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"Over 21,000 health centres for mothers and children receive assistance from U.N.I.C.E.F. (United Nations Children's Fund) and W.H.O. (World Health Organization). Their work and the health policies pursued jointly by the two international bodies were reviewed at a meeting held in Geneva from December 3 to 5. In the Eastern Mediterranean region, the main health problems in children with which the centres have to deal are malnutrition, diarrhoeal diseases, and respiratory and eye diseases. In Africa, also, malnutrition, particularly kwashiorkor, and malaria are very commonly seen. In the Americas the most common causes of disease and death in children are diarrhoea and respiratory infections, with nutritional disease as a probable third. These and other facts emerge from a detailed study by W.H.O. of selected mother and child health centres in all parts of the world." (W.H.O./54.)

CLINICAL AND METABOLIC STUDIES IN THYROID DISEASE*

BY

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In this lecture I shall first discuss the diagnosis and treatment of hypothyroidism. Though what I have to say will be concerned chiefly with the form which arises from primary disease of the gland, I shall also speak about post-therapy and pituitary types of hypothyroidism and about the clinical syndrome we call Hashimoto's disease. Finally, I propose to describe observations on certain changes in metabolism which take place in response to over- and under-activity of the thyroid gland.

Hypothyroidism arises from a diminution in the amount of circulating thyroid hormone and is usually the result of partial or complete destruction of the gland. I do not propose to use the terms myxoedema and hypothyroidism interchangeably. This is often done, but in my opinion myxoedema should be used to describe not a disease but a particular type of skin manifestation which occurs only in some cases of hypothyroidism. It is usually obvious in the severe forms of the disease but is rarely seen in mild cases or when hypothyroidism is secondary to hypopituitarism. When hypothyroidism is of moderate severity even experienced clinicians may differ when asked to say whether or not the physical sign myxoedema is present. The student should be taught, therefore, to recognize hypothyroidism when myxoedema is absent, and he is apt to be confused if the terms are regarded as interchangeable.

Until a few years ago the cause of the atrophy of the thyroid gland found in most cases of hypothyroidism was unknown, but there is now evidence that in many instances it may be produced through the agency of auto-immunizing mechanisms. In a small minority of cases of hypothyroidism the pituitary gland is the site of the primary lesion, but in these there is usually evidence of insufficiency of hormones other than thyrotrophic stimulating hormone (T.S.H.), and the full syndrome of panhypopituitarism (Simmonds's disease) can be distinguished clinically from primary hypothyroidism.

A common type of hypothyroidism seen in clinical practice is the result of overtreating thyrotoxicosis. This condition is of special interest, since the date of onset of the disorder can be placed within fairly narrow limits. The development of the condition is relatively rapid, and many of the clinical features of hypothyroidism tend to be accentuated so that the clinical picture differs somewhat from that of primary disease of the gland.

Recently a small group of patients has been recognized in which a genetic defect in enzyme systems has led to the production of iodinated compounds resembling the thyroid hormones but without their metabolic effects (see Stanbury and McGirr, 1957). These patients always have enlarged thyroid glands and present as goitrous cretins, though it is possible that this mechanism may also account for a proportion of adult cases of so-called sporadic goitre (McGirr *et al.*, 1959).

*The second of two Lumleian Lectures delivered before the Royal College of Physicians of London on April 14 and 16, 1959. The first lecture appeared in last week's issue.

Clinical Features of Primary Hyperthyroidism

I (Wayne, 1954) described the results of an analysis of the frequency with which the clinical features of thyrotoxicosis occur in patients with the disease, and I showed how this information could be used to throw light on the causes of diagnostic difficulty. Dr. I. P. C. Murray has carried out in my department a similar investigation on 150 cases of suspected hypothyroidism. These results indicate the relative diagnostic value of the clinical features of this disorder.

We began this investigation by listing all the information which we might subsequently require and setting it out on a comprehensive form. In order to minimize the effects of observer variation we next agreed on the criteria by which the symptoms and signs would be recognized. All patients suspected of being hypothyroid were referred to the one observer who, after completing the form, made a provisional diagnosis and arranged for special investigations to be carried out. These usually indicated the correct diagnosis, but it was confirmed by observing the patient's progress with or without specific therapy. In this way the 150 patients were separated into two groups: 55 cases of definite hypothyroidism in which the diagnosis was never in doubt, and a group of 95 cases termed "doubtful" in which it was not immediately clear whether the patient was or was not hypothyroid. After the final diagnosis was known this second group was divided into two subgroups: 45 cases ultimately proved to be hypothyroid which we have called "doubtful hypothyroid," and a group of 50 "doubtful euthyroid" cases in which hypothyroidism had been suspected by at least one physician but which were finally shown to be euthyroid.

One hundred cases of proved hypothyroidism were therefore investigated, of which 55 were "definite" and 45 "doubtful." A separate analysis of these groups revealed some interesting features, but they did not differ greatly and I have pooled the results. They are given in Table V, under the heading of "hypothyroidism." We also investigated 55 control cases matched by age and sex to the "definite hypothyroid" group, and the figures for these subjects are also shown in Table V. These subjects were not patients and were not attending a hospital or clinic; their average age was 55 years and 82% were women. When inspecting the figures in Table V it should be remembered that patients with hypothyroidism are predominantly middle-aged females.

TABLE V.—*Incidence of Signs and Symptoms in Cases of Proved Hypothyroidism, Suspected Hypothyroidism Shown Finally to be Euthyroid ("doubtful" Euthyroid), and in Normal Control Subjects*

Symptoms	Hypothyroidism (100 Cases) %	"Doubtful" Euthyroid (50 Cases) %	Normal Controls (55 Cases) %	Signs	"Doubtful" Hypothyroidism (100 Cases) %	"Doubtful" Euthyroid (50 Cases) %	Normal Controls (55 Cases) %
Tiredness (physical)	98	88	42	Voice hoarse ..	87	42	15
Lethargy (mental)	85	26	9	Cerebration slow	48	16	2
Paraesthesiae	56	18	13	Movements slow	73	22	7
Deafness ..	40	22	9	Skin coarse ..	70	14	5
Cold intolerance ..	95	64	16	Skin dry ..	79	42	11
Decreased sweating	68	24	11	,, cold ..	81	38	29
Hair loss ..	41	34	9	,, yellow ..	48	22	16
Skin dry ..	77	22	7	Malar flush ..	55	18	5
Appetite increased	4	12	4	Periorbital puffiness ..	86	46	11
Appetite decreased	40	22	9	Puffiness supraclavicular fossa and/or wrists ..	57	24	4
Weight increased	76	34	38	Pulse rate <60	8	2	0
Weight decreased	9	30	16	60–9 ..	39	30	20
Constipation	54	16	5	70–9 ..	32	28	38
Hoarseness	74	28	9	80+ ..	21	40	42

From the large amount of information obtained in this study I propose to discuss here only those features which show significant differences in frequency between the groups. It may be taken that symptoms or signs commonly found in hypothyroidism which do not appear in Table V—for example, brittleness of the nails —are found with almost equal frequency in either the "doubtful euthyroid" or control groups, and so cannot be regarded as having high diagnostic significance.

Cases making up the "doubtful euthyroid" group are of special interest since they had been referred for investigation because at least one clinician suspected they were suffering from hypothyroidism. It can be seen that the classical symptoms of hypothyroidism such as cold intolerance, decreased sweating, gain in weight, and constipation, occurred much more often in patients with the disease than in the others, though a complaint that the hair has a tendency to fall out is not very significant. On the other hand, among the physical signs, the examining physician recorded a dry cold skin and periorbital puffiness in a sufficiently large proportion of cases in the control groups to show that as isolated phenomena the diagnostic significance of these features should not be overestimated. These findings show how diagnostic error may occur, and emphasize the danger of diagnosing "subclinical" or "masked" hypothyroidism on the basis of the clinical features alone.

A large proportion of all the patients studied complained of physical tiredness, and it is only because 98% of those patients with proved hypothyroidism have this symptom that it has any diagnostic value at all. Mental lethargy, if of recent onset, is much more significant, and we include under this heading a disinclination to undertake familiar tasks as well as an inability to concentrate on the more important intellectual activities of our age, such as reading the newspaper, listening to the wireless, or watching television.

The physical signs which were most valuable diagnostically were those affecting the skin and the central nervous system.

