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THE DIAGNOSIS OF THYROTOXICOSIS*

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Parry first described an association between thyroid enlargement and cardiac disease in 1825, and in 1835 Graves published his account of three cases of "violent and long-continued palpitations in females in each of which the same peculiarity presented itself, viz., enlargement of the thyroid gland." Each cited a case in which exophthalmos was present. It is, however, to Basedow, in 1840, that we owe the first complete clinical description of the disease which, in Europe, still bears his name. All the symptoms except tremor and most of the physical signs were described so vividly and accurately that little of importance has been added since. By comparison Sattler's book, published in 1908, though invaluable in providing information about the progress of the disease before any effective treatment was available, gives a picture which is out of perspective.

Perhaps I should apologize for retreading in this lecture much well-trodden ground. I hope, however, to deal in particular with the problem of diagnosis in the doubtful case and to discuss the value of modern laboratory tests, especially those which make use of radioactive iodine. I shall also consider some of the manifestations of thyrotoxicosis in more detail, especially where recent work has shed light on their mechanism.

Thyrotoxicosis is a relatively common disorder. It occurs in all parts of the world, but is especially frequent where endemic goitre is prevalent. Derbyshire has for long been recognized as such a district, and many of our cases have come from this region. It was this local concentration of patients that aroused my interest and provided the clinical opportunities for these studies.

The importance of suspecting the presence of thyrotoxicosis and of carrying out full clinical and laboratory investigations to establish the diagnosis cannot be overemphasized. The advance in therapeutic measures to deal with this disease has been exceedingly rapid. It is now ten years since Astwood (1943) first treated thyrotoxicosis successfully with thiourea, and the drugs in this series have given us a powerful tool with which we can almost always confirm or refute the diagnosis without subjecting the patient to forms of therapy which permanently destroy a large portion of the gland. Once the diagnosis has been firmly established other forms of treatment are available and we can offer our patients an excellent prospect of permanent recovery. Improved surgical and anaesthetic techniques have greatly reduced the risks of operation, and no patient is too ill to drink a therapeutic dose of radio-iodine. These rich opportunities in the therapeutic field impose a duty on the physician not to overlook any case in which thyrotoxicosis may be present.

In a florid case the diagnosis is obvious and can be made by the junior clinical clerk who has spent only a few weeks in the ward. On the other hand, some cases of thyrotoxicosis do not present all the classical features of the disease, and in them the diagnosis may be overlooked. This especially happens when the more prominent facial signs are lacking and there is no gross enlargement of the thyroid gland. In such circumstances the diagnosis may be difficult, for it is common knowledge that many of the clinical features associated with thyrotoxicosis may occur in a wide variety of disorders. I refer to such non-specific features as, for example, loss of weight, "nervousness," and tachycardia. Furthermore, the more definite manifestations which are often clearly associated with thyrotoxicosis may occasionally be seen in persons with normal thyroid function. Signs such as goitre, exophthalmos, and lid lag fall into this category.

Grouping of Patients

As the suspicion of the presence of thyrotoxicosis must first be assessed by the presence of some of these signs and symptoms, their incidence and diagnostic significance have been investigated more fully. This has involved dividing the patients with suspected thyrotoxicosis into two definite categories, "toxic" and "non-toxic." Such a distinction may be difficult to make and yet is essential for the practising physician. The former group essentially comprises those who will be benefited by specific therapy for thyrotoxicosis, while in the latter it is clearly not indicated. It is also of interest and importance to inquire into the prevalence of some of the clinical features often associated with thyrotoxicosis amongst people not suspected of having any thyroid disorder. We have accordingly studied the following three groups of subjects.

Group 1.—Patients referred to the thyroid clinic and shown after full investigation to be indisputably thyrotoxic. Some of these patients had clinically obvious thyrotoxicosis, but the majority had presented diagnostic difficulties to at least one clinician. The diagnosis was based on at least two radio-iodine criteria—namely, the four-hour uptake by the gland

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and the 48-hour protein-bound activity in the plasma. If these were inconclusive or if the patient had received previous therapy, the cases were further investigated before a final decision was made. There were 90 patients in this group.

Group 2.—Patients referred to the thyroid clinic as possible cases of hyperthyroidism but finally shown to be non-toxic—72 patients fell into this group.

Group 3.—This comprised 90 normal individuals drawn so far as possible from the same social class and with the same age and sex distribution as the thyrotoxic cases. None was receiving medical attention.

The individuals in these three groups have been asked a standard set of questions and the presence or absence of certain physical signs has been recorded. Only two clinicians carried out the investigation. Fig. 1 shows

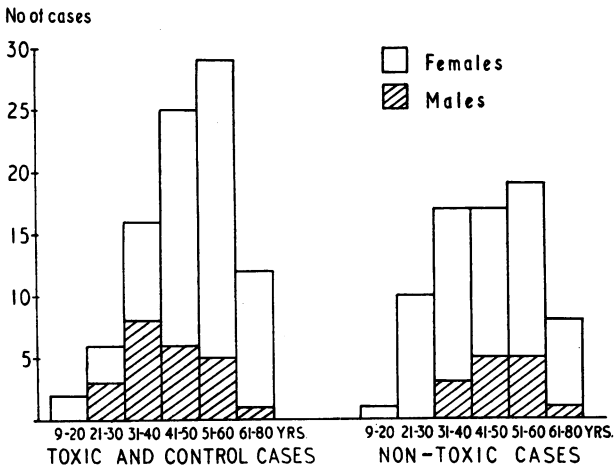

FIG. 1.—Age and sex distribution in non-toxic, and toxic and normal cases.

the age and sex distribution in the normal controls and the thyrotoxic cases and in the non-toxic group. The distribution follows the usual pattern in thyrotoxicosis. Details of the investigation will be published elsewhere (Weetch, 1954) and I shall give only a selection of the figures and a summary of our conclusions. Table I

TABLE I.—*Incidence of Signs and Symptoms in Thyrotoxic (T.), Non-toxic (N.T.), and Control (C.) Cases*

Symptoms	T.	N.T.	C.	Signs	T.	N.T.	C.
	%	%	%		%	%	%
Dyspnoea on exertion	81	61	40	Goitre ..	87	56	11
Palpitation ..	75	75	26	Diffuse enlargement	49	37	11 (slight)
Tiredness ..	80	68	31	Nodular ..	32	14	0
Preference for cold	73	53	41	Single adenoma	4	5	0
Excessive sweating	68	54	31	Exophthalmos	34	11	2
"Nervousness"	59	54	21	Lid lag ..	62	24	16
Appetite:				Hyperkinetic	39	22	9
Increased ..	32	1	2	Finger tremor	66	54	26
Diminished ..	13	14	3	Hands:			
Weight:				Sweating ..	72	54	22
Loss	52	27	2	Hot ..	76	40	44
Gain	4	7	16	Auricular fibrillation	19	8	0
Bowels:				Regular pulse rate over 90/min.	68	47	19
Diarrhoea ..	8	2	0				
Constipation ..	15	20	21				
Menses:							
Excessive ..	3	12	6				
Scanty ..	18	9	3	Average pulse rate. Beats/min.	100	85	78

shows a selection of the results of the analysis of symptoms and signs in the different groups. The signs recorded are necessarily only those which could be elicited without a full physical examination on the normal control group.

