

Answer 11-3

(1) Red blood cells coated with anti-red blood cell antibodies bind to splenic macrophages via Fc receptors, inducing phagocytosis of the red blood cell by receptor-mediated endocytosis. (2) Red blood cells bound by anti-red blood cell antibodies fix complement, which causes deposition of C3b on the red blood cell surface. C3b then binds to the receptor CR1 on splenic macrophages, inducing red blood cell phagocytosis. (3) Anti-red blood cell antibody triggers the complement cascade and the formation of membrane-attack complexes on the red blood cell, leading to cell lysis.

Answer 11-4

Antibodies and complement bound to neutrophil surfaces do not impair the normal function of these cells. In addition, white blood cells are far less susceptible to the formation of membrane-attack complexes, owing to continual production of complement regulatory proteins in these nucleated cells. Hence, the mechanism that destroys the antibody-targeted neutrophils is phagocytosis by splenic macrophages via Fc receptors and the complement receptor CR1. Splenectomy would reduce the rate at which neutrophils are destroyed because splenic macrophages are the major site of antibody and complement-coated cell clearance.

Answer 11-5

First, endocrine glands synthesize tissue-specific proteins unique to that gland. These proteins are not normally found in primary lymphoid organs where lymphocyte maturation occurs. Hence, the population of T and B lymphocytes is not tolerant to some endocrine gland-specific proteins, and these self proteins are thus recognized as foreign antigens. Second, endocrine glands are highly vascularized because their products need to gain access to the circulation. This feature gives leukocytes relatively easy access to endocrine tissue.

Answer 11-6

Both Hashimoto's and Graves' diseases disrupt normal production of the thyroid hormones tri-iodothyronine (T3) and thyroxine (T4), derived from thyroglobulin in thyroid follicles. Formation of T3 and T4 requires engagement of the thyroid-stimulating hormone receptor (TSHR) with thyroid-stimulating hormone (TSH) secreted from the pituitary gland, a key step in the regulation of thyroid hormone production. This step malfunctions for these two diseases.

In Hashimoto's disease, anti-thyroid antigen antibodies and T_H1 effector cells are involved. Large numbers of lymphocytes take up residence in the gland tissue, establishing germinal centers that resemble those in lymph nodes. Eventually the thyroid tissue is destroyed and thyroid follicles are no longer able to respond to TSH and make T3 or T4, a condition called hypothyroidism.

Graves' disease, in contrast, results in hyperthyroidism. Anti-TSHR antibodies act agonistically mimicking TSH, even in the absence of TSH. The thyroid follicle is chronically overstimulated by these antibodies and overproduces T3 and T4. The effector T cells are of the T_H2 type and the absence of lymphocyte infiltration retains the thyroid gland in operable condition. Therefore T3 and T4, no longer regulated by TSH, are secreted continuously in excess of concentrations required by the body.

Answer 11-7

Hashimoto's and Graves' diseases are treated differently because, although they both affect the thyroid gland, they exert opposing effects on the production of thyroid hormones—inhibition and overproduction, respectively. Hashimoto's disease is treated by administering synthetic thyroid hormones orally to replace the deficiencies in T3 and T4. Graves' disease is treated either by suppressing thyroid function with inhibitory drugs, or by thyroidectomy combined with thyroid hormone replacement therapy.

Answer 11-8

- A. The negative selection of developing autoreactive T cells in the thymus.
- B. The underlying genetic defect is in a gene encoding a protein called AIRE (autoimmune regulator). This is a transcription factor that, when working normally, causes several hundreds

of proteins otherwise expressed only in particular peripheral tissues to be expressed by medullary epithelial cells in the thymus. This induces the negative selection of T cells specific for these proteins and their deletion from the T-cell repertoire. The T cells emerging from the thymus are therefore tolerant to a large number of antigens found primarily on organs and tissues elsewhere in the body. When AIRE is defective and these proteins are not expressed in the thymus, the population of naive T cells that develops will contain T cells reactive against these antigens of peripheral tissues.

Answer 11-9

These cells are called regulatory CD4 T cells (T_R). When activated by encounter with their corresponding self antigen they become able to suppress the activation of naive autoreactive T cells. This active suppression of autoreactive T cells in the periphery is now thought to be an important method of preventing autoimmune reactions.

