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62 • CLINICAL IMMUNOLOGY to protect against infection (Fig. 4.1). Immune defences are normally categorised into the innate immune response, which provides immediate protection against an invading pathogen, and the adaptive or acquired immune response, which takes more time to develop but confers exquisite specificity and long-lasting protection. The innate immune system Innate defences against infection include anatomical barriers, phagocytic cells, soluble molecules such as complement and acute phase proteins, and natural killer cells. The innate immune system recognises generic microbial structures present on non-mammalian tissue and can be mobilised within minutes. A specific stimulus will elicit essentially identical responses in different individuals, in contrast with adaptive antibody and T-cell responses, which vary greatly between individuals. Physical barriers The tightly packed keratinised cells of the skin physically limit colonisation by microorganisms. The hydrophobic oils that are secreted by sebaceous glands further repel water and microorganisms, and microbial growth is inhibited by the skin’s low pH and low oxygen tension. Sweat also contains lysozyme, an enzyme that destroys the structural integrity of bacterial cell walls; ammonia, which has antibacterial properties; and several The immune system has evolved to identify and destroy pathogens while minimising damage to host tissue. Despite the ancient observation that recovery from an infectious disease frequently results in protection against that condition, the existence of the immune system as a functional entity was not recognised until the end of the 19th century. More recently, it has become clear that the immune system not only protects against infection but also regulates tissue repair following injury, and when dysregulated, governs the responses that can lead to autoimmune and auto-inflammatory diseases. Dysfunction or deficiency of the immune response can lead to a wide variety of diseases that may potentially involve every organ system in the body. The aim of this chapter is to provide a general understanding of the immune system, how it contributes to human disease and how manipulation of the immune system can be put to therapeutic use. A review of the key components of the immune response is followed by sections that illustrate the clinical presentation of the most

common forms of immune dysfunction: immune deficiency, inflammation, autoimmunity and allergy. More detailed discussion of individual conditions can be found in the relevant organ-specific chapters of this book. Functional anatomy and physiology The immune system consists of an intricately linked network of lymphoid organs, cells and proteins that are strategically placed Fig. 4.1 Anatomy of the immune system. Adenoids Lymph nodes Tonsils Thoracic duct Spleen Bone marrow Liver Appendix Germinal centre Proliferating B cells after antigen exposure Afferent lymph Paracortex T cells Dendritic cells Cortex B cells in primary lymphoid follicles Efferent lymph Medulla Plasma cells Sinuses with macrophages Blood vessels Capsule Lymph node section Lymphatics Neutrophil Eosinophil Cells of the innate immune system Natural killer cell Basophil Mast cell Monocyte Macrophage T lymphocyte Cells of the adaptive immune system Antigen-presenting cell B lymphocyte Thymus Peyer’s patches in small intestine

the specific soluble proteins and cells of the innate immune system are activated. Phagocytes Phagocytes (‘eating cells’) are specialised cells that ingest and kill microorganisms, scavenge cellular and infectious debris, and produce inflammatory molecules that regulate other components of the immune system. They include neutrophils, monocytes and macrophages, and are particularly important for defence against bacterial and fungal infections. Phagocytes express a wide range of surface receptors, including pattern recognition receptors (PRRs), which recognise pathogen-associated molecular patterns (PAMPs) on invading microorganisms, allowing their identification. The PRRs include Toll-like receptors, nucleotide oligomerisation domain (NOD) protein-like receptors and mannose receptors, whereas the PAMPs they recognise are molecular motifs not present on mammalian cells, including bacterial cell wall components, bacterial DNA and viral double-stranded RNA. While phagocytes can recognise microorganisms through PRRs alone, engulfment of microorganisms is greatly enhanced by opsonisation. Opsonins include acute phase proteins produced by the liver, such as C-reactive protein and complement. Antibodies generated by the adaptive immune system also act as opsonins. They bind both to the pathogen and to phagocyte receptors, acting as a bridge between the two to facilitate phagocytosis (Fig. 4.2). This is followed by intracellular pathogen destruction and downstream activation of pro-inflammatory genes, resulting in the generation of pro-inflammatory cytokines as discussed below. antimicrobial peptides such as defensins. Similarly, the mucous membranes of the respiratory, gastrointestinal and genitourinary tracts provide a physical barrier to infection. Secreted mucus traps invading pathogens, and immunoglobulin A (IgA), generated by the adaptive immune system, prevents bacteria and viruses attaching to and penetrating epithelial cells. As in the skin, lysozyme and antimicrobial peptides within mucosal membranes directly kill invading pathogens, and lactoferrin acts to starve invading bacteria of iron. Within the respiratory tract, cilia directly trap pathogens and contribute to removal of mucus, assisted by physical manœuvres such as sneezing and coughing. In the gastrointestinal tract, hydrochloric acid and salivary amylase chemically destroy bacteria, while normal peristalsis and induced vomiting or diarrhoea assist clearance of invading organisms. The microbiome, which is made up of endogenous commensal bacteria, provides an additional constitutive defence against infection. Approximately 1014 bacteria normally reside at epithelial surfaces in symbiosis with the human host (p. 102). They compete with pathogenic microorganisms for scarce resources, including space and nutrients, and produce fatty acids and bactericidins that inhibit the growth of many pathogens. In addition, recent research has demonstrated that commensal bacteria help to shape the immune response by inducing specific

regulatory T cells within the intestine. Eradication of the normal flora with broad-spectrum antibiotics commonly results in opportunistic infection by organisms such as Clostridium difficile, which rapidly colonise an undefended ecological niche. These constitutive barriers are highly effective, but if external defences are breached by a wound or pathogenic organism, Fig. 4.2 Phagocytosis and opsonisation. Phagocytosis of microbes can be augmented by several opsonins, such as C-reactive protein, antibodies and complement fragments like C3b, which enhance the ability of phagocytic cells to engulf microorganisms and destroy them. Phagocytes also recognise components of microbes, such as lipopolysaccharide, peptidoglycans, DNA and RNA, collectively as pathogen-associated molecular patterns (PAMPs). These activate pattern recognition receptors (PRRs), such as Toll-like receptors and nucleotide oligomerisation domain (NOD)-like receptors, which promote inflammatory gene expression through the nuclear factor kappa beta (NFκB) pathway. Uric acid and other crystals can also promote inflammation through the NOD pathway. Microbes C3b Antibody C-reactive protein Fc receptor Toll-like receptors NOD-like receptors Lipopolysaccharide Bacterial DNA Bacterial RNA Peptidoglycans Crystals NFκB NFκB Lysosome C3b receptor Phagocytic cell Pro-inflammatory gene expression Response genes

 constitute about 5% of leucocytes. From the blood stream they migrate to peripheral tissues, where they differentiate into tissue macrophages and reside for long periods. Specialised populations of tissue macrophages include Kupffer cells in the liver, alveolar macrophages in the lung, mesangial cells in the kidney, and microglial cells in the brain. Macrophages, like neutrophils, are capable of phagocytosis and killing of microorganisms but also play an important role in the amplification and regulation of the inflammatory response (Box 4.1). They are particularly important in tissue surveillance and constantly survey their immediate surroundings for signs of tissue damage or invading organisms. Dendritic cells Dendritic cells are specialised antigen-presenting cells that are present in tissues in contact with the external environment, such as the skin and mucosal membranes. They can also be found in an immature state in the blood. They sample the environment for foreign particles and, once activated, carry microbial antigens to regional lymph nodes, where they interact with T cells and B cells to initiate and shape the adaptive immune response. Cytokines Cytokines are signalling proteins produced by cells of the immune system and a variety of other cell types. More than 100 have been identified. Cytokines have complex and overlapping roles in cellular communication and regulation of the immune response. Subtle differences in cytokine production, particularly at the initiation of an immune response, can have a major impact on outcome. Cytokines bind to specific receptors on target cells and activate downstream intracellular signalling pathways, ultimately leading to changes in gene transcription and cellular function. Two important signalling pathways are illustrated in Figure 4.3. The nuclear factor kappa B (NFκB) pathway is activated by tumour necrosis factor (TNF), by other members of the TNF superfamily such as receptor activator of nuclear kappa B ligand Neutrophils Neutrophils, also known as polymorphonuclear leucocytes, are derived from the bone marrow and circulate freely in the blood. They are short-lived cells with a half-life of 6 hours, and are produced at the rate of 1011 cells daily. Their functions are to kill microorganisms, to facilitate rapid transit of cells through tissues, and to amplify the immune response non-specifically. These functions are mediated by enzymes contained in granules, which also provide an intracellular milieu for the killing and degradation of microorganisms. Two main types of granule are recognised: primary or azurophil granules, and the more numerous secondary or specific granules. Primary granules contain myeloperoxidase and other enzymes important for intracellular killing and digestion of ingested microbes. Secondary granules are smaller and contain

lysozyme, collagenase and lactoferrin, which can be released into the extracellular space. Enzyme production is increased in response to infection, which is reflected by more intense granule staining on microscopy, known as ‘toxic granulation’. Changes in damaged or infected cells trigger local production of inflammatory molecules and cytokines. These cytokines stimulate the production and maturation of neutrophils in the bone marrow, and their release into the circulation. Neutrophils are recruited to specific sites of infection by chemotactic agents, such as interleukin 8 (IL-8), and by activation of local endothelium. Up-regulation of cellular adhesion molecules on neutrophils and the endothelium also facilitates neutrophil migration. The transit of neutrophils through the blood stream is responsible for the rise in neutrophil count that occurs in early infection. Once present within infected tissue, activated neutrophils seek out and engulf invading microorganisms. These are initially enclosed within membrane-bound vesicles, which fuse with cytoplasmic granules to form the phagolysosome. Within this protected compartment, killing of the organism occurs through a combination of oxidative and non-oxidative killing. Oxidative killing, also known as the respiratory burst, is mediated by the nicotinamide adenine dinucleotide phosphate (NADPH)–oxidase enzyme complex, which converts oxygen into reactive oxygen species such as hydrogen peroxide and superoxide that are lethal to microorganisms. The myeloperoxidase enzyme within neutrophils produces hypochlorous acid, which is a powerful oxidant and antimicrobial agent. Non-oxidative (oxygen-independent) killing occurs through the release of bactericidal enzymes into the phagolysosome. Each enzyme has a distinct antimicrobial spectrum, providing broad coverage against bacteria and fungi. An additional, recently identified form of neutrophil-mediated killing is neutrophil extracellular trap (NET) formation. Activated neutrophils can release chromatin with granule proteins such as elastase to form an extracellular matrix that binds to microbial proteins. This can immobilise or kill microorganisms without requiring phagocytosis. The process of phagocytosis and NET formation (NETosis) depletes neutrophil glycogen reserves and is followed by neutrophil death. As the cells die, their contents are released and lysosomal enzymes degrade collagen and other components of the interstitium, causing liquefaction of closely adjacent tissue. The accumulation of dead and dying neutrophils results in the formation of pus, which, if extensive, may lead to abscess formation. Monocytes and macrophages Monocytes are the precursors of tissue macrophages. They are produced in the bone marrow and enter the circulation, where they 4.1 Functions of macrophages Amplification of the inflammatory response • Stimulate the acute phase response (through production of IL-1 and IL-6) • Activate vascular endothelium (IL-1, TNF-α) • Stimulate neutrophil maturation and chemotaxis (IL-1, IL-8) • Stimulate monocyte chemotaxis Killing of microorganisms • Phagocytosis • Microbial killing through oxidative and non-oxidative mechanisms Clearance, resolution and repair • Scavenging of necrotic and apoptotic cells • Clearance of toxins and other inorganic debris • Tissue remodelling (elastase, collagenase, matrix proteins) • Down-regulation of inflammatory cytokines • Wound healing and scar formation (IL-1, platelet-derived growth factor, fibroblast growth factor) Link between innate and adaptive immune systems • Activate T cells by presenting antigen in a recognisable form • T cell-derived cytokines increase phagocytosis and microbicidal activity of macrophages in a positive feedback loop (IL = interleukin; TNF = tumour necrosis factor)

