The Clinical Significance of Autoantibody Detection

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In the past twenty years there have been many reports on the presence of autoantibodies in the blood in a wide variety of human diseases, and tests for autoantibodies are now extensively used in clinical practice. This article is concerned with the indications for, and interpretation of, those autoantibody tests which I believe are of real practical value in the diagnosis, prognosis, or treatment of patients. The value of autoantibody tests in the investigation and management of the haemolytic anaemias is already well known and will not be dealt with here.

It is necessary for the clinician to be aware of the great variation in the methods and apparatus employed by different laboratories to detect autoantibodies, and to know that there are serious problems, only now beginning to be solved, in the standardisation of some of the reagents used, such as fluorescein-labelled antiglobulin antibodies. Because of the variables involved, different laboratories may produce rather different results with what appears to be the same test. Accordingly, the results quoted in the ensuing paragraphs are for general guidance. For detailed interpretation of results the physician should consult his own clinical immunologist.

Thyroid Antibody Tests

Thyroid autoantibody in the serum nearly always indicates the presence of chronic thyroiditis. Most clinicians who have used them agree that tests for thyroid antibody are of practical value in the diagnosis of severe forms of thyroiditis such as Hashimoto’s disease and primary non-goitrous hypothyroidism. Unfortunately, to obtain the greatest diagnostic accuracy, separate sensitive tests have to be performed for autoantibody to three distinct thyroid-specific antigens (thyroid microsomes, thyroglobulin, and a second antigen in the thyroid colloid), and, when positive, further tests are required to determine the titre of the antibody. The subject is well reviewed by Doniach and Roitt (1968) whose results, quoted below, are based on a battery of tests including immunofluorescence, agglutination of tanned red cells coated with thyroglobulin, and complement fixation tests.

The main indications for tests for thyroid antibody are as follows:
1. The Distinction of Hashimoto's Disease from Simple Non-toxic Goitre

This distinction is of practical importance owing to the desirability of avoiding surgery in patients with Hashimoto's disease and of treating them for the remainder of their lives with thyroid hormone. Although it is established that partial thyroidectomy leads rapidly to the development of hypothyroidism in Hashimoto's disease (Woolner et al., 1959), it is of interest that there is no accurate information on the incidence of subsequent hypothyroidism in patients who first present with euthyroid Hashimoto's disease and remain untreated. Table 1 shows that high titre antibodies to thyroglobulin and/or thyroid microsomes are almost diagnostic of Hashimoto's disease in goitrous patients who do not have thyrotoxicosis, while Hashimoto's disease can confidently be excluded when the sensitive tests for antibody to the various thyroid antigens are negative, provided that the patients have received little or no treatment at the time of testing. The presence of weak thyroid antibodies in half the cases of simple non-toxic goitre is nearly always due to clinically insignificant mild focal thyroiditis; the 19 per cent of Hashimoto patients with weak thyroid antibody must be recognised by other abnormalities such as elevated serum immunoglobulin levels, abnormal serum flocculation reactions, or evidence of a small thyroidal iodine pool demonstrated by radioiodine studies.

2. The Distinction of Hashimoto's Disease from Carcinoma of Thyroid

The finding of high titre thyroid antibodies again points to the diagnosis of Hashimoto's disease (Table 1). It is noteworthy that Hashimoto's disease and thyroid carcinoma not infrequently occur together in the same patient, which explains the presence of high titre thyroid antibodies in 11 per cent of patients

| Table 1. Incidence of Thyroid Autoantibodies (after Doniach and Roitt, 1968) |
|---------------------------------|-----------------|-----------------|
|                                 | Percentage of cases with |
|                                 | Strong antibody | Weak antibody | No antibody |
| Hashimoto's disease             | 80              | 19             | 1            |
| Non-toxic goitre                | 2               | 47             | 51           |
| Thyroid cancer                  | 11              | 34             | 55           |
| Primary hypothyroidism          | 40              | 53             | 7            |


with thyroid carcinoma. In practice, the serological distinction between Hashimoto’s disease and thyroid carcinoma should be restricted to those cases in which the clinical suspicion of a tumour is based only on the presence of a uniform firm goitre; if a tumour is suspected for any other reason the serological findings should be disregarded and a biopsy obtained. This useful rule is illustrated by the case of a female aged 57 with recent enlargement of the right lobe of thyroid which had developed in a small goitre of many years’ duration. Serological (and other) investigations pointed to the diagnosis of Hashimoto’s disease, but scanning of the neck following radioiodine administration showed markedly diminished uptake over the lesion, which was found, at operation,

![Image](Fig 1. Thyroid carcinoma associated with Hashimoto’s disease—a diagnostic pitfall for the unwary.)

to be a rather anaplastic papillary carcinoma associated with Hashimoto’s disease (Fig. 1).

