The diagnosis of thyrotoxicosis

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Summary

Thyrotoxicosis is a clinical syndrome due to excessive amounts of thyroid hormone in the circulation and tissues. Graves' disease, goitre and exophthalmos, is the commonest variety, but in some parts of the world thyrotoxicosis supervenes on the background of a long standing nodular goitre. Other varieties such as ectopic TSH syndromes are very rare.

The diagnostic sequence in practice starts with clinical suspicion and a decision can often be made on the symptoms and signs alone. It is, however, always advisable to confirm the presence or absence of thyrotoxicosis. There has been re-orientation in the simple test procedure used in this respect. Measurements such as serum TSH and serum TSH response to TRH and measurements of serum LATS levels are available only in a few centres and are not discussed in detail.

Tests based on the carriage of thyroid hormones in the blood are preferable to *in vivo* radionuclide studies, particularly when the patient is thought to be euthyroid. We advise a serum $PB^{127}I$ and serum total thyroxine estimation in all patients. If the data are abnormal we add a serum T3 resin estimation to check whether the values are due, for example, to iodine contamination or altered binding.

We advise radionuclide studies in all doubtful cases and measurements such as the 4 hr or 24 hr ^{131}I uptake and the 48 hr serum $PB^{131}I$ are very helpful. A thyroid uptake suppression test may be required if there is still doubt. In general those patients going for thyroidectomy or ^{131}I therapy should have a scan performed. With improved technology much safer radionuclides, such as ^{123}I or ^{99m}Tc , may be usable when thyrotoxicosis is suspected in children or during pregnancy.

Causation

Thyrotoxicosis is a common clinical disorder and a consequence of too much thyroxine (tetraiodothyronine—T4) and/or triiodothyronine (T3) in circulation and tissues. There are a number of rare causes; exceptionally it arises because there is a true

intrinsically overactive discrete adenoma in the thyroid, as distinct from a toxic multinodular goitre (see below). Rarely, thyrotoxicosis is the result of metastatic untreated follicular carcinoma, and over-treatment of hypothyroidism may cause some of the clinical features. Very occasionally thyrotoxicosis is seen in patients with trophoblastic tumours or other visceral tumours, and this is usually attributed to the artificial production of thyroid stimulating hormone (TSH) or TSH-like substances by the deranged tumour cells (ectopic TSH syndromes). Sometimes patients with active acromegaly are also thyrotoxic, but this does not seem to be due to excess TSH stimulation; other rare types of thyrotoxicosis probably include some people whose hypothalamus is unresponsive to a high normal blood thyroid hormone level and they proceed to secrete an inappropriate amount of TSH-releasing hormone (TRH) and consequently the blood TSH is raised, leading to thyrotoxicosis.

The very great majority of thyrotoxic patients have, however, either toxic goitre with exophthalmos (Graves' disease) or toxic multinodular goitre without exophthalmos. In Western Europe and the U.S.A., for example, Graves' disease is much more common than toxic multinodular goitre, but the latter is not rare in older patients; there is usually a history of long-standing goitre and recent thyrotoxicosis. Toxic multinodular goitre is more commonly seen in countries such as Norway and Tasmania with epidemiological but moderate iodine deficiency, and there is evidence that when this has been corrected the prevalence of thyrotoxicosis increases; presumably the iodine deficiency curtails the potentially thyrotoxic thyroid.

The fundamental cause of Graves' disease is not known but it seems that the primary disorder lies outside the thyroid. Certainly it is not due to too much pituitary TSH (in fact TSH is not detectable in the blood of people with active Graves' disease and the pituitary responds poorly to TSH-releasing

hormone—TRH). The syndrome of Graves' disease also has extrathyroidal tissue abnormalities; the exophthalmos and periorbital swelling are almost invariable, but sometimes there is in addition pretibial myxoedema, finger clubbing and acropachy. In young people there may be slight enlargement of neck lymph nodes, a just palpable spleen and, if special X-rays are carried out, the thymus may be seen to be enlarged too. Some insight into those apparently linked observations has been given by the discovery of an unusual 7S IgG immunoglobulin in the neat sera of 50%, or the concentrated sera of 80%, of patients with active Graves' disease. This substance, when tested in appropriately prepared mice or guinea pigs causes prolonged thyroid stimulation (long acting thyroid stimulator—LATS). Its prevalence and titres are high in those patients with extrathyroidal tissue manifestations of Graves' disease and the peripheral lymphocytes from the same patients can be induced to synthesise LATS *in vivo*. There is, however, a generally poor correlation between blood LATS titres and the severity of thyrotoxicosis, the degree of exophthalmos and the response to therapy whether by antithyroid drugs, operation or radioiodine. Nevertheless, the discovery of LATS should open new avenues of thought and research. Included in the general problem area is the need to explain the inheritance of the tendency to develop the condition, its association with common conditions such as pernicious anaemia and rheumatoid arthritis, the mode of action of LATS in the thyroid itself and its association with other antithyroid antibodies.