IKK, which in turn leads to phosphorylation of the inhibitor of nuclear factor kappa B protein (IκB), causing it to be degraded, and allowing NFκB to translocate to the nucleus and activate gene transcription. The Janus kinase/signal transducers and activators of transcription (JAK-STAT)

pathway is involved in (RANKL; p. 985), and by the Toll-like receptors and NOD-like receptors (see Fig. 4.2). In the case of TNF superfamily members, receptor binding causes the inhibitor of kappa B kinase (IKK) complex of three proteins to be recruited to the receptor by binding TNF receptor-associated proteins (TRAF). This activates Fig. 4.3 Cytokines signalling pathways and the immune response. Cytokines regulate the immune response through binding to specific receptors that activate a variety of intracellular signalling pathways, two of which are shown. Members of the tumour necrosis factor (TNF) superfamily and the Toll-like receptors and NOD-like receptors (Fig. 4.2) signal through the nuclear factor kappa B (NFκB) pathway. Several other cytokines, including interleukin-2 (IL-2), IL-6 and interferons, employ the Janus kinase/ signal transducer and activator of transcription (JAK-STAT) pathway to regulate cellular function (see text for more details). (IκB = inhibitor of kappa B; IKK = I kappa B kinase; P = phosphorylation of the signalling protein; TRAF = tumour necrosis factor receptorassociated factor) JAK JAK inhibitor Response genes Response genes JAK Cytokines Cytokine receptor P P P P P STAT STAT P P STAT STAT DNA TNF TNF receptor TRAF IκB P IκB NFκB NFκB IKKκ IKKα IKKβ IFN-γ IL-6 IL-2 4.2 Important cytokines in the regulation of the immune response Cytokine Source Actions Biologic therapies Interferon-alpha (IFN-α) T cells and macrophages Antiviral activity Activates NK cells, CD8+ T cells and macrophages Recombinant IFN-α used in hepatitis C and some malignancies Interferon-gamma (IFN-γ) T cells and NK cells Increases antimicrobial activity of macrophages Regulates cytokine production by T cells and macrophages Used in chronic granulomatous disease Tumour necrosis factor alpha (TNF-α) Macrophages, NK cells and others, including T cells Pro-inflammatory Increases expression of other cytokines and adhesion molecules Causes apoptosis of some target cells Directly cytotoxic TNF-α inhibitors used in rheumatoid arthritis, inflammatory bowel disease, psoriasis and many other inflammatory conditions Interleukin-1 (IL-1) Macrophages and neutrophils Stimulates neutrophil recruitment, fever, and T-cell and macrophage activation as part of the inflammatory response IL-1 inhibitors used in systemic juvenile rheumatoid arthritis, periodic fever syndromes and acute gout Interleukin-2 (IL-2) CD4+ T cells Stimulates proliferation and differentiation of antigenspecific T lymphocytes Interleukin-4 (IL-4) CD4+ T cells Stimulates maturation of B and T cells, and production of IgE antibody Antibodies to IL-4 receptor used in severe atopic dermatitis Interleukin-6 (IL-6) Monocytes and macrophages Stimulates neutrophil recruitment, fever, and T-cell and macrophage activation as part of the inflammatory response, stimulates maturation of B cells into plasma cells Antibodies to IL-6 receptor used in rheumatoid arthritis Interleukin-12 (IL-12) Monocytes and macrophages Stimulates IFN-γ and TNF-α release by T cells Activates NK cells Antibody to p40 subunit of IL-12 used in psoriasis and psoriatic arthritis Interleukin-17 (IL-17) Th17 cells (T helper), NK cells, NK-T cells Pro-inflammatory cytokine Involved in mucosal immunity and control of extracellular pathogens, synergy with IL-1 and TNF Antibody to IL-17 used in psoriasis, psoriatic arthritis and ankylosing spondylitis Interleukin-22 (IL-22) Th17 cells Induction of epithelial cell proliferation and antimicrobial proteins in keratinocytes (IgE = immunoglobulin E; NK = natural killer)

 important in the defence against encapsulated bacteria such as Neisseria spp. and Haemophilus influenzae. Complement fragments generated by activation of the cascade can also act as opsonins, rendering microorganisms more susceptible to phagocytosis by macrophages and neutrophils (see Fig. 4.2). In addition, they are chemotactic agents, promoting leucocyte trafficking to sites of inflammation. Some fragments act as anaphylotoxins, binding to complement receptors on mast cells and triggering release of histamine, which increases vascular permeability. The products of complement activation also help to target immune complexes to

antigen-presenting cells, providing a link between the innate and the acquired immune systems. Finally, activated complement products dissolve the immune complexes that triggered the cascade, minimising bystander damage to surrounding tissues. A monoclonal antibody directed against the central complement molecule C5, eculizumab, has been developed for therapeutic use in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndromes (p. 408). Invasive infection, including meningococcal sepsis, has been reported with eculizumab therapy, highlighting the importance of the complement system in preventing such infections. Mast cells and basophils Mast cells and basophils are bone marrow-derived cells that play a central role in allergic disorders. Mast cells reside predominantly in tissues exposed to the external environment, such as the skin and gut, while basophils circulate in peripheral blood and are recruited into tissues in response to inflammation. Both contain large cytoplasmic granules that enclose vasoactive substances such as histamine (see Fig. 4.14). Mast cells and Fig. 4.4 The complement pathway. The classical pathway is activated by binding of antigen–antibody complexes to C1 but is blocked by C1 inhibitor (C1inh), whereas mannose-binding lectins, which are macromolecules that bind to various microorganisms, activate the pathway by binding C4. Bacteria can directly activate the pathway through C3, which plays a pivotal role in complement activation through all three pathways. Smooth muscle contraction Activation of cells Vascular permeability Lysis of bacteria Membrane attack complex (MAC) Opsonisation of bacteria Direct activation Lectin pathway Mannosebinding lectin Classical pathway Antibody–antigen complexes Alternate pathway C4 C2 C3 C3a C1inh C5a C5 C3b C5b C6 C7 C8 C1 C9 transducing signals downstream of many cytokine receptors, including those for IL-2, IL-6 and interferon-gamma (IFN-γ). On receptor binding, JAK proteins are recruited to the intracellular portion of the receptor and are phosphorylated. These in turn phosphorylate STAT proteins, which translocate to the nucleus and activate gene transcription, altering cellular function. The function and disease associations of several important cytokines are shown in Box 4.2. Cytokine inhibitors are now routinely used in the treatment of autoimmune diseases, most of which are monoclonal antibodies to cytokines or their receptors. In addition, small-molecule inhibitors have been developed that inhibit the intracellular signalling pathways used by cytokines. These include the Janus kinase inhibitors tofacitinib and baracitinib, which are used in rheumatoid arthritis (p. 1026), and the tyrosine kinase inhibitor imatinib, which is used in chronic myeloid leukaemia (p. 959). Integrins Integrins are transmembrane proteins that play important roles in cell–cell and cell–matrix interactions. They mediate attachment of the cell to the extracellular matrix, signal transduction and cell migration. Their role in autoimmune disease has been extensively studied. Targeted therapy with a recombinant humanised anti-α4 integrin antibody, natalizumab, is an effective treatment for multiple sclerosis, which works by preventing immune cells from traversing the vascular endothelium and entering the central nervous system (p. 1109). Complement The complement system comprises a group of more than 20 tightly regulated, functionally linked proteins that act to promote inflammation and eliminate invading pathogens. Complement proteins are produced in the liver and are present in inactive form in the circulation. When the complement system is activated, it sets in motion a rapidly amplified biological cascade analogous to the coagulation cascade (p. 918). There are three mechanisms by which the complement cascade can be activated (Fig. 4.4): • The alternate pathway is triggered directly by binding of C3 to bacterial cell-wall components, such as lipopolysaccharide of Gram-negative bacteria and teichoic acid of Gram-positive bacteria. • The classical pathway is initiated when two or more IgM or IgG antibody molecules bind to antigen. The associated conformational change exposes binding sites on the antibodies for the first protein in the classical pathway, C1, which is a multiheaded molecule that can bind up to six antibody molecules. Once two or more

‘heads’ of a C1 molecule are bound to antibody, the classical cascade is triggered. An important inhibitor of the classical pathway is C1 inhibitor (C1inh), as illustrated in Figure 4.4. • The lectin pathway is activated by the direct binding of mannose-binding lectin to microbial cell surface carbohydrates. This mimics the binding of C1 to immune complexes and directly stimulates the classical pathway, bypassing the need for immune complex formation. Activation of complement by any of these pathways results in activation of C3. This in turn activates the final common pathway, in which the complement proteins C5–C9 assemble to form the membrane attack complex (MAC). This can puncture the cell wall, leading to osmotic lysis of target cells. This step is particularly

Lymphoid organs The primary lymphoid organs are involved in lymphocyte development. They include the bone marrow, where T and B lymphocytes differentiate from haematopoietic stem cells (p. 914) and where B lymphocytes also mature, and the thymus, the site of T-cell maturation (see Fig. 4.1). After maturation, lymphocytes migrate to the secondary lymphoid organs. These include the spleen, lymph nodes and mucosa-associated lymphoid tissue. These trap and concentrate foreign substances and are the major sites of interaction between naïve lymphocytes and microorganisms. The thymus The thymus is a bi-lobed structure in the anterior mediastinum, and is organised into cortical and medullary areas. The cortex is densely populated with immature T cells, which migrate to the medulla to undergo selection and maturation. The thymus is most active in the fetal and neonatal period, and involutes after puberty. Failure of thymic development is associated with profound T-cell immune deficiency (p. 79) but surgical removal of the thymus in childhood (usually during major cardiac surgery) is not associated with significant immune dysfunction. The spleen The spleen is the largest of the secondary lymphoid organs. It is highly effective at filtering blood and is an important site of phagocytosis of senescent erythrocytes, bacteria, immune complexes and other debris, and of antibody synthesis. It is important for defence against encapsulated bacteria, and asplenic individuals are at risk of overwhelming Streptococcus pneumoniae and H. influenzae infection (see Box 4.5). Lymph nodes These are positioned to maximise exposure to lymph draining from sites of external contact, and are highly organised (Fig. 4.1) • The cortex contains primary lymphoid follicles, which are the site of B-lymphocyte interactions. When B cells encounter antigen, they undergo intense proliferation, forming germinal centres. • The paracortex is rich in T lymphocytes and dendritic cells. • The medulla is the major site of antibody-secreting plasma cells. • Within the medulla there are many sinuses, which contain large numbers of macrophages. Mucosa-associated lymphoid tissue Mucosa-associated lymphoid tissue (MALT) consists of diffusely distributed lymphoid cells and follicles present along mucosal surfaces. It has a similar function to the more organised, encapsulated lymph nodes. They include the tonsils, adenoids and Peyer’s patches in the small intestine. Lymphatics Lymphoid tissue is connected by a network of lymphatics, with three major functions: it provides access to lymph nodes, returns interstitial fluid to the venous system, and transports fat from the small intestine to the blood stream (see Fig. 14.13, p. 372). The lymphatics begin as blind-ending capillaries, which come together to form lymphatic ducts, entering and leaving regional lymph nodes as afferent and efferent ducts, respectively. They eventually coalesce and drain into the thoracic duct and left subclavian vein. Lymphatics may be either deep or superficial, and follow the distribution of major blood vessels. basophils express IgE receptors on their cell surface, which bind IgE antibody. On encounter with specific antigen, the cell is triggered to release histamine and

other mediators present within the granules and to synthesise additional mediators, including leukotrienes, prostaglandins and cytokines. An inflammatory cascade is initiated that increases local blood flow and vascular permeability, stimulates smooth muscle contraction, and increases secretion at mucosal surfaces. Natural killer cells Natural killer (NK) cells are large granular lymphocytes that play a major role in defence against tumours and viruses. They exhibit features of both the adaptive and the innate immune systems in that they are morphologically similar to lymphocytes and recognise similar ligands, but they are not antigen-specific and cannot generate immunological memory. NK cells express a variety of cell surface receptors, some of which are stimulatory and others inhibitory. The effects of inhibitory receptors normally predominate. These recognise human leucocyte antigen (HLA) molecules that are expressed on normal nucleated cells, preventing NK cell-mediated attack, whereas the stimulatory receptors recognise molecules that are expressed primarily when cells are damaged. This allows NK cells to remain tolerant to healthy cells but not to damaged ones. When cells become infected by viruses or undergo malignant change, expression of HLA class I molecules on the cell surface can be down-regulated. This is an important mechanism by which these cells then evade adaptive T-lymphocyte responses. In this circumstance, however, NK cell defences becomes important, as down-regulation of HLA class I abrogates the inhibitory signals that normally prevent NK activation. The net result is NK attack on the abnormal target cell. NK cells can also be activated by binding of antigen–antibody complexes to surface receptors. This physically links the NK cell to its target in a manner analogous to opsonisation and is known as antibody-dependent cellular cytotoxicity (ADCC). Activated NK cells can kill their targets in various ways. They secrete pore-forming proteins such as perforin into the membrane of the target cell, and proteolytic enzymes called granzymes into the target cell, which cause apoptosis. In addition, NK cells produce a variety of cytokines such as TNF-α and IFN-γ, which have direct antiviral and anti-tumour effects. The adaptive immune system If the innate immune system fails to provide effective protection against an invading pathogen, the adaptive immune system is mobilised (see Fig. 4.1). This has three key characteristics: • It has exquisite specificity and can discriminate between very small differences in molecular structure. • It is highly adaptive and can respond to an almost unlimited number of molecules. • It possesses immunological memory, and changes consequent to initial activation by an antigen allow a more effective immune response on subsequent encounters. There are two major arms of the adaptive immune response. Humoral immunity involves the production of antibodies by B lymphocytes, and cellular immunity involves the activation of T lymphocytes, which synthesise and release cytokines that affect other cells, as well as directly killing target cells. These interact closely with each other and with the components of the innate immune system to maximise effectiveness of the immune response.

