AUTO-IMMUNITY AND THYROID DISORDERS

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A considerable amount of new knowledge has accumulated about the immune phenomena associated with lymphoid infiltration of the thyroid gland since the first reports (Roitt *et al.*, 1956; Witebsky *et al.*, 1957) that patients with lymphadenoid goitre have serum antibodies reacting specifically with certain proteins from the human thyroid. A large number of patients with various thyroid diseases have now been examined for auto-antibodies both in this country and the United States and the whole subject was well reviewed by Owen (1958). More recent papers include those of Roitt and Doniach (1958), Owen and Smart (1958), Anderson *et al.* (1959, a and b), Hubble (1959), Blizzard *et al.* (1959), Cline *et al.* (1959), Beierwaltes *et al.* (1959), and Belyavin and Trotter (1959).

High titres of serum antibodies have been found in classical Hashimoto's disease, in less typical cases previously classed as non-specific chronic thyroiditis, in early forms of the disease termed lymphocytic thyroiditis, and even in some cases of subacute thyroiditis. Adult primary myxoedema is probably a variant of the same pathological process, although the gland does not react by goitre formation but undergoes involutive atrophy with fibrosis. All these conditions are extreme or advanced forms of auto-immune thyroiditis, but milder lesions, represented by various degrees of focal lymphoid invasion of the gland and associated with low titre antibodies, are common in all types of underlying goitre, particularly in Grave's disease, and are even found in 10 to 15 per cent. of apparently normal thyroids in elderly women. The chain of events leading to progressive destruction of the thyroid gland is not understood but appears to be connected with the auto-immune phenomena observed in the patients.

Recent work has shown that several other granulomatous and atrophic glandular diseases in which lymphoid replacement is a prominent feature are connected with auto-immune reactions. Thus Barrie Jones (1958) demonstrated precipitating auto-antibodies against lacrimal and salivary glands in the serum of patients with Sjögren's syndrome, of which chronic parotitis or Mikulicz's disease is

probably a variant. Sperm agglutinins have been found in certain cases of infertility and in some testicular granulomas (Rumke, 1954; Cruickshank and Stuart-Smith, 1959). Addison's disease associated with 'toxic' atrophy of the adrenal is thought to arise from auto-immune destruction of the gland, since complement fixing antibodies against adrenal extracts were found in a few cases (Anderson *et al.*, 1957 and 1959) and the lesion has been successfully reproduced by the immunization of animals with homologous adrenal extracts (Colover and Glynn, 1958) thus paralleling the thyroid lesions produced by Witebsky and Rose (1956) in rabbits and other laboratory animals.

The work of Mackay and Gajdusek (1958) on lupoid hepatitis has shown that certain forms of cirrhosis also belong to the wide spectrum of auto-immune phenomena. The association of Hashimoto's disease with cirrhosis was pointed out by Luxton and Cooke (1956) and was studied immunologically by Doniach, Roitt and Vaughan Hudson (1959). Lupus erythematosus (L-E) cells have been reported occasionally in patients with thyroid disease (Hijmans *et al.*, 1958), and Heaton (1959) has recently brought together the evidence for the association of Sjögren's syndrome with lupus erythematosus phenomena and with thyroid disease. Apart from these associations, Hashimoto's disease and myxoedema are sometimes found with Paget's disease (Luxton, 1957) with rheumatoid arthritis (Beare, 1958), and isolated cases occur in association with nephrosis and with acquired haemolytic anaemia. Systemic lupus erythematosus itself has been extensively studied with immunological methods in the past few years, and it has been shown that the serum factors characteristic of this disease are antibodies against deoxyribonucleic acid (DNA) and other nuclear constituents (see Deicher *et al.*, 1959). Since patients with systemic L-E have a wide variety of other auto-antibodies, it is thought that the disease arises from a disturbance of the mechanisms responsible for the regulation of immunological tolerance in general. Although chronic thyroiditis has been considered quite separate until now, its association with other auto-immune

phenomena has to be sought in the clinical observation of patients, if we are to understand the true nature of these abnormal reactions and their relation to each other.