Answer 11-10

- A. Genes of the HLA complex, specifically the HLA class I and class II genes. Associations with HLA class II genes are most common. Various alleles of these genes are associated with a higher or lower susceptibility to particular autoimmune diseases compared with the incidence of the diseases in the population as a whole.
- B. The polymorphic HLA genes encode the proteins that present peptide antigens to T cells. It has been proposed that particular alleles of these genes are associated with particular autoimmune diseases because of their ability to present the required peptide epitope(s) to autoreactive T cells. Associations with HLA class II genes are more common than those with HLA class I because CD4 T cells rather than CD8 T cells are most commonly involved in autoimmunity.

Answer 11-11

The condition is precipitated by food antigens—the gluten proteins in wheat, barley, and rye—which makes it similar to a hypersensitivity reaction. But, unlike other common food allergies, the condition does not involve sensitization to the antigen and production of IgE antibodies. Instead, the disease is considered to result from a loss of the normal oral tolerance to gluten. The inflammatory reaction in the gut could be caused both by the indirect effects of the reaction to gluten (as in a type IV hypersensitivity reaction) and by autoimmune reactions mounted against gut tissue antigens. As in a hypersensitivity reaction, T_H1 cells specific for peptides from the gluten proteins are found in the inflammatory lesions. However, autoantibodies against a tissue enzyme—tissue transglutaminase—are also produced.

Answer 11-12

- A. Molecular mimicry refers to the phenomenon in which a pathogen expresses an antigen that bears a chemical similarity to a host-cell antigen. Once pathogen-specific antibodies or effector T cells are generated, they have the potential to cross-react with self antigen.
- B. An autoimmune disease involving molecular mimicry is rheumatic fever. Infection with *Streptococcus pyogenes* (for example 'strep throat') results in the production of antibodies specific for the bacterial cell-wall proteins. These antibodies cross-react with chemically similar (but not identical) self antigen expressed on heart tissue. This is followed by complement activation and production of inflammatory mediators, which cause damage to heart tissue and valves and the formation of scar tissue, which can lead to cardiovascular complications later in life. This type of immunological aftermath can be avoided if antibiotics are administered early during infection.

Answer 11-13

- A. Epitope spreading is the phenomenon in which the immune response, having initially targeted a particular epitope on an antigen molecule, progressively involves other cross-reactive epitopes on the same molecule.

- B. Pemphigus foliaceus. Autoantibody production against the protein desmoglein, a component of desmosomes, initially involves epitopes that do not result in any tissue damage or symptoms. Only when additional desmoglein epitopes become involved, as a result of epitope spreading, does the autoimmune response cause damage to desmosomes and the resulting lesions in the skin (the disease pemphigus).

Chapter 12

Answer 12-1

- Inactivated virus vaccines are made of virus particles that are not able to replicate because they have been chemically or physically treated (for example, heat treatment) in a way that inactivates the nucleic acid. Examples: Salk polio vaccine, rabies vaccine, influenza vaccine.
- Live-attenuated virus vaccines are made of viruses that have lost their pathogenicity and ability to reproduce efficiently in human cells through mutations accumulated as a result of growing the virus in non-human cells. Examples: Sabin polio vaccine (oral), measles vaccine, mumps vaccine, yellow fever vaccine, rubella vaccine, varicella vaccine.
- Subunit vaccines are composed only of particular antigenic pathogen components known to induce protective immune responses. Recombinant DNA technology enables the production of antigenic proteins in the absence of other pathogen gene products. Examples: hepatitis A vaccine, hepatitis B vaccine, pertussis vaccine.
- Toxoid vaccines are made from chemically inactivated toxins purified from pathogenic bacteria. Toxin activity is eliminated but not antigenic activity, so an immune response is generated in the absence of pathological damage. Examples: diphtheria vaccine, tetanus vaccine.
- Conjugate vaccines are made by covalently coupling antigenic polysaccharide found in bacterial capsules to a carrier protein (often a toxoid). This converts the otherwise T-independent bacterial polysaccharide antigen into a T-dependent antigen. T cells respond to an epitope on the protein carrier, whereas B cells respond to epitopes on the polysaccharide portion of the conjugate. This ensures that T-cell help is provided to B cells making anti-capsule antibodies. Example: *Haemophilus influenzae* type B vaccine (HIB).

