Middle Articles

CLINICAL PROGRESS

Thyroid Disorders

In the articles below two contributors discuss recent progress in pathogenesis, management, and diagnosis of some thyroid disorders. Dr. Reginald Hall summarizes the evidence that long-acting thyroid stimulator is an antibody, speculating that after reacting with a thyroid chalone it may trigger off Graves's disease. Dr. R. N. Smith discusses management, and emphasizes that recent progress has concentrated on minimizing the complications of established methods of treatment.

Hyperthyroidism—Pathogenesis and Diagnosis

REGINALD HALL,* B.SC., M.D., M.R.C.P.

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Hyperthyroidism is the clinical condition resulting from an increase in the circulating levels of the thyroid hormones (L-thyroxine or L-triiodothyronine, or both). Normal people given doses of thyroxine above 0.3 to 0.4 mg. per day or 100 to 140 µg. daily of triiodothyronine will develop hyperthyroidism, but in the elderly or in those with ischaemic heart disease much lower doses may cause side-effects. Spontaneous hyperthyroidism may be due either to autonomous thyroid overactivity or to the action of stimulating agents on the thyroid. The first cause includes toxic adenoma and toxic multinodular goitre. There are probably two varieties of the latter.¹ In the first, hyperthyroidism develops in a patient with a pre-existing nodular goitre; eye signs may be present, and histologically the thyroid shows hyperplasia of the paranodular tissue. In the second type one or usually several nodules in a multinodular gland become autonomous and produce excess thyroid hormone.

Excess production of the thyroid-stimulating hormone secreted by the pituitary has never been convincingly shown to cause hyperthyroidism.² In acromegaly goitres are not infrequent, but the levels of thyroid stimulating hormone (T.S.H.) are not raised and the occasional cases of hyperthyroidism are coincidental. Moreover, if a goitre is present in a patient with acromegaly the hypermetabolism seen in the latter may lead to the erroneous diagnosis of hyperthyroidism. Some trophoblastic tumours do produce a substance resembling thyroid-stimulating hormone, which possibly gives rise to a form of hyperthyroidism,³ though in most cases the evidence for hyperthyroidism has not been very convincing.

Graves's Disease

In the United Kingdom most cases of hyperthyroidism fall into the category of Graves's disease, an eponym best retained to describe a syndrome comprising goitre, hyperthyroidism, eye signs, and, rarely, localized myxoedema and acropachy, though not all of these features are usually present in an individual patient. Both the goitre and hyperthyroidism are now known to be due to the action of a humoral agent acting on the thyroid,⁴ which because its action is prolonged under laboratory conditions has been designated the long-acting thyroid stimulator (L.A.T.S.). Standard bioassays have shown that this substance is present in 30 to 70% of patients with

Graves's disease, but after concentrating the serum specimens L.A.T.S. can be found in 80 to 90% of cases.⁵ Levels of L.A.T.S. are usually very high in patients with pretibial myxoedema, and they provide the main source of this material for bioassay standards and research procedures.

L.A.T.S.

L.A.T.S. is an IgG (7S γ-globulin) molecule⁶ with a molecular weight of about 150,000. Its higher molecular weight compared with that of T.S.H. is probably why it has a longer action. In patients with Graves's disease, the source of L.A.T.S. has finally been shown to be the lymphocyte.⁷ Hence since L.A.T.S. is an IgG molecule produced by lymphocytes it seems likely that L.A.T.S. is an antibody to some thyroid antigen. The evidence that L.A.T.S. is an antibody and reacts with some thyroid antigen is summarized in Table I⁸ and that L.A.T.S. is active in man is shown in Table II.⁸

TABLE I.—Evidence that L.A.T.S. is an Antibody and Reacts With a Thyroid Antigen.

- (1) Bound by thyroid homogenates or microsomes to a greater extent than by liver or spleen homogenates or microsomes
- (2) Can be dissociated from thyroid homogenates by procedures known to separate antigen-antibody complexes
- (3) Activity is an inherent part of the IgG molecule
- (4) Can be produced by lymphocytes of patients with Graves's disease
- (5) L.A.T.S.-like activity can be produced by immunizing rabbits with human thyroid extracts

TABLE II.—Evidence that L.A.T.S. is Active in Man.