It is argued that a contradiction exists in calling any lesion 'auto-immune,' since immunity has hitherto implied protection from diseases. However, the reaction to bacterial infection is fundamentally similar to that which comes into play whenever the body is confronted by a substance not recognized as a 'self' constituent, and the term 'immune response' has undergone a modification in meaning to cover the more general phenomenon of reaction to any stimulus treated as foreign. The other terms suggested for these abnormalities are 'auto-antibodization' (Fan, 1959) and 'antigenation' (Gooch, 1959). As regards the thyroid, Hubble's term, 'auto-immunizing thyroiditis,' seems the most acceptable.

The thyroid gland is perhaps the easiest organ in which auto-immune reactions may be studied, owing to the fact that one of the antigens involved is a well-characterized protein, thyroglobulin, and that extremely high concentrations of antibodies are present in the serum of some patients with auto-immune thyroiditis. The methods used for the detection of thyroid antibodies are applicable to the investigation of as yet undiscovered auto-immune phenomena and might, therefore, be usefully reviewed, with the results obtained in thyroid diseases.

Methods Employed for the Detection of Auto-antibodies, and Their Applications

When fairly high concentrations of auto-antibodies are present, the classical methods of immunology can be employed. These include the precipitin-reaction and the complement-fixation test (CFT). In some instances, however, auto-antibodies are of the 'non-precipitating' so-called 'incomplete' kind, or else they do not fix complement or are present in amounts undetectable by these tests. More sensitive recent methods include the tanned red cell agglutination test (TRC) of Boyden (1951), and the fluorescent antibody technique of Coons and Kaplan (1950). The 'anti-human-gamma-globulin consumption' test devised by Steffen (1954) may be used for the detection of antibodies to cell-bound auto-antigens.

Precipitin Reaction

When certain antibodies come in contact with their specific antigen in suitable proportions, they combine to form large protein aggregates giving a visible precipitate. To improve sensitivity, the test is usually done in agar gel and is simple to perform. Thyroglobulin antibodies are easily

demonstrated either in small tubes or in Petri dishes, provided there is about 0.2 mg. or more of antibody protein per ml. of serum. About 65 per cent. of Hashimoto patients and 20 per cent. of 'primary' myxoedemas have sufficient antibody for this test. In other thyroid diseases positive precipitins are rare (2 per cent. in thyrotoxicosis). Many Hashimoto patients have so much anti-thyroglobulin in their serum that quantitative precipitin curves can be made. The highest level so far recorded was 18.9 mg. of antibody protein per ml. but, more commonly, levels are of the order of 5 mg./ml. Positive precipitin reactions have been obtained in a few patients with Sjögren's syndrome, using not only saline extracts of lacrimal and salivary glands but also human liver, kidney and muscle.

The Complement-fixation Test (CFT)

This method classically used in the Wassermann Reaction (WR) depends on the fact that antigen-antibody complexes may combine with a group of proteins termed complement (C') normally present in the serum. The 'fixation' of complement to such complexes can be detected by the addition of an indicator system of sensitized sheep red cells which become lysed in the presence of complement. Thus the absence of lysis in the indicator system implies the presence of antibody in the serum to which antigen was added. This test is extremely important for studies on auto-immunity, since some antibodies cannot readily be demonstrated by any other method. Although it has many difficulties, the CFT has been widely used with many different immune systems for over 50 years and it is reasonably sensitive.

In its application to thyroid diseases, the test has provided extremely interesting information. It was shown by Trotter *et al.* (1957) that the antigen involved is distinct from thyroglobulin and that it is most abundant in thyrotoxic gland extracts. It has now been possible to localize this complement-fixing antigen to the 'microsome' fraction of actively secreting thyroid epithelium (Roitt and Doniach, 1958). The antigen is not specifically connected with Graves's disease for it is also present in normal glands and in the TSH over-stimulated thyroids of goitrous cretins (Anderson *et al.*, 1959) who develop compensatory hyperplasia owing to imperfect hormone synthesis, associated with a congenital enzyme defect in the gland.