I have now seen several patients with clinical, immunological, and histological evidence of simple Hashimoto’s disease who had recurrent laryngeal nerve palsy or adhesion of thyroid to the strap muscles of the neck. I believe that surgical exploration of the neck was justified in these cases although they were eventually shown not to have malignant disease.

3. The Diagnosis of Mild Non-goitrous Primary Hypothyroidism
Serological studies are indicated only when clinical examination and chemical measurements give equivocal results. High titre thyroid antibodies that indi-
cate thyroiditis likely to be so extensive as to impair thyroid function are found in 40 per cent of patients with primary hypothyroidism, while absence of thyroid antibodies is against the diagnosis (Table 1). Weak thyroid antibodies may be found in at least a sixth of female hospital patients over the age of 50 years due to the presence of clinically insignificant amounts of focal thyroiditis (Goudie et al., 1959), and the presence of low antibody titres does not help with the diagnosis in females of this age group. Low antibody titres lend some support to the diagnosis in doubtful cases of primary hypothyroidism in younger females and in males, for in these groups symptomless focal thyroiditis is uncommon.

4. In Patients with Thyrotoxicosis where Partial Thyroidectomy is Contemplated

Thyrotoxic patients who will develop hypothyroidism following partial thyroidectomy nearly always have high titre thyroid autoantibodies, especially to thyroid microsomal antigen (Irvine et al., 1962). Antibody tests thus provide a useful contra-indication to surgical treatment when there is a desire to avoid or anticipate the development of postoperative hypothyroidism. It should be noted that tests for autoantibodies are of no value in predicting hypothyroidism following radioiodine or antithyroid drug therapy.

5. The Recognition of Endocrine Exophthalmos

Positive thyroid antibody tests favour this diagnosis, which can be difficult, especially in euthyroid patients with unilateral exophthalmos.

Because of the complexity and expense of thyroid antibody tests, they should not be performed in obvious cases of primary hypothyroidism nor in thyrotoxic patients who are to be treated with antithyroid drugs or radioiodine. There is little to be said for routine investigative refinement without commensurate therapeutic progress.

Gastric Autoantibody Tests

While it is probable that autoimmune gastritis is the basic defect in most cases of Addisonian pernicious anaemia, in my opinion this disorder should normally be diagnosed by the demonstration of histamine-fast achlorhydria, appropriate haematological changes, and low serum levels of vitamin B12. If, for some reason, tests for gastric acid production cannot be carried out, the demonstration of antibody to gastric parietal cells is better than nothing. Parietal cell antibody is present in 86 per cent of cases of pernicious anaemia (i.e. a negative test does not exclude the diagnosis) and in 11 per cent of the 'normal' adult population (Taylor et al., 1962). Its presence points to the
existence of autoimmune gastritis but it does not indicate whether the disease has proceeded to the severe gastric atrophy that accompanies pernicious anaemia.

In cases where the diagnosis is in doubt and there is difficulty in deciding whether to embark on life-long vitamin B₁₂ therapy, positive tests for antibody to intrinsic factor are virtually diagnostic. Unfortunately, tests for this antibody are negative in 43 per cent of cases of pernicious anaemia (Ardeman and Chanarin, 1963).

**Antibodies to Adrenal Cortex**

These are present in the serum of half the cases with non-tuberculous chronic adrenocortical insufficiency and are virtually diagnostic except in rare cases of idiopathic hypoparathyroidism, which presumably also have subclinical autoimmune adrenalitis. Non-tuberculous Addison’s disease is, of course, best diagnosed routinely by appropriate endocrinological and radiological examination. The demonstration of adrenal antibody gives reassurance that the adrenal lesion is not tuberculous, and it can be of considerable value in rare cases of special difficulty. In two patients who developed the electrolyte disturbances of Addison’s disease while receiving prolonged prednisolone therapy for steatorrhoea, the presence of adrenal antibody gave evidence of irreversible adrenocortical damage (Goudie et al., 1969).

