chapter 5:

DISORDERS OF THE IMMUNE SYSTEM

OBJECTIVES

After studying this chapter you should be able to:

- describe the features and explain the clinical consequences of immunodeficiency diseases;
- describe the features and explain the clinical consequences of autoimmune diseases;
- describe the features and explain the clinical consequences of immunological hypersensitivity;
- outline the ways in which immunological disorders are investigated and treated.

5.1 INTRODUCTION

A fully functioning immune system is essential for maintaining health (*Chapter 4*) but, like all body systems, the immune system itself is subject to many clinical disorders. Immunological disease can occur for one of three reasons. Firstly, **immunodeficiency diseases** occur in individuals whose immune systems are inadequate, perhaps due to the absence or malfunction of essential components, making them susceptible to infectious disease and even to certain types of cancer. Secondly, **autoimmune diseases** can occur as a result of the immune system mounting an immune response against 'self' components. Finally, **immunological hypersensitivity** occurs when immune responses, often mounted against seemingly innocuous immunogens, result in tissue damage. Indeed, immunological hypersensitivities are among the commonest of immunological disorders. This chapter will examine the variety, etiologies, diagnoses and treatments of these three groups of immunological disorders.

5.2 IMMUNODEFICIENCY DISEASES

Immunodeficiency diseases result from a failure of one or more components of the immune system and may involve the absence or malfunction of organs, cells or proteins of the immune system. Where the immunodeficiency results from a direct defect within the immune system, the disease is classified as a **primary immunodeficiency (PID)**. All PIDs are inherited or have a genetic component. Most, but not all, primary deficiencies are congenital, that is are present from birth, although some do not manifest themselves until later in life. **Secondary immunodeficiencies (SIDs)** arise as a consequence of other conditions. For example, some viruses are associated with an immunosuppression, which may be transient, as for example in measles, or permanent, as in HIV infection. Conditions that can give rise to secondary immunodeficiency are listed in *Table 5.1*. This chapter will concentrate on the primary immunodeficiencies.

Contributing factor	Comments
Malnutrition	a proper functioning immune system requires a supply of essential nutrients (*Chapter 10*)
Physical trauma	for example extensive burns and surgery are associated with an immunosuppression
Immunosuppressive drugs	drugs given to prevent transplant rejection (*Chapter 6*); chemotherapeutic therapy for cancer (*Chapter 17*)
Infectious diseases	for example HIV (*Chapter 2*); measles; cytomegalovirus
Hematologic disease	for example myeloma (*Chapter 4*); leukemia (*Chapter 17*)
Immaturity of immune system	for example in premature infants
Aging of the immune system	all body systems start to malfunction with aging, the immune system is no different (*Chapter 18*)
Metabolic and hereditary disorders	for example diabetes mellitus (*Chapter 7*)
Stress	stress hormones, such as cortisol (*Chapter 7*) can be immunosuppressive

Table 5.1 Some factors contributing to secondary immunodeficiency

Patients with immunodeficiency diseases invariably suffer infections more frequently and with increased severity although the type of infection depends to a large extent on the nature of the immune deficit. Some general rules to guide diagnoses are given in *Table 5.2*. Other types of disorder may also arise as a consequence of a PID. So, for example, deficiencies of some complement proteins may lead to systemic lupus erythematosus (SLE), an autoimmune disorder (*Section 5.2*). Certain types of cancer, such as non-Hodgkins lymphoma, a tumor of the lymph glands, and Kaposi's sarcoma, a tumor derived from blood vessels and which frequently shows in the skin, are also more frequent in the immunodeficient patient, because these tumors are linked to infections with certain viruses (*Chapter 17*).

PRIMARY IMMUNODEFICIENCY DISEASE

Primary immunodeficiencies are classified according to the site of the immunological defect. The 100 or so inherited PIDs were classified into eight groups or tables (*Table 5.3*) at a meeting of the International Union of Immunological Societies in 2003.

Deficiencies of:	Consequences
T lymphocytes	viral and fungal infections (for example herpes simplex; *Pneumocystis carinii*) opportunistic infections such as *Candida albicans* infections with intracellular bacteria, e.g. Mycobacteria Kaposi's sarcoma (a tumor derived from blood vessels)
Antibodies	bacterial infections causing recurrent chest infections and boils in the skin
Phagocytic cells	bacterial infections causing boils and abscesses
Complement	recurrent meningococcal meningitis bacterial pneumonia , septicemia systemic lupus erythematosus (SLE, an autoimmune disorder)

Table 5.2 Diseases associated with PIDs of different origins

Table	Deficiencies in:	*Examples
I	T and B lymphocytes	severe combined immunodeficiency (SCID)
II	antibody deficiencies	X-linked agammaglobulinemia
III	other well-defined immunodeficiency syndromes	Wiskott Aldridge syndrome DiGeorge anomaly
IV	diseases of immune dysregulation	Chediak-Higashi syndrome
V	congenital deficiencies of phagocyte numbers and/or function	X-linked neutropenia/myelodysplasia leukocyte adhesion deficiencies (LADs) types I and II chronic granulomatous disease
VI	defects in innate immunity	mannose binding lectin (MBL) deficiency
VII	autoinflammatory disorders	hyper IgD syndrome
VIII	complement deficiencies	C4 deficiency C2 deficiency C1 inhibitor deficiency

* examples only, many more disorders are known

Table 5.3 Classification of PIDs

Combined T and B deficiencies

Deficiencies that affect both B and T lymphocyte (*Chapter 4*) numbers and/or their functions are life threatening. Such deficiencies are termed **severe combined immunodeficiency (SCID)**. The term SCID represents a group of disorders associated with more than 20 different mutations and with a frequency of between one in 50 000 and one in 500 000 births. As some forms of SCID are inherited in an X-linked fashion (*Chapter 15*), more boys than girls are affected, with the male : female ratio of approximately 3 : 1.

Depending on the mutation involved, T and B cells may both be decreased (T^-B^- SCID) or B cells numbers may be normal or increased (T^-B^+SCID). In the latter, the absence of T cells renders B cells functionally inactive, owing to the need for the cytokines produced by T_H cells for antibody production as described in *Chapter 4*. In either case, the disorder becomes apparent in the first few weeks

BOX 5.1 Laboratory tests for lymphocyte function

It is theoretically easy to test for lymphocyte function ***in vivo*** by immunizing a patient with immunogens known to stimulate cell-mediated or humoral immunity and monitoring the response of their immune systems. A test for humoral immunity would involve measuring the levels of specific antibody ***in vitro***. Tests for cell-mediated immunity might involve injecting a small amount of immunogen subcutaneously and looking for delayed **hypersensitivity** (*Section 5.4*). However, such tests are not necessarily appropriate or, indeed, ethical, especially for sick babies. Fortunately, there are tests that can be used to measure the function of lymphocytes *in vitro*. For example, small lymphocytes can be incubated with antigens to which the patient has been exposed. If the child is immune, the small lymphocytes will respond by starting to proliferate. The amount of cell division can be measured by determining the amount of radiolabeled thymidine incorporated into the DNA of the dividing cells. Of course, an antigen will only stimulate those cells which bear specific receptors, perhaps only one in 100 000 cells and so the test may not be sufficiently sensitive. However, some proteins and other types of molecules, such as lipopolysaccharide, act as **mitogens** and stimulate many lymphocytes to divide and are known as polyclonal activators because they stimulate many different clones of lymphocytes. Mitogens are examples of **lectins**, which stimulate lymphocyte proliferation by binding to carbohydrate residues on the lymphocyte membrane. Lectins are frequently of plant origin (*Table 5.4*) although some are derived from other groups of organisms. It is also possible to stimulate lymphocytes to divide by incubating them with antibodies directed at cell surface receptors. Thus, an antibody to CD3 will stimulate all mature T lymphocytes to divide.

A typical response of T lymphocytes to the lectin phytohemagglutinin (PHA) from runner beans in a healthy individual is shown in *Figure 5.1*. A failure to respond in this way is indicative of a lymphocyte defect. In patients with SCID, the proliferative response is less than 10% of control values.

Mitogen	Derived from	Small lymphocytes stimulated
Phytohemagglutinin (PHA)	*Phaseolus vulgaris*	T lymphocytes
Concanavalin A (ConA)	*Canavalia ensiformis*	T lymphocytes
Poke weed mitogen (PWM)	*Phytolacha americana*	B lymphocytes
Lipopolysaccharide (LPS)	*Escherichia coli*	B lymphocytes
AntiCD3	monoclonal antibody originating from mice	T lymphocytes
Anti-immunoglobulin	monoclonal antibody originating from mice	B lymphocytes

Table 5.4 Polyclonal activators of small lymphocytes

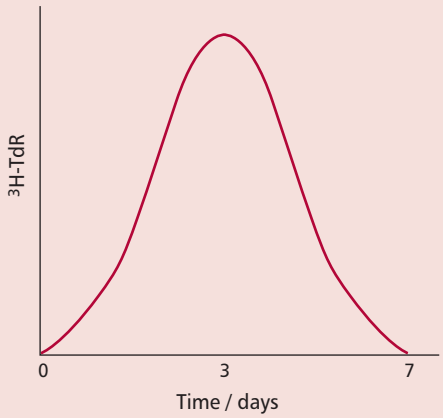

Figure 5.1 The stimulation of T lymphocytes with phytohemagglutinin (PHA), which stimulates all T cells to divide as measured by the uptake of tritiated thymidine (^{3}H-TdR) into dividing cells.

or months of life with the mean age at diagnosis being 6.5 months. The disease is characterized by chronic viral and fungal infections. Chronic diarrhea and oral Candida infections are common and in the presence of other infections, the child fails to thrive. Affected infants may suffer generalized viral infections if given live viral vaccines, such as the MMR and polio vaccines. Laboratory tests show fewer than 3000 per mm^3 circulating lymphocytes (where the reference range for an infant of six months is between 4000 and 13 500 per mm^3). The lymphocytes present are functionally inactive and do not respond *in vitro* to known **mitogens** (*Box 5.1*). Chest X-rays show an abnormally small or absent thymus.

Approximately 20% of T^-B^- SCID arises from mutations in the gene encoding adenosine deaminase (ADA). The absence of this enzyme results in the accumulation of metabolites, such as ADP, GTP and dATP, which are toxic to

small lymphocytes. A similar syndrome arises from deficiency of the purine nucleoside phosphorylase (PNP) that results in an accumulation of dGTP. Approximately 40% of cases of T^-B^+ SCID are X-linked and arise from mutations in a polypeptide that forms part of the receptor for several interleukins (ILs), so that affected lymphocytes are unable to respond to interleukin signals.

If not diagnosed early and treated appropriately, children with SCID usually die from infections in the first few years of life. Management of this condition includes administering antiviral, antibacterial and antifungal drugs and measures must be taken to avoid infection. Keeping such infants in totally aseptic conditions is neither feasible nor ethical, since this would preclude direct contact with other humans. Their immune system may be restored with a bone marrow transplant. This can lead to long-term survival but is not without danger, chiefly graft versus host disease (GVHD; *Chapter 6*). Gene therapy has been attempted with some ADA deficient patients and, in a few cases, has been reported to be successful.

Antibody deficiencies

The normal concentration ranges for the five immunoglobulin classes, IgM, IgG, IgA, IgE and IgD (*Chapter 4*), in adults are shown in *Table 5.5*. Deficiencies involving immunoglobulins of all classes are commonly referred to as **agammaglobulinemias** or **hypogammaglobulinemias**, depending on the level of deficiency. However, with some disorders there may be a selective deficiency of a single immunoglobulin class, as in selective IgA deficiency, or a dysregulation, where some antibody classes are reduced while others are increased.