Auto-antibodies to this microsomal antigen are nearly always present in Hashimoto's disease, together with anti-thyroglobulin. The separate nature of the two systems is well demonstrated by the fact that all the precipitins can be removed with thyroglobulin from such sera without alter-

ing the complement-fixation titres. Apart from advanced auto-immune thyroiditis, positive CFT using thyrotoxic gland extracts are also found in about 40 per cent. of thyrotoxic patients and more rarely in non-toxic goitres and thyroid carcinoma, as well as in elderly women without overt thyroid disease. The titres are, however, much lower in these conditions: whereas Hashimoto patients often have titres of 512 or even up to 2048, thyrotoxics yield a titre of 16 to 64 as a rule. Myxoedema cases lie somewhere in between with titres of up to 128 or so. Diagnostically this test is important because many cases of thyroiditis have no precipitins and sometimes not even traces of anti-thyroglobulin antibody detectable by the TRC test to be described below. A certain number of Hashimoto patients (about 8 per cent.) fix complement not only with thyrotoxic thyroid but also with normal thyroid and sometimes with other human organs including liver, kidney, brain, suprarenal or salivary glands. This finding again points to interesting connections with systemic lupus erythematosus and Sjögren's syndrome and perhaps with other 'collagen' diseases. However, it must not be forgotten that the great majority of Hashimoto and myxoedema patients show no evidence of systemic involvement and are usually healthy people once their hormone deficiency is corrected.

The Tanned Red Cell Agglutination (TRC) Test

Red cells treated with dilute tannic acid can be coated with various soluble proteins, in this instance purified thyroglobulin. If the coated cells are then placed in contact with patient's serum containing antibodies to thyroglobulin, they become agglutinated and form a diffuse mat. The TRC test is about 1,000 times more sensitive than the precipitin reaction, although it detects the same antibody. Apart from being positive in 93 per cent. of Hashimoto patients and 65 per cent. of primary myxoedemas, usually in titres of 25,000 to several million, it also shows up the traces of anti-thyroglobulin associated with small foci of lymphoid infiltration in all types of goitre, which are probably of no clinical significance since these lesions are of very low-grade activity and may well remain stationary throughout the patient's life. In cases with focal thyroiditis, the tanned-cell titres are of the order of 250 to 2,500 or even less. Precipitins are detectable when the TRC titre is 25,000 or upwards, although there are exceptions where no precipitins are obtained in the presence of a high TRC titre or vice versa. This is possibly due to the effect of 'incomplete' antibodies, which might produce red cell agglutination, although they are incapable of giving complexes large enough to become visible, or to the

presence of yet another antibody, but for clinical purposes this is not important as the dilutions are in steps of 10 and the exact titre does not correspond to any major clinical differences. It is far more important to combine the tanned-cell test with the CFT in the investigation of thyroid patients, since the presence of both antibodies, even in low titres, suggests a lesion which might produce clinical symptoms at some time. Precipitins are always of clinical significance as they imply a fairly widespread lymphadenoid replacement in the thyroid. In a thyrotoxic patient, precipitins suggest that myxoedema is likely to occur after surgical treatment, although severe toxicity is compatible with auto-immune thyroiditis.

The tanned-cell test was laborious and difficult to perform until Dr. A. J. Fulthorpe, of Burroughs Wellcome, developed a stable preparation of formalized sheep cells for use in clinical thyroid work. The formalized cells keep for many months and agglutinate specifically when added to suitable serial dilutions of the patient's serum, previously absorbed with uncoated cells from the same sheep to eliminate heterophile agglutinins.

In the foreseeable future it will be possible to coat tanned formalized cells with many other human antigens, provided they can be prepared in reasonably purified soluble form. This will undoubtedly be of great value in the investigation of obscure diseases which may be connected with auto-immune processes.

The Fluorescent Antibody Technique

This method was first developed by Coons and Kaplan (1950) for the study of foreign antigens, but it has proved of great importance in thyroid auto-immunity and will find many other applications in the future.

The method relies on the fact that certain fluorescent dyes such as fluorescein isocyanate and Rhodamin B can be conjugated with proteins, including serum antibodies which are mostly in the gamma globulin fraction. The conjugated serum is then applied to a histological frozen section; the antibodies combine with their specific antigen in the tissue cells and, after removing the excess serum proteins, the section can be viewed with a microscope using an ultra-violet light source. This provides a method of localizing antigens in various parts of cells and also makes it possible to find unknown antibodies in serum. The method was first applied to the problem of thyroiditis by White (1957). He was able to demonstrate that Hashimoto serum, conjugated with fluorescein, specifically stained the colloid in thyroid sections, and also that colloid escapes from injured thyroid follicles in areas affected by lymphadenoid lesions,

both in Hashimoto glands and in thyrotoxic glands with focal thyroiditis. It is not known whether the escape of intrafollicular thyroglobulin is a factor in initiating the auto-immune lesion or whether it escapes following an underlying disruption of the thyroid basement membrane due to unknown causes, in which case the circulating antibodies might only be a reflection of the injury and not responsible for the perpetuation of the lesion.

