroidism, carried out by the method previous described, are shown in Tables 6 and 7. It should be noted that because of the small number of cases, large differences in the percentage incidence of symptoms and signs are necessary before statistical significance between this and other groups is achieved. Thus, a difference of about 40% is usually necessary before statistical significance (P = 0.05) is attained. Nevertheless, it can be seen that the incidence of symptoms in the primary and secondary forms is very similar. Differences are only really present in the relative frequency with which paraesthesiae, hoarsensss and a sensation of puffiness occurred. In the "pituitary" hypothyroid group, weight increase and dryness of the skin was rather less often encountered. On the other hand, considerable differences are apparent in the incidence of physical signs. The skin was generally smooth, the hair soft and fine rather than dry, and the appearance of "puffiness" was much less frequently noted. The systolic blood pressure was less than 110mm.Hg in 9 patients; the diastolic reading was below 70mm.Hg in 10.

Discussion

Ever since Simmonds showed in 1914 that a syndrome of ill-health might result from a destructive lesion of the anterior pituitary, this disorder has been thoroughly studied.

In particular, the observations by Sheehan (1939) served to delineate its characteristics. He demonstrated that hypopituitarism frequently resulted from necrosis of the pituitary following post-partum haemorrhage. He also called attention to the variability of the clinical manifestations depending on the degree of pituitary destruction. Many excellent studies of the clinical features have been carried out, for example by Fraser and Smith (1941) and Querido et al (1954). It is clear that in the complete picture the patient will present evidence of hypothyroidism, hypogonadism and hypocorticalism and increased insulin sensitivity. Such a picture is not always encountered. When the degree of pituitary destruction is relatively mild the clinical manifestations are proportionately less defined. In general, gonadal failure is the first to occur. Thyroid failure usually follows next and then adreno-cortical insufficiency ensues. This order is not invariable and any one of the three may cause the predominant clinical picture. Usually, however, as Escamilla and Lisser (1942) pointed out, some of the stigmata resulting from each of the various glandular insufficiencies will be encountered.

When, therefore, hypothyroidism occurs as part of the syndrome of panhypopituitarism, the clinical features may differ in several respects from those seen in the primary form of the disease. This is illustrated by the analysis of symptoms and signs. Those manifestations which depend on alterations in integumentary structures were less marked. The skin was less coarse and less frequently had a yellow tinge. The appearance of "myxoedema" was less common and it may be noted that symptoms which to a large extent are caused by infiltration by "myxoedematous tissue", such as paraesthesiae and hoarseness, were less frequently encountered. Nevertheless, although less obvious clinically, the deposition of this abnormal substance does occur and the histological appearances of the skin are similar to those seen in primary hypothyroidism. The differences in the integumentary structure seem, therefore, to be the result, in part at least, of the other hormonal deficiencies. Such deficiencies in themselves are associated with changes in the skin. In pure pituitary dwarfism, lack of growth hormone produces a soft delicate skin with silky hair. A smooth, soft, pale skin is also typically encountered in hypogonadism, as in Klinefelter's syndrome. Since, in hypopituitarism it is likely, as Hubble (1952) suggests, that the production of growth and gonadotrophic hormones is first reduced, the eventual thyroid hormone deficiency will affect skin and related structures that are already abnormal.

It is of considerable practical importance to be aware of these differences in the clinical features between primary and secondary hypothyroidism. It is essential that differentiation of the two conditions is made since Castleman and Hertz (1939) and Means et al (1940) have pointed out the possibility that the administration of thyroid alone to patients with pituitary failure may precipitate a crisis of adrenal insufficiency. Even if this does not occur, full vigour will not usually be restored until treatment with adrenal steroids is also instituted. It must, therefore, be emphasised that in some cases of partial hypopituitarism, as in 4 patients in this series, the clinical picture may be very similar to that occurring in primary hypothyroidism. Clinical signs of other glandular deficiencies may be minimal. Indeed, Richardson (1956) states that "any patient who is suspected of being myxoedematous must also be regarded as a possible example of hypopituitarism". Furthermore, when hypothyroidism is due to pituitary insufficiency, full reliance cannot be placed on many of the laboratory procedures commonly employed to demonstrate impaired thyroid function.

It is essential, therefore, in any case of hypothyroidism, to enquire into any history of post-partum haemorrhage with the characteristic failure to lactate and menstruate thereafter. A pituitary cause should also be considered if hypotension is found, or if impaired fields of vision are present.

Conclusions

When thyroid failure is caused by pituitary insufficiency the clinical features of hypothyroidism are modified by the accompanying evidence of other endocrine insufficiencies. The consequent picture, however, does in most instances present a typical pattern. Little clinical difficulty, therefore, is usually experienced in making the diagnosis, especially if the cause of the pituitary destruction can be ascertained. In some cases, the hypothyroid state may be dominant, being almost indistinguishable from primary hypothyroidism and the pituitary origin only suspected by obtaining a history of post-partum haemorrhage, or by demonstrating evidence of a pituitary tumour. The differentiation of the two forms of hypothyroidism is necessary since the treatment of each differs.

CHAPTER 5

THE CLINICAL PICTURE

Since the early reports by Gull (1874) and Ord (1878) the clinical features of hypothyroidism have been frequently described so that the findings typical of the disorder are now well recognised. In the advanced case the physical signs are usually obvious, but at earlier stages they may be much less clear-cut and difficulty may arise in deciding whether or not they are present. As pointed out in a previous chapter, it is in these circumstances that errors may arise through observer variation. This may be overcome by laying down strict criteria for the symptoms and signs. The use of these, however, necessitates the appreciation of the characteristics of each feature. Thus, for example, when eliciting any symptom, appropriate supplementary questions may only be asked if the observer is aware of the manner in which the symptoms may affect the patient's everyday life. It is from this aspect, therefore, that the clinical features of hypothyroidism are reviewed in this chapter. Particular attention is paid to those which were shown in the foregoing analyses to be of diagnostic importance. The frequency with which each feature was encountered is indicated in parenthesis.

In the Report of the Myxoedema Committee of the Clinical Society of London (1888) 94 of the 109 patients were women and 15 men. In most subsequent series at least 80% of the patients have been female.

In this study 121 patients were women and 22 were men. The age at which the condition was diagnosed varied greatly, as shown in Figure 1.

The most frequently encountered symptom resulting from the generalised effect of decreased thyroid hormone is "tiredness" (98%), although as has been already seen, it is not specific to hypothyroidism. It has been used here to describe the sensation of exhaustion experienced after undertaking tasks previously undertaken without difficulty. Since the majority of patients are women, their ability to carry out housework provides a good reference standard on which to base questions. Thus, they typically state that they are unable to complete the work that usually has been a daily routine for years. This is in part due to the exhaustion that overtakes them and in part because of their disinclination even to start work. In addition, they frequently note how much longer they require to finish even a simple task. Complaints of "slowing up" are very typical, especially in the milder cases, and are therefore of considerable significance. They vary from generalisations such as "my housework has become a mountain" to more precise examples. Thus, one patient noted that her earnings as a piece-worker had gradually, but steadily diminished, being, of course, directly proportional to her production. Another patient was forced to abandon a part-time occupation as a dance-band leader because of inability to "keep the beat". The slowing may manifest in many ways that affect the tenor of everyday life even presenting, for example, as difficulty in crossing the road in safety. In many instances it reflects the changes in cerebral function, in particular the impairement of reaction time. In addition, however, the stiffness and weakness of the muscles that frequently develop plays an important part. This was apparent in a joiner, whose first symptom was inability to climb scaffolding. "Weakness" (61%) is difficult to distinguish from tiredness, but may in fact be noted as decreased strength in lifting objects such as pails and furniture. Impairment of grip of the hands is commonly recognised, although as will be seen later (Chapter 6), this probably arises for different reasons. Thus, some patients had noted an increased tendency to drop objects, as for example a building labourer, who was endangering his workmates by his inability to hold bricks. Many hypothyroid individuals observed some difficulty in performing simple tasks requiring a firm grip, such as peeling potatoes. Clumsiness of movements arise from this weakness in association with other changes, particularly the myxoedematous infiltration causing typically "swollen" hands. Consequent loss of precision leads to inability to carry out intricate movements such as knitting or typewriting. Changes in the quality of handwriting may be obvious. If the patient is observed while removing clothes, clumsy, ponderous and fumbling movements (73%) may be recognised and are as important diagnostically as the hyperkinesis of the thyrotoxic subject. The muscles themselves, especially the larger groups, may feel "tense" and some patients complain of a sensation of "tightness" in them. "Cramps" (36%) may cause considerable discomfort, although, as previously shown, these are more commonly encountered in "iatrogenic hypothyroidism". They may occur at rest, especially during the night, but are often precipitated by exercise, especially of a repetitive nature, such as brushing the hair.

Mental torpor was one of the features noted by Gull(1874) and various other mental changes were soon recognised as being of considerable importance. Thus in the Myxoedema Committee's Report (1888), delusions and hallucinations were found in nearly half the cases. In a large number insanity was also noted, taking the form of acute or chronic mania, dementia, or melancholia with a marked predominance of suspicion and self-accusation. Psychoses of this nature, for which Asher (1949) coined the alliterative term "myxoedematous madness", usually only occurs when the disease is very advanced. Consequently, they are infrequently encountered today and may be overlooked when they do in fact arise. Thus, hypothyroidism was only suspected in one patient with depressive psychosis when she failed to derive any apparent benefit from a full course of electro-convulsive therapy.

Since adequate circulating hormone is essential for normal cerebral function, any reduction will quickly result in mental change. Consequently, at an early stage in the development of hypothyroidism, evidence of impaired cerebration will become apparent. Although this may take various forms, these are all very typical of the disorder and are most important diagnostic features. The most frequently encountered symptom of this nature is "lethargy" (85%), a disinclination to start any tasks which have previously been carried out routinely. It is important to distinguish this mental tiredness, present before any work is even started, from the physical exhaustion resulting after exertion. Whereas many patients complaining of being easily tired are frustrated at being unable to complete their work, the hypothyroid subject becomes indifferent to whether it is done or not. She may remark that she has become lazy and that she "just cannot be bothered to get on with things". Changes of this nature in a previously active person are of considerable significance and may show in various ways. The patient, or especially the relatives, may observe the difference in the cleanliness or tidiness of the house. Even small tasks like washing dishes or clothes may suffer from this characteristic procrastination. In the early stages the patient is often able to "drive herself" to carry out her duties, but as the condition develops she is more and more loathe to leave her chair to do anything. Marked somnolence may be noted. This is often marked during the day, even in subjects who also complain of insomnia.

Frequently the changes in mental function may show as increasing indifference and disinterest. This may be reflected in the personal appearance and is often of importance in the younger woman who has previously been "dress-conscious", but who no longer takes any care in being tidy or neat. Similar changes in habit may be shown by loss of interest either in general pursuits or in special hobbies. One man, for example, had played football for many years and later had been a referee. When he became too old for this he had become a spectator attending regularly every week. With the onset of hypothyroidism, however, his life-long interest in this sport waned and he no longer attended any match or even watched the game on television. The inventions of this age, such as wireless and television command such universal attention that listening and viewing have become national habits so widespread that it is well worth questioning any patient about any differennes in their adherence to these forms of entertainment.

The retardation of cerebral function, however, may especially affect those processes in which intellectual agility is involved. In general, such changes are most apparent where the intellectual exercise required is greatest. For this reason, the earliest abnormality noted by one patient, a chartered accountant, was difficulty in carrying out complex calculations which previously had presented no trouble. This in part was due to impaired concentration which more frequently may be recognised by such symptoms as disinclination to read or difficulty in solving crossword puzzles. A more unusual presentation was illustrated by the pharmacist who found herself unable to decipher doctors' prescriptions, a feat for which she had previously been renowned. Impaired memory (65%) may also be apparent and be of variable degree. In the earlier stages it usually is seen as mild forgetfulness, so that the housewife forgets important items when shopping, or mislays her handbag frequently. Difficulty in remembering recent events is common and may be embarrassing, especially if the patient is working. It resulted in considerable difficulty for a civil servant in whom the increasing hypothyroid state was accompanied by an increasing inability to remember correctly the governmental forms appropriate for various situations.

The hypothyroid patient may be unaware of the mental slowing until specific questioning results in recollection of the changes that have insidiously affected everyday life in work and play. They are, however, highly characteristic and, of course, diagnostically important since they will be present at an early stage in the development of the disorder. The clinician is, therefore, well rewarded for the patience required to obtain adequate history. The impaired cerebration (48%) soon becomes apparent as the poor memory of the patient results in long cogitation before any answers are provided. The personality of the hypothyroid subject varies greatly. In some cases there is stubborness which is accompanied by a refusal to admit to anything. The majority, however, are of a very cheerful disposition, almost childlike in their willingness to be amused at the simplest remarks. Often too they are very garrulous, talking incessantly of minor affairs of little relation to their symptoms. It is often only with difficulty that they can be interrupted and the conversation brought back to matters relevant to their condition. As the condition progresses they become increasingly apathetic and depressed, with resulting indifference to the observer's questioning. Ultimately the patient will be more and more stuporose and finally hypothyroid coma will result from the combination of advanced mental changes, hypothermia and adrenal failure.

The hypothyroid state may also manifest by other alterations in the nervous system. Thus, for example, impaired hearing is common (40%). Howarth and Lloyd (1956) showed that this deafness is frequently perceptive, but it may also be of a middle-ear type, presumably due to local myxoedematous infiltration. It is clearly of considerable diagnostic significance especially when of recent onset in younger women. In such circumstances hypothyroidism must be considered as a possible cause since treatment will produce rapid relief. Other sensory disturbances may be experienced and not uncommonly the hypothyroid patient complains of a "bad taste". Dizziness and vertigo may also be encountered although rarely of a distressing degree.

It is clear from the symptom analysis that a symptom which occurs with considerable frequency is paraesthesiae (56%). This has been previously recorded as occurring in hypothyroidism but is usually ascribed to "peripheral neuritis" and little attention has been paid to it. This symptom was, therefore, studied in a special investigation which will be discussed separately in the next chapter. More attention has previously been paid to the tendon reflexes which may be found to be prolonged, with a characteristic delay in relaxation. This was first noted by Chaney (1924), but is now generally referred to as "Woltman's sign of myxoedema". Although these changes are usually obvious in the advanced case, they are less easy to demonstrate unequivocally by conventional clinical methods at earlier stages and are, therefore, of limited diagnostic value. In many studies of this phenomenon, for example that by Lambert et al (1956), elaborate equipment has been required. Lawson (1958), however, described a much more simple technique and suggested its use as a diagnostic procedure. Subsequently two types of apparatus have now become commercially available in the United States and are fairly extensively employed in the routine investigation of suspected hypothyroidism.

The apathy of the hypothyroid patient leads also to a disinclination to eat. The loss of appetite (40%) is in addition due to the general hypometabolism with resulting lowered food requirements. Just as decreasing weight despite excessive appetite should suggest thyrotoxicosis, so the finding of a combination of anorexia with rising weight should suggest hypothyroidism. Although it must be remembered that an increased weight may be found in many patients in the post-menopausal years, this is even more frequently encountered in hypothyroid patients, as shown by the symptom analysis. Means (1948) considered that some degree of slight obesity was present in over 80% of patients. Although Spence (1950) stated that obesity is not the rule, most authors do agree that the hypothyroid subject is usually overweight. Since obesity is difficult to define, they have therefore studied the excess weight over the normal average. Thus, Plummer (1940) found that 62% of 200 patients with hypothyroidism were above the mean of normals, the average excess being 10.1 lbs. After treatment there was an average loss of 13 lbs. Baron (1956) also studied the weight before and after therapy and concluded that there had been an average gain of 6 lbs. as the result of hypothyroidism. He noted that 63% of hypothyroid patients were above the standard mean, but pointed out that 43% of normals were also above the mean because of the positive skewness of the distribution curve. Because of this, it is fairly generally accepted that significant obesity is only present when the patient's weight is over 20% above the normal average. Figure 2 shows the distribution of the weights of 88 hypothyroid patients in the present study expressed as a percentage of the average weight for sex, age and height (Appendix IV). This has been obtained by using the nomogram relating height and weight at different ages devised by Wang (1957) from the tables of the American Medico-Actuarial Mortality Investigation. It may be seen that the weight of 25% of these patients was greater than 20% above the normal mean, indicating a significant degree of obesity. Moreover, the majority (73%) do lie above the mean and it is of interest therefore to observe that in the symptom analysis 76% of all the patients considered that their weight had increased. Nevertheless, it should be remembered that some patients were underweight, although only one was less than 20% below the normal average. There was no apparent relationship between the amount that patients were overweight or underweight and the severity of the hypothyroidism. Baron (1956) was also unable to demonstrate any such correlation. The patients themselves frequently are aware of the increase in weight either by weighing records or by becoming conscious of increasing constriction by their clothes. They may complain of a sensation of "tightness" around the abdomen. The development of the typical facies, however, is so gradual that the patient, her relatives and friends and even the doctor, may be unaware of the change, until a certain degree is reached at which the alterations are suddenly recognised. The stage at which this occurs varies greatly and depends to a large extent on the severity of the mental changes. Often there is realisation that the features have become different only when attention is specifically directed to them by direct questioning by a hospital physician to whom, seeing the patient for the first time, the appearance is pathognomonic. Several patients in this series had become aware of facial alterations by chance when perusing old photographs. Comparison of photographs was recommended by Asher (1955) and this "photograph test" is particularly of value in assessing the response to a therapeutic trial. In the advanced case the physiognomy is, of course, characteristic and has been variously described, such terms as "bloated" and "mask-like" being common. In particular, the periorbital tissues become so infiltrated that the eyelids become swollen and have a peculiar watery or pearly lustre. The upper lid may become so enlarged as to encroach on the visual fields. This periorbital puffiness (86%) often is apparent at an early stage, especially being evident as sacs of loose skin below the eyes. This sign is less liable to observer variation than an impression of "puffiness of the face" (95%).

Pallor (50%) may be present suggesting a much greater degree of anaemia than the mild degree that usually exists. As will be seen later, varying degrees of carotenaemia are frequently present and result in a yellowish pigmentation (48%). These changes in the skin colouration may have been noted by the patient herself because of difficulty in obtaining cosmetics of the appropriate shade with consequent changes from those previously used.

In his original description of cretinism, Curling (1850) was markedly impressed by the supraclavicular pads of fat.

Indeed, his report is titled "Two cases of absence of the thyroid body, and symmetrical swelling of fat tissues at the sides of the neck, connected with defective cerebral development". The reasons why these particular pads should appear remains obscure. Although it is not a consistent finding in hypothyroid subjects (57%), it is much less frequently present in obese patients in whom diagnostic difficulty is not uncommonly encountered. Similarly, "puffiness" at the wrists is more often found in hypothyroid patients. This possesses a firm, spongy quality when pressed. A similar firm sensation may also be experienced on palpation of the upper chest. These findings indicate infiltration with myxoedematous tissue. This also results in thickening of the skin, so that, on pinching, difficulty is experienced in lifting a loose fold. The skin is also cold (80%), dry (79%), and rough (70%). The coarseness may be demonstrated most readily by examining the elbows where the skin is normally thicker and wrinkled. In hypothyroidism, however, it becomes very keratotic, resembling "elephant-hide". The patient frequently has noted the scaling herself (77%) by observing flakes of dry skin falling when removing her stockings. These dry scales may be produced by gentle rubbing, especially on the back of the forearms.

Other integumentary structures may be affected by the lack of thyroid hormone. The nails, for example, may have been noted to require paring less often and to be more liable to break easily (41%). On examination they may be seen to be brittle (24%), thickened and often have rough, longitudinal striations (31%). The hair typically becomes dry (62%) and tends to fall readily (41%). Loss of hair is difficult to evaluate unless of a gross degree, such as usually only occurs in the advanced case. A change in the quality of the hair is of greater significance. Thus the patient may have noticed that her hair has become lifeless and limp and that as long as she retains any interest in her appearance, she has increasing difficulty in keeping it tidy. In particular, many observe that "permanent waves" preserve their shape for much shorter periods. Haircuts become necessary only at very long intervals. The loss of hair may manifest first as thinning of the eyebrows (84%), but as previously discussed, this sign is too frequently encountered in normal subjects (58%) for it to retain much diagnostic significance. Enlargement of the tongue is also commonly found in hypothyroid subjects (60%), but again is of limited diagnostic significance, in view of the difficulty in deciding whether or not the sign is present. This enlargement plays a part in the production of the typical speech of the hypothyroid patient causing slowness (56%) and slurring of words. In addition, infiltration of the vocal cords and nasal passages results in the thick, nasal deep quality of the voice (87%) which Asher (1949) described as resembling "a bad gramophone record, running down, of a drowsy, slightly intoxicated person with a bad cold and a quinsy". At earlier stages, weakness or huskiness are typical changes (74%). Consequently, several patients had noted that they were no longer able to sing and others observed that their voices had become so husky that there had been difficulty in being heard on the telephone. The thickening of the nasal passages also may result in an increased tendency to snore. This does appear to be present frequently, but was not included in the symptom analysis in view of the obvious potential witness variations. In fact, several relatives spontaneously mentioned that they heard the noisy snoring and one patient had actually been told about it by her next-door neighbour. It was so marked in another case that she had to be moved out of the ward to a lecture-room at night in order to permit the rest of the patients to sleep.

The general hypometabolism is accompanied in most cases by an increase in intolerance of cold (95%). This symptom is usually elicited easily by specific questioning regarding any changes in clothing habits, need for more blankets or the use of hot water bottles. As the condition advances, so the desire for heat increases to an inordinate degree which is much more marked than the normal preference for warmth existing in most subjects in this country. The patient, therefore, admits that she spends much of her time huddled over the fire. Confirmation may frequently be obtained by finding "erythema ab igne" on the legs. In bed, characteristically the patient may be seen hiding under a mound of bed-clothes with only her eyes and nose to be seen, the "snug sign" described by Asher (1955). Specific questioning also may elicit the fact that sweating has markedly decreased or virtually disappeared even in circumstances that would have produced it previously (68%).

The effect of hypothyroidism on the cardio-vascular system produces remarkably few changes apparent on clinical examination. As has been seen, bradycardia may be present, 47% of the patients in this series having casual pulse rates less than 69 per minute. Nevertheless, the rate was over 80 per minute in 21%. The diagnostic value of counting the sleeping pulse rate is considered separately (Chapter 7). The changes in the blood pressure have been studied by various authors. Most have considered, like Means (1948), that the pressure is extremely variable from case to case. He considered that although the classic finding is probably hypotension with low pulse pressure, both the systolic and diastolic pressure may be elevated in a considerable number of patients. In the present series similar findings have been encountered. The results have, however, not been fully analysed since it is clear that the blood pressure is of little diagnostic significance as moderate hypertension, especially systolic, is so frequently found in euthyroid patients in the same age groups as most of the hypothyroid cases. It may be noted, however, that Thompson et al (1931) showed that in patients who had previously been hypothyroid, the incidence of hypertension after treatment is higher than in the general population. The heart sounds often are distant and of poor quality. This is in part due to the obesity which also makes difficult any convincing clinical demonstration of cardiac enlargement. Slight ankle swelling may be encountered but a full picture of congestive cardiac failure is rarely seen. Means (1948) considered that it only occurs in hypothyroidism when another heart lesion is present. Thus, although pitting ankle oedema has been recorded by various authors and was found in 5 patients in this series, it was only found in one subject to a marked degree. She also had marked venous congestion, pleural effusions and ascites. Treatment with thyroxine, digitalis and mercurial diuretics resulted in improvement in these features as well as her thyroid state. Attempts to withdraw the diuretic therapy, however, resulted in deterioration of the cardiac condition once again. Even when she became euthyroid it was clear that thyroxine therapy alone was inadequate and that she required continued digitalis and diuretics.

Peripheral vaso-motor disturbances resulting in complaints of a Raynaud-type phenomenon occurred in some patients. This symptom was initially included in the symptom-analysis, but was later discarded because of the difficulty in discriminating accurately between it and cold intolerance.

The effect of hypothyroidism on other systems may similarly result in changes of a vague and inconstant nature. Thus, constipation (54%) is the only evidence of alimentary upset found with any significant regularity. It is, of course, only of diagnostic importance if of recent onset or markedly increased in severity. Flatulence, however, may in some be an embarrassing and distressing symptom.

The symptom analysis showed that menstrual upset may occur; abnormal uterine bleeding was present in 6 of 18 pre-climacteric women. Goldsmith et al (1952) showed that in 7 of 10 hypothyroid subjects there was no evidence of ovulation and considered that this resulted in a continuous oestrogen effect. Their findings also explain the low fertility of hypothyroid women, although this is also the result of impaired libido. Decreased sexual desire was in fact an early symptom in many of the men and pre-climacteric women and was restored by treatment. Although there is no convincing evidence that thyroid therapy is of any value in the treatment of sterility in general, the studies of King and Herring (1939) do suggest that it may be indicated in some cases of habitual abortion. Hoet et al (1959) also consider that mild degrees of maternal hypothyroidism are responsible for a number of congenital abnormalities. In such circumstances, therefore, if no other aetiological factor can be discovered, investigation of thyroid function is warranted. It should be remembered that although amenorrhoea may occur in primary hypothyroidism, this is much more commonly encountered when the impaired function is the result of pituitary insufficiency.

Conclusions

The clinical picture as it has been observed in varying degrees of severity in the course of this investigation has demonstrated that, although many of the symptoms and signs of hypothyroidism may be ill-defined, others result in characteristic alterations producing changes either in the everyday life, or in appearance. Such an alteration permits greater accuracy in the identification of a clinical feature. Accordingly, in any patient suspected of being hypothyroid especial attention should be paid to deciding whether any such feature is present or absent, particularly if it is also among these symptoms and signs most frequently occurring in proven hypothyroidism. For this reason, it is suggested that the changes in cerebral function produced by thyroid hormone deficiency play a considerable part in clinical assessment.

Nevertheless, since similar symptoms and signs may occur in conditions other than hypothyroidism, the finding of any one by itself is only really of significance in that it should lead to the condition being suspected. It is when these features are present in association that they build up a composite pattern typical of the disorder.

CHAPTER 6

ACROPARAESTHESIA IN HYPOTHYROIDISM

Paraesthesia is not generally recognised as being a symptom commonly encountered in hypothyroid states. However, as has been shown in the symptom analysis, it does in fact occur frequently, 56% of the patients studied having this specific complaint. Although various authors have noted the presence of paraesthesia or similar symptoms, few have paid much attention to it. When therefore the high incidence of this complaint became evident at an early stage in this study, it was considered that closer examination was warranted. The clinical and experimental findings obtained in this special investigation are presented in this chapter.

Subjects and Methods

This investigation comprises 35 consecutive patients observed in the course of the general study. The diagnosis of hypothyroidism was established in each as previously described. In these patients, particular care was taken in determining the exact nature of any sensory phenomena and in the examination of motor and sensory function in the hands. The cases were classified at this stage as minimal, mild, moderate or severe, on the basis of the general clinical picture and the

B.M.R. It may be noted that to facilitate presentation in this chapter the patients have been numbered in the order studied rather than by the numbers finally allotted and used in the appendices.

Examination by an electromyographic method (Simpson, 1956) was carried out in 11 patients. The conduction velocity of the median and ulnar nerves was measured by recording the time delay of the muscle-action potential (of the abductor pollicis brevis and of the abductor digiti minimi muscles respectively) after supramaximal electrical stimulation of the nerve at elbow and wrist. Coaxial needle-electrodes or silver-disc surface electrodes were used with conventional amplification and cathode-ray oscilloscope recording techniques. The method and the type of record obtained are illustrated in Figure 3.

Results

Paraesthesia - of the 35 patients, 26 complained of paraesthesia of the fingers. This was usually described as numbness or pins-and-needles and tended to occur either during certain activities, e.g. sewing, knitting or washing clothes, or during the night when the tingling was often sufficient to prevent sleep or to rouse the patient from sleep. It was usually present on waking in the morning and passed off soon after rising. Sometimes an "electric shock" sensation was noticed if an affected finger suddenly touched a hard object. Both hands were involved in 20 patients. Seventeen patients stated that the little finger and sometimes also the ring finger were not affected by paraesthesia. Seven described involvement of all their fingers and 2 patients described numbness restricted to the ulnar side of the hand. Motor symptoms were more difficult to assess. Most of the patients described the clumsiness of manipulation which is well recognised in hypothyroidism, but 8 patients described marked loss of power of finger-thumb grip and wasting of the hand suggestive of genuine paresis. Only 2 patients mentioned occasional tingling of the toes.

Sensory Impairment - Clinical examination showed evidence of sensory impairment to be present in 8 cases. Six of these and 2 further cases without sensory loss showed muscle atrophy. The sensory impairment was invariably on the radial side of the hand. Appreciation of pin-prick was reduced on the pads of the thumb, index and middle fingers and there was hypoaesthesia for light touch on the same fingers and the radial half of the ring finger, sometimes extending proximally to the palm of the hand. In one case, the dorsum of the radial part of the hand was similarly affected, but in all the others the changes were confined to the palmar surfaces. No demonstrable sensory changes were noted in the distribution area of the ulnar nerve.

<u>Motor Changes</u> - The motor changes usually consisted in weakness and atrophy of the abductor pollicis brevis and the opponens pollicis muscles. One patient had wasting of the first dorsal interosseous muscle of the right hand, and in another fasciculation of the flexor pollicis brevis was observed. All these muscles are wholly or in part supplied by the median nerve. Thus all the objective sensory and motor findings pointed to a lesion of the median nerve.

<u>Electromyography</u> - On electromyography with coaxial needle-electrodes, the classical signs of partial denervation (spontaneous fibrillation and reduced motor-unit activity) were noted in 5 cases with objective weakness. These manifestations were confined to the radial border of the thenar eminence, except in one case with fibrillation of the first dorsal interosseous muscle, which sometimes receives fibres from the median nerve (Rowntree, 1949).

<u>Conduction Velocity</u> - Conduction velocity determined by the method described was examined in 11 cases. Table 8 shows that the conduction-time of the median nerve was much increased in 3 cases, and that this increase was always due to a delay peripheral to the wrist-stimulating cathode. The conduction time between the two points on the nerve, obtained by subtraction, was normal in every case. In 4 other cases the conduction-time in the distal part of the median nerve was a little longer than

is found in normal subjects, but the equipment used in the present work did not allow for measurement to an accuracy greater than 1 m.sec. However, it is important to state that no unusual retardation was ever detected in the ulnar nerve, even in the first 3 cases mentioned.

Carpal Tunnel Syndrome - The clinical and electromyographic findings indicate that the neuropathy is restricted to that part of the median nerve distal to the wrist and is comparable in every way to the common carpal tunnel syndrome. In one patient, acroparaesthesia of the right hand had been promptly relieved by division of the flexor retinaculum six months previously. When she came under medical supervision moderate hypothyroidism was apparent. Weakness of her right abductor pollicis brevis was still present. She had recently begun to complain of tingling of the finger-tips of her left hand at night. No objective clinical or electromyographic changes were found. The symptoms disappeared when her hypothyroidism responded to treatment.

Relation of Neuropathy to Severity of Hypothyroidism - No correlation was noticed between the presence of neuropathy and the severity of the hypothyroidism. Indeed, many patients with neuropathy were only considered to have mild hypothyroidism whereas the most severely hypothyroid patient in the whole series had no neuropathy. On the other hand, a clear relationship was established between the clinical response to treatment of the hypothyroidism and the disappearance of the acroparaesthesia.

Follow-up - At the last survey 30 of the 35 patients had become euthyroid. Only 3 of these 30 still noticed occasional nocturnal paraesthesia. One had atrophy of the thenar muscles and this was unchanged. The other 27 were normal. Four patients were still graded as "mild hypothyroidism"; one of these had no change in the acroparaesthesia, the 3 others still having it occasionally. One case was still considered to be "moderately severe" with acroparaesthesia unchanged.

One of the histories is of particular interest (Table 9, Case 12). Bilateral median paraesthesia had been very persistent in a woman with moderate hypothyroidism. When this was treated with tri-iodothyronine the neuropathy disappeared. When treatment was changed to thyroxine she had a temporary relapse, during which paraesthesia returned, but it finally disappeared when control of hypothyroidism was regained.

Body weight - The patient's weight appears to be of greater significance than the degree of hypothyroidism. Selected cases illustrating this trend are shown in Table 9, which shows that severe hypothyroidism without excessive body weight is not accompanied by acroparaesthesia (Case 6), whereas, very slightly hypothyroid patients have this symptom if they are overweight (Case 4), and good metabolic response to treatment is not associated with recovery from acroparaesthesia if there is not significant loss of weight (Cases 4, 8 and 14). One man (Case 13) with severe myxoedema and bilateral median paraesthesia, with clumsiness of the hands, lost 14 lbs. weight in three weeks when treated intensively with tri-iodothyronine. Within that period his paraesthesiae disappeared and have not returned.

Restoration of Nerve-conduction Velocity - This was seen in one of the most severely affected patients (Case 2). The patient, a woman with "moderately severe" hypothyroidism had bilateral paraesthesia and sensory loss of median distribution in her right hand. Movements of her thumbs were clumsy, but quite powerful. No obvious wasting was present, but electromyography disclosed partial denervation of the right abductor pollicis brevis muscle. Conduction velocity of the right median nerve distal to the proximal palmar crease was greatly diminished, though the velocity above this point was normal (Table 8). Treatment with thyroxine achieved clinical cure of hypothyroidism, the patient lost 19 lbs. weight, the median nerve symptoms disappeared and the conduction velocity returned to normal (Table 10).

Discussion

Peripheral-nerve disorders in hypothyroidism are not widely recognised. The standard textbooks on neurology (Wilson, 1955; Brain, 1955) list hypothyroidism among the causes of peripheral neuritis, but no references to original papers are given, and it is not clear whether the tabulation represents the personal experience of the writers. From the context, it appears that generalised peripheral neuritis is intended rather than the more restricted syndrome termed "acroparaesthesia" which is, by usage, confined to paraesthesia of the hands (Kremer et al, 1953). The diagnosis of hypothyroidism is doubtful in the two cases reported by Currier and Brink (1948) to show correlation between multiple neuritis and hypothyroidism. Their first case developed a neuropathy ten years after thyroidectomy. The B.M.R. was -27%, but the blood-cholesterol was 80mg per 100ml. There was also a history of macrocytic anaemia. Free hydrochloric acid was present in the gastric juice, but steatorrhoea was not excluded. Treatment with thyroid extract caused "little change", but there was delayed improvement. In their second case hypothyroidism was diagnosed although the B.M.R. was only -8%, because the yellow colour of the patient's hands was considered characteristic of carotenaemia. This patient had an acute paresis of all limbs, with retention of tendon reflexes and a zone of sensory deficit along the dorsal spine. This unusual syndrome was regarded by

Currier and Brink as a manifestation of polyneuritis, but they admit that neither of their cases conforms to accepted criteria.

Paraesthesia of the hands in hypothyroid patients has been mentioned by some workers (Williams, 1950; Werner, 1955; Soffer, 1956), but has not been studied in detail. Few patients presented with paraesthesia as their primary complaint, but it was spontaneously mentioned by several others. On questioning it became clear that in most of them the paraesthesiae were indeed distressing, but the degree of disability was difficult to assess in some in view of the mental lethargy. The mental state also made the determination of sensory disturbances difficult in many patients. Nevertheless, investigation disclosed a high incidence of symptomatic disturbances and many demonstrable motor and sensory changes confined to the hands. Sensory loss occurred exclusively in the part of one or both hands supplied by the median nerve; motor phenomena involved only muscles in the hand supplied completely, or in part, by the median nerve. A few patients complained of paraesthesia involving the ulnar part of the hand. It is impossible to be dogmatic about subjective phenomena, but it should be noted that similar complaints are common in the carpal tunnel syndrome (Kremer et al, 1953).

The clinical findings thus indicated a lesion of the median nerve in its distal part in all respects similar to that recognised as the carpal tunnel syndrome. It was therefore of interest to find that the electromyographic study revealed that some of these patients had slowing of conduction restricted to the most peripheral part of the median nerve, but not involving the ulnar nerve. The changes are those described by Simpson (1956) in the carpal tunnel syndrome.

In none of the patients was there any evidence of a generalised diminution of the rate of conduction of the nerve impulse. This confirms the observations of Lambert et al (1951). These workers considered that the action potential elicited reflexly by tapping a tendon appeared after a normal delay, suggesting that the reflex arc and hence the nervefibres, conducted with normal velocity. Further evidence that metabolic change in the nerve does not provide an explanation for the peripheral nerve symptoms is seen in the lack of correlation between acroparaesthesia and the severity of hypothyroidism. On the other hand, there does appear to be a strong relationship between the symptoms and weight gain. Since the abnormalities found in both the clinical and experimental studies are identical with those encountered in the carpal tunnel syndrome, it is reasonable to conclude that acroparaesthesiae in hypothyroid subjects result from pressure on the median nerve by myxoedematous tissue under the flexor retinaculum. This view gains support from the relief obtained by operation in one case. Consequently, in view of the frequency with which this complaint was encountered in hypothyroid subjects, it must also be suggested that in any patient in whom the carpal tunnel syndrome is discovered, the possibility of hypothyroidism should be considered and excluded.

Conclusions

Median nerve acroparaesthesiae and paresis are common in hypothyroidism. There is no generalised abnormality of nerve conduction, but slowed conduction in the median nerve at the wrist can often be demonstrated. The clinical and experimental findings indicate compression of the median nerves in the carpal tunnels.

The paraesthesiae and paresis are probably caused by accumulation of myxoedematous tissue under the flexor retinaculum of the wrist.

CHAPTER 7

THE SLEEPING PULSE RATE IN HYPOTHYROIDISM

For many years sleeping pulse rate has been considered a useful diagnostic feature in thyrotoxicosis, most authorities agreeing that thyrotoxic tachycardia is distinguishable from the functional variety by the fact that it does not fall in sleep. A study of the sleeping pulse rate in thyrotoxicosis carried out by Crooks and Murray (1958) established the ranges of normality and showed its value as an aid to the diagnosis of thyrotoxicosis. It appeared likely to be of interest to extend this investigation by studying the sleeping pulse rate in hypothyroidism, not merely since this is the antithesis of thyrotoxicosis, but also because a bradycardia may be found in hypothyroid patients when awake.

Subjects and Method

Of the 197 subjects studied, 63 were hypothyroid, 25 being initially in the "Doubtful Hypothyroid" group. Sleeping pulse rates were also obtained in 134 euthyroid subjects; 27 were in the "Doubtful Euthyroid" group and the remaining 107 were hospital patients with varied disorders, but without evidence of any thyroid disorder.

Nurses were instructed to count the radial pulse for one minute at any time during the night that they were satisfied that the patient was asleep. The sleeping pulse rate of patients admitted to hospital for full investigation of their thyroid function was taken as the mean of the three lowest figures recorded.

Results

The distribution of the sleeping pulse rates is shown in Figure 4. It can be seen that although the pulse rates of the hypothyroid patients are in general slower than these of euthyroid individuals, there is a considerable overlap between the two groups. Thus in the range 60 to 72 beats per minute there are 40 (63%) of the 63 hypothyroid patients and 81 (59%) of the 137 euthyroid patients. Outwith this range, however, the sleeping pulse rate is of some diagnostic significance. Rates of less than 60 beats per minute were found in 20 (32%) hypothyroid patients, but only in 3 (2%) of all the euthyroid subjects. Conversely, 50 (37%) of the latter group had pulse rates greater than 72 beats per minute; whereas only 3 (5%) of the hypothyroid cases lay in this range. There was no significant difference in the distribution between the two hypothyroid groups.

Discussion

Crooks and Murray (1958) pointed out that although the recording of the sleeping pulse rate has for many years been recommended in the investigation of thyrotoxicosis, its use was limited since no ranges of normality have been provided. 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. In the latter group the lowest rates recorded for males were 53 beats per minute and for females 58 per minute. The use of a cardiotachometer, however, converted 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. Freeman and Mattingly (1956) have suggested that an accurate recording of the sleeping pulse rate might be obtained by strapping a microphone to the subject's great toe and in this way overcome the possibility of waking the patient. This is perhaps also unnecessarily complicated and the conventional method of counting the radial pulse was considered to be of greater practical value. The risk of errors in obtaining sleeping pulse rates was accepted, and was minimised by careful instructions to night nurses. Nevertheless, it is apparent that, despite these instructions, many nurses only counted the pulse for half or quarter minutes.

The results show that it is unusual for a sleeping pulse greater than 72 beats per minute to be encountered in a hypothyroid patient and the finding of a rate greater than this makes the diagnosis of hypothyroidism unlikely. On the other hand, normal subjects only rarely have sleeping pulse rates less than 60 beats per minute. Rates in this range, therefore, in a patient suspected of hypothyroidism are strongly in favour of the diagnosis provided other causes of bradycardia are excluded. Nevertheless, only 32% of the hypothyroid patients actually had slow rates. It is therefore considered that although slow or rapid pulse rates do have considerable diagnostic significance, the value of the recording of sleeping pulse rate is limited since so many hypothyroid patients lie in the intervening range.

Conclusion

The recording of the sleeping pulse rate is a simple procedure which may occasionally provide useful information in a patient in whom hypothyroidism is suspected.

CHAPTER 8

THE CLINICAL DIAGNOSTIC INDEX

In the preceding chapters an attempt has been made to show that of the many symptoms and signs which may be present in hypothyroidism some are of greater diagnostic significance than others. If the clinician appreciates the importance of these particular features and especially the characteristic manner in which they may affect a patient's health or appearance, he will be able to diagnose correctly most cases of hypothyroidism. Even so, errors in diagnosis will still arise since the process of making a clinical diagnosis is complicated and involves more than just history-taking and examination, however carefully these may be carried out. No single symptom or sign is diagnostic and it is only when they occur in combination that the typical clinical picture is built up. The clinician must, therefore, sift and evaluate multiple features and ultimately select the clinical syndrome which accounts best for the findings. Since, however, different clinicians place varying emphasis on these findings, their conclusions are also liable to considerable variation. By adopting a statistical procedure incorporating the principles of discriminant analysis, it has been found possible to reduce the variability of such interpretative conclusions and increase the accuracy of the clinical diagnosis. This was done by allocating a positive or negative value to each clinical feature, the values being based on the analysis of the frequency of symptom and signs. In this way a total score, or clinical diagnostic index, was obtained for each patient. It will be shown that these scores are helpful in distinguishing between hypothyroid and euthyroid patients.

