Occasional Survey

Aetiology of Hyperthyroidism—II*

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What Precipitates Graves's Disease?

Acute precipitation of hyperthyroidism by stressful external events has been accepted by many authorities ever since Parry's description in 1825 of the case of Elizabeth S.,⁸¹ aged 21, who "was thrown out of a wheelchair in coming fast downhill . . . and was very much frightened but not much hurt" and who went on to develop acute swelling of the thyroid gland, "palpitation of the heart, and various nervous affections." Only a few months ago, Forteza⁸² remarked that it was "almost universally accepted fact that stress of any sort may precipitate hyperthyroidism," and went on to support this contention by demonstrating psychologically stressful factors in 65% of younger patients who developed the disease, and physical stress in many of the older. Emotional disturbance, characteristically in the sense of loss or deprivation of a loved friend or relative, is often incriminated, but infection, surgery, trauma, and acute illness have all been blamed. In careful serial studies Alexander *et al.*⁸³ found evidence of relapse (clinical and biochemical) in a previously hyperthyroid patient after a double bereavement, in another after a severe throat infection, but no relapse in a third patient who had undergone cardioversion. A causal relationship of the bereavement in the first case is far from certain, as two months elapsed before the hyperthyroidism became apparent, and it went on to remission without treatment.

Other authors have postulated similar provocation of acute hyperthyroidism by psychic stress,⁶⁵ but the evidence for this is largely anecdotal and there is a deplorable lack of adequate controls in most papers on the subject. Brown and Hetzel⁶⁸ and Hermann and Quarton⁸⁴ could find no reason to incriminate psychological factors from their studies in which control euthyroid and hypothyroid patients appeared to have suffered equivalent stressful life situations. Before dismissing the role of stress one should perhaps refer to the slight but significant increase in circulating PBI levels found in some studies of stressed human subjects⁸⁵ and in sheep exposed to the barking of a dog.⁸⁶

Catecholamines might reasonably be thought to play a part in some of these thyroid responses,⁸⁷⁻⁸⁹ and it is tempting to incriminate these in the evolution of hyperthyroidism—not least because it would provide an opportunity for me to link this lecture with George Oliver, whose pioneer studies of the effects of adrenaline—and of thyroxine—are described in the first of these Oliver-Sharpey lectures, given by him in 1904.⁹⁰ Despite this temptation and the observation that 5-hydroxytryptamine and other amines can stimulate synthesis and release of thyroid hormones,⁹¹ one has to conclude there is little to support a

causal role for catecholamines in the precipitation of hyperthyroidism.

Evidence of stress-induced epidemics of the disease is even less convincing. Iverson⁹² drew attention to a remarkable rise in thyrotoxicosis in Copenhagen during the years of the second world war and psychic strain was proposed as a possible factor. A decreased incidence of the disease in Holland and Belgium during the same period would argue against this, and other factors such as exposure to cold (after three severe winters), altered nutritional status, or infection may well have been responsible. Furszyfer *et al.*⁴⁶ were unable to show any change in the incidence of Graves's disease in Olmsted County despite the stress periods of the economic depression (1935-9) and the second world war (1942-5).

It seems in general that a slight increase in thyroid function may succeed some types of stress in some (? predisposed) individuals. The part this plays in the acute precipitation of thyrotoxicosis remains far from convincing.

What Causes Graves's Disease?

For about 15 years the shadow of the long acting thyroid stimulator (LATS) has loomed large over the problem of what causes Graves's disease. Many of the arguments about its role, if any, in hyperthyroidism are to be found in reviews⁹³⁻⁹⁷ and I shall try to summarize its present status.

There is widespread disagreement about the frequency with which LATS is found in sera from hyperthyroid patients, figures ranging from 14% to 76%.⁹⁸ These differences are largely explained by patient selection, modifications of assay technique, and statistical treatment of assay results. For practical purposes, and applying strict criteria for positivity, LATS has been found only in sera from patients hyperthyroid at the time of testing or in the past or, exceptionally, in those about to develop the disease. A convincing exception—with important implications—is the finding of Wall *et al.*⁷⁶ that nine of 43 euthyroid relatives of patients with Graves's disease had LATS-positive sera; some of these people had mild clinical features of hyperthyroidism and serum PBI concentrations above normal. Bonnyns *et al.*⁹⁸ have recently confirmed the high incidence of LATS in the families of some patients with Graves's disease in whom overt hyperthyroidism was not apparent.