History-taking

It should be emphasized that this investigation was not made in an attempt to discover the commonest symptoms and signs in obvious cases of thyrotoxicosis, but to try to find out why there had been difficulty in separating doubtful cases into toxic and non-toxic groups on purely clinical grounds. It was decided to include a group of normal individuals when it became apparent that with some symptoms there was often remarkably little difference in the replies given by the toxic and non-toxic groups. The questions were asked in the form, "Do you become unduly breathless on exertion?"; "Do you tire easily?"; "Do you prefer hot or cold weather?"; and it is the answers to these questions which are recorded in the tables. Patients could usually give a date of onset of their symptoms, but the answers of the normal controls to the same questions varied, some having "always been like that" and others stating that "it has come on recently."

An incidental illuminating feature of this investigation was the light it threw on the art of history-taking. I can strongly recommend to any physician with a special interest in some disease, as, for example, pulmonary tuberculosis, that he put his usual questions to a group of patients with chronic anxiety or to women at the menopause. He will be surprised at the number of positive answers he receives. Yet I do not think that the experienced physician would misinterpret these replies. It is, however, this problem which confuses our clinical clerks and house-physicians, who find it far more difficult to know whether a positive answer to a question is significant. They also have less skill in framing the appropriate supplementary questions, and little experience in assessing the patient's personality as a whole. My experience in completing the forms which were used has confirmed my suspicion that methods of history-taking which involve the use of a set list of symptoms are inherently unsatisfactory.

The two surprising features of the analysis are the high incidence of many symptoms in both the non-toxic and the control groups. We believe the explanation lies in the large number of women, and especially of women at or not far past the menopause, that are present in both groups, and in the high proportion of patients with anxiety states in the non-toxic group. We have analysed separately the figures for males and females, and Figs. 2, 3, and 4 illustrate the relative frequency of three symptoms in the toxic, non-toxic, and control groups when they are broken down in this way. In the control group positive answers were given much less frequently by males. In the non-toxic group this was true of most but not of all symptoms. In thyrotoxicosis, on the other hand, the proportions of males and females with symptoms were roughly equal. This was true of all symptoms except hot flushes, which were, as would be expected, much commoner in females in all the groups. A separate analysis of the answers of women over the age of 50 showed with most symptoms a still greater difference from the males, but the numbers were too small to be able to show a statistically significant difference between women of different ages.

I shall discuss the significance of the various signs and symptoms individually, indicating those which have the greatest diagnostic value, but it may be helpful to emphasize again that the comparison is essentially between a group of thyrotoxic patients, many of whom were not severely ill, a cross-section of the community of similar age and sex distribution, and a group of patients, usually with goitre, exophthalmos, auricular fibrillation, or persistent tachycardia, many of whom had in addition the symptoms of chronic anxiety or of the menopause.

Clinical Manifestations of Thyrotoxicosis Considered Separately

I now propose to discuss the clinical aspects of thyrotoxicosis so far as they illustrate points of special diagnostic value.

Family History

There is an undoubted familial tendency to thyrotoxicosis (Rundle, 1941), but this is also true of simple goitre (Brain, 1926). The disease has been reported in identical and in dissimilar twins (Neff, 1932; Bowers, 1948; Bartels, 1953). Martin (1945) and Bartels (1953) conclude that Graves's disease is inherited in a dominant manner. Martin and Fisher (1951) could, however, find no evidence of a hereditary influence in toxic nodular goitre, but Bartels disagrees with this conclusion. Occasionally the presence of thyroid disease in a relative may direct the physician's attention towards a correct diagnosis, but usually little help is derived from the family history.

Psychological Features

In his Bradshaw Lecture last year Bomford (1953) drew attention to the importance of studying disease by psychological as well as by physical methods. Thyrotoxicosis would certainly seem to qualify as a disease with psychological aspects. Sitting in a clinic devoted to the supervision of treated cases, one can hardly fail to be impressed by the unusual temperament of those who have been cured of the somatic side of their disorder. Moreover, a previously thyrotoxic patient who has developed hypothyroidism tolerates the condition far less well than one who has developed the disease spontaneously and becomes irritated with a body which refuses to carry out efficiently the dictates of a still relatively active mind. A psychosomatic theory of thyrotoxicosis has been developed by Ham *et al.* (1951). They find that the condition tends to occur in individuals frustrated in early life who make continued efforts towards premature self-sufficiency, and when these fail develop chronic anxiety. However sympathetic one may be to the psychosomatic approach one cannot help feeling that its exponents would strengthen their case if they could foretell, even occasionally, which of the many patients with early frustration and anxiety will develop thyrotoxicosis and which are more likely to develop some other psychosomatic manifestation such as peptic ulcer, colitis, or asthma. In the few people I have known personally before they developed thyrotoxicosis I certainly would have ventured no prophecy.

A history of mental shock or emotional strain is relatively common in this disease, although patients who develop anxiety states may have been subjected to equally severe stress. It is said that the disease tends to occur at the landmarks in a woman's sexual life—puberty, engagement, marriage, pregnancy, and the menopause—but few women are far removed from one of these events. Some acute cases are clearly associated with psychical trauma or pregnancy, but in many the history of a direct emotional stimulus is absent.

It is clear that though the psychological features may be of considerable importance in the management of a case of thyrotoxicosis they are of little or no assistance in the establishment of a diagnosis.

Goitre

The high proportion of our cases in the non-toxic group who are recorded as having a goitre indicates that this is the commonest sign which gives rise to the suspicion of thyrotoxicosis. It must, however, be remembered that Sheffield lies at the tip of an area in which goitre is known to be common (Campbell, 1927), and this presenting feature may not be so common in other parts of the country. A bruit over the gland is frequently heard in severely thyrotoxic individuals but is often absent in milder cases and in toxic nodular goitres. The 11 patients in the control group recorded as having diffuse enlargement of the thyroid gland were all women, and though the abnormality was slight it might have been regarded as significant if they had presented other features of toxicity.

