CLINICAL PATHOLOGY IN GENERAL PRACTICE

TESTS OF THYROID FUNCTION

BY

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At times the diagnosis of disordered thyroid function is obvious on the first examination, but often the clinical signs do no more than suggest such a diagnosis, and it is then that further tests are needed. Several tests of thyroid function are available for the clinician, a fact which itself indicates that none is both easy and universally valid alone. However, if the best test is chosen for the problem which the patient presents, the laboratory can usually supply a useful measurement. But misleading inferences may be drawn unless the test is chosen in the light of the patient's clinical condition, and its results interpreted in the light of both the patient's history of recent drugs and his or her general clinical condition.

Not all hospitals can have facilities for all the tests; radio-iodine tests, in particular, require costly apparatus. In the larger centres where the latter is available, radio-iodine offers the simplest initial test for most patients; but careful use of the other tests can usually circumvent the need for this test. Where all tests are available one may summarize their uses as follows. With nervous patients the basal metabolic rate (B.M.R.) is apt to be high and the radio-iodine test is therefore preferable for assessing thyroid function. With patients who have had, within the six previous months, some thyroid operation or treatment or antithyroid or iodine-containing drugs, radio-iodine tests are difficult to interpret and are best avoided. Otherwise radio-iodine is the best test for recognizing or excluding thyrotoxicosis, and the B.M.R. combined with plasma cholesterol the best test for recognizing or excluding myxoedema.

Basal Metabolic Rate Test

This test measures the main effect of the thyroid hormone. It is most commonly done on in-patients; but with suitably equipped laboratories the out-patient can be tested, after being instructed on the day before. The patient attends fasting on the morning of the test, and has the measurement made after half an hour's rest on a bed or couch in a suitably screened and quiet alcove of the laboratory or ward. The usefulness of the test depends on the technician's ability to get the patient calm and restful both before and during the test. To achieve this it is usually necessary to have a routine involving two or more measurements on successive mornings, the first test being preceded by a trial run to accustom the patient to the procedure. The two main readings should agree within 10% of each other and the patient should have been calm, otherwise it is likely that the reading has not been "basal." The test consists in recording the patient's oxygen consumption during a period of six or more minutes. This is usually done with a spirometer connected by two wide-bore tubes to a mouthpiece, into and from which the patient breathes with a nose-clip applied; soda lime is in the apparatus to remove the carbon dioxide, and a drum records the change in spirometer level and so the oxygen consumption.

The result is calculated with the aid of tables; first the oxygen consumption is converted to its equivalent in heat production per unit of surface area (calories per square metre per hour), and then by reference to age and sex tables this is usually converted to "percentage normal."

Till recently the standards commonly used were from American surveys (Dubois, Benedict, or Boothby) based on the tests made on the first visit to the laboratory—that is, with little special effort to make the patient basal. Recently Robertson has published an English series of standards based on duplicate tests agreeing within 5%. With equivalently careful technique the latter standards should be used; their values are about 10% lower than the American standards. With careful technique the normal range is $\pm 10\%$, but in most laboratories it is $\pm 15\%$. The laboratory should therefore state on its report the normal limits for its technique and standards.

There are two main limitations to the usefulness of the B.M.R. test—the difficulty of ascertaining whether the patient really was basal during the test, and the possibility of non-thyroid causes of raised or lowered B.M.R.; the former is the more serious. The "basal" state means as nearly as possible at complete muscular, mental, and digestive rest (12 hours after food covers the last requirement); with nervous patients, in whom the problem commonly arises, this is difficult and sometimes impossible to achieve, and the nearness of the achievement is always hard to assess; inadequacies here can only raise the result. The important non-thyroid factors which may also cause a truly raised B.M.R. are fever, increased respiratory effort (notably that of circulatory failure, in which the rate may be raised up to +25%), phaeochromocytoma, leukaemia, and polycythaemia. The non-thyroid causes of a lowered B.M.R. are usually readily recognized—starvation, severe oedema, and Addison's disease. Obesity also alters the B.M.R., mainly by affecting the standards; if the standard is derived from the actual weight a lowering down to -25% is usual, while it will be nearly equivalently raised if the previously normal weight is used. With seriously abnormal general nutrition it is usually unsafe to infer the level of thyroid function from the B.M.R., except when it is raised in a wasted patient showing no evidence of another primary disease.

Clearly it is difficult definitely to diagnose hyperthyroidism on the basis of a raised B.M.R., but such a suspicion can usually be eliminated by finding a normal result, and a lowered value confirms a suspicion of myxoedema. Thus the B.M.R. is a good screening test for confirming myxoedema or for eliminating the suspicion of thyrotoxicosis when other tests are impracticable; however, if the rate is raised one must be sure that it was basal before accepting it. With nervous patients when this is in doubt it is helpful to estimate a "somnolent B.M.R."—that is, an estimate after an intravenous sedative given to induce sleep—there can then be no doubt that the patient was basal, and if the value is still raised or still normal it can be accepted.