The Skin

In hypothyroidism there is an extracellular deposition in the connective tissue of the skin of a metachromatically stained material which probably consists of combinations of a protein with the mucopolysaccharides hyaluronic acid and chondroitin sulphuric acid. The difference between myxoedematous and normal skin is, however, quantitative rather than qualitative (Gabrilove and Ludwig, 1957). The presence of this material is not clinically obvious in the early stages of hypothyroidism. It first becomes apparent round the eyes, where it produces the baggy swelling we have called periorbital puffiness. Later the dorsum of the hands, the wrists, and the supraclavicular fossae become puffy and look oedematous, though on pressure the skin does not pit. In a fully developed case this "myxoedema" is obvious, but in the early stages of hypothyroidism its presence may be revealed only by

comparing a contemporary photograph of the patient with one taken a year or so previously. A further photograph after a month's treatment with an active thyroid preparation will often show a change in the patient's facial appearance and may be diagnostically helpful. The precise nature of the changes which lead to the formation of myxoedematous tissue is not known.

Apart from the myxoedema, the skin is usually coarse, dry, cold, and yellow. Pallor and a malar flush were present in about half our cases, and were recorded much less often in the control groups. The coldness of the skin, in so far as it indicates vasoconstriction, and also its dryness, serve a purpose in reducing loss of heat, but the mechanisms by which these are brought about are unknown. The yellow colour of the skin is probably due to carotinaemia (Escamilla, 1942), and we found blood-levels of carotene greater than 120 mg./100 ml. in 57% of our cases of proved hypothyroidism. Carotene is the precursor of vitamin A in the body, and low serum values of this vitamin in hypothyroidism have been reported (Stanley, 1955). There is, however, little evidence that vitamin-A deficiency plays any part in the pathology of the disease, including its cutaneous manifestations.

Other ectodermal structures are also affected in hypothyroidism. Patients complain that the nails grow more slowly and that they are brittle and ridged. We were able to show this trend, but the differences between the hypothyroid and control groups were not statistically significant. In definite cases the hair tends to become sparse; it is drier and looks untidy even after careful attention, but these features are also seen to some extent in many middle-aged women.

A physical sign of hypothyroidism in which most students firmly believe, thinning of the outer third of the eyebrows, was present in about 80% of cases, but it was also seen in 70% of the "doubtful euthyroid" group and in 47% of the normal euthyroid controls. It is thus valueless as a diagnostic sign.

A distinctive type of hoarseness occurs in severe cases of hypothyroidism, and is chiefly due to thickening of the vocal cords. In severe cases the tongue tends to be larger than normal, and this, together with dryness of the throat, gives rise to that peculiar throaty hoarseness which is highly characteristic of the full syndrome.

The Nervous System

Most cases of hypothyroidism show some disturbance of cerebral function. This may be of all degrees of severity from a slowing of activity which has to be demonstrated by objective tests to psychotic states such as acute myxoedematous madness. The average case shows some loss of memory and somnolence, and in our series mental lethargy as indicated by a disinclination for physical or mental effort was especially common. Slowness and clumsiness of movement is a valuable sign, since it is not usually found in normal subjects, even in the older age-groups.

Slowness of cerebration is a significant feature of hypothyroidism. Though we elicited this sign on physical examination in only half the cases, a much higher incidence is found if more sensitive techniques are used. For example, a more precise method of assessing defects in the higher mental processes is to estimate the *reaction time*. Murray (1958), working in my department, has devised a simple and rapid method of doing this. It involves relatively little co-operation from the patient and is well within the capacity of even the most severe case. He found that the reaction time was lengthened in 46 out of 50 hypothyroid patients. It decreased in 25 patients who were tested before and after treatment and diminished in parallel with other evidence of improvement (Fig. 9). Measurements of the reaction time provide, therefore, a relatively rapid method of assessing the response to therapy. Murray also showed that dexamphetamine sulphate shortens the reaction time of hypothyroid patients, and administration of this drug, by masking some of the features of the disease, may increase diagnostic difficulties.

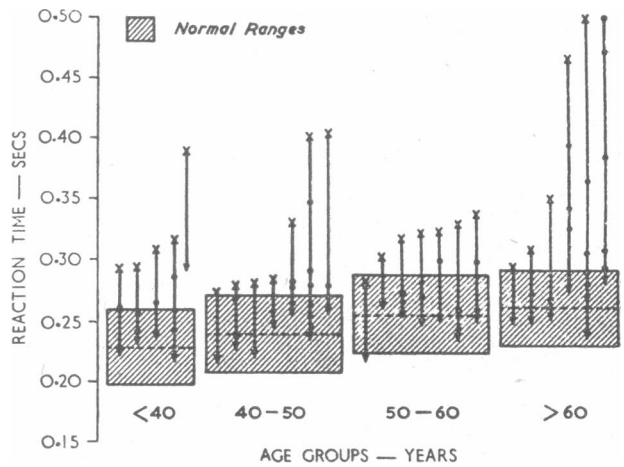

FIG. 9.—Effect of therapy on reaction times of 25 hypothyroid patients; ×, initial reading; ●, readings during period of control; ↓, final reaction time when patient was euthyroid.

The changes in reaction time almost certainly reflect changes in cerebral function rather than alterations in nerve conduction or delay in the reflex arc. There are, however, alterations in the peripheral nerves in hypothyroidism, and these may produce symptoms and hence be of practical importance in diagnosis. Acroparaesthesiae in hypothyroid subjects have been noted by several observers and have been attributed to a peripheral "neuritis" or "neuropathy." Numbness or "pins and needles" in the hands was reported by 56% of our cases and was a diagnostically useful feature. These symptoms often tended to occur in the course of activities which involved the hands, or during the night, preventing sleep. Murray and Simpson (1958) have made a clinical and electromyographic study of this phenomenon. The median nerve was usually involved, and in addition to the paraesthesiae there was often some evidence of motor paresis. There was no generalized abnormality of nerve conduction, but slowing of conduction in the median nerve in the neighbourhood of the wrist was often demonstrated.

All the findings pointed to compression of this nerve in the carpal tunnel similar to that found in the well-known carpal-tunnel syndrome. The evidence suggested that the accumulation of myxoedematous tissue under the flexor retinaculum was the cause of the compression. There was no correlation between the severity of the hypothyroidism and the presence of paraesthesiae. The impairment of conduction seemed to occur more often in those who were overweight, and was relieved after treatment with thyroxine. This syndrome is of more than theoretical interest. Until it is

generally recognized that an incomplete carpal-tunnel syndrome may be a manifestation of hypothyroidism some patients will be subjected to unnecessary operations.

Deafness

Deafness was given as a symptom by 40% of our cases, and objective tests confirmed its presence in a high proportion of these. The deafness of hypothyroidism has been investigated by Howarth and Lloyd (1956), who conclude that it is perceptive in type, and that if a conductive type of deafness is also present some other factor should be sought. Great improvement follows treatment with thyroxine, and for this reason it is important that hypothyroidism should be considered as a possible cause of perceptive deafness.

Cardiovascular System

Profound alterations take place in the cardiovascular system in hypothyroidism, but few are of diagnostic help. We have already noted the coldness of the skin, which is due to a diminished blood-flow. We recorded dyspnoea on exertion in 75% of our 100 cases of hypothyroidism, but since the incidence was over 50% in the control subjects this symptom is of little diagnostic value. Angina of effort occurred in 16% of hypothyroid cases and in 9% of the control group. Pulse rates below 60 a minute were found in only 8% of hypothyroidism, but when found tend to confirm the diagnosis. Pulse rates above 80 a minute were found twice as often in euthyroid as in hypothyroid subjects, and are therefore of some diagnostic value.

A Clinical Diagnostic Index for Hypothyroidism

We have used our analysis of the clinical features to produce a diagnostic index for hypothyroidism similar to the one I have already described for thyrotoxicosis. Weighting factors have been allotted to 15 symptoms and 11 signs according to their relative frequency in the different groups of patients. For example, physical tiredness, which has relatively little value diagnostically, is allocated a score of +1. On the other hand, mental lethargy scored +3 points and paraesthesiae +2 points. Negative scores were awarded to clinical features which are infrequently found in hypothyroidism. Thus a preference for cold scored −3 points and a loss of weight −2 points. The algebraic sum of the scores gives the diagnostic index.

I do not propose to reproduce our full scoring system or to describe the rigid criteria laid down for the recognition of symptoms and signs. Most of the results have been obtained by one observer, and have not yet been fully subjected to observer-variation studies. When these are complete they may show that it is necessary to modify some of the weighting factors—that is, the scores for individual clinical features.