The Construction of the Clinical Diagnostic Index

The clinical features were reviewed in the 110 cases which had given rise to no clinical diagnostic difficulty, the two "Definite" groups. Those which provided a contrast between the normal and hypothyroid groups were weighted by allocating a score to each. The positive or negative value of these scores were initially allocated on the basis of their relative diagnostic significance. The scores were then modified to diminish the effects of observer variation. This was done in part by reducing the value of the highest scores, because although these were attached to features of great diagnostic importance, differences between observers in noting their presence or absence would give rise to considerable variation in the total score. Some of the features were discarded as it was considered they were especially liable to observer variation. The clinical diagnostic indices, i.e. the total scores, were then calculated. These produced a good separation between the normal and hypothyroid subjects.

The features were then reviewed with regard to their respective incidence in the 95 patients in the two "Doubtful" groups. On the basis of this the weighting factors attached to them were then further modified. The "Definite" group was then re-scored using these revised values. A good separation between the normal and hypothyroid subjects persisted and these scores were accepted. The symptoms and signs selected are shown in Table 11 with their respective positive or negative values.

The Application in Routine Clinical Practice

The practical application was assessed in a further group of 37 patients, most of whom presented similar difficulty in diagnosis. The final diagnosis in these subjects, termed "test group", was again only made after full investigation and observation. In the examination of these patients, the criteria for the presence or absence of symptoms and signs were the same, where relevant, as for the preceding Symptom Analysis (Appendix I).

Results

Definite Groups - When the clinical diagnostic indices of the 55 normal and 55 hypothyroid subjects were analysed, the values were found to range from -21 to +4 for the former and from +11 to +39 for the latter (Appendix IV). Figure 5 illustrates the distribution of these unequivocally euthyroid and hypothyroid subjects. The separation between them will be seen to be from -1 to +15 with the exception of two cases. There was a clear division between the two groups at +10. Thus an index of less than +5 indicated hormality, while indices of +15 or over indicated hypothyroidism. Only one of the 100 subjects in this group had a score between +5 and +15. This has been called the "Equivocal" range.

<u>Doubtful Groups</u> - The distribution of the 95 subjects of this group is shown in Figure 6. A good division persisted between the cases finally shown to be euthyroid and those proved to be hypothyroid (Table 12), 98% of the former and 91% of the latter lying on either side of +10. Although 18 cases had scores in the equivocal range, and one hypothyroid subject lay within the normal range, 76 (80%) of the 95 cases were correctly diagnosed by this method. Thus 84% of those proved euthyroid had indices of less than +5, while the scores of 76% of those shown to be hypothyroid were above +15.

<u>Test Group</u> - Ten of the 37 subjects studied after completion of the scoring system were finally shown to be euthyroid. All

of these subjects had indices within the normal range. The remaining 27 were later proved to be hypothyroid. Three patients had scores in the equivocal range, but only one of these had an index below +10. The indices of other subjects all lay within the hypothyroid range.

When the indices of all the 242 cases studied are considered together there is almost complete separation at +10 (Table 13). Even when the equivocal range is introduced, the accuracy of diagnosis is still of a high degree. Thus 107 (93%) of the 115 euthyroid subjects and 112 (88%) of the 127 hypothyroid cases were correctly diagnosed. Only one case was completely wrong, the remaining 22 having indices in the equivocal range.

Statistical Analysis -

The distribution curves for the definite groups are shown in Figure 7. Statistical analysis of the results allowed the probabilities corresponding to the observed percentages to be calculated. These showed that a score greater than +5 is extremely unlikely in a healthy normal individual (P = 0.0003). It is almost as remote a possibility that an index of +15 or less should be encountered in a patient in whom hypothyroidism is obvious (P = 0.0006).

Distribution curves of the indices of those patients in whom diagnostic difficulty had been found, the doubtful and test groups, are illustrated in Figure 8. Probabilities have also been calculated for these cases and are shown in Table 14. These figures multiplied by 100 indicate the percentage of cases that might be expected to fall within the various ranges. Thus indices within the normal range (less than +5) would be found in 87.9% of euthyroid cases presenting diagnostic difficulty. The remainder would fall within the equivocal range since an index greater than +15 would only be encountered in one in every 200 such patients. Similarly, in doubtful hypothyroid subjects indices within the equivocal range might be expected in 19.9%, but the correct diagnosis (greater than +15) would be provided by the method in 78.23%. Only 1.79% of cases would have an index of less than +5. When all cases providing diagnostic difficulty are considered together, remembering that in the present series the approximate ratio of hypothyroid to euthyroid subjects is 6:5, the true potential accuracy of the index can be estimated. A correct diagnosis would probably be obtained in 82.6% and a wrong one in only 1.2%. The remaining 16.2% would likely fall in the equivocal zone, two-thirds of these probably being hypothyroid. This diagnosis is more likely if the index is greater than +10, since 14.28% of all hypothyroid cases would lie between +10 and +15 and only 2.55% of euthyroid subjects. Between +5 and

+10, the respective figures would be 5.7% and 9.06%.

Discussion

In evaluating the clinical evidence in an effort to make a diagnosis, a clinician combines his 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 eleven 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 13 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 obtained by 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.

The value of this technique in clinical diagnosis was first demonstrated by Crooks et al (1959) in a study of thyrotoxicosis. In this it was shown that by application of the method the diagnostic accuracy of the clinical diagnosis was not significantly different from that of radioiodine studies and basal metabolic rate estimations. The personal experience obtained in that study has proved invaluable in the present investigation, and knowledge of the problems previously encountered has permitted improvements to be made in the method.

The allocation of values to the various symptoms and signs was based on their relative diagnostic importance as shown by study of the symptom analysis. Thus a highly characteristic symptom, such as lethargy, was heavily weighted, while only a low value was placed on dryness of the hair, a sign found in a considerable number of normal subjects. The presence of many of these symptoms and signs results in an accumulation of positive weighting factors producing a high total score which is indicative of hypothyroidism.

When clinical diagnosis is taught, or practised, emphasis tends to be placed on the presence of certain symptoms and signs. In many instances, however, the absence of these features may be of equal importance. Thus the absence of lethargy favours the diagnosis of normal thyroid function to the same extent that its presence favours hypothyroidism.

In order to make the greatest possible use of the clinical evidence, therefore, both positive and negative scores must be allocated to the features. For example, in the initial weightings based on the definite groups, slow movements scored +4 while normal movements scored -3, since the former was present in 84% of the hypothyroid patients, but in only 7% of the normals. It was recognised that this feature was subject to considerable observer variation, and the score was therefore modified to +3 and -2. When the doubtful groups were considered, however, only 60% of the hypothyroid patients were recorded as having slow movements, while this was noted in 22% of those later proved euthyroid. The scores allocated to the presence or absence of this sign were therefore finally altered to +2 and -2.

In this way the weighting factors were developed for each of the symptoms and signs. The decrease in the values was based not only on the different frequency with which the features occurred in the doubtful groups as compared with the definite groups, but also on the liability of each to observer variation. This has previously been discussed and the importance of laying down criteria emphasised. In the course of this study it had become obvious that the recognition of some of the features was very difficult and liable to considerable variation. This was due to the fact that no adequate criteria could be provided for these features. A typical example is "largeness of the tongue" which has been omitted although noted in 60% of all hypothyroid patients and in only 17% of euthyroid subjects. In arriving at the final values for each feature, an attempt has been made 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 hypothyroid to the euthyroid range, or vice versa.

The cumulative effect of diagnostically significant features may be illustrated by the scores attached to the findings on examination of the skin. Each sign is not heavily weighted, but when they are all present (cold +2, dry +1, coarse +1, yellow +1) the total score of +5 does reflect the diagnostic importance of the typical picture of the skin in hypothyroidism.

It should also be noted that in selecting the features to which scores were allocated, an attempt has been made to preserve a balance between the symptoms and signs reflecting the effect of the hypothyroid state on the different systems. Thus, for example, in order to avoid too heavy weighting being placed on the changes in the nervous system, impairment of memory has been excluded. It is in fact rather an ill-defined symptom and the clinician may have difficulty in being certain about its presence or absence. Lethargy provides much more definite changes in the individual's everyday life and has consequently been preferred. Similarly, to avoid over-loading the importance of the changes in integumentary structures, "periorbital puffiness" has been chosen rather than the more vague sign of "facial puffiness".

Since the weightings allocated to the clinical features were initially based on their incidence in the control groups of normal and frankly hypothyroid subjects, it is not surprising that these two groups have been widely separated by the use of the clinical diagnostic index. In such cases presenting an unequivocal clinical picture, the index possesses no diagnostic value over normal clinical procedures. The importance of a separate study of cases presenting diagnostic difficulty has been stressed previously. The results of the index in correctly diagnosing the patients in the doubtful groups are therefore of greater significance in assessing the value of the diagnostic index. In these patients, 98% of those later shown to be euthyroid had indices of less than +10 while 91% of those proved hypothyroid had indices greater than +9. Since there is no gap between the groups, however, several of the scores lying close to +10, the separation is less valuable than might appear. A simple erroneous observation could result in a hypothyroid patient being placed in the normal range and vice versa. The distribution curves also illustrate this danger. Accordingly the "equivocal" range was introduced. As a result an incorrect observation can only result in a shift from the normal or hypothyroid ranges to this range. The introduction of this range will reduce the total number of correct diagnoses, but even so 84% of the euthyroid subjects in the doubtful group had indices of less than +5, and 76% of those proved hypothyroid had indices greater than +15. All but one of the remainder lay within the equivocal range.

The statistical analysis of the results shows that in any future series the diagnostic accuracy of the method would be very similar to that in the present series. The likelihood of an index falling into the wrong range is small. Thus it has been calculated from the distribution curve of the indices of all the hypothyroid patients in this study that the probability of an index less than 0 being encountered in a hypothyroid subject is slight. Indeed, only 18 in any 1000 hypothyroid subjects would be likely to have indices less than +5. Conversely, a score of more than +15 would be found in only 5 of every 1000 euthyroid patients suspected of being hypothyroid. Considerably fewer would have indices greater than +20. It may therefore be confidently concluded that the finding of a score of more than +20 establishes the diagnosis of hypothyroidism so firmly that no further investigation is required. Similarly, the diagnosis is excluded if the index is less than 0. Scores lying between 0 and +4 and between +16 and +20 also strongly favour respective diagnoses of normal and impaired thyroid function. It is, however, desirable when such indices are found, to carry out a single further investigation. If this agrees with the diagnosis indicated by the index, this diagnosis is amply confirmed. If not, further tests of thyroid function should be performed. The necessity for full investigation is indicated by the finding of an index in the equivocal range of +5 to +15. As will be seen later, the laboratory tests in such patients often do provide results which are borderline or of doubtful significance. It is clear that no single test is completely infallible, and more than one procedure therefore should be employed. In interpreting the results, however, it may be remembered that a score of greater than +9 is more likely to indicate hypothyroidism.

The true value of the clinical diagnostic index can only be assessed by using it in routine clinical practice. For this reason, 37 additional patients were studied. The index resulted in the correct diagnosis in 34 of these, the remaining 3 having scores in the equivocal range. Further studies to observe the accuracy of the index in the hands of independent observers would be of great interest. In the previous study of the method in thyrotoxicosis, it was shown that no statistically significant difference existed between the scores obtained by observers if they had some experience of thyroid disease, or had received clear instructions in the technique and criteria for examination. In the recording of individual symptoms and signs, there was usually some disagreement between observers, but that was usually insufficient to alter significantly their mean score. When the accuracy of the index in diagnosing thyrotoxicosis was tested by clinicians in four separate hospitals, there was no significant difference in the results obtained. Since precautions taken in this study to minimise observer variation have been similar to those employed in the previous investigation, it may be suggested that any differences in the total indices obtained by other observers will also be slight.

It could be suggested that the clinical diagnostic index can add little to the accuracy of the diagnosis made by conventional clinical methods. This is almost certainly true of the definite group in this study where the diagnosis was obvious. When the doubtful groups are considered, the method does appear to have a definite advantage. All the 95 patients had already caused diagnostic difficulty and have been considered separately because one or more clinicians had been unable to make a definite diagnosis. With the use of the index, however, a correct diagnosis was made in 76 (80%). It is likely that, if there had been no laboratory facilities available and a definite decision had had to be made purely on clinical grounds, the physician would have diagnosed many of these cases correctly. It is equally possible, however, that in some he would have reached the wrong conclusion. In others, even physicians experienced in thyroid disease would have hesitated to make a definite diagnosis and suspended judgement until a full therapeutic trial had been carried out. This is especially likely when the condition is seen at an early and mild stage in its development. A careful review of the histories permits the suggestion that there would have been such reluctance in diagnosing hypothyroidism in a considerable number of cases and certainly in a greater number of patients than the 22 in whom the index, by falling in the equivocal range, indicated the need for further investigation. It may be emphasised that a "normal" index was encountered in only one hypothyroid patient, but even this fell in the range where it has been suggested that a confirmary test is desirable. It appears highly probably therefore that the application of the diagnostic index does provide an overall diagnostic accuracy of an order greater than could be achieved by ordinary clinical examination.

The assessment of clinical severity of hypothyroidism has always presented difficulties since this also must be based on the relative value placed by individuals on the clinical features and on their overall impression. Although the values allocated to the symptoms and signs are based on their importance in differentiating normal from abnormal, it is obvious that the more of these features that are present, as occurs in more advanced hypothyroidism, the higher will be the total score. Consequently the diagnostic index will, to a certain extent, reflect the severity of the condition. Modifications of weighting factors so as to express the degree of abnormality of individual features, could be carried out to improve this aspect. Nevertheless, as it stands, the numerical value of the index does allow its use as a measure of clinical severity. It may, therefore, be employed to compare the clinical state with objective measures of thyroid function and, as is shown later, to correlate its degree with the results of these tests. Moreover, the use of a quantitative index allows other clinicians acquainted with the method to appreciate the clinical status of a patient in any report of studies of hypothyroid states, without having to study full details of a case history.

Conclusions

By applying a statistical technique to routine clinical procedures it has been possible to construct a 'clinical diagnostic index". This reduces the errors arising from observer variation and individual interpretive conclusions and thus increases the accuracy of the clinical diagnosis. It is of value in day to day practice as it is a rapid, reliable and simple method. By its use the number of patients in whom any further investigation is required is greatly reduced.

CHAPTER 9

THE APPLICATION OF THE CLINICAL DIAGNOSTIC INDEX

In the preceding chapter it was suggested that the use of the clinical diagnostic index provides greater overall diagnostic accuracy than can be obtained by ordinary clinical assessment. It should therefore be particularly valuable in those cases where difficulty has been experienced in reaching a diagnosis by conventional means. In this chapter selected cases are reviewed which illustrate some of the reasons why reluctance to make a definite diagnosis existed and demonstrate how, by overcoming these, the index did indeed prove useful.

It was apparent in the analysis of symptoms and signs that many of the clinical features encountered in hypothyroid patients could also be found in normal subjects, although with a lower incidence. Consequently it is not surprising to find that a common cause of difficulty in those patients later proved to be euthyroid was the presence of many symptoms. This may be illustrated in the following example:-

Female, aged 48 years

Symptoms

Tiredness	1	Skin unchanged	-1
Lethargy	3	Weight increased	2
Paraesthesiae	2	Constipation absent	-1
Cold intolerance	1	Hoarseness absent	-1
Hair untidy	2	Hearing unchanged	0

SYMPTOM SCORE 8

Signs

Cerebration normal	-1	Supraclavicular puffiness	2
Movements normal	-2	Hair dry	1
Skin normal	-3	Casual pulse rate 88/minute	-2
Periorbital puffiness absent	-2		

SIGN SCORE -7

DIAGNOSTIC INDEX 1

Final Diagnosis (obtained as defined in Chapter 2) -- EUTHYROID.

The symptoms in this patient were menopausal in origin. The high symptom score is not supplemented by a raised sign score and the diagnostic index is within the normal range. Since hypothyroidism frequently becomes apparent in the late forties or early fifties, many post-menopausal women, in whom there are similar symptoms, are suspected of being hypothyroid. Careful examination should make the diagnosis clear. Nevertheless, this group accounts for a large proportion of the patients referred for radioiodine studies in whom the tests prove negative.

Many physicians tend to regard positive signs as more important than positive symptoms. This is generally true. In hypothyroidism, however, there may be a tendency to place too much emphasis on an impression of the subject's appearance - the "hypothyroid facies". This became obvious when many of the euthyroid patients causing difficulty were studied. The following example is typical of this group:-

Female, aged 61 years

Symptoms

Tiredness	1	Constipation	3
Lethargy absent	-3	Hoarseness	2
Paraesthesiae absent	-1	Sweating, hair,	
Temperature indifference	-1	hearing, appetite,	
Skin unchanged	-1	weight- unchanged	0

SYMPTOM SCORE 0

Signs

Hoarse voice	1	Periorbital	
Cerebration normal	-1	puffiness	2
Movements normal	-2	Supraclavicular	
Skin dry	1	puffiness	2
Skin warm	-2	Casual pulse rate	
Hair dry	1	80/minute	0

SIGN SCORE 2

DIAGNOSTIC INDEX 2

Final Diagnosis -- EUTHYROID

This patient was very obese and looked "puffy". However, in addition to the absence of several typical signs, there were no important symptoms, apart from constipation and hoarseness. The symptom score thus compensated for the signs. As shown by these examples, it is apparent that the difficulties in diagnosis arose from the clinician tending to place undue importance on the presence of signs or symptoms and not paying enough attention to their absence. Often there was a tendency to be influenced by the symptoms alone, or vice versa, and thus fail to maintain a balance between the symptoms and signs.

In the hypothyroid patient, the difficulties appear to be the reverse. They arise mainly from the absence of features considered to be of importance with less emphasis being placed on the presence of equally important findings. In the following example, although all the signs are present, there has been reluctance to reach a definite diagnosis because of the lack of symptomatology.

<u>Male, aged 58 years</u>

<u>Symptoms</u>

Tiredness	1	Constipation absent	-1
Lethargy absent	-3	Hoarseness absent	-1
Paraesthesiae absent	-1	Sweating, hair, appetite, hearing - unchanged	0
Cold intolerance	1		
Skin dry	3		
Weight increased	2		

SYMPTOM SCORE 1

<u>Signs</u>

Speech hoarse	1	Periorbital puffiness	2
Cerebration slow	2	Supraclavicular "	2
Movements slow	2	Hair dry	1
Skin - coarse, dry, cold, yellow	5	Casual pulse rate 64/minute	1

SIGN SCORE 16

DIAGNOSTIC INDEX 17

Final Diagnosis - HYPOTHYROID

Although this is an extreme case, which nevertheless is correctly diagnosed by the index, in general the reluctance to make a diagnosis in those finally shown to be hypothyroid was similarly caused by the absence of typical symptoms of hypothyroidism rather than of signs. The following subject, however, complained of nearly all the more important symptoms but several typical signs were absent. The index, however, gave the correct diagnosis.

Female, aged 45 years

Symptoms

Tiredness	1	Skin dry	3
Lethargy	3	Weight decreased	-2
Paraesthesiae	2	Constipation	3
Deafness	1	Hoarseness	2
Heat preference	1	Sweating, appetite - unchanged	0
Hair untidy	2		

SYMPTOM SCORE 16

Signs

Hoarseness	1	Supraclavicular puffiness	2
Cerebration slow	2	Hair dry	1
Movements slow	2	Casual pulse rate 72/minute	0
Skin - warm,	-2		
moist	-1		
Periorbital puffiness absent	-2		

SIGN SCORE 3

DIAGNOSTIC INDEX 19

Final Diagnosis - HYPOTHYROID.

Full appreciation of the clinical features may still lead to diagnostic difficulty since undue emphasis may be placed on those symptoms and signs which are known to be most important. Consequently, when these features are absent there may be considerable reluctance to make a clinical diagnosis of hypothyroidism, whatever other clinical evidence is present.

Since the diagnostic index was constructed on the basis of the relative frequency and diagnostic importance of the clinical features, it is clear that it is also liable to this tendency to imbalanced evaluation. Indeed, the absence of symptoms and signs of high value is evidently the reason why diagnostic indices of hypothyroid subjects did fall into the equivocal zone, as illustrated by the following case:-

Female, aged 54 years

Symptoms

Tiredness	1	Skin unchanged	-1
Lethargy	3	Weight increased	2
Paraesthesiae	2	Constipation absent	-1
Temp. indifference	-1	Hoarseness	2
Hair untidy	2	Sweating, hearing, appetite - unchanged	0

SYMPTOM SCORE 9

Signs

Hoarseness	1	Periorbital puffiness	2
Cerebration normal	-1	Supraclavicular puffiness	2
Hair dry	1	Casual pulse rate 68/minute	1
Movements normal	-2		
Skin - warm	-2		
moist	-1		
yellow	1		

SIGN SCORE 2

DIAGNOSTIC INDEX 11

Final Diagnosis - HYPOTHYROID

Nevertheless, although the index did not provide an outright "correct" diagnosis in this case, it did, by falling within the equivocal zone, indicate the need for full further investigation.

Euthyroid subjects falling within the equivocal zone often had either an accumulation of many features of low value, or of high symptom scores associated with one or two heavily weighted signs. Negative scores arising from the physical examination did not compensate for the positive symptom scores as shown by the following case:-

Female, aged 50 years

Symptoms

Tiredness	1	Weight increased	2
Lethargy	3	Constipation absent	-1
Paraesthesiae absent	-1	Hoarseness absent	-1
Temp.indifference	-1	Hearing, sweating, appetite -unchanged	0
Hair dry	2		
Skin dry	3		

SYMPTOM SCORE 7

Signs

Hoarseness absent	0	Periorbital puffiness	2
Cerebration normal	-1	Supraclavicular puffiness	-2
Movements normal	-2	Hair normal	0
Skin - cold	2	Casual pulse rate 72/minute	0
dry	1		

SIGN SCORE 0

DIAGNOSTIC INDEX 7

Final Diagnosis - EUTHYROID

These cases have been selected to illustrate most clearly the reasons for diagnostic difficulty. They are, therefore, the most obvious and extreme examples, but show the trends typically found in many of these patients. It is evident that in most there has been a reluctance to make a diagnosis because the clinical picture has been considered incomplete, usually because of the absence of certain features which an individual clinician has personally considered to be of great significance. It is probable that patient history-taking and examination would have revealed the true diagnosis in many instances, provided the findings were carefully assessed. This is exactly what is accomplished by the diagnostic index since it eliminates the errors arising from individual interpretative conclusions. Its success is illustrated by its diagnostic accuracy in the preceding examples. The index was completely wrong in only one case. On general clinical assessment also this patient was considered probably to be euthyroid. Investigations, however, indicated impaired thyroid function. The final diagnosis of hypothyroidism was made after observing a therapeutic trial with thyroxine which produced complete relief of all symptoms and signs. It was because the latter were of low value and were outweighted by the negative scores attached to the absent features that the index gave an incorrect result.

Female, aged 79 years

Symptoms

Tiredness	1	Appetite decreased	1
Lethargy absent	-3	Weight decreased	-2
Paraesthesiae absent	-1	Constipation	3
Cold intolerance	1	Hoarseness absent	-1
Hair dry	2	Hearing, sweating unchanged	0
Skin unchanged	-1		

SYMPTOM SCORE 0

Signs

Hoarseness absent	0	Periorbital puffiness	-2
Cerebration normal	-1	Supreclavicular puffiness	-1
Movements slow	2		
Skin - cold	2	Hair dry	1
moist	-1	Casual pulse rate 76/minute	0

SIGN SCORE 0

DIAGNOSTIC INDEX 0

Hypothyroidism was only suspected in this patient after full gastro-intestinal investigation had failed to reveal any cause for her constipation, which despite her age was considered to be significant in view of its short duration. The signs that were present were slight and the other symptoms were only elicited after full supplementary questions were asked.

In most cases of hypothyroidism one or two symptoms will usually be especially troublesome. Fortunately those most frequently encountered are those which produce the most characteristic alterations in the patient's life, as has already been seen. Thus, the findings of such complaints as lethargy and "slowing up" or even cold intolerance, should immediately result in the possibility of hypothyroidism being considered. Other symptoms may then be elicited, but since they are mild at the earlier stages, the appropriate supplementary questions must be asked. However, it is when these less important and often less characteristic symptoms dominate the clinical picture that hypothyroidism may fail to be considered. Consequently there will be no attempt to enquire about the more typical symptoms, which may very well be present also, although not causing the patient as much distress as her primary complaints. Thus it has already been shown how one patient underwent operative treatment for her acroparaesthesiae six months before hypothyroidism was diagnosed and explained her general ill-health. In the same way, many patients had been observed for considerable periods and had received treatment directed towards the relief of symptoms which were in fact the result of hypothyroidism. Admittedly many of these complaints could not be considered to be typical of hypothyroid states, but in fact when eventually it was considered, the diagnosis became clear-cut with careful history-taking and examination. With specific therapy the initial symptoms receded. Although it is desirable, therefore, that clinicians should be aware of these atypical presentations, any of the many "minor" symptoms previously mentioned may dominate the clinical picture in this way. Some are well recognised as producing the picture of "masked" hypothyroidism. In particular, the disturbances of ovarian function previously discussed may distract the clinician's attention. Thus one patient had undergone dilatation and curettage because of menorrhagia twice in 18 months before hypothyroidism was suspected. Another had had two miscarriages and one stillbirth before the diagnosis of hypothyroidism was made. The complaint of one patient of diminished libido had been dismissed as psychological only six months previously. It is clear, therefore, that the onus for diagnosing hypothyroidism does not rest with the physician alone. In many other instances the patients in this series had initially been seen in other clinics.

In some hypothyroidism had been suspected and the patient referred for investigation. In others the initial complaint had been treated along other lines for considerable periods and only when there had been no improvement was the possibility considered that a generalised disorder might be responsible for a local complaint. For example, one patient had previously undergone full investigation by ear, nose and throat specialists because of persistent dizziness which was later completely relieved by thyroid therapy. On the other hand, in one subject attending the Ear, Nose and Throat Clinic complaining of recent deafness, hypothyroidism was suspected as the result of routine examination which showed the vocal cords to be white and swollen, appearances considered to be typical of myxoedematous infiltration.

In many patients in the present study there appeared to be symptoms of a Raynaud-type phenomenon, but it was difficult to distinguish these from the general cold-intolerance. The converse was, however, true and a number of patients had attended clinics where attention was directed only to their peripheral vascular complaints. In these patients, as in the others mentioned above, once the possibility of hypothyroidism had been considered, careful examination revealed the other clinical features. This may be illustrated by a single example:-

A female, aged 64 years, was first seen at a Vascular Clinic in November, 1955 with a complaint of "bad circulation in the hands", and a diagnosis of Raynaud's syndrome was made. "Ronicol" was prescribed and she also received two courses of baths and one of ultrasonic therapy. When, by January 1957 there was no appreciable benefit, it was considered that her persistently low voice might be of significance. She was therefore referred to the Endocrine Clinic. The features elicited there were:-

Symptoms

Tiredness	1	Skin changes absent	-1
Lethargy	3	Constipation absent	-1
Paraesthesiae absent	-1	Hoarseness	2
Deafness	1	Weight and appetite unchanged	0
Cold intolerance	1	Hair changes	2
Decreased sweating	2		

SYMPTOM SCORE 9

Signs

Hoarseness	1	Supraclavicular puffiness	2
Cerebration normal	-1	Hair dry	1
Movements slow	2	Casual pulse rate 80/minute	0
Skin - cold, dry	3		
Periorbital puffiness	2		

SIGN SCORE 10

DIAGNOSTIC INDEX 19

Final Diagnosis - HYPOTHYROIDISM

It was clear that many of these symptoms had in fact only been noted by the patient subsequent to her first visit to hospital and were still of a mild degree. Similarly the signs were slight.

In many of the patients like this in whom the diagnosis of hypothyroidism was initially overlooked, the changes were not obvious. Often the symptoms had not bothered the patient unduly and certainly to a lesser extent than the primary complaint. It is possible that without the careful history-taking that has been laid down as part of the procedure for the diagnostic index, these symptoms might not have been elicited. In the same way, the use of the strict criteria for the presence of signs is likely to result in more careful observation of these significant features. It may therefore be suggested that although the index may only be applied when hypothyroidism is suspected, acquaintance with the technique does lead to an increased appreciation of the importance of the clinical features. Consequently there will be an increased awareness of the possibility of the condition existing whenever the significant findings are met in the course of the routine examination of any patient, whatever the presenting complaint. This may be illustrated by the following case:-

Male, aged 50 years, who had been troubled for many years with varicose veins which had intermittently ulcerated. Healing had usually taken place spontaneously. In the preceeding 12 months, however, the varicose ulcers had failed to respond to all local measures. When complaints of lethargy and cold intolerance were also mentioned, attention was directed to his thyroid state. The findings were:-

<u>Symptoms</u>

Tiredness	1	Hair changes absent	0
Lethargy	3	Skin changes absent	-1
Paraesthesiae absent	-1	Appetite decreased	1
Deafness	1	Weight unchanged	0
Cold intolerance	1	Constipation	3
Decreased sweating	2	Hoarseness absent	-1

SYMPTOM SCORE 9

<u>Signs</u>

Hoarseness	1	Supraclavicular puffiness	-1
Cerebration normal	-1		
Movements normal	-2	Hair normal	-1

Skin - cold	2	Periorbital puffiness	2
dry	1	Casual pulse rate 80 per minute	0
yellow	1		

SIGN SCORE 2

DIAGNOSTIC INDEX 11

In this case the index fell within the equivocal range. This, however, indicated the necessity for further investigations. These showed unequivocal evidence of impaired thyroid function. Unfortunately the man failed to report back after treatment was commenced and the therapeutic response could not be observed. Cohen (1934) reported a similar case in whom therapy resulted in healing in five weeks of leg ulcers which had shown no tendency to heal for the previous six years.

Where another organic disorder is coincidentally present there may be a tendency to overlook the accompanying hypothyroidism. This is particularly liable to happen when the patient is anaemic. The finding of low blood levels in an individual may result in the assumption that these are responsible for symptoms which are in fact caused by hypothyroidism. If it is not remembered that impaired thyroid function may result in a mild anaemia, the cause of the anaemia may be overlooked. It is only when there is a failure to respond to haematinics that hypothyroidism may be suspected. Thus several cases of "unresponsive anaemia" were encountered in this study. Most had previously been treated with liver extract or cyanocobalamin by their own practitioners often for considerable periods. The resemblance of the clinical picture of hypothyroidism and pernicious anaemia has previously often been noted and in these cases had clearly also caused difficulty. In both, such features as yellowness of the skin and paraesthesiae may be encountered in addition to symptoms like tiredness, chilliness and dyspnoea. However, careful history-taking and examination should differentiate the two conditions. It must, of course, be remembered that although the "anaemia" of hypothyroidism is typically normocytic, the finding of microcytic or macrocytic blood pictures does not exclude the diagnosis. There may also be iron deficiency, especially if there has been blood loss due to menorrhagia. Moreover, Tudhope and Wilson (1960) consider that in hypothyroidism there is a relatively high incidence of megaloblastic anaemias which is usually of a typical Addisonian pernicious anaemia type. On the other hand, the vague history of ill-health encountered in many anaemic patients not infrequently causes a clinician to consider hypothyroidism as a possible cause of symptoms. Thus several patients with anaemia may be found in the "Doubtful Euthyroid" group. The index, however, provided assessment as illustrated by the following example:-

Female, aged 60 years

Symptoms

Tiredness	1	Skin changes absent	-1
Lethargy absent	-3	Appetite unchanged	0
Paraesthesiae absent	-1	Weight unchanged	0
Cold intolerance	1	Constipation absent	-1
Sweating unchanged	0	Hoarseness absent	-1
Hair changes absent	0		

SYMPTOM SCORE -5

Signs

Hoarseness	1	Periorbital puffiness	2
Cerebration normal	-1	Supraclavicular " absent	-1
Movements slow	2		
Skin - dry	1	Hair dry	1
warm	-2	Pulse rate 66/minute	1
yellowish	1		

SIGN SCORE 5

DIAGNOSTIC INDEX 0

Sometimes the impaired thyroid function will result in changes in the accompanying condition which may be spotted by the alert clinician. For example, the development of hypothyroidism in a diabetic subject is usually accompanied by decreased insulin requirements. This may manifest by frequent hypoglycaemic incidents which persist despite reduction in insulin dosage. This pattern was observed in all three diabetic patients in this series. At the time that hypothyroidism was diagnosed, the daily total dosages of insulin mixtures which in the past had given satisfactory control, had been reduced from 34, 34 and 48 units to 12, 17 and 18 units respectively.

It has been recognised for a long time that there are certain disorders that simulate the hypothyroid state and may therefore be mistaken for it. In the present series these conditions have once again been the cause of clinical difficulty in diagnosis. Thus it has been shown earlier that among those patients suspected of being hypothyroid but later proved euthyroid, were many women with post-menopausal symptoms and others with simple obesity. Another condition frequently considered to cause difficulty is nephrosis, since in this disorder the facial appearance may also resemble the hypothyroid facies. In one subject in the "Doubtful Euthyroid" group, a male aged 74 years, this was in fact the actual diagnosis. The findings were:-

Symptoms

Tiredness	1	Hair changes	2
Lethargy absent	-3	Skin dry	3
Paraesthesia absent	-1	Appetite unchanged	0
Deafness absent	0	Weight increased	2
Heat intolerance	-3	Constipation absent	-1
Sweating unchanged	0	Hoarseness absent	-2

SYMPTOM SCORE -2

Signs

Hoarseness present	1	Periorbital puffiness	2
Cerebration normal	-1	Supraclavicular " absent	-1
Movements normal	-2		
Skin - coarse, dry	2	Hair dry	1
warm	-2	Pulse rate 76/minute	0

SIGNS SCORE 0

DIAGNOSTIC INDEX -2

Final Diagnosis - Euthyroid.

In this man the facies did indeed suggest hypothyroidism and the diagnostic difficulty was increased by the presence of a scaling dermatitis. Despite this, however, the diagnostic index provided the correct diagnosis. In these subjects the finding of gross pitting oedema should lead the clinician to suspect nephrosis rather than hypothyroidism in which oedéma is rarely encountered. Similarly, gross albuminuria is uncommon in hypothyroidism. Although traces were occasionally found, there were significant amounts of albumin (two parts Esbach or more) in only five hypothyroid patients.

Hypothyroidism is usually suspected in other disorders because of the occurrence in them of many of the symptoms and signs that are found in hypothyroid subjects. It must, however, be remembered that these other disorders will also be accompanied by additional features typical of each which, when identified, will permit hypothyroidism to be excluded. This will be, in addition, readily accomplished by an impartial evaluation of the clinical findings by avoiding undue emphasis being placed on any single feature. The examples of such cases quoted in this chapter shows that the clinical diagnosis will provide such an evaluation. It is considered, therefore, that the success of this technique in separating these cases which had, for a variety of reasons, caused diagnostic difficulty when conventional clinical assessment was employed, illustrates its value as a diagnostic measure.

Conclusions

When the application of the diagnostic index to those cases in whom diagnostic difficulty had been found with routine clinical methods is studied, many of the causes for this difficulty have become obvious. It is clear, however, that these may be overcome by the use of the index. It was of equal value in those cases where the clinician had been reluctant to make up his mind because he considered the clinical picture incomplete and in those subjects suffering from other disorders, but in whom the presence of some of the clinical features frequently found in hypothyroidism had made the exclusion of this diagnosis difficult. The index does, in addition, provide an increased appreciation and awareness of the symptoms and signs of hypothyroidism which consequently permits the disorder to be suspected more readily when presenting in atypical forms, and thereafter be accurately diagnosed.

CHAPTER 10

SECTION I - THE CLINICAL EVALUATION

Summary

A clinical study has been carried out in 310 subjects. Hypothyroidism was shown to be present in 195 patients. In 53 it followed treatment of thyrotoxicosis and in 15 resulted from pituitary insufficiency. The disorder was either primary or associated with Hashimoto's thyroiditis in 127. Sixty patients had initially been suspected of being hypothyroid, but were finally shown to be euthyroid. The remaining 50 were normal healthy individuals used as control subjects.

An analysis of the incidence of symptoms and signs which are generally considered typical of the hypothyroid state was carried out. A comparison of the frequency with which these features occurred in both euthyroid and hypothyroid subjects revealed their relative importance. A study of the clinical picture as it was observed in the hypothyroid individuals showed which of these symptoms and signs also produced the most characteristic changes in general health and appearance. It was thus possible to evaluate the diagnostic significance of the clinical features and on this basis to allocate numerical values to each. The aggregate score in the individual case has been termed the clinical diagnostic index.

These indices have been shown to be of assistance in

discriminating between euthyroid and hypothyroid subjects. By the use of this method the number of patients in whom further investigation is required is greatly reduced. The technique is of particular value in the mild and early case, but is also useful in identifying atypical forms of the disorder.

SECTION II

THE LABORATORY CONFIRMATION

CHAPTER 11

THE LABORATORY CONFIRMATION

Introduction

No laboratory procedure has yet been devised which will define exactly and infallibly the level of the secretory activity of the thyroid. Those commonly employed, however, may be of considerable value as aids in the diagnosis of thyroid disorders. They may be divided into several groups each of which provide information regarding the functional state of the thyroid by assessing different aspects. The activity of the gland may be studied directly either by measuring its avidity for iodine with the use of radioactive iodine studies, or by estimating the amount of circulating hormone produced by the gland, the serum protein bound iodine. Indirect evidence may be provided by studying the effects of deficiency of the hormone. This will, of course, influence not only metabolism in general, causing lowering of the basal metabolic rate, but may cause biochemical changes, such as those in the serum cholesterol, and affect specific target organs with resulting abnormalities which may be demonstrated by means of ancillary means such as the electrocardiograph. All of these tests do possess their own particular disadvantages. By careful selection from each group, however, a combination of tests, each reflecting a different aspect of the state of thyroid function should be able to provide a high degree of diagnostic accuracy.

Few clinicians would support the suggestion that the clinical diagnosis in every case of hypothyroidism should be confirmed by investigations (Galbraith, 1953). When the clinical picture is characteristic, such tests should be unnecessary since the proof of the diagnosis is provided by the dramatic response to therapy. There is, however, even among clinicians who realise this, a tendency to request confirmatory investigations, since these are now generally so readily available. Usually these will merely confirm their clinical impression, although they do provide a record of the state of hypothyroidism which may be of value if the diagnosis is later questioned after all the signs have disappeared following treatment. The danger exists, not unfortunately purely theoretically, that some physicians may allow their clinical judgement to be swayed by the results of these tests, and even place more reliance on them. As Bauer (1956) said, "for these clinicians the clinical evaluation lacks that one tangible asset, a figure reported in per cent elevation, per cent uptake or gamma per cent". They do, in fact, fail to realise that the tests are just as liable to fallacies as the clinical diagnosis. It is because no one test is completely reliable in the diagnosis of thyroid function that so many different procedures have been devised. Such investigations, of course, are really of value when required to assist in the diagnosis of these subjects in whom there is an incomplete or atypical clinical picture. Unfortunately it is in this group that they all too often provide results that are inconclusive and fall on the borderline between normality and abnormality. Moreover, when several tests are employed, the conclusion to be drawn from each may vary so much that the clinician has difficulty in knowing on which test to place the most reliance. It is difficult to compare the tests by studying in the literature the reports of their use, since in each series the selection of cases varies and usually there is no separation of the subjects with obvious hypothyroidism from those causing diagnostic difficulty. It is obvious that the accuracy of any procedure may be greatly enhanced by the inclusion of a majority of the former group. This is also true of the few attempts that have been made to compare the diagnostic accuracy of the investigations and in these the numbers of patients have been small. The difficulty in expressing clinical severity has also tended to invalidate any comparison of the accuracy of the investigations and the clinical diagnosis.

The object in this section, therefore, has been to evaluate which test or combination of tests will provide confirmation of the clinical diagnosis most accurately, most rapidly and with the minimal inconvenience to the patient.

The investigations which have been studied in this series are those which can be carried out in most centres rather than those procedures which, although possibly of greater diagnostic accuracy, require considerable technical skill and special laboratories, or which involve undue expense. For this reason such procedures as the measurement of plasma protein-bound iodine and the erythrocyte uptake of ^{131}I labelled iodothyronines have not been evaluated. A new procedure, the measurement of reaction time, has, however, been introduced. The large number of patients studied has allowed a confident assessment to be made of the diagnostic value of each test. Moreover, since most tests were carried out in the same subjects, it has been possible to compare the accuracy of the tests not only with each other, but also with the clinical diagnosis using the clinical diagnostic index.

CHAPTER 12

RADIOACTIVE IODINE STUDIES

Since radioactive iodine has become generally available it is now possible to study the fate of the administered iodine at any of the many stages in its metabolism. Following the initial studies of thyroidal handling of ^{131}I by Hertz et al (1938), it has been used extensively in diagnostic procedures, and a very extensive literature has resulted. This has been reviewed by Beirwaltes et al (1957) and Wayne and Macgregor (1957). The tests fall into four main groups, the dynamic rate of accumulation of radioiodine by the gland, the percentage of the dose taken up at a fixed time, the measurement of serum protein-bound radioactivity and the amount of radioactivity found in the urine. The relative value of the different tests still remains a matter of controversy. Some are of greater value in the diagnosis of hyperthyroidism than of hypothyroidism and vice versa. It is clear from the literature, however, that the standard tests all have a high degree of diagnostic accuracy, but no one test is infallible. A comparison between them is made difficult by the varying selection of cases in the series which advocate different procedures.

The tests of most value in demonstrating impaired function of the thyroid are those reflecting the decreased avidity of the gland for iodine. This may be demonstrated by measuring the gland uptake at various times after the administration of the dose. Hamilton and Soley (1940) pointed out that the thyroid and kidney compete for circulating iodide and that there is inverse relationship between the uptake and the excretion of radioiodine. The total urinary excretion during 48 hours is therefore high in hypothyroidism, but, as Skanse (1949) pointed out, there is a considerable overlap between normal and hypothyroid subjects. In attempts to overcome this and other problems such as the impairment of renal iodide clearance which may occur in hypothyroidism, numerous improvements with divided urinary collections and analysis of excretion rates have been developed. The difficulties of obtaining accurate urine collections are, however, increased by such procedures and do reduce their feliability. An attempt, therefore, has been made to evaluate which procedures will provide the most information regarding the functional state of the thyroid in terms of their ease of administration and operation, as well as diagnostic precision.

Methods and Subjects

In 173 subjects the gland uptake of radioiodine was measured after an oral dose of 25 microcuries of radioiodine (^{131}I).

Fifty of these were the Doubtful Euthyroid group previously defined. The diagnosis was unequivocal in 53 of 100 patients with primary hypothyroidism and the remaining 47 were in the Doubtful Hypothyroid group. A diagnosis of Hashimoto's thyroiditis was established in a further 26 hypothyroid subjects. The uptake was measured at 24 hours after the dose in 73 of the hypothyroid subjects and at 48 hours in 50. In 23 it was also estimated at 4 hours.