Radio-iodine Tests

These tests assess thyroid-cell activity by measuring the speed of iodine metabolism. During the past ten years radio-iodine tests have become an important addition to the tests of thyroid function. Fortunately their limitations are largely covered by previously available tests, and radio-iodine tests are reliable and particularly useful where the other tests tend to be unsatisfactory.

There are various methods by which radio-iodine may be used to measure the speed of movement of iodine atoms through the body, and so the thyroid cellular activity; all these methods differ only in lesser detail—the important advantages and disadvantages of this type of test apply to

them all. The great advantage of this type of test is its independence of the nervous condition of the patient, and its great disadvantage is its liability to modification by previous drugs. The radiation given to the patient does not exceed that given the patient in such standard x-ray diagnostic investigations as a barium meal. The procedure for the patient is equally simple; after drinking what appears to be water or receiving an intravenous injection, he usually attends for two measurements comparable to having an x-ray examination (see Fig. 1), for a blood sample, or collects some urine samples (see Fig. 2).

The principle of the test is to "label" the body's extracellular fluid (E.C.F.) iodide pool by an intravenous or oral "tracer" dose of radioactive iodide—that is, a dose so small in weight that it is an insignificant addition—whose radioactivity, however, permits its subsequent measurement in various sites such as the thyroid region of the neck, the

FIG. 1.—Apparatus used for measuring radioactivity in the neck. (1) Counter at standard distance from neck. (2) Ratemeter activated by counter which records on both dial (3) and paper (4). The "standard" (1/10 of the dose to be given intravenously) (5) is being counted in front of the patient's neck: later the counter will record over the neck alone.

thigh, or in blood or urine samples at chosen times. This test is really measuring the speed of the movement of iodine atoms through their cycle in the body (Fig. 3); usually by measuring the speed of thyroid uptake (the rate at step B in Fig. 3) or sometimes by measuring the speed of thyroid uptake plus secretory discharge (step B + step C). A simple but clinically adequate theory of the functional basis is as follows. The administered radioactive iodide rapidly comes into equilibrium with the circulating iodide of the E.C.F., whence it is extracted at constant rates (expressed as percentage of the pool per hour) only into the urine and thyroid; after mixing with the thyroid's store the latter is discharged from the thyroid at a rate (percentage of store discharged per hour) depending jointly on the size of the thyroid store and on thyroid secretory activity. As radio-iodine tests involve no measurement of the absolute amount of natural iodide in the body they can give no measure of the absolute amounts of iodine involved; but useful inferences can be derived merely from the rates of these percentage transfers. Two or more measurements are usually taken from which can be calculated these rates of percentage transfer, or, in the simpler

tests, a single measurement may be made of the concentration reached in one site by a standard time, which will give a less specific index of these rates.

There are three main procedures by which radio-iodine is used clinically to assess thyroid function: (a) Measurement of the uptake in the neck (this is the most sensitive), the thyroid clearance (rate at step B), or, as a fairly adequate test, the total thyroid concentration reached at 24 or 48 hours; if the last is used, it is assumed that renal function is approximately normal. (b) Equivalent measurements of the urinary excretion—that is, to obtain either a rate index or a total excretion in a standard time, each of which gives a reflection of thyroid uptake. From three samples of the 48-hour excretion can be derived the "T" index, a rate index of thyroid uptake independent of renal function. (c) Measurements of the appearance of hormonal or protein-bound radio-iodine in the plasma; a sample at 48 hours suffices for this test. Provided a type of test giving a rate is used, the two former are equally sensitive with patients who can collect urine accurately; for recognizing hyperthyroidism the third test is equally sensitive, but it involves too small amounts of radio-iodine for use in the recognition of myxoedema. Thus the tests are approximately equivalent, and are subsequently considered together.

All clinically confirmable, untreated thyrotoxicosis is readily recognized, the average uptake being about 10 times the normal (cf. a B.M.R. of 1,000%). Some other hyperplastic glands, apparently non-toxic goitres, may give similarly raised uptakes; but little harm would come if these were treated as toxic glands, which they may become later.

FIG. 3.—The body's iodine cycle. Radio-iodine tests measure the speed of this cycle, usually by measuring at step B, C, or F.

FIG. 2.—Apparatus for measuring radioactivity of urine. (1) Ratemeter. (2) Bin in which has been placed Winchester containing patient's urine. (3) "Standard" containing 1/10 dose given to the patient. The result is expressed as a percentage of the administered dose of I^{131} .

Slightly increased uptake by this test is therefore probably best treated as a normal value. However, any patient who has taken an antithyroid drug such as thiouracil for some months, or has had a recent thyroidectomy, will also show a high thyroid uptake owing to iodine depletion. And conversely any patient who has had iodine in any form will show a lowered uptake—thus thyrotoxicosis may be masked for this test. This inapplicability after iodine, antithyroid drugs, or other thyroid treatment is the main limitation of tests with radioactive iodine; but the B.M.R. test is valid in these circumstances. The test can also be used for the recognition of thyroid deficiency, but here it is not as sensitive; while all patients with absent thyroid function will be recognized, a proportion of those with partial failure will not give abnormal results. Again the results may be invalidated by previous drugs. The test cannot therefore be used to exclude myxoedema, though it may help to confirm its presence; but the B.M.R. test can be safely used to recognize myxoedema not discernible by this test.