Answer 12-2

- Some potential antigens will evoke a very weak or no immune response when injected into an animal or human in their pure form. Immunogens, in contrast, are antigens that are able to evoke a strong immune response when introduced into an animal or human.
- Adjuvants are substances that when mixed with any antigen increase its immunogenicity. They are commonly used in experimental immunology and in vaccines. Adjuvants work by inducing a nonspecific antigen-independent inflammation, which helps to drive the immune response forward. Adjuvants delay the release of antigen at the injection site, and prevent its rapid clearance from the body, by converting soluble antigen into particulate material. The most effective adjuvants also activate Toll-like receptors on macrophages and tissue dendritic cells, which then produce inflammatory cytokines, chemokines, and co-stimulatory molecules (B7) that help drive the immune response to the antigen itself.
- The following adjuvants are used in humans: alum, a form of aluminum hydroxide; MF59, a squalene-oil-water emulsion; and bacterial components included as part of some vaccines, for example, whole *Bordetella pertussis* as part of the DTP (diphtheria, tetanus, and pertussis) vaccine.

Immune stimulatory complexes (ISCOMS) are non-toxic adjuvants that might one day be used in humans. They are composed of lipid micelles that fuse with plasma membranes and deliver proteins enclosed within the micelles to the

cytosol of antigen-presenting cells. Other powerful adjuvants, such as Freund's complete adjuvant, are not used in humans because of their adverse side-effects.

Answer 12-3

Live-attenuated virus vaccines are mutant viruses that can replicate, albeit inefficiently, in human cells, thus simulating conditions of a normal viral infection. The attenuated vaccine strains of virus have been obtained by growing the virus over many generations in non-human cells (for example, monkey cells), so that it acquires multiple mutations that allow it to replicate but prevent it from spreading in the human body and causing disease. When introduced into humans as a vaccine, there is small chance that some or all of the mutations may revert to the original nucleotide sequence, restoring the properties of the virulent strain of the virus. Very rarely, this occurs with the poliovirus used in the trivalent oral polio vaccine (TVOP) and, now that polio is very rare in the United States, this vaccine is no longer recommended and an inactivated polio virus vaccine is used instead.

The more rounds of replication the vaccine virus undergoes in the human host before being contained by the immune response, the greater is the potential for genetic reversion. This is why individuals who suffer from inherited or acquired immunodeficiencies should never receive live-attenuated virus vaccines.

Answer 12-4

Acute rejection is due chiefly to immune responses made by the recipient's T cells against HLA class I and II molecules of the graft that are different from those of the recipient and which the recipient's immune system perceives as 'foreign.' The differences can be due to the HLA molecules, the self-peptides they bind or both. Transplantation between identical twins and transplantation of autografts are the only situations where the graft and the recipient are genetically identical and there are no differences in either the HLA molecules or the bound peptides. In these situations graft rejection does not occur. Transplantation between donors and recipients who have identical HLA class I and II molecules, usually HLA-identical siblings, almost always involves differences in the peptides that are bound by the HLA molecules. These differences trigger peptide-specific alloreactive T cells to cause graft rejection through the direct pathway of allorecognition. Although it is possible to match donor and recipient for many HLA class I and II alleles, in practice most clinical transplants involve one or more mismatched HLA loci. For these differences in HLA type, alloreactive T-cell clones activated by either the direct or indirect pathway of allorecognition cause graft rejection. Destruction of the grafted organ is effected through a type IV delayed-type hypersensitivity response.

Answer 12-5

- The organ would be rejected immediately by the process of hyperacute rejection as a result of the presence in the recipient's blood of preformed antibodies against the A and B blood group antigens present on the tissues of the graft. Such antibodies are made early in life as a result of exposure to common bacteria that carry surface carbohydrates similar to those on human cells. A person of O blood group would have made antibodies against bacterial 'A' and 'B' antigens, because the person does not have these antigens on their own cells and is thus not tolerant to them. These preexisting anti-A and anti-B antibodies in the recipient's blood will immediately attack the endothelium of blood vessels throughout the transplant, which expresses the A and B blood group antigens. Blood vessels become occluded through thrombus formation. The graft is deprived of oxygen and becomes engorged with blood hemorrhaging from leaky blood vessels. Hyperacute rejection occurs almost immediately after transplantation and cannot be treated once it has started.
- Other examples of combinations that will induce hyperacute rejection: O recipient, A donor; O recipient, B donor; A recipient, B donor; B recipient, A donor; A recipient, AB donor; and B recipient, AB donor.