 Humoral immunity Humoral immunity is mediated by B lymphocytes, which differentiate from haematopoietic stem cells in the bone marrow. Their major functions are to produce antibody and interact with T cells, but they are also involved in antigen presentation. Mature B lymphocytes can be found in the bone marrow, lymphoid tissue, spleen and, to a lesser extent, the blood stream. They Fig. 4.5 B-cell activation. Activation of B cells is initiated through binding of an antigen with the immunoglobulin receptor on the cell surface. For activation to proceed, an interaction with T-helper cells is also required, providing additional signals through binding of CD40 ligand (CD40L) to CD40; an interaction between the T-cell receptor (TCR) and processed antigenic peptides presented by human leucocyte antigen (HLA) molecules on the B-cell surface; and cytokines released by the T-helper cells. Fully activated B cells undergo clonal expansion with differentiation towards plasma cells that produce antibody. Following activation,

memory cells are generated that allow rapid antibody responses when the same antigen is encountered on a second occasion. (CD = cluster of differentiation; IL = interleukin) T-helper cell Immunoglobulin receptor Antigen CD40L CD40 TCR HLA B-cell activation B cell Clonal expansion Plasma cells Antibodies Memory B cells IL-4 IL-5 Fig. 4.6 The structure of an immunoglobulin (antibody) molecule. The variable region is responsible for antigen binding, whereas the constant region can interact with immunoglobulin receptors expressed on immune cells. Variable region (Fab) Constant region (Fc) Light chain Heavy chain 4.3 Classes and properties of antibody Antibody Concentration in adult serum Complement activation* Opsonisation Presence in external secretions Other properties IgG 6.0–16.0 g/L IgG1 +++ IgG2 + IgG3 +++ IgG1 ++ IgG3 ++ ++ Four subclasses: IgG1, IgG2, IgG3, IgG4 Distributed equally between blood and extracellular fluid, and transported across placenta IgG2 is particularly important in defence against polysaccharides antigens IgA 1.5–4.0 g/L – – ++++ Two subclasses: IgA1, IgA2 Highly effective at neutralising toxins Particularly important at mucosal surfaces IgM 0.5–2.0 g/L ++++ – + Highly effective at agglutinating pathogens IgE 0.003–0.04 g/L – – – Majority of IgE is bound to mast cells, basophils and eosinophils Important in allergic disease and defence against parasite infection IgD Not detected – – – Function in B-cell development *Activation of the classical pathway, also called ‘complement fixation’. express a unique immunoglobulin receptor on their cell surface, the B-cell receptor, which binds to soluble antigen targets (Fig. 4.5). Encounters with antigen usually occur within lymph nodes. If provided with appropriate cytokines and other signals from nearby T lymphocytes, antigen-specific B cells respond by rapidly proliferating in a process known as clonal expansion (Fig. 4.5). This is accompanied by a highly complex series of genetic rearrangements known as somatic hypermutation, which generates B-cell populations that express receptors with greater affinity for antigen than the original. These cells differentiate into either long-lived memory cells, which reside in the lymph nodes, or plasma cells, which produce antibody. Memory cells allow production of a more rapid and more effective response on subsequent exposure to that pathogen. Immunoglobulins Immunoglobulins (Ig) play a central role in humoral immunity. They are soluble proteins produced by plasma cells and are made up of two heavy and two light chains (Fig. 4.6). The heavy chain determines the antibody class or isotype, such as IgG, IgA, IgM, IgE or IgD. Subclasses of IgG and IgA also occur. The antigen is recognised by the antigen-binding regions (Fab) of both heavy and light chains, while the consequences of antibody binding are determined by the constant region of the heavy chain (Fc) (Box 4.3). Antibodies have several functions.

and production of antibody is decreased to 2–3 days, the amount of antibody produced is increased, and the response is dominated by IgG antibodies of high affinity. Furthermore, in contrast to the initial antibody response, secondary antibody responses do not require additional input from T lymphocytes. This allows the rapid generation of highly specific responses on re-exposure to a pathogen and is an important mechanism in vaccine efficacy. Cellular immunity Cellular immunity is mediated by T lymphocytes, which play important roles in defence against viruses, fungi and intracellular bacteria. They also play an important immunoregulatory role, by orchestrating and regulating the responses of other components of the immune system. T-lymphocyte precursors differentiate from haematopoietic stem cells in the bone marrow and are exported to the thymus when they are still immature (see Fig. 4.1). Individual T cells express a unique receptor that is highly Fig. 4.7 T-cell activation. Activation of T cells is initiated when an antigenic peptide bound to a human leucocyte antigen (HLA) molecule on antigenpresenting cells

interacts with the T-cell receptor expressed by T lymphocytes. Additional signals are required for T-cell activation, however. These include binding of the co-stimulatory molecules CD80 and CD86 with CD28 on the T cell, and interleukin 2 (IL-2), which is produced in an autocrine manner by T cells that are undergoing activation. Other molecules are present that can inhibit T-cell activation, however, including cytotoxic T-lymphocyte-associated protein 4 (CTLA4), which competes with CD28 for binding to CD80 and CD86; and PD1, which, by binding PDL1, is also inhibitory. Following activation, T cells proliferate and, depending on their subtype, have various functions with distinct patterns of cytokine production, as indicated. Memory cells are also generated that can mount a rapid immune response on encountering the same antigen. (CD = cluster of differentiation; CD40L = CD40 ligand; IFN-γ = interferon-gamma; IL = interleukin; PD1 = programmed cell death 1; PDL1 = programmed death ligand 1; TGF-β = transforming growth factor beta; TNF-α = tumour necrosis factor alpha) CD80 CD86 CD4+ T cells Th2 cells Cytokines IL-4, IL-5, IL-10, IL-13 Function B-cell activation Eosinophil activation Th1 cells Cytokines TNF-α, IFN-γ, IL-2 Function Pro-inflammatory Th17 cells Cytokines IL-17 Function Mucosal immunity Pro-inflammatory Regulatory T cells Memory T cells Memory T cells Cytokines Fas ligand TNF-α, IFN-γ Function Direct cell killing CD8+ T cells Cytokines IL-10, TGF-β Function Anti-inflammatory PDL1 HLA T-cell receptor T-cell activation Antigenic peptide PD1 CTLA4 CD28 Antigen-presenting cell IL-2 They facilitate phagocytosis by acting as opsonins (see Fig. 4.2) and facilitate cell killing by cytotoxic cells, particularly NK cells by antibody-dependent cellular cytotoxicity. Binding of antibodies to antigen can trigger activation of the classical complement pathway (see Fig. 4.4). In addition, antibodies can directly neutralise the biological activity of their antigen target. This is a particularly important feature of IgA antibodies, which act predominantly at mucosal surfaces. The humoral immune response is characterised by immunological memory, in which the antibody response to successive exposures to an antigen is qualitatively and quantitatively improved from the first exposure. When a previously unstimulated or ‘naïve’ B lymphocyte is activated by antigen, the first antibody to be produced is IgM, which appears in the serum after 5–10 days. Depending on additional stimuli provided by T lymphocytes, other antibody classes (IgG, IgA and IgE) are produced 1–2 weeks later. If the memory B cell is subsequently re-exposed to the same antigen, the lag time between exposure

 molecules that down-regulate T-cell activity. One such inhibitory molecule, CTLA4, has been harnessed therapeutically in the form of abatacept, which is a fusion protein comprised of the Fc fragment of immunoglobulin linked to CTLA4. This is used to inhibit T-cell activation in rheumatoid arthritis and solid organ transplantation. The inflammatory response Inflammation is the response of tissues to injury or infection, and is necessary for normal repair and healing. This section focuses on the general principles of the inflammatory response and its multisystem manifestations. The role of inflammation in specific diseases is discussed in many other chapters of this book. Acute inflammation Acute inflammation is the result of rapid and complex interplay between the cells and soluble molecules of the innate immune system. The classical external signs include heat, redness, pain and swelling (Fig. 4.8). The inflammatory process is initiated by local tissue injury or infection. Damaged epithelial cells produce cytokines and antimicrobial peptides, causing early infiltration of phagocytic cells. Production of leukotrienes, prostaglandins, histamine, kinins, anaphylotoxins and inducible nitric oxide synthase also occurs within inflamed tissue. These mediators cause vasodilatation and increased vascular permeability, causing trafficking of fluid and cells into the affected tissue. In addition, pro-inflammatory cytokines, such as IL-1, TNF-α and IL-6 produced at the site of injury, are released systemically and act on the hypothalamus to cause fever, and on the liver to stimulate production of acute phase

proteins. The acute phase response The acute phase response refers to the production of a variety of proteins by the liver in response to inflammatory stimuli. These proteins have a wide range of activities. Circulating levels of C-reactive protein (CRP) and serum amyloid A may be increased 1000-fold, contributing to host defence and stimulating repair and regeneration. Fibrinogen plays an essential role in wound healing, and α1-antitrypsin and α1-antichymotrypsin control the pro-inflammatory cascade by neutralising the enzymes produced by activated neutrophils, preventing widespread tissue destruction. In addition, antioxidants such as haptoglobin and manganese superoxide dismutase scavenge for oxygen free radicals, while increased levels of iron-binding proteins such as ferritin and lactoferrin decrease the iron available for uptake by bacteria (p. 941). Immunoglobulins are not acute phase proteins but are often increased in chronic inflammation. Septic shock Septic shock is the clinical manifestation of overwhelming inflammation (p. 196). It is characterised by excessive production of pro-inflammatory cytokines by macrophages, causing hypotension, hypovolaemia and tissue oedema. In addition, uncontrolled neutrophil activation causes release of proteases and oxygen free radicals within blood vessels, damaging the vascular endothelium and further increasing capillary permeability. Direct activation of the coagulation pathway combines with endothelial cell disruption to form clots within the damaged vessels. The specific for a single antigen. Within the thymus T cells undergo a process of stringent selection to ensure that autoreactive cells are destroyed. Mature T lymphocytes leave the thymus and expand to populate other organs of the immune system. It has been estimated that an individual possesses 107–109 T-cell clones, each with a unique T-cell receptor, ensuring at least partial coverage for any antigen encountered. Unlike B cells, T cells cannot recognise intact protein antigens in their native form. Instead, the protein must be broken down into component peptides by antigen-presenting cells for presentation to T lymphocytes in association with HLA molecules on the antigen-presenting cell surface. This process is known as antigen processing and presentation, and it is the complex of peptide and HLA together that is recognised by individual T cells (Fig. 4.7). The structure of HLA molecules varies widely between individuals. Since each HLA molecule has the capacity to present a subtly different peptide repertoire to T lymphocytes, this ensures enormous diversity in recognition of antigens by the T-cell population. All nucleated cells have the capacity to process and present antigens, but cells with specialised antigenpresenting functions include dendritic cells, macrophages and B lymphocytes. These carry additional co-stimulatory molecules, such as CD80 and CD86, providing the necessary ‘second signal’ for full T-cell activation. T lymphocytes can be divided into two subgroups on the basis of function and recognition of HLA molecules. These are designated CD4+ and CD8+ T cells, according to the ‘cluster of differentiation’ (CD) antigen number of key proteins expressed on their cell surface. CD8 + T lymphocytes These cells recognise antigenic peptides in association with HLA class I molecules (HLA-A, HLA-B, HLA-C). They kill infected cells directly through the production of pore-forming molecules such as perforin and release of digesting enzymes triggering apoptosis of the target cell, and are particularly important in defence against viral infection. CD4 + T lymphocytes These cells recognise peptides presented on HLA class II molecules (HLA-DR, HLA-DP and HLA-DQ) and have mainly immunoregulatory functions. They produce cytokines and provide co-stimulatory signals that support the activation of CD8+ T lymphocytes and assist the production of mature antibody by B cells. In addition, their close interaction with phagocytes determines cytokine production by both cell types. CD4+ lymphocytes can be further subdivided into subsets on the basis of the cytokines they produce: • Th1 (T helper) cells typically produce IL-2, IFN-γ and TNF-α, and support the development of delayed-type hypersensitivity responses (p. 83). • Th2 cells typically produce IL-4, IL-5, IL-10 and IL-13, and promote allergic responses (p. 84). • T-regulatory cells (T regs) are a

further subset of specialised CD4+ lymphocytes that are important in actively suppressing activation of other cells and preventing autoimmune disease. • Th17 cells are pro-inflammatory cells defined by their production of IL-17. They are related to regulatory T cells, and play a role in immune defence at mucosal surfaces T-cell activation is regulated by a balance between co-stimulatory molecules, the second signal required for activation, and inhibitory

Chronic inflammation In most instances, the development of an active immune response results in clearance and control of the inflammatory stimulus and resolution of tissue damage. Failure of this process may result in chronic inflammation, with significant associated bystander damage, known as hypersensitivity responses. Persistence of microorganisms can result in ongoing accumulation of neutrophils, macrophages and activated T lymphocytes within the lesion. If this is associated with local deposition of fibrous tissue, a granuloma may form. Granulomas are characteristic of tuberculosis and leprosy (Hansen's disease), in which the microorganism is protected by a robust cell wall that shields it from killing, despite phagocytosis. Laboratory features of inflammation Inflammation is associated with changes in many laboratory investigations. Leucocytosis is common, and reflects the transit of activated neutrophils and monocytes to the site of infection. The platelet count may also be increased. The most widely used laboratory measure of acute inflammation is CRP. Circulating clinical consequences include cardiovascular collapse, acute respiratory distress syndrome, disseminated intravascular coagulation, multi-organ failure and often death. Septic shock most frequently results from infection with Gram-negative bacteria, because lipopolysaccharide produced by these organisms is particularly effective at activating the inflammatory cascade. Early recognition and appropriate early intervention can improve patient outcome (p. 196). Resolution of inflammation Resolution of an inflammatory response is crucial for normal healing. This involves active down-modulation of inflammatory stimuli and repair of bystander damage to local tissues. Extravasated neutrophils undergo apoptosis and are phagocytosed by macrophages, along with the remains of microorganisms. Macrophages also synthesise collagenase and elastase, which break down local connective tissue and aid in the removal of debris. Normal tissue homeostasis is also associated with reversion of parenchymal cells to a non-inflammatory phenotype. Macrophage-derived cytokines, including transforming growth factor-beta (TGF-β) and platelet-derived growth factor, stimulate fibroblasts and promote the synthesis of new collagen, while angiogenic factors stimulate new vessel formation. Fig. 4.8 Clinical features of acute inflammation. In this example, the response is to a penetrating injury and infection of the foot. Hypothalamus: Change in temperature set point Fever Sweating Neuro-endocrine and autonomic stress responses Flushing ↑Respiratory rate ↑Heart rate, flow murmur Adrenal release of glucocorticoids and catecholamines Release of insulin from pancreas Bone marrow: ↑Production and mobilisation of neutrophils Vasodilatation ↑Local vascular permeability Neutrophils + Macrophages Inflammatory mediators and cytokines Tissue damage Bacteria Local infection Skin rupture Phagocytosis Cytokine production Vasodilatation ↑Local vascular permeability ↑Leucocyte influx Headache Delirium Anorexia Low blood pressure Liver: ↑Synthesis of acute phase proteins Enlarged draining lymph nodes Ascending lymphangitis Local cellulitis Pain Redness Swelling Nail