We found that the total scores were quite different in a series of 55 definitely hypothyroid patients and a series of normal euthyroid persons. Members of the first group, with one exception, scored more than +15 and all those in the second group less than +5. We have also applied these scores to the two series of cases we have called "doubtful euthyroid" and "doubtful hypothyroid"; that is to say, cases in which some clinician had found diagnostic difficulty. Discrimination was good, though 19% of the cases fell in the range between +5 and +15 which we call the "equivocal range" and which indicates that further investigation is necessary. These findings, together with those in thyrotoxicosis, confirm the generally accepted view that hypothyroidism is more difficult to diagnose clinically in the doubtful case.

Clinical Features of Post-Therapy and Pituitary Hypothyroidism

We have also studied the incidence of some of the clinical features of hypothyroidism in two other series of cases. The first of these consisted of 53 cases in which hypothyroidism followed the treatment of thyrotoxicosis: 35 had received ^{131}I, 14 had been subjected to operation, and 4 had been treated with antithyroid drugs. The second series consisted of 15 cases of panhypopituitarism; two of these were examples of pituitary necrosis (Sheehan's syndrome) and three had chromophobe adenomas. Table VI shows the results

TABLE VI.—*Incidence of Symptoms and Signs in Primary, Post-therapy, and Pituitary Hypothyroidism*

Symptoms	Hypothyroidism			Signs	Hypothyroidism		
	Primary (100 Cases) %	Post-therapy (53 Cases) %	Pituitary (15 Cases) %		Primary (100 Cases) %	Post-therapy (53 Cases) %	Pituitary (15 Cases) %
Muscle pain	36	72	13	Voice hoarse ..	87	86	33
,, weakness	61	81	13	Skin coarse ..	70	42	7
Paraesthesiae	56	47	13	,, yellow ..	48	9	7
Deafness	40	17	26	Malar flush ..	55	8	0
Nails brittle	41	20	16	Periorbital puffiness ..	86	85	40
Weight increased	76	93	47	Puffiness supra-clavicular fossa and/or wrists	57	40	20
Weight decreased	9	2	26				

for those clinical features, the incidence of which differed significantly from that found in our main series of 100 cases of primary hypothyroidism. It should be noted that because of the small number of cases of panhypopituitarism large differences in the percentage incidence of symptoms and signs are necessary before statistical significance between this group and the other groups is achieved. For example, differences of about 40% between the last and first columns are usually necessary before statistical significance ($P<0.05$) is obtained. On the other hand, a difference of 20% between the first two columns is usually significant. These percentages are given as a rough guide; the actual figures depend, of course, on the number of cases showing a given phenomenon, and tests of significance must be applied separately to each clinical feature.

The results reveal several points of interest. When thyrotoxicosis is overtreated the patient is relatively quickly subjected to a change from over- to under-activity of the thyroid gland and symptoms therefore appear rapidly. Since she is usually under medical supervision the condition is recognized at an early stage and there is less time for the more chronic manifestations to develop. This explains the smaller proportion of patients in this group with cutaneous manifestations such as coarseness and yellowness of the skin and brittleness of the nails. Nevertheless, an equal proportion had a hoarse voice and periorbital puffiness. A much smaller number were deaf and a much greater proportion complained of muscle pain. The latter is

a curious phenomenon to which attention has been drawn before (Blomfield *et al.*, 1955) but upon the existence of which doubt has recently been cast (Blomfield *et al.*, 1959). The present survey, however, confirms its existence, though the mechanism of its production is not clear. Werner (1955) also refers to muscle spasm as an early symptom of developing hypothyroidism after ^{131}I therapy or thyroidectomy and points out that Kocher (1883) made this observation in the classic paper in which he described this operation for the first time.

When hypothyroidism occurs as part of the syndrome of panhypopituitarism the clinical features differ in several respects from those seen in primary disease of the thyroid. Thus those manifestations which depend on alterations in the skin are less marked. Table VI shows that in our series the skin was less often coarse and less frequently had a yellow tinge; a malar flush was not present in any of the cases and periorbital puffiness was less common. The histological appearance of the skin is, however, similar to that in primary hypothyroidism (Gabrilove and Ludwig, 1957). In hypopituitarism fewer cases have brittle nails and the voice is rarely hoarse. These differences may be due to the fact that the skin in panhypopituitarism is influenced by deficiencies of several hormones. We know, for example, that in pure pituitary dwarfism lack of the growth and gonadotrophic hormones is associated with a soft delicate skin and silky hair. Hubble (1959) suggests that in panhypopituitarism the secretion of the growth and gonadotrophic hormones is first diminished and this is followed by a diminution in the secretion of corticotrophin and thyrotrophic stimulating hormone. In panhypopituitarism, therefore, the eventual deficiency of thyroid hormone will affect skin and related structures which are already abnormal.

It is important that the clinician should always consider the possibility that any case of hypothyroidism may be secondary to panhypopituitarism, since treatment of the two conditions differs. Many patients in this group are parous women with a history of postpartum haemorrhage, failure to lactate, and subsequent amenorrhoea. There are, however, a variety of other aetiological factors, and the true nature of the underlying cause of the hypothyroidism may be overlooked. Extensive laboratory investigation is often necessary and the interpretation of the results is not always easy, since hypothyroidism may itself lead to secondary depression of gonadal and adrenal function.

Special Tests for Hypothyroidism

When the clinician fails to recognize an obvious case of hypothyroidism it is often because the possibility of this condition has not entered his mind. Once suspicion is aroused, a full history and examination will confirm the diagnosis. Mild degrees of hypothyroidism, however, may be difficult to recognize, and our "doubtful" group of patients—that is to say, those about which doubt has arisen in at least one observer's mind—finally divided itself into 45 hypothyroid and 50 euthyroid cases. It is in this group that laboratory investigations are time-saving, since the only alternative is to observe the response to specific therapy. When hypothyroidism is the result of the overtreatment of thyrotoxicosis or is secondary to panhypopituitarism special problems of diagnosis arise, and much recent work has been directed to tests for use in these conditions.

We have attempted to determine the relatively reliability of a large number of tests for hypothyroidism. Full details will be published later. Fig. 10 shows in summary form the results in cases of untreated proved hypothyroidism of all degrees of severity. We have included only those tests which we found to be diagnostically valuable, and there seems to be no significant difference in their reliability. Estimation of the reaction time correlates equally well with the final diagnosis and is a relatively simple method of following the progress of patients under treatment.

Basal Metabolic Rate.—We used the same technique as in the investigation of thyrotoxicosis. Using the reference standards of Robertson and Reid (1952), we found that the basal metabolic rate (B.M.R.) agreed with the final diagnosis in 77% of cases. If a less rigid technique was used and fewer measurements were made we found that the correlation was less satisfactory.

Chemical Estimation of Protein-bound Iodine.—Macgregor and Farrell (1958) estimated the P.B.^{127}I in 82 hypothyroid patients and found that only nine had values greater than 3 μg./100 ml. We have adopted their method and have already found it of diagnostic

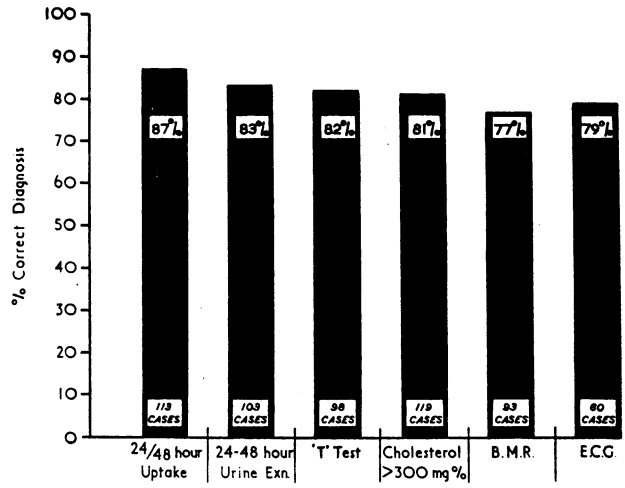

FIG. 10.—Comparison of the diagnostic accuracy of various laboratory tests for hypothyroidism. The first three columns refer to tests using ^{131}I.

value in patients with suspected mild hypothyroidism. In this we agree with Fraser (1956), but we have found that the 24- or 48-hour uptake of ^{131}I is at least as reliable an index in this type of case. We have little doubt, however, that as our experience of the estimation of P.B.^{127}I increases we shall come to rely upon it to a greater extent.