- (1) Present in neonatal Graves's disease, and disappears as the disease remits
- (2) Neonatal Graves's disease occurs only in the children of mothers with high circulating levels of L.A.T.S.
- (3) Can stimulate thyroid uptake of radioiodine in man
- (4) Levels correlate with thyroid turnover of radioiodine (P.B.¹³¹I at 48 hours) and with thyroid gland mass

The nature of the thyroid component reacting with L.A.T.S. is at present being actively studied; it is known to be a low molecular weight compound present in high activity in the cell sap.⁹ One tempting speculation is that this agent is a thyroid chalone—that is, one of the tissue-specific inhibitors of mitosis which are thought to be concerned in regulating organ size and growth. Thus when L.A.T.S. reacts with a mitotic inhibitor it might trigger off the thyroid hyperplasia and overactivity characteristically seen in Graves's disease. On the other hand, it is now certain that pituitary T.S.H. is not directly concerned in the pathogenesis of Graves's disease (Table III).⁸ T.S.H. and L.A.T.S. are compared in Table IV.⁸

* Consultant physician and senior lecturer in medicine, Royal Victoria Infirmary, Newcastle upon Tyne.

TABLE III.—Evidence that T.S.H. is Not Involved in Pathogenesis of Graves's Disease.

- (1) Levels in circulation are low or normal in Graves's disease (by radioimmune assay)
- (2) Pituitary histology suggests suppression of the thyrotroph cells
- (3) Graves's disease can occur after total hypophysectomy
- (4) Overtreatment with antithyroid drugs in Graves's disease can cause goitre from overproduction of T.S.H., hence the feedback mechanism is intact. Such a goitre can be reduced by thyroid hormone, which lowers T.S.H. levels
- (5) Triiodothyronine given in doses of 120 µg./day for one week fails to suppress ¹³¹I uptake in patients with Graves's disease, whereas normally such suppression occurs. Since the T.S.H. feedback mechanism is intact, this suggests that a substance other than T.S.H. is stimulating thyroid overactivity

TABLE IV.—Comparison of T.S.H. and L.A.T.S.

	L.A.T.S.	T.S.H.
Peak of action in mouse assay (hr.)	10–12	2–3
Structure and molecular weight	IgG, 150,000	Glycoprotein 26,000–30,000
Inhibition of activity	By anti-IgG serum	By anti-T.S.H. serum
Source	Lymphocytes	Anterior pituitary
Action	Stimulates thyroid	Stimulates thyroid
Circulating level reduced by	High doses of corticosteroids	Thyroid hormone
Overproduction in	Graves's disease	Trophoblastic tumours may produce T.S.H.-like material

Eye Signs

The pathogenesis of the eye signs in Graves's disease has long defied solution. There is no good correlation with the presence or the titre of L.A.T.S. or other thyroid antibodies, though serum from exophthalmic patients may cause prominence of the eyes in fish. Nevertheless, most assays based on this action yield variable and not entirely convincing results. Recently a factor has been found in the IgG fraction of serum from patients with exophthalmos. This is distinct from L.A.T.S., and induces an increase in weight of the Harderian gland in the orbit of the guinea pig.¹⁰ So a distinct immunoglobulin may be responsible for at least some of the eye signs of Graves's disease.

Autoimmune Thyroid Diseases

Graves's disease falls into the class of autoimmune thyroid disease,¹¹ which also includes Hashimoto's disease and its atrophic variant, myxoedema. In all these diseases antibodies to thyroid tissue (for example, L.A.T.S.) are found in the circulation and lymphocytic infiltration of the thyroid gland is present.

There is an increased prevalence of goitre, Graves's disease, hypothyroidism, and thyroid antibodies in the relatives of patients with Graves's disease—particularly their sisters and mothers. Other organ-specific autoimmune diseases—for example, idiopathic Addison's disease and pernicious anaemia—are also significantly associated with Graves's disease. Genetic factors are probably concerned in the pathogenesis of Graves's disease; certainly the tendency to develop thyroglobulin antibodies^{12,13} and probably L.A.T.S.¹⁴ is genetically determined. Possibly the autoimmune thyroid diseases arise as a result of a genetically determined disturbance of immune tolerance,¹⁵ a view supported by the finding of histological changes in the thymus.¹⁶ The role of environmental factors, particularly emotional stress, in triggering off overt disease in genetically predisposed people has long been suggested, and W. D. Alexander and his colleagues have provided evidence for this.¹⁷

Clinical Diagnosis

In most patients with hyperthyroidism the diagnosis is obvious, particularly when the presence of eye signs or a goitre indicate the likelihood of thyroid disease. J. Crooks¹⁸ has pointed out that the first step in diagnosis is usually made by the general practitioner who asks the question, "Is this patient hyperthyroid or not?" Despite the fact that a goitre may indicate the presence of thyroid disease, enlargement of the

thyroid is not uncommon in normal women; thus it is present in about 12% of women in the north-east of England.¹⁹

Once the patient is referred to hospital the diagnostic criteria are changed and the endocrinologist asks the question, "Is this patient really hyperthyroid?" The presence of a goitre is now less important but finding even minor ocular abnormalities of Graves's disease, such as lid retraction, is very significant. Over half the patients referred to some hospital clinics for hyperthyroidism have some psychiatric disorder—usually an anxiety state—and are clinically euthyroid. Hence a psychiatric history must be obtained from patients with suspected hyperthyroidism—in fact, apart from increased appetite most of the symptoms of hyperthyroidism are frequently recorded from patients with psychiatric disease. Hyperthyroid patients usually have a less neurotic personality and fewer hysterical symptoms; there is less often a psychiatric precipitant; and the age of onset is later.