The problem of the distinction between thyrotoxicosis with diffuse glandular enlargement, with multiple nodules, or with a single adenoma is a difficult one. Cope *et al.* (1947) have produced evidence that some single adenomata may take up most of a tracer dose of radio-iodine while the remainder of the gland takes up very little. It is suggested that such tumours are analogous to the physiologically overactive adenomata of the islets of Langerhans or of the parathyroids, and function independently of the pituitary gland. They are rare, constituting, as in the present series, about 5% of all goitres. The common toxic multinodular goitre, on the other hand, contains nodules which have usually lowered functional activity, and the thyrotoxicosis arises from overactivity of the paranodular tissue. It is, moreover, not unusual to find adenomata in the apparently diffusely enlarged gland of Graves's disease. There is often no clear distinction, and the manifestations of thyrotoxicosis, apart from a few such as the eye signs and muscular weakness, are the result of an excess of circulating thyroid hormone and can be imitated in the normal individual by heavy dosage with thyroxine. Crile (1949), writing from a surgeon's point of view, concludes that the "fundamental issue is the age of the patient rather than the presence or absence of nodules in the thyroid." I feel sure that this is the correct approach and that the distinction between thyrotoxicosis with diffuse goitre and exophthalmos, on the one hand, and toxic nodular goitre, on the other, is worth making only when it affects the management of the case.

Eye Signs

Exophthalmos was present in about a third of our thyrotoxic cases, and, though present in 11%, was found in equal degree in only 8% of the non-toxic group, which included some cases of previously treated thyrotoxicosis. Two members of the control series showed exophthalmos of slight degree, and it should be remembered that this may be a family characteristic. We have not recorded lid retraction separately, but the distinction between lid retraction and exophthalmos, which was first pointed out by Pochin (1938), is important, since the former is much more likely to disappear after therapy (Eden and Trotter, 1942).

It has long been clear that exophthalmos is not caused simply by excess of circulating thyroid hormone, since it is absent in many cases of severe thyrotoxicosis and may be present in its most virulent form in persons with normal thyroid function. It was pointed out by Russell Brain (1945) that males are far more liable than females to develop severe exophthalmos, especially after thyroidectomy. In our series exophthalmos was twice as common in males as in females. So far as the mechanism of exophthalmos is concerned it has been suggested that the thyroid-stimulating hormone of the anterior pituitary (T.S.H.) exerts an influence not only on the thyroid gland but also on the retro-orbital tissues. Rawson *et al.* (1946) have shown that T.S.H. is normally inactivated but not destroyed by the cells of the thyroid gland and that in thyrotoxicosis the degree of inactivation is increased. Some patients, however, are thought to have thyroids less capable of effecting this oxidation, and the excess of active T.S.H. is then capable of affecting the retro-orbital tissues. No simple explanation can cover all the cases nor explain in particular why patients with intact pituitary function developing myxoedema do not exhibit exophthalmos. The possibility that two separate hormones are involved has been greatly strengthened by the recent observations of Dobyns and Steelman (1953), who have been able to obtain from extracts of anterior pituitary two hormones, one of which stimulates the thyroid gland of chickens and another which produces exophthalmos in *Fundulus*, a type of minnow. If further work confirms these separate effects in mammals, much that is at present obscure will be explained.

The tendency for exophthalmos to become progressive in a case of thyrotoxicosis seems to be related to the speed with which the concentration of circulating thyroid hormone is reduced. In our cases orbitonometric observations of the degree of exophthalmos have shown that after radio-iodine treatment, which produces its effects slowly, there is less tendency for exophthalmos to increase than after methylthiouracil or thyroidectomy (Ferguson, 1951).

Lid Lag

This was present in all our toxic and non-toxic cases with exophthalmos, but was also seen in an equal number of patients without exophthalmos. We have therefore confirmed Jackson's (1949) observations that at least 10% of normal people exhibit this phenomenon. If exophthalmos and lid retraction cannot be recognized by simple inspection of the patient it is doubtful if special signs, such as lid lag or failure of convergence of the eyes on accommodation, yield any further information of value.

Nervous and Mental Symptoms

Severe cases of thyrotoxicosis almost always show emotional instability, and milder cases may have phobias and swings of emotional tone. It is probable that the biochemical disturbance unmasks a basic personality defect. It is easy to regard some patients as primarily psychotic unless the physician or psychiatrist has the possibility of thyrotoxicosis in mind.

In our series we asked the questions, "Are you a nervous person?" and "Are you irritable?" and, if the answer was positive, inquired whether this had always been so. About a quarter of the normal controls answered "yes" to both questions, and several members of the older age groups declared that the symptoms were of comparatively recent onset. Females gave a positive answer much more often than males (Fig. 2). In the non-toxic group as many females gave a positive answer as in the toxic group, but the complaints were usually long-standing except in females at or about the menopause. Neither of these symptoms therefore carried much weight diagnostically except in males. Hyperkinetic movements were significantly more frequent in toxic cases, and this sign has some diagnostic value when it is present. Finger tremor was recorded whether it was fine or relatively coarse. It is very common in apprehensive persons and in the older age groups. A fine rapid tremor was much more often seen in the thyrotoxic group, but may occur in normal people. Jackson (1949) found it in about 2% of his series. Unfortunately, this type of tremor, usually considered to be characteristic of thyrotoxicosis, tends to grade imperceptibly into the slightly coarser types seen in anxiety states, and is of little diagnostic help in separating the two groups.

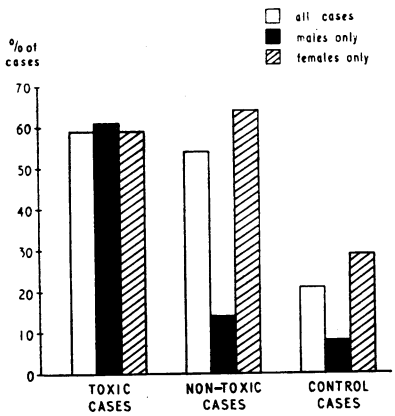

FIG. 2.—Incidence of nervousness in all cases, in males only, and in females only.

Muscular System

Muscular weakness and easy liability to fatigue are frequent accompaniments of the thyrotoxic state. The muscles may show histological changes which are probably due to excess of T.S.H. rather than of thyroxine (Dobyns, 1946). About a third of the control series said that they tired easily, and as large a proportion of the non-toxic as of the toxic patients had the symptom. Here again a positive answer to the question is of value in the male but of little help in the female unless there has been a definite alteration of recent date.

Cardiovascular Manifestations

I have recently discussed the circulatory adjustments which take place in thyrotoxicosis (Wayne, 1952), and I shall not deal with them in detail here. They are all due to excess of circulating thyroid hormone and can be reproduced in animals. It is, however, still uncertain whether there is a specific type of heart disease caused by thyrotoxicosis or whether an excess of thyroid hormone acts merely as a precipitating factor in hearts already predisposed to failure from other causes. Levine (1951) takes the former view, but the balance of evidence is in favour of the latter. A distinction between thyrotoxicosis and thyrotoxic heart disease is worth making, since auricular fibrillation or congestive failure, when it occurs in thyrotoxicosis, becomes more important than the purely metabolic effects of the hormone. This is, however, one of the few forms of heart disease which can be treated by removing the cause.