 by the composition of plasma proteins and the morphology of circulating erythrocytes. These factors govern the propensity of red cells to aggregate, the major

determinant of the ESR. Erythrocytes are inherently negatively charged, which prevents them from clumping together in the blood stream. Since plasma proteins are positively charged, an increase in plasma protein concentrations neutralises the negative charge of erythrocytes, overcoming their inherent repulsive forces and causing them aggregate, resulting in rouleaux formation. Rouleaux have a higher mass-to-surface area ratio than single red cells, and therefore sediment faster. The most common reason for an increased ESR is an acute phase response, which causes an increase in the concentration of acute phase proteins, including CRP. However, other conditions that do not affect acute phase proteins may alter the composition and concentration of other plasma protein (Box 4.4). For example, immunoglobulins comprise a significant proportion of plasma proteins but do not participate in the acute phase response. Thus any condition that causes an increase in serum immunoglobulins will increase the ESR without a corresponding increase in CRP. In addition, abnormal red cell morphology can make rouleaux formation impossible. For these reasons, an inappropriately low ESR occurs in spherocytosis and sickle-cell anaemia. Plasma viscosity Plasma viscosity is another surrogate measure of plasma protein concentration. Like the ESR, it is affected by the concentration of large plasma proteins, including fibrinogen and immunoglobulins. It is not affected by properties of erythrocytes and is generally considered to be more reliable than the ESR as a marker of inflammation. levels of many other acute phase reactants, including fibrinogen, ferritin and complement components, are also increased in response to acute inflammation, while albumin levels are reduced. Chronic inflammation is frequently associated with a normocytic normochromic anaemia (p. 943). C-reactive protein C-reactive protein (CRP) is an acute phase reactant synthesised by the liver, which opsonises invading pathogens. Circulating concentrations of CRP increase within 6 hours of the start of an inflammatory stimulus. Serum concentrations of CRP provide a direct biomarker of acute inflammation and, because the serum half-life of CRP is 18 hours, levels fall promptly once the inflammatory stimulus is removed. Sequential measurements are useful in monitoring disease activity (Box 4.4). For reasons that remain unclear, some diseases are associated with only minor elevations of CRP despite unequivocal evidence of active inflammation. These include systemic lupus erythematosus (SLE), systemic sclerosis, ulcerative colitis and leukaemia. An important practical point is that if the CRP is raised in these conditions, it suggests intercurrent infection rather than disease activity. Since the CRP is a more sensitive early indicator of the acute phase response, it is generally used in preference to the erythrocyte sedimentation rate (ESR). If both ESR and CRP are used, any discrepancy should be resolved by assessing the individual determinants of the ESR, which are discussed below. Erythrocyte sedimentation rate The ESR is an indirect measure of inflammation. It measures how fast erythrocytes fall through plasma, which is determined 4.4 Conditions commonly associated with abnormal C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) Condition Consequence Effect on CRP1 Effect on ESR2 Acute bacterial, fungal or viral infection Stimulates acute phase response Increased (range 50–150 mg/L; in severe infections may be

> 300 mg/L) Increased Necrotising bacterial infection Stimulates profound acute inflammatory response Greatly increased (may be 300 mg/L) Increased Chronic bacterial or fungal infection Localised abscess, bacterial endocarditis or tuberculosis Stimulates acute and chronic inflammatory response with polyclonal increase in immunoglobulins, as well as increased acute phase proteins Increased (range 50–150 mg/L) Increased disproportionately to CRP

> Acute inflammatory diseases Crohn’s disease, polymyalgia rheumatica, inflammatory arthritis Stimulates acute phase response Increased (range 50–150 mg/L) Increased Systemic lupus erythematosus, Sjögren’s syndrome, ulcerative colitis Chronic inflammatory response Normal Increased Multiple myeloma Monoclonal increase in serum immunoglobulin without acute inflammation Normal Increased Pregnancy, old age, end-stage renal disease Increased fibrinogen Normal Moderately increased 1Reference range < 10 mg/L. 2Reference range: adult males < 10 mm/hr, adult females < 20 mm/hr.

4.5 Immune deficiencies and common patterns of infection Phagocyte deficiency Complement deficiency Antibody deficiency T-lymphocyte deficiency Bacteria Staphylococcus aureus Pseudomonas aeruginosa Serratia marcescens Burkholderia cenocepacia Nocardia Mycobacterium tuberculosis Atypical mycobacteria Neisseria meningitidis Neisseria gonorrhoeae Haemophilus influenzae Streptococcus pneumoniae Haemophilus influenzae Streptococcus pneumoniae Staphylococcus aureus Mycobacterium tuberculosis Atypical mycobacteria Fungi Candida spp. Aspergillus spp. – – Candida spp. Aspergillus spp. Pneumocystis jirovecii Viruses – – Cytomegalovirus (CMV) Enteroviruses Epstein–Barr virus (EBV) Herpes zoster virus Human papillomavirus Human herpesvirus 8 Protozoa – Giardia lamblia Toxoplasma gondii Cryptosporidia Presenting problems in immune disorders Recurrent infections Infections can occur in otherwise healthy individuals but recurrent infection raises suspicion of an immune deficiency. Depending on the component of the immune system affected, the infections may involve bacteria, viruses, fungi or protozoa, as summarised in Box 4.5. T-cell deficiencies can involve pathogens from all groups. Aetiology Infections secondary to immune deficiency occur because of defects in the number or function of phagocytes, B cells, T cells or complement, as described later in this chapter. Clinical assessment Clinical features that may indicate immune deficiency are listed in Box 4.6. Frequent or severe infections, or ones caused by unusual organisms or at unusual sites are typical of immune deficiency. Investigations Initial investigations should include full blood count and white cell differential, CRP, renal and liver function tests, urine dipstick, serum immunoglobulins with protein electrophoresis, and HIV testing. Additional microbiological tests, virology and imaging are required to identify the causal organism and localise the site of infection, as outlined in Box 4.7. If primary immune deficiency is suspected on the basis of initial investigations, more specialised tests should be considered, as summarised in Box 4.8. Management If an immune deficiency is suspected but has not yet been formally characterised, patients should not receive live vaccines because of the risk of vaccine-induced disease. Further management depends on the underlying cause and details are provided later. 4.6 Warning signs of primary immune deficiency* In children In adults ≥ 4 new ear infections within 1 year ≥ 2 new ear infections within 1 year ≥ 2 serious sinus infections within 1 year ≥ 2 new sinus infections within 1 year, in the absence of allergy ≥ 2 months on antibiotics with little effect Recurrent viral infections ≥ 2 pneumonias within 1 year ≥ 1 pneumonia per year for more than 1 year Failure of an infant to gain weight or grow normally Chronic diarrhoea with weight loss Recurrent deep skin or organ abscesses Recurrent deep skin or organ abscesses Persistent thrush in mouth or elsewhere on skin after infancy Persistent thrush or fungal infection on skin or elsewhere Need for intravenous antibiotics to clear infections Recurrent need for

intravenous antibiotics to clear infections ≥ 2 deep-seated infections such as sepsis, meningitis or cellulitis Infection with atypical mycobacteria A family history of primary immune deficiency A family history of primary immune deficiency *The presence of two or more of the above features may indicate the presence of an underlying primary immunodeficiency. © Jeffrey Modell Foundation.

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respectively. Imaging may be required to exclude occult infection. If these investigations provide no evidence of infection or another cause, then genetic analysis should be considered to confirm the diagnosis of a familial fever syndrome (p. 81). Negative genetic testing does not, however, entirely exclude a periodic fever syndrome. Management Symptomatic management with non-steroidal anti-inflammatory drugs (NSAIDs) should be initiated, pending the results of investigations. If the response to NSAIDs is inadequate, glucocorticoids can be tried, provided that infection has been excluded. If a familial fever syndrome is confirmed, then definitive therapy should be initiated, depending on the underlying diagnosis (p. 81).

leading to hypotension, and bronchoconstriction, as summarised in Box 4.9. It can be difficult to distinguish IgE-mediated anaphylaxis clinically from non-specific degranulation of mast cells on exposure to drugs, chemicals or other triggers where IgE is not involved, previously known as anaphylactoid reactions. Common triggers are shown in Box 4.10. Clinical assessment The clinical features of anaphylaxis and ‘anaphylactoid’ reactions are indistinguishable and are summarised in Figure 4.9. Several other conditions can mimic anaphylaxis and these are listed in Box 4.11. It is important to assess the severity of the reaction, and the time between allergen exposure and onset of symptoms provides Anaphylaxis Anaphylaxis is a potentially life-threatening, systemic allergic reaction characterised by circulatory collapse, bronchospasm, laryngeal stridor, often associated with angioedema, and urticaria. The risk of death is increased in patients with pre-existing asthma, particularly if this is poorly controlled, and in situations where treatment with adrenaline (epinephrine) is delayed. Aetiology Anaphylaxis occurs when an allergen binds to and cross-links membrane-bound IgE on mast cells in a susceptible individual, causing release of histamine, tryptase and other vasoactive mediators from mast cells. These mediators have a variety of effects, including vasodilatation, increased capillary permeability 4.10 Common causes of systemic allergic reactions Anaphylaxis: IgE-mediated mast cell degranulation Foods • Peanuts • Tree nuts • Fish and shellfish • Milk • Eggs • Soy products Insect stings • Bee venom • Wasp venom Chemicals, drugs and other foreign proteins • Intravenous anaesthetic agents (suxamethonium) • Penicillin and other antibiotics • Latex Anaphylactoid: non-lgE-mediated mast cell degranulation Drugs • Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) • Opiates • Radiocontrast media Physical • Exercise • Cold Idiopathic • No cause is identified in 20% of patients with anaphylaxis 4.9 Clinical features of mast cell degranulation Mediator Biological effects Pre-formed and stored within granules Histamine Vasodilatation, chemotaxis, bronchoconstriction, increased capillary permeability and increased mucus secretion Tryptase Bronchoconstriction, activates complement C3 Eosinophil chemotactic factor Eosinophil chemotaxis Neutrophil chemotactic factor Neutrophil chemotaxis Synthesised on activation of mast cells Leukotrienes Increase vascular permeability, chemotaxis, mucus secretion and smooth muscle contraction Prostaglandins Bronchoconstriction, platelet aggregation and vasodilatation Thromboxanes Bronchoconstriction Platelet-activating factor Bronchoconstriction, chemotaxis of eosinophils and neutrophils Fig. 4.9 Clinical manifestations of anaphylaxis. In this example, the response is to an insect sting containing venom to which the patient is allergic. This causes release of histamine and other vasoactive mediators, which cause the characteristic features of anaphylaxis that are illustrated. Itching of palms, soles of feet and genitalia Feeling of impending doom, loss of consciousness Conjunctival injection Flushing Sweating Hypotension Urticaria Wheeze, bronchoconstriction Angioedema of lips and mucous membrane Abdominal pain Diarrhoea Cardiac arrhythmias Laryngeal obstruction

Stridor Wasp sting

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Prevents hypoxia Administer adrenaline (epinephrine) promptly: 0.3–1.0 mL 1 : 1000 solution IM in adults Repeat at 5–10-min intervals if initial response is inadequate Intramuscular route important because of peripheral vasoconstriction Acts within minutes Increases blood pressure Reverses bronchospasm Administer antihistamines: Chlorphenamine 10 mg IM or slow IV injection Blocks effect of histamine on target cells Administer glucocorticoids: Hydrocortisone 200 mg IV Reduces cytokine release Prevents rebound symptoms in severe cases Provide supportive treatment: Nebulised β2-agonists IV fluids Oxygen Reverses bronchospasm Restores plasma volume Reverses hypoxia (IM = intramuscular; IV = intravenous) 4.11 Differential diagnosis of anaphylaxis Causes of hypotension • Vasovagal syncope • Cardiac arrhythmia • Cardiogenic shock Causes of respiratory distress • Status asthmaticus • Pulmonary embolus Causes of laryngeal obstruction • C1 inhibitor deficiency • Idiopathic angioedema Causes of generalised flushing • Systemic mastocytosis • Carcinoid syndrome • Phaeochromocytoma

antifungal agents. The most important examples are illustrated in Figure 4.10 and discussed below. Chronic granulomatous disease This is caused by mutations in genes that encode NADPH oxidase enzymes, which results in failure of oxidative killing. The defect leads to susceptibility to catalase-positive organisms such as Staphylococcus aureus, Burkholderia cenocepacia and Aspergillus. Intracellular killing of mycobacteria in macrophages is also impaired. Infections most commonly involve the lungs, lymph nodes, soft tissues, bone, skin and urinary tract, and are characterised histologically by granuloma formation. Most cases are X-linked (p. 48). Leucocyte adhesion deficiencies These very rare disorders of phagocyte migration occur because of failure to express adhesion molecules on the surface of leucocytes, resulting in their inability to exit the blood stream. The most common cause is loss-of-function mutations affecting the ITGB2 gene, which encodes the integrin β-2 chain, a component of the adhesion molecule LFA1. They are characterised by recurrent bacterial infections but sites of infection lack evidence of neutrophil infiltration, such as pus formation. Peripheral blood neutrophil counts may be very high during acute infection because of the failure of mobilised neutrophils to exit blood vessels. Specialised tests show reduced or absent expression of adhesion molecules on neutrophils. Immune deficiency The consequences of immune deficiency include recurrent infection, autoimmunity as a result of immune dysregulation, and increased susceptibility to malignancy, especially malignancy driven by viral infections such as Epstein–Barr virus. Immune deficiency may arise through intrinsic defects in immune function but is much more commonly due to secondary causes, including infection, drug therapy, malignancy and ageing. This section gives an overview of primary immune deficiencies. More than a hundred such deficiencies have been described, most of which are genetically determined and present in childhood or adolescence. The presentation of immune deficiency depends on the component of the immune system that is defective (see Box 4.5). There is considerable overlap and redundancy in the immune network, however, and some diseases do not fall easily into this classification. Primary phagocyte deficiencies Primary phagocyte deficiencies typically present with recurrent bacterial and fungal infections, which may involve unusual sites. Affected patients require aggressive management of infections, including intravenous antibiotics and surgical drainage of abscesses, and long-term prophylaxis with antibacterial and Fig. 4.10 Normal phagocyte function and mechanisms of primary phagocyte deficiency. Under normal circumstances, neutrophils traverse the endothelium to enter tissues by the cell surface molecule lymphocyte function-associated antigen 1 (LFA1), which binds to intercellular adhesion molecule 1