The clearance rate of radioiodine was estimated by a modification of the technique described by Berson et al (1952) and was studied in 25 hypothyroid patients. After the injection of 25uc of ^{131}I intravenously, the counting rate over the gland was recorded at one minute intervals for 10 minutes and thereafter at every two minutes for a further 20 minutes. A correction factor was applied to allow for backscatter of radiation. The clearance rate was calculated, taking into account the loss of ^{131}I in the urine, and expressed as millilitres per minute per square metre of surface area.

Estimations of the serum protein-bound radioactivity were carried out 48 hours after the administration of radioiodine using the resin extraction method of Zieve et al (1956).

The urinary excretion of radioactivity was measured after collecting the urine in periods. In 53 cases the periods were those advocated by Fraser et al (1953), namely

0-8 hours, 8-24 hours and 24-48 hours. In 60 subjects the periods were 0-6 hours, 6-24 hours and 24-48 hours, as used by Mason and Oliver (1949). The 'T' index (Fraser et al, 1953) was calculated for both groups.

Results

Detailed results of all the radioactive iodine studies are given in Appendix V.

1. Gland Uptake -- It can be seen from Table 15 that this provides a marked separation of the patients with primary hypothyroidism from the euthyroid group. Forty-nine (98%) of the 50 in the latter group had uptakes greater than 19% of the dose. On the other hand, 97 of the 100 patients with primary hypothyroidism had uptakes less than 20% of the dose. The 3 subjects with normal uptakes were in the Doubtful Hypothyroid group.

Although there was no difference between the results of the uptakes carried out at 24 and 48 hours, in 9 of the 23 subjects in which the uptake at 4 hours was measured, it was greater than 19%. By 24 or 48 hours it was less than 20% in all 23 patients.

When the 26 patients who were hypothyroid as the result of Hashimoto's thyroiditis are considered, it can be seen that only 10 had uptakes less than 19%. If this group were to be included with the patients with primary hypothyroidism the diagnostic accuracy of the gland uptake would fall from 97% to 85%.

2. <u>Clearance Rate</u> -- In 24 of the 25 subjects with hypothyroidism in whom this procedure was carried out, the clearance rate was less than 15.0ml/min/square metre of body surface. In normal subjects the rate is always greater than this using this method.

3. <u>Protein-bound Radioactivity</u> -- The serum protein-bound radioactivity was within normal limits (less than 0.3% of the dose per litre) in all but one of the patients with primary hypothyroidism.

4. Urine Studies -- <u>a. 0-48 hours</u> - There was a considerable scatter of the results of the urinary excretion in this period both in euthyroid and hypothyroid subjects. Although all but 2 of the 31 patients in the former group excreted less than 69% of the dose in this period, values in this range were also found in 25 (30%) of the 82 hypothyroid cases. Table 16 shows that even in the Definitely Hypothyroid group only 37 (78%) excreted more than 69% of the dose. Values in this range were found in only 20 (57%)

of the 35 subjects in the Doubtful Hypothyroid group.

b. 6/8-24 hours - Table 17 shows that in the hypothyroid subjects there is no significant difference in the diagnostic accuracy of the results obtained in either the 8-24 hour or 6-24 hour periods. Thus, in the former period 31 (89%) of 35 patients excreted more than 20% of the dose and in the latter period 43 (90%) of 48 patients excreted more than 25% of the dose. The results of the two groups can therefore be combined. It can be seen that 89% of both the definite and doubtful hypothyroid patients excreted amounts of radioactivity outwith the normal range. High values were, however, also found in 12 (40%) of the 30 subjects in the Doubtful Euthyroid group.

c. 24-48 hours - The excretion of radioactivity in this period does not normally exceed 10% of the dose. It can be seen in Table 18 that 30 (88%) of 34 subjects in the Doubtful Euthyroid group did excrete less than this. Excretion of radioactivity greater than 10% was found in 73 (87%) of the 84 hypothyroid subjects.

d. 'T' Index - Since two different collecting periods were employed, the T index which is derived from these periods was different for each group. The results are shown in Table 19. It can be seen that the index derived from the group in which the middle period was 8-24 hours (T_8) is superior to that based on the 6-24 hour period (T_6), both in the hypothyroid and euthyroid subjects. Thus in the former, 30 (94%) of 32 patients had indices less than 2.7 while only 4 (22%) of the euthyroid cases had similarly low indices. When the indices based on the 6-24 hour collecting periods (T_6) are examined, the respective figures are 83% and 36%. If the two indices are combined, however, the overall diagnostic accuracy is still satisfactory. Seventy (88%) of the 80 hypothyroid cases had low indices, while normal indices were found in 21 (72%) of 29 euthyroid subjects.

5. Combination of Radioiodine Studies -- The results show that the diagnostic accuracy of the radioiodine tests is generally of a high order. This may be increased if more than one test is employed. These most often used in conjunction are the gland uptake and the 'T' index. In 79 hypothyroid patients in whom these two investigations were carried out, and in all of whom one or other proved abnormal, both were abnormal in 68 (86%). Similarly, when the results of the gland uptake and 24-48 hour urine excretion are considered together (Figure 9) abnormal results by both tests were found in 80 (85%) of 82 subjects, but in only one hypothyroid patient were both normal. It is of interest to note that in 17 hypothyroid patients with Hashimoto's thyroiditis, although these two tests were in agreement in

only 6, in a further 6 one or other gave abnormal results.

6. <u>Comparison with the Clinical Diagnosis</u> -- The use of the clinical diagnostic index permits a comparison to be made of the accuracy of the various methods of investigation with that of clinical evaluation. Thus when the index is considered with the results of the gland uptake in 96 hypothyroid subjects (Table 20) it can be seen that a correct diagnosis was made by both methods in 83 (87%) and that one or other favoured the diagnosis in all but one of the remaining 13 subjects. The table does suggest that the uptake has a significantly higher diagnostic accuracy than the index, but it must be remembered that only one of the 11 cases which were not correctly diagnosed by the index was in fact wrong; the remainder merely fell within the equivocal range. All 50 subjects in the Doubtful Euthyroid group were correctly diagnosed by the use of the two procedures.

A similar comparison between the index and the 24-48 hour urine excretion is shown in Table 21 and Figure 10. It can be seen that both procedures were abnormal in 64 (80%) of 80 hypothyroid subjects. One test was abnormal in 14 (17%) of the remaining 16. In the Doubtful Euthyroid group both were normal in 22 (73%) of 30 subjects and both abnormal in only one.

Since the results of the gland uptake in hypothyroid subjects fell within such a small range it is not likely that there would be any correlation between gland uptake and clinical severity. No significant correlation ($r = +0.185$) exists between the 24-48 hour urine excretion of radioactivity and the diagnostic index when the latter is employed as a measure of clinical severity.

Discussion

The measurement of the gland uptake of radioiodine is probably the most simple and rapid of all the diagnostic procedures employing radioiodine. Nevertheless, opinions regarding its reliability in the diagnosis of hypothyroidism are varied. This is in part due to the fact that the values for normal subjects vary with the techniques employed and with the geographical location. Thus, reported normal values in the eastern United States range from 10 to 45% (Werner et al, 1950) while in the mid-western States the lower limit is 6% (Keating et al, 1947). In this country, however, the normal ranges are higher, values less than 20% generally being regarded as abnormal (Goodwin et al, 1951). Most observers agree that whereas the uptake at 4 hours is of considerable value in the diagnosis of thyrotoxicosis, it is much less useful in the investigations of hypothyroidism in view of the considerable body background from circulating iodide unexcreted at this period. McConahey et al (1956), however, did find that there was less overlap between normal and hypothyroid subjects using the 6 hour uptake than with the 24 hour uptake. The present series, on the other hand, makes it clear that an uptake at either 24 or 48 hours is much more reliable than at 4 hours. There is no difference in the accuracy of the procedure when carried out at either of these former times.

The precision of the gland uptake in separating euthyroid subjects from those with primary hypothyroidism is of a high order. It must be remembered, however, that in some hypothyroid states other than the primary disorder, the gland uptake and indeed all the radioiodine tests, may be much less reliable. For example, when impaired thyroid function is secondary to pituitary failure, normal values for the uptake may be found, as did occur in 9 of 17 patients in whom hypothyroidism secondary to hypopituitarism was demonstrated during the period of this study. The gland uptake was also within normal limits in 13 of 28 patients who became hypothyroid following treatment of thyrotoxicosis with ^{131}I. The uptake may be elevated when hypothyroidism results from overdosage by antithyroid drugs and high values are also found in cases of goitrous cretinism. In these circumstances however, the preceding history will usually provide sufficient warning that the results of radioiodine studies should be interpreted with caution. The condition that is possibly most likely to lead to difficulty is Hashimoto's thyroiditis since the clinical picture is indistinguishable from primary hypothyroidism except that a goitre is present. The use of radioiodine studies in the diagnosis of this disorder has been examined by Murray and McGirr (1960). The results showed that even when the patient is frankly hypothyroid, all the radioiodine studies may be in the normal range. It is essential, therefore, that the diagnosis of Hashimoto's thyroiditis be made in order to separate these subjects from cases of primary hypothyroidism. In the majority of patients suspected of hypothyroidism, the finding of enlargement of the thyroid should provide adequate warning that the studies may be of little value in showing impaired thyroid function. In some patients, however, the goitre may be minimal and difficult to palpate and Hashimoto's thyroiditis may consequently not be suspected. It is especially in these circumstances that radioiodine studies may be misleading. It is of interest, therefore, to note that abnormal thymol turbidity tests and elevated serum globulin levels were found in two of three subjects, apparently with primary hypothyroidism, but in whom the gland uptake was greater than 19%. These subjects were thus in fact probable cases of "auto-immunising thyroiditis", but being apparently agoitrous could not be diagnosed as such except by the finding of abnormal biochemistry. It seems possible that varied inclusion of such cases as these in certain of the reported series accounts to a great extent for the varying results in studies of radioiodine investigations in the diagnosis of hypothyroidism.

The gland uptake is rarely low in the absence of hypothyroidism unless, as will be seen later, the patient has received thyroid therapy or iodide in any form. Low uptakes will also be found in patients with acute and subacute thyroiditis, but the clinical picture is so different that errors in diagnosis should not be encountered.

Myant et al (1949) and Keating et al (1949) proposed that a direct measure of thyroid activity may be obtained by testing the thyroid clearance rate. This does provide an index of thyroid iodide utilisation, but as Riggs (1952) pointed out, it is less specific than even uptake estimations as a measure of hormone secretion, as it is influenced to a considerable extent by the renal clearance of iodide. The method described by Myant et al, moreover, is cumbersome, involving estimations of the plasma radioiodine as well as serial measurements of gland uptake. Other procedures designed to reflect the dynamic changes in iodide metabolism have therefore been introduced. Many of these are also unduly complex, as for example, that advocated by Haig and Reiss (1950). The technique described by Berson et al (1952) has probably been most widely used. Coenegracht and Fraser

(1955) found a good correlation between this test and the 'T' index, but suggested that it was less sensitive than the urine excretion studies or the 24 or 48 hour gland uptake in lesser grades of hypothyroidism. Although McConahey et al (1956) considered that determination of thyroidal iodide clearance was quite useless in the diagnosis of hypothyroidism, the present study suggests that it is just as accurate as the gland uptake. It was noted in fact that in one hypothyroid subject the clearance rate was low although the gland uptake was normal. Apart from this one case, however, there is little to suggest that this technique, so much more time consuming, is to be preferred to the gland uptake. It will, however, provide diagnostic information within 30 minutes and, if rapidity is required, will obviously be of value. With the introduction of the shorter-lived isotope ^{132}I and the use of an automatic recorder (Farran, 1958), there is a possibility that the procedure may become more acceptable as a routine clinical investigation.

The sensitivity of counting equipment at present available does not permit discrimination between the very low normal levels of circulating serum protein bound radioactivity and the negligible amounts in hypothyroidism.

The estimation of protein-bound radioactivity is therefore of no value in the diagnosis of hypothyroidism. Elevated levels, however, are frequently found in Hashimoto's thyroiditis even in hypothyroid patients and if present should suggest the possibility of this diagnosis.

Since there is an inverse relationship between the gland uptake and urinary excretion of radioiodine, it is not surprising that as a result of the decreased avidity of the gland in hypothyroidism a large amount of radioactivity is found in the urine. There are, however, differences in opinion regarding the reliability of the urine excretion as an index of impaired function. It is generally agreed that the output in the first 24 hours is of little value since there is considerable overlap between normal and hypothyroid subjects. Skanse (1949) for example, showed that in the former the output varied from 39.9 to 81.3% with an average of 60.6%. In hypothyroidism he found the average excretion to be 61.4%. When the 48 hour excretion was examined the respective average figures were 65.9% and 83.6%. Fraser et al (1953) also showed that there was a separation between euthyroid and hypothyroid subjects using this period, but considered it too insensitive to detect slighter degrees of altered thyroid function.

The experience in the present series has been similar, since the output in 30% of hypothyroid subjects lay within the normal range. It should be noted, however, that only 6% of the normal individuals excreted more than 69% and a value higher than this must favour a diagnosis of hypothyroidism.

Keating et al (1947) first noted that the sensitivity of the urinary excretion of radioiodine as a test of thyroid function could be considerably increased by the collection of urine over selected time intervals. This procedure has been developed (Arnott et al, 1949; Martinelli et al, 1948; Mason and Oliver, 1949), but the technique described by Fraser et al (1953) has, certainly in this country, been most generally accepted. The periods advocated by these workers were 0-8 hours, 8-24 hours and 24-48 hours. The largest amount of radioactivity was excreted in the middle period. It seemed likely that this would be increased by extending the period to 6-24 hours and thus provide better separation between normal and hypothyroid values. The results show that there is, however, no significant increase in the diagnostic accuracy of the two periods. The normal upper limits of 20% in the 8-24 hour period and 25% in the 6-24 hour period were exceeded in 89% and 90% of hypothyroid subjects respectively. When the 'T' index, however, was derived from the two series it was clear that the index based on the 6-24 hour collection was less sensitive in detecting impaired thyroid function than that based on the 8-24 hour period. The 'T' index was introduced by Fraser et al (1953) and advocated as a method which would help to overcome the fallacies resulting from renal and cardiac impairment that may render urinary tests of thyroid function unreliable. They found it of value in the diagnosis of hyperthyroidism, but considered that it was slightly less sensitive in the detection of hypothyroidism. The present series, however, shows that in fact it is the most accurate of all the tests based on the urinary excretion in indicating impaired thyroid function.

The accuracy of all these investigations depends on exact urine collection. This is often difficult in a general hospital ward, but the risk of errors is increased when collections are to be carried out by outpatients. In the hands of intelligent patients this risk is often slight but it must be remembered that in hypothyroid subjects cerebration is very frequently impaired. The likelihood of erroneous collections is increased if divided periods are required. It is claimed that by the use of these divided periods faulty collection can readily be detected and thus erroneous conclusions avoided. This merely emphasises the chances of invalidating this method of assessment. Since the 'T' index requires three periods of collection it may be affected by mistakes in any of them.

Ideally the routine procedure of choice is that which gives the most diagnostic information while being the simplest to carry out. It is obvious that if a single collection will suffice the patient is more likely to understand and follow the instructions. It has already been shown that in the 0-24 hour and 0-48 hour periods there is considerable overlap between euthyroid and hypothyroid subjects. If a single period is required, the choice therefore lies between the 6/8-24 hour and the 24-48 hour periods. Using either of these there is relatively little difference when applied to hypothyroid subjects, abnormal results were found in 89% using 6/8-24 hour collections and 87% with 24-48 hour.

The true diagnostic value is best assessed by considering all the patients causing initial diagnostic difficulty, whether euthyroid or hypothyroid. Using the 6/8-24 hour period, results agreeing with the final diagnosis were obtained in 50 (76%) of 66 patients, while with the 24-48 hour collections agreement was found in 63 (90%) of 70 cases. It would appear, therefore, that the latter provides greater diagnostic precision. Moreover, collections are much easier to carry out in a 24 hour period. Although this procedure is probably not quite so accurate as the 'T' index and may occasionally produce results difficult to interpret in view of concomitant renal or cardiac disease, it is nevertheless suggested that it is the most useful urine test in routine practice. If gland uptake measurements are not possible, as for example when the patient is at a distance from a hospital with radioiodine facilities, this procedure will provide a reliable and simple method of assessing thyroid function.

Although a single test may be sufficient for diagnosis, greater reliability can be placed on two procedures when these are in agreement. This can be illustrated by examining the results of the gland uptake and the 24-48 hour urine excretion. Both tests were abnormal, thus providing strong evidence of impaired thyroid function, in 85% of subjects proved to be hypothyroid. In the remainder, one or other was abnormal in all but one case. The use of the two tests introduces a group in whom the results are not in agreement, but reduces the number of patients who would have been wrongly diagnosed if only one test had been carried out. The finding of results not in agreement merely should indicate the necessity for carrying out further investigations. It has been shown that the use of the clinical diagnostic index along with either or both of these procedures, produces a high degree of diagnostic accuracy. Thus, for example, when the index and uptake are used together one or other was abnormal in 95 of 96 hypothyroid subjects. It is even more significant that the diagnosis suggested by the uptake proved ultimately to be the correct diagnosis in 18 of 22 subjects who had indices within the equivocal range.

When the clinical index, uptake and 24-48 hour excretion are considered, all three were abnormal in 60 of 77 patients. Abnormal results were present in two out of the three procedures in 15 of the remaining 17 subjects. The use of this combination therefore provided very strong evidence in favour of the diagnosis of hypothyroidism in 97% of the patients. Similarly, when the Doubtful Euthyroid group is examined, it can be seen that, using these three parameters, at least two normal results were found in 32 of 33 subjects in which they were carried out.

It must be remembered, however, that all these radioiodine techniques are subject to fallacies. The problems that may arise when hypothyroidism results from a certain specific aetiological factor have already been discussed.

In interpreting the results of radioiodine studies, it is important to bear in mind the fact that there is a decrease in thyroid uptake with increasing age. Perlmuther and Riggs (1949) found that in a group of 162 euthyroid cases the mean "accumulation gradient" fell with each decade. Quimley et al (1950) also detected a small, but significant decrease in the 24 hour thyroid uptake with increasing age. More recently, Macgregor (1958) has shown that with advancing years there is an increase in the urinary excretion of radioiodine both in the 8-24 hour and the 0-48 hour periods. As a result, there is a statistically significant correlation between a decrease in the T index and increase in age. Macgregor pointed out the importance of these findings with regard to possible errors in the diagnosis of hyperthyroidism, but it is obviously equally significant as a potential source of error in the diagnosis of hypothyroidism. In the Doubtful Euthyroid group, 13 subjects were over 60 years of age. In three, abnormal results of urine studies were found. In two the 6-24 hour value was higher than normal and in the other the 24-48 hour was abnormal. It is important therefore that in this age group the urine excretion values should be intrepreted with caution. The gland uptake results in these three cases were within normal limits.

The most likely source of errors in these procedures arises from concurrent or past administration of drugs. Iodine in organic or inorganic form results in saturation of the gland and subsequent inhibition of the uptake of ^{131}I. It is not infrequently taken for medicinal reasons as for example in the form of cough mixtures or lozenges for chronic chest disease so common, especially in winter, in the West of Scotland. It is essential that patients should be questioned regarding recent ingestion of such remedies. Indeed, it is now recognised that, in some individuals, continued administration of iodide usually in these forms, may produce thyroid enlargement. In the course of this study 6 such "iodide goitres" were encountered. Three of these patients were frankly hypothyroid. In such patients, radioiodine studies demonstrate impaired thyroid uptake and increased urinary excretion of ^{131}I. If, however, the history of chronic ingestion of iodide-containing mixtures is obtained, life-long administration of thyroid hormone can be avoided merely by ensuring that the patient discontinues taking such compounds. In this way the evidence of hypothyroidism will disappear and the goitre regress.

The barium used in gastro-intestinal investigation may contain iodide, but the quantity involved is not large. In other radiological procedures, however, organic iodinated compounds are used as contrast media. Following cholecystograms, intravenous or retrograde pyelography, arteriography and similar investigations, therefore, the gland uptake may be low and of little diagnostic value. Whereas following the ingestion of inorganic iodide compounds there will usually be a return to normal uptake levels in euthyroid subjects in 4-6 weeks, the depression of uptake following these radiological procedures is much more persistent and the effect may last from three to six months. When Lipiodol has been employed in bronchographic studies, inhibition will continue as long as the compound is present in the body and Carter et al (1959) have shown more than 445 days may elapse before normal uptake values are again found. Iodised salt contains less than 0.01% of iodine. Normally this is insufficient to effect the radioiodine studies, but may do so occasionally depending on the daily ingestion. When it is suspected that there has been administration of iodide, chemical analysis of the urine may show an increase in the iodide content.

The administration of thyroid, thyroxine and tri-iodothyronine is followed by a reduction in the uptake of ^{131}I by the normal thyroid. Uptake is diminished throughout the period of therapy and for a variable time after treatment is discontinued. All too often this presents a problem in patients suspected of hypothyroidism, since their own practitioner has often prescribed thyroid before referring them to hospital. A minimum of four to six weeks is required after therapy has been stopped before ^{131}I procedures can be used with any confidence being placed on the findings. The depression of thyroid function produced by thyroid and thyroxine, however, can be differentiated from true hypothyroidism by means of the administration of thyroid stimulating hormone (T.S.H.).

The possibility that fallacious results may be produced by the previous administration of iodide or thyroid is far from theoretical. There is a constant risk that, in any patient suspected of hypothyroidism, radioiodine studies will not be of any value. A clinician should not place complete reliance on them and must therefore have other investigations available.

Although this study shows that the use of radioactive iodine provides a useful method in detecting impaired thyroid function, it would appear that the tests are less sensitive than in the diagnosis of hyperthyroidism. The results may be compared with those of Crooks et al (1959). A series of patients was studied who presented difficulty in the diagnosis of thyrotoxicosis and it was shown that, using a combination of the 4 hour uptake and 48 hour protein-bound radioactivity, agreement between these two tests existed in 97% of cases. A significant correlation was found between clinical severity of thyrotoxicosis and both the 4 hour gland uptake and 48 hour protein-bound radioactivity. No such correlation between severity and the radioiodine studies exists in hypothyroidism.

Various other procedures involving the use of radioactive iodine have been devised in attempts to increase the diagnostic accuracy in hypothyroidism. Ingbar and Freinkel (1955), for example, showed that the degradation rate of radio-thyroxine was decreased in hypothyroid states. However, like many other tests advocated, the procedure is complex and has little practical value as a routine diagnostic method. Although simpler techniques are required for the measurement of the uptake of ^{131}I-labelled tri-iodothyronine by erythrocytes (Hamolsky et al, 1957) or by resins (Sterling and Tabachnick, 1961) the labelled compound remains at present too expensive for use in a routine diagnostic procedure. Consequently it would appear that the diagnostic accuracy obtained with the combined use of gland uptake and 24-48 hour urine output of ^{131}I cannot at the present time be improved on by any other similar investigation without greatly increasing the complexity and difficulty of application of the tests.

Conclusions

This study has confirmed the value of radioactive iodine (^{131}I) studies in demonstrating hypofunction of the thyroid. The most useful procedure for use in routine investigation is the measurement of the gland uptake at 24 or 48 hours. Decreased glandular avidity for ^{131}I can also be shown by the $\frac{1}{2}$-hour clearance rate which, although

involving a more complex technique, can be employed when diagnostic information is rapidly required.
Discrimination between normal and impaired thyroid function can also be obtained by studying the urinary excretion of ^{131}I. Several procedures may be used for this, but the measurement of the excretion in the 24-48 hour period is preferred since it is considered to be least liable to the possible errors that may arise from incorrect collections. All these tests may be invalidated by the recent administration of iodine or thyroid. Misleading results may also occur in certain instances when the thyroid failure is the result of certain specific causes. Accordingly, although these procedures can be regarded as being of great assistance in confirming the clinical diagnosis, complete reliance must not be placed on them. In the routine investigation of suspected hypothyroidism, therefore, complementary tests of thyroid function should be performed.

CHAPTER 13

THE BASAL METABOLIC RATE

Over many years, the estimation of the basal metabolic rate (B.M.R.) has been a standard method of assessing thyroid function. With the advent of more recent diagnostic procedures, however, its usefulness has been questioned, since its diagnostic accuracy is dependent on many variable factors, such as the techniques employed and the standard of normality chosen. In this study, therefore, particular attention has been paid to these and the extent to which they may influence the diagnostic precision of the procedure.

Methods and Subjects

The B.M.R. was estimated in 131 people, all of whom were admitted to hospital. The standard Benedict-Roth apparatus was used, but two different procedures were employed. In the first, termed Method A, the patients were given 200mg of butobarbitone twelve hours before each test. The estimation was carried out by the same experienced technician in every case. The test was done in duplicate on two days and the lowest of the four values was accepted. No standard sedation was administered in the second series, Method B, and the estimation was performed by any technician available. The results in both series were expressed as the percentage deviations from the normal means in terms of the standards of Robertson and Reid (1952) and Aub and Du Bois (1917).

Method A was employed in 40 hypothyroid patients of whom 17 were in the Doubtful Hypothyroid group, and in 30 subjects in the Doubtful Euthyroid group. In 53 subjects Method B was used. Twenty-three were in the Doubtful Hypothyroid group. Only 8 of the Doubtful Euthyroid group were investigated in this way. In all the hypothyroid subjects, the condition was either primary or resulted from Hashimoto's thyroiditis.

Results

A comparison of the results obtained by the two procedures (Appendix IV) is shown in Table 22. It is clear that the use of a standard technique carried out by a careful observer improves the accuracy of B.M.R. estimations considerably. In the 40 hypothyroid patients investigated by Method A, the B.M.R. was less than -15% (Robertson and Reid) in 31 (77%). Similar low readings were obtained in only 28 (53%) of the 53 patients in whom Method B was employed. The numbers of euthyroid patients are too small to permit a significant conclusion to be drawn.

Table 22 also shows that in the patients presenting diagnostic difficulty, the B.M.R. is less accurate than in those in whom there was no clinical doubt. This is obvious in both series, although it is more marked using Method B. If they are considered together, the B.M.R. lay outwith the normal range in 38 (72%) of the 53 subjects in the Definite Hypothyroid group, but was below -15% in only 21 (53%) of the 40 Doubtful Hypothyroid cases.

Since these studies show that the B.M.R. estimations are most unreliable unless a standard and uniform technique is adopted, the results of Method B have been omitted from the subsequent analyses.

The effect on the diagnostic accuracy of the B.M.R. produced by the use of different ranges of normal metabolic rate is shown in Table 23. It can be seen that the use of the Aub and Du Bois standard, taking the lower limit of normal as -20%, possesses little advantage over the Robertson and Reid standards. Thus in 40 hypothyroid subjects 33 (83%) were correctly diagnosed by the former compared with 31 (77%) by the latter. When, however, the lower limits of the Aub and Du Bois standards are raised to -15% and -10%, 36 (88%) and 39 (97%) respectively of these same subjects had B.M.R.s outwith the normal range. It must be noted, nevertheless, that when these limits are used a larger number of euthyroid subjects were incorrectly diagnosed. As a result there is little change in the overall accuracy of the B.M.R. diagnostic procedure. In the 70 patients in whom the test was carried out 60 (86%) were correctly diagnosed using the Robertson and Reid standards. The comparable figures using -20%, -15% and -10% (Aub and Du Bois) are 61 (87%), 59 (84%) and 60 (86%).

The B.M.R. estimation was repeated after therapy in 5 subjects who, when hypothyroid, had B.M.R.s within the normal range (mean value -8% Robertson and Reid). In all the B.M.R. increased and when they were euthyroid the mean value was +12%. These changes in the B.M.R. are illustrated in Figure 11. In none of these subjects was there any evidence of overdosage with thyroxine.

When the results of the B.M.R. estimations are compared with those of the clinical diagnostic index (Table 24) it can be seen that one or other was abnormal in all 40 hypothyroid subjects in whom Method A was used. Both tests were in agreement in 29. The index provided the correct diagnosis in 9 patients whose B.M.R. lay within the normal range. Two subjects had equivocal indices but abnormal B.M.R.s. There is no correlation ($r = -0.254$) between the B.M.R. and diagnostic index in the hypothyroid group.

Discussion

Many conflicting opinions exist regarding the usefulness of B.M.R. estimations in assessing the state of thyroid function.

Comparisons between various series are, however, made difficult in view of the varied selection of cases and the different techniques and standards of normality employed.

It is clear, however, that the most important factor that influences the accuracy of the procedure in the diagnosis of hypothyroidism is the method by which determinations are carried out. Nearly all the errors inherent in the technique are in favour of producing a fallaciously high result. Means (1948) pointed out that the value of a single determination of B.M.R. is analogous to a single observation of pulse rate, temperature or blood pressure. Robertson (1944) advocated repeated readings until the second of two duplicate estimations differed by no more than 5% from the first duplicate on the same day. Boothby et al (1936) on the other hand, took as their level the first determination, arguing that it is not possible to obtain truly basal readings in clinical practice. The procedure employed in this series is a compromise between these two views. Nervous tension is not uncommon at the initial test and the initial reading is frequently higher than later readings. This is, of course, particularly of importance in the investigation of thyrotoxicosis, but is also of significance when hypothyroid subjects are being studied. Although in advanced hypothyroidism the patient is typically somnolent and obtaining a true basal reading presents no difficulty, milder cases may well be nervous and apprehensive as the symptom analysis has already shown. As a result, the B.M.R. may be fallaciously raised unless strict attention is paid to the technique. The comparison between the two procedures by which the B.M.R. was estimated illustrates the extent to which the technique may influence the result. It is of interest to observe that Werner (1955) considered that the B.M.R. determination offered not much more than a 50% correlation with the clinical appraisal of thyroid activity, but that approximately 80% correspondence is attainable with special care.

Although it is obvious that the technique described as Method B is far from satisfactory, it must be remembered that there are few centres where facilities are available for B.M.R. estimations to be carried out with the scrupulous attention that was employed in Method A. This is especially true when large numbers are being investigated, and presents a strong argument against reliance on the B.M.R. estimation as a routine procedure in the assessment of thyroid function. It may further be noted that the test is less accurate in those cases where it is most required, the patients in whom diagnostic difficulty has been found on clinical grounds. It is possible that in these subjects particularly, more precision might be obtained by the use of the "sleeping metabolic rate" described by Fraser and Nordin (1955). However, the advantages gained by this method are unlikely to be commensurate with the labour involved and the inconvenience to the patient.

Even with the most exacting attention to the performance of the test, it is likely that some cases of hypothyroidism will be found to have a "normal" B.M.R. This may happen when the patient's B.M.R. in health lies at the upper limit of the normal range. This explanation gains support from the changes in the B.M.R. (Figure 11) in 5 cases in all of whom a normal B.M.R. was associated with proven hypothyroidism. Therapy, which made these patients euthyroid, was accompanied by a mean rise in the B.M.R. of +20%.

The diagnostic accuracy of the B.M.R. reported in various series varies considerably. This is partly because the different observers draw different interpretations from the results. Thus some observers consider that the finding of a normal B.M.R. is more important and indicates the absence of hypothyroidism. Others, however, state that a normal B.M.R. is of little diagnostic significance, but that a low reading is strongly in favour of impaired thyroid function. These differences arise from the use of different standards of normality. In an admirable review of this subject, Skanse (1949) points out that in various series the limits of normality have been $\pm 10\%$, $\pm$ 12%, $\pm$ 13%, $\pm$ 15% and $\pm$ 20% of the mean standards laid down by Aub and Du Bois (1917). Robertson and Reid (1952) concluded that the standards of Aub and Du Bois were too high for this country, either because of population differences or differences in technique or a combination of both. Accordingly they produced new standards for the basal metabolism of normal people in Britain based on a study of 987 males and 1323 females aged between 3 and 80 years. Their normal ranges for age and sex were calculated on the basis of ± 2 S.D. from the mean values (about $\pm$ 15%). An estimate of B.M.R. expressed in terms of these standards will be about 7-10% higher than an estimate based on those of Aub and Du Bois. The results show that, when the two standards are compared, low readings are found in hypothyroid subjects more frequently when the Aub and Du Bois standards are used. This difference is not significant when -20% is taken as the lower limit of normal as is perhaps now most commonly done (Baron 1956). When -15% and -10% are considered as the lower limits, the increase is more marked. Thus 39 (97%) of the 40 patients studied had readings less than -10%, the level advocated by Soffer (1956). There was, however, a reciprocal increase in the number of euthyroid subjects whose B.M.R.s were outwith the normal range, 9 (30%) of 30 cases. It is clear, therefore, that the diagnostic significance of the results obtained when using the two standards must be evaluated differently. Thus with Aub and Du Bois standards a normal B.M.R. (greater than -10%) will provide strong evidence against the diagnosis of hypothyroidism. If the Robertson and Reid standards are employed, a normal B.M.R. will not necessarily indicate normal thyroid function, but a low reading is likely to be incompatible with this. There is no difference in the overall accuracy of the two in separating normality from abnormality and accordingly little to favour the choice of either for a routine use in the diagnosis of hypothyroidism. However, a comparison of the two standards by Crooks et al (1958) in the diagnosis of thyrotoxicosis did show that the British standard provided greater reliability. It may be suggested, therefore, that the Robertson and Reid standards should be universally adopted in this country.

An objection to the use of B.M.R. estimations is the occurrence of "hypometabolism without hypothyroidism". In various series the proportion of patients in whom low B.M.R.s have been found without any other evidence of impaired thyroid function differs considerably. These differences may again be largely due to the use of different standards of normality. It is obvious that if the lower limit is considered to be -10% many more "low" B.M.R.s will be found in euthyroid subjects than if -20% is used. An alternative reason in some individuals may be the result of the method of estimating the

B.M.R. As long ago as 1922 Boothby and Sandiford suggested that heat-production is proportional to the active protoplasmic mass of the body and that this in turn is related to surface area. The possibility existed, therefore, that an increase in fat results in an increase in surface area without a proportionate change in basal oxygen consumption. This effect of depot fat on the B.M.R. as calculated from surface area was supported by the findings of Krebs and Johnson (1948) who considered that depot fat has a very low rate of oxygen utilisation and this was also recognised by Keys and Brozek (1953) and Bernstein et al (1956). Recent studies, however, suggest that fat is considerably more metabolically active than previously thought (Kekwick, 1960). Nevertheless, it is of interest to note that of 58 euthyroid subjects in whom Baron (1956) found low B.M.R.s, 17 were cases of simple obesity and it must still be considered possible that their B.M.R.s were fallaciously low because they were calculated from an abnormally high surface area.

It must be remembered that hypometabolism may occur in patients with disturbances of endocrine glands other than the thyroid (Baron 1956). The conditions most frequently encountered are eunuchoidism and anorexia nervosa, while low values are also occasionally found in subjects with Addison's disease. These disorders are, however, usually easily distinguished on clinical grounds.

This study has shown that the estimation of basal metabolic rate is of limited value in confirming the diagnosis of hypothyroidism, although a low reading is of significance. Serial estimations after the initiation of treatment may, however, be considerably valuable since, as will be shown in a later section, the effect of therapy may often be demonstrated by changes in the B.M.R. before any significant improvement is apparent in the clinical state.

Conclusions

The hypometabolism typical of hypothyroidism may be demonstrated by the estimation of the basal metabolic rate. The results, however, are only of significance if a truly basal reading is obtained. This requires a scrupulous attention to technique such as is not generally obtainable or practical. The diagnostic accuracy obtained in any series will also depend both on the standards and ranges of normality employed. The results in this study favour the adoption of the Robertson and Reid standards, particularly since low values will be found less frequently in euthyroid subjects. Nevertheless, in view of other inaccuracies that may be encountered, such as the association of "normal" B.M.R.s with proved hypothyroidism, the application of the procedure as a routine test in diagnosis is limited.

CHAPTER 14

SERUM CHOLESTEROL

Although there is considerable experimental evidence of an association between thyroid function and the metabolism of cholesterol, the value of the alterations in blood cholesterol levels as indices of the thyroid state has been the subject of controversy for many years. It is now generally accepted that significantly low values are not encountered sufficiently frequently in thyrotoxic subjects to make its estimation of use in the routine investigation of hyperthyroidism. Considerable disagreement, however, persists regarding its place in the diagnosis of primary hypothyroidism. In this chapter the results obtained in this study are presented and an attempt made to assess the usefulness of the serum cholesterol as a diagnostic procedure.

Method and Subjects

The serum cholesterol was estimated in 281 subjects using the method of Bloor (1916). Hypothyroidism was proved in 119 cases. The diagnosis was clear-cut in 68, but was not obvious in the remaining 51, the Doubtful Hypothyroid group. Diagnostic difficulty was also present in 59 patients shown later to be euthyroid, the Doubtful Euthyroid group. The estimation was also carried out in 103 normal healthy subjects of approximately the same age group in order to provide a range of normal values.

In 39 subjects with hypothyroidism the serum cholesterol estimation was repeated when, following treatment, they had become unequivocally euthyroid.

Results

In both the euthyroid and hypothyroid subjects there was a considerable scatter of results but it can be seen (Figure 12) that the values are higher in the latter group. Thus 132 (81%) of the 162 euthyroid subjects had serum cholesterol levels below 300mg%, whereas it was higher than this in 97 (81%) of the 119 hypothyroid patients (Table 25). Even high levels (greater than 350mg%) were present in 66 (56%) of these cases, but such values were only found in 8 (5%) of the euthyroid cases. Conversely only 7 (6%) of hypothyroid patients had values less than 250mg% compared with 98 (60%) of the euthyroid group.

There is a close correspondence in the distribution of results in the "Definite" and "Doubtful" groups of both euthyroid and hypothyroid subjects. If 300mg is taken as the dividing line, 95 of 110 doubtful cases (86%) could be correctly categorised.

The serum cholesterol fell after treatment in all of the 39 hypothyroid subjects in whom serial estimations were made (Figure 13), although in 2 patients the fall was less than 50mg%. The mean fall was 45.5%. In 32 subjects the value before therapy was greater than 300mg%, but in all but 2 was below this when they because euthyroid. In these two, initially very high values of 614mg% and 556mg% fell to only moderately raised levels of 334mg% and 321mg%, falls of 45% and 42% respectively. Considerable reduction of serum cholesterol was also apparent in four subjects who initially had values below 300mg%. An ultimate level of 185mg% was found in 3 of these in whom the levels prior to treatment had been 292mg%, 287mg% and 256mg%. One subject is of special interest since repeated estimations before treatment showed values of 200mg%, while after treatment the level was 138mg% which is below the lower limit of the normal range.

When the results of the cholesterol estimations are compared with the clinical diagnostic index (Table 26) it can be seen that agreement existed between the two parameters in 81 (69%) of 117 hypothyroid subjects. One or other was abnormal in all but one of the remaining 36 patients. Ten of the 12 hypothyroid patients with indices in the equivocal range had high serum cholesterol levels as had the only case incorrectly diagnosed by the index. In 49 cases in the

Doubtful Euthyroid group, agreement existed in 37 (79%) with only one case having both tests abnormal.

No significant correlation ($r = +0.043$) was present between the degree of elevation of cholesterol and the values of the index in the hypothyroid patients. There was also no correlation between the values of serum cholesterol and of basal metabolic rate estimated by the Method A previously described ($r = -0.244$). In 39 hypothyroid patients studied with these procedures both provided the correct diagnosis in 26. Of the remaining 13, the cholesterol was correct in 6, the B.M.R. in 4, while both were wrong in 3.

Discussion

The observations by Mason et al (1930) that the serum cholesterol was frequently elevated in hypothyroidism led many investigators to study its value as a diagnostic aid. Their conclusions were often contradictory. Some authors, for example Boyd and Connell (1936), doubted its reliability. On the other hand, Hurxthal (1934) considered it more valuable in indicating hypothyroidism than the B.M.R. The procedure gained greater support following the comprehensive study by Gildea et al (1939). These authors found that a serum cholesterol of over 300mg% was greatly in favour of hypothyroidism while this diagnosis was practically excluded by finding a value less than 275mg%. They pointed out that, if the cholesterol was below this level, thyroid therapy would be most unlikely to relieve symptoms suggestive of hypothyroidism or to produce a significant decrease in the cholesterol. They concluded that in patients with a high cholesterol and a low B.M.R. the diagnosis of hypothyroidism should be made until disproved by a failure to improve after an adequate period of therapy. Most clinicians would not now place quite so much reliance on the test. In general, however, the results of the present study do in fact support the views of Gildea et al (1939).

It has been found that, while 81% of the euthyroid subjects have cholesterol values below 300mg%, the same proportion of hypothyroid patients showed values above this level. There is obviously still a considerable overlap between the two groups, but this mainly lies in the range 250-350mg%. Thus in a patient suspected to be hypothyroid the finding of a cholesteol value of more than 300mg% favours hypothyroidism and if greater than 350mg% the diagnosis is practically certain, provided certain other conditions discussed later can be excluded. Conversely, the possibility that a patient suffers from primary hypothyroidism is extremely unlikely if the cholesterol is less than 250mg%. However, 102 (31%) of the total 281 subjects studied had cholesterol values within the intermediate range of 250-350mg%. In particular it may be noted that although 35% of the definite hypothyroid group lay within this range, a higher percentage (43%) of the doubtful hypothyroid patients had similar values.

One objection to the use of cholesterol estimations in the investigation of thyroid disorders is the wide scatter of normal values. In different centres the normal range may vary greatly, depending on their technique and the number of "normal" estimations carried out. The selection of the normal subjects is also important in view of the rise in serum cholesterol that may accompany increasing age. It may be noted, however, that the levels found in this study in euthyroid subjects of approximately the same ages as the hypothyroid patients are very similar to those reported by Peters and Man (1943a). These authors found a scatter of results from 107-320mg% with the majority lying between 130 and 280mg%. Similarly, Wooten and King (1953) stated that 99% of normal individuals had figures between 123 and 324mg%. The consequence of this scatter is that a hypothyroid subject may have a serum cholesterol within the normal range although in fact it may be considerably elevated above the "normal" value for this individual. Peters and Man (1943b) concluded that the level to which the cholesterol rises is roughly related to the concentration in the individual when healthy. This is illustrated by the effect of treatment in 3 of the patients in whom the initial readings were less than 300mg%. Therapy resulted in falls of 27 to 36%. One other patient had a very low "normal" concentration of 138mg% which was reached after treatment from an initial level of only 200mg%. Obviously this explanation applies equally to the hypothyroid patients of both definite and doubtful groups since it depends on the individual "normal" level. It is not surprising, therefore that there is no correlation between the serum cholesterol and the degree of clinical severity as assessed by the diagnostic index. No correlation existed between the cholesterol and B.M.R., as has also been previously shown by other investigators, such as Mason et al (1930).