Radioactive Iodine.—Though in the diagnosis of thyrotoxicosis we found the four-hour uptake of ^{131}I by the gland and the plasma activity at 48 hours very helpful, they are of little assistance in hypothyroidism. The uptake of ^{131}I by the gland 24 or 48 hours after administration of the dose is as good a measure of diminished thyroid function as other tests using radioactive iodine and has the advantage that it is simple to carry out. The lower limit of our normal range at these times is 20% of the administered dose. Other useful indices are the proportion of ^{131}I excreted during

the 24–48 hours after the isotope has been given, and Fraser's 'T' test (Fig. 10). The intravenous clearance test also gives accurate results, and has the advantage that the short-lived isotope ^{132}I can be used instead of ^{131}I. When Hashimoto's disease is suspected, special considerations apply and these are considered later.

Serum Cholesterol.—This estimation, which is of little diagnostic value in thyrotoxicosis, is helpful in hypothyroidism. It has the advantage of being readily available to any clinician who has access to a biochemical laboratory. We found that 81% of our cases had serum cholesterol levels above 300 mg./100 ml. (Fig. 10), and in only 6% of cases was the level below 250 mg. It should be remembered that high levels of serum cholesterol are found in numerous other conditions—for example, in the nephrotic syndrome, xanthomatosis, diabetes mellitus, and pregnancy. A high total serum cholesterol is only specifically indicative of hypothyroidism if the cholesterol-phospholipid ratio remains normal (Peters and Man, 1950). The fall of serum cholesterol which occurs when hypothyroidism is treated with thyroxine may be used as an additional diagnostic test.

Electrocardiogram in Hypothyroidism.—The electrocardiogram is a valuable and too-little-used aid to diagnosis. It is easy to carry out and involves no discomfort to the patient. In hypothyroidism the curves show a relatively slow heart rate and the voltage is reduced; the T waves are flattened, isoelectric, or inverted; sometimes there are alterations in the ST segment. Repetition of the investigation after several weeks' treatment with L-thyroxine sodium may show a reversion towards normal and thus confirm the diagnosis. One experienced observer examined electrocardiograms from our series of hypothyroid and control euthyroid cases. He did not know the final diagnosis at the time. Of 60 cases which proved eventually to be hypothyroid he concluded that 37 (62%) had electrocardiograms characteristic of hypothyroidism. In 10 cases (17%) he thought that the curves were strongly suggestive of the disease. This shows that a surprisingly high proportion (79%) of electrocardiograms yield confirmatory evidence of hypothyroidism (Fig. 10).

Tests of Thyroid Function in Post-Therapy Hypothyroidism.—Serial electrocardiograms and estimations of serum cholesterol are the simplest methods of confirming early post-therapy hypothyroidism, and if doubt remains estimations of the B.M.R. should be made. In my first lecture I pointed out that tests using radioactive iodine are apt to be misleading in patients who have been treated and rendered euthyroid by thyroidectomy or ^{131}I. This is also true if mild hypothyroidism develops, and those tests which depend on the plasma radioactivity are especially unreliable. The uptake of the gland 24 or 48 hours after the administration of the dose is more dependable, but we find that the most useful guide is the chemical estimation of P.B.^{127}I. It should be remembered that after treatment with ^{131}I some patients pass through a phase of temporary depression of thyroid function and also that a few cases may develop permanent hypothyroidism years after operation or ^{131}I therapy.

Tests of Thyroid Function in Pituitary Hypothyroidism.—Panhypopituitarism causes failure of target organs other than the thyroid gland, and special tests which measure adrenal or gonadal function are necessary. Thus when panhypopituitarism occurs in post-menopausal females, estimation of F.S.H. is said be to one of the best tests (VanArsdel and Williams, 1956). Thyroid function often diminishes more slowly in hypopituitarism than when there is primary disease of the thyroid gland; it is not surprising, therefore, that many tests tend to give inconclusive results. We have found, as others have done, that there are patients with panhypopituitarism who show clinical evidence of hypothyroidism and in whom several tests of thyroid function may give normal results. Primary and pituitary hypothyroidism are best distinguished by measuring the ^{131}I uptake by the gland before and after the administration of T.S.H. We measure the actual uptake by the gland 24 hours after the dose has been given, but other indirect indices which depend on thyroid uptake may be used. A control test is carried out and the test is repeated after the administration of 10 units of T.S.H. A significant response is indicated by an increase in the 24-hour gland uptake of more than 15% of the original uptake. We found that all 17 cases of primary hypothyroidism tested showed less than a 5% increase in uptake after T.S.H. administration, whereas six out of nine cases of pituitary hypothyroidism gave a significant response. This test may also be used to decide whether a patient who is receiving thyroid hormone really requires it. T.S.H. increases the uptake of ^{131}I in the normal gland in which function has been suppressed by the administration of thyroxine or thyroid extract, but cannot do so in the functionless gland of true hypothyroidism. The response of T.S.H. is also greatly impaired in Hashimoto's disease with or without hypothyroidism.

Treatment of Hypothyroidism

In 1891 Murray reported the successful treatment of myxoedema by thyroid extract given subcutaneously. The patient received daily injections for 30 years and died at the age of 74. Fox (1892) and MacKenzie (1892) independently showed that oral administration of thyroid was equally effective. After Harington (1926) and Harington and Barger (1927) had isolated and synthesized thyroxine the racemic compound was for a time included in the *British Pharmacopoeia,* but the preparation was little used, since it was expensive and was said to be erratically absorbed. L-Thyroxine sodium, which is in the current *British Pharmacopoeia,* was shown by Hart and Maclagan (1950) to be an effective and reliable alternative to thyroid extract. It has the great merit of being a well-defined chemical compound of constant composition, and for this reason I have used it since it first became commercially available. Thyroid *B.P.* is standardized on the basis of its iodine content and is known to diminish in potency if kept for a long time and especially if exposed to moisture and heat. Macgregor and Farrell (1958) have collected a series of cases with clinical evidence of hypothyroidism and with low P.B.^{127}I levels though they were receiving thyroid. When they were given L-thyroxine sodium in recognized equivalent doses (1 gr. (65 mg.) of thyroid is equivalent to 0.1 mg. of L-thyroxine sodium) clinical improvement occurred, the serum cholesterol fell, and the P.B.^{127}I rose to normal values. We have confirmed Macgregor's findings using other tests of thyroid function.

Treatment with thyroxine is said to be expensive (Goodman and Gilman, 1955). The cost of the usual

maintenance dose is, however, one-fiftieth of that of the usual maintenance dose of cortisone, and the difference between treating a patient with thyroid *B.P.* (1 g. (65 mg.) a day) and L-thyroxine sodium (0.1 mg. a day) at hospital prices is about 2s. 6d. a year. There seems no justification for the continued use of thyroid.

Thyroxine should always be given cautiously in hypothyroidism. Low doses, with a very gradual increase, are necessary in older patients, especially when there is either a history of angina or an electrocardiogram which suggests the presence of coronary disease. I have seen and heard of several patients with hypothyroidism whose lives have been dramatically shortened by the over-enthusiastic administration of thyroid in an attempt to afford rapid relief of their symptoms. It should also be remembered that patients with panhypopituitarism may react adversely to thyroid or thyroxine, and as a rule it is wise to treat any adrenocortical insufficiency first.

Several compounds with a similar action to thyroxine have recently been discovered, most notably triiodothyronine and triiodothyroacetic acid (Gross and Pitt-Rivers, 1952; Haringon and Pitt-Rivers, 1952; Pitt-Rivers, 1953). The amount of triiodothyronine equivalent to 0.1 mg. of L-thyroxine sodium is 20 μg. and it acts much more rapidly than thyroxine. Apart from its value in making observations in the course of clinical investigations in which rapid effects are required, it is used in the treatment of "myxoedema coma," a rare complication of hypothyroidism. The effect of this drug passes off rapidly when administration ceases, and it is therefore of value in the management of cases of carcinoma of the thyroid receiving repeated doses of ^{131}I (Halnan and Pochin, 1958). It would seem to have no advantages over thyroxine in the routine treatment of hypothyroidism.

