1. **Tissue specific autoimmune diseases**

1. **Introduction**

The aim of this chapter is not to provide an exhaustive account of all the autoantibodies associated with autoimmune disease but to highlight the important autoantibody associations with disease, and their diagnostic significance. Measurement of autoantibodies is not a replacement for clinical diagnosis. Like any investigation, interpretation of an autoantibody result must be made by considering the sensitivity and specificity of the test, and the likelihood or the diagnosis before the test is ordered. For example, it would be wrong to make a diagnosis of systemic lupus erythematosus (SLE) on the basis of a positive anti-nuclear antibody in a patient with few clinical features to support the diagnosis. However, sometimes measurement of autoantibodies can dramatically change the clinical perspective. For example, a positive anti-glomerular basement membrane (GBM) antibody test in a patient with rapidly progressive glomerulonephritis would allow the diagnosis of Goodpasture's syndrome to be made with a high degree of certainty, and provide an indication for specific and aggressive therapy with cytotoxic agents and plasmapheresis. The distinction between organ and systemic autoimmune can sometimes be artificial. Where it possible, the investigation of clinical syndromes rather than individual diseases is discussed.

Autoantibodies should be interpreted with reference to:

1. Clinical findings
2. Patients age. Most autoantibodies increase with age. Two exceptions are anticardiolipin antibodies and smooth muscle antibodies.
3. Antibody titre
4. Antibody isotype. IgM antibodies are usually not pathogenic. Two exceptions are rheumatoid factor and anti-red cell antibodies in cold haemolytic anaemia.

2. **Endocrine Disorders**

In autoimmune thyroid disease, the presence of autoantibodies may precede the appearance of clinical disease by many years. Autoantibodies to thyroglobulin or thyroid peroxidase are very commonly present, and antibodies directed against different epitopes may either stimulate or block the TSH receptor → hyperthyroidism or hypothyroidism respectively.

In type 1 Insulin-Dependent Diabetes Mellitus (IDDM), β-cells in the pancreatic islets of Langerhans are the targets of autoimmune attack. A number of autoantigens have been identified as targets for both antibody and T-cell responses in both humans and a commonly used mouse model (NOD, or non-obese diabetic mice who spontaneously develop IDDM). Three antigens (GAD [glutamic acid decarboxylase], insulin, and Hsp [heat shock protein] 60) are leading candidates. Autoantibodies to pancreatic islet cells are present in the serum of >90% of patients with IDDM at diagnosis and disappear over the following year or so, but the immunopathology is thought to be due mainly to cell-mediated immune responses.

The most common cause of Addison's disease is autoimmune destruction of the adrenal cortex. Patients present with hyperpigmentation, weakness, hypotension, electrolyte disturbances, diarrhoea and death. The major autoantigen is the 21-hydroxylase enzyme involved in steroid biosynthesis. A significant percentage of patients with Addison's disease also have autoantibodies against other steroid-producing cells - for example ovarian autoantibodies.

3. **Bullous skin disorders**

The skin is involved in many systemic autoimmune diseases, particularly vasculitides (e.g. SLE, scleroderma, vasculitis). In lupus, there is a characteristic deposition of antibodies at the dermo-epidermal junction in both normal and involved skin. This deposition is not obviously related to local pathology. By contrast, there are a number of potentially life-threatening blistering skin conditions where antibodies can be identified in the dermis or epidermis, usually at the level at which the layers of the skin separate to form the blister. Thus, in pemphigus autoantibodies are directed towards the intercellular desmosomes between
epidermal cells resulting in fragile blisters. In pemphigoid they are directed towards the epidermal basement membrane, resulting in tense blisters. There are also a number of similar conditions listed below.