When hypothyroidism is secondary to impaired pituitary function the serum cholesterol is of much less value in reflecting impaired thyroid function as Peters et al (1949) pointed out. In half of the patients of this type in one series reported by van Arsdel and Williams (1956), the cholesterol was below 200mg%. In the present study values of less than 300mg% were found in 6 of 13 patients suffering from hypopituitarism.

The results of cholesterol estimations must be interpreted with caution in light of the state of nutrition. Means(1948) pointed out that there may be a marked lowering of the serum cholesterol in malnutrition and that in certain cases of hypothyroidism with added malnutrition the expected elevation might not be found.

Abnormal elevated values of serum cholesterol may also be found in conditions other than hypothyroidism, for example diabetes mellitus, the nephrotic syndrome, obstructive jaundice, xanthomatosis and pregnancy. The occurrence of elevated values in such conditions is considered by many to reduce considerably the reliability of the estimation of total cholesterol as a diagnostic tool in the investigation of hypothyroidism. In many of these disorders there is usually a disturbance of the ratios both of esterified to free cholesterol and of total cholesterol to phospholipids, while in hypothyroidism the normal ratios are maintained (Peters and Man, 1943b, 1950). The finding of abnormal total cholesterol values in these conditions, however, should not in fact cause great diagnostic difficulty since in most cases differentiation from hypothyroidism should be possible on clinical grounds. The increased complexity of the biochemical procedures involved in the estimation of the cholesterol fractions and phospholipids would not, therefore, appear likely to produce a commensurate increase in the diagnostic accuracy from that provided by the simple measurement of total cholesterol.

Conclusions

The changes in cholesterol metabolism provide a useful method of demonstrating the metabolic effect of deficiency of thyroid hormone. An increase in blood cholesterol levels almost inevitably occurs in primary hypothyroidism and, in the majority of cases, results in abnormally high values. Normal levels may be found in some hypothyroid subjects and elevated values may also be caused by extra-thyroidal factors. Objections such as these do not, however, detract sufficiently from the usefulness of the estimation to preclude its employment in the routine investigation of suspected hypothyroidism.

CHAPTER 15

SERUM CAROTENE

In clinical reports of patients with hypothyroidism the skin is often described as "yellowish". Terms such as "like old wax" are frequently found in the Report on Myxoedema (1888). The symptom analysis, previously discussed in Chapter 2, showed that this feature was present in 48% of hypothyroid subjects. Its presence in adult hypothyroidism was first explained by the finding by Escamille et al (1935) of carotenemia in a case of hypothyroidism. In a subsequent report Escamilla (1942) showed that high serum carotene levels were present in seven further hypothyroid patientsand that the administration of thyroid resulted in a gradual decrease in these levels. Subsequently, the occurrence of carotenemia in hypothyroid subjects has been reported by other authors, Stepp and Wendt (1937) and Cohen (1958). Experimental studies have confirmed the relationship between the thyroid gland and the metabolism of carotene and vitamin A. These have, however, often been contradictory (Goodwin, 1952) and there is still dispute whether the disturbed metabolism of these compounds in hypothyroidism is the result of alterations in absorption or produced by a direct effect on the enzyme carotenase which controls the oxidative conversion of carotene into vitamin A. No previous attempts, however, have been made to determine the value of the estimation of serum carotene in the diagnosis of clinical hypothyroidism. Such a study has, therefore, been carried out.

Methods and Subjects

Estimations of serum carotene, using the method of Pett and Le Page (1940), were carried out in 116 subjects. The specimens of blood were removed at the clinic without the individuals being in a fasting state. Forty-nine hypothyroid patients were investigated, 20 being in the Doubtful Hypothyroid group. Thirty-five subjects in the Doubtful Euthyroid group were studied and the test was also performed in 32 normal healthy individuals to provide ranges of normality. In 27 of the hypothyroid cases estimations were repeated when the patients had become euthyroid.

Results

The results are shown in Appendix IV, and illustrated in Figure 14. It can be seen that in the euthyroid subjects the values varied from 29ug% to 156ug%, while in the hypothyroid patients the range was from 40 to 229ug%. In the 32 control subjects (Table 27) the level was below 90ug% in 22 (68%) and below 110ug% in 26 (81%), but in 4 (13%) values greater than 130ug% were found. There was a similar distribution of the results in the Doubtful Euthyroid group. Among the 49 hypothyroid subjects 22 (45%) had a carotene level greater than 130ug%, while in only 8 (16%) was it below 90ug%; 28 (57%) showed values above 110ug%.

With therapy, the serum carotene level fell in all 27 hypothyroid patients studied (Figure 15), although in 3 subjects the fall was less than 20ug%. In 17 of 19 subjects with an initial level greater than 110ug%, the level was below this figure when they were euthyroid. Twenty-three patients initially had values greater than 90ug%; in 19 therapy was accompanied by a fall below this level. It may be noted that there was some decrease even in the 4 subjects in whom the initial levels were 90ug% or less. The mean fall in serum carotene following treatment for the 27 patients was 44%.

Discussion

In most textbooks dealing with thyroid disease, statements can be found that the serum carotene is elevated in hypothyroidism. These, however, usually refer to the observations of Escamilla (1942) which were based on 7 cases using the "icteric index" of the petroleum ether extract of serum as the measure of carotenemia. The method employed in the present study does provide a more reliable quantitative value. It does, however, involve a colorimetric comparison with a standard solution of potassium dichromate. The fact that yellow colour changes are particularly difficult to detect may in part account for the wide range of values found in euthyroid subjects. Greater accuracy might have been obtained if all specimens had been removed from fasting subjects, since the dietary carotene content of foods may vary considerably. Indeed, carotenemia may be encountered when excessive amounts of carotene have been ingested, usually in the form of carrots. This is, however, uncommon since Cohen (1958) states that 4 to 8lbs of raw carrots must be eaten for several months daily before marked elevation of serum carotene is observed. It is more important to note that elevated levels may be found in some cases of diabetes and can occur in association with malnutrition as demonstrated by Dally (1959) in a case of anorexia nervosa.

The results of this study do in general confirm the previous observations that there is abnormal carotene metabolism in adult hypothyroidism. When, however, 110ug% is taken as the upper limit of normality, there is too great an overlap between normal and hypothyroid subjects for the result of a carotene estimation to be of any diagnostic value. If the range 90ug% to 130ug% is considered as an "equivocal range", values lying on either side will be of much greater significance. Thus a serum carotene of more than 130ug% will strongly favour a diagnosis of hypothyroidism since such values were found in only 9% of normal subjects. Hypothyroidism is unlikely to be present if the serum carotene in an individual is less than 90ug%, only 8 (16%) of the 49 hypothyroid patients having such values. However, 35 (30%) of all the individuals studied had serum carotene values in the range 90 to 130ug%. When both doubtful groups are considered, only 31 (56%) of 55 patients were correctly diagnosed by falling on the respective sides of this range. Thus, although a high or low reading will be of value, the overall accuracy of the serum carotene in discriminating between normal and hypothyroid subjects is inadequate for the procedure to be of value in the routine investigation of hypothyroidism.

Conclusions

The serum carotene was higher in the majority of 49 patients with hypothyroidism than in 67 euthyroid patients.

Although a carotene level greater than 130ug% favours a diagnosis of hypothyroidism and this diagnosis is unlikely if a value of less than 90ug% is found, there is a considerable overlap between the two groups. The procedure is not considered to be of any practical value in the investigation of suspected hypothyroidism.

CHAPTER 16

THE ELECTROCARDIOGRAM IN HYPOTHYROIDISM

Ever since White and Aub (1918) and Zondek (1918) reported changes in the electrocardiogram which have come to be recognised as characteristic of hypothyroidism, most clinicians include the procedure in the routine investigation of suspected hypothyroidism, considering that the presence of the typical changes provides confirmation of the diagnosis. Surprisingly few attempts, however, have been made to assess the frequency with which the characteristic electrocardiographic pattern does in fact occur. In this chapter, therefore, this aspect has been considered.

Method

Electrocardiographic examination was carried out in nearly all the patients in this study, but an accurate comparison of the records proved somewhat difficult since different instruments, with consequent differences in standardisation, had been used. Although in the majority of cases abnormalities were noted, the tracings in only 60 hypothyroid subjects have been considered in detail. In all of these 60 cases the same standard limb, chest and unipolar (1-6) leads were employed and care was taken to ensure accurate standardisation. The tracings were all studied independantly by the same two observers after the final diagnosis of hypothyroidism had been established. Attention was paid particularly to the changes in the T waves and to the decrease in the voltage of the QRS complexes. It was possible to grade the changes into four groups, as follows:-

1. ++ A pattern of changes typical of hypothyroidism.
2. \+ Changes of a lesser degree, but still in favour of the diagnosis of hypothyroidism.
3. ± Abnormalities present, but of doubtful significance and not of diagnostic value.
4. \- No changes at all suggestive of hypothyroidism.

The diagnosis was obvious in 35 patients, the remaining 25 being in the Doubtful Hypothyroid group. In all, hypothyroidism was either primary or due to Hashimoto's thyroiditis. The results of the E.C.G. studies carried out following treatment will be discussed later.

Results

The E.C.G. showed abnormalities of diagnostic value in 47 patients (79%). It can be seen (Table 28) that marked changes (++) were present in 37 (62%), but that these were more often present in the Definite Hypothyroid group than in those patients causing diagnostic difficulty, usually because the severity was of lesser degree. In 13 patients the procedure provided no significant diagnostic information, although equivocal changes were present in 9.

Discussion

Abnormal T waves which returned to normal with thyroid therapy were described by White and Aub (1918) in two cases of hypothyroidism. In 14 further patients Thacher and White (1926) drew attention to the diminished size of QRS complexes and the general decrease in potential. Thacher (1924) had also noted similar abnormalities in 8 cretins and observed the improvement following treatment. Since then it has been recognised that in hypothyroidism these changes are indeed commonly found and form a characteristic pattern typically with low voltage in all complexes and flattening and often inversion of T waves. Other changes occasionally noted are reduction in the amplitude of the P wave, a prolongation of the PR interval or a widened QRS complex. These latter alterations in conduction may indicate myxoedematous infiltration of either the bundle of His or one of the branch bundles. The other changes have been attributed by Kern (1949) to the presence of pericardial effusion on the basis of experimental evidence that the introduction of sodium chloride into the pericardium is accompanied by electrocardiographic changes similar to those found in hypothyroidism, but this is most unlikely to be the complete explanation. The possibility that the alterations are simply due to the altered resistance of myxoedematous skin has been shown to be untrue by White (quoted by Means, 1948), who found persistent changes when using needle electrodes.

Although it is generally accepted that these abnormal tracings are frequently associated with hypothyroidism, there is some disagreement as to their diagnostic significance. Some authors, for example Werner (1955) and Soffer (1956), considered that the E.C.G. changes are not diagnostic. White (1951), among many others, states that they are almost pathognomonic. Means (1948) is even more emphatic, considering that the abnormalities should be looked on as being specific to athyreosis, and suggests that they are as much a sign of hypothyroidism as any of the cardinal signs and symptoms.

The present study shows that the electrocardiogram is not normal in the majority of hypothyroid subjects. Further it is clear that, in many of these patients, the changes are of the typical pattern associated with the disorder and thus provide a firm basis for confident diagnosis. The frequency with which the tracings show this pattern unequivocally is however disappointingly low. Not surprisingly, it is more frequently encountered in the patients where the diagnosis is clear-cut on clinical grounds than in those where the condition is milder. In the latter group, many do in fact show changes strongly in favour of the diagnosis. In some of these patients, however, these changes, being less marked, may be obscured by other abnormalities not directly associated with the hypothyroid state. It must be remembered that in the age range in which hypothyroidism is most common, disorders such as hypertension and myocardial ischaemia may be encountered with their accompanying electrocardiographic abnormalities. On this account, in 9 (15%) of the 60 patients studied here the abnormality in the E.C.G. could not be considered to be of any value in determining their thyroid state. Tracings which were not considered to be at all suggestive of hypothyroidism were in fact found in 4 patients who were proved unequivocally to be hypothyroid. This is perhaps surprising and difficult to explain, but may be related to varying sensitivity of the target organ to thyroid hormone. It may be noted that Williams and Haines (1925) considered that significant changes were present in only 28 (54%) of 52 hypothyroid patients.

The selection of the 60 patients whose E.C.G. tracings have been carefully reviewed was unrelated to the degree of severity of their hypothyroidism. The frequency with which abnormal findings were reported in the other hypothyroid patients investigated was similar, although the criteria were possibly less strict. The reversion of the changes following therapy, as will be seen later, does provide a simple method of assessing the control of the individual. The diagnosis is, however, not entirely excluded if the typical abnormalities are not found, and this unfortunately is most likely to happen when diagnostic information is most urgently required, namely in the early and atypical case. This disadvantage is to a considerable extent balanced by the fact that abnormal E.C.G. tracings of the characteristic hypothyroid pattern were not found in any of the Doubtful Euthyroid group. Nevertheless, this study tends to support the view expressed by Means (1948) that "electrocardiography is a diagnostic luxury, not a necessity".

Conclusions

The demonstration of electrocardiographic abnormalities of a typical pattern provides strong evidence in favour of the diagnosis of hypothyroidism. The changes reflect the clinical severity to a certain extent since they are more frequently observed in advanced cases. When the condition is milder they may be less marked or obscured by other accompanying abnormalities, or may even be absent. The investigation is, therefore, considered to be a useful method of confirming the clinical diagnosis of hypothyroidism, but to be of limited value in routine diagnostic investigation, since the absence of typical changes does not exclude the diagnosis.

CHAPTER 17

THE REACTION TIME IN HYPOTHYROIDISM

The reaction time, the measure of the interval between the application of a stimulus to a sensory organ and the voluntary response, is known to be influenced by various factors. Increasing age and fatigue, for example, lengthen it, as do depressant drugs such as alcohol and the barbiturates. It seemed possible that the reaction time would also be prolonged in hypothyroidism, and that it might be correlated with the degree of thyroid underactivity. A simple and rapid method of measuring the reaction time to a visual stimulus was therefore devised and has been used in patients with hypothyroidism and also, as controls, in healthy people and in anaemic patients. The effects of thyroid therapy and of dextroamphetamine sulphate on the reaction time have also been studied.

The investigation was carried out in two parts. The first showed that there is a significant prolongation of the reaction time in many hypothyroid subjects. The study was then continued in order to assess the value of the procedure in the investigation of hypothyroidism and to compare its diagnostic accuracy with that of the standard tests.

Method

The apparatus used to measure reaction time is shown in Figure 23 and the circuit illustrated in Figure 24. After the subject has depressed key 2, the observer depresses key 1, thus closing the relay contacts AB and CD. As a result, the red lamp lights, and the scaling unit is operated by the relay contacts AB and key 2 acting via the electronic gate. The scaling unit records pulses at twice the mains frequency (100 c.p.s.) until key 2 is released by the subject, when the scaler stops (again using the electronic gate) and records the reaction time in seconds up to 9.99 seconds.

The subject is instructed to depress the button (key 2) and, immediately he sees the red light, to remove his finger from the button as rapidly as possible. The operator continues to keep his key depressed until after the scaler has stopped and then resets the scaler. Several practice tests were made with each subject to ensure that the instructions were understood. Reaction times were measured at intervals from 5 to 10 seconds in order to avoid anticipation. Long intervals were avoided to prevent the subject's attention from wandering. In the initial stages of this study a minimum of two hundred consecutive readings were taken in 5 healthy people and in 4 hypothyroid patients. It was found that after the first ten to fifteen tests had been made there was little difference between the mean of each suceeding group of ten. Accordingly the practice was adopted of taking fifty readings, the first twenty being discarded, and the mean of the last thirty recorded as the reaction time. A visual stimulus was used rather than aural, because hypothyroidism may cause impaired hearing.

PART I

Control subjects - This group consisted of 101 healthy people aged 17 to 83 years and included medical staff, laboratory personnel and patients in whom there was no evidence of thyroid dysfunction. A further 10 persons with normal thyroid function, but with anaemia from various causes (haemoglobin less than 60%) were also studied. In 5 healthy people the test was repeated at intervals of several weeks.

Hypothyroid patients - Fifty patients were studied. The condition was idiopathic in most cases, but in some it was secondary to hypopituitarism, Hashimoto's thyroiditis, thyroidectomy or radioiodine therapy. Twenty of the patients were reviewed at intervals during therapy and repeated estimations of B.M.R., serum cholesterol level and reaction times were made. To eliminate the possible effects of practice, the reaction times were determined only before and after return to the euthyroid state in 5 patients. Reaction times were also estimated in a further 9 patients previously proved hypothyroid, but who had been euthyroid on thyroxine therapy for periods of six months to two years. In all cases it was ascertained that no barbiturate was being administered.

Dextroamphetamine sulphate - This drug was administered orally in a dosage of 15mg to 6 healthy people and 7 hypothyroid patients and the reaction time was recorded at intervals for the following 4 to 4½ hours.

PART II

The investigation was continued using the same procedure until 124 hypothyroid subjects had been studied. In 45 the hypothyroidism was secondary to pituitary insufficiency or radioactive iodine therapy. The diagnosis in 42 of the remaining 79 patients in whom the condition was primary or due to Hashimoto's thyroiditis, was unquestionable, but 37 were in the Doubtful Hypothyroid group. In addition, the test was carried out in 45 subjects of the Doubtful Euthyroid group.

Results -- Part I

The mean reaction times of the healthy people for the four age-groups analysed are shown in Table 29. The pooled standard deviation is ± 0.0156 seconds. If M is the mean of a group and S the pooled standard deviation, then if the members are normally distributed the range M ± 2S is one in which 95% of the normal reaction times will lie. These normal ranges are also shown in Table 29. There was no statistically significant difference between repeated readings in healthy people on different dates. The reaction times of the 10 severely anaemic patients all fell within these normal ranges. The mean values for the reaction times of the 50 hypothyroid patients for each age-group are also shown in Table 29. There is a significant difference between each and the corresponding normal mean. It can be seen from Figure 18 that the reaction times of 46 of these patients lay outside the normal ranges. The reaction times of the 9 hypothyroid patients who had been euthyroid for a considerable period were all within the normal ranges for their ages. During therapy the reaction times of the hypothyroid patients decreased and it can be seen (Figure 19) that when 23 of the 25 patients had become euthyroid, their reaction times lay within the normal ranges. This happened both in the patients observed at intervals and in those in whom the test was repeated only when they were euthyroid, and thus demonstrated that practice was not of importance. These changes are statistically significant. One patient, while hypothyroid, had a reaction time just within the normal range, but after treatment her "normal" reaction time was faster than normal for her age. In a cretin, aged 14 years, who had neglected to continue her treatment, there was also an improvement on further therapy, but when she was euthyroid her reaction time was still much prolonged. This improvement corresponded to a clinical impression of increased alertness, although she still remained mentally retarded. Table 30 shows the mean reaction times (excluding this case) before and after therapy. For each age-group the values when the patients had become euthyroid approached the mean for healthy people. The improvement in the reaction times in the hypothyroid patients after treatment paralleled the changes in B.M.R. and serum cholesterol levels. This pattern is illustrated by Figure 20, which shows the response to tri-iodothyronine in a hypothyroid female, aged 44 years. The reaction time improved rapidly and within four days was within the normal range. Normal values were subsequently found on repeated occasions for over a year when this patient remained under observation on therapy. One patient stopped therapy on her own initiative and her reaction time, which had kept within the normal range for five months while euthyroid, again became prolonged. Resumption of therapy was followed by a return of the reaction time to normal.

In both the healthy people and the hypothyroid patients dextroamphetamine sulphate decreased the reaction time. However, as can be seen in Figure 21, this decrease was greater and more prolonged in the hypothyroid patients than in the healthy people. The mean maximal quickening for the patients was 0.0524 seconds, compared with 0.0248 seconds for healthy people.

Results -- Part II

The results of the investigation in all 124 hypothyroid subjects can be seen in Table 31 which shows that the reaction time was prolonged in 106 (86%) patients. It may be noted that a normal value was found in only one of the Definite Hypothyroid group. Nine (24%) of 37 patients in whom diagnostic difficulty was found also had reaction times within the normal range, but it was prolonged in the remaining 28 (76%). On the other hand, abnormal results were only found in 5 (11%) of the 45 subjects in the Doubtful Euthyroid group. When the two doubtful groups are considered together, a total of 82 patients, a correct diagnosis was obtained in 68 (83%).

The combined use of the diagnostic index and this test produced high diagnostic accuracy. Thus, one or other favoured the correct diagnosis in all but 2 of 79 subjects, although there was agreement between the two procedures in only 60 (76%) (Table 32). The Table shows that there is no significant difference between the accuracy of the two methods. It must be remembered that where the index is not correct (in only one instance did it actually indicate a wrong diagnosis) it merely fell within the equivocal range. In the one case with a completely wrong diagnostic index, the reaction time was prolonged, correctly favouring the diagnosis of hypothyroidism. In none of the 45 patients in the Doubtful Euthyroid group were both procedures wrong and agreement between them existed in 34 (76%).

The results of the measurement of reaction time are compared with the clinical diagnostic index, using this a measure of clinical severity, in Figure 22. No significant correlation exists between the two parameters within the separate age groups of "less than 40 years," "40 to 50 years" and "greater than 60 years". The respective correlation co-efficients are + 0.294, +0.374, +0.306. A significant correlation was present in the 50 to 60 age group (r =+0.437). These differences may be the function of the numbers in the groups, since, when age is disregarded, there is significant correlation between reaction time and in the index over all the cases (r =+0.3157). No correlation (r = +0.15) is present between the reaction time and the basal metabolic rate in 28 patients in whom the latter was estimated by the Method A previously discussed.

Discussion

The method of measuring reaction time used in this study has many advantages over other methods. In particular the apparatus is portable and inexpensive and allows considerable accuracy in timing. The rapidity with which observations may be repeated also permits allowance to be made for the effects of practice, which Forbes (1945) and others have demonstrated. The validity of the method has been confirmed in separate unpublished studies by demonstrating in a sensitive manner the changes expected after the administration of drugs affecting the central nervous system, for example the prolongation after barbiturates.

The symptom analysis showed that mental sluggishness, lethargy, impaired memory and lack of concentration are common complaints of patients with frank hypothyroidism, and even mild cases may present with symptoms of this type. Since the reaction time reflects higher mental processes (Evans, 1947) it is not surprising to find it lengthened in hypothyroidism. In a few patients with gross mental apathy resulting from hypothyroidism, the test was made more difficult as a result of their inability to understand the instructions. In many of the other cases the diagnosis of hypothyroidism could be made only after full investigation, including the response to a therapeutic trial. In such patients the mental and physical slowing is much less which, as already shown, often gives rise to diagnostic difficulty. However, in 46 of these 50 patients the reaction times were prolonged. The possibility that the anaemia which may be associated with hypothyroidism might play a part in the prolongation of the reaction time was eliminated by the finding of normal reaction times in severely anaemic, but euthyroid, patients.

In the initial study, 4 hypothyroid subjects had reaction times within the normal ranges. One, an electric welder, a skilled occupation involving quick and rapid movements of the hands, noted that he was not producing such good work as formerly. The reaction time of another of these patients lay just within the upper limit of the normal range, but when she became euthyroid her "normal" reaction time lay below the lower limit of the normal range, suggesting that there had originally been a considerable prolongation. The two other patients had only recently become hypothyroid as a result of radioactive iodine therapy. It seemed possible, from these and other patients studied subsequently, that the hypothyroid state must be present for some time before the reaction time slows.

The subsequent studies have supported this view. It was noted that 8 (24%) of the patients hypothyroid following treatment of thyrotoxicosis had normal reaction times. In all of these overdosage with radioactive iodine had caused hypothyroidism. Normal values were found more frequently in the patients in the Doubtful Hypothyroid group where the condition was milder than in those where the diagnosis was unequivocal. In one patient the true diagnosis of hypothyroidism was suspected only after she failed to obtain any clinical benefit from a full course of electro-convulsive therapy for a reputed depressive psychosis. It is of interest to observe that her reaction time was well within the normal range, although she was proved hypothyroid by all other procedures.

On the completion of the first part of this investigation it was considered reasonable to suggest (Murray, 1958a) that, in cases of suspected hypothyroidism, the measurement of reaction time is a simple and rapid aid to diagnosis which causes minimal inconvenience to the patient. Moreover, a useful index of the response to therapy by the patient is provided by the improvement in reaction time. In general this parallels the changes in the clinical picture, the B.M.R. and the serum cholesterol level (Figure 20).

Following the publication of these observations a method of measuring reaction time with even less apparatus than the one employed in this study was suggested by Magnus (1958). It was apparent, however, that the increase in observer error using this procedure would reduce the diagnostic accuracy.

The changes in reaction time in hypothyroidism probably reflect the changes in cerebral function. The results are comparable with those of Gantt and Fleischmann (1948), who studied the conditioned-reflex function in a cretin and showed that after successful therapy there was an improvement which reached a level in two months, but did not change further over two years. Other workers have studied the changes in cerebral function in hypothyroidism using recognised psychological techniques, and have found evidence of impairment, for example Reitan (1953) who used the Rorschach test. Further evidence that the effect is on the higher centres is provided by the results of the studies of the effect of dextroamphetamine sulphate (Figure 28). The quickening of reaction time produced by this drug lasted considerably longer in hypothyroid than in healthy individuals.

The possibility exists that the impairment of reaction time might be influenced by delay in the peripheral component of the arc, but this is unlikely in view of the findings described earlier (Chapter 6) showing that the conduction velocity in peripheral nerves was not appreciably altered in hypothyroidism. Similarly, Lambert et al (1951) concluded that although the total time taken for the ankle-jerk in hypothyroidism was increased, there was no appreciable difference in the speed of conduction through the reflex arc in healthy people and in hypothyroid patients. They emphasised that this reflex took place over a two-neurone arc which does not involve the more complex activity of the central nervous system, as does the reaction time pathway.

Further experience with the procedure has confirmed the conclusions of the initial study. Indeed, the results obtained in the larger number of patients provide stronger evidence that accurate discrimination between hypothyroid and euthyroid subjects may be obtained by the estimation of reaction time. In particular, it is of value in assessing these patients who cause diagnostic difficulty on clinical grounds. In 83% of this group correct separation was achieved. This diagnostic accuracy is comparable with most of the other standard tests, but the simplicity of the test makes it particularly suitable in providing rapid confirmation of the diagnosis suggested by the clinical diagnostic index. The results show that the combination of these two procedures provide a high degree of diagnostic precision. It may be recalled that 17 of the 124 patients studied had indices outwith the normal or hypothyroid ranges. The correct diagnosis was provided by the estimation of reaction time in 15 of these including the one patient in whom the index was wrong.

It was noted in the symptom analysis that the mental changes were of considerable diagnostic importance in hypothyroidism and these features were consequently given heavy weighting in the construction of the diagnostic index. It is therefore not altogether surprising that there is a significant correlation between the index and reaction time, since the latter reflects the impairment of mental activity. Nevertheless, the existence of such a correlation does further emphasise the diagnostic importance of the changes in cerebral function. Moreover, it may be concluded that the measurement of reaction time provides not only useful diagnostic information, but is also, to a considerable extent, a quantitative index of the clinical severity of the hypothyroid state.

Conclusions

Prolongation of the reaction time reflects the impaired mental activity frequently encountered in hypothyroidism. The reaction time provides a quantitative measurement of these changes in cerebral function and may be used as a diagnostic test in the investigation of suspected hypothyroidism and in the assessment of response to therapy. The method that has been employed provides diagnostic precision of the same order as many conventional tests, but may be carried out more rapidly and with less inconvenience to the patient than most of these. The estimation of reaction time is considered to be a very useful method of confirming the diagnosis made by the

clinical diagnostic index and to be of value in the investigation of those patients in whom this index lies in the equivocal range.

CHAPTER 18

"THE CHOICE OF TESTS"

The studies reported in the previous chapters have shown that the accuracy provided by the various tests in confirming the diagnosis of hypothyroidism varies considerably. Although in some it is of a high degree, no single procedure is infallible. A comparison of the frequency of abnormal results encountered with the different tests in hypothyroid subjects is shown in Figure 23. From this it can be seen that the procedures employing radioactive iodine most frequently provided results agreeing with the final diagnosis. Indeed, this agreement is so good that it might be suggested that only these tests should be required to confirm the diagnosis. However, as previously pointed out, there are possible fallacies inherent even in these tests, as for example in the normal results which may be encountered in hypothyroidism due to Hashimoto's thyroiditis. Moreover, the use of radioiodine is invalidated if the patient has received iodide in any form, or recent thyroid therapy. Other tests must, therefore, be available not only to replace the radioactive iodine studies in such circumstances, but also to provide corroborative evidence of the state of thyroid function.

It is obviously desirable to reduce the number of investigations to the minimum that will provide adequate and accurate information. In the selection of those to be used in the routine investigation several considerations must be borne in mind. In the first place the relative diagnostic accuracy is obviously important. On this account procedures such as the estimation of serum carotene or the recording of the sleeping pulse rate may be excluded since, although impaired thyroid function may produce abnormal values, normal results are seen in such a large proportion of hypothyroid subjects.

In the course of this study several other investigations were performed in a number of hypothyroid patients. It was apparent that with many of these tests abnormalities could be demonstrated, but similarly not with sufficient frequency to be relied upon. Thus for example, the typical alterations of hypothyroidism in the electro-encephalogram, the lowered voltage and slow alpha rhythm, were found in 5 of 24 hypothyroid patients. Changes of doubtful significance were present in 9, but in 10 patients the record was considered to be within normal limits. Moreover, with some investigations the alterations encountered were similar to those that may occur in other conditions. Examples of changes which are not specific to hypothyroidism were the demonstration of a mild anaemia (haemoglobin less than 12.0G%) in 18 of 65 hypothyroid patients, a histamine fast achlorhydria in 10 of 25 patients and an elevated erythrocyte sedimentation rate (greater than 15mm in the first hour) in 44 of 60 patients.

Of the numerous other tests available, there are many in which the frequency of occurrence of abnormal results is comparable. From these the choice of routine procedures must be selected. In any hypothyroid individual normal values are rarely found with more than one or two of these tests. Such apparently divergent results are probably explained by the fact that the various procedures reflect differing aspects of thyroid deficiency. In selecting the tests to be used therefore it is obviously desirable to pick those that do demonstrate various aspects of impaired thyroid function.

In the choice of any test the ease with which it may be carried out is obviously important. Thus any procedure should be chosen in preference to another if, their diagnostic accuracy being comparable, it can provide the required information more rapidly and with less inconvenience to the patient. On these grounds many of the investigations that have been advocated in the past may be discarded. For this reason, for example, skin biopsy cannot be advocated. This procedure was carried out in 14 hypothyroid patients. The changes considered by Gabrilove and Ludwig (1957) to be characteristic of hypothyroidism, namely the presence of extracellular metachromatic material stained with toluidine blue, was noted in the corium of 11 patients. In the remaining 3, although the deposits were not stained, there was undoubted disruption of collagen fibres. The procedure does, however, cause some discomfort to the patient and cannot be considered to be a justifiable routine procedure.

It was not possible to include the estimation of the protein-bound iodine in this survey of diagnostic procedures. It is, of course, widely considered to be the most diagnostically accurate of all tests of thyroid function. Macgregor and Farrell (1958) for example estimated the $PB^{127}I$ in 82 hypothyroid patients and found that only 9 of them had values greater than 3.0ug/100ml. The use of this investigation, however, in routine practice is limited by the considerable difficulties that arise in the estimation. The determination is difficult, tedious and time-consuming, factors that make it extremely prone to error from contamination. Werner (1955) points out that the procedure does require facilities and proficiency not available in the average clinical laboratory. In addition, it is not infallible since misleading results may arise from various causes which unfortunately in many instances are the same ones that often invalidate ^{131}I studies, such as the use of organic iodinated contrast media and the administration of inorganic iodides which, as Man et al (1951) showed, may be particularly confusing since the resulting errors are capricious and of varying magnitude. Low values of $PB^{127}I$ that may be misleading may be encountered in conditions other than hypothyroidism, such as nephrosis (Recant and Riggs, 1954), cirrhosis of the liver (Kydd and Man, 1951) and malnutrition (Durham et al, 1954). In particular, it is important to note that Riggs et al (1945) showed that the $PB^{127}I$ may fall to hypothyroid concentrations for a variable period after cessation of thyroid therapy to normal individuals. Consequently, as personal experience in the Massachusetts General Hospital, Boston, has confirmed, this estimation is considered in many centres to be of value, but certainly not to provide an increase in diagnostic precision commensurate with the difficulties in its estimation compared with the routine tests of thyroid function.

In evaluating the diagnostic accuracy of any investigation consideration must be given not only to the frequency with which abnormal results are found in abnormal subjects, but also whether such abnormal results occur in healthy subjects. In addition it is desirable to discover the efficiency of the tests in determining correctly those cases presenting clinical diagnostic difficulty. Figure 24 shows the overall accuracy of the selected tests in the two "doubtful" groups together.

Bearing the considerations regarding the practicability of the procedures in mind, it may be concluded from the results that the investigation of hypothyroidism can be restricted to only a few tests without any loss in diagnostic precision. Radioiodine studies are clearly the most sensitive in detecting impaired function provided their limitations are remembered. A gland uptake at 24-hours causes little inconvenience to the patient and is easily carried out. If a more rapid answer is required this may be obtained by the use of intravenous clearance techniques, although at the expense of some increase in complexity. Should the uptake be impracticable because of distance or contra-indicated in view of the patient's general state, a simple urine collection in the period 24-48 hours after the dose of ^{131}I provides an adequate replacement. The estimation of serum cholesterol is a sensitive and relatively simple biochemical procedure to demonstrate the changes in metabolic process associated with primary myxoedema. In addition, as will be seen in Section III, the fall that characteristically follows the administration of thyroid provides a useful index of therapeutic response. Since radioiodine studies cannot be relied on to demonstrate hypothyroidism produced by auto-immunising thyroiditis, it is desirable, when this disorder is suspected on clinical grounds, to carry out a flocculation test, such as the measurement of serum thymol turbidity, or a precipitin test or similar procedure to show the presence of antibodies.

It is suggested that of all the procedures that reflect the effect of lack of thyroid hormone or end-organ function, the measurement of reaction time fulfils most adequately the criteria discussed above. An electrocardiogram may provide useful information and, of course, it is much more readily available. However, it must be interpreted with care, preferably by a skilled observer, since the changes may be of an equivocal nature. It is also of value, of course, as a reminder of the caution that must be employed in the treatment of hypothyroidism.

In the first part of this thesis it was shown that the use of the diagnostic index could result in a considerable reduction in the number of patients in whom confirmatory investigations are required. An index of less than 0 provided strong evidence that a patient was euthyroid, while an index of greater than +20 indicated hypothyroidism. Values between 0 and +4 strongly favoured normal and between +16 and +20 impaired thyroid function, but in view of the statistical possibility of an incorrect diagnosis arising from scores in these ranges, a simple confirmatory investigation was considered desirable. From the results of the selected tests carried out in the 33 patients who fell within these ranges, it is possible to judge which is the most useful in providing this confirmatory information. It will be seen (Table 33) that 15 of the 16 patients whose indices lay between 0 and +4 were finally shown to be euthyroid. In all of these the uptake of ^{131}I was normal. It was also within normal limits in the one hypothyroid subject, but in this case, as previously pointed out, the discovery of abnormal flocculation tests suggested that the diagnosis was auto-immunising thyroiditis. This patient, however, had an elevated cholesterol and a prolonged reaction time. Elevated cholesterol levels were found in two euthyroid subjects, but a prolonged reaction time was present in only one normal individual.

When the 17 hypothyroid subjects with indices between +16 and +20 are considered (Table 34) it can be seen that normal ^{131}I uptakes were encountered in only 3 patients, two of whom had Hashimoto's thyroiditis. Normal cholesterol values were also found in 3 subjects, but the reaction time was normal in only two patients in this group.

In view of the previous studies, it is not altogether unexpected that when these 33 patients are considered together it can be concluded that there is little to indicate the superiority of any single test, although again the radioiodine studies appear to be slightly more reliable. The measurement of reaction time, however, is suggested as the procedure of choice to confirm the diagnosis when such scores are found, in view of the rapidity with which it may be carried out. Whereas radioiodine studies may necessitate a certain delay according to laboratory arrangements, the reaction time may be estimated within minutes of the completion of the clinical examination. By using the test in combination with the diagnostic index in 29 of these patients, a firm diagnosis was established in 25.

The need for any further investigation was thus excluded in all but the 4 subjects in whom the two parameters disagreed. When the other tests were carried out, they provided support for the diagnosis favoured by the index in three patients. In the remaining subject, however, it became evident that the index had been wrong.

Further evidence in favour of the selection of these tests as those of most value in the routine investigation of hypothyroidism is provided by the results of their use in those cases in whom diagnostic indices fell within the equivocal range (Table 35). It will be recalled that even when values were found in this range, scores greater than +10 favoured hypothyroidism while those less than +10 favoured normal thyroid function. It can be seen that only 3 of 11 subjects with scores below +10 were finally shown to be hypothyroid. In 2 all tests were abnormal, the other had a normal uptake, but this once more was associated with Hashimoto's thyroiditis which was suspected clinically. The three tests were carried out in 6 other subjects with indices in this range, all of whom were finally shown to be euthyroid. In at least two of the tests the results favoured normal function.

The results in all but one of the 7 patients who were finally shown to be hypothyroid, but who had indices between +10 and +15 agreed with the presumptive diagnosis of hypothyroidism indicated by the index. In the odd case, the reaction time was normal, the serum cholesterol was borderline (300mg%) but the uptake was low.

In view of the equivocal diagnostic index and this low uptake a therapeutic trial was clearly warranted. This resulted in a dramatic improvement which confirmed the diagnosis of hypothyroidism.

It is clear therefore that the investigations that have been advocated for routine use in the investigation of suspected hypothyroidism will provide a high degree of accuracy when used in combination. It has been shown that this is true in those patients in whom these tests are particularly indicated, namely those subjects in whom, as the result of finding a diagnostic index within the equivocal zone, considerable doubt remains as to the thyroid status. On conclusion of the investigations, the diagnosis in the majority of these cases will be evident. However, it is suggested that in such patients, even if only one investigation is outwith normal values, a therapeutic trial with thyroxine must be carried out.

Conclusions

In the majority of cases, the diagnosis of primary hypothyroidism may be established by the use of the clinical diagnostic index. In some, a single confirmatory investigation is desirable. The measurement of reaction time will provide such confirmation most rapidly. Further investigations are only indicated if the result is not in agreement with the index.

It is suggested that the only investigations necessary in those patients in whom the diagnostic index falls within the equivocal range are radioiodine studies with measurement of the gland uptake or of the excretion of activity in the period 24-48 hours after the dose, the measurement of reaction time and the estimation of serum cholesterol.

CHAPTER 19

SECTION II - THE LABORATORY CONFIRMATION

Summary

A study has been carried out to determine the accuracy of some of the investigations that demonstrate the state of thyroid function when hypothyroidism is suspected. It is clear that no one test is infallible. The clinical diagnosis may most readily be confirmed by the measurement of reaction time, since in hypothyroid states this characteristically shows a prolongation which is corrected by specific therapy. In the small minority of cases in which the diagnostic index does not provide a clear-cut answer, the radioactive iodine studies, in particular the measurement of gland uptake, provide the most accurate assessment. Complete reliance, however, cannot be placed on these tests since they may be misleading in some circumstances. The estimation of serum cholesterol is, therefore, a useful supplementary test and electrocardiography may also be helpful. The diagnostic precision that may be achieved by the use of these procedures in combination makes it unnecessary to employ further investigations. If on completion of these investigations there is still any doubt, a therapeutic trial with l-thyroxine sodium is indicated, since only in this way may a final diagnosis be established.

SECTION III

THE THERAPEUTIC TRIAL

CHAPTER 20

THE THERAPEUTIC TRIAL

Introduction

The ultimate object of all the clinical observations and of the investigations which have been discussed hitherto is to determine whether in any individual patient the administration of thyroid hormone will alleviate the symptoms present and cause the physical signs to disappear. The final diagnosis in any case, therefore, depends on the response to such therapy. Whatever the conclusions reached on the basis of investigations, hypothyroidism can only be considered to have been present in any individual if a return to normal health is procured by treatment. This effect of treatment is of special diagnostic value in the early case, especially since, as previously seen, the tests of thyroid function may in these subjects produce equivocal or even conflicting results. In these patients, however, the assessment of the response to therapy may not be easy as the clinical features are so mild that it may be difficult to be certain of any change in them. In this final chapter, therefore, the methods by which a therapeutic trial may be evaluated have been briefly considered.

There should be little dispute as to the preparation that should be prescribed for the routine treatment of primary hypothyroidism. The dramatic effect of the subcutaneous injection of sheep's thyroid was demonstrated by Murray in 1891 and the following year MacKenzie and Fox independently showed that the disorder could be satisfactorily treated by the oral administration of dried thyroid hormone. This form of therapy has retained great popularity throughout the years but, especially in recent years, many clinicians have experienced difficulties in maintaining satisfactory control of patients. In the course of this study the unreliability of dried thyroid tablets has also been noted. Since there is this danger of variation in the potency of dried thyroid Macgregor (1961) has recently concluded that there is ample pharmacological, therapeutic and economic justification for recommending that thyroxine be used for all thyroid replacement therapy, to the exclusion of preparations of dried thyroid, including thyroid B.P.

The only other hormone occurring in the human thyroid with significant metabolic activity is 3-5-3'-1-triiodothyronine. The high biological potency observed by Gross and Pitt-Rivers (1952) in rats and by Gross et al (1952) has been amply confirmed. The speed with which the calorigenic effects of this hormone are produced in man do, however, make it unsuitable for the routine treatment of the hypothyroid subject in view of the dangers inherent in too rapid an acceleration of metabolism in such individuals. It does, of course, remain invaluable in the treatment of myxoedema coma and in carefully observed experimental studies such as those described in Chapter 17. Recently a preparation containing both thyroxine and a small amount of triiodothyronine has become available (Tayler, 1961), but there has not as yet been a clear demonstration that it possesses any significant advantage over thyroxine alone. In recent years many analogues of thyroxine and triiodothyronine have been synthesised, but have gained no accepted place in the practical therapy of hypothyroidism. Similarly, there is no indication for the use of any of the twenty-one proprietary preparations containing thyroid hormone in varying amounts that are listed in the Extra Pharmacapoeia (1958).