Cases have been described which have low basal metabolic rates and which respond to triiodothyronine but not to thyroid extract or in a few cases to thyroxine (Kurland *et al.*, 1955; Tittle, 1956). It is suggested that there may be a failure of target-organ response at the cellular level, and the clinical syndrome of metabolic insufficiency—"hypometabolism without hypothyroidism"—has been invented to explain the findings. The symptoms of this disorder, which are said to be "lethargy, easy fatigability, nervousness, irritability, sensitivity to cold, headache, musculo-skeletal pain, diminished sexual potency and menstrual irregularity" (Kurland *et al.*, 1955), are so similar to those which are also alleged to be cured by vitamin supplements, "tonics," and "ataraxics," that the relief by triiodothyronine can hardly be regarded as convincing evidence of the existence of a specific syndrome. It would be necessary to carry out a double-blind trial before this concept could be accepted. Some patients to whom the label hypometabolism has been attached may well be examples of genuine hypothyroidism treated with preparations of thyroid of low biological activity. Their response to triiodothyronine would then be at least as striking as that noted by Macgregor, who used the more slowly acting thyroxine.

Hashimoto's Disease

A most important and dramatic recent discovery in the field of thyroid disorders has been the demonstration that autoimmune processes may play a part in the production of Hashimoto's disease. Evidence has been produced which suggests that patients with this disease become immunized to their own thyroglobulin so that a progressive destruction of the gland occurs from the interaction of thyroglobulin with auto-antibodies which can be identified in the blood. The train of events leading to this discovery, which was made by Roitt *et al.* in 1956, and the important repercussions on our attitude to many other disease processes have been reviewed in several recent articles (*Lancet*, 1958, 1959; *Scottish Medical Journal*, 1959).

Hashimoto's disease is known by several other names—for example, lymphadenoid goitre, Hashimoto's thyroiditis, struma lymphomatosa, chronic lymphoid thyroiditis, and autoimmunizing thyroiditis. Hashimoto (1912) described a condition which is comparatively rare and is characterized by hypothyroidism and a diffuse goitre which sometimes gives rise to pressure symptoms. It was subsequently realized that hypothyroidism is not an essential feature of the condition, but until recently the diagnosis has rested on histological evidence obtained by biopsy or operation. It is now known that, provided a sensitive enough test is used, such as the tannic acid haemagglutination technique, about 80% of patients with this disease can be shown to have in their sera antibodies to thyroid protein.

It is, however, the application of these tests to hypothyroid patients without goitre—that is, those clinically diagnosed as primary cases—which has produced startling results, since about the same proportion give a positive serological reaction (Owen and Smart, 1958; Roitt and Doniach, 1958). Similarly, workers in Glasgow (Buchanan *et al.*, 1958) have shown that some patients who have hypothyroidism without goitre give, in response to the intradermal injection of an extract of human thyroid tissue, a skin reaction which may be as strongly positive as that of patients with Hashimoto's disease. It is difficult to avoid the conclusion that some cases of hypothyroidism which have in the past been regarded as due to an idiopathic atrophy of the gland are in fact the end-result of an autoimmune process. In those cases of Hashimoto's disease in which the patient is euthyroid it seems probable that the process of destruction of the gland is incomplete and enough healthy thyroid tissue remains to produce in response to T.S.H. a normal quantity of thyroid hormone.

It is important to recognize the clinical syndrome which is called Hashimoto's disease. It usually occurs in middle-aged women, and many patients seek advice because of a swelling in the neck. The clinician may mistake this for a simple non-toxic goitre and may even consider operation, especially if there are pressure symptoms. Some patients have a superadded anxiety state and may at first sight appear to be thyrotoxic. Once suspicion is aroused there are several aids to diagnosis. Thus Hubble (1959) gives seven diagnostic criteria for auto-immunizing thyroiditis. He regards a positive serological reaction to thyroid extract together with a positive finding in any one of another six investigations as adequate to establish the diagnosis. In these tests he includes the clinical findings, flocculation tests, three tests using ^{131}I, and histological examination. We use essentially the same criteria, but we place more emphasis on the value of tests using ^{131}I. For the detection of circulating antibodies we use the precipitin test instead of the more sensitive tanned red-cell haemagglutination test. Complement-fixing

antithyroid antibodies are also present in more than 80% of cases of Hashimoto's disease (Anderson *et al.*, 1959), but they are also found in the sera of nearly 6.8% of all hospital patients and of 16.2% of elderly female patients with no clinical evidence of thyroid disease (Goudie *et al.*, 1959). The results of this test must therefore be interpreted cautiously.

In Hashimoto's disease with hypothyroidism a slightly elevated P.B.^{131}I at 48 hours is occasionally associated with a low or normal gland uptake of ^{131}I. When this combination is found in any case of hypothyroidism Hashimoto's disease should be suspected. More usually, however, the gland uptake at 24 or 48 hours is less than 20% and the P.B.^{131}I at 48 hours is negligible. In euthyroid cases of Hashimoto's disease the usual findings are a normal or a moderately high uptake of ^{131}I at four hours with a high P.B.^{131}I at 48 hours—that is, they may closely resemble those found in thyrotoxicosis.

Two additional observations using ^{131}I are of value. We have found that the thyroxine-suppression test gives useful information in those euthyroid patients with Hashimoto's disease who have relatively high gland uptakes. The uptake is suppressed as it is in normal euthyroid patients and those with simple goitres; in other words, the gland does not behave like that of a thyrotoxic patient.

The second test which uses ^{131}I was first described by Morgans and Trotter (1957). They found that potassium perchlorate rapidly discharged radioactive iodine from the glands of patients with Hashimoto's disease and that this did not occur in patients with simple goitres or in normal subjects in whom iodine is firmly bound to protein. The test is carried out by giving 500 mg. of potassium perchlorate one hour after a dose of ^{131}I, and we have confirmed its diagnostic value, though the results may be misleading.

The results of treating Hashimoto's disease with thyroxine are gratifying. Not only are the symptoms of hypothyroidism relieved but even in their absence the gland diminishes in size. Pressure symptoms if present diminish or disappear. It is of some theoretical interest but of less practical importance that prednisolone will also cause a rapid diminution in the size of the gland and an improvement in the biochemical abnormalities (Murray, 1958). This drug might on occasion be used along with thyroxine to afford a more rapid relief of pressure symptoms, though in our experience these are infrequent.

Metabolic Studies

The thyroid hormones have important metabolic actions. When they are present in excess metabolic processes proceed at an increased rate; a decrease in the amount of circulating hormones has the reverse effect. The two clinical conditions of over- and under-activity of the thyroid gland are especially suitable for controlled metabolic studies, since observations can be made on the same patient before and after appropriate treatment has rendered them euthyroid. On the whole we have found that thyrotoxicosis is more suitable than hypothyroidism for this type of investigation since complications tend to be introduced by the deposition of the mucopolysaccharide described as myxoedematous tissue.

We have investigated three aspects of metabolism which are altered in thyrotoxicosis and hypothyroidism—namely, changes in the red-cell mass, alterations in total exchangeable electrolytes, and disturbances of calcium metabolism.

Early in the course of our metabolic studies we decided that lean body mass (L.B.M.) would theoretically be a better reference standard than body weight, since depot fat is a relatively inert material. Krebs and Johnson (1948) have shown that it has a very low rate of oxygen utilization, and Hastings and Eichelberger (1937) that it has a relatively low content of electrolytes. Thyrotoxicosis usually causes a loss of weight which is partly due to loss of metabolically inactive fat and partly due to loss of metabolically active lean tissue. It is clear, therefore, that changes in metabolic processes in this condition would be easier to interpret if the relative amounts of fat and lean tissue were known. This is also true of hypothyroidism.

In recent years several techniques for determining lean-body mass have been devised and we have used the estimation of total body water for this purpose, since methods for its estimation can be readily applied in clinical practice. Lean-body mass is derived by assuming that 73% of the total body water is associated with the metabolically active cell mass. This has been shown to be so in guinea-pigs and rats (Pace and Rathbun, 1945), and direct analysis of human cadavers suggests that the same relationship holds in man (Widdowson *et al.*, 1951; Forbes and Lewis, 1956). We have estimated total body water by a dilution technique using antipyrine. We have converted the figures for total body water to lean-body mass, since the concept of lean-body mass often enables us to understand the mechanisms underlying our findings. It should, however, be noted that these figures differ by a constant factor of 0.73 and that all the correlations I shall describe are equally valid if the figures for total body water are used instead of the derived lean-body mass.