1. Classification of Autoimmune Skin Disease by Location of Autoantibodies

<table>
<thead>
<tr>
<th>Location</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Epidermis</td>
<td>Pemphigus vulgaris, Pemphigus foliaceus</td>
</tr>
<tr>
<td>II Basement membrane</td>
<td>Bullous pemphigoid, Epidermolysis bullosa acquisita, Linear IgA Bullous dermatosis</td>
</tr>
<tr>
<td>III Dermis</td>
<td>Dermatitis herpetiformis</td>
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4. Neurological disorders

**Multiple Sclerosis** (MS) is the most common cause of neurological disability in young adults. The clinical manifestations vary widely, and the symptoms and signs may fluctuate over time. The pathology is characterised by small patches of demyelination (plaques) throughout the CNS. The plaques represent a cellular immune response directed against an autoantigen, presumably in the myelin of the CNS. However, the identity of the antigen remains a mystery. One difficulty is that autoreactivity to the major candidate glycoproteins MOG (myelin oligodendrocyte glycoprotein), MAG (myelin associated glycoprotein), MBP (myelin basic protein) and PLP (proteolipid protein) has been reported both in patients who have MS and normal individuals. In order reliably to incriminate a target molecule, there should be a difference in immune responses against the putative antigens in patients with the disorder and normal individuals. A number of environmental factors have been implicated in the pathogenesis of MS. The prevalence of MS is greater in temperate than tropical climates, which strongly suggests that it may be related to infection with a microbe more prevalent in temperate climates. Other putative but unconfirmed associations include childhood measles, and exposure to cats.

Evidence of activation of lymphocytes in the CNS is obtained by demonstrating the presence of oligoclonal bands of IgG in the CSF but not the serum is helpful in diagnosis. The oligoclonal nature of the response suggests that there is an antigen-driven B cell response occurring. Oligoclonal bands are helpful in establishing the diagnosis of MS, along with other modalities such as MRI and evoked potentials. Oligoclonal bands can be detected in CSF of patients with other conditions, including AIDS dementia complex and neurosyphilis.

**Myasthenia gravis** is a disorder of neuromuscular transmission where skeletal muscle becomes easily fatigued. It is caused by antibodies against the Acetylcholine Receptor (AChR) at the neuromuscular junction. Binding of these antibodies leads to blockade of neurotransmission, inflammation at the post synaptic membrane, and a reduction in the number of AChRs. Some patients (who have more severe disease) may be improved by thymectomy, and it is associated with thymoma in some patients. The Lambert-Eaton (myasthenic) syndrome (LES), which is rarer than myasthenia gravis, is also characterised clinically by muscle weakness. LES is usually a paraneoplastic syndrome. That is, it occurs in association with malignancy such as small cell lung cancer. It is caused by antibodies against pre-synaptic voltage-gated calcium channels which cause reduced amounts of neurotransmitter to be released by action potentials at the neuromuscular junction.
Guillain-Barre syndrome (GBS) is an acute or subacute ascending motor polyneuropathy due to inflammation involving the myelin sheaths of peripheral nerves. GBS has been linked with a number of different infectious agents, including enteroviruses, EBV, HIV, mycoplasma and Campylobacter jejuni which appear to trigger an autoimmune response directed against myelin. The predominant clinical manifestation is progressive weakness, although patchy sensory deficits are also common early in the disease. Most patients make a recovery over 4-8 weeks. However, the disease may be life-threatening if nerves to the muscles of the chest wall and diaphragm become involved, in which case artificial ventilation may be necessary. The clinical benefit derived from plasmapheresis or intravenous immunoglobulin treatment in the early stages of the disease suggest that autoantibodies may be chiefly responsible for the immunopathology. However, the refractoriness in later stages suggest that a cellular response may subsequently dominate. Although this is essentially a disease of the peripheral nervous system, CSF mononuclear pleocytosis may be found due to inflammation in the nerve roots.