(ICAM1) on endothelium. In order for macrophages to engulf and kill microorganisms, they need to be activated by cytokines and also require nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to generate free radicals. Primary phagocyte deficiencies can occur as the result of leucocytes being unable to traverse endothelium due to defects in LFA1, because of mutations in cytokines or their receptors, or because of defects in NADPH oxidase. (IFN-γ = interferon-gamma; IL = interleukin) Neutrophils traverse endothelium through binding of LFA1 to ICAM1 Normal Primary phagocyte deficiency Leucocyte adhesion deficiency Neutrophils cannot traverse endothelium due to defects in ITGB2, a component of LFA1 Chronic granulomatous disease Cytokines activate macrophages Destruction of microorganisms through NADPH oxidase-mediated killing Cytokine defects LFA1 IL-23 IL-12 IFN-γ Phagocytes cannot be activated due to defects in cytokines or their receptors Microorganisms cannot be destroyed in lysosomes due to NADPH oxidase deficiency IL-23 IL-12 IFN-γ IL-23 IL-12 IFN-γ ICAM1

78 • CLINICAL IMMUNOLOGY Management Patients with complement deficiencies should be vaccinated with meningococcal, pneumococcal and H. influenzae B vaccines to boost their adaptive immune responses. Lifelong prophylactic penicillin to prevent meningococcal infection is recommended, as is early access to acute medical assessment in the event of infection. Patients should also carry a MedicAlert or similar. At-risk family members should be screened for complement deficiencies with functional complement assays. The management of C1 esterase deficiency is discussed elsewhere. Primary antibody deficiencies Primary antibody deficiencies occur as the result of abnormalities in B-cell function, as summarised in Figure 4.11. They are characterised by recurrent bacterial infections, particularly of the respiratory and gastrointestinal tract. The most common causative organisms are encapsulated bacteria such as Streptococcus pneumoniae and H. influenzae. These disorders usually present in infancy, when the protective benefit of placental transfer of maternal immunoglobulin has waned. The most important causes are discussed in more detail below. X-linked agammaglobulinaemia This rare X-linked disorder (p. 48) is caused by mutations in the BTK gene, which encodes Bruton tyrosine kinase, a signalling protein that is required for B-cell development. Affected males present with severe bacterial infections during infancy. There is a marked reduction in B-cell numbers and immunoglobulin levels are low or undetectable. Management is with immunoglobulin replacement therapy and antibiotics to treat infections. Selective IgA deficiency This is the most common primary antibody deficiency, affecting 1 : 600 northern Europeans. Although IgA deficiency is usually asymptomatic with no clinical sequelae, about 30% of individuals experience recurrent mild respiratory and gastrointestinal infections. The diagnosis can be confirmed by measurement of IgA levels, which are low or undetectable (< 0.05 g/L). In some Defects in cytokines and cytokine receptors Mutations of the genes encoding cytokines such as IFN-γ, IL-12, IL-23 or their receptors result in failure of intracellular killing by macrophages, and affected individuals are particularly susceptible to mycobacterial infections. Complement pathway deficiencies Loss-of-function mutations have been identified in almost all the complement pathway proteins (see Fig. 4.4). While most complement deficiencies are rare, mannose-binding lectin deficiency is common and affects about 5% of the northern European population, many of whom are asymptomatic (see below). Clinical features Patients with deficiency in complement proteins can present in different ways. In some cases, the presenting feature is recurrent infection with encapsulated bacteria, particularly Neisseria spp., reflecting the importance of the membrane attack complex in defence against these organisms. However, genetic deficiencies of the classical complement pathway (C1, C2 and C4) also present with an increased risk of autoimmune disease, particularly SLE (p. 1034). Individuals

with mannose-binding lectin deficiency have an increased incidence of bacterial infections if subjected to an additional cause of immune compromise, such as premature birth or chemotherapy. The significance of this condition has been debated, however, since population studies have shown no overall increase in infectious disease or mortality in patients with this disorder. Deficiency of the regulatory protein Cl inhibitor is not associated with recurrent infection but causes recurrent angioedema (p. 87). Investigations Screening for complement deficiencies usually involves specialised functional tests of complement-mediated haemolysis. These are known as the CH50 (classical haemolytic pathway 50) and AP50 (alternative pathway 50) tests. If abnormal, haemolytic tests are followed by measurement of individual complement components. Fig. 4.11 B lymphocytes and primary antibody deficiencies (green boxes). (Ig = immunoglobulin) Failure of lymphocyte precursors: Severe combined immune deficiency Stem cells Lymphoid progenitors Bone marrow Failure of production of IgG antibodies: Common variable immune deficiency Specific antibody deficiency IgM-producing B cells Failure of B-cell maturation: X-linked agammaglobulinaemia Immature B cells IgG IgE IgA Plasma cells Failure of IgA production: Selective IgA deficiency

IgG level just prior to an infusion) within the normal range. This has been shown to minimise progression of end-organ damage and improve clinical outcome. Treatment may be self-administered and is life-long. Benefits of immunisation are limited because of the defect in IgG antibody production, and as with all primary immune deficiencies, live vaccines should be avoided. Primary T-lymphocyte deficiencies These are a group of diseases characterised by recurrent viral, protozoal and fungal infections (see Box 4.5). Many T-cell deficiencies are also associated with defective antibody production because of the importance of T cells in providing help for B cells. These disorders generally present in childhood. Several causes of T-cell deficiency are recognised. These are summarised in Figure 4.12 and discussed in more detail below. DiGeorge syndrome This results from failure of development of the third and fourth pharyngeal pouches, and is usually caused by a deletion of chromosome 22q11. The immune deficiency is accounted for by failure of thymic development; however, the immune deficiency can be very heterogeneous. Affected patients tend to have very low numbers of circulating T cells despite normal development in the bone marrow. It is associated with multiple developmental anomalies, including congenital heart disease, hypoparathyroidism, tracheo-oesophageal fistulae, cleft lip and palate. Bare lymphocyte syndromes These rare disorders are caused by mutations in a variety of genes that regulate expression of HLA molecules or their transport to the cell surface. If HLA class I molecules are affected, CD8+ lymphocytes fail to develop normally, while absent expression of HLA class II molecules affects CD4+ lymphocyte maturation. In addition to recurrent infections, failure to express HLA class I is associated with systemic vasculitis caused by uncontrolled activation of NK cells. Severe combined immune deficiency Severe combined immune deficiency (SCID) results from mutations in a number of genes that regulate lymphocyte development, with failure of T-cell maturation, with or without accompanying B- and NK-cell maturation. The most common cause is X-linked SCID, resulting from loss-of-function mutations in the interleukin-2 receptor gamma (IL2RG) gene. The gene product is a component of several interleukin receptors, including those for IL-2, IL-7 and IL-15, which are absolutely required for T-cell and NK development. This results in T-cell-negative, NK-cell-negative, patients, there is a compensatory increase in serum IgG levels. Specific treatment is generally not required. Common variable immune deficiency Common

variable immune deficiency (CVID) is characterised by low serum IgG levels and failure to make antibody responses to exogenous pathogens. It is a heterogeneous adult-onset primary immune deficiency of unknown cause. The presentation is with recurrent infections, and bronchiectasis is a recognised complication. Paradoxically, antibody-mediated autoimmune diseases, such as idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemia, are common in CVID. It is also associated with an increased risk of malignancy, particularly lymphoproliferative disease. Functional IgG antibody deficiency This is a poorly characterised condition resulting in defective antibody responses to polysaccharide antigens. Some patients are also deficient in the antibody subclasses IgG2 and IgG4, and this condition was previously called IgG subclass deficiency. There is overlap between specific antibody deficiency, IgA deficiency and CVID, and some patients may progress to a more global antibody deficiency over time. Investigations Serum immunoglobulins (Box 4.15) should be measured in conjunction with protein and urine electrophoresis to exclude secondary causes of hypogammaglobulinaemia, and B- and T-lymphocyte subsets should be measured. Specific antibody responses to known pathogens should be assessed by measuring IgG antibodies against tetanus, H. influenzae and S. pneumoniae (most patients will have been exposed to these antigens through infection or immunisation). If specific antibody levels are low, immunisation with the appropriate killed vaccine should be followed by repeat antibody measurement 6–8 weeks later; failure to mount a response indicates a significant defect in antibody production. These functional tests have generally superseded IgG subclass quantitation. Management Patients with antibody deficiencies generally require aggressive treatment of infections and prophylactic antibiotics may be indicated. An exception is deficiency of IgA, which usually does not require treatment. The mainstay of treatment in most patients with antibody deficiency is immunoglobulin replacement therapy. This is derived from plasma from hundreds of donors and contains IgG antibodies to a wide variety of common organisms. Replacement immunoglobulin may be administered either intravenously or subcutaneously, with the aim of maintaining trough IgG levels (the 4.15 Investigation of primary antibody deficiencies Serum immunoglobulin (Ig) concentrations Circulating lymphocyte numbers IgM IgG IgA IgE B cells T cells Test immunisation Selective IgA deficiency Normal Often elevated Absent Normal Normal Normal Not applicable* Common variable immune deficiency Normal or low Low Low or absent Low or absent Variable Variable No antibody response Specific antibody deficiency Normal Normal Normal Normal Normal Normal No antibody response to polysaccharide antigens *Test immunisation is not usually performed in IgA deficiency but some patients may have impaired responses.

 include lymphadenopathy, splenomegaly and a variety of other autoimmune diseases. Susceptibility to infection is increased because of the neutropenia. Secondary immune deficiencies Secondary immune deficiencies are much more common than primary immune deficiencies and occur when the immune system is compromised by external factors (Box 4.16). Common causes include infections, such as HIV and measles, and cytotoxic B-cell-positive SCID. Another cause is deficiency of the enzyme adenosine deaminase (ADA), which causes lymphocyte death due to accumulation of toxic purine metabolites intracellularly, resulting in T-cell-negative, B-cell-negative and NK-cell-negative SCID. The absence of an effective adaptive immune response causes recurrent bacterial, fungal and viral infections soon after birth. Bone marrow transplantation (BMT; p. 936) is the treatment option of first choice. Gene therapy has been approved for treatment of ADA deficiency when there is no suitable donor for BMT and is under investigation for a number of other causes of SCID. Investigations The principal tests for T-lymphocyte deficiencies are a total lymphocyte count and quantitation of individual lymphocyte

subpopulations. Serum immunoglobulins should also be measured. Second-line, functional tests of T-cell activation and proliferation may be indicated. Patients in whom T-lymphocyte deficiencies are suspected should be tested for HIV infection (p. 310). Management Patients with T-cell deficiencies should be considered for antiPneumocystis and antifungal prophylaxis, and require aggressive management of infections when they occur. Immunoglobulin replacement is indicated for associated defective antibody production. Stem cell transplantation (p. 936) or gene therapy may be appropriate in some disorders. Where a family history is known and antenatal testing confirms a specific defect, stem cell therapy prior to recurrent invasive infection can improve outcome. Autoimmune lymphoproliferative syndrome This rare disorder is caused by failure of normal lymphocyte apoptosis, most commonly due to mutations in the FAS gene, which encodes Fas, a signalling protein that regulates programmed cell death in lymphocytes. This results in massive accumulation of autoreactive T cells, which cause autoimmune-mediated anaemia, thrombocytopenia and neutropenia. Other features Fig. 4.12 T-lymphocyte function and dysfunction (green boxes). (HLA = human leucocyte antigen) Failure of lymphocyte precursors: Severe combined immune deficiency Stem cells Lymphoid progenitors Bone marrow Failure of expression of HLA molecules: Bare lymphocyte syndromes Failure of thymic development: DiGeorge syndrome Proliferation and maturation of thymocytes Export of mature T lymphocytes to periphery T-lymphocyte activation and effector function Apoptotic cell death Failure of apoptosis: Autoimmune lymphoproliferative syndromes Thymus Failure of cytokine production: Cytokine deficiencies 4.16 Causes of secondary immune deficiency Physiological • Ageing • Prematurity • Pregnancy Infection • HIV infection • Measles • Mycobacterial infection Iatrogenic • Immunosuppressive therapy • Antineoplastic agents • Glucocorticoids • Stem cell transplantation • Radiation injury • Antiepileptic agents Malignancy • B-cell malignancies including leukaemia, lymphoma and myeloma • Solid tumours • Thymoma Biochemical and nutritional disorders • Malnutrition • Renal insufficiency/dialysis • Diabetes mellitus • Specific mineral deficiencies (iron, zinc) Other conditions • Burns • Asplenia/hyposplenism