- C. A recipient's preformed antibodies against an HLA class I antigen expressed on the endothelial cells of the transplant can also cause hyperacute rejection. Such antibodies can be generated in pregnancies in which the fetus expresses a paternal HLA allotype different from the maternal HLA allotype. These antibodies can also arise from HLA-incompatible blood transfusions or previous transplants.
- D. Hyperacute rejection can be prevented by typing and cross-matching donor and recipient for the A,B,O blood groups and HLA antigens. The recipient's serum antibodies are assayed *in vitro* for their ability to bind to donor white blood cells.

Answer 12-6

- A. Class 1: Corticosteroids. Examples: hydrocortisone, prednisone.
Class 2: Cytotoxic drugs. Examples: azathioprine, cyclophosphamide, methotrexate.
Class 3: T-cell activation inhibitors. Examples: cyclosporin A, tacrolimus (FK506), rapamycin.
- B. Class 1: Side/toxic effects: fluid retention, weight gain, diabetes, bone demineralization, thinning of the skin.
Class 2: Side/toxic effects: nonspecifically prevent DNA replication in all mitotic cells causing, for example, diarrhea, hair loss. More specific effects are liver damage caused by azathioprine, and bladder damage caused by cyclophosphamide.
Class 3: Side/toxic effects: nephrotoxicity, suppression of B-cell and granulocyte activation.

Answer 12-7

Cyclosporin A prevents the production of IL-2 and its high-affinity receptor, and thus prevents the activation of T cells and their proliferation and differentiation. It acts by inactivating the protein calcineurin. Calcineurin is a serine/threonine protein phosphatase that is activated by the first part of the T-cell receptor pathway and that dephosphorylates the transcription factor NFAT. This modification is necessary for NFAT, which normally resides in the cytoplasm, to enter the nucleus and stimulate transcription of the genes for IL-2 and the IL-2 receptor α chain. Inactivation of calcineurin by cyclosporin thus prevents the production of IL-2 and its high-affinity receptor.

Answer 12-8

- A. Anti-CD3 MoAbs are often administered to patients to suppress T-cell activity when signs of graft rejection are observed. Because CD3 is expressed only on T lymphocytes, this therapy is extremely specific. Anti-CD3 antibodies cross-link CD3:T-cell receptor complexes, leading to a reduction in the number of these complexes on the cell surface and a reduction in the number of T cells in the circulation. Suppression of effector T-cell activity protects the graft.
- B. Mouse MoAbs are antigenic in species other than mice and stimulate anti-MoAb responses. Repeated doses will exacerbate this situation and lead to the formation and clearance of MoAb:anti-MoAb immune complexes before the antibody can bind to the T cells, thus rendering the mouse antibody ineffective. A type III hypersensitivity reaction resembling serum sickness can also result when small immune complexes are formed, that is, when MoAb levels exceed anti-MoAb levels. Hence, repeated doses are discouraged, and physicians must restrict this form of immunosuppressive therapy to one episode of rejection.

Answer 12-9

Matching HLA between donor and recipient will reduce undesirable and harmful allo reactions that may cause graft-versus-host disease (GVHD) when mature donor-derived T cells in transplanted bone marrow react against the recipient's alloantigens in tissues and organs. In addition, the thymic epithelium of the recipient, and thus recipient MHC molecules, will positively select a new T-cell repertoire derived from the donor bone marrow. Therefore, matching is

essential to ensure that the donor T cells are selected on the same MHC molecules that will be used to present foreign antigen during infection in peripheral lymphoid organs. Foreign antigen will be presented by donor-derived professional antigen-presenting cells. Failure to match MHC molecules between donor and recipient will result in the development of a useless T-cell repertoire in the host after transplantation.

Answer 12-10

- A. Graft-versus-host disease is caused by T cells in the transplanted bone marrow making an immune response against antigens on the recipient's tissues. This can happen even though donor and recipient are HLA matched, because there are proteins other than HLA antigens that can differ between people and provoke an immune response. Such antigens are known as minor histocompatibility antigens. In a bone marrow transplant from a female to a male, the minor histocompatibility antigens most likely to cause a problem are male-specific proteins (which are encoded on the Y chromosome) which a female's T cells will not be tolerant to and will see as 'foreign' or non-self.
- B. CD8 cytotoxic T cells. The proteins that act as minor histocompatibility antigens are mainly intracellular proteins. Intracellular proteins of the recipient's cells are processed into peptides by proteasomes as part of normal protein degradation and turnover. These peptides are transported into the endoplasmic reticulum and thus are eventually presented on the surface of the recipient's cells by HLA class I molecules. Any peptides that are different from those in the donor may be recognized as non-self by the donor's cytotoxic T cells, which recognize peptides bound to HLA class I molecules. The naive CD8 T cells in the bone marrow can be activated to effector status by the presentation of minor histocompatibility peptides by dendritic cells in secondary lymphoid organs.
As the brother and sister share HLA class I type, the sister's T cells will be able to recognize non-self peptides presented by her brother's HLA molecules.