**The Connective Tissue Diseases**

In the diseases mentioned above it is possible, in certain circumstances, to relate the results of autoantibody tests to immediate therapeutic decisions. This is seldom so with immunological tests in the connective tissue diseases, i.e. rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, and allied disorders. In these conditions the demonstration of antibodies to antigens shared by a wide variety of tissues (hence called non-organ-specific antibodies) gives confirmation of the general nature of the disease, but the detailed management depends mainly on other features of the illness.

Of the many autoantibody tests described in the connective tissue diseases the following are of practical importance.

1. **The Immunofluorescence Test for Antinuclear Antibody (ANF)**

The test demonstrates reactions with several distinct nuclear antigens, including desoxyribonucleoprotein and desoxyribonucleic acid (DNA). In my opinion, immunofluorescence tests for ANF should now replace the LE cell test which indicates the presence of anti-desoxyribonucleoprotein antibody in a complex and insensitive way; homogeneous nuclear fluorescent staining,
often in high titre, is nearly always found in patients reputed to have a positive LE cell test. If the ANF test is negative in an untreated patient thought to have systemic lupus erythematosus, the diagnosis is probably wrong. As shown in Pollack’s review of the literature in 1964 (Table 2), the presence of ANF is not diagnostic of systemic lupus erythematosus—not for that matter is a positive LE cell test. ANF is found in a third of cases with discoid lupus erythematosus and does not suggest that the disease is likely to become systemic (Beck and Rowell, 1966); it is also present in a quarter of patients with rheumatoid arthritis, usually those with severe disease but without features peculiar to systemic lupus erythematosus (Goudie and Buchanan, 1967). The finding of ANF, especially in high titre, generally points to the presence of a connective tissue disease, and is particularly valuable in patients with unexplained pleurisy, pericarditis, or renal disease.

2. Antibody to DNA
Best recognised by special tests using purified antigen, this antibody is said to be almost pathognomonic of systemic lupus erythematosus, and is especially related to active renal disease. Serial measurement of this antibody has been proposed as a guide to steroid dosage, high titres foreshadowing further renal damage (Schur and Sandson, 1968).

3. Rheumatoid Factor
This group of antibodies, essentially anti-gammaglobulins, is found not only in the connective tissue diseases but also in chronic infections. Tests for rheumatoid factor are of prognostic value in polyarthritis of rheumatoid type, the
disease being twice as likely to become inactive in patients with negative tests as in those with rheumatoid factor (Duthie et al., 1964); high titres are especially associated with extra-articular manifestations of the disease such as subcutaneous nodules, vascular involvement, and neuropathy.

4. Biological False Positive Wassermann Reactions
Certain patients with active or latent connective tissue disease have non-organ-specific autoantibodies that fix complement with the cardiolipin Wassermann antigen (Harvey, 1962). In these individuals, the demonstration of a negative treponemal immobilisation test and the finding of other antibodies suggestive of a connective tissue disease will ensure against the inappropriate diagnosis of syphilis.

LIVER DISEASE
The biochemical evidence of biliary tract obstruction in primary biliary cirrhosis frequently gives rise to anxiety on the part of the clinician lest a remediable form of extrahepatic biliary tract obstruction may be present. The finding of mitochondrial antibody, present in over 90 per cent of primary biliary cirrhosis (Doniach et al., 1966), is very strong evidence that exploratory laparotomy is unnecessary. To my knowledge, mitochondrial antibody has never yet been found in a case of extrahepatic biliary tract obstruction.

The clinical significance of autoantibody detection in chronic active hepatitis (antinuclear antibody has been reported by Doniach et al. (1966) in 77 per cent, antibody to smooth muscle in 67 per cent, and mitochondrial antibody in 28 per cent) remains unknown, and therapy should probably be dictated by the clinical state of the patient (Geall et al., 1968).