Total Red-cell Mass in Thyrotoxicosis and Hypothyroidism

Muldowney (1957) has shown that in normal persons total red-cell mass is related more closely to lean-body mass than to total body weight. If the lean-body mass is known the red-cell mass may be predicted with 95% confidence limits of $\pm$75 ml. This relationship holds for both sexes and over a wide range of age and of body weight. He suggested that the basis for this correlation was that oxygen-carrying power, or red-cell mass, is regulated by the basal oxygen requirements of the actively metabolizing lean-body mass. If this is true, then in conditions such as thyrotoxicosis and myxoedema, where basal oxygen consumption is altered, the red-cell mass might show parallel changes. Thus thyrotoxicosis would be accompanied by an increase and hypothyroidism by a decrease in red-cell mass. We have made observations which suggest that this is the case and that the red-cell mass is regulated by changes in the basal oxygen consumption of the tissues (Muldowney *et al.*, 1957).

Seven thyrotoxic and eight hypothyroid subjects were studied. Lean-body mass was derived from the total body water, and confirmation of the estimate was obtained from the Keys–Brozek equation for fat-free

weight including minerals. The results are shown in Figs. 11 and 12. In thyrotoxicosis there was an increase in the red-cell mass relative to lean-body mass. Furthermore, the relationship of red-cell mass to lean-body mass returned towards normal in the three thyrotoxic subjects studied after treatment. Since the mean cell haemoglobin concentrations did not vary

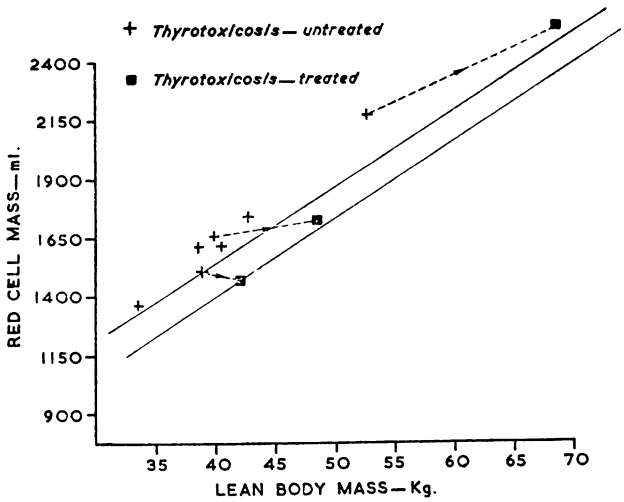

FIG. 11.—Red-cell mass and lean-body mass in thyrotoxicosis. The parallel lines represent the 95% confidence limits in 36 normal subjects.

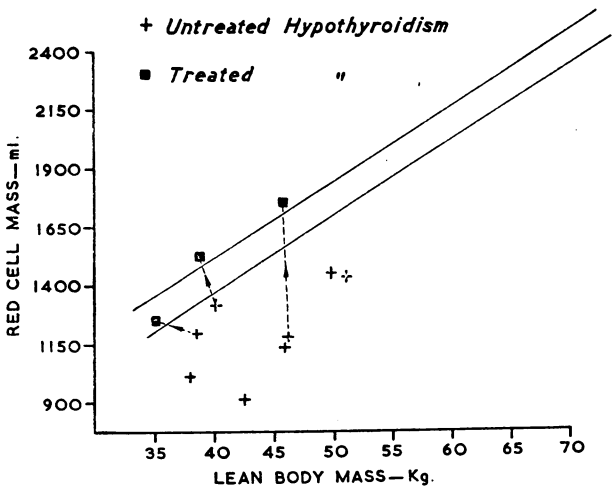

FIG. 12.—Red-cell mass and lean-body mass in hypothyroidism. The parallel lines represent the 95% confidence limits in 36 normal subjects.

after treatment, the changes in red-cell mass reflect the changes in total circulating haemoglobin. The time taken to reach the euthyroid state varied from 6 to 12 weeks, but the picture after treatment was complicated by considerable increases in lean-body mass. This was most marked in the case of one subject whose lean-body mass increased by 14 kg. In this subject, though an absolute rise of 375 ml. of red-cell mass occurred, the red-cell mass per kg. of lean-body mass fell from +15% to 5.8% of the normal mean.

Our observations are an extension of those of Gibson and Harris (1939), who showed that the blood-volume tends to be increased in thyrotoxicosis and decreases after treatment. The increase in total red-cell mass found in thyrotoxicosis in our present series implies increased bone-marrow activity, and Axelrod and Berman (1951) have described erythroid hyperplasia at the expense of fat in patients with the disease. Functioning cellular marrow may extend even into the long bones in the adult.

The changes in lean-body mass and red-cell mass in the hypothyroid patients are the reverse of those found in thyrotoxicosis. Thus the total red-cell mass relative to lean-body mass was less than normal and increased with treatment.

In normal persons the basal oxygen consumption varies with the lean-body mass (Miller and Blyth, 1952), and this in its turn correlates with the red-cell mass (Muldowney, 1957). These correlations suggest that there is a physiological relationship between the oxygen

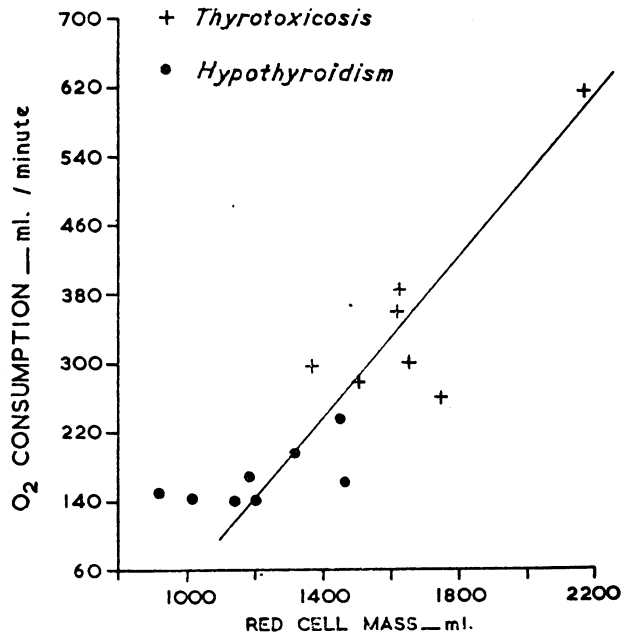

FIG. 13.—Red-cell mass and basal oxygen consumption in thyrotoxicosis and hypothyroidism.

requirements of the tissues and the total number of red cells carrying oxygen to them. Great changes in the oxygen requirements of the body occur in thyrotoxicosis and in hypothyroidism, and we have measured both basal oxygen consumption and the red-cell mass in 15 examples of these diseases. Fig. 13 shows the good correlation ($r=0.88$) which was obtained. Since we know that in these diseases alterations in oxygen consumption are not accompanied by parallel changes in lean-body mass, our results tend to confirm the view that the red-cell mass is determined by the oxygen requirements of the tissues, and this is true even when they are well outside the normal range.

It could be argued, however, that the regulation of red-cell mass is not achieved directly by change in basal oxygen consumption but by a coincident action of the thyroid hormone on the bone-marrow. It was therefore thought desirable to study the effect on red-cell mass of an increase in basal oxygen consumption in the absence of any increase in circulating thyroid hormone. This was done by the administration of dinitrophenol to a myxoedematous subject, since this drug has been shown

to stimulate oxygen consumption without increasing thyroid function. Twenty-one days after treatment had begun the B.M.R. had risen by 43% and the red-cell mass by 11%. The uptake of ^{131}I was unaffected. Thus the red-cell mass had increased significantly in association with a rise in basal oxygen consumption and in the absence of increased production of thyroid hormone. This is further evidence that the marrow responds primarily to changes in basal oxygen demands.

The changes in red-cell mass in thyrotoxicosis and hypothyroidism must be re-examined in the light of this concept. Thus thyrotoxicosis is accompanied by an increase in the total red-cell mass and in the amount of circulating haemoglobin; in other words, there is a hypertrophy of the oxygen-carrying tissues in response to increased metabolic demands. In this condition there is also evidence that the erythrocytes of at least some patients have a diminished life-span (McClellan *et al.*, 1958). An excessive rate of red-cell destruction would explain the moderate increase in faecal urobilin which may occur in this disease (Wallerstein and Castle, 1955). It could, however, result equally well from the increase in the total red-cell mass which we have shown to occur, and it is doubtful if an increased rate of destruction of red cells is of any clinical significance in thyrotoxicosis.