Answer 12-11

- A. Tumor-specific antigens are antigens found exclusively on tumor cells and are not expressed by normal cells.
- B. They can originate as the result of: (1) mutations in normal genes in the tumor cell that cause changes in amino acid sequence that generate new epitopes; (2) the generation of hybrid genes through genetic recombination, with the consequent production of a new protein unique to the tumor cell; or (3) viral proteins expressed as a result of viral infection or integration in the host cell genome.
- C. Examples: Mucin-1 (MUC-1)—breast and pancreatic cancer; human papilloma virus—cervical carcinoma.

Answer 12-12

- A. Tumor-associated antigens are antigens expressed in tumor cells as well as some normal cells, but often at higher levels in tumor cells.
- B. They can originate from: (1) proteins involved in mitosis that are produced at higher concentrations because the cells are continually dividing; (2) proteins expressed during embryogenesis that have become deregulated and reactivated transcriptionally; or (3) proteins expressed continuously at high levels in tumor cells that are normally expressed at low levels or transiently.
- C. Examples: Melanoma Antigen Encoding -1 and -3 (MAGE-1 and MAGE-3)—melanoma, glioma, and breast cancer; cyclin-dependent kinase 4—melanoma.

Answer 12-13

First, the patient's tumor-specific T cells could be expanded *in vitro* to generate a large number of tumor-specific effector T cells. To achieve this, the patient's tumor-specific T cells would be co-cultured with

tumor antigen, antigen-presenting cells, and cytokines. Second, the patient's purified dendritic cells could be loaded with tumor antigen *in vitro* and then be placed back in the patient, where they would stimulate tumor-specific T cells *in vivo*. Both of these techniques require the tumor antigen to have been characterized and purified so that it can be used in the co-culture *in vitro*.

Answer 12-14

Tumor-specific MoAbs are useful tools for the oncologist because of their ability to home in on tumor cells *in vivo*. The size, location, and extent of metastasis can be evaluated. The MoAb can be coupled covalently to a radioactive tag (for example, iodine-131) that is detectable by diagnostic imaging equipment.

MoAbs can be used not only to identify and characterize tumors but also to target the tumor for destruction. This can occur through several different mechanisms. First, if MoAbs are coupled to radioisotopes (iodine-131 or yttrium-99), the tumor cell's DNA is damaged and the cell dies. Coupling MoAbs to cytotoxic drugs is another way of destroying tumor cells. Drugs coupled to antibodies are cleaved from their MoAb transporter only after they have bound to and been internalized by the tumor cell. Finally, alerting the host immune system to tumors coated with MoAb can lead to the destruction of tumors. MoAb bound to tumor cell surfaces will activate the classical complement pathway, which will induce opsonization by phagocytes, lead to the production of inflammatory mediators which will recruit additional phagocytes, and form membrane-attack complexes on tumor cell surfaces. NK cells can also participate in tumor eradication through antibody-dependent cell-mediated cytotoxicity (ADCC).

Glossary

$\alpha\beta$ T cells T cells that express an antigen receptor made up of α and β chains. This majority population of T cells includes all T cells that recognize peptide antigen presented by MHC class I and II molecules.

$\alpha\beta$ T-cell receptor *see* T-cell receptor

Acquired immune deficiency syndrome (AIDS) the disease caused by infection with the human immunodeficiency virus (HIV). It involves a gradual destruction of the CD4 T-cell population and increasing susceptibility to infection.

Acquired immunity *see* adaptive immunity

Activated dendritic cells *see* dendritic cells

Acute rejection rejection of transplanted cells, tissues, or organs that is due to a T-cell response stimulated by the transplant.

Acute-phase proteins plasma proteins made by the liver whose synthesis is rapidly increased in response to infection. They include mannose-binding lectin (MBL), C-reactive protein (CRP), and fibrinogen.

Acute-phase response a response of innate immunity that occurs soon after the start of an infection and involves the synthesis of acute-phase proteins by the liver and their secretion into the blood.