The demonstration of LATS has certainly explained why some mothers with treated or untreated thyrotoxicosis produce babies with congenital or neonatal hyperthyroidism. The LATS immunoglobulin passes the placenta, and if in high enough titre stimulates the young thyroid. This thyrotoxicosis remits spontaneously, although temporary drug control may be necessary, as the LATS disappears from the circulation. This usually takes place within a few weeks of birth.

These comments are made to emphasize our relative ignorance about the processes involved in the initiation and maintenance of the commonest syndrome of clinical thyrotoxicosis. Although direct measurements of blood TSH, blood TSH response to TRH and blood LATS levels are likely to clarify some aetiological problems and even help with diagnostically difficult cases, they are still research tools.

The ordinary clinician responsible for making diagnostic and therapeutic decisions about large numbers of patients, only some of whom will have thyrotoxicosis, really wants to know what there is in the laboratory to help him. This article attempts to

orientate the busy doctor in this respect. Emphasis will, of course, be put on simple tests and those using radionuclides, but it is hoped this will be done in the context of the general diagnostic process.

Clinical diagnosis

Nobody would disagree that the most important first step in making a diagnosis of thyrotoxicosis is to suspect it. Obviously a previous or family history is helpful and the presence of eye signs and a goitre have high diagnostic value too. The clinical index (Table 1) described by Crooks, Murray & Wayne (1959) is very helpful to the general physician, in that patients can be segregated into three general categories on the basis of the symptoms and signs. There will be those who appear to be definitely not thyrotoxic (total diagnostic score less than 11), those who appear to be unequivocally thyrotoxic (total diagnostic score greater than 19) and those in whom the diagnosis is doubtful (total diagnostic score between 11 and 19). Patients who have a history of treated thyrotoxicosis are a special group where the index is not applicable, since some signs such as goitre and exophthalmos are residual even when the patient is in remission. This index is also not applicable to those patients with unusual forms of thyrotoxicosis, such as ectopic TSH syndrome. The rarer forms of thyrotoxicosis will not be further discussed. Thyrotoxicosis in the newborn and in pregnancy pose special diagnostic problems and thyrotoxicosis occurring in underprivileged regions or severe iodine deficiency also give rise to diagnostic difficulty.

The best physicians are not infallible; since thyrotoxicosis can be corrected, if not cured, and each of the three treatments have their respective hazards and two are destructive (operation and radioiodine), it is essential that at least one reliable test is carried out even when the situation seems clear. The choice of a single test obviously depends on local, regional and sometimes national resources. Nevertheless a few guiding principles can be laid down.

Serum PB¹²⁷I, total thyroxine and T3 resin tests (Figs. 1–4 and Tables 2 and 3).

The author's view is that enough is now known about *in vitro* measurements of blood hormone levels to advise their application in the first stage of diagnostic decision making. In our view all patients should have chemical estimations of the serum protein bound iodine (PB¹²⁷I), preferably carried out by autoanalyser; they should also have an estimation of the serum total thyroxine using, for example, a competitive binding assay system of the type produced by the Radiochemical Centre, Amersham (Thyopac 4). When the serum PB¹²⁷I or the serum total thyroxine give values outside the range for

TABLE 1. Diagnostic index for thyrotoxicosis (Crooks *et al.*, 1959)

Symptom	Score		Sign	Score	
	Present	Absent		Present	Absent
Breathless on exertion	+1	0	Palpable thyroid	+3	-3
Palpitations	+2	0	Thyroid bruit	+2	-2
Tiredness	+2	0	Exophthalmos	+2	0
Preference for heat	0	-5	Lid retraction	+2	0
Preference for cold	+5	0	Lid lag	+1	0
			Hyperkinesia	+4	-2
			Finger tremor	+1	0
			Hands		
			Hot	+2	-2
			Moist	+1	-1
Excessive sweating	+3	0	Pulse rate		
Nervousness	+2	0	80/min	0	-3
			90/min	+3	0
Appetite			Atrial fibrillation	+4	0
Increased	+3	0			
Decreased	0	-3			
Weight					
Increased	0	-3			
Decreased	+3	0			
Totals			Totals		
Total symptom score			Total sign score		
			Final score =