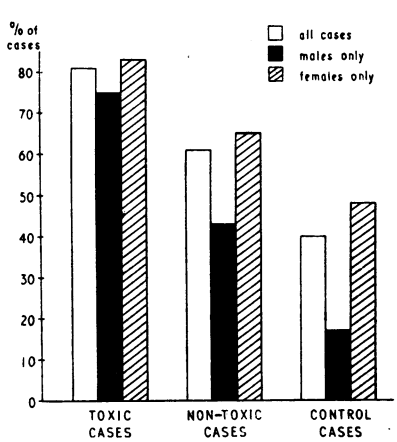

FIG. 3.—Incidence of dyspnoea on exertion in all cases, in males only, and in females only.

Cases of thyrotoxic heart disease may present with established auricular fibrillation or attacks of paroxysmal fibrillation. Clinical examination of the heart sometimes gives rise to the suspicion that mitral stenosis is present, since the first sound at the apex may be accentuated and so roughened as to suggest a presystolic murmur; systolic murmurs are also often heard. It is in such cases and in cases with congestive failure that tracer tests with radio-iodine may be the only method of making a diagnosis without subjecting the patient to a prolonged therapeutic trial. One feature which may suggest that auricular fibrillation is secondary to thyrotoxicosis is its not infrequent failure to respond by a fall in rate to the administration of digitalis in full doses.

In our series of cases the average pulse rate in patients with regular rhythm was significantly higher than in the non-toxic and control groups, but there was considerable overlap between individual cases. We have, however, seen cases of undoubted thyrotoxicosis with resting pulse rates below 80 beats a minute. A slowing of the pulse rate during sleep occurs in normal and neurotic individuals but not in thyrotoxic patients. This is one of the most valuable differentiating features after admission to hospital. Breathlessness on exertion and palpitation occur so frequently in anxiety states and in normal women that they have little differential diagnostic value (Fig. 3).

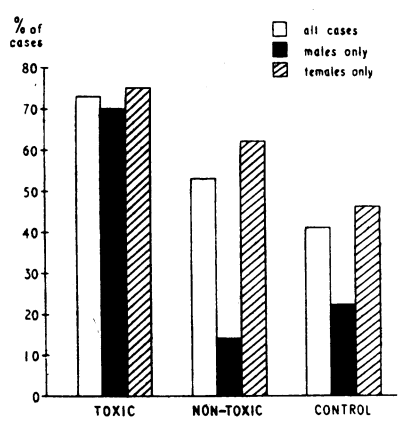

FIG. 4.—Incidence of preference for cold weather in all cases, in males only, and in females only.

The Skin

Because the metabolic rate is high and excess heat must be eliminated, the skin of the thyrotoxic patient is typically hot and moist. Patients often say that they dislike the heat, and they may complain of hot flushes. A surprisingly large proportion of our group of normal individuals expressed a preference for cold weather, but, as Fig. 4 shows, it is chiefly women who dislike a hot environment. Thyrotoxic patients in general expressed their dislike of hot weather much more

vehemently than the non-toxic and control groups and complained more convincingly of excessive sweating. These two symptoms have a diagnostic value even in the female if the questions are properly framed.

Although hot and sweating hands are a characteristic feature of the florid thyrotoxic case, they may, of course, be seen in normal persons, and the nature of the environment must be taken into account. If the atmosphere is relatively dry and cool and the hands are sweating they may be cool to the touch. It is very rare for them to be cold except occasionally in cases with severe congestive failure, although we have noted cold feet, especially in elderly patients.

Appetite and Loss of Weight

Although only a third of the patients with thyrotoxicosis said that their appetite had increased, this symptom is so uncommon in the other groups that it has special diagnostic value. Patients with anxiety state usually have diminished appetites. No fewer than 14% of toxic cases, however, said that their appetite was diminished, and these were often the severer cases. Loss of weight is also a valuable differential diagnostic feature, although 4% of toxic patients gave evidence of gain of weight. We adopted the arbitrary figure of a loss of 7 lb. (3.2 kg.) or more. Greene (1953) has recorded a loss of weight in 44% of patients and a gain in weight of 10% of patients with goitre, not all of whom, however, were toxic. Conway (1950) investigated the weights of 50 cases of active Graves's disease and found that 7 were heavier and 33 lighter than the expected weight. Appetite was increased in 38 of the cases and poor in 1. The combination of loss of weight with increased appetite when present is diagnostic of thyrotoxicosis and was not found in any of our non-toxic or control groups.

Bowel Function

Diarrhoea occurred in about 8% of the patients with thyrotoxicosis. Very rarely it may be the presenting symptom. Constipation, on the other hand, is by no means uncommon. It is of some interest that 20% of the normal controls and of the non-toxic group were constipated and most of them took purgatives regularly. This no doubt explains the preponderance of advertisements for purgatives among the medicaments offered to the public in the popular press.

Menses

Irregularity of menstruation was found in about one-fifth of the premenopausal patients in both toxic and non-toxic groups, but scanty periods were more common in the former. The numbers of patients are, however, small. Riisfeldt (1948), in a series of 340 women, found menstrual abnormalities in 31% of cases of toxic diffuse goitre, 21% of toxic nodular goitre, and 10% of patients with non-toxic goitre. Diminution in the menstrual loss was more common than increase.

The Spleen

We have been unable to confirm the belief that clinically determinable enlargement of the spleen occurs in thyrotoxicosis, although Williams (1946) found it in 10% of 247 cases. In the few instances in which it has been present in cases of thyrotoxicosis which have passed through our hands there has always been some other cause, such as chronic microcytic anaemia.

General Conclusions

We had hoped, when we began this survey in our three series of cases, that we might be able to discover some signs or symptoms which would enable a distinction to be made between thyrotoxic and non-toxic cases on purely clinical grounds. In fact, we discovered that most of the classical signs and symptoms are a reliable guide in thyrotoxic males, but that the problem was far more difficult in females. Women, especially women at the menopause, will often say they have symptoms such as breathlessness on exertion or fatigue even if they are carrying out a full day's work. When in addition they have an anxiety state it is impossible to distinguish thyrotoxic from non-toxic cases on symptoms alone. The problem, however, becomes difficult chiefly when these symptoms are associated with some objective feature usually associated with the thyrotoxic state, such as goitre, exophthalmos, auricular fibrillation, congestive failure, or persistent tachycardia. The most helpful diagnostic features when they are present are increased appetite, loss of weight, preference for cold weather, hot and sweating hands, persistent tachycardia especially during sleep, and hyperkinesis. The value of any diagnostic feature is greatly enhanced if it is of relatively recent onset.