Eye signs, particularly of recent onset, may indicate Graves's disease and suggest that the patient's illness is more likely to be thyroid than psychiatric in origin. Eye signs may be found in euthyroid patients with no previous history of hyperthyroidism; this condition is called ophthalmic Graves's disease.²⁰ Hyperthyroidism can occur without thyroid enlargement, but in most patients some asymmetry, undue firmness, thyroid nodularity, or retrosternal swelling can be elicited. If no abnormality of the thyroid gland can be found one should always review the diagnosis. Probably the single most important physical sign is a thyroid bruit indicating thyroid vascularity—and hence hyperplasia—this may occur after treatment with antithyroid drugs and in certain dysmorphogenetic goitres, but these situations are usually easy to differentiate.

The clinical diagnosis has been put on a sounder basis by using a diagnostic index,²¹ where the important symptoms and signs are allocated scores. As mentioned before, discrimination of euthyroid patients from those with hyperthyroidism is helped by taking a psychiatric history.

Laboratory Tests

Even in the most florid case of hyperthyroidism it is worth confirming the diagnosis with at least one and preferably two tests of thyroid function, since often the course of the disease is prolonged and the treatment not without risks. The tests chosen depend on individual preference and the facilities available. Routinely I use the estimation of serum protein-bound iodine (P.B.I.) and the uptake of radioiodine by the thyroid six hours after it has been given. W. D. Alexander and his colleagues²² rely largely on blood tests—the P.B.I. and the resin uptake of ¹³¹I-labelled triiodothyronine (T-3 resin uptake). J. Crooks¹⁸ uses the thyroidal radioiodine uptake at four hours and the 48-hour plasma protein-bound radioactivity. Needless to say, the normal range and standard deviations for each test must be determined in an individual laboratory.

In patients where the clinical diagnosis is uncertain these limited investigations usually settle the diagnosis. When the situation is still not clear it is best to reassess the clinical picture and question the patient further about drugs which might have modified the results of tests. Protein-bound iodine estimations may be invalidated by iodides, which may be taken in a wide variety of preparations.²³ The iodine contained in certain radiological contrast media may invalidate P.B.I. tests for over a year. Salicylates and hydantoin-like drugs compete with thyroxine for binding sites on thyroxine-binding globulin and lower the P.B.I. The level of this globulin (and hence of the P.B.I.) is raised by oestrogens in oral contraceptives or during pregnancy. Likewise measurements of thyroidal radioiodine uptake are affected by iodides and by salicylates. A rise in the P.B. ¹³¹I may indicate hyperthyroidism, but it is also found whenever the intrathyroidal iodine pool is

reduced—for example, after thyroidectomy or radioiodine therapy and in the presence of thyroiditis.

Further tests for solving difficult problems include estimating the absolute iodine uptake rate²⁴ by the thyroid; the triiodothyronine suppression test²⁵ is helpful in distinguishing those raised thyroid radioiodine uptakes which are caused by iodine deficiency or early autoimmune thyroiditis. If the radioiodine uptake is found to be suppressed, this virtually excludes a diagnosis of hyperthyroidism; nevertheless, failure of suppression is also seen in ophthalmic Graves's disease, in some euthyroid patients with Graves's disease, and in the presence of one or more autonomous nodules in the thyroid. Thyroid antibody tests are also useful since they give a clue to the presence and extent of autoimmune thyroiditis. Subclinical thyroiditis is not infrequent in the general population—high thyroglobulin antibody titres were found in 4.6% of women and 1.6% of men in a general practice in the north-east of England.¹⁹

Special Diagnostic Problems

During Antithyroid Therapy.—The level of thyroid function during a course of antithyroid drugs is best assessed clinically. Radioiodine uptake measurements 2½ hours or more after the tracer dose are not helpful, though those done 20 minutes after intravenous tracer doses of ¹³¹I give a measure of thyroid iodide trapping which is independent of drugs.²⁶ Measurements of P.B.I. may be misleadingly low, since the thyroid depleted of iodine produces more triiodothyronine than normal during antithyroid therapy and this is less well bound to thyroxine-binding globulin.