The anti-human-gamma-globulin consumption test has not yet been applied to thyroid problems but has been used for the detection of antibodies present in the sera of some patients with progressive hepatitis and with obscure renal and rheumatic lesions, which react with cell-bound antigens in liver, kidney, heart or connective tissue. In essence this method has applications similar to the Coons fluorescent antibody technique. The latter has the advantage of giving a visual localization of cell-bound antigens but the globulin-consumption test is semi-quantitative and can be used to follow the progress of disease processes. It remains to be seen which of these methods proves the most sensitive, or the least difficult.

Some Clinical Aspects of Thyroid Auto-immunity

The clinical picture of classical lymphadenoid goitre and of advanced myxoedema are well known, but since applying immunological tests to all thyroid patients a surprising number of early or mild cases of auto-immune thyroiditis have been uncovered, which made it possible to observe the disease in its incipient stages. These cases can be roughly divided into patients with small shrunken thyroid glands and those with a goitre of small, medium or large size.

Cases without Goitre

A survey of sera sent for cholesterol estimations from medical, dermatological and psychiatric clinics revealed a number of cases of early myxoedema with symptoms of chronic tiredness and depression or sometimes merely with dry skin, loss of hair or an unexplained gain in weight, in whom either the B.M.R. or the radioiodine uptake tests or both, gave equivocal results and who would have been difficult to diagnose on clinical grounds. Some of these had been sent to psychiatrists for their persistent complaints often extending over several years. These patients frequently had firm thyroids which could easily be felt if specially looked for. Their symptoms improved on 2 to 3 gr. of thyroid daily. A combination of the tanned-cell test with the complement fixation reaction will probably prove to be the most sensitive and specific way of establishing the presence of early thyroid deficiency, especially in patients with

added psychiatric complications, in whom it is difficult to obtain a reliable B.M.R.

Cases with Goitre

In the surgical clinic patients are usually seen for a noticeable goitre, and early cases of thyroiditis are often mistaken for non-toxic colloid goitres. Owing to the frequent asymmetry of the two thyroid lobes, or to prominent grooves between the lateral lobes and the enlarged isthmus, the gland may feel nodular on external palpation, even if the entire gland is involved in the lymphadenoid process. Rarely the gland is truly nodular and the auto-immune lesion is superimposed on a long-standing colloid goitre. The consistency of lymphadenoid goitre in the early stages is not as uniformly firm and rubbery as in the more advanced classical forms of the disease, and this is sometimes misleading. A common and helpful finding is the palpable pyramidal lobe. The B.M.R. is normal or slightly raised at this stage and the radioiodine uptake can be surprisingly high with an elevated plasma value at 48 hours. The topographical survey produces a symmetrical picture or one that corresponds with the outlines of the goitre. Although a positive precipitin is almost diagnostic of Hashimoto's disease the test has been positive in a few patients where a thyroid cancer was surrounded with lymphadenoid changes (Stuart and Allan, 1958). In such cases the character of the goitre and the presence of lymph node invasion may help to establish the diagnosis, but the most helpful test is the topographical survey of I^{131} distribution which nearly always shows an area of low or absent uptake over a malignant tumour. On the other hand, the absence of detectable antibodies does not completely exclude Hashimoto's disease, although in the few cases with negative immunological tests the serum flocculation values and gamma globulins have been markedly raised, suggesting the possible presence of antibodies in the form of complexes or directed against an unidentified antigen.

Changes due to Treatment

Thyroid extract in doses of 2 to 4 gr. or L-thyroxine 0.3 to 0.5 mg. daily is the treatment of choice for lymphadenoid goitre once the diagnosis is established. In many cases the goitre shrinks and disappears completely after one to two years or even less. The narrowed trachea opens out once more. In some patients a small goitre remains, although pressure symptoms have subsided. Occasionally a Hashimoto goitre fails to respond to large doses of thyroid, in which case the histology may show an excessive preponderance of thick collagen reminiscent of keloid tissue.