FIG. 2. Diagram of thyroxine (T₄) transport in blood. Note that most of the T₄ is bound to thyroxine binding globulin (TBG) but the TBG capacity for T₄ is not wholly occupied even in thyrotoxicosis.

and 48 hr serum protein bound radioiodine—serum PB¹³¹I). Radioiodine studies are not, however, strictly necessary if the patients are not thyrotoxic on clinical grounds and the blood hormone measurements are normal. The exception to this rule is the patient with a non-toxic goitre where a scan may be useful.

When the patient is obviously thyrotoxic and measurements of blood hormone levels confirm this there are two indications for radioiodine studies. The first is when a single toxic adenoma or a toxic multinodular goitre is suspected and this can be shown by scanning and uptake measurements, and the second indication is when a patient is being considered for operation or radioiodine therapy. When patients may be going for partial thyroidectomy it is useful to have a scan showing the size and

FIG. 1. Diagram outlining current views on the mature regulation of thyroid function and the basis of some tests.

healthy non-pregnant adults, not on any medication, a serum T₃ resin test should be carried out on the same serum sample. This allows some decision to be taken as to whether the high values are the result of iodide contamination or abnormal binding (Figs. 1–4 and Tables 2 and 3).

Because of our research interest in thyrotoxicosis we also arrange for patients to have direct radioisotope (¹³¹I) studies (24 hr thyroid uptake and scan

FIG. 3. Principles of competitive protein binding (CPB) assay for T4 as employed in various commercial kits. When all the T4 (total T4) is extracted from a patient's sera (horizontal axis) and added to a system containing TBG bound ^{131}I -T4 there is an equilibrium reaction whereby some of the ^{131}I -T4 is displaced. The displaced radioactivity is proportional to the amount of T4 added.

FIG. 4. Illustration of alterations in T3 resin test due to changes in TBG binding of T4. Note that in pregnancy and in the perinatal period for example, both serum total T4 and T3 resin (% normal) are high, whereas in the nephrotic syndrome both are low (the serum total T4 and the T3 resin test are, therefore, complementary and should and can be done on each single blood sample to allow for anomalous data due to changes in TBG).

shape of the goitre before antithyroid drugs are commenced. When radioiodine therapy is being planned a measure of the tracer uptake and a scan (Fig. 5) are essential so that the appropriate therapeutic dose may be calculated. In patients where the diagnosis is in doubt, either clinically or because the serum PB^{127}I , the serum total thyroxine and the serum T3 resin test give apparently anomalous values we advise radioiodine studies. If there is still diagnostic doubt we proceed to a thyroid suppression test. The thyroid uptake of patients who are thyrotoxic fails

TABLE 2. An outline of some causes of altered serum PB^{127}I not due to thyroid disease; note that some also alter serum total thyroxine

1. Estimation of iodine not in T4—high values.
 - (a) Excessive iodide intake, e.g. potassium iodide in cough mixtures and iodopyrine in asthma remedies.
 - (b) Abnormal iodide intake, e.g. diiodohydroxy quinolones, antidiarrhoeal mixtures and iodoforms in skin antiseptics.
 - (c) Artificial iodine intake, e.g. administration of organic iodine compounds for radiology (effects on serum PB^{127}I last for months to years).
2. Interference with chemical estimation of PB^{127}I —low values, e.g. traces of mercury, gold and silver.
3. Alteration in TBG binding of T4 (also applies to serum total T4 assays).
 - (i) High values.
 - (a) Oestrogen effects—e.g. pregnancy, newborn, oestrogen therapy.
 - (b) Congenital variation—familial.
 - (c) Unknown mechanism—porphyria.
 - (ii) Low values.
 - (a) Drugs leading to low TBG—e.g. androgen and corticosteroid therapy.
 - (b) Replacement of T4 on TBG—e.g. salicylate and diphenyl hydantoin therapy.
 - (c) Low TBG as result of disease—e.g. nephrotic syndrome, portal cirrhosis, severe malnutrition.
 - (d) Congenital variation—familial.
 - (e) Altered binding of T4 associated with acute or severe illness in general.

Footnotes.