The Therapeutic Trial

The dangers of inducing too rapid an acceleration of metabolism by the administration of large amounts of thyroid hormone to hypothyroid individuals has long been recognised. In general, therefore, it is recommended that treatment should be commenced with small doses which should be gradually and cautiously increased until the patient is euthyroid. The evidence of clinical improvement will only appear correspondingly slowly, and may cause difficulties in assessing such minor changes, especially those of a subjective nature. It may, therefore, not be easy to ascertain whether or not the patient has unequivocally benefitted from treatment unless this is continued for a considerable period. This constitutes a considerable problem in the evaluation of a therapeutic trial particularly when carried out in the patient in whom there is only a mild degree of hypothyroidism. An attempt has therefore been made to assess the pattern of changes in the clinical picture of hypothyroidism occurring in the course of routine treatment with l-thyroxine sodium. The value of the changes in the abnormal laboratory findings in confirming such a response has also been examined.

Methods

The effect of treatment on the clinical features was closely observed in 29 subjects in whom the diagnosis of hypothyroidism had been made by the procedures previously discussed. The patients were seen at monthly intervals. At each visit a conventional clinical assessment of their thyroid state was made. At the same time a record sheet similar to that used in the initial symptom and sign analysis was completed for the presence or absence of the clinical features.

Each feature was noted to be present and unchanged, diminished or absent. In patients over 50 years the initial dosage of l-thyroxine sodium was 0.025mg, but in younger subjects it was 0.05mg. The dosage was increased monthly. In the older group the initial increase was 0.025mg, but thereafter, like the younger patients, the monthly increment was 0.05mg. In two males the final increase was 0.1mg. The dosage continued to be increased in this way until the patient was considered to be euthyroid on conventional clinical grounds. If on two subsequent visits control was considered to be remaining satisfactory, the dose was maintained at the level being given at that time. In this way the amount of thyroxine required in each subject was determined on general assessment only. Only when they were considered euthyroid were the record sheets reviewed and diagnostic index scores calculated from the clinical features noted on each visit. The value attached to any feature was only deducted from the total score when the symptom or sign had completely disappeared. One point was deducted for each 4 lbs. of weight lost. The evaluation of the clinical state was also uninfluenced by the results of any investigations since these were also recorded separately. The procedures used in the investigations -- B.M.R., serum cholesterol, carotene, reaction time and E.C.G. -- which were carried out in many of the patients at their monthly visit were the same as those previously described. For the estimation of B.M.R. the subjects were admitted overnight and the lowest of two tracings (obtained by the procedure termed Method A in Chapter 13) accepted as representing the current rate.

Results

Clinical Observations - It was found impossible to obtain a quantitative comparison of the rate of disappearance of the various clinical features. This difficulty in part arose because the symptoms and signs initially present differed from patient to patient. It was, however, clear with each feature that there was a considerable variation in the time at which it diminished or was no longer observed in relation to the period of treatment. From the study it has, however, been possible to note the general pattern of change in the clinical picture. Particular attention was paid to those symptoms and signs incorporated in the diagnostic index. The observations have been summarised as follows:-

Symptoms

Tiredness: Often increases during initial months of treatment, possibly as the result of an increase in activity produced by a decrease in lethargy. Some fatiguability persists for a considerable time, even after patient is otherwise clinically euthyroid.

Lethargy: Usually dramatic improvement even on small doses. Manifested by increased desire to undertake work and by return of former interests. Alterations in other evidence of cerebral changes, e.g. impairment of memory, are more gradual.

Paraesthesia: Persists until significant weight loss occurs.

Muscle cramps: Variable; occasionally increase or even appear de novo in early period of treatment.

Deafness: Variable, although rapid improvement unusual.

Cold intolerance: Slight diminution usually follows initial therapy, but completely normal tolerance rarely returns until euthyroid.

Sweating: Similar pattern to cold intolerance.

Hair changes: Initially often increased loss for a short time, but thereafter no further loss; quality improves very gradually.

Skin changes: Frequently increased scaling at first, but followed by rapid improvement.

Appetite: Returns to normal quickly.

Weight: Variable; usually gradual loss until approaching euthyroid state, when it may fall fairly rapidly.

Constipation: Often very persistent.

Voice: Strength improves rapidly, but slight huskiness remains for several months.

<u>Signs</u>

<u>Speech</u>: Slowness soon becomes less obvious, with loss of typical hypothyroid tone, but some huskiness often persists.

<u>Cerebration</u>: A rapid increase in alertness observed in nearly all patients, but the rate at which normal cerebration returns depends greatly on the degree of impairment initially present.

<u>Movements</u>: Often a considerable delay before any marked change is observed.

<u>Skin</u> - <u>Coarseness</u>: initially scaling frequently increased, but thereafter a rapid improvement noted.

<u>Dryness</u>: little evidence of sweating, especially of the palms, observed until the patient is euthyroid.

<u>Coldness</u>: some increase in warmth noted early, but the exposed areas such as hands, usually remain cool until nearly euthyroid.

<u>Periorbital puffiness</u>: Early and marked diminution common.

<u>Supra-clavicular puffiness</u>: more persistent, usually reflects weight changes.

<u>Hair</u>: Change in quality is not often obvious until euthyroid for a variable period.

<u>Pulse rate</u>: In those patients in whom a bradycardia has initially been noted the rate usually remains slow until a dose of 0.1mg daily is given.

In support of these observations it may be pointed out that the pattern noted in those features represented by both a symptom and sign was very similar. For example, the characteristic complaint of lethargy was considered to diminish rapidly while a marked increase in mental alertness and brightness was recorded early in the course of treatment. The skin changes also show parallel alterations. Thus, the disappearance of scaling or flaking, after an initial increase, was noted at an early date both by the patient and observer, while the continued objective finding of dryness was accompanied by the persistence of the subjective complaint of diminished sweating.

These observations permitted the study of the changes in the diagnostic index scores that accompanied treatment (Table 36). If it is remembered that the score attached to any feature was only deducted when it was considered to have disappeared completely, it may be noted that in the first months of treatment there was often only a slight fall. This continued elevation of the score is greatly due to the persistence of clinical features to which high values were attached. It can therefore be seen that the diagnostic index in 16 of the 29 cases only became absolutely normal (less than 0) at the same time as the patient was considered to be euthyroid by conventional clinical assessment. In the remainder, normal values of the index were obtained when the patients did still appear by conventional clinical assessment to be slightly hypothyroid, but a single increase in dose was sufficient in each case to produce complete control.

Investigations

The administration of thyroxine resulted in a correction of the abnormalities demonstrated by all the procedures employed. The rate at which the different investigations showed this return to normal varied, but for each procedure was remarkably constant in all the patients. Thus, a rapid rise in the B.M.R. was noted in 14 of the 17 patients in whom it was repeated at intervals (Table 37). In 14 subjects in whom abnormal levels were initially recorded, normal values were obtained in 10 when they were receiving only 0.025mg or 0.05mg daily. The B.M.R. was also within normal limits in the other 4 patients before they were considered euthyroid clinically. Similarly, it was observed that only small doses of thyroxine were required to produce a fall in serum cholesterol (Table 38). The administration of 0.025mg or 0.05mg daily was sufficient to produce a fall to within normal limits in 11 of the 18 patients studied. It may be noted that the rapidity with which normal levels are attained depends to a certain extent on the initial elevation.

Thus the patient in whom the highest value was obtained when hypothyroid was also the only one in whom the level was not normal until the visit when clinically euthyroid.

The changes in the reaction time presented a rather different pattern. Small doses (0.025mg or 0.05mg) produced a return to within the normal ranges in only 5 of the 21 patients investigated (Table 39). In most of the others there was some quickening initially, but normal values were not recorded until the patient was almost euthyroid. When the E.C.G.s were considered, it was also clear that although the abnormalities lessened on the commencement of therapy, the tracings could not be considered to be within normal limits in most instances until complete control had been established. The results of the serum carotene estimations (Table 40) show that although a fall does follow therapy, this was capricious and so variable that no reliance could be placed on the procedure.

Discussion

Although this study was designed to enable observations to be made of the changes in the clinical picture and investigations following the administration of thyroxine, it must be admitted that it is not entirely typical of the routine management of the hypothyroid patient, since the therapy was probably over-cautious. Normally the dosage may be safely increased at shorter intervals than the monthly periods employed. These were chosen, however, to ensure that the complete effect of each dosage level had become apparent.

It is clear that the alterationsin the clinical picture vary from patient to patient. This study has, however, demonstrated the general trend of improvement which may be expected. As attempt should therefore be made to observe this pattern in any individual. It may be noted that the disappearance of most symptoms precedes the disappearance of signs. This is not, of course, surprising since the physical signs demonstrate the organic changes resulting from thyroid deficiency which has been usually present over a considerable period.

The difficulty in assessing the significance of the improvement or relief of subjective features is well-known and such changes must be accepted cautiously in the absence of placebo therapy. Since this is impracticable in these circumstances, it is particularly important to attempt to obtain objective evidence favouring the response. The improvement in the mental changes are usually quickly apparent, but the change in the facial appearance may be even more dramatic. The evaluation of the disappearance of the typical "puffiness", however, is rendered rather difficult by the intervals elapsing between each visit. The necessity of attempting to remember the previous appearance is obviated by obtaining a photograph of each patient when hypothyroid. By comparing this with the appearance on each visit the observer error is obviously reduced.

Although therapy produced a rapid improvement in most of the clinical features, many persisted in minor degrees until the patient became completely euthyroid. This, of course, is logical since any individual was only considered euthyroid when the symptoms had been relieved and the signs had become absent. It is therefore not surprising that the diagnostic indices showed little change initially. Their return to normal only when the patient was virtually euthyroid is also to be expected since the score attached to each feature was only deducted when it had disappeared. The method is therefore of little value in indicating the initial response to treatment. It must, however, be remembered that it was designed to provide a wide separation between normality and abnormality. A "therapeutic" index could probably be constructed by allocating different scores to each feature reflecting its severity. As the results show, however, the index in its present form does provide a quantitative method of assessing when the patient is euthyroid. By reducing observer variation, it does possess some advantage over the assessment by conventional clinical examination. It is obviously both simpler and safer than the method of arriving at a maintenance dose advocated by Spence (1959). He suggested that the dose should be increased weekly until signs of overdosage, such as tachycardia and irritability, appeared and that treatment should then be discontinued for two weeks, being resumed in doses of 1gr a day less than the overdose. Starr (1954) considered that the optimum method of achieving control was to increase the dosage until the $PB^{127}I$ was 7ug%. He also suggested that the maintenance dose was that which kept the $PB^{127}I$ at 6ug%. The difficulties in this estimation have already been discussed and clearly make this method impracticable in routine practice.

It may, therefore, be suggested that the diagnostic index does indeed provide a useful technique that can be routinely employed to indicate when an adequate dosage level has been attained. Thus, when the index falls below 0 it should be considered likely that no further increase in the dose of thyroxine is likely to be required unless further observation shows the persistence of some features. It may be noted that in the patients in this study, as indeed in the other subjects observed throughout the investigation, the dosage of thyroxine required by the great majority of females was 0.15 or 0.2mg daily. Males, however, usually required 0.2 to 0.3mg daily. This difference may to a great extent be explained by the differences in lean body mass, the main oxygen-consuming component of the body, which Muldowney (1957) has shown to be generally greater in the male than in the female. Certainly when these respective dosages have been reached, any further increase should be considered unlikely to be required and only administered after a longer period of observation.

Although the successful restoration of health to the hypothyroid patient can be accomplished by clinical observation alone, it must be admitted that the laboratory investigations can play a useful part in the assessment of a therapeutic trial. The results show that the rate at which the various abnormalities are corrected varies. An example of the typical pattern of response shown by the different parameters is illustrated in Figure 25. It is clear therefore that each test may be of most use to the clinician at different stages during the course of treatment. Thus, the measurement of reaction time and the E.C.G. are of most value in confirming that the patient has become euthyroid. On the other hand, the B.M.R. and cholesterol provide a more sensitive guide to the effect of thyroxine in the early period after commencement of therapy.

As indeed would be expected, even very small doses induce an increase in metabolism reflected by a rise in the B.M.R. The technical difficulties that must be surmounted before this test may be relied upon have already been emphasised. It is therefore always difficult to evaluate the significance of changes in the B.M.R. The procedure has, moreover, little place in the therapeutic trial since it necessitates admission to hospital. It is of little assistance in determining when a patient is euthyroid, since the range of normality is so wide that it is difficult to know the "normal" value for any individual without repeated readings. Although this objection also applies to the estimation of serum cholesterol, this procedure is of considerable value in the therapeutic trial since the results do show that in most instances small doses of thyroxine produce a rapid fall in the cholesterol level. A decrease in cholesterol values found to be elevated in disorders other than hypothyroidism may also be induced by thyroid therapy, as shown for example by Barnes (1959), but is unlikely to be as dramatic or as profound as in hypothyroidism. These changes are especially of value since it has already been pointed out that the diagnostic index does not provide a measure of the improvement in the early stages of treatment. By using these two procedures it is possible to assess both the initial response and the adequacy of treatment in any patient. Their complimentary use is illustrated in Figure 26 which shows the respective mean values of the 18 patients in whom both were estimated on each visit. It can be clearly seen that the cholesterol demonstrates the efficacy of treatment while the index indicates when control is satisfactory.

The diagnostic index, serum cholesterol and reaction time may, therefore, be considered to be of value in overcoming the problems that may be encountered in the treatment of hypothyroidism since they provide quantitative methods of confirming the changes noted by clinical observations. Their use did permit the accurate demonstration of the unreliability of dried thyroid as a therapeutic measure. In the course of this study 7 patients were encountered in whom frank hypothyroidism was apparent although they were all reputed to be receiving this preparation. There was no reason to disbelieve their claim that the medication was in fact being taken since they had previously been well controlled for at least two years on the same dosage. When they were transferred to equivalent doses of l-thyroxine sodium there was a dramatic improvement. This phenomenon is illustrated in Figure 27, where it can be seen that the diagnostic index, cholesterol and reaction time were all abnormal at the time that the patient was actually receiving dried thyroid (gr.2 daily). These parameters, however, all returned to normal levels within six weeks of the institution of thyroxine (0.2mg daily). Such observations as these and those described earlier in this chapter do, it may be suggested, provide further evidence regarding the validity of the clinical diagnostic index and, therefore, additional justification for its adoption, as has been advocated throughout this thesis, for use in the routine assessment of any patient in whom hypothyroidism may be suspected.

CHAPTER 21

THE THERAPEUTIC TRIAL

Summary

The final proof that any individual is hypothyroid is provided by the response to therapy.

The administration of gradually increasing doses of l-thyroxine sodium provides the safest method of restoring the hypothyroid patient to health. The evaluation of the therapeutic response may be difficult since the improvement resulting from the cautious therapy will be gradual. It will, however, be observed by careful clinical assessment especially if the clinician is aware of the pattern of changes in the symptoms and signs that may be expected. Confirmation that thyroxine has had a therapeutic action may best be provided by the fall in serum cholesterol that typically follows the institution of treatment. The diagnostic index shows little initial alteration, but is of value in indicating when the dosage is adequate to maintain the patient in a euthyroid state. The return to normal of the reaction time and E.C.G. provides useful methods of confirming that satisfactory control has been established.

EPILOGUE

The observations recorded in this thesis provide little support for the tenet proposed by Starr (1954) that "the practice of medicine guided by symptoms and signs is not enough to give the patient health". Indeed, these studies have emphasised the importance of careful history-taking and clinical examination by showing the high degree of diagnostic precision that may be attained by clinical assessment. It must be admitted that in some instances valuable assistance can be obtained from the laboratory investigations, if those employed are carefully selected. These tests, however, are not infallible and can be misleading if they are not interpreted in light of the clinical picture. It has therefore become apparent that the clinical findings and the results of the tests of thyroid function must always be considered in conjunction. Only in this way is it possible to demonstrate accurately mild degrees of thyroid insufficiency and permit the diagnosis of hypothyroidism to be established at an early stage in its development. This complementary use of the traditional art of medicine and the scientific discoveries of the twentieth century provide a vivid illustration of the truth of the dictum laid down by Roger Bacon in the thirteenth century -

"All sciences are connected; they lend each other material aid as part of one great whole, each doing its work not for itself alone, but for the other parts, as the eye guides the whole body and the foot sustains it and leads it from place to place. As with an eye torn out or a foot cut off, so it is with the different departments of knowledge; none can attain its proper result separately, since all are parts of one and the same complete wisdom".

THE DIAGNOSIS OF PRIMARY HYPOTHYROIDISM

A Critical Evaluation

of

The Clinical Features

and

Laboratory Aids to Diagnosis

by

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Table 1

Percentage Incidence of Symptoms

	Control Euthyroid	Control Hypo.	Equivocal Euthyroid	Equivocal Hypo.	All Euthyroid	All Hypo.
No. of cases	55	55	50	45	105	100
Dyspnoea	40	75	66	69	52	72
Tiredness	42	98	88	98	64	98
Lethargy	9	87	26	82	17	85
Muscle weakness	13	65	30	55	21	61
Muscle pain	11	36	24	35	17	36
Joint pain	24	23	24	35	24	29
Paraesthesia	13	63	18	46	15	56
Deafness	9	45	22	35	15	40
Impaired memory	16	75	46	54	31	65
Cold intolerance	16	100	64	89	39	95
Heat intolerance	15	0	10	5	12	2
Temperature indifference	69	0	26	7	49	3
Sweating decreased	11	78	24	55	17	68
" unchanged	47	20	58	42	52	30
" increased	42	2	18	2	31	2

Percentage Incidence of Symptoms (continued)

	Control Euthyroid	Control Hypo.	Equivocal Euthyroid	Equivocal Hypo.	All Euthyroid	All Hypo.
No. of cases	55	55	50	45	105	100
Hair untidy	13	57	46	66	28	62
" loss	9	45	34	35	21	41
Skin dry	7	85	22	66	14	77
Nails brittle	16	45	24	35	20	41
Appetite increased	4	2	12	6	8	4
" decreased	9	45	22	33	15	40
" unchanged	87	53	66	60	77	56
Weight increased	38	82	34	68	36	76
" decreased	16	5	30	14	23	9
" unchanged	46	13	36	18	39	15
Constipation	5	51	16	57	10	54
Hoarseness	9	80	28	66	18	74
Angina	2	20	16	12	9	16
Palpitations	11	22	30	25	20	23
Nervousness	36	51	48	51	42	51
Depression	33	56	50	65	41	60
Puffiness	2	87	32	91	16	89

Table 2

Percentage Incidence of Signs

	Control Euthyroid	Control Hypo.	Equivocal Euthyroid	Equivocal Hypo.	All Euthyroid	All Hypo.
No. of cases	55	55	50	45	105	100
Speech slow	2	65	12	46	7	56
" hoarse	15	95	42	77	28	87
Cerebration slow	2	54	16	42	9	48
Movements slow	7	84	22	60	14	73
Skin coarse	5	84	14	53	10	70
" dry	11	87	42	68	26	79
" cold	29	78	38	83	33	80
" pale	5	51	24	49	14	50
" yellow	0	51	12	44	6	48
Nails brittle	16	22	22	27	19	24
" striated	22	24	42	40	31	31
Face puffy	5	96	50	93	27	95
" malar flush	5	63	18	44	11	55

Percentage Incidence of Signs (continued)

	Control Euthyroid	Control Hypo.	Equivocal Euthyroid	Equivocal Hypo.	All Euthyroid	All Hypo.
No. of cases	55	55	50	45	105	100
Eyes puffy	11	90	46	80	28	86
Extremities) Supra-clav.) puffy	4	51	24	58	13	57
Exophthalmos	2	18	6	4	4	11
Tongue large	9	58	26	62	17	60
Pulse rate - <60	0	9	2	7	1	8
60-69	20	43	30	33	25	39
70-79	38	29	28	36	33	32
>80	42	18	40	24	41	21
Oedema	2	9	2	0	2	5
Hair - very sparse	0	5	12	4	6	5
" sparse	15	31	18	16	16	24
" dry	25	75	62	76	43	75
Eyebrows sparse	47	87	70	80	58	84

Table 3

Comparison of Incidence of various clinical features reported in different series.

	Lerman 77 cases %	Present Study 100 cases %	Sheedy & Lienhard 20 cases %
Weakness (Tiredness)	99	98	95
Lethargy	91	85	100
Sensation of cold	89	95	60
Decreased sweating	89	68	60
Memory impairment	66	65	55
Constipation	61	54	
Gain in weight	59	76	
Loss of hair	57	41	
Dyspnoea	55	72	
Hoarseness	52	74	45
Anorexia	45	40	
Nervousness	35	51	35
Menorrhagia	32	33 (18 cases)	50
Palpitation	31	23	
Deafness	30	40	55
Loss of weight	13	9	
Dry skin	97	79	90
Coarse skin	97	70	
Slow speech	91	56 (hoarse 87)	
Oedema of eyelids	90	86	75
Cold skin	83	80	
Thick tongue	82	60	
Coarseness of hair (dryness)	76	75	60
Oedema of face	79	95	75
Peripheral "oedema"	55	57	
Pallor of lips	57	50	

Table 4

Percentage Incidence of Symptoms in Iatrogenic Hypothyroidism

	Iatrogenic Hypothyroidism	All Hypothyroid	All Euthyroid
No. of Cases	53	100	105
Dyspnoea	57	72	52
Tiredness	93	98	64
Lethargy	83	85	17
Muscle Weakness	81	61	21
Muscle Pain	72	36	17
Joint Pain	23	29	24
Paraesthesia	47	56	15
Deafness	17	40	15
Impaired Memory	66	65	31
Cold Intolerance	79	95	39
Heat Intolerance	4	2	12
Temperature Indifference	17	3	49
Sweating Decreased	58	68	17
" Unchanged	40	30	52
" Increased	2	2	31
Hair untidy	72	62	28
Hair loss	32	41	21
Skin dry	79	77	14
Nails Brittle	49	41	20

Table 4 (cont.)

Appetite Increased	8	4	8
" Decreased	53	40	15
" Unchanged	39	56	77
Weight Increased	93	76	36
" Decreased	2	9	23
" Unchanged	5	15	39
Constipation	45	54	10
Hoarseness	85	74	18
Angina	9	16	9
Palpitations	21	23	20
Nervousness	42	51	42
Depression	64	60	41
Puffiness	86	89	16

Table 5

Percentage Incidence of Signs in Iatrogenic Hypothyroidism

	Iatrogenic Hypothyroidism	All Hypothyroid	All Euthyroid
No. of Cases	53	100	105
Speech Slow	68	56	7
Speech Hoarse	86	87	28
Cerebration Slow	53	48	9
Movements Slow	56	73	14
Skin Coarse	42	70	10
" Dry	68	79	26
" Cold	79	80	33
" Pale	17	50	14
" Yellow	9	48	6
Nails Brittle	30	24	19
Nails Striated	28	31	31
Face Puffy	81	95	27
Face - Malar Flush	8	55	11
Eyes Puffy	85	86	28
Extremities) Supra-clav.) puffy	40	57	13
Exophthalmos	38	11	4
Tongue Large	32	60	17

Table 5 (cont.)

Pulse Rate <60	4	8	1
60-69	36	39	25
70-79	36	32	33
>80	24	21	41
Oedema	0	5	2
Hair V. Sparse	0	5	6
" Sparse	17	24	16
" Dry	79	75	43
Eyebrows Sparse	36	84	58

Table 6

Percentage Incidence of Symptoms in 'Pituitary' Hypothyroidism

	Pituitary Hypothyroidism	All Hypothyroid
No. of Cases	15	100
Dyspnoea	73	72
Tiredness	100	98
Lethargy	80	85
Muscle Weakness	73	61
Muscle Pain	13	36
Joint Pain	26	29
Paraesthesia	13	56
Deafness	26	40
Impaired Memory	67	65
Cold Intolerance	93	95
Heat Intolerance	0	2
Temperature Indifference	7	3
Sweating Decreased	80	68
" Unchanged	20	30
" Increased	0	2
Hair Untidy	60	62
Hair Loss	13	41
Skin Dry	47	77
Nails Brittle	20	41
Appetite Increased	0	4
" Decreased	53	40
" Unchanged	47	56
Weight Increased	47	76
" Decreased	26	9
" Unchanged	26	15
Constipation	33	54
Hoarseness	13	74
Angina	7	16
Palpitations	13	23
Nervousness	47	51
Depression	73	60
Puffiness	20	89

Table 7

Percentage Incidence of Signs in 'Pituitary' Hypothyroidism

	Pituitary Hypothyroidism	All Hypothyroid
No. of Cases	15	100
Speech Slow	67	56
Speech Hoarse	33	87
Cerebration Slow	67	48
Movements Slow	60	73
Skin Coarse	7	70
" Dry	60	79
" Cold	60	80
" Pale	87	50
" Yellow	7	48
Nails Brittle	13	24
Nails Striated	40	31
Face Puffy	53	95
Face Malar Flush	0	55
Eyes Puffy	40	86
Extremities) Supra-clav.) Puffy	20	57
Exophthalmos	0	11
Tongue Large	20	60
Pulse Rate <60	20	8
60-69	26	39
70-79	47	32
>80	7	21
Oedema	0	5
Hair V. sparse	0	5
" Sparse	7	24
" Dry	40	75
Eyebrows Sparse	80	84

Table 8

Median Nerve Conduction Velocity in Hypothyroid Patients

Case No.	Length (cm.)		Delay+ (msec.)		Difference (Elbow to wrist)(msec.)	Electro-myography	Paraesthesia
	Elbow	Wrist	Elbow to muscle	Wrist to muscle			
1	30	6	20	14	6	Denervation	+
2	26.5	4.5	21	16	5	"	+
3	33	6	18	12	6	"	+
4	28	5	12	6	6	"	+
5	22	4	12	66	6	"	+
6	27	5	11	6	5	Normal	-
7	22	5	11	6	5	"	+
8	23	5	9	5	4	"	+
9	22	4	8	4	4	"	+
10	24	5	8	4	4	"(?)	+
11	27	6	9	4	5	"	-

Length measured from centre of stimulating cathode on median nerve to proximal recording electrode on abductor pollicis brevis muscle.

+ Time interval from stimulus to nerve to onset of action potential in muscle. Normal range - elbow 8-12 msec., wrist 3-5 msec.

Table 9

Relation of Body-Weight to Acroparaesthesia

Case No.	Weight lbs.	Change in weight (lbs)	B.M.R. %	Acro-paraesthesia	Comment
12	171 155 165 147	 -16 +10 -18	-31 +12 - 9 +21	++ - + -	Hypothyroidism relapsed when treatment changed, with transient return of acroparaesthesia
2	170 151	 -19	-36 - 2	++ -	Complete remission and restoration of conduction velocity (Table 10)
13	179 165	 -14	-26 + 1	++ -	Rapid response to tri-iodothyronine (3 weeks), no relapse.
6	140 136	 - 4	-28 - 3	- -	Severe hypothyroidism, but patient not overweight.
4	186 182	 - 4	- 5 +21	++ +	Good metabolic response but remains overweight.
8	150 147	 - 3	-30 - 8	+ +	Good metabolic response but remains overweight.
14	173 160	 -13	-17 + 3	+ +	Good metabolic response but remains overweight.
15	141 146	 + 5	- -	+ +	Hypothyroidism improved but patient gained weight.

Table 10

Restoration of Nerve-Conduction Velocity

	Weight (lbs)	Length (cm.) Elbow	Wrist	Delay (msec.) Elbow to muscle	Wrist to muscle	Difference (elbow to wrist)(msec)
When hypothyroid	170	26.5	4.5	21	16	5
Following therapy	151	25.5	5	12	7.5	4.5

Table 11

Values allocated to the selected symptoms and signs

SYMPTOMS (recent onset or increased severity)	Present	Absent
Physical Tiredness	+1	
Mental Lethargy	+3	-3
Paraesthesiae	+2	-1
Deafness	+1	0
Cold Intolerance	+1	0
Heat Intolerance	-3	0
Temp. Indifference	-1	0
Decreased Sweating	+2	0
Increased Sweating	-3	0
Hair — untidy and/or loss	+2	0
Skin dry	+3	-1
Appetite Increased	-2	0
Appetite Decreased	+1	0
Weight Increased	+2	0
Weight Decreased	-2	0
Constipation	+3	-1
Hoarseness	+2	-1
Totals		
Total Symptom Score		

SIGNS	Present	Absent
Speech Hoarse	+1	0
Cerebration Slow	+2	-1
Movements Slow	+2	-2
Skin Coarse	+1	0
" Dry	+1	-1
" Cold	+2	-2
" Yellow	+1	0
Periorbital puffiness	+2	-2
Puffiness of supra-clav. fossa and/or wrists	+2	-1
Hair Dry	+1	0
Pulse Rate <61	+3	0
61-69	+1	0
70-80	0	0
>80	-2	0
Totals		
Total Sign Score		

TOTAL SCORE

Table 12

Diagnostic Index — Distribution of Results

	Definite Group		Doubtful Group	
Ranges	Final Diagnosis Euthyroid	Final Diagnosis Hypothyroid	Final Diagnosis Euthyroid	Final Diagnosis Hypothyroid
<10	55 (100%)	0 (0%)	49 (98%)	4 (9%)
>9	0 (0%)	55 (100%)	1 (2%)	41 (91%)
<5	55 (100%)	0 (0%)	42 (84%)	1 (2%)
>15	0 (0%)	54 (98%)	0 (0%)	34 (76%)
Total	55	55	50	45

Table 13

Diagnostic Index — Overall Diagnostic Accuracy

Ranges		$<+10>$	$<+5 \; - >+15$		
Diagnosis	No. of Cases	Correct	Correct	Equivocal	Wrong
All Euthyroid	115	114 (99%)	107 (93%)	8 (7%)	0 (0%)
All Hypothyroid	127	122 (96%)	112 (88%)	14 (11%)	1 (1%)
All Cases	242	236 (98%)	219 (90%)	22 (10%)	1 (1%)

Table 14

Distribution of Indices -- probabilities based on observed percentages

a. Euthyroid subjects presenting diagnostic difficulty.

0 or over	-	0.321
+5 " "	-	0.121
+10 " "	-	0.0304
+15 " "	-	0.0049

b. Hypothyroid patients presenting diagnostic difficulty.

+15 or less	-	0.2177
+10 " "	-	0.0749
+5 " "	-	0.0179
0 " "	-	0.0030

Table 15

^{131}I Gland Uptake — Distribution of results

Gland Uptake	Definite Hypothyroid	Doubtful Hypothyroid	All Hypothyroid	Doubtful Euthyroid	Hashimoto Hypothyroid
<20%	53 (100%)	44 (94%)	97 (97%)	1 (2%)	10 (38%)
>19%	0 (0%)	3 (61%)	3 (3%)	49 (98%)	16 (62%)
No. of Cases	53	47	100	50	26

Table 16

0-48 hr. Urine ^{131}I Excretion - Distribution of results

Urine Excretion 0-48 hr.	Definite Hypothyroid	Doubtful Hypothyroid	All Hypothyroid	Doubtful Euthyroid
$<69\%$	10 (21%)	15 (43%)	25 (30%)	29 (94%)
$>69\%$	37 (79%)	20 (57%)	47 (70%)	2 (6%)
No. of Cases	47	35	82	31

Table 17

6/8 hr. Urine ^{131}I Excretion - Distribution of results

Urine Excretion	Definite Hypothyroid	Doubtful Hypothyroid	All Hypothyroid	Doubtful Euthyroid
a. 8-24hrs.				
>20%	20 (87%)	11 (92%)	31 (89%)	6 (33%)
<20%	3 (13%)	1 (8%)	4 (11%)	12 (67%)
No. of cases	23	12	35	18
b. 6-24hrs.				
>25%	22 (92%)	21 (88%)	43 (90%)	6 (50%)
<25%	2 (8%)	3 (12%)	5 (10%)	6 (50%)
No. of cases	24	24	48	12
c. 6/8-24hrs.				
>'N'	42 (89%)	32 (89%)	74 (89%)	12 (40%)
<'N'	5 (11%)	4 (11%)	9 (11%)	18 (60%)
No. of cases	47	36	83	30

'N' represents the upper limit of the percentage of ^{131}I excreted by normal individuals, i.e. 20% in 8-24 hour period and 25% in 6-24 hour period.

Table 18

24-48 hr. Urine ^{131}I Excretion - Distribution of results

Urine Excretion 24-48hrs.	Definite Hypothyroid	Doubtful Hypothyroid	All Hypothyroid	Doubtful Euthyroid
>10%	40 (83%)	33 (92%)	73 (87%)	4 (12%)
<10%	8 (17%)	3 (8%)	11 (13%)	30 (88%)
No. of cases	48	36	84	34

Table 19

"T" Index — Distribution of results

T Index	Definite Hypothyroid	Doubtful Hypothyroid	All Hypothyroid	Doubtful Euthyroid
a. T_8				
<2.7	20 (95%)	10 (91%)	30 (94%)	4 (22%)
>2.7	1 (5%)	1 (9%)	2 (6%)	14 (77%)
No. of cases	21	11	32	18
b. T_6				
<1.5	20 (83%)	20 (83%)	40 (83%)	4 (36%)
>1.5	4 (17%)	4 (17%)	8 (17%)	7 (64%)
No. of cases	24	24	48	11
c. T_8&T_6				
<'N'	40 (89%)	30 (86%)	70 (88%)	8 (28%)
>'N'	5 (11%)	5 (14%)	10 (12%)	21 (72%)
No. of cases	45	35	80	29

T_8 and T_6 represent the indices calculated when the urinary collections on which the 'T' Index was based included 8-24 and 6-24 hour periods respectively. 'N' represents the lower limit of normality for both T_8 and T_6 and has been employed to permit study of the two indices together.

Table 20

Comparison of Diagnostic Index and Gland Uptake with Final Diagnosis in 96 Hypothyroid Patients

Index Correct, Uptake Correct 83 (87%)	Index Correct, Uptake Wrong 2 (2%)
Index Wrong, Uptake Correct 10 (10%)	Index Wrong, Uptake Wrong 1 (1%)

Table 21

Comparison of Diagnostic Index and 24-48 hr. Urine ^{131}I Excretion with Final Diagnosis in 80 Hypothyroid Patients

Index Correct / Urine Correct 64 (80%)	Index Correct / Urine Wrong 8 (10%)
Index Wrong / Urine Correct 6 (8%)	Index Wrong / Urine Wrong 2 (2%)

Table 22

Effect of Sedation and Technique on Accuracy of Basal Metabolic Rate (Robertson and Reid Standards)

	Definite Hypothyroid $<-15\%$	Doubtful Hypothyroid $<-15\%$	All Hypothyroid $<-15\%$	Doubtful Euthyroid $>-15\%$
Method A	19/23 (83%)	12/17 (71%)	31/40 (77%)	29/30 (97%)
Method B	19/30 (63%)	9/23 (39%)	28/53 (53%)	8/8 (100%)

Table 23

Effect of Different Standards and Ranges of Normality on Accuracy of Basal Metabolic Rate

Final Diagnosis	No. of Cases	Diagnosis correct by			
		Robertson and Reid	Aub and Du Bois		
			<-10%	<-15%	<-20%
Hypothyroid	40	31 (77%)	39 (97%)	36 (88%)	33 (83%)
Euthyroid	30	29 (97%)	21 (70%)	23 (77%)	28 (93%)
All Cases	70	60 (86%)	60 (86%)	59/70 (84%)	61/70 (87%)

Table 24

Comparison of Index and Basal Metabolic Rate with Final Diagnosis in 40 Hypothyroid Patients

Index Correct, B.M.R. Correct: 29 (72.5%)	Index Correct, B.M.R. Wrong: 9 (22.5%)
Index Wrong, B.M.R. Correct: 2 (5%)	Index Wrong, B.M.R. Wrong: 0 (0%)

Table 25

Serum Cholesterol - Distribution of results

Ranges mg%	Definite Group Final Diagnosis Euthyroid	Definite Group Final Diagnosis Hypothyroid	Doubtful Group Final Diagnosis Euthyroid	Doubtful Group Final Diagnosis Hypothyroid	All Hypothyroid
>300	24 (23%)	55 (81%)	6 (10%)	42 (82%)	97 (81%)
<300	79 (77%)	13 (19%)	53 (90%)	9 (18%)	22 (19%)
>350	3 (2%)	39 (57%)	5 (10%)	27 (53%)	66 (56%)
<250	56 (54%)	5 (7%)	42 (71%)	2 (4%)	7 (6%)
Total	103	68	59	51	119

Table 26

Comparison of Diagnostic Index and Serum Cholesterol with Final Diagnosis in 117 Hypothyroid Subjects

Index Correct, Cholesterol Correct: 81 (69%)	Index Correct, Cholesterol Wrong: 23 (20%)
Index Wrong, Cholesterol Correct: 12 (10%)	Index Wrong, Cholesterol Wrong: 1 (1%)

<u>Table 27</u>

<u>Serum Carotene -- Distribution of results</u>

Ranges µg%	Definite Group: Final Diagnosis Euthyroid	Definite Group: Final Diagnosis Hypothyroid	Doubtful Group: Final Diagnosis Euthyroid	Doubtful Group: Final Diagnosis Hypothyroid	All Hypothyroid
>110	6 (19%)	18 (62%)	7 (20%)	10 (50%)	28 (57%)
<110	26 (81%)	11 (38%)	28 (80%)	10 (50%)	21 (43%)
>130	4 (13%)	14 (48%)	2 (5%)	8 (40%)	22 (45%)
<90	22 (68%)	4 (14%)	23 (66%)	4 (20%)	8 (16%)
Total	32	29	35	20	49

Table 28

E.C.G. Abnormalities found in Hypothyroid Patients

Group	No.	Grade of Changes			
		++	+	±	-
"Definite"	35	23	5	6	1
"Doubtful"	25	14	5	3	3
All Cases	60	37 (62%)	10 (17%)	9 (15%)	4 (6%)

Table 29

Mean Reaction Times

	Healthy			Hypothyroid	
Age	No. of persons	Mean (sec.)	Normal Range	No. of persons	Mean
<40	34	0.2286	0.1974-0.2598	7	0.3200
40-50	21	0.2396	0.2084-0.2708	10	0.3053
50-60	26	0.2546	0.2234-0.2858	18	0.3141
60-	20	0.2598	0.2286-0.2910	15	0.4313
Total	101			50	

Table 30

Effect of Thyroxine on Mean Reaction Times of Hypothyroid Patients

Age	Mean Reaction Time (sec.)			
	No. of persons	Before therapy	After therapy	Normal Mean
<40	4	0.303	0.2287	0.2286
40-50	7	0.322	0.2374	0.2396
50-60	7	0.317	0.2466	0.2546
>60	6	0.423	0.2570	0.2598

Table 31

Reaction Time - Distribution of results

	No. of Cases	Normal	Prolonged
'Definite' Hypothyroid	42	1 (2%)	41 (98%)
'Doubtful' Hypothyroid	37	9 (24%)	28 (76%)
'Iatrogenic' Hypothyroid	33	8 (24%)	25 (76%)
'Pituitary' Hypothyroid	12	0 (0%)	12 (100%)
All Hypothyroid	124	18 (14%)	106 (86%)
'Doubtful' Euthyroid	45	40 (89%)	5 (11%)

Table 32

Comparison of Index and Reaction Time with Final Diagnosis in 79 Hypothyroid Patients

Index Correct, Reaction Time Correct: 60 (76%)	Index Correct, Reaction Time Wrong: 8 (10%)
Index Wrong, Reaction Time Correct: 9 (11%)	Index Wrong, Reaction Time Wrong: 2 (3%)

Table 33

Comparison of Diagnostic Accuracy of Selected Investigations in Patients with Indices 0 to +4.

Score	Final Diagnosis	Case No.	Reaction Time	^{131}I Uptake	^{131}I Urine	Cholesterol
0	E	113	-	o	o	o
0	E	129	o	o	-	x
0	E	149	o	o	o	o
0	H	91	x	o	o	x
1	E	107	o	o	x	o
1	E	128	o	o	o	o
1	E	150	-	o	o	o
2	E	109	o	o	o	x
2	E	135	x	o	o	o
2	E	142	o	o	x	o
2	E	143	o	o	o	x
2	E	147	o	o	-	o
3	E	108	-	o	o	o
3	E	148	-	o	o	o
4	E	119	o	o	-	o
4	E	137	o	o	o	o

o = Normal result
x = Abnormal result

E = Euthyroid
H = Hypothyroid
H* = Hypothyroid with Hashimoto's thyroiditis

Table 34

Comparison of Diagnostic Accuracy of Selected Investigations in Patients with Indices of +16 to +19

Score	Final Diagnosis	Case No.	Reaction Time	^{131}I Uptake	^{131}I Urine	Cholesterol
16	H*	34	x	x	o	o
16	H	84	x	x	x	x
17	H	53	x	x	o	x
17	H	63	x	x	x	x
17	H	67	x	o	x	o
18	H	16	x	x	x	x
18	H	43	x	x	x	x
18	H*	62	o	x	x	x
18	H*	64	o	o	x	x
18	H	82	x	x	o	x
19	H	44	x	-	x	x
19	H	54	x	x	o	x
19	H	59	x	x	x	x
19	H	72	x	x	x	o
19	H*	77	x	o	x	x
19	H	90	x	x	x	x
19	H	96	x	x	x	x

o = Normal result
x = Abnormal result

E = Euthyroid
H = Hypothyroid
H* = Hypothyroid with Hashimoto's thyroiditis

Table 35

Comparison of Diagnostic Accuracy of Selected Investigations in Patients with Indices in 'Equivocal Range' (+5 to +15)

Score	Final Diagnosis	Case No.	Reaction Time	^{131}I Uptake	^{131}I Urine	Cholesterol
5	E	112	o	o	-	o
6	E	122	o	x	o	o
6	E	144	o	o	o	o
7	E	126	o	o	x	o
7	E	133	o	o	o	o
8	E	139	o	o	o	o
9	E	124	-	o	o	o
10	E	125	-	o	-	x
5	H*	86	x	o	-	x
7	H	76	x	x	-	x
8	H	94	x	x	x	x
10	H	97	x	x	x	x
11	H	39	x	x	x	x
11	H	65	-	x	x	x
12	H	68	x	x	-	x
12	H*	87	x	o	o	x
12	H	95	-	x	x	x
13	H	61	o	x	o	o
13	H	69	x	x	x	x

o = Normal result
x = Abnormal result

E = Euthyroid
H = Hypothyroid
H* = Hypothyroid with Hashimoto's thyroiditis

Table 36

Changes in Diagnostic Index Following Thyroxine Therapy

Thyroxine mg/day	Nil	0.025	0.05	0.1	0.15	0.2	0.25	0.3
Case No.								
16	18	14	12	-10*				
45	30	27	10	- 6*				
77	19	20	13	- 4*				
21	23	17	6	-12	-17*			
85	36	29	18	- 1	- 7*			
180	27	22	9	- 3	- 7*			
5	25		14	10	- 8*			
20	25	27	19	8	- 1*			
69	13	21	18	3	-15*			
70	31	30	11	2	-18*			
18	32		22	12	- 7	-13*		
63	17	10	7	2	- 2	-14*		
64	19		15	2	- 5	-13*		
84	16	21	17	2	- 8	-16*		
90	19	20	12	3	- 5	-12*		
93	27		17	14	- 9	-13*		
94	9		20	4	-11	-16*		
13	33	24	21	17	11	- 3*		
17	23	23	26	10	5	- 3*		
19	26		20	9	1	- 9*		
27	28	25	19	18	5	- 6*		
80	25	30	19	15		- 2*		
82	19		16	14	1	-10*		
43	17		18	19		-13*		
202	35		30	20	9	- 4*		
198	22		19	3		- 4	-12*	
25	28		14	10		-10		-14*
36	24		23	23		- 1		- 8*
168	19		26	19		7		- 9*

* Indicates when patient considered euthyroid by conventional clinical assessment.