It is clear that in the doubtful case laboratory help is needed, and I shall now discuss the various tests which have been devised to assist the clinician.

Special Tests of Thyroid Function

Further evidence that it is not always easy to arrive at a diagnosis of thyrotoxicosis on clinical evidence alone is provided by the variety of laboratory methods which have been used to assess thyroid function. Some of these are now only of historical interest, but I shall review briefly those which are still in vogue, devoting, however, most of my time to a discussion of the help which may be afforded by tests using radio-iodine.

Estimation of the Basal Metabolic Rate.—This is still the standard laboratory investigation used by most clinicians in an attempt to confirm or refute a diagnosis of thyrotoxicosis. It has the merit that it is comparatively easy to carry out, and it gives some idea of the severity of the thyrotoxic state in clear-cut cases. It is essentially a measure of hypermetabolism, and a raised basal metabolic rate is therefore found in a variety of other conditions, as, for example, leukaemia, phaeochromocytoma, cardiovascular disease, and anxiety states. In the last two conditions it may be impossible to achieve truly basal conditions without heavy sedation (Rapport *et al.*, 1951). Thyrotoxic patients may, moreover, have basal metabolic rates lying within the statistically acceptable "normal" range. In our experience (Goodwin *et al.*, 1951) as many as 33% of patients with proved thyrotoxicosis may have basal metabolic rates lying below +20%, and Foote *et al.* (1952), who took special care to obtain reliable estimates, found that 23% of thyrotoxic patients had basal metabolic rates lying within the normal range. Werner and Hamilton (1951) also report 15 cases of hyperthyroidism without hypermetabolism. Robertson (1952) has pointed out that a specially careful technique and standards derived from normal persons in Great Britain should be used, and Robertson and Reid (1952) emphasized the value of carrying out further tests after the administration of iodine in doubtful cases. An estimation of the basal metabolic rate is of undoubted help in a suspected case of thyrotoxicosis, but conditions must be truly basal and observations on out-patients are often unsatisfactory. Duplicate determinations on two or more days are desirable, and in border-line cases further investigation after the administration of iodine may be necessary.

Estimation of Serum Protein-bound Iodine.—This estimation measures the amount of circulating iodine bound to protein molecules, and is generally regarded as an accurate index of the amount of circulating thyroxine. Several groups of workers in the U.S.A. (Salter *et al.*, 1941; Starr *et al.*, 1950; and Hallman *et al.*, 1951) regard a raised level as the most reliable laboratory evidence of thyrotoxicosis. De Mowbray and Tickner (1952), on the other hand, in this country found that the level was raised in only two-thirds of cases of proved hyperthyroidism, and regard the estimation as inadequate in itself as a test of thyroid function. The previous administration of iodine-containing compounds produces a spurious increase in the serum protein-bound iodine figures. We have encountered serious technical difficulties with the method of Barker *et al.* (1951). It is doubtful if this estimation, which is in any case time-consuming, will ever become generally available to the clinician. It is chiefly of interest because it may give a

more complete picture of iodine and thyroxine metabolism when the results of simultaneous studies with radio-iodine are available (Riggs, 1952).

Estimation of Serum Cholesterol.—The serum cholesterol is lower than normal in the majority of cases of thyrotoxicosis. There is an increased rate of hepatic synthesis of cholesterol, but this is accompanied by an even greater rate of destruction and intestinal excretion. The changes are not related directly to changes in metabolic rate (Rosenman *et al.*, 1952). The fall in blood cholesterol level is small in degree, but under treatment a steady rise occurs (McGavack and Drekter, 1945). We have found the estimation of serum cholesterol of little diagnostic help in thyrotoxicosis although it is valuable in suspected cases of myxoedema. Our experience thus agrees with that of Peters and Man (1950) and Bartels (1950).

Estimation of Serum Creatine.—Creatinuria undoubtedly occurs in all patients with thyrotoxicosis, but its degree bears no relation to the severity of the disease. Griffiths (1951) has suggested that a knowledge of the height of the fasting serum creatine is of diagnostic value in thyrotoxicosis, especially when considered in conjunction with the basal metabolic rate. Unfortunately, however, he appears to have accepted a level of 0.6 mg. of creatine per 100 ml. as the upper limit of normal in spite of the observation of Tierney and Peters (1943) that normal women often have a serum creatine higher than this figure. Because of the high degree of overlap which exists between thyrotoxic and normal men and women it is unlikely, even if a more sensitive method of estimating serum creatine could be devised, that the differences would be clear-cut enough to be of diagnostic value. Similar considerations apply to creatine-tolerance tests.

Blood Picture.—"Leucopenia is fairly common, and it has been claimed that relative or absolute lymphocytosis is a constant finding in hyperthyroidism" (Whitby and Britton, 1950). If this were true an examination of the blood would clearly be diagnostically helpful. My colleague Dr. E. K. Blackburn (1953, personal communication) has studied the peripheral blood in 51 of our proved cases of thyrotoxicosis. In none of these was there a leucopenia or an absolute lymphocytosis, taking the respective normal ranges as 4,000–11,000 per c.mm. and 1,000–4,500 per c.mm. (Osgood *et al.*, 1939). In his view the concept of relative lymphocytosis should be abandoned. The bone marrow has, however, shown a lymphocytic reaction in some cases. This is probably a manifestation of the general tendency to hyperplasia of lymphoid tissue in this disease. Anaemia, when it occurs, is usually of iron-deficiency type unrelated to the thyrotoxicosis, except in so far as the latter predisposes to achlorhydria.

Use of Radio-iodine in Diagnosis of Thyrotoxicosis

Pochin (1950), in his Oliver-Sharpey Lectures, described the ways in which radio-iodine may be used to investigate fundamental problems of iodine metabolism, and Myant (1952) has described and critically reviewed the different types of test which may be used to assess thyroid function. These tests fall into two main groups: they either measure directly or indirectly the capacity of the thyroid gland to take up radio-iodine, or they attempt to measure the output of radioactive thyroxine from the gland. The avidity of the thyroid for iodine, which is greatly increased in thyrotoxicosis, can be estimated by determining the proportion of a given dose taken up by the gland at a fixed time or the maximum amount taken up by the gland. Alternatively, the rate at which the dose is taken up at a given plasma concentration of radio-iodine may be measured, a figure which is termed the thyroid clearance rate by analogy with renal clearance rates. Theoretically this should be a more reliable index of thyroid activity than the total radio-iodine uptake. Since the administered radio-iodine is shared between the thyroid and the kidneys, an estimation of the amount of radioactivity in the urine will give an indirect measure of the capacity of the thyroid to absorb iodine. Samples of urine taken at various times after the test dose are usually analysed separately.