5. Autoimmune Liver Disease/Viral Hepatitis/Gut Disorders

Pernicious anaemia (PA) is predominantly a disease of European whites. It is leads to malabsorption of vitamin B12. Histologically it is characterised by type A gastritis involving the fundus and body of the stomach. There is selective loss of parietal and chief cells and a submucosal lymphocytic infiltrate. The gastric secretions contain anti-gastric parietal cell antibodies (AGPCAs) and anti intrinsic factor antibodies (IF Abs). AGPCAs occur in > 90% of patients with pernicious anaemia and in 30% of their relatives. These antibodies bind to gastric cell canaliculi and parietal cell microsomes. They are specific for the β subunit of proton pump or H⁺/K⁺ ATPase which consists of a membrane channel, the β subunit, and a cytoplasmic catalytic component. How the antibodies gain access to these molecules which are cytoplasmic and luminal is unclear.

Ulcerative colitis and Crohn's disease are inflammatory bowel diseases of unknown cause in which it seems likely that immunological effector mechanisms may cause pathology. Infectious causes have been assiduously sought but there remains no explanation as to the cause of the underlying diseases. There are no specific immunological investigations to aid in the diagnosis, although some patients have a positive atypical ANCA. It is of interest that inflammatory bowel disease has been observed in mice deficient in IL10.

Autoimmune Chronic Active Hepatitis (AI-CAH) must be distinguished from other causes such as chronic infection with hepatitis B or C viruses, drugs, Wilson's disease, haemachromatosis, and α-1 antitrypsin deficiency. In particular, hepatitis C must be distinguished from autoimmune hepatitis because hepatitis C is treated with interferon, and exacerbated by immunosuppression, while autoimmune hepatitis is treated with immunosuppression, and is exacerbated by interferon.

The pathology reveals lymphocytes and plasma cells infiltrating the portal tracts and thence the liver parenchyma with characteristic piecemeal necrosis. Cirrhosis may follow. There are three patterns of AI-CAH:

Type I

CAH which may be associated with other autoimmune diseases. Mostly occurs in middle aged women. Associated with smooth muscle antibodies (directed against a variety of cytoskeletal antigens including actin), antinuclear antibodies and hypergammaglobulinemia (IgG).

Smooth muscle antibodies occur in 40-70% of patients with AI-CAH, 50% with of patients with PBC (see below) and 30% of patients with cryptogenic cirrhosis. Also occur with acute viral illnesses, asthma and malignancy. However, in these conditions they are usually present in lower titre. They occur in less than 2% of the normal population.

Type II

Less common than type I, but also occurs in women, and responds well to prednisone. Associated with LKM 1 antibodies that bind to cytochrome P-450 II D6. Cross-reactivity with antibodies to HCV noted.

Type III
Recently described specificity. Antigen identified as UDP glucuronodyl transferase and significant cross-reactivity with antibodies to hepatitis D.

**Primary biliary cirrhosis** differs from other forms of AI-CAH because the inflammation leads to progressive destruction of bile ducts rather than the hepatocytes. The infiltrate comprises lymphocytes and macrophages, which may form granulomata. Hepatocyte function is maintained until late in the disease. However, the manifestations of biliary obstruction (itch and osteopenia) can be extremely debilitating.

Antimitochondrial antibodies (AMA) are present in >95% of patients with PBC. Even in the absence of abnormal LFTs, a titre of 1:40 for AMA is predictive of PBC. AMA disappears within about one month of orthotopic liver transplant suggesting that it is antigen driven. AMAs may be observed in other forms of liver disease, however, there are differences in the precise antigen specificity depending on the nature of the liver disease. In PBC, AMA (classified as M2) is targeted at part of the pyruvate dehydrogenase complex. A similar enzyme is present in E.coli and UTIs with E.coli have been associated with the development of PBC. PBC patients also have a polyclonal increase in IgM.

6. **Haematological disorders**

Autoantibodies can be directed against circulating cells and Immune Thrombocytopenia (ITP), autoimmune haemolytic anaemia (AIHA), autoimmune neutropenia and lymphopaenia can result. The latter two are uncommon, but do occur e.g. sometimes in association with RA and SLE respectively. They can respond to treatment with high doses of intravenous immunoglobulin, which blocks the Fc receptors of phagocytes which phagocytose the autoantibody-coated cells.

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