Underlined figures indicate first normal value obtained following treatment.

Table 37

Changes in Basal Metabolic Rate Following Thyroxine Therapy

Thyroxine mg/day	Nil	0.025	0.05	0.1	0.15	0.2	0.25	0.3
Case No.								
16	-29		$\underline{-10}$	- 5*				
21	$\underline{-6}$	+11		+10	*			
20	-28		-47	$\underline{-13}$	- 5*			
85	-25		$\underline{-4}$		+ 2*			
27	$\underline{-5}$		+26	+14	+21	*		
93	$\underline{-7}$		+ 8		+13	+24*		
63	-27	$\underline{-13}$	+ 8	- 8	- 3	+ 2*		
84	-25	$\underline{-14}$		+ 9	- 1	- 2*		
90	-27	$\underline{-10}$	- 4	+18	+12	+ 1*		
13	-36	-21	$\underline{-8}$	+12	- 2	+ 9*		
80	-25	-21	$\underline{-9}$	- 4		*		
82	-22		$\underline{-12}$	- 4	- 9	+ 7*		
202	-17		$\underline{-13}$	+27		+ 3*		
43	-34		-31	$\underline{-10}$		+ 5*		
17	-16		-27		$\underline{-5}$	*		
168	-21		$\underline{-11}$	+ 2				*
36	-17		-29	$\underline{-12}$		+ 3		*

.* Indicates when patient considered euthyroid by conventional clinical assessment.

Underlined figures indicate first normal value obtained. (% Robertson and Reid)

Table 38

Change in Serum Cholesterol
Following Thyroxine Therapy

Thyroxine mg/day	Nil	0.025	0.05	0.1	0.15	0.2	0.25	0.3
Case No.								
16	347		278	249*				
20	740	314	282	172	238*			
21	300	334	256	278	249*			
85	340	361	175	211	*			
5	614		386	285	334*			
84	427	282		205	273	151*		
13	491	303	213	245	239	278*		
43	326		225	159		203*		
80	642	303	222	198		177*		
82	303		196	170	185	141*		
90	303	334	245	235	238	205*		
17	410		416	416	252	187*		
93	490		340	386	263	211*		
202	439		439	339	256	303*		
63	832	648	416	321	340	222*		
198	334		278	303		298	177*	
36	278		340	278		143		149*
168	406			340		278		238*

*Indicates when patient considered euthyroid by conventional clinical assessment.

Underlined figures indicate first normal value obtained. (Mg.%)

Table 39

Changes in Reaction Time Following Thyroxine Therapy

Thyroxine mg/day	Nil	0.025	0.05	0.1	0.15	0.2	0.25	0.3
Case No.								
16	.350	.354	.264	.252*				
21	.391	.303	.282	.271	.267*			
287	.284		.256	.264	.245*			
5	.334		.294	.264	.243*			
180	.330	.280	.276	.262	.255*			
181	.371		.277	.274	.246*			
20	.959	.610	.494	.385	.292*	(- .283)		
63	.321	.280	.269	.248		.250*		
90	.293	.296	.248			*		
19	.308		.294	.270	.248	*		
43	.320		.289	.250		.237*		
82	.291		.260	.223	.233	.222*		
202	.323		.299	.250	.246	.250*		
13	.411	.511	.516	.309	.278	.270*		
17	.290		.347	.308	.242	.232*		
84	.338	.365	.296	.294	.259	.250*		
93	.320		.311	.287	.260	.237*		
27	.466	.394	.534	.341	.325	.275*		
80	.343	.323	.307	.297		.270*		
198	.294		.267	.240		.233	*	
36	.279		.267	.236	.235		.230	*

*Indicates when patient considered euthyroid by conventional clinical assessment.

Underlined figures indicate first normal value obtained. (Secs.)

<u>Table 40</u>

Changes in Serum Carotene
<u>Following Thyroxine Therapy</u>

Thyroxine mg/day	Nil	0.025	0.05	0.1	0.15	0.2	0.25	0.3
Case No.								
16	192		187	<u>63*</u>				
20	172	<u>84</u>	116	76	81*			
85	127	<u>67</u>	108	75	*			
5	175		<u>89</u>	101	95*			
21	157	157	190	<u>45</u>	74*			
43	<u>57</u>		101			40*		
13	144		<u>84</u>	80	78	46*		
63	174	148	<u>71</u>	126	67	75*		
80	130	131		<u>62</u>		38*		
82	104		91	<u>68</u>	97	76*		
84	127	154		130	<u>68</u>	96*		
17	130		119	148	122	<u>55*</u>		
90	145	154	173	112	120	<u>82*</u>		
202	180		175	93	124	<u>61*</u>		
198	<u>75</u>		64	50		49	44*	
36	<u>79</u>		64			57		34*
168	108			<u>76</u>				*

*Indicates when patient considered euthyroid by conventional clinical assessment.

Underlined figures indicate first normal value obtained. (ug%)

FIGURES 1 - 27

AGE DISTRIBUTION—PRIMARY HYPOTHYROIDISM

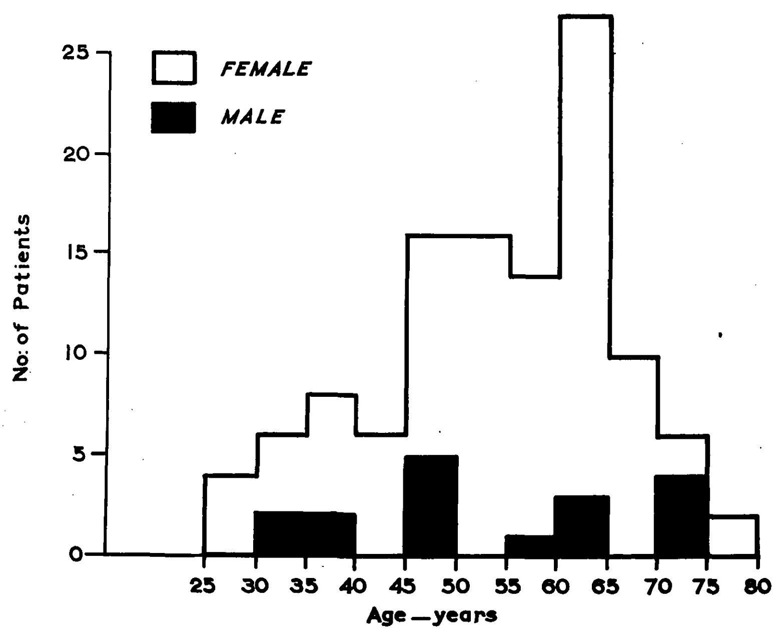


Figure 1 - Distribution of the ages at which the diagnosis was established in hypothyroid subjects.

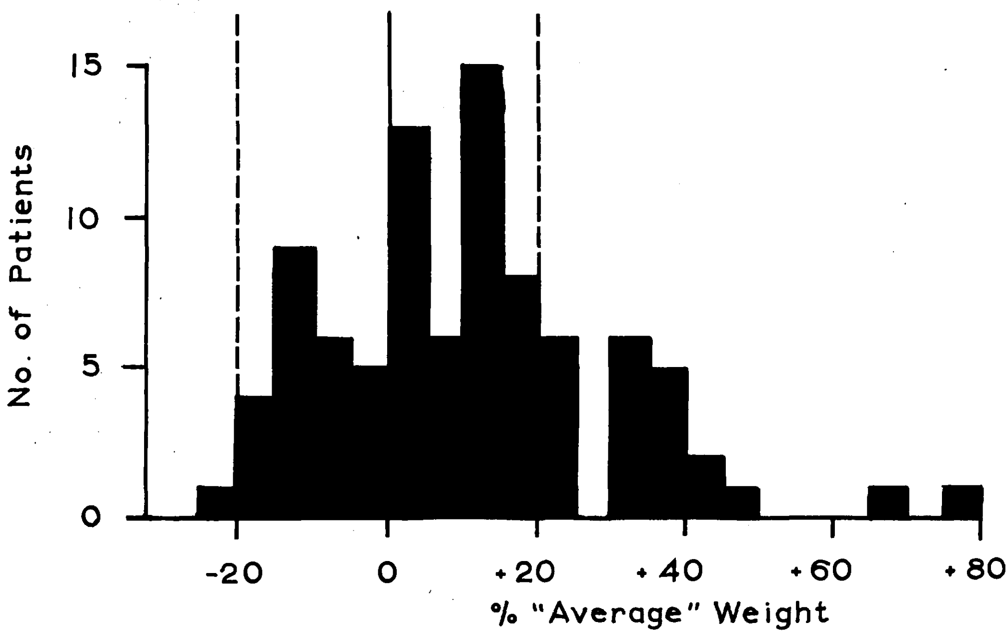
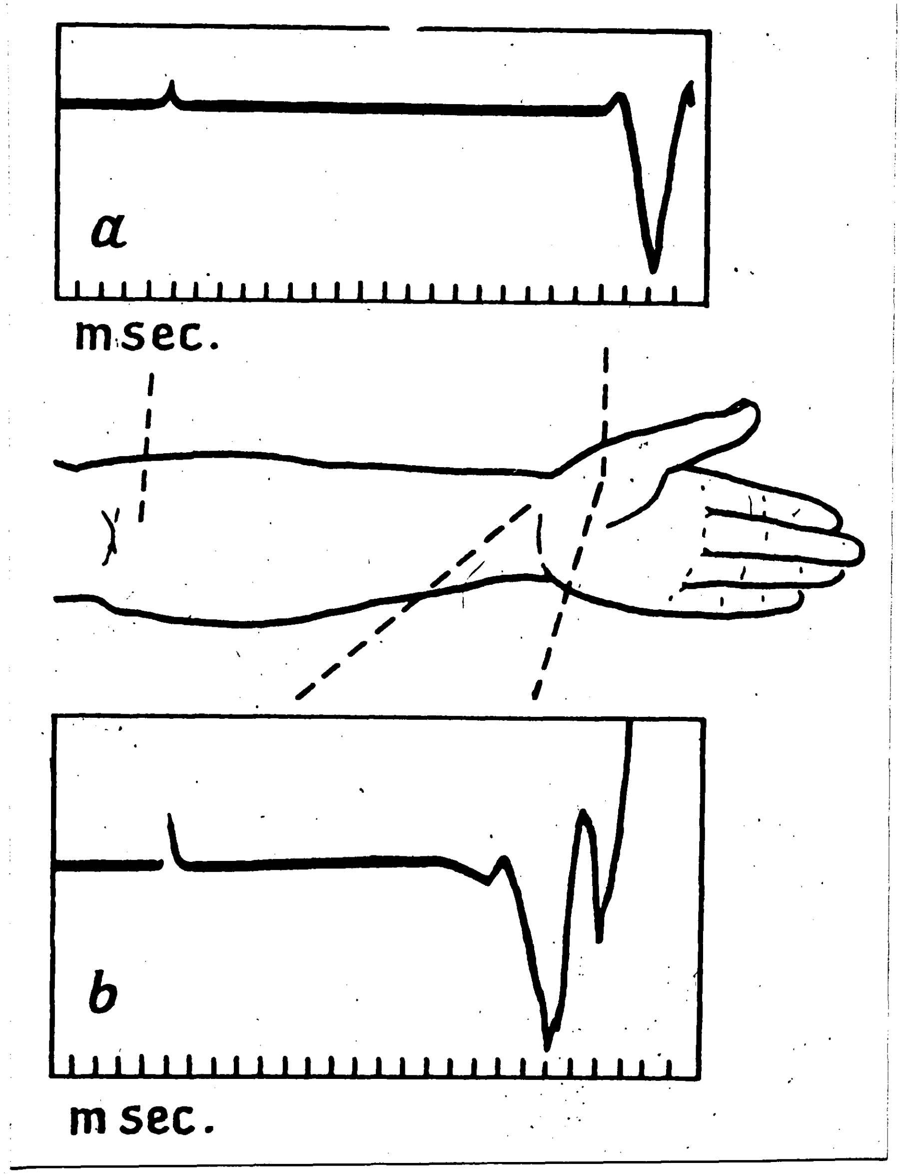


Figure 2 - Distribution of the weights of 88 hypothyroid patients in relation to their "average" weights for age, sex and height.



<u>Figure 3</u> - Shock artefact shows time of stimulus at cathode on median nerve at a) elbow, b) wrist. After delay due to conduction along nerve this is followed by muscle-action potential recorded by co-axial needle-electrode in abductor pollicis brevis muscle.

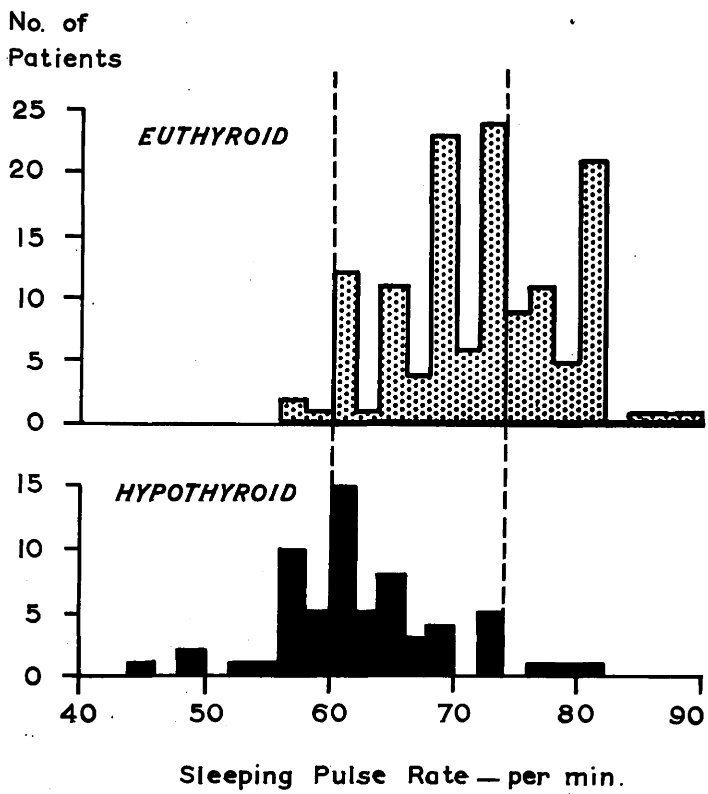


Figure 4 - Distribution of the sleeping pulse rates in 134 euthyroid individuals and in 63 hypothyroid patients.

DIAGNOSTIC INDEX — CORRELATION WITH FINAL DIAGNOSIS

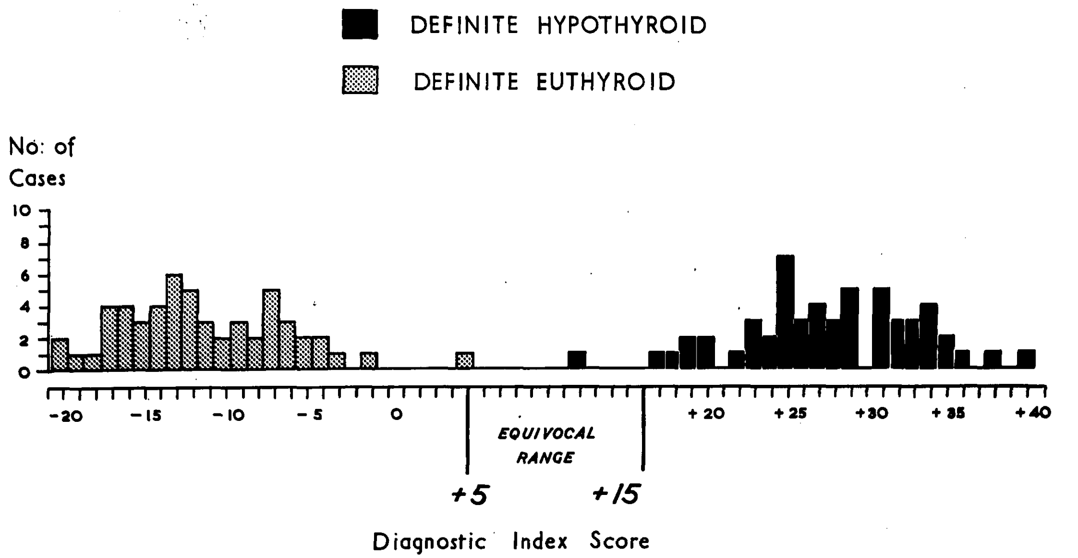


Figure 5 - Distribution of the diagnostic indices of 55 individuals in the "Definite Euthyroid" group and of 55 patients in the "Definite Hypothyroid" group.

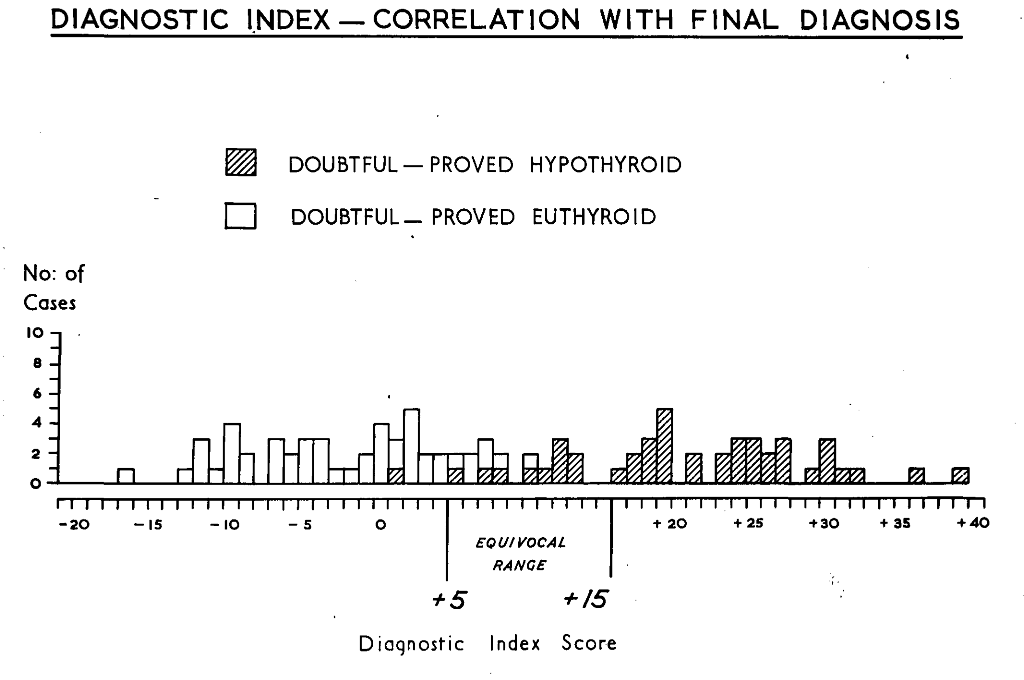


Figure 6 - Distribution of the diagnostic indices of patients in whom diagnostic difficulty had been encountered; 50 were finally shown to be euthyroid and hypothyroidism proved in 45.

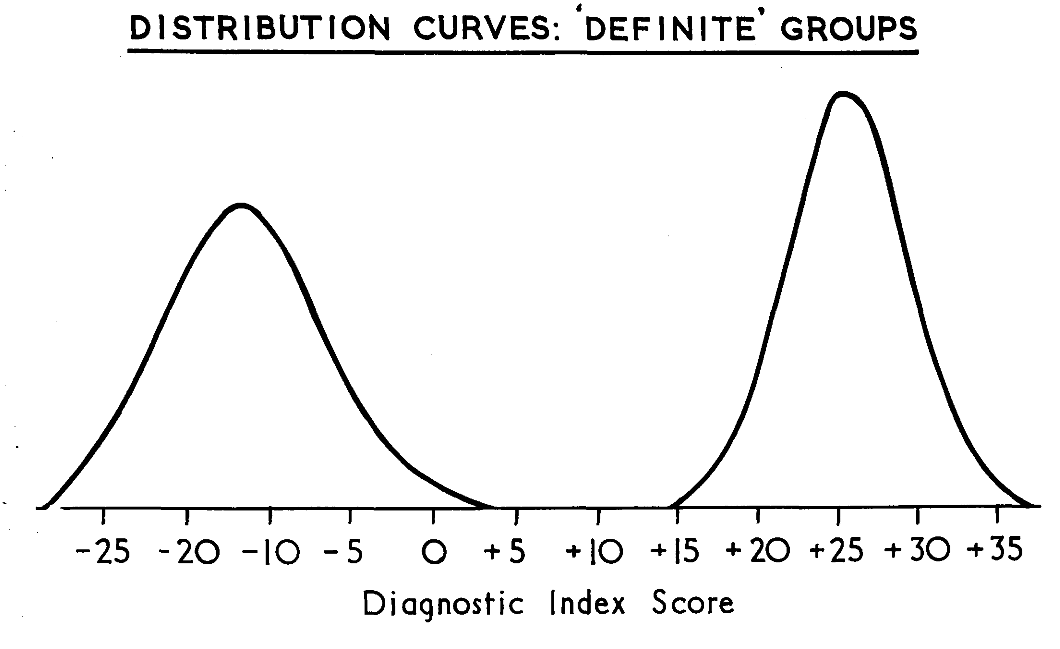


Figure 7 - Distribution curves based on the observed clinical diagnostic indices of the "Definite" group.

DISTRIBUTION CURVES: 'DOUBTFUL' GROUPS

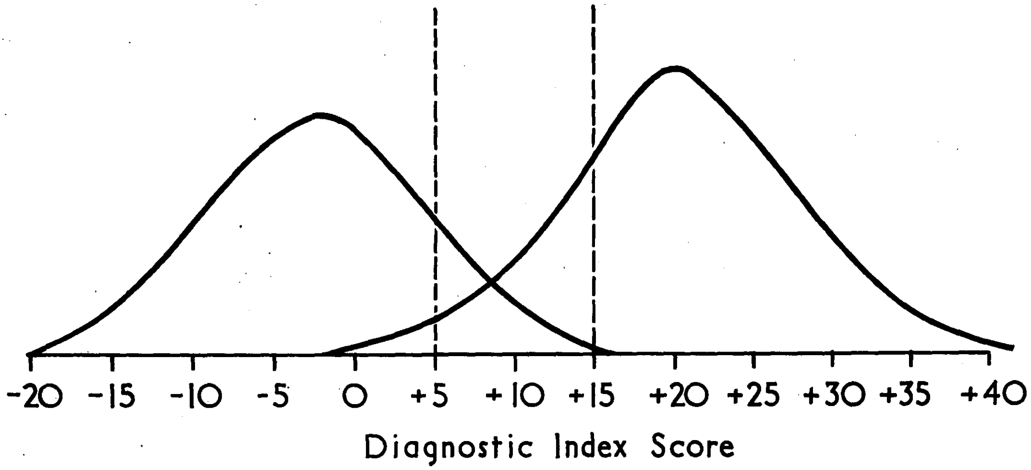


Figure 8 - Distribution curves based on the observed clinical diagnostic indices of the "Doubtful" group.

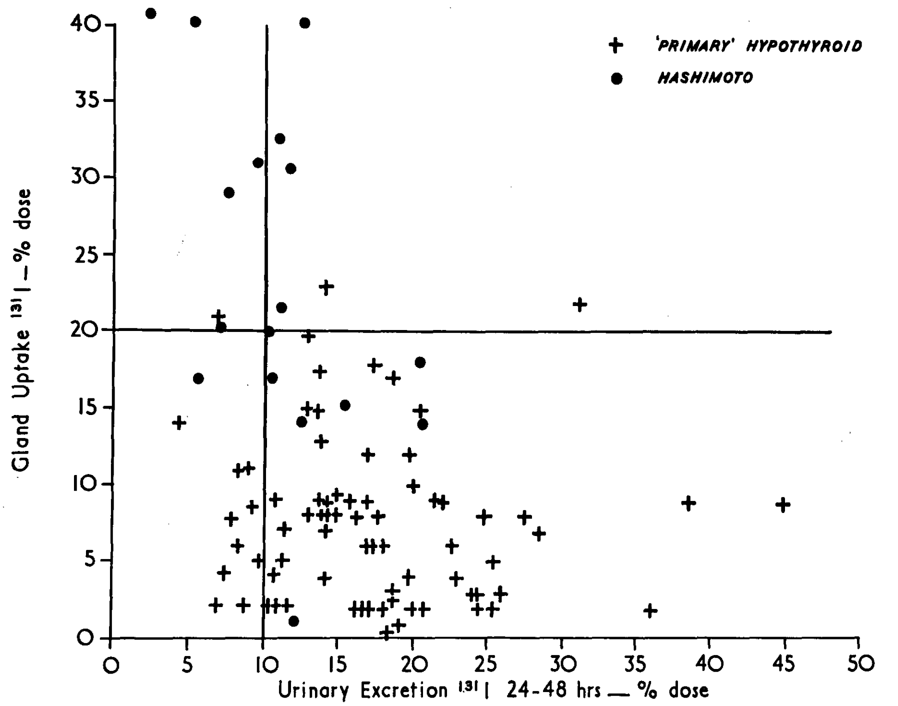


Figure 9 - Relationship of the gland uptake and urinary excretion in 24-48 hour period after tracer dose of ^{131}I in hypothyroid patients.

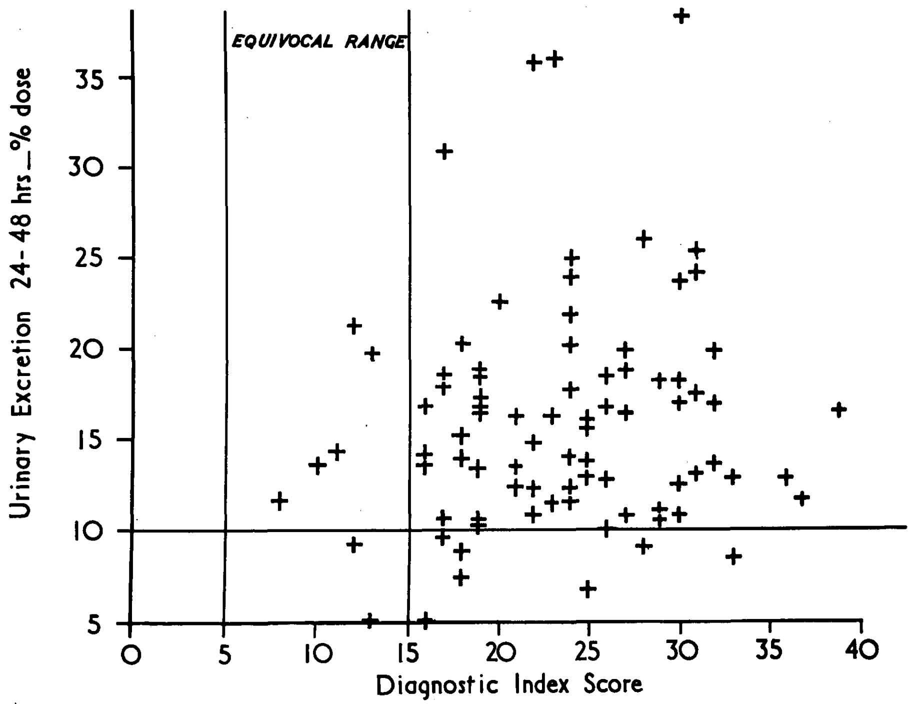
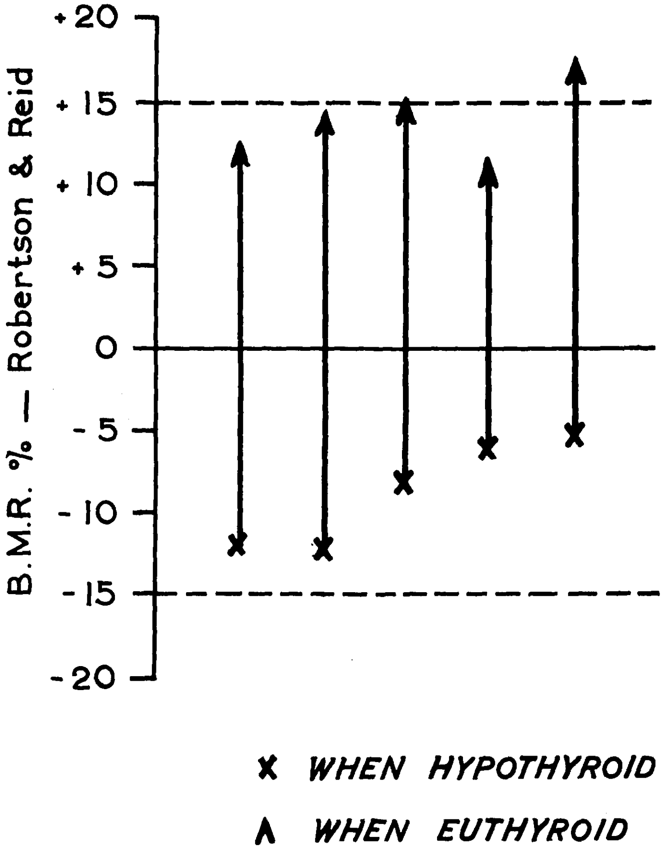
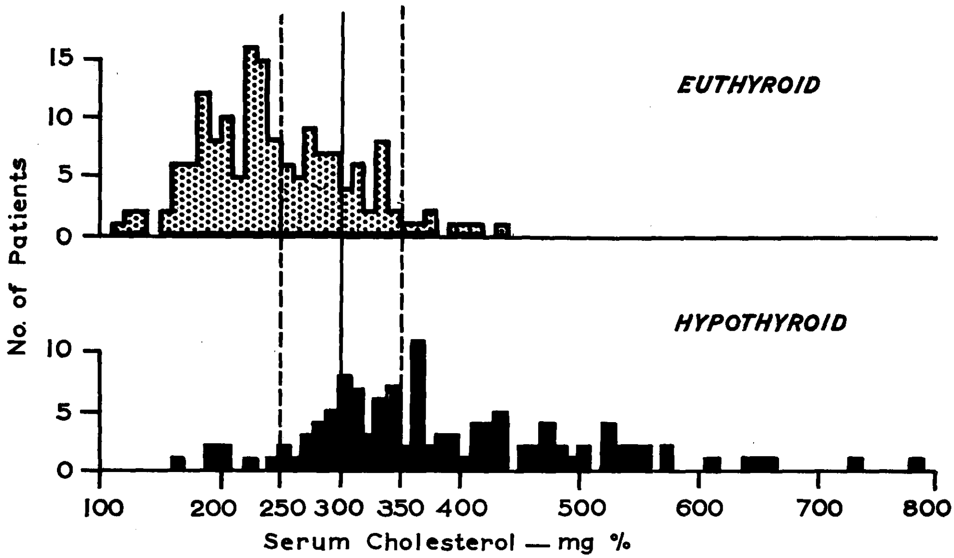


Figure 10 - Relationship of the clinical diagnostic indices and the urinary excretion of ^{131}I in 24-48 hour period after tracer dose in hypothyroid patients.



<u>Figure 11</u> - Changes in the basal metabolic rate following thyroxine therapy in 5 patients in whom hypothyroidism was demonstrated but whose B.M.R. initially lay within the "normal" range.



<u>Figure 12</u> - Distribution of serum cholesterol levels in euthyroid and hypothyroid subjects.

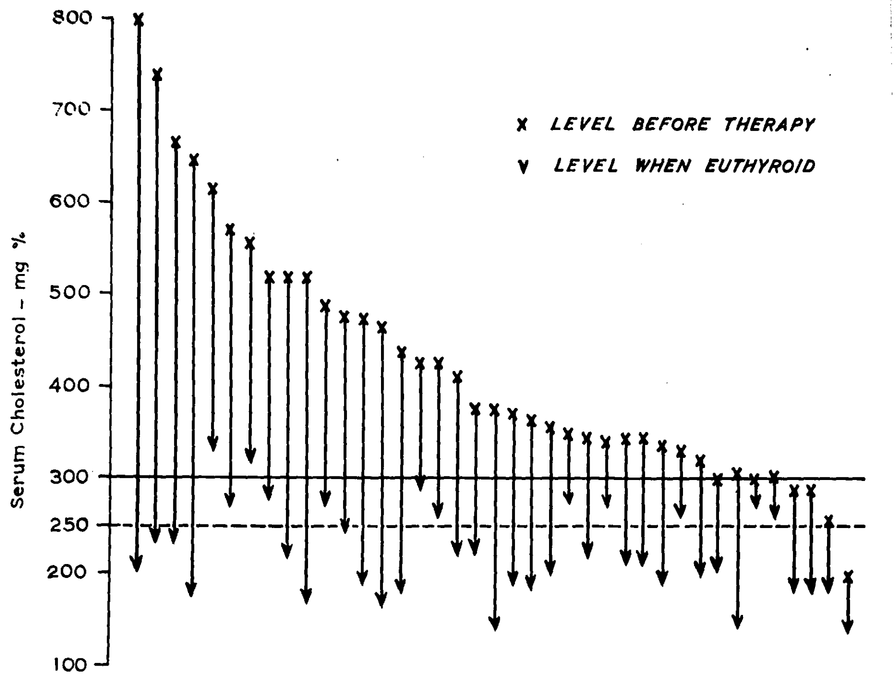


Figure 13 - Changes in the serum cholesterol level following thyroxine therapy in 39 hypothyroid patients.

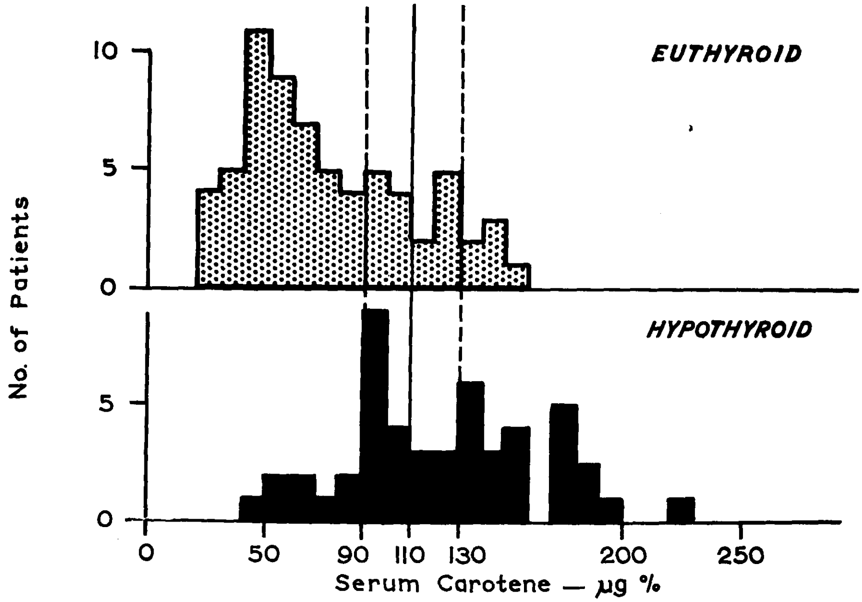


Figure 14 - Distribution of serum carotene levels in euthyroid and hypothyroid subjects.

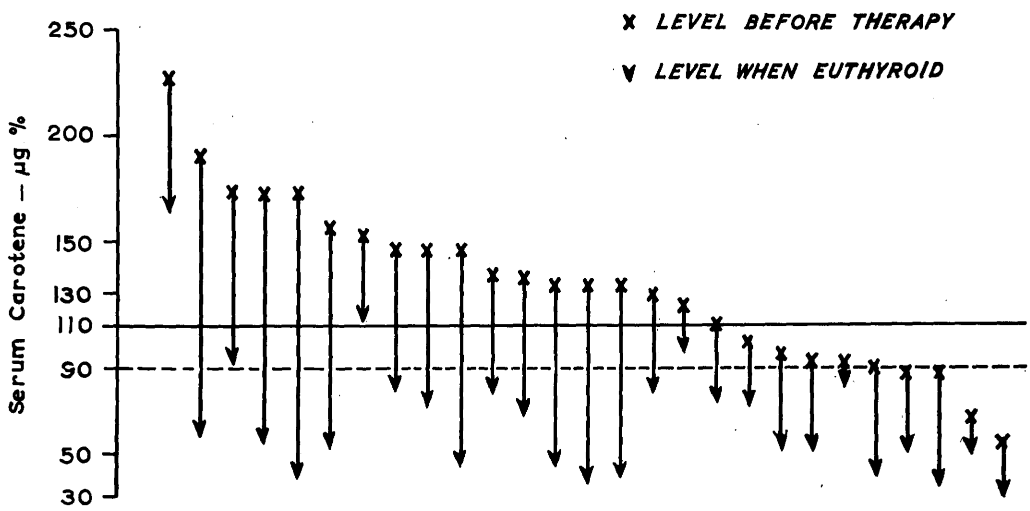
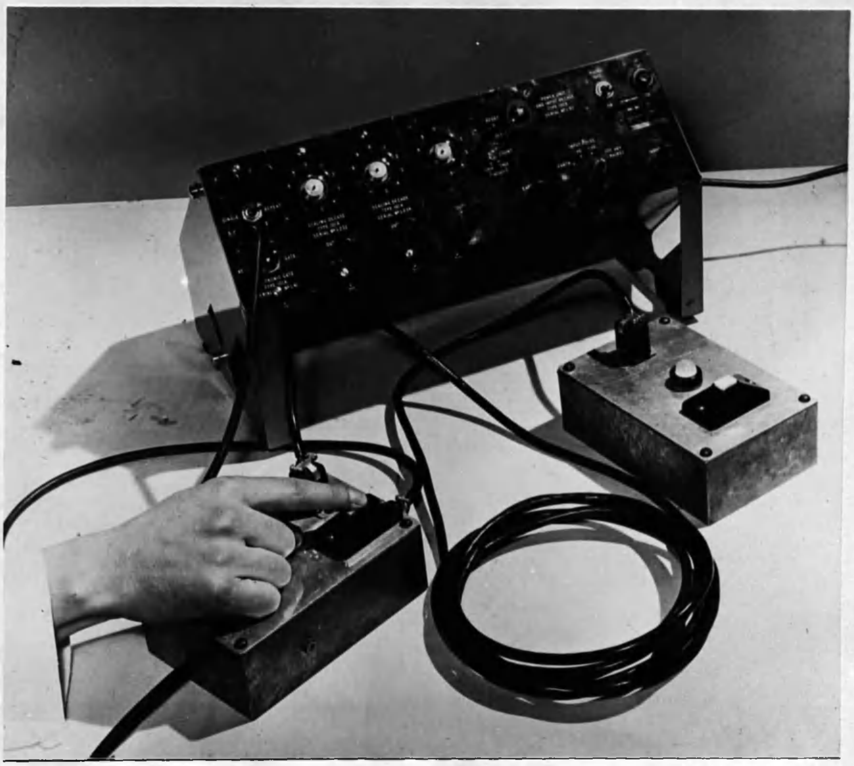


Figure 15 - Changes in the serum carotene level following thyroxine therapy in 27 hypothyroid patients.



<u>Figure 16</u> - The apparatus used to measure reaction time.

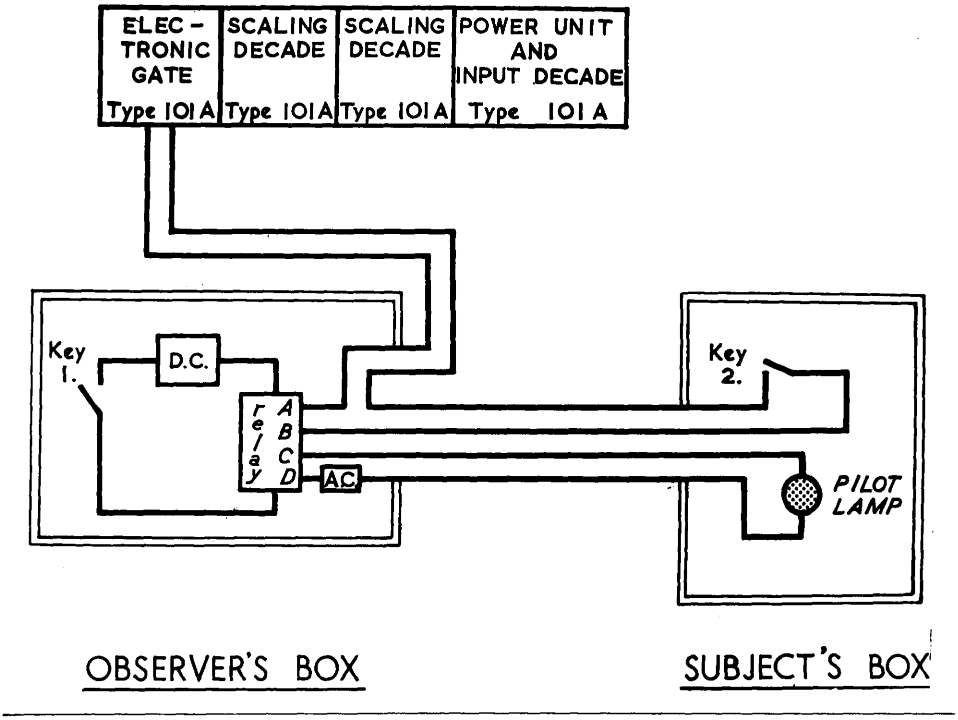


Figure 17 - Circuit plan of the apparatus.