After Antithyroid Therapy.—Tests of thyroid function may also give misleading results. The uptake of radioiodine by the thyroid may be raised as a result of the iodine deficiency which follows antithyroid drugs.²⁷ Usually, however, the results of the P.B.I. or the T-3 resin uptake tests are satisfactory indicators of thyroid abnormality.

Pregnancy.—During pregnancy there are complex alterations in iodine metabolism and thyroid function.²⁸ The renal

loss of iodine is increased, the plasma inorganic iodide falls, and the thyroid clearance of iodide increases maintaining the absolute iodide uptake within the normal range. Thyroxine-binding globulin levels rise in response to the high levels of circulating oestrogens causing a rise in the P.B.I. The nature of the pituitary T.S.H. response and the role of placentally-produced T.S.H.-like material²⁹ is not yet well understood. It is best to avoid administering radioiodine, even ¹³¹I, to the pregnant woman. Estimating the free thyroxine index,³⁰ which is the product of the P.B.I. (raised) and the T-3 resin uptake (lowered), indicates the true level of thyroid function.

Renal Failure.—This, with the characteristic pallor, lethargy, and fluid retention, may simulate hypothyroidism. Moreover, it may itself complicate tests of thyroid function; there may be retention of iodide, an increase in plasma inorganic iodide, and (because of isotope dilution) the thyroidal uptake of radioiodine tends to be reduced, though this may be balanced by failure of excretion of the isotope, which tends to increase uptake. The actual uptake recorded will depend on the balance of these and many other factors. In the nephrotic syndrome the loss of thyroxine-binding globulin (T.B.G.) will lower the P.B.I., though thyroid function remains normal because the free thyroxine level is maintained.

Toxic Adenomas of the Thyroid.—These cause about 5% of cases of hyperthyroidism in the United Kingdom. Nodules may be single or multiple, their secretory capacity depending on their size³¹ and on the iodine content of the diet. Some autonomous nodules may produce sufficient thyroid hormone to suppress the output of T.S.H. by the pituitary—and hence the uptake of iodine by the rest of the thyroid—without causing hyperthyroidism. Surface counting of the thyroid after giving radioiodine (a thyroid scan) is helpful since a "hot" nodule is very rarely malignant whereas a "cold" nodule may represent a non-functioning adenoma, a thyroid cyst, a thyroid carcinoma, or even a localized enlargement of a gland affected by thyroiditis. Many apparently single nodules are found at operation to be the largest nodule in a multinodular gland.

Management

R. N. SMITH,† B.SC., M.D., M.R.C.P.ED.

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Several developments in the management of thyroid disorders have been discussed in recent articles in the *British Medical Journal*—concerning radioiodine therapy,³² antithyroid drug treatment,³³ and thyroid hormones.³⁴ To enable him to make the correct choice of treatment and subsequent management of a patient the doctor should be familiar with recent therapeutic studies.

Thyrotoxicosis

Antithyroid Drugs

Blocking iodine metabolism in the thyroid gland reduces the output of iodinated thyroid hormones and relieves both the symptoms and some of the signs of thyrotoxicosis. Nevertheless, it is doubtful whether antithyroid drugs alter the underlying mechanism of thyrotoxicosis. Spontaneous remission of thyrotoxicosis does occur,³⁵ and prolonged treatment with anti-

thyroid drugs may only control the patient's symptoms until normal thyroid function recovers spontaneously.

Thyrotoxicosis frequently recurs after antithyroid medication, the percentage of recurrences varying from 50 to 70 in different studies, and the relapse can be hastened by iodide repletion.²⁷ The fact that triiodothyronine (T-3) suppresses the uptake of radioiodine (¹³¹I) by the thyroid suggests that the autonomous metabolism characteristic of thyrotoxicosis is absent. Moreover, the development of T-3 suppression in a previously thyrotoxic patient while receiving antithyroid drugs may indicate that normal thyroid function has been re-established.³⁶

Antithyroid drugs are often used inadequately, the common errors being to allow long intervals between doses or to produce hyperplasia of the thyroid with unduly large doses of these goitrogenic compounds. The metabolism of commonly-used antithyroid drugs, carbimazole and propylthiouracil, differs, and several factors—including renal function—determine their therapeutic efficacy.³⁷ The dosage of these compounds must be adjusted according to the patient's response to therapy, and the doses divided, not according to mealtimes,

† Lecturer in Pharmacology and Therapeutics, University and Royal Infirmary, Sheffield S6 3DA.