In hypothyroidism the diminished oxygen requirements of the tissues results in a shrinkage of red-cell mass and of total circulating haemoglobin. Bomford (1938), who studied the blood changes in this condition by conventional haematological methods, came to essentially the same conclusion—namely, that the uncomplicated anaemia is a physiological compensation for the diminished need of the tissues for oxygen. This diminished erythropoiesis is associated with the peripheral blood picture of a normocytic normochromic anaemia. Sometimes, however, iron deficiency is also present and a microcytic hypochromic anaemia results. There is also in hypothyroidism a relatively high incidence of megaloblastic anaemia which is usually of typical Addisonian pernicious anaemia type (Wilson and Tudhope, 1959).

Total Exchangeable Electrolytes in Thyrotoxicosis and Hypothyroidism

Physiologists have long appreciated that comparisons of the electrolyte content of various tissues are invalidated by variations in the proportion of lipid since the latter is poor in electrolytes (Hastings and Eichelberger, 1937). For this reason they have usually expressed their measurements of electrolytes on the basis of fat-free weight rather than of tissue weight. Thyrotoxicosis results in a variable loss of lean tissues and fat (Moore *et al.*, 1952), and a study of the changes in the exchangeable electrolytes produced by the disease should take this factor into account. This cannot be satisfactorily achieved if body weight is used as the standard of reference.

Notwithstanding the findings of physiologists, clinical workers have not used lean-body mass or total body water as a standard of reference for exchangeable electrolytes either in normal subjects (Corsa *et al.*, 1950; Ikkos *et al.*, 1955) or in patients with thyrotoxicosis (Munro *et al.*, 1958). Even the normal variation in the proportions of lean tissue and fat found in health may produce certain fallacies of interpretation. For example, Aikawa *et al.* (1952) found that the exchangeable potassium (K_e) in females had a lower value per kg. body weight than Corsa *et al.* (1950) found in males. This is probably due to the greater proportion of adipose tissue in females, since we have shown that this difference between the sexes disappears when lean-body mass is used as the reference standard (Wayne *et al.*, 1958; Crooks *et al.*, 1959). Fig. 14 illustrates the poor correlation between K_e and body weight, and Fig. 15 the much better correlation which is obtained when

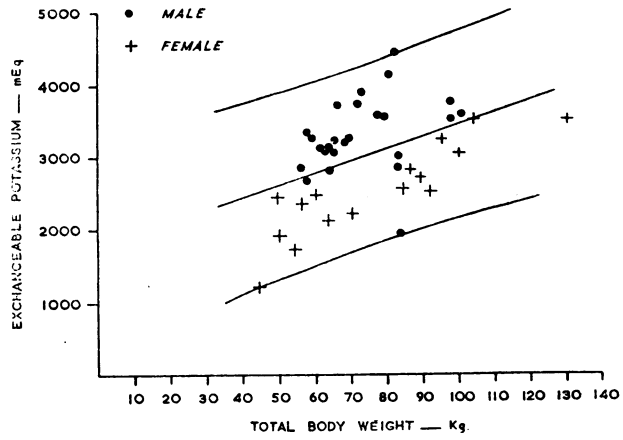

FIG. 14.—Correlation of total exchangeable potassium with total body weight in normal subjects, showing the regression line and its 95% confidence limits.

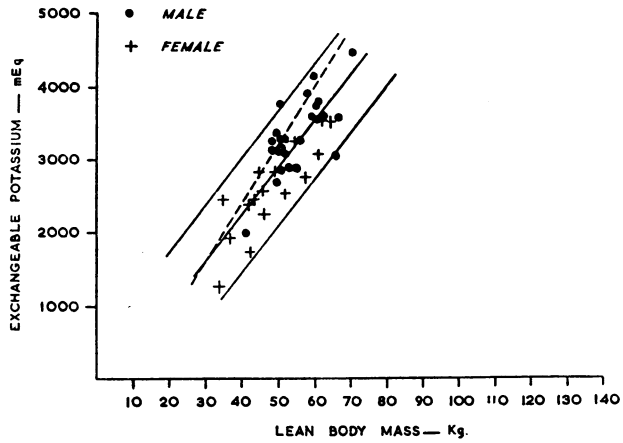

FIG. 15.—Correlation of total exchangeable potassium with lean-body mass in normal subjects, showing the regression line and its 95% confidence limits. The interrupted line is a regression line derived from the data of Ikkos *et al.* (1956) in a series of normal subjects.

lean-body mass derived from total body water is used as a reference standard. Similar but less striking improvement is found in the correlation for Na_e and Cl_e.

We have therefore measured the total body water as well as the total exchangeable electrolytes in our thyrotoxic patients and have repeated the observations after treatment. We found that the figures for K_e when referred to lean-body mass were the same in thyrotoxic and normal individuals (Fig. 16). After treatment both K_e and lean body mass increased. Danowski and Elkinton (1951) and Munro *et al.* (1958) have shown that there is a diminution of K_e in thyrotoxicosis. Our

results suggest that this can be wholly accounted for by a corresponding loss of lean tissue. In other words, the changes in body potassium are related directly to the diminution in cell mass which occurs when the disease is active and to the increase which takes place when the patient is treated.

When similar studies of total exchangeable (Na_e) were made in thyrotoxic subjects the points tended to fall significantly above the regression line for normal persons. No significant trend in individual patients was shown on successful treatment. The results are similar to those of Munro *et al.* (1958). The increase of Na_e in thyrotoxicosis is probably associated with the increased plasma volume which is present in this disease. We found also that the ratio of sodium space to chloride space is unaltered in thyrotoxicosis, and this makes it unlikely that the increase in Na_e is due to an increase in the exchangeable sodium of bone.

We have also made a number of observations on total exchangeable electrolytes in hypothyroidism. The results are much more difficult to interpret. There is

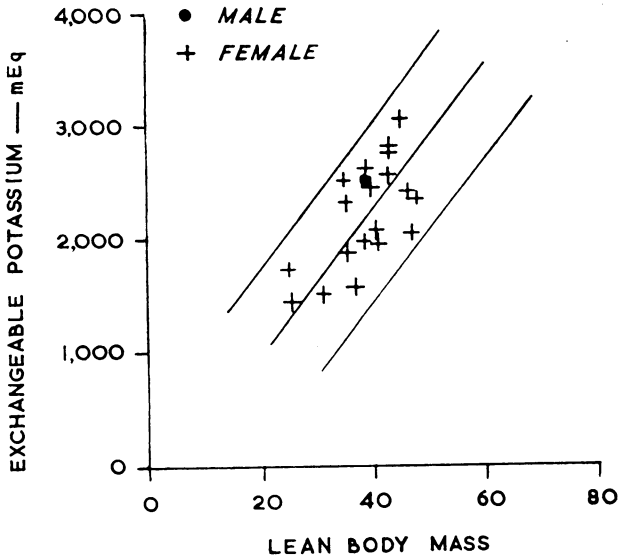

FIG. 16.—Total exchangeable potassium plotted against lean-body mass derived from total body water in thyrotoxic subjects, also showing the regression line and its 95% confidence limits for normal subjects.

no doubt that there is a substantial and rapid loss of weight when hypothyroid patients are treated with thyroxine, and it is necessary to take this into account. We were unable to show any change in the K_e in hypothyroidism when we used lean-body mass derived from total body water as a reference standard (Fig. 17), and both K_e and total body water fell with treatment. This is the reverse of what occurs in thyrotoxicosis and explains the findings of Munro *et al.* (1958).

Calcium Metabolism in Thyrotoxicosis

It has long been known that osteoporosis may occur in the course of thyrotoxicosis (von Recklinghausen, 1891). As in other forms of osteoporosis, trabecular bone is mainly affected and hence the vertebral bodies are principally involved. Nowadays, however, thyrotoxicosis is a rare cause of radiologically identifiable osteoporosis, probably because the disease is seldom allowed to continue for a long period without some form of treatment. Thyrotoxic osteoporosis is commonly attributed to a deficiency of the protein matrix of the skeleton with consequent reduction in the rate of new bone formation, in accordance with the well-known views on the genesis of osteoporosis of Albright

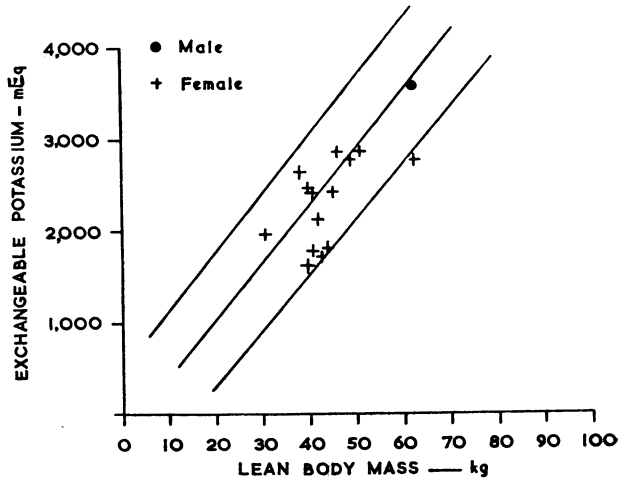

FIG. 17.—Total exchangeable potassium plotted against lean-body mass derived from total body water in hypothyroid subjects, also showing the regression line and its 95% confidence limits for normal subjects.

and Reifenstein (1948). There are, however, some facts which do not accord with this view. For example, Follis (1953) has shown that the histological picture may be that of an osteitis; thus in these cases there is active destruction of bone. Krane *et al.* (1956), using ^{45}Ca, have shown that thyrotoxicosis is associated with an increase in the turnover rate of skeletal calcium and have pointed out that some patients who are in strongly negative calcium balance may be almost in nitrogen equilibrium. The demonstration by Puppel *et al.* (1945) that positive calcium balance can be achieved simply by giving thyrotoxic patients calcium supplements is also difficult to reconcile with the concept of protein matrix deficiency.