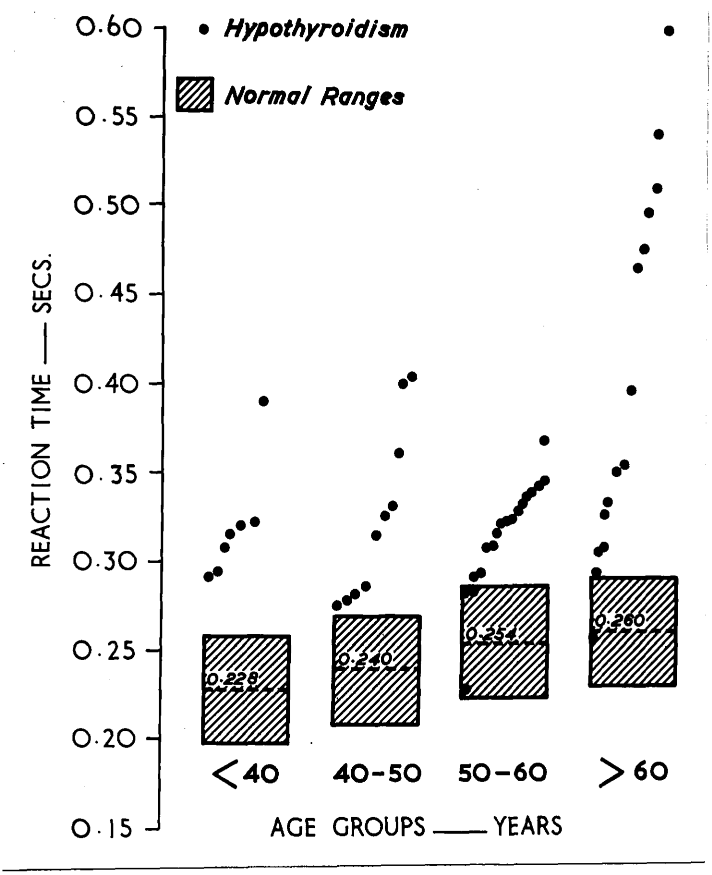


Figure 18 - Reaction times of 50 hypothyroid patients showing the prolongation outside normal ranges.

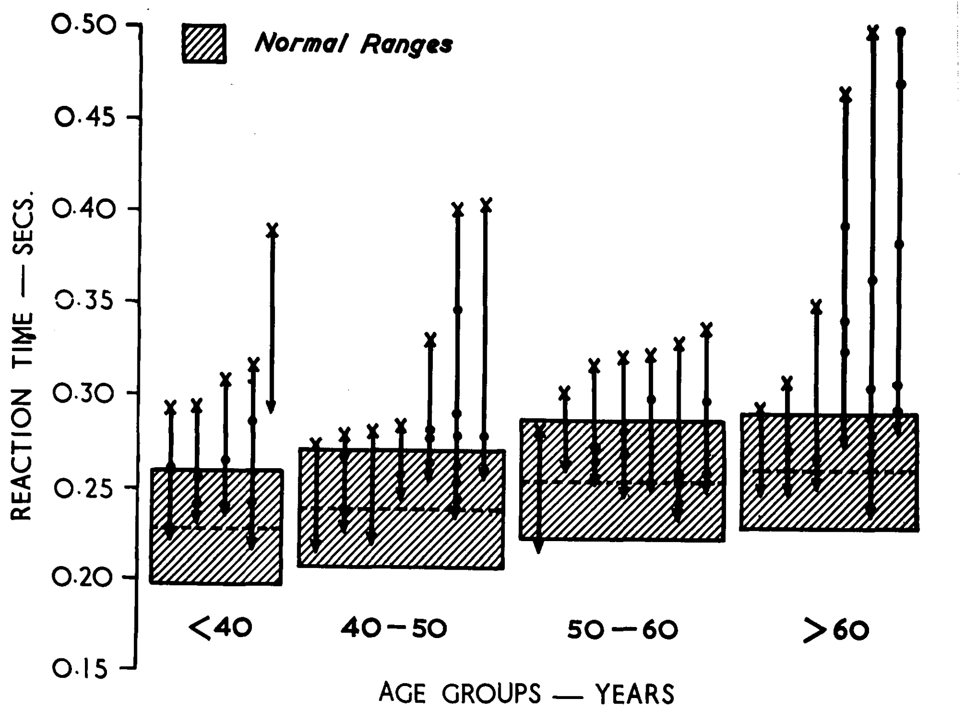
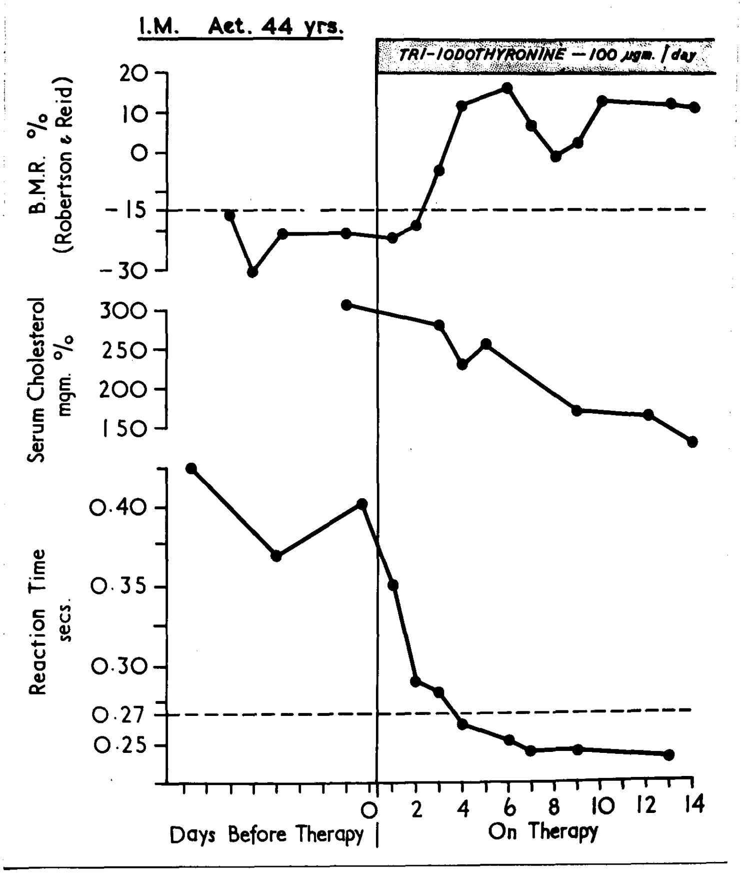


Figure 19 - Effect of therapy on reaction times of 25 hypothyroid patients: x, initial reading; •, readings during period of control; v, final reaction time when patient was euthyroid.



<u>Figure 20</u> - Effect of triiodothyronine on B.M.R., serum cholesterol level and reaction time in a hypothyroid patient.

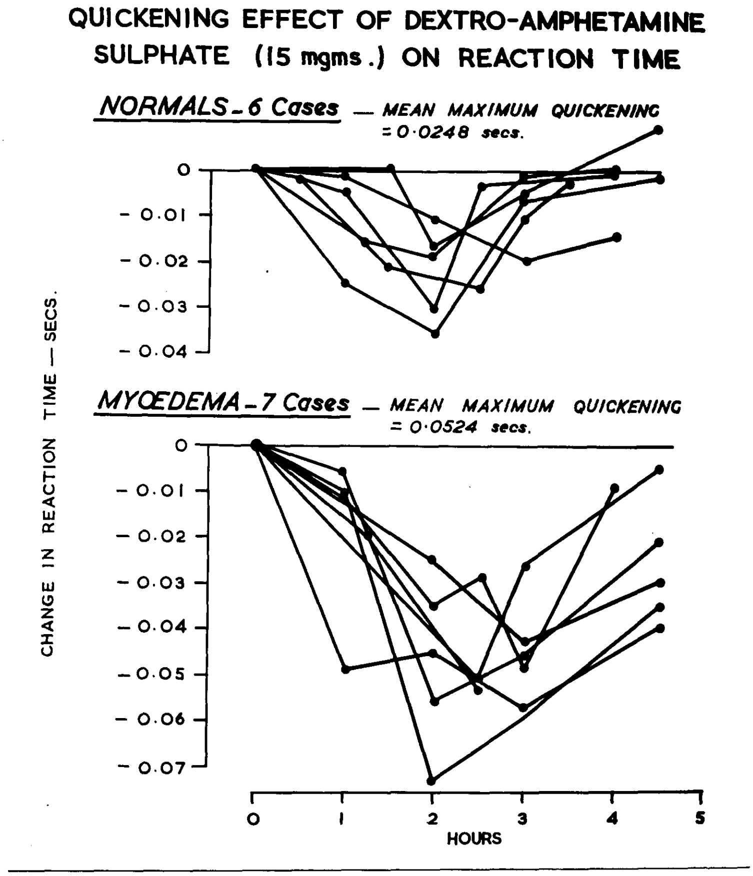
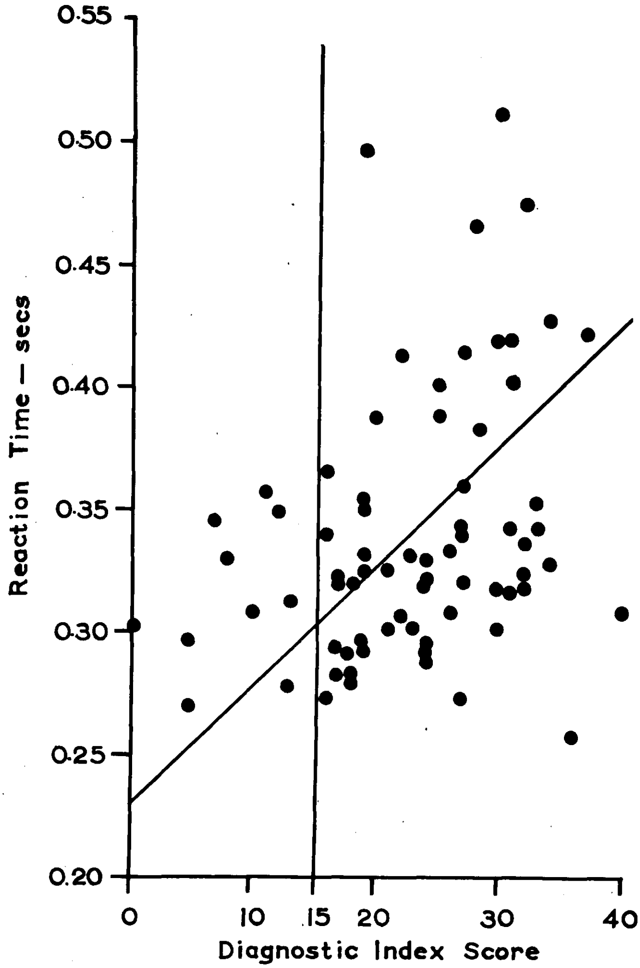
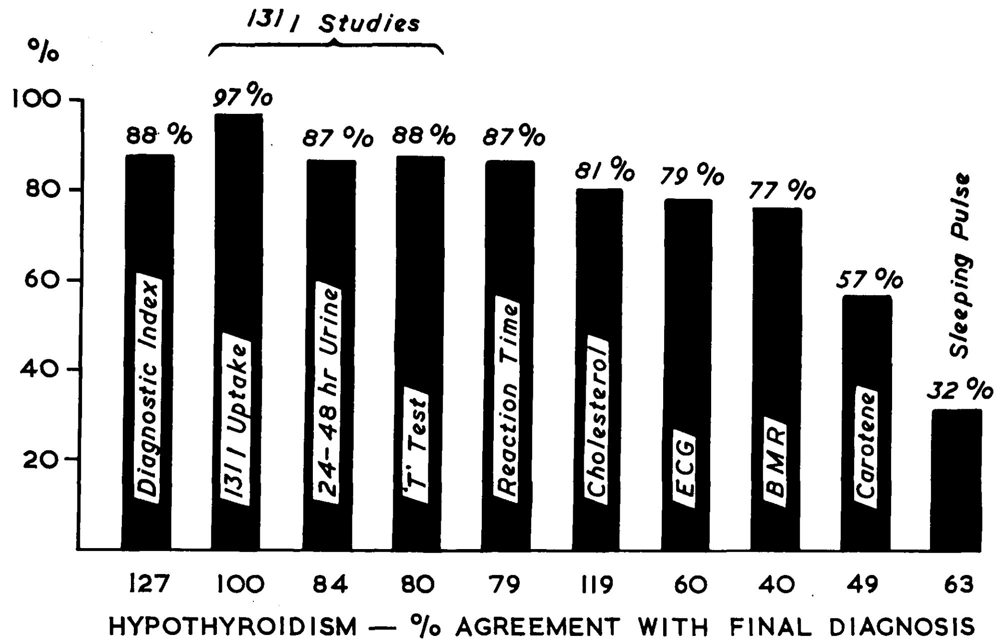


Figure 21 - Changes in reaction time following administration of dextroamphetamine sulphate to 6 healthy people and 7 hypothyroid patients.



<u>Figure 22</u> - The clinical diagnostic index used as a measure of severity and correlated with the reaction time of hypothyroid patients. The regression line of the index on the reaction time is shown.



<u>Figure 23</u> - Comparison of the accuracy with which the various procedures indicated the diagnosis of hypothyroidism in patients finally proved to be hypothyroid. The number of patients in which each was carried out is indicated below the respective bars.

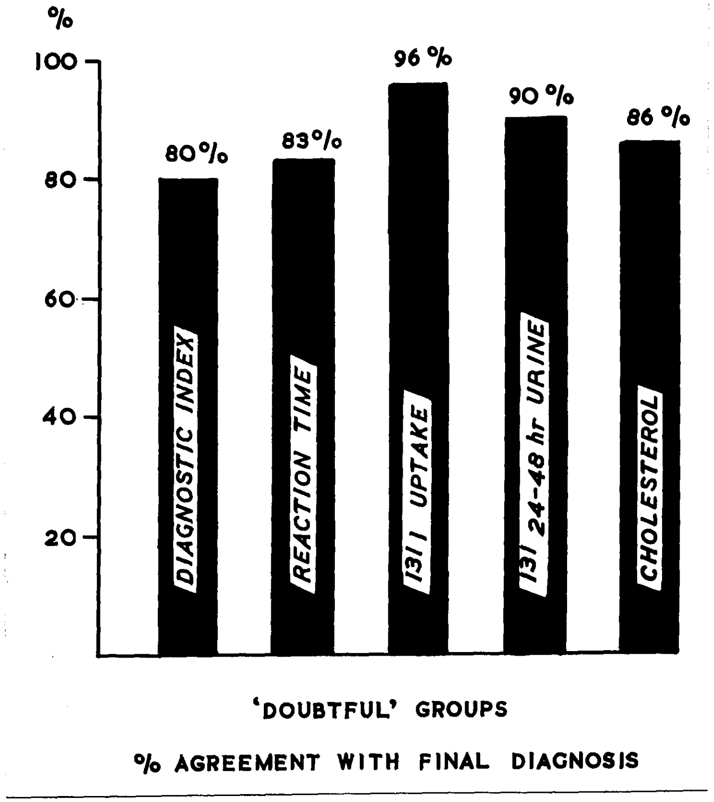
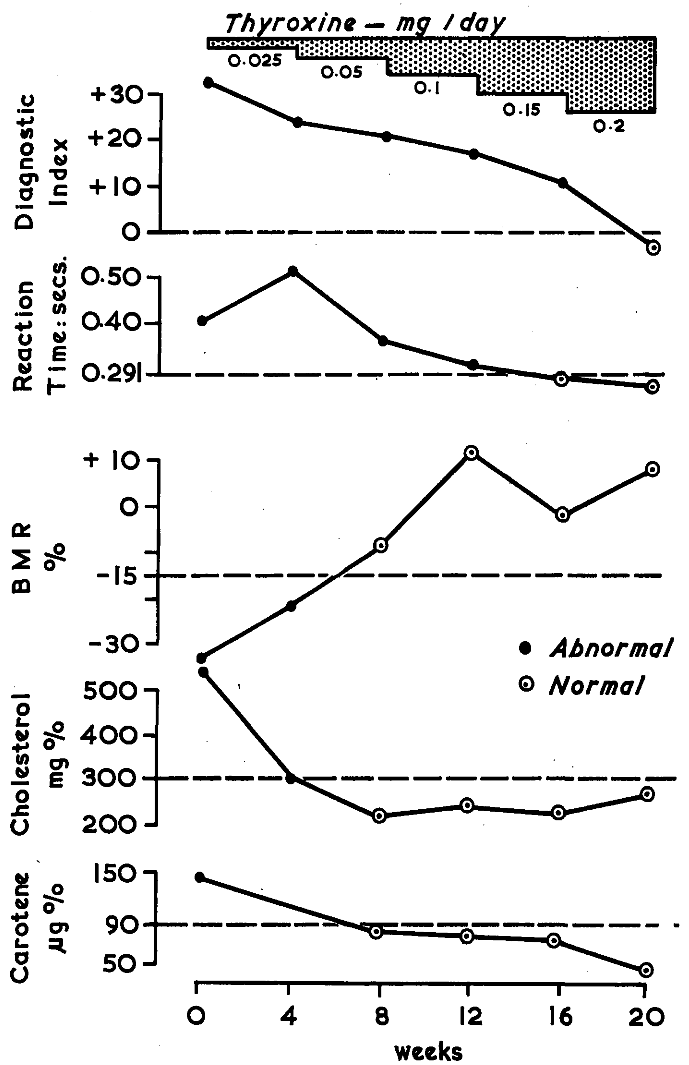
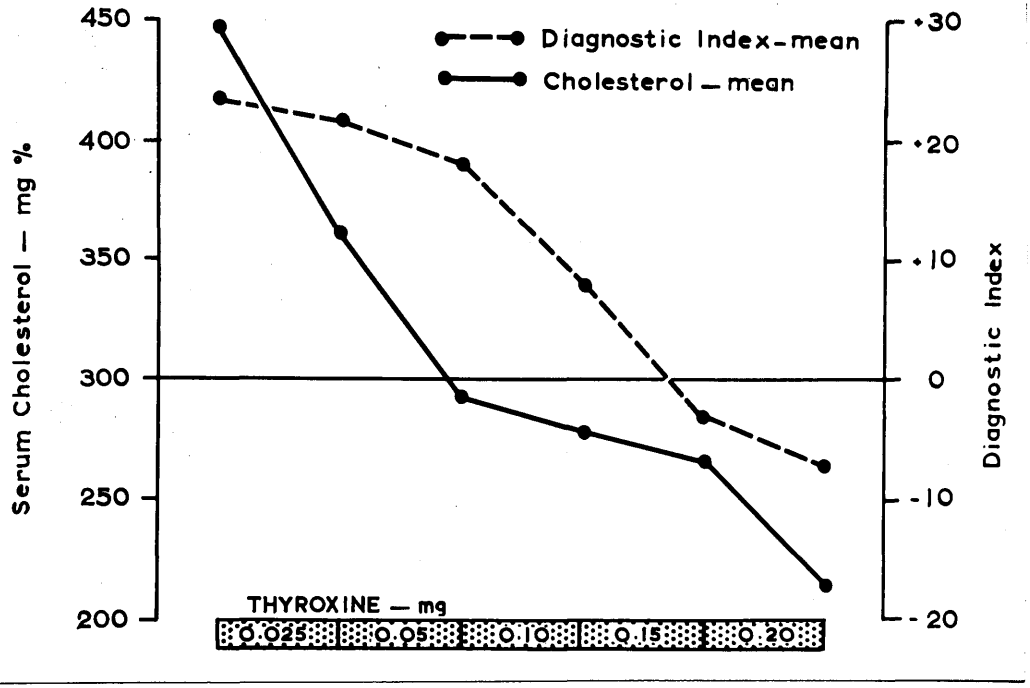


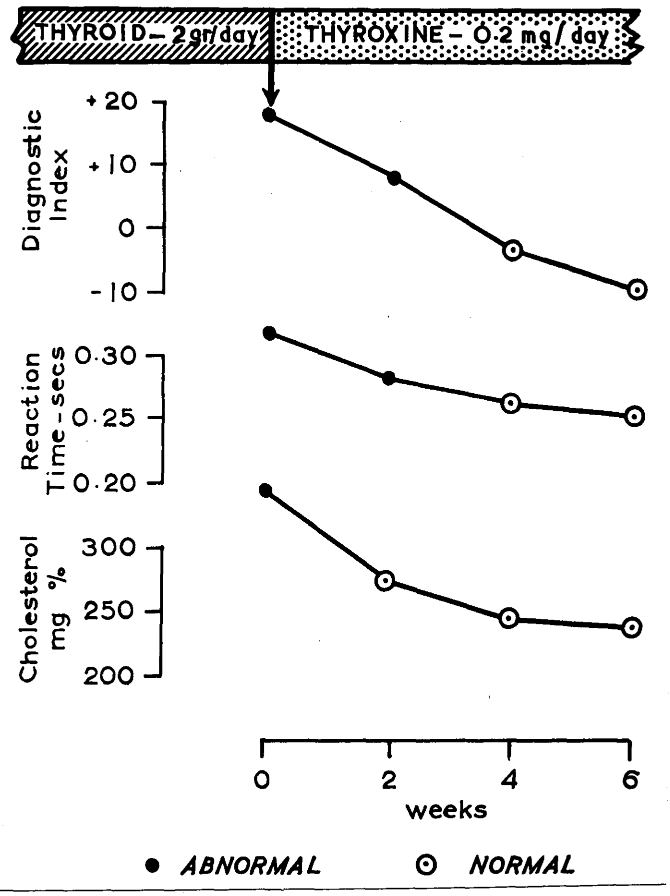
Figure 24 - Comparison of the accuracy with which the procedures correctly categorised the patients of the "Doubtful" groups either as euthyroid or hypothyroid.



<u>Figure 25</u> - The effect of gradually increasing dosage of l-thyroxine sodium on the diagnostic index, reaction time, B.M.R., serum cholesterol and serum carotene in a hypothyroid patient. The open circles indicate when a value within normal ranges was obtained.



<u>Figure 26</u> - Comparison of the effect of l-thyroxine sodium on the mean values of the diagnostic index and serum cholesterol of 18 hypothyroid patients.



<u>Figure 27</u> - The effect of l-thyroxine sodium on the diagnostic index, reaction time and serum cholesterol in a patiant who had become clinically hypothyroid while continuing to take Thyroid B.P. which had previously provided satisfactory control.

REFERENCES TO THE LITERATURE

REFERENCES

ARNOTT, D.G., EMERY, E.W., FRASER, R. and HOBSON, Q.J.G. (1949) Lancet, ii, 460.

ASHER, R. (1949) Brit. med. J., 2, 555.

ASHER, R. (1955) Brit. med. J., 1, 471.

AUB, J.C. and Du BOIS, E.F. (1917) Arch. intern. Med., 19, 823.

BACON, Roger (1214-1294) Quoted by Sir Henry Brackenbury in "Patient and Doctor" (1935) Hodder and Stoughton, London.

BARNES, B.O. (1959) Lancet, ii, 149.

BARON, D.N. (1956) Lancet, ii, 277.

BARTEL S. (1953) J. clin. Endocr., 13, 95.

BAUER, R.E. (1956) Ann. intern. Med., 44, 207.

BEIRWALTES, W.H., JOHNSON, P.C. and SOLARI, A.J. (1957) "Clinical Use of Radioisotopes", Saunders, London.

BERNSTEIN, L.M., JOHNSTON, L.C., RYAN, R., INOUYE, T. and HICK, F.K. (1956) J. appl. Physiol., 9, 241.

BERSON, S.A., YALOW, R.S., SORRENTINO, J. and ROSWIT, B. (1952) J. clin. Invest., 31, 141.

BLOMFIELD, G.W., ECKERT, H., FISHER, M., MILLER, H., MUNRO, D.S. and WILSON, G.M. (1959) Brit. med. J., 1, 5114.

BLOMFIELD, G.W., JONES, J.C., MACGREGOR, A.G., MILLER, H. and WAYNE, E.J. (1951) Brit. med. J., 2, 273.

BLOOR, W.R. (1916) J. biol. Chem., 24, 227.

BOAS, E.P. (1932) Amer. Heart J., 8, 24.

BOOTHBY, W.M., BERKSON, J. and DUNN, H.L. (1936) Amer. J. Physiol., 116, 468.

BOOTHBY, W.M. and SANDIFORD, I. (1922) J. biol. Chem., 54, 767.

BOYD, E.M. and CONNELL, W.F. (1936) Quart. J. Med., 5, 455.

BRAIN, W.R. (1955) Diseases of the Nervous System, London.

BURNSTEIN, N. (1948) New Orleans Med. and Surg. J., 100, 374.

CARTER, A.C., WEISENFELD, S. and WALLACE, E. (1959), J. clin. Endocr., 19, 234.

CASTLEMAN, B. and HERTZ, S. (1939) Arch. Path. (Chicago), 27, 69.

CHANEY, W.C. (1924) J. Amer. med. Ass., 82, 2013.

CLINICAL SOCIETY OF LONDON (1888) Report of a Committee nominated December 14, 1883 to investigate the subject of myxoedema. Trans. clin. Soc. Lond., 21 Suppl.

COCHRANE, A.L., CHAPMAN, P.J. and OLDHAM, P.D. (1951) Lancet, i, 1007.

COENEGRACHT, J. and FRASER, R. (1955) J. Endocr., 12, 185.

COHEN, Lord (1958) Ann. intern. Med., 48, 219.

COHEN, M.H. (1934) J. Amer. med. Ass., 102, 283.

CROOKS, J. and MURRAY, I.P.C. (1958) Scot. med. J., 3, 120.

CROOKS, J., MURRAY, I.P.C. and WAYNE, E.J. (1958) Lancet, i, 604.

CROOKS, J., MURRAY, I.P.C. and WAYNE, E. J. (1959) Quart. J. Med., 28, 211.

CURLING, T.B. (1850) Med.-chir. Trans., London, 33, 303.

CURRIER, F.P. and BRINK, J.R. (1948) Dis. nerv. Syst., 9, 144.

DALLY, P.J. (1959) Brit. med. J., 1, 1333.

ESCAMILLA, R.F. (1942) J. clin. Endocr., 2, 33.

ESCAMILLA, R.F. and LISSER, H. (1942) J. clin. Endocr., 2, 65.

ESCAMILLA, R.F., LISSER, H. and SHEPARDSON, J. (1935) Ann. intern. Med., 9, 297.

EVANS, C.L. (1947) "Principles of Human Physiology", London.

EXTRA PHARMACOPOEIA, The (Martindale) (1958) Vol.1, 24th edition. London; The Pharmaceutical Press.

FARRAN, H.E.A. (1958) Brit. med. J., 2, 1060.

FLETCHER, C.M. (1952) Proc. roy. Soc. Med., 45, 576.

FORBES, G. (1945) J. exp. Psychol., 35, 153.

FOX, E.L. (1892) Brit. med. J., 2, 941.

FRASER, R., HOBSON, Q.J.G., ARNOTT, D.G. and EMERY, E.W. (1953) Quart. J. Med., 22, 99.

FRASER, R. and NORDIN, B.E.C. (1955) Lancet, i, 532.

FRASER, R. and SMITH, P.H. (1941) Quart. J. Med., 40, 297.

FREEMAN, A.G. and MATTINGLY, D. (1956) Lancet, i, 965.

GABRILOVE, J.L. and LUDWIG, A.W. (1957) J. clin. Endocr., 17, 925.

GALBRAITH, H-J. B. (1953) St. Bartholomew's Hospital Journal, 57, 311.

GANTT, W.H. and FLEISCHMANN, W. (1948) Amer. J. Psychiat., 104, 673.

GILDEA, E.F., MAN, E.B. and PETERS, J.P. (1939) J. clin. Invest., 18, 739.

GLASSER, E.M. and WHITTOW, G.C. (1954) Clin. Sci., 13, 199.

GOLDSMITH, R.E., STURGIS, S.H., LERMAN, J. and STANBURY, J.B. (1952) J. clin. Endocr., 12, 846.

GOODWIN, J.F., MACGREGOR, A.G., MILLER, H. and WAYNE, E.J. (1951) Quart. J. Med., 20. 353.

GOODWIN, T.W. (1952) "The Comparative Biochemistry of Carotenoids", London, Chapman and Hall.

GROSS, J. and PITT-RIVERS, R. (1952a) Lancet, i, 439.

GROSS, J. and PITT-RIVERS, R. (1952b) Lancet, i, 593.

GROSS, J., PITT-RIVERS, R. and TROTTER, W.R. (1952) Lancet, i, 1044.

GULL, W.W. (1873) Trans. clin. Soc. Lond., 7, 180.

HAIG, C.P. and REISS, M. (1950) Brit. J. Radiol., 23, 527.

HAMILTON, J.G., and SOLEY, M.H. (1940) Amer. J. Physiol., 131, 135.

HAMOLSKY, M.W., STEIN, M. and FREEDBERG, A.S. (1957) J. clin. Endocr., 17, 33.

HERTZ, S., ROBERTS, A. and EVANS, R.D. (1938) Proc. Soc. exp. Biol., 38, 510.

HOET, J.P., HOET, J.J. and GOMMERS, A. (1959) J. Endocr., 18, XXVI.

HOWARTH, A.E. and LLOYD, H.E.D. (1956) Brit. med. J., 1, 431.

HURXTHAL, L.M. (1934) Arch. intern. Med., 53, 762.

HUBBLE, D. (1952) Lancet, i, 1123.

INGBAR, S.H. and FREINKEL, N. (1955) J. clin. Invest., 34, 808.

KEATING, F.R., POWER, M.H., BERKSON, J. and HAINES, S.F. (1947) J. clin. Invest., 26, 1138.

KEATING, F.R., WANG, J.C., LUELLEN, T.J., WILLIAMS, M.M.D. POWER, M.H. and McCONAHEY, W.M. (1949) J. clin. Invest., 28, 217.

KEKWICK, A. (1960) Brit. med. J., 2, 407.

KELLGREN, T.H., BALL, J. and TUTTON, C.K. (1952) Quart. J. Med., 21, 405.

KERN, R.A. (1949) Amer. J. med. Sci., 217, 609.

KEYS, A. and BROZEK, J. (1953) Physiol. Rev., 33, 245.

KING, E.L. and HERRING, J.S. (1939) J. Amer. med. Ass., 113, 1300.

KOCHER, E.T. (1883) Arch. klin. Chir., 29, 254.

KREBS, H.A. and JOHNSON, W.A. (1948) Tabul. biol. Hague., 19, 139.

KREMER, M., GILLIAT, R.W., GOLDING, J.S.R. and WILSON, T.G. (1953) Lancet, ii, 590.

KYDD, D.M. and MAN, E.B. (1951) J. clin. Invest., 30, 874.

LAWSON, J.D. (1958) New Engl. J. Med., 259, 761.

LAMBERT, E.H. (1960) Personal Communication.

LAMBERT, E.H. and SAYRE, G.P. (1955) Amer. J. Physiol., 183, 636.

LAMBERT, E.H., UNDERDAHL, L.U., BECKETT, S. and MEDEROS, L.O. (1951) J. clin. Endocr., 11, 1186.

LERMAN, J. (1948) Quoted by Means, J.H. "The Thyroid and Its Diseases", 2nd Edition. Lippincott Co., London.

LLOYD, W.H. (1959) Brit. med. J., 1, 1208.

McCONAHEY, W.M., OWEN, C.A. and KEATING, F.R. (1956) J. clin. Endocr., 16, 724.

MACGREGOR, A.G. (1961) Lancet, i, 329.

MACGREGOR, A.G. and FARRELL, L.P. (1958) Scot. med. J., 3, 277.

MACGREGOR, A.G. and WAYNE, E. J. (1957) "Modern Trends in Endocrinology", Butterfield, London.

MACGREGOR, G.A. (1958) Lancet, ii, 612.

MACKENZIE, H.W.G. (1892) Brit. med. J., 2, 940.

MAGNUS, E. (1958) Lancet, ii, 749.

MAN, E.B., KYDD, D.M. and PETERS, J.P. (1951) J. clin. Invest., 30, 531.

MARTINELLI, L.D., QUIMBY, E.H. and HINE, G.J. (1948) Amer. J. Roentgenol., 59, 260.

MASON, A.S. and OLIVER, R. (1949) Lancet, ii, 456.

MASON, R.L., HUNT, H.M. and HURXTHAL, L.M. (1930) New Engl. J. Med., 203, 1273.

MEANS, J.H. (1948) "The Thyroid and Its Diseases", 2nd Edition, J.B. Lippincott, London.

MEANS, J.H., HERTZ, S. and LERMAN, J. (1940) Trans. Ass. Amer. Phycns., 55, 32.

MEANS, J.H. and RICHARDSON, E.P. (1929) The diagnosis and treatment of diseases of the thyroid. Oxford Monographs on Diagnosis and Treatment, IV, New York.

MULDOWNEY, F.P. (1957) Clin. Sci., 16, 163.

MURRAY, G.R. (1891) Brit. med. J., 2, 796.

MURRAY, I.P.C. (1958) Lancet, ii, 384.

MURRAY, I.P.C. and McGIRR, E. M. (1960) Brit. med. J., 1, 838.

MURRAY, I.P.C. and SIMPSON, J.A. (1958) Lancet, i, 1360.

MYANT, N.B., POCHIN, E.E. and GOLDIE, E.A.G. (1949) Clin. Sci., 8, 109.

ORD, W.M. (1878) Med-chir. Trans., 61, 57.

OYAMA, T. and TATSUOKA, M. (1956) Amer. Rev. Tuberc., 73, 472.

PERLMUTHER, M. and RIGGS, D.S. (1949) J. clin. Endocr., 16, 724.

PETERS, J.P., GERMAN, W.J. and MAN, E.B. (1949) J. clin. Endocr., 9, 1292.

PETERS, J.P. and MAN, E.B. (1943a) J. clin. Invest., 22, 707.

PETERS, J.P. and MAN, E.B. (1943b) J. clin. Invest., 22, 715.

PETERS, J.P. and MAN, E.B. (1950) J. clin. Invest., 29, 1.

PETT, L.B. and LePAGE, G.A. (1940) J. biol. Chem., 132, 585.

PLUMMER, H.S. (1923) J. Amer. med. Ass., 80, 1955.

PRICE'S TEXTBOOK OF MEDICINE (1956) Edited by D. Hunter, London, Oxford University Press.

QUERIDO, A., VAN DER WERFF, T.E.N., BOSCH, J.J., BLOM, P.S. and VAN GILSE, H.A. (1954) Acta med. scand., 144, 291.

QUIMLEY, E.H., WERNER, S.C. and SCHMIDT, C. (1950) Proc. Soc. exp. Biol., N.Y., 75, 537.

RECANT, L. and RIGGS, D.S. (1952) J. clin. Invest., 31, 789.

REITAN, R.M. (1953) Arch. Neurol. Psychiat. (Chicago), 69, 436.

RICHARDSON, J.S. (1956) "The Practice of Medicine", London, Churchill.

RIGGS, D.S., MAN, E.B., and WINKLER, A.W. (1945) J. clin. Invest., 24, 722.

RIGGS, D.S. (1952) Pharmacol. Rev., 4, 284.

ROBERTSON, J.D. (1944) Brit. med. J., 1, 617.

ROBERTSON, J.D. and REID, D.D. (1952) Lancet, i, 940.

ROWNTREE, T. (1949) J. Bone Jt. Surg., 31B, 505.

SCHILLING, R.S.F., HUGHES, J.P.W. and DINGWALL-FORDYCE, I. (1955) Brit. med. J., 1, 65.

SCHULTZ, A.L. and ZIEVE, L. (1956) Amer. J. Med., 20, 30.

SHEEDY, J.A. and LIENHARD, W.F. (1957) Ann. intern. Med., 47, 1184.

SHEEHAN, H.L. (1939) Quart. J. Med., 8, 277.

SIMMONDS, M. (1914) Dtsch. med. Wschr., 40, 322.

SIMPSON, J.A. (1956) J. Neurol. Psychiat., 19, 275.

SKANSE, B. (1949) Acta med. scand. Suppl. 235, 1.

SOFFER, L.J. (1956) "Diseases of the Endocrine Glands", London, Kimpton.

SPENCE, A.W. (1953) Clinical Endocrinology, Cassell, London.

SPENCE, A.W. (1959) Brit. med. J., 1, 706.

STARR, P. (1954) "Hypothyroidism - An Essay on Modern Medicine", Thomas, Springfield.

STEPP, W. and WENDT, H. (1937) Deut. Arch. klin. Med., 180, 640.

STERLING, K. and TABACHNICK, M. (1961) J. clin. Endocr., 21, 456.

STURGIS, C.C. (1922) Med. Clin. N. Amer., 11, 1251.

TAYLOR, S. (1961) Lancet, 1, 341.

THACHER, C. (1924) Amer. J. Dis. Child., 28, 25.

THACHER, C. and WHITE, P.D. (1926) Amer. J. Med. Sci., 171, 61.

THOMPSON, W.O., DICKIE, L.F.N., MORRIS, A.E. and HILKEVITCH, B.H. (1931) Endocrinology, 15, 265.

TUDHOPE, G.R. and WILSON, G.M. (1960) Quart. J. Med., 29, 513.

VAN ARSDEL, P.P. and WILLIAMS, R.H. (1956) Amer. J. Med., 20, 4.

WANG, I. (1957) Scot. med. J., 2, 165.

WAYNE, E.J. (1954) Brit. med. J., 1, 411.

WERNER, S.C. (1955) "The Thyroid", London, Cassell & Co.

WERNER, S.C., HAMILTON, H.B., LEIFER, E. and GOODWIN, L.D. (1950) J. clin. Endocr., 10, 1054.

WHITE, P.D. (1951) "Heart Disease", 4th Edition, New York, Macmillan.

WHITE, P.D. and AUB, J.C. (1918) Arch. intern. Med., 22, 766.

WILLIAMS, F.A. and HAINES, S.F. (1925) Amer. Heart J., 1, 67.

WILLIAMS, R.H. (1950) "Textbook of Endocrinology" London, Saunders.

WILSON, S.A.K. (1955) "Neurology", Vol. 1, Arnold, London.

WOOTON, I.D.P. and KING, E.J. (1953) Lancet, i, 470.

ZIEVE, L. and HILL, E. (1955a) Gastroenterology, 28, 759.

ZIEVE, L. and HILL, E. (1955b) Gastroenterology, 28, 785.

ZIEVE, L. and HILL, E. (1955c) Gastroenterology, 28, 914.

ZIEVE, L., VOGEL, W.C. and SCHULTZ, A.L. (1956) J. Lab. clin. Med., 47, 663.

ZONDEK, H. (1918) Munch. med. Wschr., 65, 1180.

APPENDICES I - VI

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 weather preference the patient should be asked first "What type of weather do you prefer?", rather than "Do you feel the cold unduly?". A suitable supplementary question would be "Do you sit nearer to, or further from the fire than you used to?".

Only symptoms of recent onset, or recently increased severity should be recorded, bearing in mind the duration of the main complaint. Where there is any doubt about the presence of a symptom, it should not be recorded. The criteria for individual symptoms are as follows:- (the features underlined indicate those later adopted for the clinical diagnostic index)

Dyspnoea on exertion - the age of the patient should be taken into account, the symptom only being significant if of recent onset.

Physical Tiredness refers to a feeling of unusual physical exhaustion during or after familiar physical effort, e.g. housework.

Mental Lethargy is shown by a disinclination to undertake tasks previously carried out routinely.

Muscle Weakness is a feeling of recent impairment of strength in arms or legs on performing familiar tasks.

Muscle Pain refers particularly to a tight constricting sensation or frequent cramps produced by familiar tasks.

Paraesthesiae are defined as sensations of tingling or numbness in the extremities.

Deafness - the age of the patient and the known presence of aural disease should be taken into account.

Memory (impaired mental power) may be noted as impairment of memory, often for minor matters, e.g. when shopping; loss of concentration, e.g. at work with difficulty in calculation; or in loss of interest in previous habits, e.g. reading, sewing, etc.

Temperature Preference is of high diagnostic significance and a decision should be reached only after supplementary questions. Suitable ones elicit comparison of habits with those of friends or relatives, discomfort when outside in cold weather, the habit of sitting close to the fire or the increased use of bed clothing or hot water bottles.

Hair changes - Untidiness refers to a change in the hair which produces difficulty in keeping it in place. A rapid loss of "permanent waves" may have been noticed.

Loss of hair should not be recorded in the male unless it is severe and there is no family history of baldness. In the female it is only of significance if considerable increase has been noted.

Decrease

Dryness of the skin should have been noted by the patient, not only on the hands, but on the back of the arms or front of the legs. The latter may be noted when removing stockings.

Nails - brittleness refers to greater tendency to break especially.

Appetite change - the question "How is your appetite?" should be an enquiry as to whether it is regarded as less than normal, normal or increased.

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

Constipation should be recorded only if there has been a recent change in bowel habits or much larger doses of purgatives have been necessary.

Hoarseness - the patient, friends or relatives, should have noticed a change in the quality of the voice which may have become huskier, deeper, or weaker especially if talking for prolonged periods.

Anginal Pain and Palpitations are only of significance if of recent onset.

Nervousness

Depression is important if there has been recent change in the attitude and reaction of the patient to matters, often minor, that previously would have caused no emotional upset.

Puffiness should be recorded if a change in the features has been noted by the patient or friends with swelling, especially of the eyes or submandibular region.

SIGNS

The following criteria should be fulfilled before a positive sign is recorded.

Speech - the voice should have a deep, croaking and monotonous quality and speech should be slow.

Slow Cerebration is defined as delay in answering questions or poorness of memory.

Movements Slow - the patient should be observed for slowness and fumbling while removing and replacing clothing. Movements may convey an impression of over-deliberation.

Skin - Coarse - the forearms should be examined for roughness and scaling.

Dry - no sensation of moisture should be present on the palms.

Cold - the palms are compared with those of the examiner taking into account the environmental temperature.

Yellowness - should be present in the face, but not the conjunctivae

Pallor - should be immediately obvious.

Nails - the edges should be examined for irregularity, breaks or roughness and the surfaces for longitudinal striations.

Periorbital Puffiness is a swelling of the periorbital tissues and is usually most evident in the infraorbital region.

Facial Puffiness - the face should appear swollen and puffy with the normal folds less apparent. The periorbital tissues should appear "full" with infraorbital swelling. The presence or absence of a "malar flush" should be noted.

Tongue - this should be recorded as large if, on protrusion, it appears broad and rounded, filling the breadth of the open mouth and at the same time appears unduly thick when viewed from the side.

Puffiness of the supraclavicular fossae or wrists - the fullness or the tissues in these sites should be sufficient to obliterate bony prominences.

Hair dry - the hair appears lustreless, hangs limply and, when felt between the finger tips, feels dry and gives no sensation of smoothness or oiliness. Sparseness should be marked; it should not be recorded in a male.

Pulse Rate - this is counted for one minute at the end of the examination.