- (i) Production of abnormal iodoprotein by thyroiditis will give high PB^{127}I values.
- (ii) Chemical estimation of total serum ^{127}I should not give a value different from PB^{127}I by more than 1 $\mu\text{g}/100\text{ ml}$.
- (iii) Always think of drug or metal interference and altered TBG binding of T4 when PB^{127}I or serum total T4 values are quite inconsistent with the suspected diagnosis.
- (iv) TBG cannot itself be absolutely measured; only its capacity to bind T4.

to suppress with administered thyroid hormone (Table 4). Some of these patients with normal blood thyroxine values and radioiodine metabolism may be examples of thyrotoxicosis due to a selective increase in T3 secretion by the thyroid. If a facility for measuring the absolute blood level of T3 is available it should be used; this facility is, however, still only within the province of special research teams.

Other measurements such as the thyroxine binding capacity (TBC) of the thyroxine binding globulin (TBG) and direct estimation of the free serum T4 (of the order of 0.05% of the total) are also highly specialized facilities ranking with estimations of the 24 hr urine excretion of T4, assay of blood TSH and of LATs.

It is now appropriate to discuss the routine *in vivo* test procedures and to discuss some of the pitfalls which the busy diagnostician must appreciate. Since the conventional radioiodine study (uptake and

TABLE 3. A summary of thyroid test values in non-pregnant adults, during pregnancy and at various ages after birth. Note that these are approximate values and are subject to variations depending on techniques and the population under study

Group	Thyroid function tests in health					
	Adult non-pregnant	Adult pregnant	Premature	Perinatal	Childhood	Adolescence
Serum PB ¹³¹ I %	4-8	6-10	7-12	6-12	5-9	5-9
Serum total T4 %	5-12	8-14	9-15	7-13	6-12	6-12
Serum T3 resin %	90-120	>120	>120	100-120	90-120	90-120
Serum TBG T4 capacity %	15-30	30-70	25-50	20-50	15-30	15-30
Serum free T4 ng %	4	3	5	5	4	4
Serum TSH IU/ml	0-5	5-10	10-15	>15	0-5	0-10
Thyroid mass (G)	25	40	>2.5	2.5	10-15	15-25
¹³¹ I uptake	20-50	30-60	15-60	15-60	20-50	20-60
% Dose—24 hr						
Serum PB ¹³¹ I	<0.3	?	?	?	<0.3	<0.3
% Dose/litre						
BE ¹³¹ I (% PB ¹³¹ I)	>85	?	?	?	>85	>85

(1) Iodo protein, Mit and Dit do not normally leave the thyroid.

(2) TSH stimulation normally increases ¹³¹I uptake by 50%.

(3) T4 or T3 suppression normally decreases ¹³¹I uptake by 50%.

(4) TRH stimulation of TSH secretion not generally available.

FIG. 5. Scan of toxic goitre 24 hr after 50 μ Ci ¹³¹I.

serum PB¹³¹I) employs ¹³¹I, which delivers an appreciable radiation dose to the thyroid, it cannot be advised for routine use in children and in pregnancy. To partly circumvent this and to diminish radiation dosage in general, and with a view to devising a one-attendance radioisotope study, attention is again being given to the use of the short half-life nuclides of iodine (Table 5) and to the use of ^{99m}Tc which is trapped but not bound in the thyroid. ^{99m}Tc has many of the ideal physical attributes for thyroid studies (see below).

TABLE 4. Thyroid (or TSH) suppression test

In health the thyroid is more or less constantly under stimulation by pituitary thyrotrophic hormone (TSH); when the blood level of thyroid hormone rises the secretion of TSH falls. This forms the basis of the thyroid (or TSH) suppression test. If the healthy thyroid uptake is measured at, for example, 2-4 hr with ¹³¹I and thyroxine 0.2 mg/day is given for the next 14 days or triiodothyronine 60 μ g/day for 7 days and the uptake re-measured, it is found to have become significantly reduced. Total or partial failure of suppression of uptake in these circumstances indicates that thyroid function is wholly or in part independent of pituitary control. This is characteristically found in untreated toxic diffuse goitre and in the autonomous overactive thyroid adenoma. Failure to suppress is, therefore, of value in confirming suspected thyrotoxicosis, but lack of suppression may also be found in other thyroid states in which the patient is euthyroid; for example, in patients with euthyroid Graves' disease and treated thyrotoxicosis.

Criteria for thyroid suppression test* (4 hr uptake of radioactive iodine, e.g. ¹³¹I)

Normal suppression

1. The second uptake falls significantly and by more than 50% of the first uptake;
or
2. The second uptake is less than 10% of the dose.

