A breakdown of the normal balance between immunity and self-tolerance can result in autoimmune disease, through the generation of an excessive level of T-cell helper function, a deficiency in the normal process of T-cell suppression, or an escape by autoreactive T-cells or B-cells from the normal process of clonal abortion. Several human diseases (and animal models) illustrate the key features of autoimmune states (thyroiditis, encephalomyelitis, myasthenia gravis, rheumatoid arthritis and SLE), and the significance of immune complexes in the pathophysiology of autoimmune disease.

An immune response to "self" antigens defines a state of autoimmunity. Clinically, autoimmune states may be mild or symptom-free, but in other cases may result in severe and fatal afflictions.

Autoimmune responses may result from two general causes. In one case, antigens normally "hidden" from the immune system ("sequestered" antigens) may be released into the circulation and trigger a response by the immune system. In this case no state of peripheral tolerance need exist (see Chapter 18), and the immune system is capable of generating an effective response on exposure to the antigen. Examples of clinical or experimentally induced autoimmunity to such sequestered antigens include those directed against thyroglobulin, eye lens protein and spermatozoa antigens. (Keep in mind, however, that sequestration of antigens within some anatomical compartment is never absolute, and that at least some degree of central and/or peripheral tolerance to such antigens is often demonstrable).

A different situation exists when the normally effective tolerant state of the immune system to "self" antigens is for some reason abrogated. The final result of such a breakdown of tolerance, however, is the same as in the case above: a damaging and potentially fatal autoimmune reaction.

Breaking of the normal tolerant state of an organism's immune system may result from a variety of influences:

i) Decrease in Treg activity.

ii) Increase in Th activity (e.g., with adjuvants).

iii) Immune response to foreign antigens which happen to cross-react with "self" (for example, the experimental induction of rabbit anti-AChR, and streptococcal-induced rheumatic fever in humans).

The mechanisms which maintain a normal state of tolerance are certainly not 100% efficient, and we have already noted in Chapter 18 that T and B-cells with potentially autoreactive antigen receptors can be found in healthy individuals. Low levels of autoantibodies can also
be commonly found in humans and other organisms, much more frequently than one can find clinically significant autoimmune disease. There are, however, many clinical and experimental situations in which autoimmune processes play a key role in active tissue destruction and disease.

We discuss below a few examples of human autoimmune diseases and identify their key features. For some of them we will also present experimental autoimmune diseases which have been central to our understanding of the underlying immunological basis of the human diseases. We will discuss little of the details of clinical treatment of different human autoimmune diseases, but will note that it often includes generalized immunosuppression by steroids or other drugs.

**HASHIMOTO’S THYROIDITIS.** Autoimmune damage to the thyroid, primarily by the humoral response, results in decreased function and clinical hypothyroidism. It is characterized by the presence of circulating antibodies to thyroglobulin and thyroid peroxidase as well as to microsomal proteins and other components of thyroid cells. A mononuclear infiltrate is also typically present within the thyroid. The etiology of this disease is generally unclear, but may include initial damage to the organ from either a viral infection or trauma. Treatment includes hormone replacement, and, as with most autoimmune diseases, there is a significant genetic component which includes contributions by HLA linked genes.

**AUTOIMMUNE THYROIDITIS OF MICE**
When healthy mice are injected with homogenized mouse thyroid tissue together with complete Freund's adjuvant, they will develop autoantibodies to thyroglobulin as well as other antigens normally hidden inside cells of the thyroid. There will also develop a cellular infiltrate of the thyroid characterizing T-cell mediated immunity, and progressive damage to the organ resulting in hypothyroidism. This is considered an example of autoimmunity by deliberately induced release of sequestered antigen (despite the fact that low amounts of thyroglobulin are normally present in the circulation.)

**GRAVE’S DISEASE.** This is also an autoimmune thyroid disorder, but is characterized by hyperthyroidism. Autoantibodies are produced which are directed against the receptor for TSH (Thyroid Stimulating Hormone) which is expressed on thyroid follicular cells, and these antibodies stimulate the chronic overproduction of thyroid hormone. This is an example of an antibody acting as an agonist for its target molecules (i.e. they stimulate TSH activity), as opposed to an antagonist (e.g. anti-AcChR antibodies which block receptor function – see below). Treatment in such cases most commonly involves reducing thyroid function by surgery or radioactive iodine.

**ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM).** This disease may follow infection by (or rarely vaccination with) a variety of viral pathogens, including measles, rubella and influenza. Cellular infiltrates representing a cellular immune response to myelin basic protein are evident, very similar to EAE, but without a humoral response. A wide variety of neurological defects can result from this autoimmune reactivity, which may be fatal.
MULTIPLE SCLEROSIS is another human disease characterized by inflammatory demyelination in the central nervous system (CMI involving CD8+ T-cells specific for myelin basic protein, or MBP). Its causes are unknown, although the appearance of high levels of antibodies to measles and other viruses suggests a connection with viral infection.

EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS (EAE) OF MICE
Mice immunized with brain tissue or with the basic protein of myelin in Freund's adjuvant develop a progressive and often fatal degeneration of myelinated nerves. It is typically characterized by the presence circulating antibodies to myelin as well as mononuclear infiltration of nervous tissue. However, the disease can be transferred to healthy mice by adoptive transfer of immune lymphocytes, but not by transfer of serum, indicating that only the cellular immune component is pathogenic. As with experimental autoimmune thyroiditis, this represents an immune response to a normally sequestered antigen following deliberate breaking of normal tolerance by use of an adjuvant.

MYASTHENIA GRAVIS. This disease of unknown etiology is associated with circulating antibodies against the AcCh receptor, resulting in progressive muscle weakening. It can be treated with anti-cholinesterase drugs together with immunosuppressive therapy. An interesting histological aspect of this disease is the frequent presence of structures resembling germinal centers within the thymus (remember that the normal thymus contains neither B-cells nor germinal centers). Thymectomy is often beneficial in treating this disease for reasons which aren’t fully clear, although cells producing anti-AcCh antibodies have been found within these ectopic germinal centers.

RABBIT AUTOANTIBODY TO ACETYLCHOLINE RECEPTOR (AcChR)
In the 1970’s, researchers immunized rabbits with purified acetylcholine receptor protein from the ray, Torpedo, in order to produce antibodies to help in studying this molecule. Much to their surprise, the rabbits rapidly developed a progressive and fatal weakening of their muscles, which was found to be the result of autoantibodies directed against their own AcCh receptor molecules. This represents autoimmunity due to a response to a cross-reactive antigen; the rabbits’ immune systems responded to the foreign protein of Torpedo, which happened to be closely enough related to their own receptor that it broke the normal state of tolerance.

Two other human autoimmune disorders are of particular importance, namely Rheumatoid Arthritis and Systemic Lupus Erythematosus. These are examples of a larger group of related disorders known as the Rheumatic Diseases, and are part of the group of "non-organ-specific" autoimmune diseases, to distinguish them from those considered "organ-specific" (which include the diseases discussed above).

RHEUMATOID ARTHRITIS (RA)
One common feature of RA is the presence of autoantibodies directed against the Fc fragment of IgG (as well as other "self" components, nuclear proteins and other intracellular molecules). The anti-IgG autoantibodies are known as rheumatoid factor, and are mostly IgM (but may be IgG). The resulting immune complexes may be deposited in various sites within the vasculature and the joints. In either location they can cause tissue damage through
the fixation of complement and the attraction of PMN's; these processes result in the synovitis and vasculitis which (among other features) characterize this disease.

**SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)**

SLE is characterized by the presence of autoantibodies to a wide variety of autoantigens, including DNA, RNA, histones, ribonucleoproteins and other nuclear and cellular elements (often with *rheumatoid factor* present as well). These antibodies are associated with a pattern of damage to an equally wide variety of tissues and organs including skin lesions (erythema) and damage to the vocal cords which results in a characteristic hoarseness (*lupus* = "wolf"). In both RA and SLE (as well as many other autoimmune diseases), the etiological connection between the autoantibodies and the disease state is far from clear; did an initial breakdown of normal tolerance result in production of autoantibodies which cause the tissue damage, or did some other process initially cause tissue damage which then caused the subsequent breakdown of tolerance?

**AUTOIMMUNITY AND IMMUNE COMPLEX DISEASE**

We've already examined (in Chapter 5) the pathological consequences of circulating immune complexes, which can result in damage to the vasculature in general, and to the kidney in particular. It is important to remember that the presence of circulating immune complexes is a common feature of many autoimmune diseases, most notably the non-organ specific ones such as RA and SLE; these autoimmune complexes exhibit the same sequelae as those formed with heterologous antigens, *i.e.* fixation of complement and local tissue damage. The kidney is an especially important target of autoimmune-mediated damage. The presence of immunoglobulins on the basement membranes of the kidney is a diagnostic feature of distinct autoimmune states, depending on whether they show a *smooth* distribution (representing antibodies directed against the basement membrane itself, as in Goodpasture's syndrome) or a granular *"lumpy-bumpy"* distribution (representing the deposition of circulating antigen-antibody complexes, as in RA and SLE). We have also discussed in Chapter 5 the crucial role that complement plays in the normal removal of circulation immune complexes, and that defects in this clearance system may predispose to the development of autoimmune disease.

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**CHAPTER 19, STUDY QUESTIONS:**

1. For three human autoimmune diseases, describe an underlying mechanism which is known from an animal model.

2. What relationships exist between the complement cascade and autoimmune disease?