Immunoglobulin	Serum concentration in adults/g dm^{-3}
IgM	0.5–2.0
IgG	7.2–19.0
IgA	0.8–5.0
IgD	trace
IgE	trace

Table 5.5 Normal adult levels of serum immunoglobulins

Transient hypogammaglobulinemia (TH) occurs when the start of production of IgG in very young children is delayed. It possibly arises when the maturation of helper T lymphocytes is itself delayed. During pregnancy, IgG is the only immunoglobulin to cross the placenta from mother to fetus. Thus a newborn baby has adult levels of IgG, most of which is maternally derived (*Figure 5.2*).

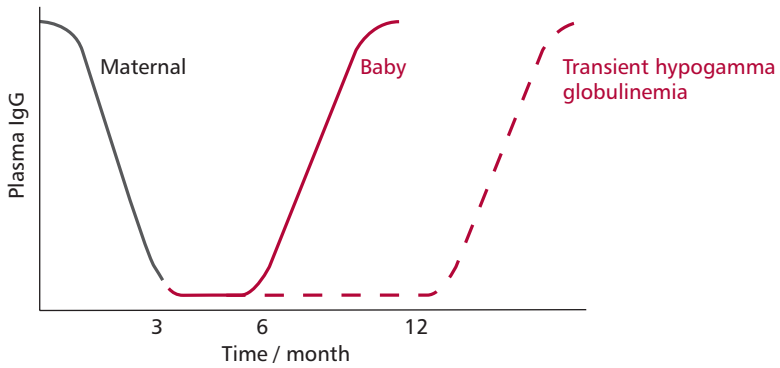

Figure 5.2 Transient hypogammaglobulinemia (TH). The production of IgG in the baby normally starts between three and six months of age by which time the maternal IgG in the baby has almost disappeared. In TH, the production of IgG by the baby is delayed.

During the first three months postpartum, the maternally derived IgG is catabolized and steadily disappears from the baby's circulation. Between three and six months, serum IgG levels may be quite low, after which the levels begin to increase, and should normally attain 'adult' levels at about 12–18 months of age. In infants with transient hypogammaglobulinemia, the production of IgG is delayed considerably, sometimes for as long as two years. During this time the child is susceptible to recurrent infections with **pyogenic** (pus producing) bacteria and antibiotics must be administered. The incidence of TH has been estimated as 23 to 61 per million births.

Common variable immunodeficiency (CVID) is the commonest primary immunodeficiency involving all classes of antibody. It is a heterogeneous group of disorders and includes a range of phenotypes. Many patients are not diagnosed until early adulthood. Most patients show low levels of IgG and IgA, with near normal or 50% of normal levels of IgM and normal lymphocyte counts. The latter allows CVID to be distinguished from other antibody deficiencies such as X-linked agammaglobulinemia (*see below*). Some patients also have impaired cell-mediated immunity (*Chapter 4*). The incidence has been estimated at one in 10 000–50 000.

The etiology of CVID is unknown and the majority of cases are sporadic. The B lymphocytes are immature and, when stimulated, do not differentiate into antibody-secreting plasma cells following the binding of an antigen (*Chapter 4*), owing to defects in their cell surface receptors or signal transduction mechanisms (*Chapter 7*). However, it is possible that in some patients there may be other defects, such as mutations in immunoglobulin regulatory genes. In addition, many CVID patients have defects in CD4+ T lymphocytes so that the T and B cell interactions required for antibody production are impaired.

Patients with CVID present with recurrent pyogenic infections, especially of the respiratory tract, commonly involving *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae* and *Moraxella catarrhalis*. This can lead to **bronchiectasis**, in which the bronchi and bronchioles are abnormally dilated. Those patients who also have some impairment in cell-mediated immunity also suffer infections with mycobacteria and the fungus *Pneumocystis carinii*. Such patients also suffer recurrent severe infections with herpes simplex and herpes zoster (*Chapter 3*), and may develop viral illness when immunized with live viral vaccines.

The diagnosis of CVID relies on the measurement of immunoglobulins, including specific antibodies to common vaccines, and ruling out other immunodeficiencies, such as X-linked agammaglobulinemia. Its treatment usually involves replacement therapy with pooled immunoglobulins obtained from healthy donors. All pooled immunoglobulin preparations are treated to inactivate viruses, such as hepatitis virus or HIV, which may be present. These preparations are available commercially and need to be given intravenously every three to four weeks to maintain plasma levels and protect against infections. The dose depends on the weight of the patient and is usually 400–600 mg kg^{-1}. Alternatively, weekly subcutaneous administration of lower doses, which can be done at home, may be more convenient. Intramuscular injection, which allows a greater volume to be administered than can be delivered subcutaneously, can also be given.

X-linked agammaglobulinemia (XLA) or Bruton's disease is caused by a deficiency in Bruton's tyrosine kinase (Btk), which is required for the maturation of preB cells in the bone marrow to form B lymphocytes. The deficiency of Btk is due to one or more of 300 different mutations in the *BTK* gene located on the X chromosome. B lymphocytes are therefore absent from the circulation and plasma cells are not present in the spleen and lymph nodes. Tonsils and adenoids may be absent, as demonstrated by radiography. However, circulating T lymphocytes are normal. Serum immunoglobulin

levels are extremely low and all classes of immunoglobulin are affected. This is a rare inherited disorder with an incidence of about one in 250 000 males. Patients present with recurrent pyogenic infections, which occur from around three to nine months of age, when maternally derived IgG is low. Infections encountered may result in pneumonia, otitis media, meningitis and diarrhea.

It is essential that patients with XLA are diagnosed as early as possible so that replacement immunoglobulin therapy can begin. Infections are treated with antibiotics. The prognosis for children diagnosed before the age of five years is good, with patients often surviving to middle age. Tests for mutations of the *BTK* gene are available, which allows for genetic counseling of affected females and prenatal diagnosis of fetal cells obtained by chorionic villus sampling or amniocentesis (*Chapter 15*), with the possibility of a therapeutic abortion.

Selective IgA deficiency, as its name implies, affects only a single class of immunoglobulin. Many IgA deficient individuals are asymptomatic, with the condition only being detected during investigation of other disorders. In contrast, other patients with selective IgA deficiency suffer recurrent infections, typically ear infections, sinusitis and pneumonia. A high proportion of sufferers also develop autoantibodies that are directed against a variety of self antigens and approximately a third present with autoimmune diseases, such as systemic lupus erythematosus (SLE) (*Section 5.3*). It is not known which features determine the severity of the disease. Selective IgA deficiency is a relatively common disorder with an incidence of one in 500 to 700 Caucasians, although the frequency is much lower in other ethnic groups.

A patient who presents with a history of recurrent infection, chronic diarrhea, and autoimmune disease should be suspected of having a selective IgA deficiency. This can be confirmed by measuring serum immunoglobulin concentrations. Values of IgA below 0.07 mg dm^{-3}, while other immunoglobulins are normal, would confirm the deficiency. Treatment of selective IgA deficiency normally involves using antibiotics to treat bacterial infections and replacement therapy is not usually necessary. If the disease presents with autoimmunity then anti-inflammatory drugs, such as corticosteroids, may be given. The prognosis is good, with patients living normal lifespans. However, approximately 10% of patients with a selective IgA deficiency also have a deficiency of the IgG_2 subclass, which is usually produced in response to polysaccharide antigens. Patients with both defects suffer more severe bacterial infections, especially with encapsulated bacteria. Immunoglobulin replacement therapy may be appropriate in these cases.

The DiGeorge anomaly and the Wiskott Aldridge syndrome

The third group of PIDs (*Table 5.3*) contains a number of well-defined immunodeficiency syndromes, of which the DiGeorge anomaly and the Wiskott Aldridge syndrome are well-known examples.

The DiGeorge anomaly (DGA) is a developmental disorder involving organs that develop from the third and fourth pharyngeal pouches of the embryo. It is associated with a deletion or partial monosomy of chromosome 22 (*Chapter 15*) that results in a range of defects. Several different patterns of inheritance have been reported, including autosomal dominant and autosomal recessive. Its incidence has been estimated to be between one in 20 000 to 66 000, depending on the country.

The DGA is characterized by facial abnormalities, hypoparathyroidism and hypocalcemia with symptoms of convulsions and tetany, congenital heart disease that may be so severe as to be life threatening, and a small underdeveloped or sometimes absent thymus that results in a profound immunodeficiency. Patients suffer severe and recurring viral and fungal infections.

Indeed, the immunological defects are the second commonest cause, after heart conditions, of death in DGA patients. The number of circulating T lymphocytes is severely reduced leading to defects in cell-mediated immunity. T cell proliferative responses to mitogens vary in DGA patients, such that they can be classified either as partial or complete. In the former, proliferation is reduced but in the latter it is completely absent. The absence of helper T lymphocytes reduces antibody production, so that antibacterial immunity may also be compromised, even though the number of circulating B lymphocytes is normal.

A diagnosis of DGA is based on the cardiac malformations, hypoparathyroidism resulting in hypocalcemia and a small or absent thymus. T lymphocytes in the circulation are reduced and the proliferative response to mitogens is impaired. Fluorescence *in situ* hybridization (FISH) has been used to detect deletions in chromosome 22 in the majority of patients (*Margin Note 5.1*). Other syndromes, without any apparent genetic link, but which have known environmental causes, bear some resemblance to DGA. One example is fetal alcohol syndrome, which results from prolonged exposure to alcohol during fetal development. Children with fetal alcohol syndrome also show the characteristic facial features associated with DGA.

Margin Note 5.1 Fluorescence *in situ* hybridization

Fluorescence ***in situ*** hybridization (FISH) relies on the ability of fluorochrome-labeled DNA probes to hybridize with complementary DNA in tissue sections. The hybridized probe can be seen as fluorescent 'spots' in the nuclei of target interphase cells and can be located to specific chromosomes when applied to cells in metaphase (*Chapters 17* and *18*).

Attempts have been made to treat the immunological deficit in DGA with thymus transplants, (*Chapter 6*) although results have been variable. The associated hypocalcemia is treated with calcium and vitamin D supplements, while cardiac malformations must be rectified surgically. The prognosis for patients with DGA is variable and depends mostly on the degree of cardiovascular abnormality. For patients with severe cardiac problems it is poor, with a mortality rate of over 80% at the age of six months.

The Wiskott Aldridge syndrome (WAS) arises from mutation in the *WAS* gene, which was identified on the short arm of the X chromosome in 1994. The gene codes for the cytoskeletal protein sialophorin, found in lymphocytes and platelets, that is involved in the assembly of actin filaments. The incidence of WAS is approximately one per 250 000 male births.

The syndrome is characterized by decreased levels of IgM but often with increased production of IgE and IgA. In the early stages, T and B cell numbers in the blood are normal. Since IgM is the prevalent antibody in immune responses to bacterial polysaccharides, there is an increased incidence of infections with encapsulated bacteria. Sufferers may also develop eczema. Blood platelets are small, short-lived and reduced in number, leading to thrombocytopenia and increased bleeding times which may prove fatal (*Chapter 13*). As WAS progresses, there is a loss of both humoral and cell-mediated immunity and, along with severe infections, there is also an increase in leukemia and lymphoid tumors.

The treatment for WAS includes antibiotics for infections and platelet transfusions to prevent bleeding. Immunoglobulin replacement therapy may also be given to provide some protection against infection. Bone marrow transplants (*Chapter 6*) have been successful in some cases. Unfortunately the prognosis for WAS sufferers is poor, with death commonly occurring before the age of four years usually from severe infection and bleeding. Genetic counseling is recommended for women who have had a child with WAS. Detection of the abnormal gene in cells obtained by chorionic villus sampling or amniocentesis allows a prenatal diagnosis, with the possibility of terminating the pregnancy if the fetus is found to be affected.