Appendix II — Symptom and Sign Analysis

Results (A) Hypothyroid Patients

SYMPTOMS	DEFINITE GROUP				DOUBTFUL GROUP				ALL CASES				
	Female	Male	Total		Female	Male	Total		Female		Male		Total
No. of Cases	45	10	55	%	38	7	45	%	83	%	17	%	%
Dyspnoea on Effort	36	57	41	75	27	4	31	69	63	78	9	53	72
Tiredness	44	10	54	98	38	6	44	98	82	98	16	95	98
Lethargy	38	10	48	87	31	6	37	82	69	85	16	95	85
Muscle Weakness	30	6	36	65	22	3	25	55	52	63	9	53	61
Muscle Pain	17	3	20	36	14	2	16	35	31	37	5	29	36
Joint Pain	12	1	13	23	14	2	16	35	26	32	3	17	29
Paraesthesiae	31	4	35	63	19	2	21	46	50	61	6	35	56
Deafness	19	5	24	45	15	1	16	35	34	42	6	35	40
Memory	32	9	41	75	19	5	24	54	51	62	14	82	65
Preference for Hot	45	10	55	100	34	6	40	89	79	96	16	95	95
" Cold	0	0	0	0	2	0	2	5	2	2	0	0	2
Indifferent	0	0	0	0	2	1	3	7	2	2	1	6	3
Sweating Decreased	33	10	43	78	20	5	25	55	53	64	15	87	68
" Unchanged	11	0	11	20	17	2	19	42	28	34	2	12	30
" Increased	1	0	1	2	1	0	1	2	2	2	0	0	2
Hair Untidy	30	2	32	57	27	3	30	66	57	70	5	30	62
" Loss	21	4	25	45	14	2	16	35	35	42	6	35	41
" Stopped Growing	-	0	-	-	-	-	-	-	55	67	-	-	-
Skin Dry	39	8	47	85	25	5	30	66	64	77	13	77	77
Nails Brittle	22	3	25	45	15	1	16	35	37	45	4		41
" Stopped Growing	-	-	-	-	-	-	-	-	4	5	-	-	-
Appetite Increased	1	0	1	2	3	0	3	6			0	0	4
" Decreased	22	3	25	45	12	3	15	33	34	42	6	35	40
" Unchanged	22	7	29	53	23	4	27	60	45	55	11	65	56

Results (A) Hypothyroid Patients (cont.)

	Female	Male	Total		Female	Male	Total		Female		Male		Total
Weight Increased	35	10	45	82	29	3	31	68	63	77	13	77	76
" Decreased	3	0	3	5	5	1	6	14	8	10	1	6	9
" Unchanged	7	0	7	13	5	3	8	18	12	15	3	17	15
Bowels Constipated	25	3	28	51	22	4	26	57	47	57	7	41	54
" Diarrhoea	2	0	2	4	0	0	0	0	2	2	0	0	2
Hoarseness	38	6	44	80	26	4	30	66	64	77	10	60	74
Menstruation - Post Meno.	-	-	-	-	-	-	-	-	-	-	-	-	-
Amenorrhoea	2	-	-	-	1	-	-	-	3	-	-	-	1
Oligomenorrhoea	2	-	-	-	1	-	-	-	3	4	-	-	1
Menorrhagia	2	-	-	-	4	-	-	-	6	7	-	-	6
Anginal Pain	8	3	11	20	5	0	5	12	13	16	3	17	16
Palpitations	11	1	12	22	11	0	11	25	22	27	1	6	23
Nervousness	28	0	28	51	21	2	23	51	49	60	2	12	51
Depression	30	1	31	56	25	4	29	65	55	67	5	30	60
Puffiness	40	8	48	87	34	7	41	91	74	90	15	87	89

Appendix II — Symptom and Sign Analysis

Results (A) Hypothyroid Patients

SIGNS	DEFINITE GROUP				DOUBTFUL GROUP				ALL CASES				
	Female	Male	Total		Female	Male	Total		Female		Male		Total
No. of Cases	45	10	55	%	38	7	45	%	83	%	17	%	%
Speech Slow	27	8	35	65	16	5	21	46	43	53	13	77	56
" Hoarse	42	10	52	95	28	7	35	77	70	86	17	100	87
Cerebration Slow	24	5	29	54	14	5	19	42	38	46	10	59	48
" Normal	21	5	26	46	24	2	26	58	45	35	7	41	52
Movements Slow	37	9	46	84	22	5	27	60	59	72	14	82	73
" Normal	8	1	9	16	16	2	18	40	24	29	3	18	27
Skin Coarse	37	9	46	84	19	5	24	53	56	67	14	82	70
" Dry	38	10	48	87	26	5	31	68	64	78	15	87	79
" Cold	33	10	43	78	31	6	37	83	64	78	16	95	80
" Smooth	6	1	7	13	17	2	19	42	23	28	3	17	26
" Moist	6	0	6	11	12	2	14	31	18	22	2	12	20
" Warm	10	0	10	18	7	1	8	18	17	20	1	6	18
" Pale	23	5	28	51	19	3	22	49	42	50	8	47	50
" Yellowish	21	7	28	51	15	5	20	44	36	43	12	70	48
Nails Brittle	8	4	12	22	11	1	12	27	19	23	5	30	24
" Striated	8	5	13	24	13	5	18	40	21	26	10	60	31
" Normal	-	-	-	-	-	-	-	-	-	-	-	-	-
Face Puffiness	43	10	53	96	36	6	42	93	69	85	16	95	95
" Malar Flush	32	3	35	63	18	2	20	44	50	61	5	30	55
Peri-orbit. puffiness	40	10	50	90	30	6	36	80	70	85	16	95	86
Eyes Exophthalmos	7	2	9	18	1	1	2	4	8	10	3	17	11
" Lid Retraction	1	1	2	3	0	0	0	0	1	1	1	6	2
" Lid Lag	1	0	1	2	0	1	1	2	1	1	1	6	2
Tongue Large	26	6	32	58	22	6	28	62	48	58	12	70	60

Results (A) Hypothyroid Patients (Cont.)

	Female	Male	Total		Female	Male	Total		Female		Male		Total
Thyroid Palpable	7	1	8	15	11	1	12	26	18	22	2	12	20
" Firm	3	1	4	7	8	1	9	20	11	13	2	12	13
" Diffuse	1	1	2	3	1	0	1		2	2	1	6	3
" Nodular	3	0	3	5	4	1	5		7	9	1	6	8
Pulse/min. <60	4	1	5	9	2	1	3	7	6	7	2	12	8
" 60-69	17	7	24	43	14	1	15	33	31	37	8	47	39
" 70-79	15	1	16	29	12	4	16	36	27	32	5	30	32
" >80	9	1	10	18	10	1	11	24	19	23	2	12	21
Extremities Puffiness	24	4	28	51	26	3	29	58	50	61	7	41	57
" Oedema	4	1	5	9	0	0	0	-	4	5	1	6	5
Hair Absent	0	0	0	0	0	1	1	2	0		1	6	1
" V. Sparse	2	1	3	5	2	0	2	4	4	5	1	6	5
" Sparse	14	3	17	31	4	3	7	16	18	22	6	35	24
" Dry	36	51	41	75	28	6	34	76	64	77	11	65	75
" Coarse	6	1	7	12	11	1	12	23	17	20	2	12	19
Eyebrows Sparse	40	8	48	87	31	5	36	80	71	86	13	77	84

Appendix II — Symptom and Sign Analysis

Results (B) Euthyroid Patients

SYMPTOMS	DEFINITE GROUP				DOUBTFUL GROUP				ALL CASES			
	Female	Male	Total		Female	Male	Total		Female	Male	Total	
No. of Cases	45	10	55	%	44	6	50	%	89	16	105	%
Dyspnoea on Effort	20	2	22	40	30	3	33	66	50	5	55	52
Tiredness	21	2	23	42	38	6	44	88	59	8	67	64
Lethargy	5	0	5	9	13	0	13	26	18	0	18	17
Muscle Weakness	6	1	7	13	15	0	15	30	21	1	22	21
" Pain	5	1	6	11	11	1	12	24	16	2	18	17
Joint Pain	12	1	13	24	11	1	12	24	23	2	25	24
Paraesthesiae	7	0	7	13	7	2	9	18	14	2	16	15
Deafness	4	1	5	9	10	1	11	22	14	2	16	15
Memory	8	1	9	16	19	4	23	46	27	5	32	31
Preference for Hot	9	0	9	16	28	4	32	64	37	4	41	39
" Cold	8	0	8	15	4	1	5	10	12	1	13	12
" Indifferent	28	10	38	69	12	1	13	26	40	11	51	49
Sweating Decreased	3	3	6	11	11	1	12	24	14	4	18	17
" Unchanged	25	1	26	47	24	5	29	58	49	6	55	52
" Increased	17	6	23	42	9	0	9	18	26	6	32	31
Hair Untidy	7	0	7	13	22	1	23	46	29	1	30	28
" Loss	4	1	5	9	15	2	17	34	19	3	22	21
" Stopped growing	-	-	-	-	-	-	-	-	-	-	-	-
Skin Dry	3	1	4	7	9	2	11	22	12	3	15	14
Nails Brittle	7	2	9	16	10	2	12	24	17	4	21	20
" Stopped growing	-	-	-	-	-	-	-	-	-	-	-	-
Appetite Increased	2	0	2	4	6	0	6	12	8	0	8	8
" Decreased	4	1	5	9	10	1	11	22	14	2	16	15
" Unchanged	39	9	48	87	28	5	33	66	67	14	81	77

Results (B) Euthyroid Patients (cont.)

	Female	Male	Total		Female	Male	Total		Female	Male	Total	
Weight Increased	16	5	21	38	14	3	17	34	30	8	38	36
" Decreased	8	1	9	16	14	1	15	30	22	2	24	23
" Unchanged	21	4	25	46	16	2	18	36	37	6	43	39
Bowels Constipated	3	0	3	5	7	1	8	16	10	1	11	10
" Diarrhoea	0	0	0	0	0	0	0	0	0	0	0	0
Hoarseness	4	1	5	9	12	2	14	28	18	3	19	18
Menstruation												
Post-meno.												
Amenorrhoea					0		(0)					
Oligomenorr.					5		(5)					
Menorrhagia					0		(0)					
Anginal Pain	0	1	1	2	6	2	8	16	6	3	9	9
Palpitations	5	1	6	11	15	0	15	30	20	1	21	20
Nervousness	18	2	20	36	23	1	24	48	41	3	44	42
Depression	16	2	18	33	24	1	25	50	40	3	43	41
Puffiness	1	0	1	2	15	1	16	32	16	1	17	16

Appendix II -- Symptom and Sign Analysis

Results (B) Euthyroid Patients

SIGNS	DEFINITE GROUP				DOUBTFUL GROUP				ALL CASES			
	Female	Male	Total		Female	Male	Total		Female	Male	Total	
No. of Cases	45	10	55	%	44	6	50	%	89	16	105	%
Speech Slow	0	1	1	2	5	1	6	12	5	2	7	7
" Hoarse	7	1	8	15	16	5	21	42	23	6	29	28
Cerebration Slow	1	0	1	2	7	1	8	16	8	1	9	9
" Normal	44	10	54	98	37	5	42	84	81	15	96	91
Movements Slow	3	1	4	7	8	3	11	22	11	4	15	14
" Normal	42	9	51	93	36	3	39	78	88	12	90	86
Skin Coarse	2	1	3	5	5	2	7	14	7	3	10	10
" Dry	4	2	6	11	17	4	21	42	21	6	27	26
" Cold	12	4	16	29	17	2	19	38	29	6	35	33
" Smooth	43	9	52	95	39	4	43	86	82	13	95	90
" Moist	41	8	49	89	27	2	29	58	68	10	78	74
" Warm	33	6	39	71	27	4	31	62	70	10	80	77
" Pale	3	0	3	5	11	1	12	24	14	1	15	14
" Yellowish	0	0	0	0	5	1	6	12	5	1	6	6
Nails Brittle	7	2	9	16	9	2	11	22	16	4	20	19
" Striated	9	3	12	22	19	2	21	42	28	5	33	31
" Normal	33	6	39	71	20	2	22	44	53	8	61	58
Face Puffiness	2	1	3	5	21	4	25	50	23	5	28	27
" Malar Flush	1	2	3	5	8	1	9	18	9	3	12	11
Peri-orbit. puffiness	3	3	6	11	21	2	23	46	24	5	29	28
Eyes Exophthalmos	1	0	1	2	3	0	3	6	4	0	4	4
" Lid Retraction					1	0	1	2				
" Lid Lag					1	0	1	2				
Tongue Large	2	3	5	9	9	4	13	26	11	7	18	17

Results (B) Euthyroid Patients (cont.)

	Female	Male	Total		Female	Male	Total		Female	Male	Total	
Thyroid Palpable	3	0	3	5	9	0	9	18	12	0	12	11
" Firm												
" Diffuse												
" Nodular												
Pulse/min. <60	0	0	0	0	1	0	1	2	1	0	1	1
" 60-69	9	2	11	20	12	3	15	30	21	5	26	25
" 70-79	16	5	21	38	13	1	14	28	29	6	35	33
" >80	20	3	23	42	18	2	20	40	38	5	43	41
Extremities Puffiness	2	0	2	4	11	1	12	24	13	1	14	13
" Oedema	1	0	1	2	0	1	1	2	1	1	2	2
Hair Absent	0	0	0	0	0	0	0	0	0	0	0	0
" V. Sparse	0	0	0	0	5	1	6	12	5	1	6	6
" Sparse	4	4	8	15	8	1	9	18	12	5	17	16
" Dry	7	7	14	25	27	4	31	62	34	11	45	43
" Coarse												
Eyebrows Sparse	22	4	26	47	32	3	35	70	54	7	61	58

Appendix III — Symptom and Sign Analysis

"Iatrogenic" and "Pituitary" Hypothyroidism

SYMPTOMS	Following ^{131}I Female	Following ^{131}I Male	Following ^{131}I Total	%	Following Operation or Antithyroid Drugs	All Cases Following Treatment of Thyrotoxicosis	%	"Pituitary" Hypothyroidism	%
No. of Cases	28	7	35	%	18	53	%	15	%
Dyspnoea of Effort	15	5	20	57	10	30	57	11	73
Tiredness	25	7	32	91	17	49	93	15	100
Lethargy	21	7	28	80	16	44	83	12	80
Muscle Weakness	26	6	32	91	11	43	81	11	73
Muscle Pain	21	4	25	71	13	38	72	2	13
Joint Pain	4	1	5	14	7	12	23	4	26
Paraesthesiae	14	2	16	46	9	25	47	2	13
Deafness	4	2	6	17	3	9	17	4	26
Memory	16	4	20	57	15	35	66	10	67
Preference for Hot	21	6	27	77	15	42	79	14	93
" " Cold	1	1	2	6	0	2	4	0	0
" Indifferent	6	0	6	17	3	9	17	1	7
Sweating Decreased	13	5	18	51	13	31	58	12	80
" Unchanged	15	2	17	49	4	21	40	3	20
" Increased	0	0	0	0	1	1	2	0	0
Hair Untidy	20	4	24	68	14	38	72	9	60
" Loss	10	1	11	31	6	17	32	2	13
" Stopped growing	-	-	-	-	-	-	-	-	-
Skin Dry	22	6	28	80	14	42	79	7	47
Nails Brittle	10	3	13	37	13	26	49	3	20
" Stopped growing	-	-	-	-	-	-	-	-	-

"Iatrogenic" and "Pituitary" Hypothyroidism (Cont.)

SYMPTOMS	Following ^{131}I				Following Operation or Antithyroid Drugs	All Cases Following Treatment of Thyrotoxicosis		"Pituitary" Hypothyroidism	
	Female	Male	Total						
No. of Cases	28	7	35	%	18	53	%	15	%
Appetite Increased	4	0	4	11	0	4	8	0	0
" Decreased	15	3	18	52	10	28	53	8	53
" Unchanged	9	4	13	37	8	21	39	7	47
Weight Increased	24	7	31	89	18	49	93	7	47
" Decreased	1	0	1	3	0	1	2	4	26
" Unchanged	3	0	3	9	0	3	5	4	26
Bowels Constipated	11	2	13	31	11	24	45	5	33
" Diarrhoea	0	0	0	0	0	0	0	0	0
Hoarseness	23	7	30	86	15	45	85	2	13
Menstruation Post-meno.									
" Amenorrhoea									
" Oligomenorrhoea	1				1	2	4		
" Menorrhagia	3		3	9	4	7	13		
Anginal Pain	1	2	3	9	2	5	9	1	7
Palpitations	7	0	7	20	4	11	21	2	13
Nervousness	14	0	14	40	8	22	42	7	47
Depression	16	5	21	60	13	34	64	11	73
Puffiness	23	6	29	83	17	46	86	3	20

Appendix III — Symptom and Sign Analysis

"Iatrogenic" and "Pituitary" Hypothyroidism

SIGNS	Following ^{131}I Female	Following ^{131}I Male	Following ^{131}I Total	%	Following Operation or Antithyroid Drugs	All Cases Following Treatment of Thyrotoxicosis	%	"Pituitary" Hypothyroidism	%
No. of Cases	28	7	35	%	18	53	%	15	%
Speech Slow	22	5	27	77	9	36	68	10	67
" Hoarse	27	6	33	94	13	46	86	5	33
Cerebration Slow	14	5	19	54	9	28	53	10	67
" Normal	14	2	16	46	9	25	47	5	33
Movements Slow	11	4	15	43	15	30	56	9	60
" Normal	17	3	20	57	3	23	44	6	40
Skin Coarse	11	2	13	37	9	22	42	1	7
" Dry	17	4	21	60	15	36	68	9	60
" Cold	19	6	25	72	17	42	79	9	60
" Smooth	17	5	22	63	9	31	58	14	93
" Moist	11	3	14	40	3	17	32	6	40
" Warm	9	1	10	28	1	11	21	6	40
" Pale	3	1	4	11	5	9	17	13	87
" Yellowish	2	0	2	6	3	5	9	1	7
Nails Brittle	6	3	9	26	7	16	30	2	13
" Striated	9	2	11	31	4	15	28	6	40
" Normal	14	3	17	48	8	25	47	9	60
Face Puffiness	21	5	26	74	17	43	81	8	53
" Malar Flush	0	0	0	0	4	4	8	0	0

"Iatrogenic" and "Pituitary" Hypothyroidism (cont.)

SIGNS	Following ^{131}I Female	Male	Total		Following Operation or Antithyroid Drugs	All Cases Following Treatment of Thyrotoxicosis		"Pituitary" Hypothyroidism	
No. of Cases	28	7	35	%	18	53	%	15	%
Peri-orbit. Puffiness	24	7	31	89	14	45	85	6	40
Eyes Exophthalmos	10	3	13	37	7	20	38	0	0
" Lid Retraction	9	1	10	28	1	11	21		
" Lid Lag	0	0	0	0	2	2	4		
Tongue Large	7	3	10	28	7	17	32	3	20
Thyroid Palpable	16	2	18	51	6	24	48	0	
" Firm									
" Diffuse									
" Nodular									
Pulse/minute <60	0	1	1	3	1	2	4	3	20
" " 60-69	8	2	10	29	9	19	36	4	26
" " 70-79	10	3	13	37	6	19	36	7	47
" " >80	10	1	11	31	2	13	24	1	7
Extremities Puffiness	11	1	12	34	9	21	40	3	20
" Oedema	0	0	0	0	0	0	0	0	0
Hair Absent	0	0	0	0	0	0	0	0	0
"V.Sparse	0	0	0	0	0	0	0	0	0
" Sparse	4	2	6	17	3	9	17	1	7
" Dry	22	5	27	77	15	42	79	6	40
" Coarse								2	13
Eyebrows Sparse	11	1	12	34	7	19	36	12	80
Muscle "Tense"	17	6	23	66					

Appendix IV — Clinical Data and Results of Laboratory Investigation.

(a) "Definite Hypothyroid" Group

No.	Sex	Age yrs	% Average Wt.	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time secs.	E.C.G.
1	F	69	+23	28		476			.384	++
2	F	67	+ 3	32	-18	464	129	60	.476	
3	F	48	0	24	-22	535		56	.319	
4	F	58	+13	25	-17	545		56		++
5	F	63		26	-49	614	175	56	.334	
6	F	38	+10	27	-29	485		68		
7	F	53	+22	21	- 8	432			.325	
8	F	64		34	-26	555		56	.427	++
9	F	52		23		365	176		.331	
10	F	69	+17	33	-17	439	110	60	.353	
11	F	62	+ 4	24	-37	534	181		.294	
12	M	64		31		278			.420	
13	F	64	+ 9	30	-36	491	144	60	.511	+
14	F	56	+38	33	-34	521	133	62		
15	F	56	+32	22	- 8	475	157	60		
16	F	64	+11	18	-28	476	192	64	.350	+
17*	F	51	-13	24	-16	410	130	60	.290	++
18	F	54	+30	32	-11	378		60	.324	++
19	F	65	+ 2	26	-32	292	95	60	.308	+
20	F	61	- 5	28	-28	740	172	58	.959	++
21	F	63		24	- 6	300	157	60	.391	++
22*	F	66	+10	22	-14	249	104	56	.414	

(a) "Definite Hypothyroid" Group (cont.)

No.	Sex	Age	% Average Wt.	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time Secs.	E.C.G.
23	F	80	+ 3	22	- 8	364	93	66	.306	
24	F	59	+14	32	-27	500	187	64	.336	±
25	M	49	- 9	27	-16	200		64	.343	+
26	M	74	- 1	23	- 7	308	105		.415	
27	F	65	+34	28	- 5	314	68	66	.466	+
28	F	48		33	-21	333		68	.343	-
29	F	57		31	-18	322	97	60	.343	
30	F	35	-12	24		347	177		.322	
31	F	55		25		364				
32	F	46	-12	23	-31	360		62	.389	
33	F	44	+16	30		292				
34*	F	45	-11	16	-13	280			.340	
35	F	38	+12	37	-21	364		64	.423	++
36	M	40	+14	24	-17	340	79	72	.279	±
37	F	61		34		346			.329	
38	M	31	+33	28	-29	350	112	60		++
39	F	70	-11	11		417			.356	
40	F	36	+30	29	-26	370	72	72		++
41	M	35	- 5	31	-47	287	91	48	.316	++
42	F	53	+18	30		476			.301	±
43	F	27	+ 4	18	-34	326	57	58	.320	++
44	M	47	+16	19	- 7	422			.331	++
45	F	67	+17	30	-31	572		62	.319	++
46	M	46		30	-36	267		62		
47	F	53	+20	26	-16	160		76		
48	F	54	+ 5	24		668	121	66		++

(a) "Definite Hypothyroid" Group (cont.)

No.	Sex	Age	% Average Wt.	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time Secs.	E.C.G.
49	F	48	+38	26	-24	556		72		++
50	F	67	-16	27	-47	225	40	56	.342	++
51	F	62	+44	28	-19	347	154			
52*	M	54	0	32	-20	416	151	54	.318	++
53	F	48		17	-10	362			.294	
54	M	73	- 9	19		311				
55	F	29		39	-20	400				

*Hashimoto's thyroiditis

B.M.R. values underlined = Method "A".

Appendix IV — Clinical Data and Results of Laboratory Investigations

(b) Other cases with obvious hypothyroidism

No.	Sex	Age yrs	% Average Wt.	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time secs.	E.C.G.
218	F	55	+20	18	-23	208		64		++
219	F	68	+24	20	- 2	334				++
220	F	64		29		379				++
221	F	65		29		240				++
222	F	61		23	-30	560				±
223	F	69	- 5	31	-18	412				++
224	F	63	+ 3	27		262				
225	F	65		17		408				
226	F	60		32		300				
227	F	59			-13	293				
228	F	52	+43		-18	437				
229	F	64	+16			317				
230	F	67			- 6	500		56		±
231	F	64				193				
232	F	39		19					.328	
233	F	46	- 5	18		386	93			±
234	M	72	+ 2	26						
235	F	64		17		160			.342	
249*	F	43			-18	335				
250*	F	42	+12		-16	315				
251*	F	44			- 5					
252*	F	56	+19	16		300				

(b) Other cases with obvious hypothyroidism (cont.)

No.	Sex	Age	% Average Wt.	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time secs.	E.C.G.
253*	F	50	+ 4		-20	318				
254*	F	49				244				
286	F	52		+19						
287	F	60		+30						
288	F	37		+28						
289*	M	26	+ 8		-34	250				

*Hashimoto's thyroiditis

B.M.R. values underlined = Method "A".

Appendix IV - Clinical Data and Results of Laboratory Investigations

(c) "Doubtful Hypothyroid" Group

No.	Sex	Age yrs	% Average Wt.	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time Secs.	E.C.G.
56	F	48	+68	31	- 5	520	130	64	.405	
57*	F	45	+35	21	-14			58	.309	-
58	F	49	-12	27	-12	278	109		.360	
59	F	46	+34	19	-26	416	111	60	.325	
60	M	71	+10	30	-23					+
61	F	54		13		300			.279	-
62*	F	57		18	-13	347	93		.283	
63	F	53	- 3	17	-27	832	174	44	.321	++
64*	F	52	+ 7	18	-13	348		56	.280	++
65	F	54		11	-13	544		72		
66	F	56	+10	25	+ 9	235		60		
67	M	58		17		268	90		.286	
68	M	49		12		435			.348	
69	F	44	+ 3	13	-35	525		58	.314	++
70	F	52	-10	32	-18	435		52		±
71	F	33	+86	24	-29	294		80	.295	
72	F	66	+21	19	-13	298			.297	
73	F	47		27	- 6				.274	
74	F	44	+22	30	-31	464	229	58	.420	++
75	F	46		26		361				
76	F	26		7	-21	455			.345	
77*	F	61		19	+ 6	314	84	64	.498	±
78	F	60	+36	26	-12	256		78		+
79*	F	59	+ 4	24	-30	367	96	60		++

(c) "Doubtful Hypothyroid" Group (cont.)

No.	Sex	Age	% Average Wt.	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time secs.	E.C.G.
80	F	56	+10	25	$\underline{-25}$	642	130	56		++
81	F	37	- 3	30	$\underline{-29}$	360	131	64		++
82	F	38	+ 9	18	$\underline{-22}$	303	104	65	.291	++
83	M	63	-12	29	-43	290		68		++
84	F	58	-18	16	$\underline{-25}$	427	127	48	.365	±
85	F	64	-13	36	$\underline{-25}$	340	147	56	.258	+
86*	F	54		5	$\underline{-19}$	303	80	60	.297	++
87*	F	55	+ 8	12	- 2	421	56	66	.301	++
88*	F	69	-18	23	- 3	316	69	60	.301	
89*	M	59	+13	40	$\underline{-17}$	668	145	72	.309	
90	F	65	+ 7	19	$\underline{-27}$	303		58	.296	+
91	F	79	-17	0	- 4	412			.301	
92	F	67		24		309				
93*	F	50		27	$\underline{-12}$	520			.320	+
94	M	61		8	- 2	320			.330	++
95	M	50		12		340				
96	F	45		19		488			.354	
97	F	65		10		570			.309	
98	F	60		23	-13	456			.389	
99	F	34	+39	25	- 3	193	133		.401	++
100	F	45	- 9	21		364				

*Hashimoto's Thyroiditis

B.M.R. values underlined = Method "A".

Appendix IV -- Clinical Data and Results of Laboratory Investigations

(d) Other hypothyroid cases presenting initial diagnostic difficulty

No.	Sex	Age yrs	% Average Wt.	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time secs.	E.C.G.
236	F	54		24		373			.341	++
237	F	44	-16	17		381				-
238	F	35	+18	26		286			.302	
239	F	57		15		333				
240	F	55		21		400				
241	M	61		16		250			.274	
242	F	28		16		324			.324	
243	F	57		26						
244	M	51		5		276			.270	
245	M	35	+17		-36					
246	M	50			- 8	288				
247	F	56			-18	299				
248	F	58		14		303				
255*	F	58				390	71			
257*	F	45			-19	300				

*Hashimoto's Thyroiditis

Appendix IV — Clinical Data and Results of Laboratory Investigations

(e) "Doubtful Euthyroid" Group

No.	Sex	Age yrs	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time secs.
101	F	48	- 4		222		76	
102	F	52	- 1	+16	232	98		.356
103	F	59	-10		282	47		.245
104	F	67	- 9	+12	263	136	60	.217
105	F	57	- 5		222	28		.297
106	F	63	- 5	+ 5	366			.279
107	M	51	1	+15	196	46	76	.258
108	F	68	3		272			
109	F	61	2	+ 2	416	149		.273
110	F	55	-10	+ 7	203	96		.263
111	F	54	- 4		313			.252
112	F	40	5		242	80		.253
113	F	35	0	+ 4	235	52	64	
114	F	71	- 7	+17	167			.265
115	F	70	- 2	+ 9	282	60		.251
116	F	44	- 7		181	60		.251
117	F	64	-12	+30	121	28		.260
118	F	48	-13	+32	175	28	72	.264
119	F	64	4	+19	196	59	72	.256
120	F	54	-10	+ 5	232	41	62	.244
121	F	58	- 4		198			.268
122	F	50	6	+ 8	181	48		.247
123	F	48	-11	+26	179		72	.273

(e) "Doubtful Euthyroid" Group (cont.)

No.	Sex	Age	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time secs.
124	F	53	9	+34	270		80	
125	F	53	10	- 9	362	123	68	
126	F	50	7	+18	217	112	80	.237
127	F	50	6	- 7	245		66	
128	F	66	1	- 6	232	29	68	.277
129	F	64	0	-11	353	113	76	.265
130	F	67	- 3	+11	189	33	64	
131	F	33	-17	+18	278	40	66	.251
132	F	58	- 6	+19	287	91		.266
133	F	50	7	+ 5	154	47	78	.252
134	F	69	-12	+13	200	37		.261
135	F	62	2	+12	187		68	.301
136	F	62	- 9		256			.267
137	F	44	4		245	67	60	.257
138	F	65	- 7	+ 7	245	45	56	.274
139	M	58	8	-15	232	76	60	.238
140	F	42	- 5	- 4	256	91		.259
141	M	62	-10		222	125		.265
142	M	49	2	-16	220	100		.246
143	M	74	2	+ 8	439	54	68	.265
144	F	67	6	- 7	180		68	.278
145	F	53	-12	- 1	232	54	80	.375
146	F	44	- 1	+ 7	223			.221
147	F	52	2	+11	222	88		.256

(e) "Doubtful Euthyroid" Group (cont.)

No.	Sex	Age	Diagnostic Index	B.M.R. % Rob. & Reid	Cholesterol mg%	Carotene ug%	Sleeping Pulse Rate/min	Reaction Time secs.
148	F	48	3		250		70	
149	M	60	0	<u>- 8</u>	167	125	70	.267
150	F	46	1	- 5	160		72	

*Hashimoto's Thyroiditis

B.M.R. Values underlined = Method "A".

Appendix V — Results of Radioactive Iodine Studies

(a) "Definite Hypothyroid" Group.

No.	Gland Uptake % dose 24 or 48 hrs.	I.V. Clearance ml/min/1.73m^2	Urine Output % dose 6/8–24hrs	24–48hrs	0–48hrs	'T'
1	4	-14.2	35.0	14.7	71.7	0.88
2	2					
3			21.1	17.8	66.4	2.0
4	8		41.7	15.6	80.6	0.7
5	9				58.3	
6	8		24.5	16.5	83.6	2.1
7			22.6	16.4	79.2	1.9
8	2					
9	7			36.0		
10	11.5		27.0	8.5	58.5	1.5
11	6		38.6	24.7	81.4	0.57
12	8		28.2	27.5	74.7	0.90
13	2.6		48.2	10.8	82.4	0.6
14	4.5				91.7	
15	9.5		31.2	14.8	79.3	1.35
16	15			20.4	99.2	0.03
17*	14		27.8	20.1	67.1	1.0
18	1	- 8.46	41.5			
19	12.4		26.5	16.9	63.6	1.0
20	3		6.7	26.2	33.4	0.66
21	3		32.0	24.0	70.0	0.63
22*	43		12.6	12.3	58.7	4.6
23	2		35.0	36.3	87.7	0.53
24	9		30.0	17.0	95.0	1.7

(a) "Definite Hypothyroid" Group (cont.)

No.	Gland Uptake % dose 24 or 48 hrs	I.V. Clearance ml/min/1.73m^2	Urine Output % dose 6/8-24hrs	24-48hrs	0-48hrs	'T'
52*	18		27.1	20.1	81.3	1.5
53	5		27.7	9.7	63.4	1.47
54	5	- 7.3	29.8	16.5	70.2	1.14
55	2		24.8	16.7	66.7	1.51

Values underlined indicate 6-24 hour urinary collections and 'T' index based on this period.

*Hashimoto's Thyroiditis.

Appendix V -- Results of Radioactive Iodine Studies

(b) Other cases with obvious hypothyroidism

No.	Gland Uptake % dose 24 or 48 hrs	I.V. Clearance $ml/min/1.73m^2$	Urine Output % dose			'T'
			6/8-24hrs	24-48hrs	0-48hrs	
218	11	- 1.1	30.6	8.9	81.5	1.67
219	6	-12.1	24.7	22.7	52.8	0.47
220	3			23.2		
222	2			18.7		
223	2			24.4		
224	7		48.2	18.9	85.9	0.53
225	1		67.4	19.0	93.9	0.25
226	2		36.9	20.6	75.2	0.66
228	2		43.6	25.2	77.5	0.25
229	2		43.0	8.6	69.7	0.63
230	2		44.1	20.0	78.6	0.42
231	6		46.1	8.2	78.5	0.67
233	13				77.4	
234	11					
235	8		30.1	16.6	78.6	0.7
249*	17		29.0	10.0	82.0	2.13
250*	35	+26.1				
251*	50		13.5	4.8		
252*	13					
253*	29		27.5	7.2	61.3	1.6
254*	10	+ 5.3				
286	2		36.9	20.6	75.2	0.66
289*	1		37.2	12.2	73.7	0.51

Values underlined indicate 6-24 hour urinary collections and 'T' index based on this period.

***Hashimoto's Thyroiditis.**

Appendix V — Results of Radioactive Iodine Studies

(c) "Doubtful Hypothyroid" Group

No.	Gland Uptake % dose 24 or 48 hrs	I.V. Clearance ml/min/1.73m^2	Urine Output % dose 6/8–24hrs	Urine Output % dose 24–48hrs	Urine Output % dose 0–48hrs	'T'
56	8		40.2	17.6	80.5	0.7
57*	14		38.5	12.3	55.2	0.2
58	10		31.0	20.0	56.0	0.35
59	2		38.9	16.8	87.1	0.92
60	6	- 5.7	41.6	17.0	87.1	0.79
61	14		41.3	4.4	57.0	0.46
62*	15		25.2	15.2	68.3	1.6
63	3.4		29.9	18.6	69.8	1.02
64*	23	4.0	39.6	14.0	71.0	0.62
65	8.2		26.8	14.6	62.0	1.24
66			28.6	13.0	63.2	1.2
67	22			31.0		
68	17					
69	4	13.4	43.2	19.8	79.4	0.48
70	9	- 3.68	33.5	13.7	64.4	0.8
71	8	- 8.86	25.1	14.0	53.6	1.14
72	17		41.8	18.5	70.3	1.04
73	21		27.2	10.8	73.1	1.36
74	0		33.3	18.4	89.9	1.3
75	11					
76	1					
77*	32		22.1	10.5	67.1	2.3
78	19		15.3	12.6	53.4	3.1

(c) "Doubtful Hypothyroid" Group (cont.)

No.	Gland Uptake % dose 24 or 48 hrs	I.V. Clearance ml/min/1.73m^2	Urine Output % dose 6/8-24hrs	Urine Output % dose 24-48hrs	Urine Output % dose 0-48hrs	'T'
79*	31		24.2	11.6	65.5	1.9
80	17					
81	9			38.5		
82	4		25.9	7.5	82.0	2.3
83	5	0.25	33.6	11.2	55.0	0.55
84	7		38.7	16.8	61.3	0.24
85	15		31.8	12.9	88.9	1.6
86*	40					
87*	31	39.6	28.2	9.1	74.2	1.8
88*			1.3	6.0	47.0	4.4
89*	20		25.7	10.0	48.3	1.0
90	15		31.0	13.5	72.7	1.3
91	21	2.4	32.8	6.9	57.6	0.95
92	2					
93*	49					
94	7	- 4.8	28.4	11.6	71.0	1.54
95	8		30.3	21.4	61.3	0.51
93	18		37.8	17.3	27.3	0.76
97	13		28.4	13.7	77.1	1.6
98	3	18.1	25.8	11.5	59.5	1.45
99			33.4	16.2	67.3	0.8
100	9		24.5	13.5	63.2	1.6

Values underlined indicate 6-24 hour urinary collections and 'T' index based on this period.

*Hashimoto's Thyroiditis.

Appendix V — Results of Radioactive Iodine Studies

(d) Other hypothyroid cases presenting inital diagnostic difficulty

No.	Gland Uptake % dose 24 or 48 hrs	I.V. Clearance ml/min/$1.73m^2$	Urine Output % dose 6/8–24hrs	24–48hrs	0–48hrs	'T'
236	3					
237	4	– 3.6	<u>28.6</u>	10.3	80.0	<u>1.5</u>
238	2	– 4.8				
239	11					
240	12					
241	19	+ 4.2		14.2		
242	4		<u>49.0</u>	23.0	95.9	<u>0.5</u>
243	2	– 8.4	<u>44.0</u>	10.0	94.0	<u>1.04</u>
244	11	+ 1.0				
245	12		<u>18.2</u>	19.8	54.3	<u>1.6</u>
246	7		<u>32.7</u>	28.0	82.5	<u>0.81</u>
247	2		<u>53.0</u>	18.4	86.1	<u>0.32</u>
255*	25					
256*	20		<u>27.0</u>	6.8	73.4	<u>2.0</u>
257*	62	+66.5	<u>9.9</u>	2.7		

Values underlined indicate 6–24 hour urinary collections and 'T' index based on this period.

*Hashimoto's thyroiditis.

Appendix IV — Results of Radioactive Iodine Studies

(e) "Doubtful Euthyroid" Group

No.	Gland Uptake % dose 24 or 48 hrs	Urine Output % dose 6/8–24 hrs	24–48 hrs	0–48 hrs	'T'
101	42	27.1	5.3	66.4	2.0
102	32	20.0	4.9	55.7	2.8
103	47				
104	10				
105	77	10.9	1.3	43.6	6.7
106	20		1.2		
107	35	25.0	12.0	41.7	4.5
108	30	17.7	8.2	48.8	2.7
109	35	36.0	5.5	54.0	0.64
110	65				
111	38	25.8	9.8	52.9	1.27
112	60				
113	77				
114	65	20.4	6.7	50.6	2.3
115	62				
116	57	10.3	1.5	39.2	6.8
117	50				
118	41				
119	27				
120	58	12.9	7.5	49.0	4.7
121	26				
122	20	24.5	6.6	50.9	2.3
123	43	30.6	7.8	63.7	1.3

(e) "Doubtful Euthyroid" Group (cont.)

No.	Gland Uptake % dose 24 or 48 hrs	Urine Output % dose 6/8–24 hrs	24–48 hrs	0–48 hrs	'T'
124	21	24.4	8.9	76.5	2.3
125	27.3	15.1	3.1	58.0	4.5
126	54		13.1		
127	45	15.6	6.8	40.2	2.8
128	71	14.7	3.3	34.0	3.2
129	45				
130	49				
131	52	21.8	7.2	54.9	2.3
132	55	9.7	1.6	4.8	7.5
133	35	32.2	3.6	68.3	1.47
134	57				
135	34	14.8	1.4	41.0	4.1
136	53				
137	61	3.0	0.7	34.5	
138	29	21.6	7.8	50.9	4.2
139	45	15.5	4.0	50.5	3.95
140	24	15.4	5.0	58.7	4.2
141	29		15.3		
142	24		10.3		
143	54	9.0	0.9	48.9	8.3
144	44	11.8	2.8	37.4	5.1
145	64	9.8	1.7	27.5	6.1
146	33	32.4	5.4	70.6	1.43
147	38				

(e) <u>"Doubtful Euthyroid" Group</u> (cont.)

No.	Gland Uptake % dose 24 or 48 hrs	Urine Output % dose 6/8-24 hrs	24-48 hrs	0-48 hrs	'T'
148	43	<u>28.2</u>	5.3	64.4	<u>1.7</u>
149	34				
150	67	<u>8.2</u>	1.2	41.1	<u>9.4</u>

Values underlined indicate 6-24 hour urinary collections and 'T' index based on this period.

Appendix VI — Results of Investigations in Iatrogenic Hypothyroidism

(a) Following ^{131}I Therapy

Case	^{131}I Studies: Gland Uptake % dose	^{131}I Studies: I.V. Clearance ml/min/1.73m^2	^{131}I Studies: 48hr. PB^{131}I % dose/l.	B.M.R. % Robertson & Reid	Cholesterol mg%	Reaction Time secs.	Progress
151	10	7.1	0.18		378		No remission
153	2	-6.87	0.41		520	.346	"
154	45	22.8	0.65				"
157				+ 3	250	.248	"
159	4	-6.5	0.12		257	.348	"
161				-25	439	.313	"
163	1	-1.7	0.12		310	.320	"
168				-30	406	.228	"
169					416	.248	"
170	21	8.6	0.24				"
172	6	4.3	0.20	-35	571	.365	"
176				-36	245	.320	"
179						.308	"
180				-33	298	.330	"
186	3	-10.7	0.09				"
187	1	-10.4	0.03	+ 5	348	.340	"
189	2	+ 3.0	0.04		348		"
193	2	- 7.7	0.07		445		"
194	10	- 5.3	0.40				"
195	30	10.1	0.14				"
196	30	-11.0	0		264		"
197					447	.309	"
198	3	3.86	0.03				"

(a) Following ^{131}I Therapy (cont.)

Case	^{131}I Studies: Gland Uptake % dose	^{131}I Studies: I.V. Clearance ml/min/1.73m^2	^{131}I Studies: 48hr PB^{131}I % dose/l.	B.M.R. % Robertson & Reid	Cholesterol mg%	Reaction Time secs.	Progress
200	13	6.5	0.23				No remission
152				− 1	386	.261	Partial remis.
156	5	2.31	0.09		213	.257	"
162	39	48.0	0.99				"
166	51	71.2	0.65	− 3		.259	"
167	68	41.0	0.20				"
174					386		"
175	24	20.2	0.62			.242	"
183				0	321	.328	"
185					390	.232	"
190	26	28.6	0.68				"
191	29	14.0	0				"
199	24	14.6	0.11				"
155	24	16.1	0.43				Complete remis.
158	42	17.4	0.23		186		"
160	46	38.0	0.92				"
165	31	31.9	1.34				"
178				−13	281	.315	"
181				+12	370	.371	"

Appendix VI — Results of Investigations in Iatrogenic Hypothyroidism

(b) Post-thyroidectomy

Case	^{131}I Studies: Gland Uptake % dose	^{131}I Studies: I.V. Clearance ml/min/$1.73m^2$	^{131}I Studies: 48hr $PB^{131}I$ % dose/l.	B.M.R. % Robertson & Reid	Cholesterol mg%	Reaction Time secs.
201					334	
203				- 5	334	.294
204	7			-25	314	.541
205	2		0.08			.339
207				-13	439	.323
208						.346
209	2	-1.74	0.06			.373
210		-5.1	0			
211	10	4.8	0.23			.373
213					205	.289