The thyroid converts the radio-iodine into radiothyroxine at a rate and to a degree which is determined by its functional activity. Twenty-four to forty-eight hours after a tracer dose has been given the plasma of normal individuals shows little or negligible radioactivity. On the other hand, the plasma of the thyrotoxic patient contains a significant amount of radioactive material, of which a high proportion is bound to protein. Tests of this type involve the examination of a blood sample at a fixed time after the administration of the test dose, and an estimation of the relative amount of radioactivity in inorganic and organic forms.

Many groups of observers have carried out investigations on normal individuals and on patients with thyrotoxicosis, using one or more of these methods. We (Goodwin *et al.*, 1951) compared seven different criteria in normal persons, in patients with definite thyrotoxicosis and in patients in an "intermediate" but non-toxic group with goitre, treated thyrotoxicosis, or anxiety state. We came to the conclusion that the index which correlated best with the final clinical diagnosis, arrived at independently of the results of radio-

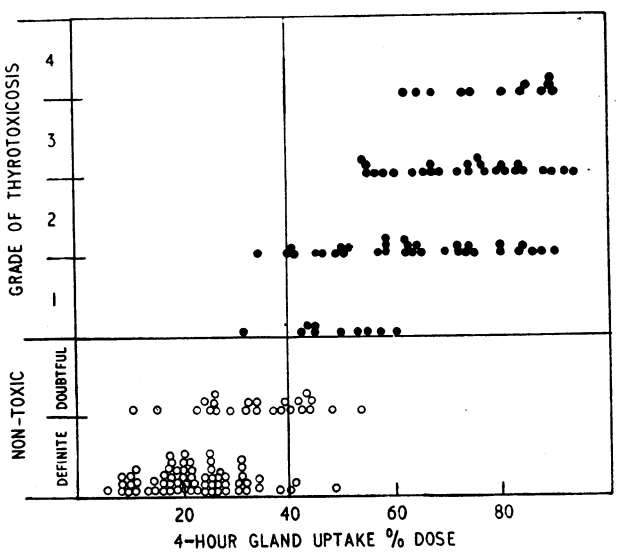

FIG. 5.—Relation of level of thyroid function to uptake of radio-iodine after four hours.

iodine tests, was the protein-bound plasma activity measured 48 hours after the administration of the dose. We thought, however, that, whenever possible, more extensive studies should be carried out. Subsequently we (Ansell *et al.*, 1953) selected three radio-iodine tests and applied them to a group of 179 persons, all of whom had been carefully and independently assessed clinically. These tests were the proportion of the dose taken up by the gland four hours after administration, the clearance rate of radio-iodine from the plasma one hour after administration, and the protein-bound plasma activity 48 hours after administration. Figs. 5 and 6 show the results which we obtained.

All thyrotoxic cases were classified into one of four grades of severity, and the non-toxic group was divided into those cases in which there was no clinical doubt that the patient had normal thyroid function and those about which there had initially been some doubt that the patient might be thyrotoxic. It is this group which any satisfactory test must separate accurately from cases of mild thyrotoxicosis. It will be seen from Fig. 5 that if a 40% uptake by the gland four hours after the radiation had been given was taken as the dividing line it separated fairly well non-toxic from thyrotoxic individuals, and that the results ran roughly parallel with the degree of severity of the disease. High uptakes did, however, occur in non-toxic individuals. If we took a clearance rate of 80 ml. a minute as the dividing line between toxic and non-toxic persons we found that several thyrotoxic patients had clearance rates well below this level. The protein-bound plasma activity, however

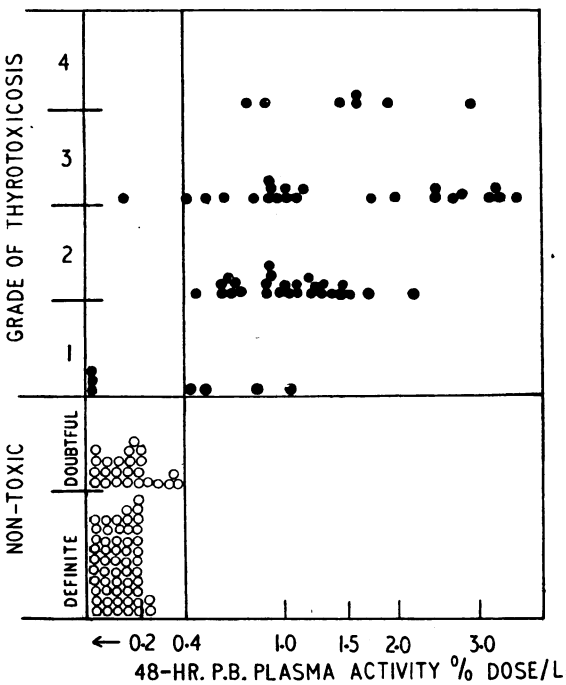

FIG. 6.—Relation of level of thyroid function to 48-hour protein-bound plasma activity. (Scale not strictly logarithmic below 0.2%.)

(Fig. 6), showed a fairly sharp division between the two groups, although thyrotoxic patients occasionally had levels well below our normal limit of 0.4% of the dose per litre. We concluded that the tests of four-hour uptake by the gland and protein-bound plasma activity at 48 hours would usually give consistent results and separate toxic from non-toxic cases.

We have now carried out more than 750 tracer tests of this type, and our conclusions, based on the smaller number of cases shown in Figs. 5 and 6, must be modified. Dr. Miller and I have correlated these figures with the clinical findings where they were available. Fig. 7 shows the results plotted so as to emphasize the cases of agreement or disagreement between the four-hour gland uptake and the 48-hour protein-bound plasma activity. Rectangles B and D contain cases in which both tests gave results which were in agreement. When this is so, it is quite exceptional to find a discrepancy between the clinical diagnosis and the radio-iodine tests, and we would place the error at less than 1%. It should be stated, however, that some cases were referred from other clinicians, and we cannot be sure that in some cases the tests have not been taken into account in arriving at a conclusion. A large proportion were, however, patients under our own care, and we can say with certainty that when the diagnosis is clear on clinical grounds the two radio-iodine criteria are always concordant and confirmatory.

We have ourseives examined the records of all the available patients in which the results of the two tests were discordant, that is to say, of cases falling in rectangles A and C. Black points appearing in rectangle A and white ones in rectangle C are examples of correct results by the plasma-activity test but incorrect as judged by the four-hour gland uptake. White points in rectangle A and black points in rectangle C indicate the converse. It will be seen that the black points fall about equally in rectangles A and C, but the white ones are mainly in rectangle C. The protein-bound plasma activity is therefore a more accurate index than the four-hour gland uptake. It is, in fact, about twice as reliable, but only because it agrees with the clinical diagnosis better in non-toxic cases. A similar analysis of the figures for the thyroid clearance rate shows that they correlate better with the clinical diagnosis than the four-hour uptake, but less well than the protein-bound plasma activity.