The Chediak-Higashi syndrome

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder first described in 1943. It is sometimes classified as a phagocytic defect.

However, even though phagocytic cells, such as neutrophils and monocytes, are defective, Natural Killer (NK) cells, which form the first line of defence against viruses, are also abnormal. The syndrome arises from a mutated form of the *CHS1* gene located on chromosome 1. The gene product is involved in the intracellular transport of proteins and the synthesis of storage granules in certain cells. The mutation results in neutrophils with abnormally large or 'giant' lysosomes (*Chapter 16*) and platelets (*Chapter 13*) with abnormal dense bodies. In addition, melanocytes, the pigment-producing cells of the skin, contain larger than normal melanosomes; the pigment storing organelles.

Chediak-Higashi syndrome presents as an immune deficiency that leads to recurrent bacterial infections, most commonly with *Staphylococcus aureus, Streptococcus pyogenes*, and *Pneumococcus* spp and viral infections, such as with Epstein-Barr virus, that frequently result in tumors of the lymph nodes (**lymphomas**). Leukocyte counts reveal neutropenia and abnormal neutrophils that do not respond to chemotactic molecules, for example activated complement proteins, and which fail to kill ingested bacteria. Infants suffer recurrent skin infections, which may result in ulcers and abscesses. The abnormalities of melanocytes means that patients are deficient in skin pigment and have blond hair and translucent blue eyes. Infants also bruise very easily, due to defective platelets. In addition, they suffer progressive neurological dysfunction, with abnormal gait, mental retardation and peripheral neuropathy. If the child survives beyond the first decade this may lead to Parkinsonism and/or dementia. Morbidity and mortality are high in CHS, with infants frequently dying before the age of 10 years, usually from overwhelming pyogenic infections attributable to poor neutrophil function.

The recommended treatment for children with CHS is a bone marrow transplant to correct the immune deficit. However, success has been variable and this treatment has no effect on the lack of pigmentation since melanocytes do not arise from bone marrow. Antibiotics are given to treat bacterial infections and antiviral drugs, such as acyclovir or interferon α, to limit infection with the Epstein-Barr virus. Patients with lymphoma are given anticancer drugs, such as vincristine.

Phagocytic defects

Phagocytic cells, such as monocytes, macrophages and neutrophils, form part of the nonspecific immune defense. These cells kill ingested bacteria using several different mechanisms as described in *Chapter 4*. A defect in any of these mechanisms can lead to increased incidences of infections. Thus, patients may be severely compromized by defective phagocytes, even if their B and T cell populations and functions are normal. Some examples of phagocytic defects are chronic granulomatous disease and leukocyte adhesion deficiency.

Chronic granulomatous disease (CGD) is named from the granulomatous inflammatory nodules that present on the skin and in the gastrointestinal and genitourinary tracts. It is an inherited disorder of phagocytic cells characterized by their inability to generate the reactive oxygen intermediates needed to produce bactericidal compounds, such as hydrogen peroxide. The formation of reactive oxygen intermediates is dependent on NADPH oxidase activity. This enzyme is composed of four subunits and a defect in any one of them can result in CGD. Approximately 65% of all CGD cases is due to a defect in the *CYBB* gene located on the X chromosome which encodes cytochrome b_{245}. The genes for the other subunits are located on autosomal chromosomes and females and males are equally affected. The incidence of CGD is estimated to be about one in 200 000 to 250 000.

Sufferers of CGD usually present before the age of five years. Skin infections, pneumonia, gastroenteritis, perianal abscesses are common. Abscesses on internal organs, such as the lungs, spleen and liver, may also be present. The

Margin Note 5.2 Hyper IgD syndrome

Hyper IgD and periodic fever syndrome (HIDS) is a rare disease which was first reported in 1984. Patients suffer recurrent attacks of fever and symptoms of inflammation and an acute phase response from about the age of one year. These attacks may last up to six days and may be triggered by surgery, trauma or vaccination. Clinical findings include, usually, elevated levels of serum IgD sometimes with higher levels of IgA. The disease is inherited as an autosomal recessive trait and sufferers have been shown to have a defective gene for mevalonate kinase. Most sufferers are of Western European origin, with the majority being Dutch or French. The mevalonate kinase enzyme is involved in the metabolism of cholesterol, although how this deficiency is related to the inflammatory condition is not known.

small amounts of hydrogen peroxide produced by CGD patients makes them resistant to catalase negative bacteria. However, catalase positive bacteria, by definition produce catalase, which catalyzes the degradation of hydrogen peroxide; hence these types of bacteria give rise to infections in CGD sufferers. Pneumonia is generally associated with fungal infections; and disseminated fungal disease also occurs.

A diagnosis of CGD takes into account the recurrent infections of early onset, granulomas, hepatosplenomegaly, that is enlarged liver and spleen, and lymphadenopathy. Laboratory investigations include the nitroblue tetrazolium (NBT) test to determine the activity of the NADPH oxidase. In neutrophils with normal levels of enzyme, the pale yellow NBT is reduced to a blue colored compound as NADPH is oxidized, and can be observed in the cytoplasm. Patients with CGD are treated with high doses of antibiotics over long periods of time. This treatment also helps to dispel the granulomas. Abscesses may need to be drained. Bone marrow transplantation has been used successfully to treat some patients.

Leukocyte adhesion deficiency (LAD) occurs in two forms, but both are caused by the failure of leukocytes to express cell adhesion molecules essential for their movement through blood vessel walls during inflammation. Thus phagocytes are unable to enter inflamed tissues and remove bacteria. In LAD I, patients do not express the integrin, CD18 on neutrophils, macrophages and lymphocytes that allows them to bind to endothelial cells lining the blood vessels. In addition, CD18 is the receptor for C3b, which is an opsonin for phagocytic cells and crucial molecule of the complement pathway. Patients suffer localized bacterial infections that may become life threatening. In LAD II leukocytes fail to express ligands for other cell adhesion molecules, namely E and P selectins. Binding of leukocytes to these ligands allows them to roll along the endothelial cell surfaces before crossing into the tissues. Both LAD I and LAD II are autosomal recessive disorders. While LAD I affects all ethnic groups, LAD II has only been reported in people of Middle Eastern origin.

Patients with LAD I suffer localized bacterial infections that may become life threatening. Children do not usually survive beyond two years of age unless they have a bone marrow transplant. Patients with LAD II also suffer repeated infections as well as severe growth and mental retardations. Blood counts from patients with either form of LAD show a leukocytosis, that is, a white blood cell count in excess of 20×10^9 dm^{-3} in the absence of infection, compared to normal values of $4–11 \times 10^9$ dm^{-3} (*Chapter 13*). Both diseases may be diagnosed by flow cytometry, to assess the presence of the cell adhesion molecule on blood leukocytes. Leukocyte adhesion deficiency I has been treated successfully with bone marrow transplantation (*Chapter 6*).

Complement deficiencies

The role of complement in immune defense was outlined in *Chapter 4*. Here it will be described in more detail. The activation of complement results in the:

- lysis of bacteria;
- stimulation of the inflammatory response;
- promotion of phagocytosis;
- clearance of immune complexes.

The value of these roles cannot be overestimated. Complement may be activated by one of three pathways: the classical pathway, which is activated by IgG or IgM, following binding to an antigen; the alternative pathway, which is stimulated principally by components of the cell walls of bacteria and yeasts; and the lectin pathway, which is initiated by the binding of mannose binding lectin (MBL) to bacteria. Complement proteins C1, 2, 3 and 4 are involved in classical activation, while Factors B, D, H, I and P are involved in

the alternative pathway activation. Activation of the lectin pathway requires MBL, MBL-associated serine proteases (MASP) 1 and 2 and C2, C3 and C4. All three pathways can lead to the production of membrane attack complexes (MACs), which are composed of C5b, C6, C7, C8 and C9. These cause lysis of the pathogen; in addition, fragments of activated complement proteins, such as C3a, C4a, C5a, promote inflammation by binding to mast cells and causing them to degranulate and release inflammatory chemicals, such as histamine (*Chapter 4*). These chemicals may also promote the chemotaxis of neutrophils out of the inflamed vessels. Other complement proteins, such as C1q, C3b and C567 act as opsonins. The absence of any of these proteins can severely compromise health. Complement is potentially very inflammatory once activated and there are a number of regulatory molecules which either prevent unregulated activation of complement, such as C1 inhibitor (C1INH), or which prevent damage to innocent bystander cells, such as Decay Accelerating Factor (DAF).

Inherited deficiencies of each complement protein have been described (*Table 5.6*). Deficiencies in several of the early classical pathway proteins result in an increased incidence of immune complex disorders, showing the role of complement in helping to remove immune complexes from the circulation. Over 90% of patients with a homozygous C1q deficiency and 10% of patients with a homozygous C2 deficiency develop SLE (*Section 5.3*). A deficiency of MBL is associated with increased incidence of infections with, for example, *Pseudomonas aeruginosa*. Newborn babies and infants are particularly at risk from this deficiency, indicating the importance of this pathway in protecting the young from infection.

Complement protein	Comments	Effects reported
C1q, C1r, C1s	autosomal recessive	increase in immune complex disorders, e.g. SLE; vasculitis* increase in pyogenic infections (Gram positive)
C4	autosomal recessive	increase in immune complex disorders, e.g. SLE; vasculitis * increase in pyogenic infections (Gram positive)
C2	autosomal recessive	increase in immune complex disorders, e.g. SLE; vasculitis * increase in pyogenic infections (Gram positive)
C3	autosomal recessive	frequent and severe bacterial infections resulting in pneumonia, septicemia and meningitis increase in immune complex disorders
C5, C6, C7, C8	autosomal recessive	recurrent neisserial infections (meningitis, gonorrhea)
C9		asymptomatic
Factor D, P		recurrent neisserial infections (meningitis; gonorrhea)
C1INH	autosomal dominant	hereditary angioedema
MBL	autosomal dominant or recessive	increased susceptibility to a variety of extracellular pathogens
Factor H	autosomal dominant	leads to depletion of C3 and symptoms similar to C3 deficiency

*inflammation of blood vessels

Table 5.6 Some complement deficiencies

Deficiencies in the classical and the alternative pathways can be detected in the laboratory by carrying out the CH_{50} and AP_{50} tests respectively. The CH_{50} test measures the ability of the patient's serum to lyse antibody-coated sheep erythrocytes, while the AP_{50} determines its ability to lyse these uncoated cells in rabbits. Results are expressed in terms of the ability of the serum to induce lysis of 50% of the target erythrocytes. Individual complement proteins can be measured by immunoassay, using specific antibodies. Thus C3 and C4 can be measured by nephelometry, single radial immunodiffusion or by ELISA (*Chapter 4*).

Hereditary angioedema (HAE) results from faults in the activity of the complement regulator, C1 inhibitor (C1INH). This protein normally functions to prevent the overactivation of the first part of the classical pathway by inhibiting C1r and C1s. The lack of the inhibitor leads to consumption of C4 and C2. Two types of HAE occur. Type I results from reduced levels of C1INH while in Type II the inhibitor is present but nonfunctional. The condition is an autosomal dominant disorder, which has an incidence of one in 50 000 to 150 000, with 85% of cases being Type I.