Absent suppression

1. The second uptake is the same as the first;
or
2. The difference between the first and second uptake is less than 14% of the mean of the two uptakes (i.e. ± 4 SD).

Partial suppression

1. The second uptake is significantly less than the first uptake but is not less than 50% of the first uptake;
or
2. A significant depression of uptake but the second uptake is more than 11% of the dose.

* Based on data by Hobbs *et al.*, 1963.

TABLE 5. Radionuclides used to assess thyroid function and structure

Isotope	Half-life	Approx thyroid dose (Rad/ μ Ci given)			Comment
		Adult	Infant	Child	
^{131}I	8.0 days	1.5	5	2.5*	Best all round for uptakes, scans and serum studies
^{132}I	2.3 hr	0.01	0.05	0.03	Useful for early uptakes and TSH stimulation/suppression tests only
^{125}I	13.3 hr	0.02	0.06	0.04	Probably best of all but not generally available
^{125}I	60.6 days	1.1	0.5	0.8	Not indicated
$^{99\text{m}}\text{Tc}$	6.0 hr	0.001	0.001	0.001	Only trapped by thyroid. Will prove very useful especially with gamma camera and dynamic studies

* When thyroid uptake is low the radiation doses are correspondingly reduced.

In vivo radionuclide studies

As might be appreciated radioactive iodine studies continue to be useful in the investigation of adult thyroid disease and the evaluation of non-pregnant adult patients with suspected or obvious thyrotoxicosis is no exception. Their great advantage is that a direct measurement is made of the thyroid iodine metabolism and an uptake measurement (at 4 hr or 24 hr) together with a turnover measurement (48 hr protein bound iodine PB^{131}I) are complementary to other tests. With ^{131}I and modern rectilinear scanners a scan can be obtained too (Fig. 5) and this is advisable if the patient is to have an operation or ^{131}I therapy. ^{131}I studies should be carried out on all cases of doubtful thyrotoxicosis and a suppression test (Table 4) can follow if the problem has not been clarified. The disadvantages of patient attendance, expensive equipment and the need for scientific and technical personnel are offset if the patients are selected for these studies and they are carried out on a regional basis.

Thyroid uptake

In routine practice, measurements of the radioactivity (^{131}I) present in the thyroid gland are made at either 2, 4, 24 or 48 hr after the oral or intravenous administration of the isotope. The quicker tests may be carried out over any interval of the day and moderate physical activity does not influence the results. It is best, if not inconvenient, to measure both the early thyroid uptake (2 or 4 hr) and a later uptake (24 or 48 hr). Many centres compromise by doing a single uptake at 24 hr. The final choice in this respect depends on local circumstances, including distance to be travelled by outpatients, staff availability and the diagnostic data required. When thyrotoxicosis is suspected a single early uptake at 20 min, 2 or 4 hr, gives better discrimination from the normal than does a single later uptake (24 or 48 hr), though a combination of the early and late measurements (4 and 48 hr) improves the diagnostic

precision in thyrotoxicosis. Technical details are, of course, critical, but are given elsewhere.

Factors influencing uptake tests

The values (percentage uptake of administered dose) depend chiefly on the iodide intake, the time after the administration of the isotope, the functional status of the thyroid in respect of its rate of clearance of the isotope from the plasma, and on other variables which include the mass and position of the gland, the volume of active follicular tissue and the previous administration of agents which modify the function of the gland and thyroid disease. Representative values for uptakes (percentage of administered dose) of the isotope found in both normal healthy people and in those with thyroid diseases are given in Table 1. It must, however, be emphasized that these values, and particularly the normal ranges, should be derived by individual laboratories since they depend on the average iodine content of the diet of the community. When the diet is rich in iodide, as it may be when the iodine content of the water, milk and bread is high, or when table salt is iodized and fish is freely eaten, the uptake of the radioactive iodide may be low, but this need not necessarily reflect the absolute amount of iodide taken up by the gland, which may be normal. For example, in the U.S.A. the average normal thyroid uptakes are lower than in the United Kingdom. In Iceland, where iodine intakes are high, the thyroid uptake of administered radioiodine is low in normal people too. Low uptake values are also found when iodides, either inorganic or organic, are administered therapeutically or as radiodiagnostic contrast media to patients. Artificially low uptake values may also be found when the gland is not fully viewed by the counter, e.g. retrosternal or ectopic thyroid tissue, or when the goitre is very large. Provided these modifying factors are remembered, an uptake test can be sensibly interpreted.