By any technique and in all reported series a core of hyperthyroid patients remains in whom LATS cannot be demonstrated. Insensitivity of the assay is often blamed for this; Carneiro *et al.*⁹⁹ and Chopra *et al.*¹⁰⁰ increased the yield of positive results by assaying a concentrated IgG fraction of such LATS-negative sera, but even this device failed to produce 100% positives and one is forced to conclude that about 20% of hyperthyroid patients have no circulating LATS (see below).

There is also no agreement about a correlation of LATS with thyroid gland size, ¹³¹I uptake or turnover (measured by PB ¹³¹I), serum T-4, serum free T-4 or clinical severity of hyperthyroidism^{98 101-103} though most positives are found when all

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three clinical components of Graves's disease are present (hyperthyroidism, exophthalmos, and pretibial myxoedema), 89% in the series of Lipman *et al.*¹⁰⁴ Several authors comment that LATS may mirror clinical fluctuations of the disease, the concentration increasing with relapse of hyperthyroidism, decreasing during remissions,¹⁰⁴⁻⁸ but this has been denied¹⁰⁹ and high levels of circulating LATS have certainly been found to persist after successful treatment of hyperthyroidism.⁹⁴

LATS has usually been found to correlate with lack of suppressibility of the thyroid gland by T-3,¹¹⁰ but there are several exceptions to this.

Perhaps the strongest evidence in favour of a causative role for LATS is in neonatal thyrotoxicosis, in which LATS is so often found in the serum of the infant and the mother, and the clinical course appears related to its activity in the former's serum.

NATURE OF LATS

To advance our discussion of LATS we must examine its nature a little more closely. One can start with the quite convincing evidence that LATS is a genuine thyroid stimulator capable of increasing thyroidal uptake of radioactive iodine, accelerating hormonal release, and producing histological changes indistinguishable from those produced by TSH. That it is an IgG seems indisputable: its effects can be neutralized by anti-IgG (not by anti-TSH) and to a large extent by anti-kappa and anti-lambda light chains.

Several features point to its antibody function: after proteolysis LATS activity has always been retained in fragments in which antigen-binding capacity characteristically resides; even isoelectric focussing fails to separate it from bands that contain other antithyroid antibodies;¹¹¹ and lymphocytes from subjects with high serum LATS levels have been shown to produce LATS *in vitro*.¹¹²⁻¹¹⁴

If LATS is an antibody, what is its antigen? Despite experiments that locate a neutralizing factor (LATS absorbing activity, LAA) in thyroid microsomes and cell sap¹¹⁵⁻¹¹⁷ no definite antigen has yet been demonstrated. LAA is found predominantly in a 4S thyroid-soluble protein fraction,¹¹⁷ and evidence suggests it has a cell-membrane origin or association.¹¹⁸⁻¹²¹ Though the current picture is confused, there is much to suggest that TSH (and LATS) act at a specific follicle cell membrane receptor site probably through an adenyl cyclase-cyclic AMP system; it seems likely but by no means definite that LATS and TSH compete for a common binding receptor.¹²²⁻¹²⁸ If LAA is simply a component of the surface receptor site for LATS, its neutralizing activity might be explained without attributing an antigenic function to it. More convincing would be a demonstration that LATS could be evoked in animals immunized against LAA. Using human thyroid homogenates and/or microsomes as immunogens, several groups claim to have shown production of LATS in rabbits,^{94 129 130} but this finding must be accepted with some reservation.

LATS PROTECTOR

Finally, mention must be made of the recently-described LATS protector (LATSP). Adams and Kennedy^{131 132} described the presence of an IgG in the serum of LATS-negative hyperthyroid patients that interfered with LATS inhibition by an extract of human thyroid gland. This IgG has been shown to stimulate colloid droplet formation in human thyroid gland but has no effect on the mouse or rhesus monkey thyroid.^{133 134} IgG thyroid stimulators are thus said to be demonstrable in *all* cases of Graves's disease, some specific for human thyroid tissue and hence negative in the mouse bioassay system for LATS.

This greatly strengthens the view that Graves's disease has an autoimmune pathogenesis. The evidence in favour of this may be summarized under four main findings.