The disorder presents as noninflammatory and painless swellings of the skin, especially that of the limbs, which is often precipitated by physical trauma and anxiety. Abdominal pain is caused by the involvement of internal organs, such as the stomach, bladder and intestines. Severe edema of the larynx can cause death. Treatment during attacks is to administer fresh frozen plasma or commercially available C1-INH. Prophylactic treatment with danazol, an androgen, has been shown to stimulate the synthesis of C1-INH, but prolonged treatment may result in unpleasant side effects, such as virilization in women and suppression of testosterone production in men (*Chapter 7*).

5.3 AUTOIMMUNE DISORDERS

The macromolecules of the body are potentially highly immunogenic but, fortunately, immune systems do not usually mount immune responses against them. In fact, we are 'tolerant' to 'self' (*Box 5.2*). Whatever mechanisms lie behind the induction and maintenance of tolerance, it is clear that a number of disorders arise when these mechanisms fail and the immune system starts to attack self antigens. Failures of immunological tolerance lie behind the development of **autoimmune disease**. Autoimmune disease affects 5 to 7% of the population and autoimmune disorders are debilitating, chronic and painful.

CLASSIFICATION OF AUTOIMMUNE DISORDERS

Autoimmune disorders are often classified according to whether they are organ-specific, affecting only one organ or are systemic that is, affecting multiple organ systems (*Table 5.7*). In addition, destruction of cells and tissues can be brought about by autoantibodies and/or cell-mediated immunity. For example, in multiple sclerosis (MS) patients produce antibodies against myelin, the fatty material surrounding the axons of nerves. In addition, MS patients have T_H and T_C lymphocytes in their blood and cerebrospinal fluid, which are specific for myelin protein. Thus, humoral and cell-mediated autoimmunity may contribute to the demyelination of nerves in MS patients. In some instances, autoantibodies can block or stimulate a cell receptor. Myasthenia gravis is an example of the former, while Graves disease (*Chapter 7*) is an example of the latter. Like most classification schemes, that of autoimmune disorders is not perfect. For example, Goodpasture's syndrome directly affects both kidneys and lungs while MS exerts systemic effects by attacking one type of tissue only.

Type of disorder	Example	Effect of disorder	Autoantibodies present	Autoreactive T cells
Organ specific	autoimmune hemolytic anemia	destruction of erythrocytes (*Chapter 13*)	antibodies to erythrocyte antigens	
	autoimmune thyroiditis	hypothyroidism (*Chapter 7*)	antibodies to thyroglobulin and thyroid peroxidase	T_H1 cells specific for thyroid antigens
	Addison's disease	adrenal insufficiency (*Chapter 7*)	antibodies to cytoplasmic antigens of cells of adrenal cortex	infiltration of adrenal cortex with autoreactive T cells
	type 1 diabetes mellitus	destruction of insulin-producing cells in pancreas; serious metabolic disturbances	antibodies to islet cells found in classical juvenile form	infiltration of pancreas with autoreactive T cells
	Goodpasture's syndrome	progressive kidney and lung damage	antibodies to basement membrane antigens of kidney and lung	
	Graves disease	hyperthyroidism (*Chapter 7*)	antibodies to thyroid stimulating hormone receptors	destruction of thyroid cells by autoreactive T lymphocytes
	myasthenia gravis	progressive muscle weakness	antibodies to acetyl choline receptors on muscle cells	
	pernicious anemia	failure to absorb vitamin B_{12} in the stomach (*Chapters 11* and *13*)	antibodies to intrinsic factor	
Systemic disease	rheumatoid arthritis (RA)	inflammatory disorder affecting joints, skin and internal organs	antibodies to IgG (rheumatoid factor)	infiltration of joints with autoreactive T lymphocytes
	systemic lupus erythematosus (SLE)	inflammatory disorder affecting multiple organ systems	antibodies to DNA, chromatin and histones; rheumatoid factor in some individuals	evidence of T cell reactivity in some of the many organs affected
	multiple sclerosis (MS)	inflammatory disorder affecting central nervous system	antibodies to myelin basic protein	destruction of myelin membrane by autoreactive T lymphocytes

Table 5.7 Some examples of autoimmune disease

Many, but not all, autoimmune disorders, affect a preponderance of female patients, with three times as many females as males presenting with autoimmune diseases. The reasons for this gender bias are unclear but may be related to sex hormone levels. Many autoimmune disorders show a link with the type of MHC antigens that are present on cells. In humans, the MHC is known as the HLA system. The links between HLA type and different diseases is described in *Chapter 6*. So, for example, patients with Goodpasture's syndrome have a higher incidence of HLA-DR2 than the healthy population.

AUTOIMMUNE DISORDERS AFFECTING ENDOCRINE GLANDS

Autoimmune disorders of the thyroid gland are among the most common autoimmune disorders. Some will be discussed in *Chapter 7*. Autoimmune thyroiditis, also known as Hashimoto's thyroiditis, results in hypothyroidism and myxedema. The disease presents, typically, in women of middle age who are overweight, lethargic, constantly feel cold, are constipated and have coarse, dry hair and skin. The thyroid is swollen with a generally painless goiter, but which has a rubbery consistency when palpated. A biopsy of the thyroid shows infiltration with both CD8+ and CD4+ T lymphocytes that progressively destroy the thyroid gland. Patients also have antibodies to thyroglobulin and to thyroid peroxidase, which can be determined by

BOX 5.2 How to recognize self

There are a number of theories to explain the development of immunological tolerance and it may indeed be that several different mechanisms are involved. It has been shown in experimental systems that rodents become tolerant to potential immunogens if they were exposed to them during fetal development. Thus mice exposed to foreign proteins *in utero* do not mount immune responses against these immunogens when adults. The suggestion that lymphocytes exposed to epitopes, including self epitopes, during fetal development are selectively removed or deleted from the immune system explains the experimental induction of tolerance, and there is certainly evidence that this happens to developing T lymphocytes in the thymus (*Figure 5.3*). However, this does not explain the development of tolerance to immunogens which are not present in the fetus but which are expressed in the adult. It may be that some immunogens are kept anatomically separate from the immune system during life, to avoid potentially immunogenic self proteins inducing an immune response. For instance, it has been shown that when rabbits are injected with lens protein they make antibodies that then bind to the lenses of their own eyes. Another example is seen in vasectomized men who may start to make antisperm antibodies, presumably because the sperm they continue to produce become exposed to their immune systems following the operation. Finally, there is evidence that some types of T lymphocytes can suppress immune responses against self antigens. These T lymphocytes have, in the past, been called suppressor T lymphocytes and were thought to belong to the CD8+ subset. However, it has been shown that both CD8+ and CD4+ cells can have suppressor activity by producing inhibitory cytokines, such as IFN γ and IL-10 respectively.

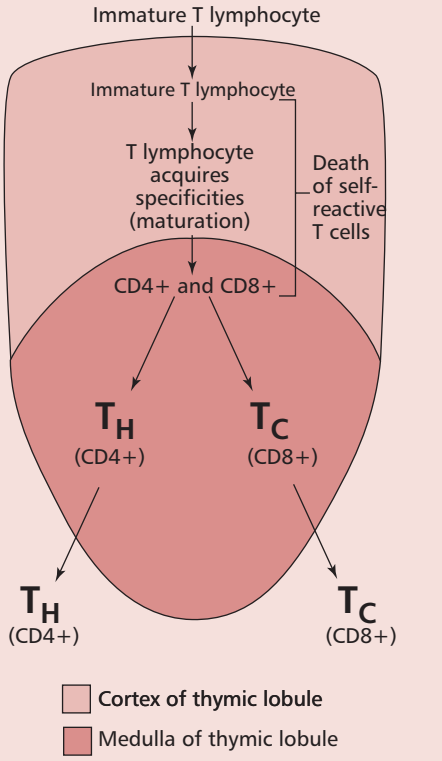

Figure 5.3 Schematic showing the development of T lymphocytes. Immature T lymphocytes enter the thymic lobule and mature as they progress through the thymic lobule into helper and cytotoxic subsets. In the cortex, cells that recognize self epitopes are deleted.

ELISA (*Chapter 4*). Immunohistochemical techniques (*Chapter 4*) can show the patient's serum to have antibodies that bind to microsomal antigens in sections of normal thyroid (*Figure 5.4*). Patients may be given thyroxine to treat the myxedema, and thyroidectomy may be required. The prognosis for patients with Hashimoto's thyroiditis is good.

In Graves disease, patients suffer symptoms of thyrotoxicosis: are thin, have a high resting pulse rate, constantly feel hot, have bulging eyes, or **exophthalmos**, due to growth of tissue around the orbit of the eye and may suffer diarrhea and general agitation. They have nodules in the thyroid that are foci of infiltrating T lymphocytes. Low levels of antibodies to thyroid microsomal antigens are seen in the plasma. However, more than 90% of patients have antibodies to the thyroid stimulating hormone (TSH) receptor on the surface of thyroid cells. These antibodies bind to the receptor and stimulate the production of thyroid hormone (*Figure 5.5*). This production is not regulated by the usual negative feedback mechanisms (*Chapter 7*) leading to the disease symptoms. Graves disease may be treated successfully by destruction of thyroid tissue. This can be achieved by its surgical removal or by giving the patient radioactive iodine that becomes concentrated in the thyroid. When women with Graves disease are pregnant, autoantibodies to TSH cross the placenta and the baby is born with thyrotoxicosis. Urgent treatment is required but, in time, the baby recovers as its levels of maternally derived antibodies drop.

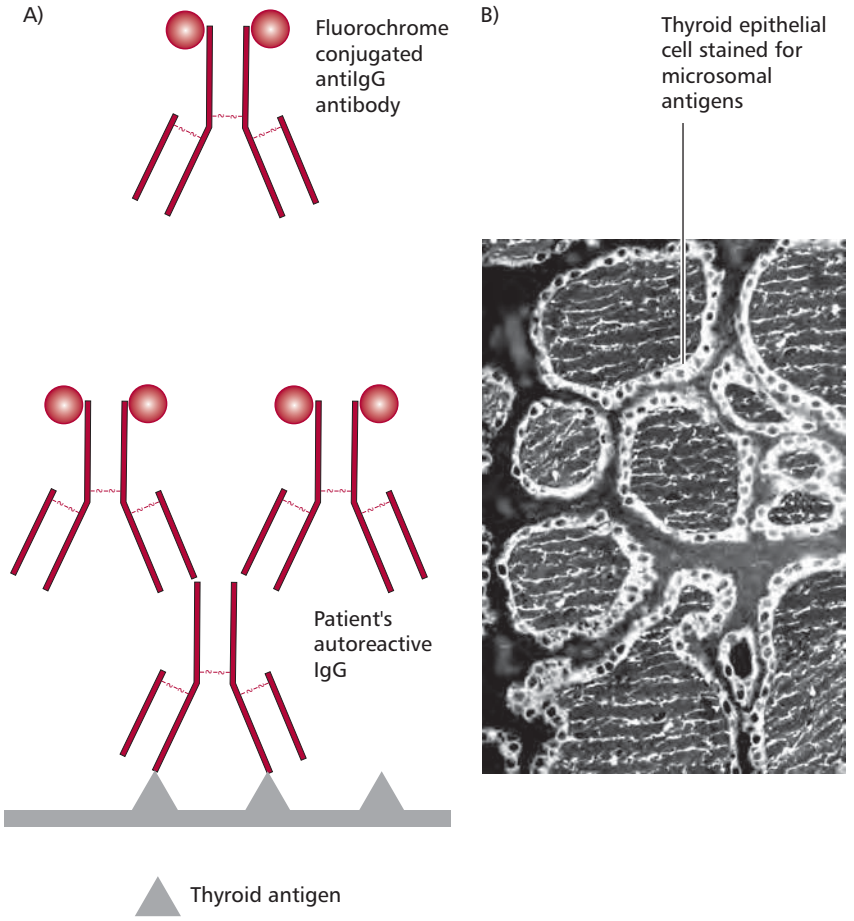

Figure 5.4 **Immunofluorescence in autoimmune thyroiditis. (A) Schematic showing the basis of indirect immunofluorescence staining of thyroid antigens by a patient's serum; (B) Photomicrograph showing thyroid microsomal antigens stained with a patient's serum by indirect immunofluorescence.** Courtesy of EUROIMMUN AG, Germany.