ADA *see* adenosine deaminase

Adaptive immune response the response of antigen-specific B and T lymphocytes to antigen, including the development of immunological memory.

Adaptive immunity the state of resistance to infection that is produced by the adaptive immune response.

ADCC *see* antibody-dependent cell-mediated cytotoxicity

Adenoids mucosa-associated secondary lymphoid tissues located in the nasal cavity.

Adenosine deaminase (ADA) enzyme involved in purine breakdown. Its absence leads to the accumulation of toxic purine nucleosides and nucleotides, resulting in the death of most developing lymphocytes within the thymus. The disease that results from a genetically determined lack of adenosine deaminase is called **adenosine deaminase deficiency**. Its symptoms are severe combined immunodeficiency.

Adjuvant substance used to enhance the adaptive immune response to any antigen. To exert its effect an adjuvant must be mixed with the antigen before injection or vaccination.

Afferent lymphatic vessels the several vessels that bring lymph draining from connective tissue into a lymph node en route to the blood.

Affinity a measure of the strength with which one molecule binds to another via a single binding site.

Affinity maturation the increase in affinity of the antigen-binding sites of antibodies for the antigen that occurs during the course of an adaptive immune response.

Agglutination the clumping together of particles, usually caused by antibody or some other multivalent binding molecule interacting with antigens on the surfaces of adjacent particles. Such particles are said to be **agglutinated**. When the particles are red blood cells, the

phenomenon is called hemagglutination. When they are white blood cells it is called leukoagglutination.

Agonist any molecule that binds to a receptor and causes it to function.

ALG *see* antilymphocyte globulin

Alleles the natural variants of a single gene.

Allelic exclusion in reference to antibody production, the case that, in a heterozygous individual, only one of the two C-region alleles at the immunoglobulin heavy-chain or light-chain loci is expressed in each B cell. In the B-cell population, for each locus roughly half of the cells express one allele and the remaining cells express the other.

Allergen an antigen that elicits hypersensitivity or allergic reactions. Allergens are usually innocuous proteins that do not inherently threaten the integrity of the body.

Allergic asthma disease caused by an allergic reaction to inhaled antigen, in which the bronchi constrict and the patient has difficulty breathing.

Allergic conjunctivitis allergic reactions in the conjunctiva of the eye, usually caused by airborne antigens.

Allergic reaction the result of a secondary immune response to an otherwise innocuous environmental antigen, or allergen. Allergic reactions can involve either antibodies or effector T cells.

Allergic rhinitis an allergic reaction in the nasal mucosa that causes runny nose, sneezing, and tears. It is also known as hay fever.

Allergy a state of hypersensitivity to a normally innocuous environmental antigen. It results from the interaction between the antigen and antibodies or T cells produced by earlier exposure to the same antigen.

Alloantibody antibody that is made by immunization of one member of a species with antigen derived from another member of the same species. Alloantibodies recognize antigens that are the result of allelic variation at polymorphic genes. Common types of alloantibody are those recognizing blood group antigens and HLA class I and class II molecules.

Alloantigen an antigen that differs between members of the same species, such as HLA molecules and blood group antigens. Alloantigens are determined by the different alleles of polymorphic genes.

Allogeneic describes two members of the same species who are genetically different.

Allograft a tissue graft made between genetically non-identical members of the same species.

Alloreaction an adaptive immune response made by one member of a species against an allogeneic antigen from another member of the same species.

Alloreactive T cell T cell in one member of a species that responds to an allogeneic antigen from another member of the same species.

Allotypes natural protein variants that are encoded by the alleles of a gene.

Alternative C3 convertase the C3 convertase of the alternative pathway of complement activation. It is composed of C3 bound to proteolytically active Bb (C3Bb) and cleaves C3 into C3a and C3b.

Alternative C5 convertase the C5 convertase of the alternative pathway of complement activation. It is composed of two molecules of C3b bound to Bb (C3b₂Bb) and cleaves C5 into C5a and C5b.

Alternative pathway of complement activation one of three pathways of complement activation. It is triggered by the presence of infection but does not involve antibody. *See also* classical pathway of complement activation; lectin pathway of complement activation.

Anaphylactic shock IgE-mediated allergic reaction to systemically administered antigen that causes circulatory collapse and suffocation due to tracheal swelling. Also called systemic anaphylaxis.

Anaphylactoid reactions reactions that are clinically similar to anaphylactic shock but do not involve IgE.