Serum protein bound radioiodine test

Radioactive iodine taken up by the thyroid

incorporated into the thyroid hormones which are secreted into the circulation. In the circulation normally more than 99% of the hormone is bound to protein. Thus the protein bound radioactive iodine serves as an index of the rate of conversion of thyroid iodide to thyroid hormone, and this principle is employed in the well-established test of thyroid function which can be carried out after the procedures for measuring the uptake have been completed. The isotope must be ^{131}I , since meaningful indices are obtained only 48 hr after the administration of the dose. The principle of the procedure is that the total radioiodine content of serum is measured before and after passage through an ion exchange column. The eluate is free of inorganic radioiodine and thus contains only the radioactivity in the protein bound fraction. Two important values are obtained: total plasma radioiodine and protein bound radioiodine. Both are calculated as percentage of the radioiodine dose administered per litre of plasma.

Depending on the sensitivity of the counting apparatus, doses of ^{131}I varying from 2 to 10 μCi may be employed. The higher doses are best if sera has to be transported or stored for counting.

The serum protein bound radioiodine has been found to be of great value in the exclusion or confirmation of thyrotoxicosis. When the value is less than 0.3% of the administered dose per litre of plasma a diagnosis of hyperthyroidism in any circumstances is unlikely. In the majority of thyrotoxic patients, whether presenting for the first time or as a relapse following therapy, the value is greater than 0.4% of the dose per litre. However, high values, i.e. greater than 0.4% of the dose per litre of plasma, are found in patients who are not thyrotoxic but who have a small intrathyroidal organic iodide pool, and consequently a rapid conversion of trapped iodide to protein bound iodine. This is obtained in post-operative thyroid remnants, when the gland is the seat of pathological destruction too, when there is concomitant autoimmune thyroiditis, or when it is small as in the solitary functioning adenoma. Sometimes, and usually in rare instances of goitre and hypothyroidism (and occasionally in autoimmune thyroiditis and thyroid carcinoma), the thyroid secretes iodoprotein (non-hormonal iodine). This disorder will give a high serum PB^{131}I but since it is not labelled hormone it will not extract into butanol, a fact which is the basis of a specialized adaptation of the serum PB^{131}I test. Butanol radioiodine extraction test— BE^{131}I ; normally 85% of protein bound hormone is extractable. Non-hormonal iodine (and radioiodine) is extracted much less efficiently.

Use of other radionuclides

^{131}I usage in pregnancy is not acceptable and is

undesirable in children except when the diagnostic information exceeds the small risk of inducing latent neoplasia. Other radionuclides of iodine can be used (Table 5). Theoretically ^{123}I is about ideal for uptakes and scans, but it is not generally available since it is cyclotron produced. It would be very useful, however, in the evaluation of thyroid function in children and possibly in pregnancy too, although in relation to the differential diagnosis of thyrotoxicosis it must be remembered that there is a relative iodine deficiency state and so physiologically a raised uptake of radioiodine.

There seems to be little information as to whether the thyroid suppression test (Table 4) is helpful in thyrotoxicosis when suspected in pregnancy, and this might be a useful area of research using ^{132}I which is quite safe in pregnancy and children. ^{132}I is not, however, a suitable radioisotope for scanning, but it is useful for measuring serially thyroid uptake and in this context has been employed also as a 20 min intravenous uptake test to follow thyroid function during carbimazole drug therapy. The 20 min uptake is not affected by the carbimazole's action *per se* within the thyroid. In attempts to devise a quick safe uptake test there has also been a renewed interest in $^{99\text{m}}\text{Tc}$ pertechnetate. $^{99\text{m}}\text{Tc}$ pertechnetate given intravenously is trapped, but not bound, in the thyroid. Furthermore, it does not emit particulate irradiation and the gamma ray spectrum is ideal for scanning. Recent work suggests that an early $^{99\text{m}}\text{Tc}$ pertechnetate uptake (within 1 hr) using a rectilinear scanner or a focused collimator might be a very useful method for screening patients for thyrotoxicosis, for following thyroid function during therapy and obtaining scans if necessary. Indeed in a general thyroid diagnostic service Hurley *et al.* (1972) have improved the accuracy and speed of determination of thyroid structure and function with a system that combines the use of $^{99\text{m}}\text{Tc}$ pertechnetate, the scintillation camera and a small general-purpose computer. With the pinhole collimator of the gamma camera over the patient's thyroid, 5 mCi of $^{99\text{m}}\text{Tc}$ pertechnetate is injected intravenously. Data are accumulated in the core memory of an Image Display and Analysis System ('IDA'). The activity of a standard amount of $^{99\text{m}}\text{Tc}$ in a thyroid phantom is also measured. Data are displayed as serial images on a video screen. The exact area and activity of the thyroid are then computed by simple programs used together with a lightpen. The activity in tissue adjacent to the thyroid is subtracted to correct for extrathyroidal activity. The entire gland and focal regions within the gland are characterized by rates of uptake of $^{99\text{m}}\text{Tc}$ pertechnetate.