Both insulin dependent diabetes mellitus Type 1 and Addison's disease are discussed extensively in *Chapter 7*. The former is caused by an autoimmune destruction of the insulin-producing cells in the pancreas; the latter by autoimmune damage to the adrenal cortex. Both diseases are fatal unless treated by replacing the missing hormones.

ANTIGLOMERULAR BASEMENT MEMBRANE DISEASE

Antiglomerular basement membrane diseases are characterized by autoantibodies to the glomerular basement membrane (antiGBM). They include Goodpasture's syndrome and Goodpasture's disease. The former disorder shows glomerulonephritis, pulmonary hemorrhage and the presence of circulating antibodies to glomerular basement membrane; the latter is similar, but without the lung involvement. Both diseases are now included under the more general heading of antiGBM disease. Tissue damage is caused by antiGBM antibodies binding to the glomerular basement membrane and activating complement. Complement-mediated inflammation then ensues. The symptoms of glomerulonephritis include proteinuria and hematuria and erythrocyte casts (*Margin Note 5.3*) are seen.

The binding of antibodies to alveolar membranes causes **hemoptysis**, that is, the coughing up of blood from the lungs and about 40% of patients experience chest pain. Hemorrhaging from the lungs may eventually lead to respiratory failure. There is some suggestion that the binding of antibodies to the alveolar basement membranes is facilitated by exposure to organic solvents, which increase the permeability of the alveolar capillaries. The incidence of antiGBM disease is rare, of the order of 0.5 cases per million in the UK. Unlike most

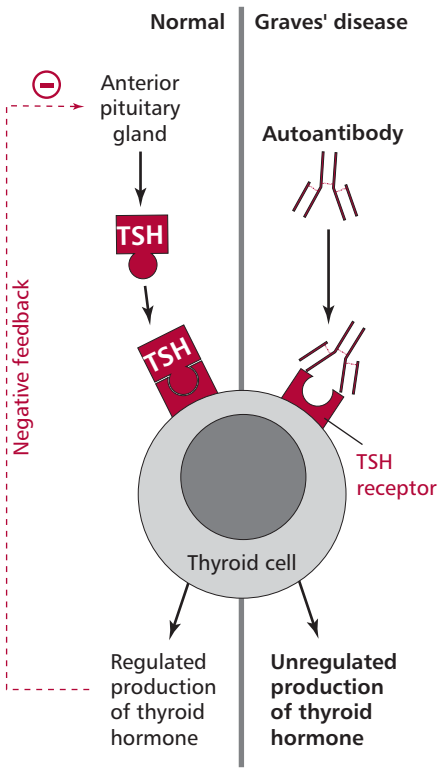

Figure 5.5 **Schematic showing how the binding of an autoantibody to the TSH receptor leads to Graves disease (right-hand side). The left-hand side shows how the production of thyroid hormone is normally regulated by a feedback mechanism.**

Margin Note 5.3 Erythrocyte casts

Erythrocyte casts are produced in the kidney when the cells become trapped in hyaline, which deposits around the kidney tubules. Healthy individuals will have a few plain hyaline casts in their urine, but finding casts containing erythrocytes or leukocytes is indicative of kidney disease.

autoimmune disease, it shows a predominance in males, with younger males generally presenting with both lung and kidney involvement.

Antiglomerular basement membrane disease can be diagnosed from linear deposits of antiGBM antibodies, which can be visualized by immunofluorescence on a kidney biopsy. An early diagnosis is essential and treatment must be started immediately. Therapy involves removal of circulating antibodies by plasmapheresis and the administration of immunosuppressive drugs (*Chapter 6*). The mortality rate for antiGBM disease is improving, and is currently at 10%, although most patients develop end stage renal disease. In the past, the disease was invariably fatal.

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an autoimmune disorder in which patients produce antibodies to acetylcholine receptors at the neuromuscular junction of striated muscle. The antibodies block the receptors so that they fail to respond to acetylcholine (*Figure 5.6*). This results in intermittent but progressive weakness of skeletal muscles, including those for breathing and the facial muscles involved in chewing, swallowing, talking and eye movements. The latter can lead to double vision and an inability to raise the eyelids, a condition known as **ptosis**. Difficulty with respiration may lead to inadequate intake of air and an inability to clear secretions from the respiratory tract. The incidence of pneumonia is increased in these patients. Approximately 75% of patients with MG also have thymic abnormalities such as hyperplasia and thymoma. The incidence of MG has been quoted as up to 14 in 100 000, with a female to male ratio of about 3 : 2.

The problems associated with movement of eye muscles are often the first sign of MG. The presence of autoantibodies may be confirmed by indirect immunofluorescence tests and the levels are a useful measure of disease progression. However, autoantibodies may not be detected in patients where the disease is confined to the facial muscles. Patients are treated with immunosuppressive drugs and cholinesterase inhibitors and with plasmapheresis (*Chapter 6*) to remove the autoantibodies. The condition is improved in the majority of patients by thymectomy. The mortality rate in

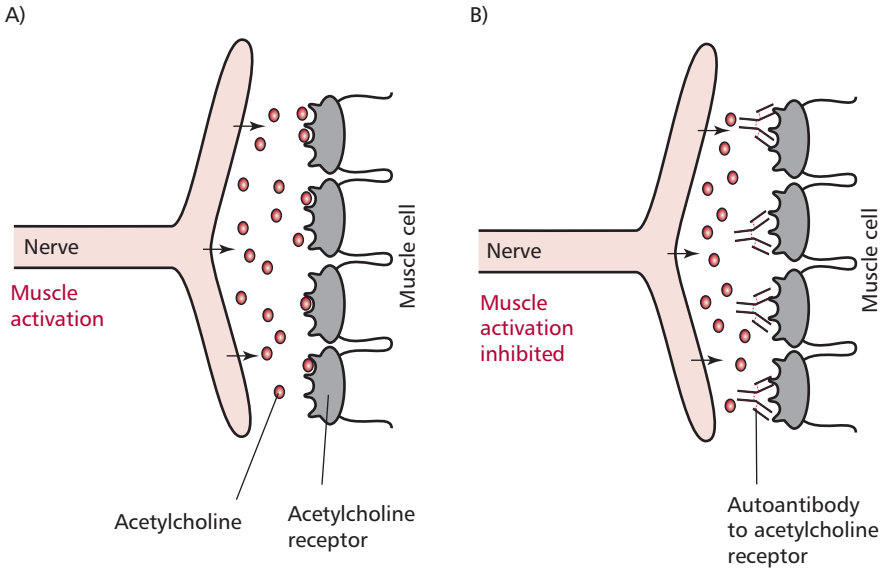

Figure 5.6 Schematics showing (A) the normal stimulation of muscle cells by the binding of acetylcholine to receptors on muscle cells and (B) the blocking of acetylcholine receptors by autoantibodies, which leads to myasthenia gravis.

MG patients is currently around 10%, which is a significant improvement on previous decades.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, painful and debilitating condition characterized by symmetrical arthritis and radiological changes to the bone. The revised classification of rheumatoid arthritis (1988) is shown in *Table 5.8*. Autoantibodies are present in the plasma of patients with RA. The commonest, occurring in 70% of cases, is an IgM class antibody directed against IgG, called **rheumatoid factor** (**RF**). However, RFs belonging to the IgA and IgG classes have also been detected. The presence of RF causes large amounts of immune complexes to be formed, since IgG is present at relatively high concentrations in the blood. The complexes may adhere to blood vessel walls, activating complement and initiating an inflammatory reaction. While a minority of patients suffer a single episode of joint inflammation with long-term remission, most have a progressive illness characterized by intermittent 'flares'. In periods of active joint inflammation, the affected joints (*Figure 5.7*) are painful, swollen, red and warm to the touch; all characteristics of the inflammation within them. The presence of RF and subsequent inflammatory disease does not, however, adequately explain the pathogenesis of RA. Cell-mediated immunity is known to be heavily involved in joint destruction. The synovial membranes of affected joints are infiltrated with small lymphocytes, especially T_H1 cells, monocytes and macrophages so that the membranes themselves become thickened. Activated macrophages within the synovial fluid produce cytokines, such as IL-1 and tumor necrosis factor α (TNF α), which mediate erosion of bone. The accumulation of inflammatory neutrophils within the synovial fluid also contributes to the damage to the cartilage. Patients may also suffer inflammation of blood vessels or vasculitis and about 20% have subcutaneous rheumatoid nodules, often on the elbows and forearms but which may also occur in internal organs. The nodules consist of a mass of monocytes, lymphocytes and plasma cells surrounding a necrotic core, and probably represent the progression of vasculitis.

The etiology of RA remains unknown, despite numerous infectious agents having been implicated over the years. However, RA remains one of the most common autoimmune disorders, with an incidence of one to two per 100. The female to male ratio is approximately 3 : 1 and the disease manifests maximally between the ages of 40 and 60, although juvenile forms also exist.

Rheumatoid factor can be detected in plasma or serum by using the Rose-Waaler test, which determines the ability of the serum to agglutinate sheep

Criteria for diagnosis
1. Stiffness of the joints in the morning
2. Arthritis in three or more joints
3. Arthritis of the joints in the hand
4. Symmetrical arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiological changes to the bone

Table 5.8 1988 Revised classification for rheumatoid arthritis. To be diagnosed with RA, the patient must have four or more of these symptoms and symptoms one to four for at least six weeks.

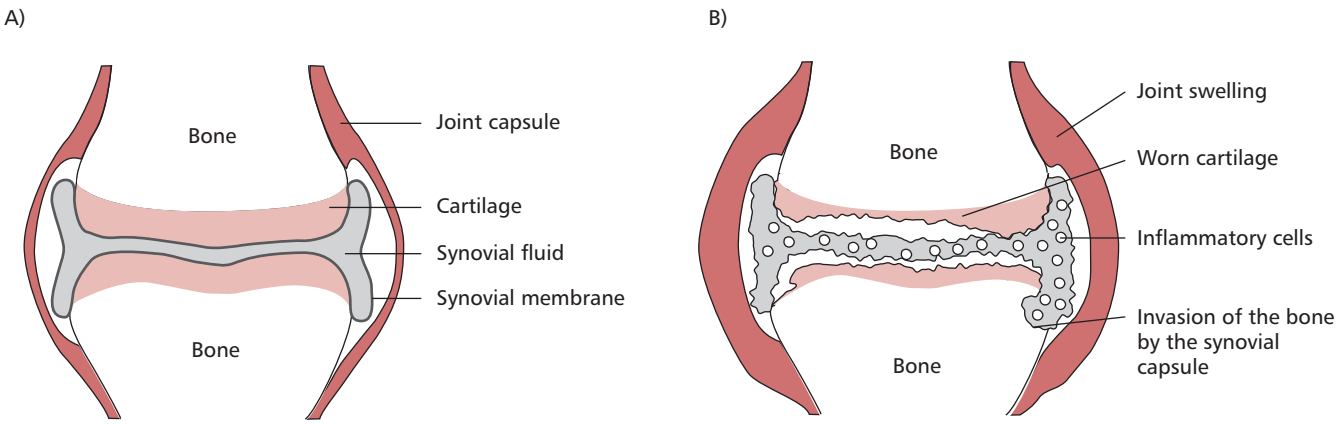

Figure 5.7 Schematics showing (A) a normal synovial joint and (B) the characteristic changes associated with rheumatoid arthritis.

erythrocytes sensitized with specific IgG antisheep erythrocyte antibody (*Figure 5.8*). Alternatively, latex particles nonspecifically coated with IgG can be used. A smaller proportion of individuals, around 40%, with RA also have **antinuclear factors** and these are also seen in patients with systemic lupus erythematosus (*see below*). Treatment of RA is with immunosuppressive agents such as methotrexate (*Chapter 6*) and anti-inflammatory drugs, including steroidal anti-inflammatory drugs (SAIDs), such as corticosteroids, and the nonsteroidal anti-inflammatory drugs, for example aspirin. New treatments aimed at blocking the effect of TNF α have been trialled. These involve either the infusion of a monoclonal antibody to TNF α, or the administration of soluble receptors for TNF α. In the latter case, the soluble receptors bind to TNF and prevent this inflammatory cytokine from binding to receptors on cells. The prognosis for patients with very severe disease is poor in terms of five-year survival. However, even with less severe disease, the condition is painful and debilitating, particularly during periods of active disease. The long-term use of immunosuppressive drugs leads to an increased susceptibility to infection.