The highest antibody levels have been found in untreated cases and prolonged thyroid administration reduces the level of both the precipitin and the complement fixation titre presumably by diminishing antigenic stimulation through TSH inhibition. The complement-fixation test may become negative after treatment, whereas precipitins never completely disappear with thyroid therapy, although they do so after subtotal thyroidectomy. Corticosteroids reduce the size of Hashimoto goitres by causing regression of lymphoid tissue and inhibition of antibody formation, but as a rule the patient feels worse unless thyroid is given simultaneously to correct the hormone deficiency.

The Association with Thyrotoxicosis

Small collections of lymphocytes are almost the rule in thyrotoxic glands and even larger patches of lymphadenoid change are not infrequent. Although a corresponding number of patients have small traces of antibody in their serum, these minor lesions are of no clinical significance, do not lead to myxoedema and are even compatible with recurrent hyperthyroidism following thyroidectomy. About 10 per cent. of thyrotoxic patients have fairly high antibody titres and of those a proportion may eventually become hypothyroid, either spontaneously several years after their thyrotoxic episode or more rapidly after subtotal removal of the goitre.

Very occasionally a rapid change to classical Hashimoto's disease may be witnessed in a thyrotoxic patient: the goitre suddenly begins to enlarge and becomes firm and horseshoe-shaped, the precipitin test becomes positive and gradually increases in titre. If the patient is still thyrotoxic at this stage, the problem of treatment becomes difficult, since anti-thyroid drugs stimulate the goitre to further growth, thyroid hormones aggravate the symptoms and thyroidectomy produces myxoedema.

A particularly high incidence of precipitins has been found in cases of malignant exophthalmos. It is possible that the lymphoid infiltration, the fragmentation of muscle fibres and increase in bulk of the extrinsic ocular muscles seen in some patients, represents an associated auto-immune myositis, although it is likely that the proptosis of endocrine exophthalmos is essentially caused by an abnormality of TSH or possible EPS (exophthalmos-producing substance). The problem is at present under investigation.

Subacute Thyroiditis of de Quervain

Subacute thyroiditis is a self-limiting disease which starts acutely with a rapid painful swelling of the thyroid, frequently unilateral at first, accompanied by fever and malaise and often asso-

ciated with tachycardia, moist skin and tremor. The disease is thought to be of viral origin and in a recent epidemic in Israel the mumps virus was cultured from the thyroid gland. Isolated cases in other countries have had raised mumps antibody titres, but it is probable that other viruses may also infect the thyroid and that different viruses operate in certain parts of the United States where the disease is particularly prevalent.

In the acute stage the B.M.R. and PBI¹²⁷ are characteristically raised owing to breakdown of thyroid follicles by the infecting virus with release of colloid into the circulation. The excess circulating hormone depresses TSH output, and this results in a completely suppressed iodine uptake by the gland for several weeks or even months according to the severity of the infection. After six to twelve weeks, or occasionally up to six to nine months, the thyroid swelling goes down completely and the patient recovers without loss of thyroid function. Since the introduction of auto-antibody studies, several patients with this disease have been tested at intervals and have shown no evidence of thyroid antibodies except for small traces which appeared in some cases eight to eleven weeks after onset and disappeared again when the patient recovered.

Acute Auto-immune Thyroiditis

There is, however, another group of patients who also complain of a fairly rapid and somewhat painful thyroid swelling, difficult to distinguish clinically from de Quervain's disease, in whom thyroid antibodies have been of high titre. In these patients the I¹³¹ uptake has been increased above normal and the B.M.R. normal or low. It is not known whether a virus infection can be a precipitating factor in these patients who appear to have 'acute auto-immunity' when first seen. In some of them the I¹³¹ uptake has slowly come down to normal and the auto-antibody titre has gradually diminished. Perhaps thyroid auto-immunizing disease can have fluctuations similar to those seen in the other auto-immune diseases. The question can only be settled by careful follow-up of auto-antibody titres in atypical cases of thyroiditis.

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