OTHER AUTOANTIBODY TESTS
Of the many other autoantibody tests that have been described, most have been found to be of little practical value in the management of patients. Some, such as tests for autoantibodies against blood platelets and leucocytes, are technically difficult; others, such as those described in myasthenia gravis, Sjögren's syndrome, ulcerative colitis, and cardiac disorders, appear to be mainly of scientific interest; yet others, such as the test for intercellular antibody in pemphigus (Lancet, 1968), promise to be useful but have yet to be fully assessed.

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The Civility of Judge Jeffreys

The labelling of medicines was a controversial subject in the eighteenth century. In 1687 the College of Physicians was concerned that the apothecaries were gaining ground in the prolonged battle for the right to treat the sick; indeed, they were increasing their influence to such an extent that some called them (and regarded them as) ‘Doctors’.

The apothecaries, said the College, were ‘aiming to acquire from physicians’ prescriptions some form and semblance of a false learning which they turn to their advantage ingratiating themselves with patients everywhere’. Accordingly, the College sealed various statutes on 28th October 1687, and one laid down that directions for the use of prescriptions must be in English and passed directly to the patient.

These new statutes were challenged by the apothecaries and surgeons: Judge Jeffreys, in his capacity as Lord Chancellor, visited the College and: ‘did civilly and privately . . . moderately reprimand the College for that having made Statutes and put them into execution they did not first (as easily they might have done) bring them to him as their Visitor and friend to give them their Sanction.’ Easily they might have done, indeed, and not only easily but wisely. The popular image of Judge Jeffreys usually omits such traits as civility and moderation, and Jeffreys had already given judgment against the College in a financial matter in 1685. In the case of the new statutes, the Visitor’s final decision is not recorded, but the statute remained in force for some years.
The Marvel of His Age

Intellectual excellence is not often an endearing quality; it is a relief to find some defect in a paragon. Thomas Young, born 1773, was an unnatural youth, being fluent in Latin, Greek, Hebrew, Chaldee, Arabic, Syriac, Persian, and, for good measure, French, Italian, and Spanish by the age of eighteen. He was elected a Fellow of the Royal Society at the age of twenty-one for his work on vision, then studied medicine at Göttingen, and went up to Cambridge in 1796 to be known by his fellow undergraduates, from whom he kept aloof, as ‘Phenomenon Young’. Appointed as Professor of Natural Philosophy at the Royal Institution in 1801, he was found to be a very bad lecturer. He then turned to the practice of medicine, becoming a Fellow of the College in 1809. Elected physician to St George’s Hospital, he showed but moderate clinical competence, and his colleagues were disappointed by his indifferent practice. Honoured for his original work on the wave theory of light, remembered as the translator of the Rosetta Stone, he still failed in treating the sick. A career that echoed the words of le Febure written a century before Young’s birth: ‘It is not a gown or degrees taken in Universities which constitute the Physician, but a solid knowledge of nature grounded upon sound reason and mature judgement, improved by practice and experience’.

Down With the College

Marchmont Nedham (in 1665) took a sour view of tradition in medicine for ‘this kept Phyfick, till of late years, as well as other Sciences, low, at a f Tay, and very heartlefs, without any growth or Advancement’ and complained that ‘men have formerly thought it wifdom not to budg an inch from the footing of the firft Masters; infomuch that when Chymiftry firft came in play, the Profefators and Operators were thought to be Mad-men; but afterwards (when they gained fome ground and entertainment in the World) the Aristotelians and Galenifts, feeling that reproach and contempt would not do the work, began to raife a fierce perfeclion, by f tirring up Princes and Magiftrates againft them, as a pack of Magicians, Mountebanks, Rogues, Cheats, Vagabonds, and I know not what; and procured Laws and Statutes to be made againft them as fuch, till the excellency of the Art it felf, and its grand Achievements, opened the eyes of the Governours, and f topp’d the mouths of gain-fayers; and even the common people to came fee, that it was the Intereft of the Collegiate Corporations of Phyficians, who lived in eafe and splendor, practifing with old Maxims and Medicines, not to permit a new laborious Sect of Philofophers, working Knowledge out of the Fire, by their Industry and Succesfes, to bring a reproach upon them for their Idlenefs, and superftitious devotion to their old heathenifh Authors.’