attacks. Standard anti-inflammatory drugs, including colchicine and glucocorticoids, are ineffective in suppressing the attacks but IL-1 inhibitors, such as anakinra, and TNF inhibitors, such as etanercept, may improve symptoms and can induce complete remission in some patients. TNF receptor-associated periodic syndrome TNF receptor-associated periodic syndrome (TRAPS) also known as Hibernian fever, is an autosomal dominant syndrome caused by mutations in the TNFRSF1A gene. The presentation is with recurrent attacks of fever, arthralgia, myalgia, serositis and rashes. Attacks may be prolonged for 1 week or more. During a typical attack, laboratory findings include neutrophilia, increased CRP and elevated IgA levels. The diagnosis can be confirmed by low serum levels of the soluble type 1 TNF receptor and by mutation screening of the TNFRSF1A gene. As in FMF, the major complication is amyloidosis, and regular screening for proteinuria is advised. Acute episodes respond to systemic glucocorticoids. Therapy with IL-1 inhibitors, such as anakinra, can be effective in preventing attacks. Amyloidosis Amyloidosis is the name given to a group of acquired and hereditary disorders characterised by the extracellular deposition of insoluble proteins. Pathophysiology Amyloidosis is caused by deposits consisting of fibrils of the specific protein involved, linked to glycosaminoglycans, proteoglycans and serum amyloid P. Protein accumulation may be localised or systemic, and the clinical manifestations depend on the organ(s) affected. Amyloid diseases are classified by the aetiology and type of

protein deposited (Box 4.18). Clinical features The clinical presentation may be with nephrotic syndrome (p. 395), cardiomyopathy (p. 538) or peripheral neuropathy (p. 1138). Amyloidosis should always be considered as a potential diagnosis in patients with these disorders when the cause is unclear. Investigations The diagnosis is established by biopsy, which may be of an affected organ, rectum or subcutaneous fat. The pathognomonic histological feature is apple-green birefringence of amyloid deposits when stained with Congo red dye and viewed under polarised light. Immunohistochemical staining can identify the type of amyloid fibril present. Quantitative scintigraphy with radiolabelled serum amyloid P is a valuable tool in determining the overall load and distribution of amyloid deposits. Management The aims of treatment are to support the function of affected organs and, in acquired amyloidosis, to prevent further amyloid deposition through treatment of the primary cause. When the latter is possible, regression of existing amyloid deposits may occur. Autoimmune disease Autoimmunity can be defined as the presence of immune responses against self-tissue. This may be a harmless phenomenon, identified and immunosuppressive drugs, particularly those used in the management of transplantation, autoimmunity and cancer. Physiological immune deficiency occurs at the extremes of life; the decline of the immune response in the elderly is known as immune senescence (Box 4.17). Management of secondary immune deficiency is described in the relevant chapters on infectious diseases (Ch. 11), HIV (Ch. 12), haematological disorders (Ch. 23) and oncology (Ch. 33). Periodic fever syndromes These rare disorders are characterised by recurrent episodes of fever and organ inflammation, associated with an elevated acute phase response (p. 74). Familial Mediterranean fever Familial Mediterranean fever (FMF) is the most common of the familial periodic fevers, predominantly affecting Mediterranean people, including Arabs, Turks, Sephardic Jews and Armenians. It results from mutations of the MEFV gene, which encodes a protein called pyrin that regulates neutrophil-mediated inflammation by indirectly suppressing the production of IL-1. FMF is characterised by recurrent painful attacks of fever associated with peritonitis, pleuritis and arthritis, which last for a few hours to 4 days and are associated with markedly increased CRP levels. Symptoms resolve completely between episodes. Most individuals have their first attack before the age of 20. The major complication of FMF is AA amyloidosis (see below). Colchicine significantly reduces the number of febrile episodes in 90% of patients but is ineffective during acute attacks. Mevalonic aciduria (mevalonate kinase deficiency) Mevalonate kinase deficiency, previously known as hyper-IgD syndrome, is an autosomal recessive disorder that causes recurrent attacks of fever, abdominal pain, diarrhoea, lymphadenopathy, arthralgia, skin lesions and aphthous ulceration. Most patients are from Western Europe, particularly the Netherlands and northern France. It is caused by loss-of-function mutations in the gene encoding mevalonate kinase, which is involved in the metabolism of cholesterol. It remains unclear why this causes an inflammatory periodic fever. Serum IgD and IgA levels may be persistently elevated, and CRP levels are increased during acute 4.17 Immune senescence • T-cell responses: decline, with reduced delayed-type hypersensitivity responses. • Antibody production: decreased for many exogenous antigens. Although autoantibodies are frequently detected, autoimmune disease is less common. • Response to vaccination: reduced; 30% of healthy older people may not develop protective immunity after influenza vaccination. • Allergic disorders and transplant rejection: less common. • Susceptibility to infection: increased; community-acquired pneumonia by threefold and urinary tract infection by 20-fold. Latent infections, including tuberculosis and herpes zoster, may be reactivated. • Manifestations of inflammation: may be absent, with lack of pyrexia or leucocytosis. • Secondary immune deficiency: common.

82 • CLINICAL IMMUNOLOGY those determining cytokine activity, co-stimulation (the expression of second signals required for full T-cell activation; see Fig. 4.7) and cell death. Many of the same gene variants underlie multiple autoimmune disorders, reflecting their common pathogenesis (Box 4.19). Even though some of these associations are the strongest that have been identified in complex genetic diseases, only by the presence of low-titre autoantibodies or autoreactive T cells. However, if these responses cause significant organ damage, autoimmune diseases occur. These are a major cause of chronic morbidity and disability, affecting up to 1 in 30 adults at some point during life. Pathophysiology Autoimmune diseases result from the failure of immune tolerance, the process by which the immune system recognises and accepts self-tissue. Central immune tolerance occurs during lymphocyte development, when T and B lymphocytes that recognise self-antigens are eliminated before they develop into fully immunocompetent cells. This process is most active in fetal life but continues throughout life as immature lymphocytes are generated. Some autoreactive cells inevitably evade deletion and escape into the circulation, however, and are controlled through peripheral tolerance mechanisms. Peripheral immune tolerance mechanisms include the suppression of autoreactive cells by regulatory T cells; the generation of functional hyporesponsiveness (anergy) in lymphocytes that encounter antigen in the absence of the co-stimulatory signals that accompany inflammation; and cell death by apoptosis. Autoimmune diseases develop when selfreactive lymphocytes escape from these tolerance mechanisms. Multiple genetic and environmental factors contribute to the development of autoimmune disease. Autoimmune diseases are much more common in women than in men, for reasons that remain unclear. Many are associated with genetic variations in the HLA loci, reflecting the importance of HLA genes in shaping lymphocyte responses. Other important susceptibility genes include 4.19 Association of specific gene polymorphisms with autoimmune diseases Gene Function Diseases HLA complex Key determinants of antigen presentation to T cells Most autoimmune diseases PTPN22 Regulation of T- and B-cell receptor signalling Rheumatoid arthritis, type 1 diabetes, systemic lupus erythematosus CTLA4 Important co-stimulatory molecule that transmits inhibitory signals to T cells Rheumatoid arthritis, type 1 diabetes IL23R Cytokine-mediated control of T cells Inflammatory bowel disease, psoriasis, ankylosing spondylitis TNFRSF1A Control of tumour necrosis factor network Multiple sclerosis ATG5 Autophagy Systemic lupus erythematosus 4.18 Causes of amyloidosis Disorder Pathological basis Predisposing conditions Other features Acquired systemic amyloidosis Reactive (AA) amyloidosis (p. 81) Increased production of serum amyloid A as part of prolonged or recurrent acute inflammatory response Chronic infection (tuberculosis, bronchiectasis, chronic abscess, osteomyelitis) Chronic inflammatory diseases (untreated rheumatoid arthritis, familial Mediterranean fever) 90% of patients present with non-selective proteinuria or nephrotic syndrome Light chain amyloidosis (AL) Increased production of monoclonal light chain Monoclonal gammopathies, including myeloma, benign gammopathies and plasmacytoma Restrictive cardiomyopathy, peripheral and autonomic neuropathy, carpal tunnel syndrome, proteinuria, spontaneous purpura, amyloid nodules and plaques Macroglossia occurs rarely but is pathognomonic Prognosis is poor Dialysis-associated (Aβ2M) amyloidosis Accumulation of circulating β2-microglobulin due to failure of renal catabolism in kidney failure Renal dialysis Carpal tunnel syndrome, chronic arthropathy and pathological fractures secondary to amyloid bone cyst formation Manifestations occur 5–10 years after the start of dialysis Senile systemic amyloidosis Normal transthyretin protein deposited in tissues Age > 70 years Feature of normal ageing (affects

> 90% of 90-year-olds) Usually asymptomatic Hereditary systemic amyloidosis 20 forms of hereditary systemic amyloidosis Production of protein with an abnormal structure that predisposes to amyloid fibril formation. Most commonly due to mutations in transthyretin gene Autosomal dominant inheritance Peripheral and autonomic neuropathy, cardiomyopathy Renal involvement unusual 10% of gene carriers are asymptomatic throughout life

Investigations Autoantibodies Many autoantibodies have been identified and are used in the diagnosis and monitoring of autoimmune diseases, as discussed elsewhere in this book. Antibodies can be quantified either by titre (the maximum dilution of the serum at which the antibody can be detected) or by concentration in standardised units using an enzyme-linked immunosorbent assay (ELISA) in which the antigen is used to coat microtitre plates to which the patient's serum is added (Fig. 4.13A). Qualitative tests are also employed for antinuclear antibodies in which the pattern of nuclear staining is recorded (Fig. 4.13B). they have very limited predictive value and are generally not useful in determining management of individual patients. Several environmental factors may be associated with autoimmunity in genetically predisposed individuals, including infection, cigarette smoking and hormone levels. The most widely studied of these is infection, as occurs in acute rheumatic fever following streptococcal infection or reactive arthritis following bacterial infection. Several mechanisms have been invoked to explain the autoimmunity that occurs after an infectious trigger. These include crossreactivity between proteins expressed by the pathogen and the host (molecular mimicry), such as Guillain–Barré syndrome and Campylobacter infection (p. 1140); release of sequestered antigens from tissues that are damaged during infections that are not usually visible to the immune system; and production of inflammatory cytokines that overwhelm the normal control mechanisms that prevent bystander damage. Occasionally, autoimmune disease may be an adverse effect of drug treatment. For example, metabolic products of the anaesthetic agent halothane can bind to liver enzymes, resulting in a structurally novel protein that is recognised as a foreign antigen by the immune system. This can provoke the development of autoantibodies and activated T cells, which can cause hepatic necrosis. Clinical features The clinical presentation of autoimmune disease is highly variable. Autoimmune diseases can be classified by organ involvement or by the predominant mechanism responsible for tissue damage. The Gell and Coombs classification of hypersensitivity is the most widely used, and distinguishes four types of immune response that result in tissue damage (Box 4.20). • Type I hypersensitivity is relevant in allergy but is not associated with autoimmune disease. • Type II hypersensitivity causes injury to a single tissue or organ and is mediated by specific autoantibodies. • Type III hypersensitivity results from deposition of immune complexes, which initiates activation of the classical complement cascade, as well as recruitment and activation of phagocytes and CD4+ lymphocytes. The site of immune complex deposition is determined by the relative amount of antibody, size of the immune complexes, nature of the antigen and local haemodynamics. Generalised deposition of immune complexes gives rise to systemic diseases such as SLE. • Type IV hypersensitivity is mediated by activated T cells and macrophages, which together cause tissue damage. 4.20 Gell and Coombs classification of hypersensitivity diseases Type Mechanism Example of disease in response to exogenous agent Example of autoimmune

disease Type I Immediate hypersensitivity IgE-mediated mast cell degranulation Allergic disease None described Type II Antibody-mediated Binding of cytotoxic IgG or IgM antibodies to antigens on cell surface causes cell killing ABO blood transfusion reaction Hyperacute transplant rejection Autoimmune haemolytic anaemia Idiopathic thrombocytopenic purpura Goodpasture's disease Type III Immune complex-mediated IgG or IgM antibodies bind soluble antigen to form immune complexes that trigger classical complement pathway activation Serum sickness Farmer's lung Systemic lupus erythematosus Cryoglobulinaemia Type IV Delayed type Activated T cells, and phagocytes Acute cellular transplant rejection Nickel hypersensitivity Type 1 diabetes Hashimoto's thyroiditis Fig. 4.13 Autoantibody testing. A Measurement of antibody levels by enzyme-linked immunosorbent assay (ELISA). The antigen of interest is used to coat microtitre plates to which patient serum is added. If autoantibodies are present, these bind to the target antigen on the microtitre plate. The amount of bound antibody is quantitated by adding a secondary antibody linked to an enzyme that converts a colourless substrate to a coloured one, which can be detected by a plate reader. B Qualitative analysis of autoantibodies by patterns of nuclear staining. In this assay, patient serum is added to cultured cells and a secondary antibody is added with a fluorescent label to detect any bound antibody. If antinuclear antibodies are present, they are detected as bright green staining. Different antinuclear antibody patterns may be seen in different types of connective tissue disease (Ch. 24). B (Nucleolar and Homogenous), Courtesy of Juliet Dunphy, Biomedical Scientist, Royal United Hospital Bath, previously of Bath Institute of Rheumatic Diseases, UK; (Speckled), Courtesy of Mr Richard Brown, Clinical Scientist in Immunology, Southwest Pathology Services, UK. Antibodies bind to target Target antigen Wash Detection of bound antibody Quantitate on plate reader Target antigen Wash Nucleolar Homogenous Speckled A B

