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LYMPHOID THYROIDITIS AS A MODEL FOR AUTO-IMMUNE DISEASE

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Many of the points raised by Prof. *Serafini* & Dr. *Torrigiani* are well illustrated by Hashimoto's disease and its atrophic variant primary myxoedema which have been the subject of intensive immunological study in recent years.

The sera of these patients contain auto-antibodies frequently of high titre, specifically directed against a number of constituents of the thyroid gland i.e. a particulate antigen localized to the cytoplasm of the acinar epithelial cells, and thyroglobulin present in the follicular lumen together with a third as yet unidentified auto-antigen (1). The methods employed for the detection of these auto-antibodies are summarized in the Table.

Tests for thyroid antibodies can be of considerable diagnostic value (2), for example in the differentiation between struma lymphomatosa and thyroid cancer or non-toxic nodular goitre, in the recognition of early primary hypothyroidism, in the choice of definitive therapy for thyrotoxicosis and sometimes in the distinction between thyrotoxicosis and anxiety states.

The presence of thyroid auto-antibodies in Hashimoto's disease poses several questions of which the most fundamental involves the causal relationship between the auto-immunization and the histopathological lesions in the thyroid gland. Is the tissue damage and lymphoid infiltration a consequence of the development of an auto-immunity directed against the thyroid,

or do the antibodies arise as a non-pathogenic result of the liberation of auto-antigens from a diseased gland?

The finding of thyroid antibodies in virtually every Hashimoto patient studied (3), the cytotoxic effect of Hashimoto sera on cultures of human thyroid cells (4) and the reproduction of the lesions by auto-immunisation of experimental animals with homologous thyroid extracts (5, 6), all argue in favour of a direct pathogenic role of auto-immunity in this disease.

It is unlikely that the typical features of lymphadenoid change arise as a non-specific inflammatory response to simple liberation of thyroid constituents since localized tissue injury accompanying haemorrhages into colloid cysts is associated with fibrosis and a mild inflammatory response but not with the presence of thyroid antibodies, whereas in multifocal lymphoid thyroiditis occurring in a variety of goitres the patient's serum almost invariably contains the same types of thyroid auto-antibodies as in the more severe form of the disease, though in much lower titres. Furthermore the massive release of thyroid constituents from damaged acini in subacute thyroiditis only rarely stimulates auto-antibody formation and then only transient low titre antibodies reacting with the colloid antigens are formed.

The mechanisms of tissue damage in auto-immune thyroiditis are not yet elucidated and there has been much inconclusive discussion on the relative roles of circulating antibody and sensitized white cells (7, 8). It is possible that a further factor may be implicated in facilitating the access of the immunological agent, be it sensitized white cell or antibody to the tissue antigens. We have shown that pretreatment of rats with Freund's adjuvant makes them susceptible to thyroiditis on injection of rabbit anti-rat-thyroglobulin serum (8). This suggests that Freund's adjuvant enhances the accessibility of antibody to its target antigen. There is as yet no evidence for the existence of such a factor circulating in Hashimoto's disease although some histological and cytological findings suggests that lymphocytes can penetrate the epithelial acinar cells of a lymphadenoid

denoid goitre. Neither has evidence yet been obtained for the presence of a genetically controlled structural defect in the cell or basement membranes which could affect tissue accessibility with similar results. Whether such a defect could underlie the familial incidence of thyroid auto-immunity seen in relatives of patients with Hashimoto's disease or whether perhaps the disturbance lies in the immunological system it yet to be determined.

TABLE
The Thyroid Antigen-Antibody Systems.

1. Microsomal Antigen	Localized in cytoplasm of thyroid epithelium. Intimate association with lipoprotein membrane of microsomal vesicles. Abundant in thyrotoxic and dys hormonogenetic glands. ? Thyroglobulin precursor.	Complement fixation test. Cytoplasmic immuno-fluorescence. Tissue culture cytotoxic test.
2. Thyroglobulin	Molecular wt. 650,000. Storage form of thyroid hormones. Constitutes ca. 75 % of protein in thyroid colloid. Contains nearly all the iodine in the gland.	Precipitin. Tanned red cell agglutination. Latex particle agglutination. Colloid immunofluorescence (floccular staining pattern). Co-precipitation with [¹³¹ I] thyroglobulin. Passive cutaneous anaphylaxis.
3. Second antigen of thyroid colloid.	Constitutes a very small % of proteins in the thyroid colloid. Present in a wide variety of glands. Contains no iodine.	Colloid immunofluorescence (uniform staining pattern).

The phenomena involved in the initiation of the thyroid auto-immunisation are still unknown. It is thought unlikely that the disorder can be triggered off by viral or bacterial infection largely because of the complete recovery of the thyroid gland after such infections.

It was previously postulated that organ-specific antigens such as those of the thyroid and other organs are isolated from the lympho-reticular system and so fail to establish immunological tolerance in the neonatal period. Although there is recent evidence that thyroglobulin circulates in the foetus at term (9) it is likely that the cytoplasmic particulate auto-antigens are confined within the tissue cells. Accessibility of the lymphoid cells to these secluded antigens in adult life could then lead to the development of an immune response. A generalized hypothetical accessibility could account for the clinical and serological overlap of Hashimoto's thyroiditis with pernicious anaemia (10, 11, 12) a disorder which provides an extremely close immunological parallel with primary myxoedema (10, 13, 14). However, evidence is accumulating that the organ specific substances are only weakly antigenic, e.g. injection of native homologous thyroglobulin into animals does not induce auto-antibody formation unless the protein is combined with an adjuvant. Thus it may be that auto-immunity arises spontaneously through factors effecting a change in the immunological responsiveness of the host. This would also be consistent with the overlap of organ-specific antibodies so frequently observed in these individuals. The finding of this overlap also tends to exclude the idea that auto-immunisation occurs as a result of alterations in the structure of the molecules since one would have to postulate alterations of the antigens in several organs.

Whatever the mechanisms underlying the development of organ-specific auto-immunity, they must clearly be different from those operating in systemic lupus erythematosus (S.L.E.) and allied conditions where characteristically the auto-antibody pattern is non-organ-specific. Whereas high titre anti-nuclear, blood cell and non-organ-specific complement fixing antibodies are commonly present in S.L.E. the incidence of organ-specific thyroid, and gastric parietal cell antibodies is not greater than in healthy controls and when present they are of extremely low titre. In contrast the incidence of anti-nuclear factors and non-organ-specific complement fixing anti-

bodies in Hashimoto's disease and pernicious anaemia is not significantly greater than in matched controls (11). Thus in S.L.E. there appears to be a central failure of the mechanisms within the lympho-reticular system which are responsible for immunological homeostasis through the 'recognition' of and maintenance of immunological tolerance to, normally circulating body constituents. These particular mechanisms are probably unaffected in the 'pure' organ-specific disorders but a number of diseases such as Sjögren's syndrome, discoid lupus erythematosus, ulcerative colitis and perhaps rheumatoid arthritis, show a combination of organ-specific lesions with non-organ-specific antibodies. It is hoped that population and family studies of the clinical and serological overlap seen in these different varieties of auto-immune disease will help to elucidate the responsible defects, particularly those determined genetically.

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