There are certain important circumstances in which radio-iodine tests give results which must be interpreted with reserve. These are the previous administration of iodine or iodine-containing compounds, the administration of drugs of the thiouracil series, previous treatment by thyroidectomy or radio-iodine, and in cases of myxoedema or cretinism. We have examined the records of 47 cases which gave discordant results in the two tests and in which one or other of these factors had to be taken into account. These are not plotted in Fig. 7.

The administration of inorganic iodine or iodides diminishes the amount of radio-iodine taken up by the gland, and it is wise to wait for three weeks after stopping these drugs before carrying out tracer tests (Keating *et al.*, 1950). Plasma activity is also reduced (Ansell and Miller, 1952). We therefore carry out a simple test described by Foote *et al.* (1952) for iodides in the urine. The organic iodine compounds used in diagnostic radiography also affect radio-iodine criteria, but do not yield enough iodine to give positive readings in this test. We have found that individuals with normal thyroid function may show complete suppression of radio-iodine uptake 18 months after they have been given iodized oil for bronchography. They should be specifically questioned about previous *x*-ray investigations.

Drugs of the thiouracil series administered over a period of time may cause an increased uptake of radio-iodine by the thyroid which can persist for as long as three years (Foote *et al.*, 1952). In our series plasma activity was a much more accurate index in such cases.

After thyrotoxicosis has been treated either by thyroidectomy or by radioactive iodine the 48-hour plasma activity tends to be higher than would be expected from clinical estimates of thyroid function. In general, it can be said that the uptake or clearance is a more reliable index than plasma activity in assessing the results of these two forms

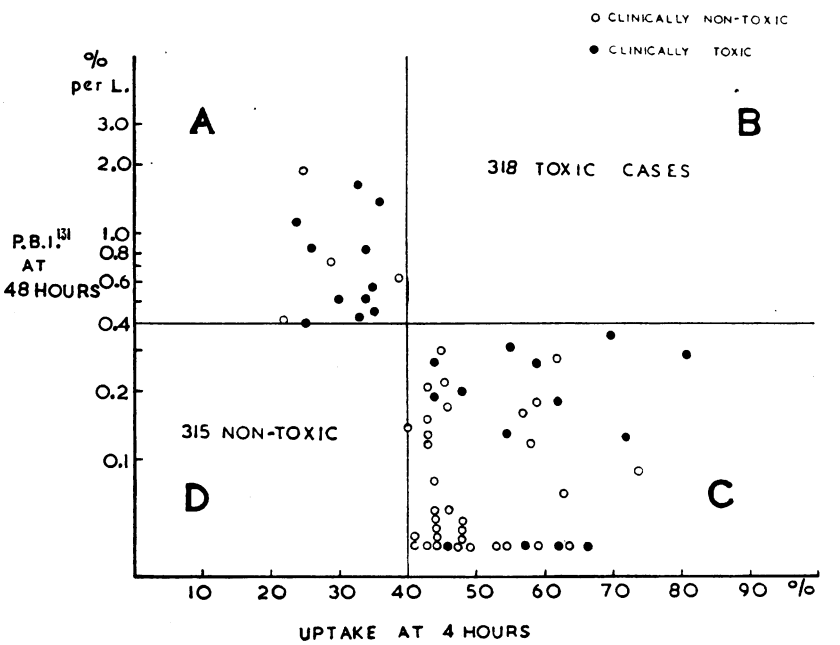

FIG. 7.—Relation of four-hour gland uptake to 48-hour protein-bound plasma activity levels.

of treatment (Ansell *et al.*, 1953). Similarly in hypothyroidism not amounting to complete myxoedema, high protein-bound plasma figures may be obtained in spite of clinical evidence of diminished thyroid function. The explanation of these exceptional results is not clear, but it seems probable that in these cases the specific activity of the circulating thyroxine is increased. The thyroid gland is working to the maximum of a diminished capacity to synthesize thyroxine and is turning over the iodine presented to it at an unusually rapid rate, so that a relatively large proportion of the circulating thyroxine molecules contain radioactive atoms. This hypothesis has been shown to be correct in two cases of hypothyroidism in which simultaneous estimations of circulating non-radioactive protein-bound iodine were carried out (Blom and Terpstra, 1953). In familial cretinism, in which hypothyroidism is associated with both a high uptake by the gland and high protein-bound radio-iodine activity, it seems more likely that there is a more fundamental disturbance in iodine or thyroxine metabolism (Hubble, 1953; McGirr and Hutchison, 1953).

We have no doubt that it is always preferable to carry out at least two and preferably three of these tests, and at Sheffield these are always done. An estimation of the 48-hour protein-bound plasma activity alone may, however, be of great diagnostic value. Since the patient need not come into contact with electronic apparatus it is possible to provide a diagnostic service for hospitals far removed from the centre at which the actual estimations are carried out. Doses of radio-iodine are dispatched weekly and a single sample of plasma is returned from each patient. Macgregor *et al.* (1953) have recently reported the results of such a co-operative effort between our centre and Nottingham. The patients were seen by two physicians, and in doubtful cases the final diagnosis was made only after therapeutic trials and follow-up.

Similar tests have been carried out at Derby and Scunthorpe, but the conditions were less rigorously controlled and the final clinical diagnosis may in some instances have been influenced by the results of the test. The correlation between the clinical and laboratory results at the three centres is summarized in Table II. It will be seen that an incorrect conclusion was given by the radio-iodine criterion in about 8% of cases, the test mainly tending to show non-toxic results in clinically toxic cases. This is especially true of borderline or doubtful cases.

TABLE II.—*Correlation Between the Final Clinical Diagnosis and the Conclusions Based on a Single Estimation of the 48-hour Protein-bound Plasma Activity*

	No. of Cases	Clinical Diagnosis	Correct	Incorrect
Nottingham	50	Toxic	25	2
		Non-toxic	22	1
Derby	77	Toxic	22	2
		Non-toxic	51	2
Scunthorpe	43	Toxic	13	6*
		Non-toxic	24	0
Total ..	170		157	13†

* 5 "mild" or "doubtful."
† 3 clinically non-toxic cases returned as toxic; 10 clinically toxic cases returned as non-toxic.