Serum or Plasma Protein-bound Iodine

This test measures the level of circulating thyroid hormone, but is technically difficult because of the small amounts involved—the normal range being 4 to 8 $\mu\text{g.}$ per 100 ml. plasma—that is, about 1/1,000 of the range of most

FIG. 4.—Multi-centred epiphyses at left femoral head in a girl of 5 with hypothyroidism.

plasma estimations. As the test can usually only be accurate to about $\pm 1 \mu\text{g.}$ per 100 ml. doubtful results may be found in doubtful cases; and it is also lowered in diseases with low plasma proteins. For these reasons, though theoretically possibly the best test of thyroid function, it is best regarded as a research tool rather than one for routine clinical work.

Other Tests

Plasma Cholesterol.—This is a useful test by which to supplement the B.M.R. estimation for the recognition of hypothyroidism. In this condition it is usually, but not always, raised (over 250 mg. per 100 ml. plasma), though of course it may also be raised from other causes—for example, in obstructive jaundice and in diabetes mellitus. In doubtful cases confirmation of the thyroid deficiency may be obtained by re-estimation of this value after two to four weeks of thyroid, 1 gr. (65 mg.) per day, when a fall of over 30% of the previous value should be expected in myxoedema, but not when plasma cholesterol is raised for other reasons. This test is of no value for the recognition of raised thyroid function.

Urinary Creatine Excretion or Plasma Creatine.—Most but not all thyrotoxic patients will show increased excretion of urinary creatine (over 200 mg. per 24 hours) or an increased plasma creatine level (over 0.6 mg. per 100 ml. plasma); but so also will patients with some other conditions involving muscular wasting. A creatine-tolerance test, based on either of these measurements, is also used but it has the same limitations.

Electrocardiographic Evidence.—Complete or nearly complete myxoedema leads to non-specific changes in the

electrocardiogram, flattening of T waves, and a general lowering of voltage. These changes can help to confirm the diagnosis, particularly if they are reversed after two to three weeks' thyroid therapy.

Radiography of Bone in Children.—Before growth is completed, x-ray pictures will always show the growth-retarding effect of thyroid deficiency, three to five or more years' retardation in bone age tending to confirm this diagnosis. In the very young a specific x-ray finding may be used to confirm the diagnosis of myxoedema—epiphyseal dysgenesis and stippled epiphyses; epiphyses formed during the deficiency will show multiple instead of single centres (Fig. 4).

Next article on Clinical Pathology.—"The Assessment of Adrenal Cortical Activity," by Dr. F. T. G. Prunty.

Reports of Societies

ANALYTICAL PSYCHOLOGY

The Section of Psychiatry of the Royal Society of Medicine met on March 9, with the president of the section, Dr. E. B. Strauss, in the chair, for a discussion on "The Theory and Practice of Analytical Psychology."

The Collective Unconscious

After referring to Frankfurt University's decision to confer the degree of Dr. nat. Phil. on Dr. Strauss, Dr. E. A. BENNET began by emphasizing the tentative nature of certain important formulations in Analytical Psychology. The hypothesis of the collective unconscious, for example, although a distinctive feature of Professor Jung's contribution to psychiatric thought, was not propounded as a dogma but as an attempt to explain the existence of impersonal elements in the mind. The symbolism found in schizophrenic thought processes had suggested to Jung that the basic structure of the human psyche was as little personalistic as the body.

Dr. Bennet, tracing the origin of this hypothesis, said that it first occurred to Jung in 1909. In that year Freud and Jung were visiting the United States to give a series of lectures. During the voyage and while in America they analysed each other. Jung, at this time, had a notable dream, containing material of an archaic character, and this he produced in the analytical sessions with Freud. Their mutual efforts, however, failed to bring meaning to the dream. Freud's interpretation, indeed, seemed not to do justice to the dream. In the dream, Jung was in an ancient house and, wondering what was downstairs, he descended to a cellar and thence to a second cellar. Gazing through a square hole in the floor of the second cellar he saw skulls and prehistoric remains. Further reflection led Jung to see in the dream a picture of the developmental stages of the human mind: the rooms, the cellars, and prehistoric remains being the cultural periods through which mankind has passed—the germ of the Collective Unconscious.

Freud, although he never accepted Jung's developed work on the impersonal collective unconscious, was well aware of non-personal psychic elements—material, he observed, which could not originate from the dreamer's adult life or from his forgotten childhood. Yet the concept of the collective unconscious played no part in the theory or the practice of psycho-analysis.

Biological motives or instincts, Jung maintained, were accepted by all, and yet the assumption that there are instincts was about as daring as the hypothesis of the collective unconscious. The Jungian archetypes, or pre-existent forms in the psyche, were close analogues of the instincts and might indeed be thought of as the unconscious images of the instincts themselves. The evidence in support of the theory of the collective unconscious came in part from the study