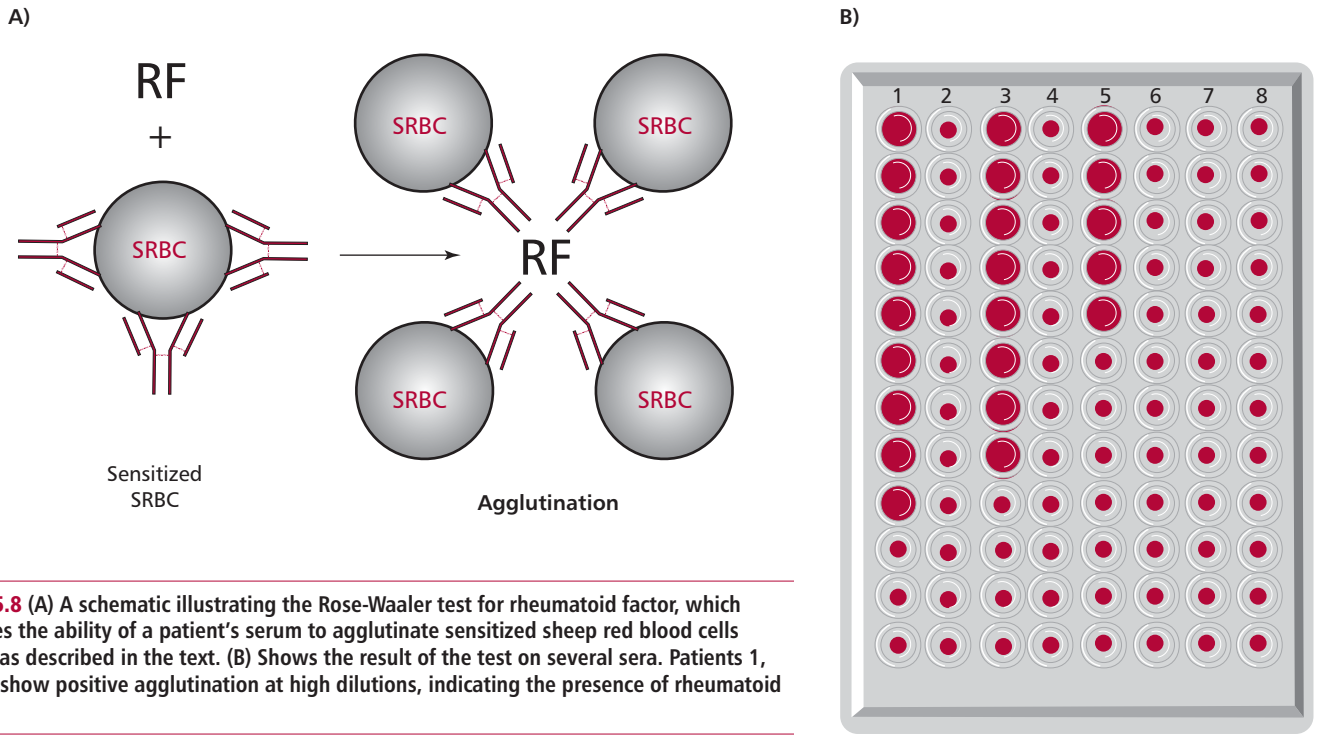

Figure 5.8 (A) A schematic illustrating the Rose-Waaler test for rheumatoid factor, which measures the ability of a patient's serum to agglutinate sensitized sheep red blood cells (SRBCs) as described in the text. (B) Shows the result of the test on several sera. Patients 1, 3 and 5 show positive agglutination at high dilutions, indicating the presence of rheumatoid factor.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease in which about 95% of patients have antinuclear antibodies (ANAs) in their plasma. The deposition of immune complexes leads to widespread inflammation that affects many organs systems within the body. Clinical features of the disease are summarized in *Table 5.9*, the commonest presentations are arthritis and skin rash, particularly the butterfly rash of the face (*Figure 5.9*). Renal disease occurs in approximately half of affected individuals, with nephritis developing early on in the disease. Although the etiology of SLE is uncertain, the systemic nature of the disease is linked to the type of autoantibodies present. The disease primarily affects women of reproductive age, although much younger and much older patients have been seen. The female to male ratio is about 4:1, although in younger patients this gender bias does not occur.

Unfortunately different patients have different patterns of symptoms and their variety in this multisystem disorder has, in the past, presented

Symmetrical arthritis involving any joint
Arthralgia (bone pain)
Erythematous rash; butterfly rash on face (*Figure 5.9*)
Mucosal ulcerations
Pleurisy
Pericarditis
Renal involvement
Fever
Nervous system involvement (psychosis, depression, convulsions, migraine)
Heart disease
Eye involvement (retinal vasculitis; corneal ulceration)
Gastrointestinal ulcers
Pancreatitis
Hepatitis
Sjogren's disease (involving autoimmune destruction of lacrimal and salivary glands)
Hemolytic anemia

Table 5.9 Clinical manifestations of SLE

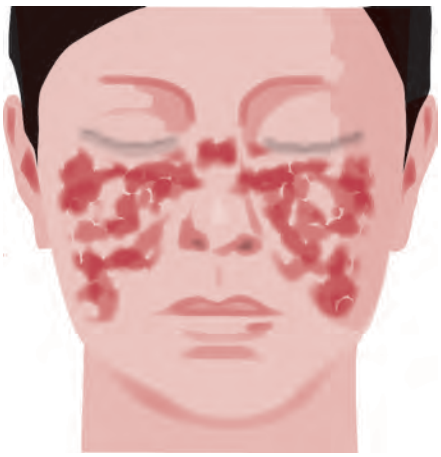

Figure 5.9 Schematic illustrating the area of face typically covered with a 'butterfly' rash in systemic lupus erythematosus.

difficulties with diagnosis, so it must take full account of the range of presentations. Diagnosis can be helped by demonstrating the presence of ANAs in samples of plasma, using indirect immunofluorescence on cultured Hep-2 cells. The commonest pattern seen is a diffuse staining throughout the nucleus due to antibodies against chromatin. It is also possible to detect different patterns of fluorescence which are indicative of antibodies to different nuclear antigens and which can help in diagnosis or in assessing prognosis (*Table 5.10*). Autoantibodies against **extractable nuclear antigens (ENA)** can also be detected by RIA or ELISA (*Chapter 4*). Positive tests for ANAs require further investigations, for example with tests for antidouble-stranded dsDNA (dsDNA) antibodies. The presence in the blood of so-called LE cells, which are neutrophils containing phagocytozed nuclei and resemble large multinucleate cells, is also indicative of SLE. Other laboratory tests used in the diagnosis of SLE include those listed in *Table 5.11*. Rheumatoid

Pattern of staining by indirect immunofluorescence (IDID)	Target antigen	Use
Homogeneous ANA	chromatin	screening but present in some normals
	double strandedDNA	specific for SLE
Speckled ANA (coarse)	Sm*	specific for SLE
Speckled ANA (coarse)	U1-RNP	found in SLE and mixed connective tissue disease

*Antibodies to the Sm (Smith) antigen were first discovered in the serum of a patient with SLE called Stephanie Smith. Antibodies to the Sm antigen bind to molecules in the nucleus called small nuclear riboproteins.

Table 5.10 Antinuclear antibodies in SLE

Laboratory test	Reasons
Full blood counts	to detect anemia, low platelet counts (*Chapter 13*)
Creatinine and electrolytes	to detect damage to kidneys (*Chapter 8*)
Erythrocyte sedimentation rate (*Chapter 13*)	increases in SLE
Urine tests	to detect proteinuria (*Chapter 8*)
Complement levels	C2 or C4 deficiency predisposes to SLE; inflammatory process in active SLE lowers complement levels

Table 5.11 Some laboratory tests for SLE

factor and the presence of antibodies against cardiolipin may also be present, although these are not specific for SLE.

Systemic lupus erythematosus is treated with immunosuppressive drugs, such as azathioprine or cyclosporine (*Chapter 6*) although the use of such drugs in patients prone to kidney disease needs careful monitoring. In addition, patients maintained on immunotherapy are more susceptible to infectious diseases. The prognosis for sufferers of SLE has improved greatly over the last 50 years because the disease is now diagnosed earlier. For example, in the 1950s, most patients died within 10 years of diagnosis, whereas today around 90% are alive 10 years after diagnosis.

5.4 IMMUNOLOGICAL HYPERSENSITIVITY

Immunological hypersensitivities are disorders in which the immune response to a foreign immunogen results in tissue damage. The term **allergy**, which originally meant 'altered reactivity', is sometimes used synonymously with hypersensitivity. In fact, allergies are only some specific types of hypersensitivity. Although the word **hypersensitivity** implies an overreaction, in fact, there is nothing essentially abnormal about the immune response in these cases. It may simply be the extent and nature of the exposure to the immunogen that results in the damage. Indeed, immunogens that provoke hypersensitivities are often 'harmless' in that they are not necessarily infectious agents. Immunological hypersensitivities represent the most common group of immunological disorders and, collectively, affect approximately 10% of the population.

In 1963, Gell and Coombs classified hypersensitivities into four 'types' based on the part of the immune system that caused the tissue damage (*Table 5.12*). This classification scheme is still used today, although not all hypersensitivities belong exclusively to one type. For example, immunological reactions to drugs can be both Types I and III, while intrinsic allergic alveolitis has components of Types III and IV. In addition, expansion of the classification to include further types has been suggested. This chapter retains the original classification.

TYPE I HYPERSENSITIVITY

Type I hypersensitivity is also referred to as **immediate**, because its effects are apparent within eight h of exposure to an immunogen. The effects can be fairly trivial, as in hay fever, or life threatening, as in atopic (*Margin Note 5.4*) or allergic asthma or anaphylactic shock. The term **allergy** is often used for Type I, although this is also used for some of the other types. Immunogens that cause allergies are often referred to as **allergens** and this is the term that will be used here.

Margin Note 5.4 Atopy

People who suffer Type I hypersensitivities are frequently referred to as being atopic. The term atopy refers to an inherited tendency to develop an allergic condition typified by rhinitis, asthma and eczema, that is Type I hypersensitivity. There is a definite genetic predisposition to atopy, with different members of the families sometimes showing different manifestations.