Firstly, in Graves's disease lymphocytic and plasma cell infiltration of the thyroid gland is common; systemic lymphocytosis, lymphadenopathy, and thymic and splenic enlargement may all be found.⁷⁹

Secondly, LATS and LATSP are both immunoglobulins, the former probably produced *in vitro* by lymphocytes from patients with Graves's disease; IgG, IgM, and IgA may be increased in the serum and IgG, IgM, IgE, and complement are often deposited in the thyroid gland of patients with Graves's disease.¹³⁵

Thirdly, specific antibodies against thyroid microsomal and thyroglobulin antigens are found in almost all patients with Graves's disease and many of their relatives;^{75 136} other organ-specific antibodies or autoimmune diseases (Hashimoto's thyroiditis, pernicious anaemia, adrenal insufficiency, myasthenia gravis, systemic lupus erythematosus) are commonly found in patients or their families.¹³⁷

Fourthly, clinical improvement and decreased LATS levels may be found in hyperthyroid patients treated with corticosteroids.^{105 108 138-140}

UNDERLYING CELLULAR ABNORMALITY

Solomon and Chopra¹⁹ argue that Milgrom and Witebsky's postulates¹⁴¹ for the autoimmune basis of a disease are not satisfied in Graves's disease, and correctly remark that the presence of immunological abnormalities does not constitute proof of an autoimmune pathogenesis. The hyperthyroid state itself may alter immunological responses—for example, by producing thymic enlargement. They propose instead an underlying abnormality of thyroid cells in this disease, either inherited and activated by an unknown mechanism or occurring spontaneously, and involving the receptor site for TSH and LATS, in which the cyclic-AMP protein-kinase complex is continuously in an activated form. The abnormal receptor provides an enhanced antigenic stimulus which evokes a polyclonal immunoglobulin response (to account for the presence of IgM and IgE as well as IgG in thyroid follicular basement membranes, as described by Werner *et al.*¹³⁸). While this theory ingeniously explains much that is known about Graves's disease, it fails adequately to explain the association of the disease with other autoimmune disorders, particularly in relatives in whom evidence of hyperthyroidism and abnormally activated thyroid cell receptors cannot be sustained.

An entirely different approach based on cell-mediated immunity is put forward by Volpé and associates.^{79 142} In favour of their thesis they adduce the following evidence: thymic enlargement and T-cell lymphocytosis¹⁴³ are common in hyperthyroidism and regress with treatment of the disease; hyperthyroid patients show reduced skin reaction to tuberculin and do not display sensitization to dinitrochlorobenzene (DNCB);¹⁴⁴ lymphocytes from patients with Graves's disease produce migration inhibition factor (MIF) in response to thyroid antigens^{142 145} and may stimulate ¹³¹I uptake by isolated bovine thyroid cells, even when taken from LATS-negative patients. The last action appears to be antibody-mediated as it is abolished by anti-IgG.¹⁴⁶ A disorder of cell-mediated immunity is therefore proposed, possibly as an inherited defect, in which T-lymphocytes situated within the thyroid gland may stimulate thyroid cells directly. Alternatively, Lamki *et al.*¹⁴² suggest that thymic lymphocytes interact with a thyroid cell antigen to stimulate B-lymphocyte production and hence humoral antibodies including LATS and other IgG thyroid stimulators.

Conclusions

In conclusion, what can one say about the aetiology of hyperthyroidism? There is a fairly long list of known non-thyroidal causes of a hyperthyroid state but together they account for not more than 1% of cases. Toxic nodular goitre has origins as

obscure as those of other functioning endocrine tumours. Graves's disease presents an enigma: it is hard to escape the conclusion that an abnormal thyroid-stimulating immunoglobulin is responsible. We know the thyroid gland is being driven in this disease by an extrahypophyseal substance; we know that LATS and LATSP are most powerful stimulators of thyroid gland function; and it now seems likely that one or other of these immunoglobulins is present in every case of hyperthyroidism. The demonstration of LATSP in LATS-negative patients has removed the last important barrier to our full acceptance of this theory. The lack of correlation between circulating levels of LATS and the degree or even presence of hyperthyroidism may be explained by variations in thyroid gland responsiveness.

Are these immunoglobulins antibodies? Of this, there can be little doubt despite our failure, as yet, to demonstrate a responsible antigen. This leaves us with two final questions: How do these antibodies stimulate thyroid cells? And why do they arise? In the present climate of opinion it would be foolhardy not to put it all down to the fashionable "failure of immunological surveillance" and to hope that the next few years will show us exactly what this means.

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