General Conclusions on Plasma Activity Tests

When we consider together the 1,000 tests of protein-bound plasma activity which we have carried out we arrive at the following general conclusions. The test alone has an error of about 10%, assuming the clinical diagnosis to be correct, but it must be remembered that this itself is not 100% accurate. When the results are supported by simultaneous estimations of clearance rates or uptake figures, great confidence can be placed in the results. If uptake and plasma activity figures are discordant the latter is more likely to be correct. It is unlikely to suggest that a patient is thyrotoxic without this being the case. It is better, however, in such instances to carry out a therapeutic trial. Little help is gained by repeating the tests, which almost always give the same results. Uptake clearance and plasma activity figures must be interpreted with reserve in patients who have received previous therapy.

All radio-iodine tests have certain drawbacks, and the ones which we use are not immune from criticism. It is possible by using a scintillation counter to determine the uptake of radio-iodine by the gland with as little as 5 microcuries of I^{131}, but to determine with reasonable accuracy the lower levels of plasma activity at least five times this amount must be used. Even so, the radiation hazard is less than that of some common diagnostic *x*-ray procedures, and the dose is less than a hundredth of that used in the treatment of thyrotoxicosis. Nevertheless, it is desirable to reduce to the absolute minimum the amount of radiation to which the gland is subjected. One way of achieving this result is to administer a drug of the thiouracil series an hour before the radio-iodine is given (Stanley and Astwood, 1948), or, alternatively, sodium iodide may be given together with the radio-iodine intravenously (Newsholme, 1952). Either the clearance rate (Newsholme) may be used or the maximum uptake of I^{131} by the thyroid together with a factor acting as an index of the initial slope of the curve (Foss and Herbert, 1952). These tests also have the advantage of being relatively unaffected by an increase in the iodine intake.

The avidity of the thyroid gland for iodine is most simply measured by determining the proportion of a dose excreted in the urine. The advantages of this method are its applicability to out-patient cases, the small dose of radio-iodine used, and the relative simplicity of the physical measurements. One disadvantage is the difficulty of ensuring that the whole of the urine output has been preserved for analysis, a difficulty which we have experienced with female patients even when they have been in our wards. We found that the excretion of radio-iodine in the urine during the 24 hours after it had been administered was a relatively poor index of thyroid function (Goodwin *et al.*, 1951). Fraser and his co-workers (1953) have, however, shown that by collecting the urine separately during the periods 0–8 hours, 8–24 hours, and 24–48 hours three indices of thyroid function could be derived. These were used to check for errors of collection and technique, and to correct for the presence of renal disease. The deductions made from them usually correlated well with the presence or absence of hyperthyroidism, and could be used to confirm the existence of myxoedema. The method appears to suffer, however, from the general defect of uptake measurements which we have also found since it tends to place non-toxic nodular goitres in the toxic range.

Fraser (1953) has recently shown that a method described by Berson *et al.* (1952) yields satisfactory results in both hyperthyroidism and hypothyroidism. The method has the disadvantage of requiring the intravenous administration of the radio-iodine, but the test, which is essentially a clearance test, can be completed in an hour.

Choice of a Radio-iodine Test

It will be seen, then, that all the tests which are at present available have both advantages and disadvantages. Our experience leads us to believe that it is best to determine both the iodine uptake of the gland and the protein-bound plasma activity. The latter measurement alone is simpler, and can be completed without the patient attending the diagnostic centre. The urine-excretion test as modified by Fraser is technically simple if appropriate samples can be delivered to the centre, and is of especial value in assessing hypothyroid states. Those who contemplate setting up a radio-iodine diagnostic service would be well advised to concentrate on one or two of the available tests, and to establish their own ranges of normal and abnormal values. We have some evidence that there are differences in the levels indicating abnormality in different countries and even in different parts of the same country. Most of our patients

come from an area which is known to be relatively iodine deficient (Murray *et al.*, 1948), and our criteria may not be generally applicable.

Relative Value of Different Tests of Thyroid Function

Each of the available tests measures a different aspect of thyroid function. Those using radio-iodine indicate either the capacity of the thyroid gland to concentrate iodine or its ability to turn out radioactive thyroxine, but they do not measure the absolute rate of iodine metabolism. The former test is affected by the variation in the plasma iodide level, and the latter by the thyroxine content of the thyroid. Both must be interpreted with reserve when the patient has received iodine-containing compounds or has been subjected to any therapeutic procedure. The basal metabolic rate, even after a hypnotic, measures hypermetabolism which may be due to a variety of "extrathyroid" causes (Meckstroth *et al.*, 1952). It does, however, give some indication of the degree of severity of the condition. The estimation of the non-radioactive serum protein-bound iodine should theoretically give the most direct measurement of circulating thyroxine, but is technically difficult. But even if we knew with certainty the absolute level of circulating thyroxine we should have to take into account the general biological phenomenon of the variability of the response of different individuals to the same stimulus.

Myant (1952) has said, "However we define normality, the limit we set between normal and pathological is an arbitrary one, and no test can tell us what this limit should be." From the point of view of the biologist this is true, and with sufficiently sensitive tests we should probably find a graded response to increasing doses of thyroxine. It is even possible that some of the symptoms of those who have an anxiety state are produced by a slight excess of the thyroid hormone. On the basis of blood iodide studies Brody (1949) has produced evidence that this may be so, and Fraser *et al.* (1953) noted a tendency for his "neurosis" group to have a relatively high gland uptake of radio-iodine. The possibility is intriguing. Yet such persons do not respond to therapeutic tests which diminish the activity of the thyroid gland. Our correlations are ultimately based on this response, and it is this aspect in which the clinician is primarily interested. Our preference for radio-iodine tests is founded on the fact that by their use we are able to make a decision quickly on whether or not specific treatment shall be instituted, and they are of minimum inconvenience to the patient. We believe that they will be widely used in the future.

Conclusion

I hope I have been able to convince you that, while it may be very easy to make a diagnosis of thyrotoxicosis from the history and physical examination alone, it is often very difficult and there will always be patients about whose thyroid function the physician remains in doubt. Some symptoms and signs have greater diagnostic value than others; diagnosis is relatively easy in the male, but difficult in the female, especially if she is in a state of chronic anxiety.

When there is any question about the diagnosis, therapeutic tests should be carried out, but much time may be saved by studies of iodine metabolism, using isotope techniques.

I wish to thank my clinical colleagues at Sheffield who have referred cases to me, and Dr. D. V. Hubble, of Derby, and Dr. J. H. D. Millar, of Scunthorpe, for detailed information about cases at these centres. The work on radio-iodine was made possible through the collaboration of Mr. G. W. Blomfield, the Director, and Dr. H. Miller, the senior physicist of the Sheffield National Centre for Radiotherapy. Figs. 5 and 6 are reproduced by permission from *Radioisotope Techniques*, Proceedings of the Isotope Techniques Conference, Oxford, Volume I. H.M.S.O., 1953.

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