Type	Names	Examples of disorder	Immune system component involved
I	immediate; anaphylactic	hay fever; allergic asthma; food allergies; anaphylactic shock	IgE
II	cytotoxic	transfusion reactions; hemolytic disease of the newborn (HDN)	IgM, IgG and complement
III	complex-mediated	intrinsic allergic alveolitis; serum sickness	antigen/antibody complexes (usually IgG)
IV	delayed-type hypersensitivity (DTH)	Mantoux reaction; contact hypersensitivity	sensitized CD4+ T lymphocytes

Table 5.12 The Gell and Coombs classification of immunological hypersensitivity

The different manifestations (*Table 5.13*) of Type I depend on the degree of previous exposure to the allergen and also on the route of exposure. The underlying cause is the production of IgE in response to an allergen. This type of antibody stimulates inflammatory responses that are aimed at eliminating parasitic worms. Atopic individuals produce IgE in response to allergens that, in nonallergic individuals, would stimulate the production of IgG. The tissue mast cells and blood basophils have receptors for the Fc region of IgE, so that IgE binds to the surface of these cells. The more sensitized an individual, the more their mast cells are coated with IgE. Further exposure to the same allergen results in the cross-linking of mast-cell bound IgE by the allergen (*Figure 5.10*). This triggers an explosive degranulation of the mast cell that releases pharmacologically active mediators, including histamine, which causes vasodilation, smooth muscle contraction and mucus secretion, depending on where they are released. In addition the subsequent release of further mediators, for example leukotrienes and prostaglandins, which are synthesized at the mast cell membrane potentiate inflammation and smooth muscle contraction. This response which evolved as a defense against multicellular parasites, causes the characteristic symptoms of the hypersensitivity.

Disorder	Effects
Allergic rhinitis (hay fever)	seen in upper respiratory tract; excess mucus; sneezing and wheezing
Atopic eczema	extensive and very itchy rash in skin; a common manifestation in atopic children
Food allergies	skin rash (hives); gastrointestinal 'cramps' and diarrhea; may sometimes result in anaphylactic shock
Allergic asthma	severe inflammation in respiratory tract; severe respiratory distress
Anaphylactic shock	sudden drop in blood pressure; respiratory distress; skin rash; gastrointestinal 'cramps' and diarrhea; may result in death within an hour of exposure
Drug allergies, e.g. penicillin, sulphonamides, salicylates	may be trivial (as in skin rash) or severe, as in anaphylactic shock

Table 5.13 Manifestations of Type I hypersensitivity

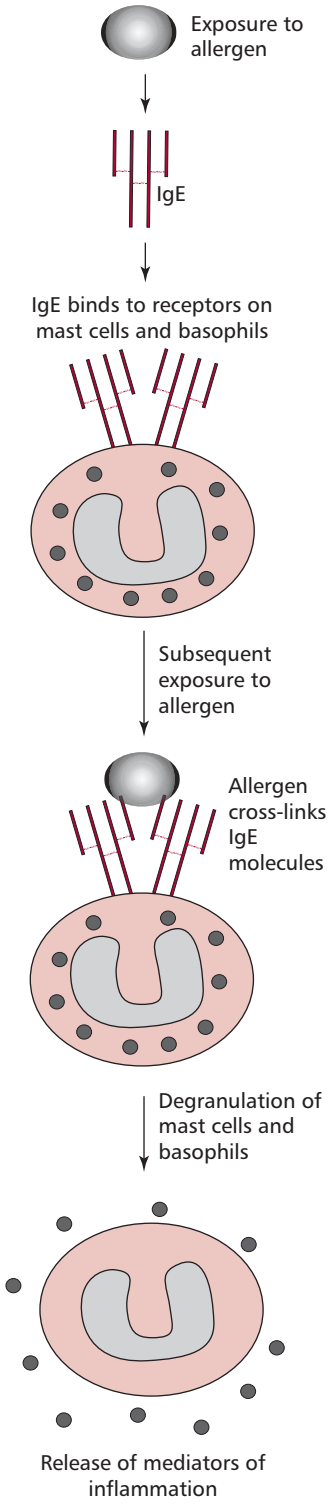

Figure 5.10 Schematic illustrating how exposure to an allergen can lead to degranulation of mast cells and basophils and Type I hypersensitivity.

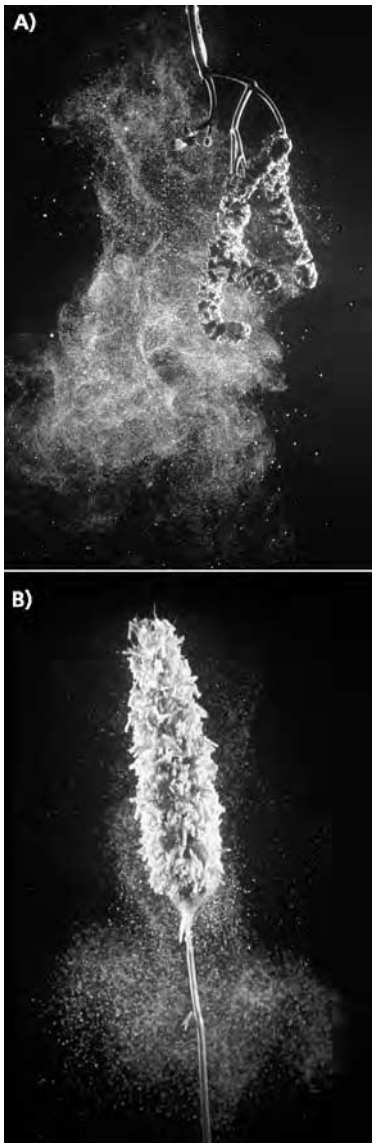

Figure 5.11 Photographs showing the release of pollen grains from (A) hazel, *Corylus avellana* and (B) Timothy grass, *Phleum pratense*.

Type I hypersensitivity is the most common form of the immunological hypersensitivities and is estimated to affect between one in 5–10 individuals, with conditions, such as allergic rhinitis, allergic asthma and food allergies.

Allergic rhinitis

Allergic rhinitis or hay fever is extremely common and its effects are well known. Seasonal allergic rhinitis typically presents in the spring and summer and is generally brought on by pollen to which the individual has been sensitized. Some individuals show sensitivity to many types of pollen (*Figure 5.11*), including well-known 'culprits' such as ragweed, while others are allergic to a single type of tree pollen. Individuals who suffer allergic rhinitis all year round are most likely to be allergic to other types of allergens, such as the dead skin cells sloughed from household pets, or the feces of house dust mites (*Figure 5.12*) which thrive in warm, carpeted dwellings. Although allergic rhinitis is not life threatening, it can be very debilitating.

Allergic asthma

Allergic asthma is a serious and potentially life-threatening condition brought on by air-borne allergens, such as those which trigger hay fever. In patients with allergic asthma, sensitization to a range of air-borne allergens stimulates inflammation in the respiratory tract, narrowing the airways and eventually leading to hyperreactivity of the muscles of the bronchial tree. The condition is very distressing particularly during an asthmatic attack, when severe respiratory distress may require emergency treatment. The incidence of asthma is increasing in children for which various explanations have been put forward. For example, it may be that increasing air pollution is predisposing patients to more frequent asthmatic attacks by increasing the hyperreactivity of the bronchial muscles.

Food allergies

Allergies to food are also seen in atopic individuals. Normally, the allergy will present as a skin rash, possibly with diarrhea, within an hour of consumption of the particular food involved. Foods known to cause allergies include eggs, shellfish, mushrooms and strawberries. Recently, much attention has focused on the extent of severe allergic reactions to nuts, especially peanuts. This may be due to the increased use of peanut paste as a thickening agent in the preparation of processed foods. Individuals who are allergic to peanuts may suffer rapid and life-threatening allergic reactions and are advised to avoid processed food unless the ingredients are clearly labeled. It has also been known for individuals to suffer severe reactions to certain fruits, such as papaya, though this is rare.

BOX 5.3 Anaphylactic shock

Anaphylactic shock is a life-threatening reaction to an allergen that may begin within minutes of exposure. Anaphylactic shock is often due to intramuscular or intravenous exposure to an immunogen as, for example, in a penicillin sensitive individual who has been given intramuscular or intravenous penicillin to treat a bacterial infection. People who are highly sensitized to bee venom may also develop anaphylactic shock following a bee sting. Anaphylactic shock may also be brought about by sensitization to latex found, for example, in rubber gloves used in hospitals, and this appears to be an increasing problem. In addition, food allergies in highly sensitized individuals occasionally result in anaphylactic shock. Typically, those affected suffer extreme respiratory distress accompanied by hypotension and may also develop a skin rash (urticaria) and diarrhea. The condition arises from a systemic release of mast cell mediators. The extensive vasodilation causes a sudden massive drop in blood pressure. The effects of mediators, in particular leukotrienes, on respiratory muscles also lead to breathing difficulties. Anaphylactic shock is a medical emergency and must be treated immediately with, for example, rapid intramuscular injection of adrenalin to relax the smooth muscle tissues.

Management of Type I hypersensitivity

The most appropriate strategy for treating Type I hypersensitivity is to identify the allergen and to avoid it. Laboratory tests to identify the allergen in question may involve skin testing (*Box 11.5*). Extracts of common allergens are injected intradermally. In sensitive individuals, the causative allergen will produce a 'wheal and flare' skin reaction within 20 min. The 'wheal' is a raised red lump, while the flare is the red inflamed area that surrounds it. Investigations of Type I hypersensitivity include the radioallergosorbent test (RAST) which measures the level of allergen-specific IgE in the blood. This involves incubating samples of serum from a patient with the potential allergen immobilized on a solid support, any IgE that becomes bound to the allergen is then detected by the addition of ^{125}I-labeled anti-IgE antibodies.

When complete avoidance of the allergen is not feasible, drugs may be used to control the symptoms. These include antihistamines, such as brompheniramine maleate and loratadine, anti-inflammatory drugs, such as corticosteroids, and 'Intal' which prevents mast cell degranulation.

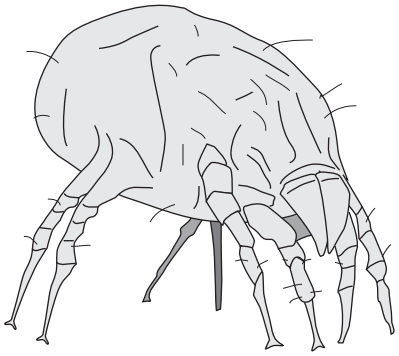

Figure 5.12 The house dust mite.

TYPE II HYPERSENSITIVITY

Type II or cytotoxic hypersensitivity refers to those situations in which antibody activates complement causing tissue damage. Examples include transfusion reactions to mismatched blood, and hemolytic disease of the newborn (HDN). In addition, autoimmune reactions that involve lysis of cells can be included here. Autoimmune diseases have already been discussed above and transfusion and HDN are described in *Chapter 6*, hence only a brief discussion of the causes and consequences of the transfusion of ABO incompatible blood will be given here.

Transfusion reactions

The ABO blood group system contains four blood groups: A, B, AB, or O, according to the types of antigens found on erythrocyte membranes (*Chapter 6*). In the plasma, there are also antibodies to the blood group antigens that are not present on the erythrocyte membranes. Thus, individuals with blood group A have anti-B antibodies in their plasma, while those of blood group B have anti-A (*Figure 5.13*). These antibodies are known as **isohemagglutinins**, and usually belong to the IgM class, which are efficient activators of complement. If a blood group A individual is transfused with group B blood, then antibodies from the donated blood will bind to recipient erythrocytes, activate complement and cause their lysis. Similarly, antibodies in the recipient will lyse the donated erythrocytes. The sudden and simultaneous lysis of cells leads to kidney failure and death.