 They comprise a range of disorders from mild to life-threatening and affect many organs. Atopy is the tendency to produce an exaggerated IgE immune response to otherwise harmless environmental substances, while an allergic disease can be defined as the clinical manifestation of this inappropriate IgE immune response. Pathophysiology The immune system does not normally respond to the many environmental substances to which it is exposed on a daily basis. In allergic individuals, however, an initial exposure to a normally harmless exogenous substance (known as an allergen) triggers the production of specific IgE antibodies by activated B cells. These bind to high-affinity IgE receptors on the surface of mast cells, a step that is not itself associated with clinical sequelae. However, re-exposure to the allergen binds to and cross-links membrane-bound IgE, which activates the mast cells, releasing a variety of vasoactive mediators (the early phase response; Fig. 4.14 and see Box 4.9). This type I hypersensitivity reaction forms the basis of an allergic reaction, which can range from sneezing and rhinorrhoea to anaphylaxis (Box 4.22). In some individuals, the early phase response is followed by persistent activation of mast cells, manifest by ongoing swelling and local inflammation. This is known as the late phase reaction and is mediated by mast cell metabolites, basophils, eosinophils and macrophages. Long-standing or recurrent allergic inflammation may give rise to a chronic inflammatory response characterised by a complex infiltrate of macrophages, eosinophils and T lymphocytes, in addition to mast cells and basophils. Once this has been established, inhibition of mast cell mediators with antihistamines is clinically ineffective in isolation. Mast cell activation may also be non-specifically triggered through other signals, such as neuropeptides, anaphylotoxins and bacterial peptides. The increasing incidence of allergic diseases is largely unexplained but one widely held theory is the 'hygiene hypothesis'. This proposes that infections in early life are critically important in

maturation of the immune response and bias the immune system against the development of allergies; the high prevalence Complement Measurement of complement components can be useful in the evaluation of immune complex-mediated diseases. Classical complement pathway activation leads to a decrease in circulating C4 levels and is often also associated with decreased C3 levels. Serial measurement of C3 and C4 is a useful surrogate measure of disease activity in conditions such as SLE. Cryoglobulins Cryoglobulins are antibodies directed against other immunoglobulins, forming immune complexes that precipitate in the cold. They can lead to type III hypersensitivity reactions, with typical clinical manifestations including purpuric rash, often of the lower extremities, arthralgia and peripheral neuropathy. Cryoglobulins are classified into three types, depending on the properties of the immunoglobulin involved (Box 4.21). Testing for cryoglobulins requires the transport of a serum specimen to the laboratory at 37°C. Cryoglobulins should not be confused with cold agglutinins; the latter are autoantibodies specifically directed against the I/i antigen on the surface of red cells, which can cause intravascular haemolysis in the cold (p. 950). Management The management of autoimmune disease depends on the organ system involved and further details are provided elsewhere in this book. In general, treatment of autoimmune diseases involves the use of glucocorticoids and immunosuppressive agents, which are increasingly used in combination with biologic agents targeting disease-specific cytokines and their receptors. Not all conditions require immune suppression, however. For example, the management of coeliac disease involves dietary gluten withdrawal, while autoimmune hypothyroidism requires appropriate thyroxine supplementation. Allergy Allergic diseases are a common and increasing cause of illness, affecting between 15% and 20% of the population at some time. 4.21 Classification of cryoglobulins Type I Type II Type III Immunoglobulin (Ig) isotype and specificity Isolated monoclonal IgM paraprotein with no particular specificity Immune complexes formed by monoclonal IgM paraprotein directed towards constant region of IgG Immune complexes formed by polyclonal IgM or IgG directed towards constant region of IgG Prevalence 25% 25% 50% Disease association Lymphoproliferative disease, especially Waldenström macroglobulinaemia (p. 966) Infection, particularly hepatitis C; lymphoproliferative disease Infection, particularly hepatitis C; autoimmune disease, including rheumatoid arthritis and systemic lupus erythematosus Symptoms Hyperviscosity: Raynaud’s phenomenon Acrocyanosis Retinal vessel occlusion Arterial and venous thrombosis Small-vessel vasculitis: Purpuric rash Arthralgia Neuropathy Cutaneous ulceration, hepatosplenomegaly, glomerulonephritis, Raynaud’s phenomenon Small-vessel vasculitis: Purpuric rash, arthralgia Cutaneous ulceration Hepatosplenomegaly, glomerulonephritis Raynaud’s phenomenon Protein electrophoresis Monoclonal IgM paraprotein Monoclonal IgM paraprotein No monoclonal paraprotein Rheumatoid factor Negative Strongly positive Strongly positive Complement Usually normal Decreased C4 Decreased C4 Serum viscosity Raised Normal Normal

of insect venom frequently stimulates the production of IgE antibodies, and thus may be followed by allergic reactions to single stings. Allergic IgE-mediated reactions vary from mild to life-threatening. Antigen-specific immunotherapy (desensitisation; see below) with bee or wasp venom can reduce the incidence of recurrent anaphylaxis from 50–60% to approximately 10% but requires up to 5 years of treatment. Peanut allergy Peanut allergy is the most common food-related allergy. More than 50% of patients present before the age of 3 years and some individuals react to their first known exposure to peanuts, thought to result from sensitisation to arachis oil in topical

creams. Peanuts are ubiquitous in the Western diet, and every year up to 25% of peanut-allergic individuals experience a reaction as a result of inadvertent exposure. Birch oral allergy syndrome This syndrome is characterised by the combination of birch pollen hay fever and local oral symptoms, including itch and angioedema, after contact with certain raw fruits, raw vegetables and nuts. Cooked fruits and vegetables are tolerated without difficulty. It is due to shared or cross-reactive allergens that are destroyed by cooking or digestion, and can be confirmed by skin prick testing using fresh fruit. Severe allergic reactions are unusual. Diagnosis When assessing a patient with a complaint of allergy, it is important to identify what the patient means by the term, as up to 20% of the UK population describe themselves as having a food allergy; in fact, less than 1% have true allergy, as defined by an IgE-mediated hypersensitivity reaction confirmed on double-blind challenge. The nature of the symptoms should be established and specific triggers identified, along with the predictability of a reaction, and the time lag between exposure to a potential allergen and onset of symptoms. An allergic reaction usually occurs within minutes of exposure and provokes predictable, reproducible symptoms such as angioedema, urticaria and wheezing. Specific enquiry should be made about other allergic symptoms, past and present, and about a family history of allergic disease. Potential allergens in the home and workplace should be identified. A detailed drug history should always be taken, including details of adherence to medication, possible adverse effects and the use of over-the-counter or complementary therapies. of allergic disease is the penalty for the decreased exposure to infection that has resulted from improvements in sanitation and health care. Genetic factors also contribute strongly to the development of allergic diseases. A positive family history is common in patients with allergy, and genetic association studies have identified a wide variety of predisposing variants in genes controlling innate immune responses, cytokine production, IgE levels and the ability of the epithelial barrier to protect against environmental agents. The expression of a genetic predisposition is complex; it is governed by environmental factors, such as pollutants and cigarette smoke, and the incidence of bacterial and viral infection. Clinical features Common presentations of allergic disease are shown in Box 4.22. Those that affect the respiratory system and skin are discussed in more detail in Chapters 17 and 29, respectively. Here we focus on general principles of the approach to the allergic patient, some specific allergies and anaphylaxis. Insect venom allergy Local non-IgE-mediated reactions to insect stings are common and may cause extensive swelling around the site lasting up to 7 days. These usually do not require specific treatment. Toxic reactions to venom after multiple (50–100) simultaneous stings may mimic anaphylaxis. In addition, exposure to large amounts Fig. 4.14 Type I (immediate) hypersensitivity response. A After an encounter with allergen, B cells produce immunoglobulin E (IgE) antibody against the allergen. B Specific IgE antibodies bind to circulating mast cells via high-affinity IgE cell surface receptors. C On re-encounter with allergen, the allergen binds to the IgE antibody-coated mast cells. This cross-linking of the IgE triggers mast cell activation with release of vasoactive mediators (see Box 4.9). B B B T T B B B B Allergen T and B cells IgE antibody IgE receptor Mast cell Histamine, tryptase and vasoactive peptides A B C 4.22 Clinical manifestations of allergy Dermatological • Urticaria • Atopic eczema if chronic • Allergic contact eczema • Angioedema Respiratory • Asthma • Atopic rhinitis Ophthalmological • Allergic conjunctivitis Gastrointestinal • Food allergy Other • Anaphylaxis • Drug allergy • Allergy to insect venom

 causes, including parasitic and helminth infections (pp. 299 and 288), lymphoma (p. 961), drug reactions and eosinophilic granulomatosis with polyangiitis (previously known as Churg–Strauss vasculitis; p. 1043). Normal total IgE levels do not exclude allergic

disease. Eosinophilia Peripheral blood eosinophilia is common in atopic individuals but lacks specificity. Eosinophilia of more than 20% or an absolute eosinophil count over 1.5 × 109/L should initiate a search for a non-atopic cause, such as eosinophilic granulomatosis with polyangiitis or parasitic infection (p. 928). Management Several approaches can be deployed in the management of allergic individuals, as discussed below. Avoidance of the allergen This is indicated in all cases and should be rigorously attempted, with the advice of specialist dietitians and occupational physicians if necessary. Antihistamines Antihistamines are useful in the management of allergy as they inhibit the effects of histamine on tissue H1 receptors. Long-acting, non-sedating preparations are particularly useful for prophylaxis. Glucocorticoids These are highly effective in allergic disease, and if used topically, adverse effects can be minimised. Sodium cromoglicate Sodium cromoglicate stabilises the mast cell membrane, inhibiting release of vasoactive mediators. It is effective as a prophylactic agent in asthma and allergic rhinitis but has no role in management of acute attacks. It is poorly absorbed and therefore ineffective in the management of food allergies. Antigen-specific immunotherapy This involves the sequential administration of increasing doses of allergen extract over a prolonged period of time. The mechanism of action is not fully understood but it is highly effective in the prevention of insect venom anaphylaxis and of allergic rhinitis secondary to grass pollen. The traditional route of administration is by subcutaneous injection, which carries a risk of anaphylaxis and should be performed only in specialised centres. Sublingual immunotherapy is also increasingly used. Clinical studies to date do not support the use of allergen immunotherapy for food hypersensitivity, although this is an area of active investigation. Omalizumab Omalizumab is a monoclonal antibody directed against IgE; it inhibits the binding of IgE to mast cells and basophils. It is licensed for treatment of refractory chronic spontaneous urticaria and also for severe persistent allergic asthma that has failed to respond to standard therapy (p. 572). The dose and frequency are determined by baseline IgE (measured before the start of treatment) and body weight. It is under investigation for allergic rhinitis but not yet approved for this indication. Adrenaline (epinephrine) Adrenaline given by injection in the form of a pre-loaded selfinjectable device can be life-saving in the acute management of anaphylaxis (see Box 4.12). Investigations Skin-prick tests Skin-prick testing is a key investigation in the assessment of patients suspected of having allergy. A droplet of diluted standardised allergen is placed on the forearm and the skin is superficially punctured through the droplet with a sterile lancet. Positive and negative control material must be included in the assessment. After 15 minutes, a positive response is indicated by a local weal and flare response 2 mm or more larger than the negative control. A major advantage of skin-prick testing is that patient can clearly see the results, which may be useful in gaining adherence to avoidance measures. Disadvantages include the remote risk of a severe allergic reaction, so resuscitation facilities should be available. Results are unreliable in patients with extensive skin disease. Antihistamines inhibit the magnitude of the response and should be discontinued for at least 3 days before testing; low-dose glucocorticoids do not influence test results. A number of other prescribed medicines can also lead to false-negative results, including amitriptyline and risperidone. Specific IgE tests An alternative to skin-prick testing is the quantitation of IgE directed against the suspected allergen. The sensitivity and specificity of specific IgE tests (previously known as radioallergosorbent tests, RAST) are lower than those of skin-prick tests. However, IgE tests may be very useful if skin testing is inappropriate, such as in patients taking antihistamines or those with severe skin disease or dermatographism. They can also be used to test for cross-reactivity – for example, with multiple insect venoms, where component-resolved diagnostics, using recombinant allergens, is increasingly used rather than crude allergen extract. Specific IgE tests can also be used post-mortem to identify allergens

responsible for lethal anaphylaxis. Supervised exposure to allergen Tests involving supervised exposure to an allergen (allergen challenge) are usually performed in specialist centres on carefully selected patients, and include bronchial provocation testing, nasal challenge, and food or drug challenge. These may be particularly useful in the investigation of occupational asthma or food allergy. Patients can be considered for challenge testing when skin tests and/or IgE tests are negative, as they can be helpful in ruling out allergic disease. Mast cell tryptase Measurement of serum mast cell tryptase is extremely useful in investigating a possible anaphylactic event. Ideally, measurements should be made at the time of the reaction following appropriate resuscitation, and 3 hours and 24 hours later. The basis of the test is the fact that circulating levels of mast cell degranulation products rise dramatically to peak 1–2 hours after a systemic allergic reaction. Tryptase is the most stable of these and is easily measured in serum. Serum total IgE Serum total IgE measurements are not routinely indicated in the investigation of allergic disease, other than to aid in the interpretation of specific IgE results, as false-positive specific IgEs are common in patients with atopy, who often have a high total IgE level. Although atopy is the most common cause of an elevated total IgE in developed countries, there are many other

diagnosis. If no obvious trigger can be identified, measurement of complement C4 is useful in differentiating hereditary and acquired angioedema from other causes. If C4 levels are low, further investigations should be initiated to look for evidence of C1 inhibitor deficiency. Management Management depends on the underlying cause. Angioedema associated with allergen exposure generally responds to antihistamines and glucocorticoids. Following acute management of angioedema secondary to drug therapy, drug withdrawal Angioedema Angioedema is an episodic, localised, non-pitting swelling of submucous or subcutaneous tissues. Pathophysiology The causes of angioedema are summarised in Box 4.23. It may be a manifestation of allergy or non-allergic degranulation of mast cells in response to drugs and toxins. In these conditions the main cause is mast cell degranulation with release of histamine and other vasoactive mediators. In hereditary angioedema, the cause is C1 inhibitor deficiency, which causes increased local release of bradykinin. Angiotensin-converting enzyme (ACE) inhibitor-induced angioedema also occurs as the result of increased bradykinin levels due to inhibition of its breakdown. Clinical features Angioedema is characterised by soft-tissue swelling that most frequently affects the face (Fig. 4.15) but can also affect the extremities and genitalia. Involvement of the larynx or tongue may cause life-threatening respiratory tract obstruction, and oedema of the intestinal mucosa may cause abdominal pain and distension. Investigations Differentiating the mechanism of angioedema is important in determining the most appropriate treatment. A clinical history of allergy or drug exposure can give clues to the underlying 4.23 Types of angioedema Allergic reaction to specific trigger Idiopathic angioedema Hereditary angioedema ACE-inhibitor associated angioedema Pathogenesis IgE-mediated degradation of mast cells Non-IgE-mediated degranulation of mast cells C1 inhibitor deficiency, with resulting increased local bradykinin concentration Inhibition of breakdown of bradykinin Key mediator Histamine Histamine Bradykinin Bradykinin Prevalence Common Common Rare autosomal dominant disorder 0.1–0.2% of patients treated with ACE inhibitors Clinical features Usually associated with urticaria History of other allergies common Follows exposure to specific allergen, in food, animal dander or insect venom Usually associated with urticaria May be triggered by physical stimuli such as heat, pressure or exercise Dermatographism common Occasionally associated with underlying infection or thyroid disease