The method was tested with respect to variations in the size, position and activity of the thyroid. There was good correlation between $^{99\text{m}}\text{Tc}$ pertechnetate

uptake and the clinical status in twenty-two normal volunteers and fifty-four patients. The method requires only 10 min of technician time; the results are available within 40 min and the patient need not return for subsequent study. Both structure and function are examined at the same time, and regional as well as total function can be measured.

Acknowledgments

FIGS. 1-4 and Table 2 are reproduced by kind permission of the Editors of *Seminars in Nuclear Medicine*, 1973, Volume 3, No. 1.

Bibliography

- ACLAND, J.D. (1971) An interpretation of the serum protein bound iodine: a review. *Journal of Clinical Pathology*, **24**, 187.
- ALEXANDER, W.D., KOUTRAS, D.A., CROOKS, J., BUCHANAN, W.W., MACDONALD, E.M., RICHMOND, M.H. & WAYNE, E.J. (1962) Quantitative studies of iodine metabolism in thyroid disease. *Quarterly Journal of Medicine*, **31**, 281.
- BURKE, G., HALKO, A., SILVERSTEIN, G.E. & Hilligoss, M. (1972) Comparative thyroid uptake studies with ^{131}I and $^{99\text{m}}\text{Tc}$. *Journal of Clinical Endocrinology and Metabolism*, **34**, 630.
- CATT, K.T. (1970) The thyroid gland. *Lancet*, **i**, 1383.
- CAUGHEY, J.E. (1970) Effects of iodation of bread. *Lancet*, **i**, 847.
- CHADD, M.A., GRAY, O.P. & DAVIES, D.F. (1970) Thyroid function tests in children. *Archives of the Diseases of Children*, **45**, 374.
- CHAN, V. & LANDON, J. (1972) Urinary thyroxine excretion as index of thyroid function. *Lancet*, **i**, 4.
- CHOICE OF THYROID FUNCTION TESTS (1970) *Drug and Therapeutics Bulletin*, **8**, 73.
- CLARK, F. (1967) The estimation of thyroid hormone binding by plasma proteins and of unbound levels of thyroxine in plasma. *Journal of Clinical Pathology* (Supplement), **20**, 344.
- CROOKS, J., MURRAY, I.P.C. & WAYNE, E.J. (1959) Statistical methods applied to the clinical diagnosis of thyrotoxicosis. *Quarterly Journal of Medicine*, **28**, 211.
- DAVIS, P. J. (1966) Factors affecting the determination of the serum protein bound iodine. *American Journal of Medicine*, **40**, 918.
- EDITORIAL (1969) Thyroxine in blood and tissues. *Lancet*, **i**, 974.
- EDITORIAL (1969) The changing iodide uptake test. *New England Journal of Medicine*, **280**, 1474.
- EDITORIAL (1970) Thyroid function tests. *Lancet*, **ii**, 806.
- EDITORIAL (1971) Thyrotrophin immunoassay. *British Medical Journal*, **4**, 761.
- EDITORIAL (1972) Thyrotoxicosis in pregnancy. *Lancet*, **i**, 886.
- EDITORIAL (1972) T3 thyrotoxicosis. *British Medical Journal*, **1**, 306.
- EDITORIAL (1972) Hypothalamic releasing hormones. *British Medical Journal*, **1**, 65.
- FISHER, D.A. (1971) Pediatric aspects of hyperthyroidism. In: *The Thyroid* (Ed. by S. C. Werner and S. H. Ingbar), 3rd edn., p. 665. Harper and Row, London.
- FISHER, D.A. (1971) Thyroid function tests in childhood. In: *The Thyroid* (Ed. by S. C. Werner and S. H. Ingbar), 3rd edn., p. 292. Harper and Row, London.
- GOOLDEN, A.W.G., GLASS, H.I. & WILLIAMS, E.D. (1971) Use of $^{99\text{m}}\text{Tc}$ for the routine assessment of thyroid function. *British Medical Journal*, **4**, 296.
- GOTTSCHALK, A. (1969) Technetium-99m in clinical nuclear medicine. *Annual Review of Medicine*, **20**, 131.