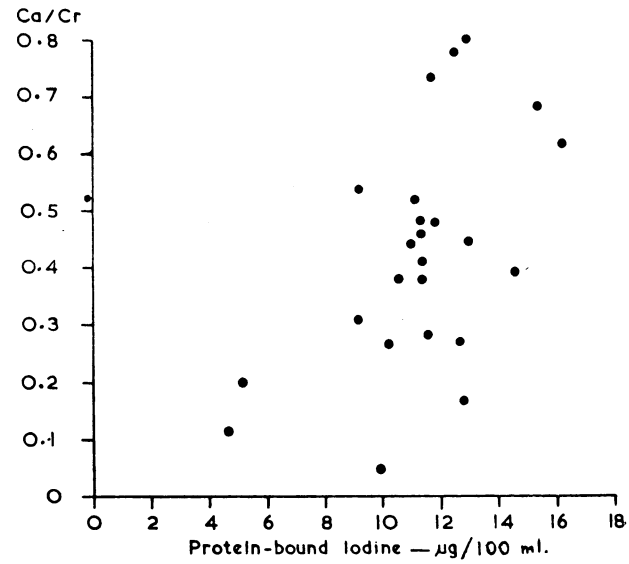

FIG. 18.—Correlation between the calcium/creatinine ratio in the urine and the serum protein-bound iodine in a series of thyrotoxic patients. (Coefficient of correlation $r=0.52$; $P<0.01$.)

There is therefore good evidence to suggest that the osteoporosis of thyrotoxicosis may be due to negative calcium balance. There is no evidence of defective absorption of calcium, but excessive excretion of calcium can be demonstrated in the urine. The measurement of the ratio of calcium to creatinine in the urine is a simple method of detecting hypercalciuria (Nordin, 1959), and there is a correlation between the degree of hypercalciuria assessed in this way and the severity of the thyrotoxicosis as reflected in the plasma P.B.^{127}I (Fig. 18) (Crooks *et al.*, 1960). The calcium/creatinine ratio was high in 15 out of 20 severely toxic patients. When they were clinically euthyroid after treatment with antithyroid drugs the calcium/creatinine ratios fell into the normal range (Fig. 19). This effect may be seen within two weeks of starting treatment and cannot be wholly accounted for by the diminution in urinary creatinine found in most cases of thyrotoxicosis.

It is thus tempting to attribute the osteoporosis of thyrotoxicosis to a continued drain of calcium in the urine. This might be due to the rise in the glomerular filtration rate which is known to occur in thyrotoxicosis (Bradley, 1955) or to the rise in plasma calcium which has been shown to take place occasionally in the disease (Kleeman *et al.*, 1958).

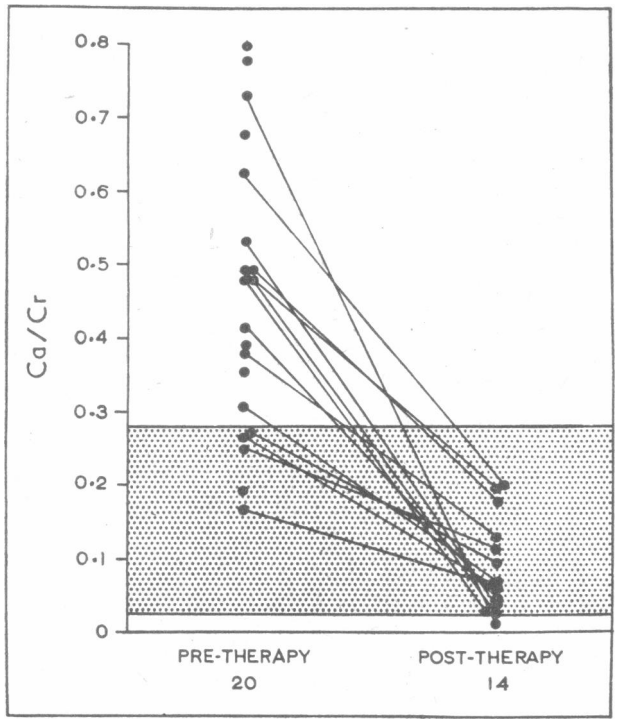

FIG. 19.—Calcium/creatinine ratio in the urine of thyrotoxic patients before and after treatment with antithyroid drugs. The shaded area indicates the normal range.

Conclusion

In these lectures I have described some new methods of handling clinical evidence. These techniques have a statistical basis, and I have little doubt that my approach to clinical problems stems from my training and experience as a pharmacologist. The concept of dealing with disease in a statistical way conflicts with much that is traditional in medicine and will not appeal to everyone. Nevertheless I believe these methods are an inevitable step in the evolution of scientific medicine. It should perhaps be emphasized that there is a substantial gain to patients who are included in investigations of this type, because the diagnosis must be established beyond doubt and the result of treatment fully assessed, even though this involves the physician in much extra work. It is, moreover, probably true that they could be carried out only in a country with a National Health Service, since intensive investigation and periods of prolonged supervision are necessary and these would be economically crippling to the patient under any other system. As it is, patients are almost invariably co-operative, and their gratitude is one of the rewards of work in a field in which treatment gives such satisfactory results.

Finally, I should like to direct your attention to some outstanding problems in the fields we have been discussing. Our present methods of diagnosing thyroid disease are probably adequate, especially since therapeutic tests can often be used in difficult cases. An intriguing problem is raised by the possibility that the disease we call thyrotoxicosis represents only a certain range on a scale of progressive thyroid activity and that we have decided quite arbitrarily to regard levels at or above a certain point on the range as abnormal. Some support for this concept is given by our studies using the therapy index, since patients who are recovering from thyrotoxicosis pass through a stage in which it is difficult to say whether or not they are "thyrotoxic." Moreover, evidence has been produced that some of the symptoms of anxiety states may be due to an excess of thyroid hormones (Brody, 1949). Nevertheless, we believe that the balance of evidence is in favour of a discontinuous process and that when patients develop thyrotoxicosis a number of features develop together, and usually fairly rapidly.

We have been interested in more recent evidence that thyrotoxicosis is a disease which does not depend for its manifestations solely on an increase in the output of thyroid hormone. When the amount of functioning thyroid tissue has been reduced, either by operation or by radioactive iodine, some abnormalities remain. For example, we have confirmed that the remnant of the gland in many patients who are clinically euthyroid continues to behave like a thyrotoxic gland in its response to T.S.H. and exogenous thyroxine. Moreover, an increased rate of utilization of thyroxine has been shown to occur in some thyrotoxic patients, and this may persist after treatment (Ingbar and Freinkel, 1958). It is clear, therefore, that the terms "euthyroid" and "cure" must be applied with some reserve to patients who have once been thyrotoxic, and we should not be complacent about our present methods of treatment, some of which are relatively crude.

Hypothyroidism also presents many unsolved problems—for example, we do not know the nature and function of myxoedematous tissue. If, however, it is true that the majority of cases are the end-result of an autoimmunizing process it may become possible to detect and treat the disease in its early stages, and when the full train of events is more precisely known we may even be able to reduce the incidence of the disease to negligible proportions.

It is, however, clear that neither of the disorders I have discussed under the labels thyrotoxicosis and hypothyroidism has yet given up its secrets, and there

is still much to be discovered about the nature and treatment of these fascinating disease processes.

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