Not associated with urticaria or other features of allergy Does not cause anaphylaxis May cause life-threatening respiratory tract obstruction Can cause severe abdominal pain Not associated with urticaria Does not cause anaphylaxis Usually affects the head and neck, and may cause life-threatening respiratory tract obstruction Can occur years after the start of treatment Investigations Specific IgE tests or skin-prick tests Specific IgE tests and skin-prick tests often negative Hypothyroidism should be excluded Complement C4 (invariably low in acute attacks) C1 inhibitor levels No specific investigations Treatment Allergen avoidance Antihistamines Antihistamines are mainstay of treatment and prophylaxis Unresponsive to antihistamines Anabolic steroids C1 inhibitor concentrate or icatibant for acute attacks ACE inhibitor should be discontinued ARBs should be avoided if possible unless there is a strong indication Associated drug reactions Specific drug allergies NSAIDs Opioids, radiocontrast media ACE inhibitors, ARBs (ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; NSAIDs = non-steroidal anti-inflammatory drugs) Fig. 4.15 Angioedema. This young man has hereditary angioedema. A Normal appearance. B During an acute attack. From Helbert M. Flesh and bones of immunology. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2006. B A

88 • CLINICAL IMMUNOLOGY should prevent further attacks, although ACE inhibitor-induced angioedema can continue for a limited period post drug withdrawal. Management of angioedema associated with C1 inhibitor deficiency is discussed below. Hereditary angioedema Hereditary angioedema (HAE), also known as inherited C1 inhibitor deficiency, is an autosomal dominant disorder caused by decreased production or activity of C1 inhibitor protein. This complement regulatory protein inhibits spontaneous activation of the classical complement pathway (see Fig. 4.4). It also acts as an inhibitor of the kinin cascade, activation of which increases local bradykinin levels, giving rise to local pain and swelling. Clinical features The angioedema in HAE may be spontaneous or triggered by local trauma or infection. Multiple parts of the body may be involved, especially the face, extremities, upper airway and gastrointestinal tract. Oedema of the intestinal wall causes severe abdominal pain and many patients with undiagnosed HAE undergo exploratory laparotomy. The most important complication is laryngeal obstruction, often associated with minor dental procedures, which can be fatal. Episodes of angioedema are self-limiting and usually resolve within 48 hours. Patients with HAE generally present in adolescence but may go undiagnosed for many years. A family history can be identified in 80% of cases. HAE is not associated with allergic diseases and is specifically not associated with urticaria. Investigations Acute episodes are accompanied by low C4 levels; a low C4 during an episode of angioedema should therefore trigger further investigation. The diagnosis can be confirmed by measurement of C1 inhibitor levels and function. Management Severe acute attacks should be treated with purified C1 inhibitor concentrate or the bradykinin receptor antagonist icatibant. Anabolic steroids, such as danazol, can be used to prevent attacks and act by increasing endogenous production of complement proteins. Tranexamic acid can be helpful as prophylaxis in some patients. Patients can be taught to self-administer therapy and should be advised to carry a MedicAlert or similar. Acquired C1 inhibitor deficiency This rare disorder is clinically indistinguishable from HAE but presents in late adulthood. It is associated with autoimmune and lymphoproliferative diseases. Most cases are due to the 4.24 Immunological diseases in pregnancy Allergic disease • Maternal dietary restrictions during pregnancy or lactation: current evidence does not support these for prevention of allergic disease. • Breastfeeding for at least 4 months: prevents or delays the occurrence of atopic dermatitis, cow’s milk allergy and wheezing in early childhood, as compared with feeding formula milk containing intact cow’s milk protein. Autoimmune disease • Suppressed T-cell-mediated immune responses in

pregnancy: may suddenly reactivate post-partum. Some autoimmune diseases may improve during pregnancy but flare immediately after delivery. Systemic lupus erythematosus (SLE) is an exception, however, as it is prone to exacerbation in pregnancy or the puerperium. • Passive transfer of maternal antibodies: can mediate autoimmune disease in the fetus and newborn, including SLE, Graves' disease and myasthenia gravis. • Antiphospholipid syndrome (p. 977): an important cause of fetal loss, intrauterine growth restriction and pre-eclampsia. • HIV in pregnancy: see p. 326. 4.25 Classification of transplant rejection Type Time Pathological findings Mechanism Treatment Hyperacute rejection Minutes to hours Thrombosis, necrosis Pre-formed antibody to donor antigens results in complement activation (type II hypersensitivity) None – irreversible graft loss Acute cellular rejection 5–30 days Cellular infiltration CD4+ and CD8+ T cells (type IV hypersensitivity) Increase immunosuppression Acute vascular rejection 5–30 days Vasculitis Antibody and complement activation Increase immunosuppression Chronic allograft failure

> 30 days Fibrosis, scarring Immune and non-immune mechanisms Minimise drug toxicity, control hypertension and hyperlipidaemia development of autoantibodies to C1 inhibitor, but the condition can also be caused by autoantibodies that activate C1. Treatment of the underlying disorder may induce remission of angioedema. As with HAE, a low C4 is seen during acute episodes. Transplantation and graft rejection Transplantation provides the opportunity for definitive treatment of end-stage organ disease. The major complications are graft rejection, drug toxicity and infection consequent to immunosuppression. Transplant survival continues to improve, as a result of the introduction of less toxic immunosuppressive agents and increased understanding of the processes of transplant rejection. Stem cell transplantation and its complications are discussed on page 936. Transplant rejection Solid organ transplantation inevitably stimulates an aggressive immune response by the recipient, unless the transplant is between monozygotic twins. The type and severity of the rejection response is determined by the genetic disparity between the donor and recipient, the immune status of the host and the nature of the tissue transplanted (Box 4.25). The most important genetic determinant

Investigations Pre-transplantation testing HLA typing determines an individual's HLA polymorphisms and facilitates donor–recipient matching. Potential transplant recipients are also screened for the presence of anti-HLA antibodies. The recipient is excluded from receiving a transplant that carries these alleles. Donor–recipient cross-matching is a functional assay that directly tests whether serum from a recipient (which potentially contains anti-donor antibodies) is able to bind and/or kill donor lymphocytes. It is specific to a prospective donor–recipient pair and is done immediately prior to transplantation. A positive cross-match is a contraindication to transplantation because of the risk of hyperacute rejection. Post-transplant biopsy: C4d staining C4d is a fragment of the complement protein C4 (see Fig. 4.4). Deposition of C4d in graft capillaries indicates local activation of the classical complement pathway and provides evidence of antibody-mediated damage. This is useful in the early diagnosis of vascular rejection. Complications of

transplant immunosuppression Transplant recipients require indefinite treatment with immunosuppressive agents. In general, two or more immunosuppressive drugs are used in synergistic combination in order to minimise adverse effects (Box 4.26). The major complications of long-term immunosuppression are infection and malignancy. The risk of some opportunistic infections may be minimised through the use of prophylactic medication, such as ganciclovir for cytomegalovirus prophylaxis and trimethoprim–sulfamethoxazole for Pneumocystis prophylaxis. Immunisation with killed vaccines is appropriate, although the immune response may be curtailed. Live vaccines should not be given. is the difference between donor and recipient HLA proteins (p. 67). The extensive polymorphism of these proteins means that donor HLA antigens are almost invariably recognised as foreign by the recipient immune system, unless an active attempt has been made to minimise incompatibility. • Hyperacute rejection results in rapid and irreversible destruction of the graft (Box 4.25). It is mediated by pre-existing recipient antibodies against donor HLA antigens, which arise as a result of previous exposure through transplantation, blood transfusion or pregnancy. It is very rarely seen in clinical practice, as the use of screening for anti-HLA antibodies and pre-transplant cross-matching ensures the prior identification of recipient–donor incompatibility. • Acute cellular rejection is the most common form of graft rejection. It is mediated by activated T lymphocytes and results in deterioration in graft function. If allowed to progress, it may cause fever, pain and tenderness over the graft. It is usually amenable to increased immunosuppressive therapy. • Acute vascular rejection is mediated by antibody formed de novo after transplantation. It is more curtailed than the hyperacute response because of the use of intercurrent immunosuppression but it is also associated with reduced graft survival. Aggressive immunosuppressive therapy is indicated and physical removal of antibody through plasmapheresis may be indicated in severe causes. Not all post-transplant anti-donor antibodies cause graft damage; their consequences are determined by specificity and ability to trigger other immune components, such as the complement cascade. • Chronic allograft failure, also known as chronic rejection, is a major cause of graft loss. It is associated with proliferation of transplant vascular smooth muscle, interstitial fibrosis and scarring. The pathogenesis is poorly understood but contributing factors include immunological damage caused by subacute rejection, hypertension, hyperlipidaemia and chronic drug toxicity. 4.26 Immunosuppressive drugs used in transplantation Drug Mechanism of action Major adverse effects Anti-proliferative agents Azathioprine, mycophenolate mofetil Inhibit lymphocyte proliferation by blocking DNA synthesis May be directly cytotoxic at high doses Increased susceptibility to infection Leucopenia Hepatotoxicity Calcineurin inhibitors Ciclosporin, tacrolimus Inhibit T-cell signalling; prevent lymphocyte activation; block cytokine transcription Increased susceptibility to infection Hypertension Nephrotoxicity Diabetogenic (especially tacrolimus) Gingival hypertrophy, hirsutism (ciclosporin) Glucocorticoids Decrease phagocytosis and release of proteolytic enzymes; decrease lymphocyte activation and proliferation; decrease cytokine production; decrease antibody production Increased susceptibility to infection Multiple other complications (p. 670) Anti-thymocyte globulin (ATG) Antibodies to cell surface proteins deplete or block T cells Profound non-specific immunosuppression Increased susceptibility to infection Basiliximab Monoclonal antibody directed against CD25 (IL-2Rα chain), expressed on activated T cells Increased susceptibility to infection Gastrointestinal side-effects Belatacept Selectively inhibits T-cell activation through blockade of CTLA4 Increased susceptibility to infection and malignancy Gastrointestinal side-effects Hypertension Anaemia/leucopenia

 arise. The ability of the immune system to kill cancer cells effectively is influenced by tumour immunogenicity and specificity. Many cancer antigens are poorly

expressed and specific antigens can mutate, either spontaneously or in response to treatment, which can result in evasion of immune responses. In addition, the inhibitory pathways that are used to maintain self-tolerance and limit collateral tissue damage during antimicrobial immune responses can be co-opted by cancerous cells to evade immune destruction. Recognition and understanding of these immune checkpoint pathways has led to the development of a number of new treatments for cancers that are otherwise refractory to treatment. For example, antibodies to CTLA4, a co-stimulatory molecule normally involved in down-regulation of immune responses, have been licensed for refractory melanoma, and antibodies to PD1 (programmed cell death protein 1) are used in melanoma, non-small-cell lung cancer and renal cell carcinoma. Potential risks include the development of autoimmunity, reflecting the importance of these pathways in the control of self-tolerance. Further information allergy.org.au An Australasian site providing information on allergy, asthma and immune diseases. allergyuk.org UK site for patients and health-care professionals. anaphylaxis.org.uk Provides information and support for patients with severe allergies. info4pi.org A US site managed by the non-profit Jeffrey Modell Foundation, which provides extensive information about primary immune deficiencies. niaid.nih.gov National Institute of Allergy and Infectious Diseases: provides useful information on a variety of allergic diseases, immune deficiency syndromes and autoimmune diseases. The increased risk of malignancy arises because T-cell suppression results in failure to control viral infections associated with malignant transformation. Virus-associated tumours include lymphoma (associated with Epstein–Barr virus), Kaposi’s sarcoma (associated with human herpesvirus 8) and skin tumours (associated with human papillomavirus). Immunosuppression is also linked with a small increase in the incidence of common cancers not associated with viral infection (such as lung, breast and colon cancer), reflecting the importance of T cells in anticancer surveillance. Organ donation The major problem in transplantation is the shortage of organ donors. Cadaveric organ donors are usually previously healthy individuals who experience brainstem death (p. 211), frequently as a result of road traffic accidents or cerebrovascular events. Even if organs were obtained from all potential cadaveric donors, though, their numbers would be insufficient to meet current needs. An alternative is the use of living donors. Altruistic living donation, usually from close relatives, is widely used in renal transplantation. Living organ donation is inevitably associated with some risk to the donor and it is highly regulated to ensure appropriate appreciation of the risks involved. Because of concerns about coercion and exploitation, non-altruistic organ donation (the sale of organs) is illegal in most countries. Tumour immunology Surveillance by the immune system is critically important in monitoring and removing damaged and mutated cells as they

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