- GREIG, W.R., BOYLE, I.T. & BOYLE, J.A. (1967) Diagnosis of thyroid disorders using radioactive iodine. *Medical Monograph* No. 5, Radiochemical Centre, Amersham, U.K.
- GREIG, W.R., GRAY, H.W., MCGIRR, E.M., KAMBAL, A. & RAHMAN, I.A. (1970) Investigation of endemic goitre in Sudan. *British Journal of Surgery*, **57**, 11.
- HALL, R. (1972) The immunoassay of thyroid stimulating hormone and its clinical applications. *Clinical Endocrinology*, **1**, 115.
- HAYEK, A. & STANBURY, J.B. (1971) The diagnostic use of radionuclides in the thyroid disorders of childhood. *Seminars in Nuclear Medicine*, **1**, 334.
- HETZEL, B.S. (1968) The aetiology and pathogenesis of hyperthyroidism. *Postgraduate Medical Journal*, **44**, 363.
- HOBBS, J.R., BAYLISS, R.I.S. & MACLAGAN, N.F. (1963) The routine use of iodine-132 in the diagnosis of thyroid disease. *Lancet*, **i**, 8.
- HURLEY, P., MAISEY, M.N., NATARAJAN, T.K. & WAGNER, H.N. (1972) A computerized system for rapid evaluation of thyroid function. *Journal of Clinical Endocrinology and Metabolism*, **34**, 354.
- KENDALL-TAYLOR, P. (1972) Hyperthyroidism. *British Medical Journal*, **2**, 337.
- MCDUGALL, I.R. & GREIG, W.R. (1971) Pathogenesis and treatment of thyrotoxicosis. *Scottish Medical Journal*, **16**, 519.
- MAYBERRY, W.E., CHARIB, H., BILSTAD, J.M. & SIZEMORE, G.W. (1971) Radioimmunoassay for human thyrotrophin—clinical value in patients with normal and abnormal thyroid function. *Annals of Internal Medicine*, **74**, 471.
- MUNRO, D.S. (1972) The long acting thyroid stimulator. *Journal of the Royal College of Physicians of London*, **6**, 308.
- MURPHY, B.E.P. (1971) *In vitro* tests of thyroid function. *Semin. Nucl. Med. Seminars in Nuclear Medicine*, **1**, 308.
- ODDIE, T.H., PIRNIQUE, F.G., FISHER, D.A. & MEADE, J.H., JR (1968) Geographic variation of radioiodine uptake in euthyroid subjects. *Journal of Clinical Endocrinology and Metabolism*, **28**, 761.
- ODELL, W.D. (1970) as Moderator for 'Symposium on Hyperthyroidism'. *California Medicine*, **113**, 35.
- REPORT OF IAEA PANEL (1970) Measurement of radioactivity in body organs. *Journal of Nuclear Biology and Medicine*, **14**, 123.
- ROBIN, N.I., REFETTOFF, S., FANG, V. & SELENKOW, H.A. (1969) Parameters of thyroid function in maternal and cord serum at term pregnancy. *Journal of Clinical Endocrinology and Metabolism*, **29**, 1276.
- ROSENBERG, I.N. (1972) Evaluation of thyroid function. *New England Journal of Medicine*, **286**, 924.
- THORNSON, S.C., MINCEY, E.K., MCINTOSH, H.W. & MORRISON, R.T. (1972) Evaluation of a new *in vitro* blood test for determining thyroid status: the effective thyroxine ratio. *British Medical Journal*, **1**, 67.
- UTIGER, R.D. (1971) Thyrotrophin radioimmunoassay: another test of thyroid function. *Annals of Internal Medicine*, **74**, 627.
- WAYNE, E.J. (1960) Clinical and metabolic studies in thyroid diseases. *British Medical Journal*, **1**, 78.
- WAYNE, E.J., KOUTRAS, D.A. & ALEXANDER, W.D. (1964) *Clinical Aspects of Iodine Metabolism*. Blackwell Scientific Publications, Oxford.
- WELLMAN, H.N. & ANGER, R.T. (1971) Radioiodine dosimetry and the use of radioiodines other than ^{131}I . *Seminars in Nuclear Medicine*, **1**, 356.
- WERNER, S.C. (1967) As Moderator for Panel Discussion on 'Hyperthyroidism' in 'The Pregnant Woman and the Neonate'. *Journal of Clinical Endocrinology and Metabolism*, **27**, 1637.