TYPE III HYPERSENSITIVITY

Type III or complex-mediated hypersensitivity is brought about by immune complexes that usually involve antibodies to soluble antigens. Immune complexes can be harmful because they activate complement, triggering inflammation and the influx of neutrophils into an area. Over a period of time, this can cause tissue damage, principally due to lytic enzymes released by dying neutrophils. As the size of immune complexes varies, depending on the relative proportions of antigen and antibody, the clinical consequences may vary. For example, in autoimmune diseases such as RA (*Section 5.3*) immune complexes between rheumatoid factor and IgG are produced in antigen excess. These complexes are small and soluble and travel in the circulation. They may adhere to the insides of blood vessels, triggering vasculitis, or terminate in the kidney and cause nephritis. In intrinsic allergic alveolitis, immune complexes produced in the alveoli are large, and precipitate in the lungs, causing alveolitis. The name 'intrinsic allergic alveolitis' covers a number of

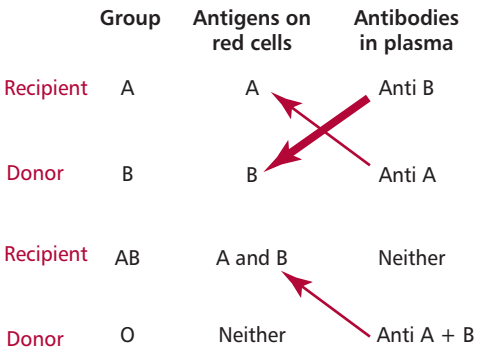

Figure 5.13 The antigens and antibodies of the ABO blood group system. The results of only two incompatible transfusions are highlighted, with the thickness of the arrows indicating the relative amounts of agglutination (***Chapter 6***).

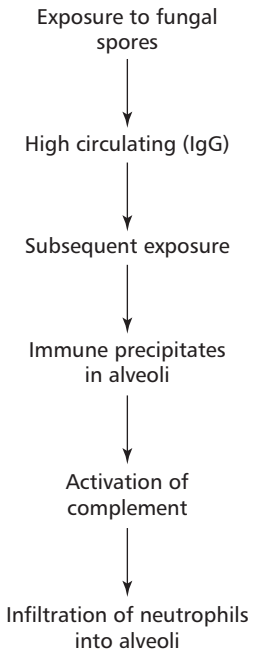

Figure 5.14 A long-term exposure to spores can cause the production of high levels of circulating antibody (IgG) which can precipitate spore antigens in the alveoli and activate complement leading to Farmer's lung.

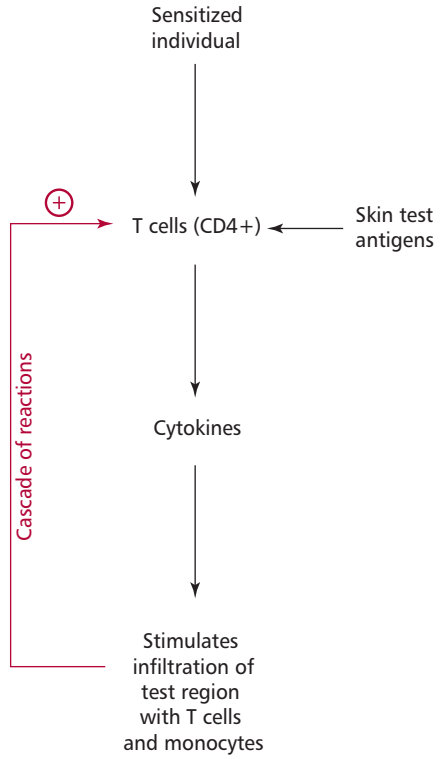

Figure 5.15 The Mantoux test for Type IV hypersensitivity. See text for details.

occupational diseases, in which workers are exposed to air-borne immunogens. A typical example of this disorder is Farmer's lung (*Figure 5.14*). This disorder typically begins in winter time, when the farmer develops a cough. Since this is not an unusual occurrence, the disease may go unrecognized for several years. However, the disease is progressive and, if untreated, will progress to emphysema. The disease is related to the farmer moving hay to feed livestock during the winter. Ascomycete fungi grow well in the warm damp conditions at the center of a haystack, and a cloud of spores are released when the hay is moved. The farmer inhales the spores and, over months and years, develops high levels of circulating IgG to immunogenic molecules which have been leached from the spores. With high levels of IgG in the blood supply to the alveoli, further exposure to spore antigens causes large immune complexes to precipitate in the lungs, setting up inflammation in the alveoli.

Successive winters may result in immune complex-mediated damage to the lungs, with fibrosis and loss of gas exchange capacity. Although Farmer's lung is classified as an antibody-mediated hypersensitivity, it is now recognized that cell-mediated immunity is also involved and that damage caused by specific T cells also contributes to the disease. It is essential that Farmer's lung be diagnosed early to avoid permanent damage to lung tissue. Treatment in the early stages may simply involve avoidance of the antigen, although corticosteroids may also be used to treat the inflammatory reaction.

TYPE IV DELAYED TYPE HYPERSENSITIVITY

Delayed-type hypersensitivity (DTH) requires more than 18 h after exposure to an immunogen for the symptoms to become apparent. This type of hypersensitivity is caused by T lymphocytes rather than antibody. The DTH reaction is typified by the Mantoux reaction. The vaccine to protect against tuberculosis (TB) consists of an attenuated form of Bacillus Calmette Guérin (BCG) which is a strain of *Mycobacterium bovis* (*Chapter 2*). Before being given the vaccine, individuals are skin tested to see if they are already sensitized by infection or previous vaccination. This involves injecting an extract of mycobacteria, called **purified protein derivative** (**PPD**) intradermally. If an individual is sensitized, then after about 18–24 h, the injection site becomes swollen and red. The swelling increases for around 48 h then subsides slowly so that this 'positive' reaction is still visible after several weeks. An individual who gives a positive Mantoux test may then be investigated to ensure that the positive result was due to prior sensitization rather than active disease.

The swelling is caused by small lymphocytes and monocytes infiltrating into the area. Initially, sensitized CD4+ T cells respond to PPD by releasing cytokines (*Figure 5.15*) that attract and retain monocytes at the site and induce inflammation, allowing the entry of more CD4+ cells. Thus a cascade reaction occurs, producing a slow but progressive swelling at the site of the injection. The reaction subsides once the phagocytic monocytes have removed all the PPD.

Delayed type hypersensitivity is also seen in **contact allergies** to a number of chemicals, including certain biological stains, some hair dyes, nickel salts in cheap jewellery, mercuric salts in some tattoo dyes, fluorodinitrobenzene and some plant biochemicals, such as urushiol in poison ivy. Typically, once sensitized, an individual will develop dermatitis approximately 18 to 24 h after further skin contact with the same chemical. Skin sensitizing chemicals are not typical immunogens, since they are neither proteins nor large molecules. However, it appears that sensitization involves their chemical binding to skin proteins to form a hapten-protein conjugate (*Chapter 4*). Langerhans cells, which are antigen presenting cells in the skin, process the 'new' antigen and present it to helper T lymphocytes, which become sensitized. Once this has

happened, any further contact with the chemical will promote cytokine release from T cells, producing a cascade similar to that of the Mantoux reaction.

Laboratory workers need to be aware of the skin sensitizing nature of many of the chemicals used in biomedical science and to conduct risk assessments for their use, since sensitization, once induced, is irreversible. The only treatment for Type IV hypersensitivy is to avoid the allergen, although corticosteroid creams may give some relief during an episode of dermatitis.

CASE STUDY 5.1

George is a nine-month-old boy who has suffered repeated bouts of upper respiratory tract infections since the age of four months. He was admitted to hospital with bacterial pneumonia. A routine examination of his throat showed his tonsils to be much smaller than usual in boys of his age, especially those who have had numerous throat infections. George has no siblings.

Questions

(a) What diagnoses might plausibly be suggested?

(b) How could these suggestions be confirmed?

(c) If confirmed, what types of treatment would be beneficial?

CASE STUDY 5.2

Peter is a teacher at a primary school. In his spare time he keeps bees and sells the honey he produces at local country fairs. At one such fair he was allowing potential customers to sample his honey. The stall became very attractive to some nearby wasps, and, in trying to keep the wasps away, Peter was stung. With a few minutes he collapsed with obvious severe breathing problems and a generalized rash.

Questions

(a) What is the most likely cause of Peter's collapse?

(b) How should he be treated?

CASE STUDY 5.3

Jane is a 24-year-old student studying for a PhD. Her first two years went well and she was hard-working and dedicated. In the last year, however, her attendance at university declined and her work suffered. Her supervisor was worried about her constant tiredness and weight gain, and, although the university is well heated, Jane was always complaining about the cold. Her supervisor advised her to consult her physician who notices that Jane has a goiter.

Questions

(a) What is the likely cause of Jane's tiredness?

(b) What clinical tests are appropriate to Jane?

5.5 SUMMARY

Disorders of the immune system include immunodeficiencies, autoimmune diseases and hypersensitivities. The lack of a component of the immune system renders the sufferer much more susceptible to infectious disease and some forms of cancer. These diseases may be treated by giving antibiotics and antiviral drugs to treat infections and, where possible, to replace the missing component by administration of antibodies or by a bone marrow transplant. Autoimmune diseases occur when the mechanisms for preventing self-

reactivity fail. These diseases can be organ specific or systemic. They can be treated with immunosuppressive drugs, although this renders the individual more susceptible to infection. Hypersensitivities are classified into four types depending on the underlying cause. They are best treated by avoiding contact with the immunogen to which the individual is sensitized.

QUESTIONS

1. Which one of the following statements is **CORRECT**?
   a) Rheumatoid factor is only present in patients with rheumatoid arthritis.
   b) All patients with rheumatoid arthritis have rheumatoid factor.
   c) Antibodies to double stranded DNA are diagnostic for SLE.
   d) Graves disease is characterized by antibodies to the acetylcholine receptor.
   e) Goodpasture's disease is a systemic disorder.

2. State whether the following statements are TRUE or are FALSE.
   a) Bruton's agammaglobulinemia is an autosomal recessive condition.
   b) Complement deficiencies result in increased neisserial infections.
   c) Deficiencies in T cells cause an increased susceptibility to viral infections.
   d) T cell deficiencies are corrected with infusions of plasma.
   e) Immunodeficiency may lead to increased risk of some cancers.

3) Which of the following statements is **INCORRECT**?
   a) In autoimmune disease generally, more women than men are affected.
   b) Transient hypogammaglobulinemia refers to a brief antibody deficiency in pregnant women.
   c) Deficiencies of C9 are asymptomatic.
   d) The classical pathway for complement action depends on the presence of antibodies.
   e) In SCID, B lymphocyte levels may be normal or decreased.

4. List three ways in which the body prevents autoimmune reactions.

5. Arrange the following two lists into their most appropriate pairings

Selective IgA deficiency	Is due to IgE
Farmer's lung	Is caused by T lymphocytes
Chediak Higashi disease	May be asymptomatic
Anaphylactic shock	Affects melanocytes
Delayed hypersensitivity	Is caused by immune complexes

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Useful web sites:

C. Lucy Park *Common Variable Immunodeficiency* http://www.emedicine.com (accessed May 2005)

http://www.hopkins-arthritis.som.jhmi.edu/rheumatoid/tnf.html (accessed June 2005)

http://emedicine.com (for up to date articles on all the diseases mentioned in this chapter)