Anaphylatoxins complement fragments C5a, C4a, and C3a, which are produced during complement activation. They recruit fluid and inflammatory cells to sites of antigen deposition.

Anchor residues residues in MHC-binding peptides that interact with pockets in the peptide-binding groove on the MHC molecule. Peptides that bind to a given MHC allotype have the same or very similar anchor residues.

Anergy a state of non-responsiveness to antigen. People are said to be anergic when they cannot mount delayed-type hypersensitivity reactions on challenge with an antigen. T and B cells are said to be anergic when they cannot respond to their specific antigen.

Angioedema swelling of the skin as a result of IgE-mediated allergic reactions, which cause increased permeability of subcutaneous blood vessels with consequent leakage of fluid into the skin.

Antagonist any molecule that binds to a receptor and prevents its function.

Antibody the secreted form of the immunoglobulin made by a B cell.

Antibody repertoire the total variety of antibodies that a person can make.

Antibody-dependent cell-mediated cytotoxicity (ADCC) the killing of antibody-coated target cells by NK cells having the FcγRIII receptor (CD16) that recognizes the Fc region of the bound antibody.

Antigen originally defined as any molecule that binds specifically to an antibody, the term now also refers to any molecule that can produce peptides that bind specifically to a T-cell receptor. *See also* epitope.

Antigen-binding site the site on an immunoglobulin or T-cell receptor molecule that binds specific antigen.

Antigen presentation the display of antigen as peptide fragments bound to MHC molecules on the surface of cells. This is the form in which antigen is recognized by most T cells.

Antigen-presenting cells cells that express either MHC class I and/or MHC class II molecules and thus display complexes of MHC molecule and peptide antigen on their surfaces.

Antigen processing the intracellular degradation of proteins into peptides that bind to MHC molecules for presentation to T cells.

Antigen receptor for a B cell, the antigen receptor is its cell-surface immunoglobulin; for a T cell the antigen receptor is a rather similar molecule called the T-cell receptor. Each individual lymphocyte bears receptors of a single antigen specificity.

Antigenic determinant *see* epitope

Antigenic drift a process by which point mutations in influenza virus genes cause differences in the structure of viral surface antigens. This causes year-to-year antigenic differences in strains of influenza virus.

Antigenic shift a process by which influenza viruses reassort their segmented genomes and change their surface antigens radically. New viruses arising by antigenic shift are the usual cause of influenza pandemics.

Antilymphocyte globulin (ALG) a preparation of antibodies made by immunizing animals with human lymphocytes. It is used clinically to prevent rejection in organ transplantation.

Antiserum (plural **antisera**) the fluid component of clotted blood from an immune individual that contains antibodies against an antigen. An antiserum contains a heterogeneous collection of antibodies that bind the antigen.

Antithymocyte globulin (ATG) a preparation of antibodies made by immunizing animals with human thymocytes. It is used clinically to prevent rejection in organ transplantation.

AP-1 a family of transcription factors, some of which participate in lymphocyte activation.

APD *see* autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

APECED *see* autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

Apoptosis a mechanism of cell death in which the cells to be killed are induced to degrade themselves from within, in a tidy manner. Also called programmed cell death.

Appendix a gut-associated secondary lymphoid tissue located at the beginning of the colon.

Arthus reaction an immune reaction in the skin caused by the injection of antigen into the dermis. The antigen reacts with specific IgG antibodies in the extracellular spaces, activating complement and phagocytic cells to produce a local inflammatory response.

ATG *see* antithymocyte globulin

Atopic allergy (atopy) the genetically determined tendency of some people to produce IgE-mediated hypersensitivity reactions against innocuous substances.

Atopic dermatitis *see* eczema

Autoantibody an antibody produced by an individual against an antigen produced by their own body.

Autoantigen a self antigen, an antigenic component of the body that provokes an immune response by the individual's own immune system.

Autocrine describes a cytokine or other secreted molecule that acts on the same type of cell as the one that secreted it.

Autograft a graft of tissue made from one anatomical site to another on the same individual.

Autoimmune disease disease in which the pathology is caused by an immune response to normal components of healthy tissue.

Autoimmune hemolytic anemia a disease characterized by reduced numbers of red blood cells (anemia). The reduction is caused by autoantibodies that bind to surface antigens of red blood cells and destroy them.

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) an autoimmune disease caused by a lack of a protein called **autoimmune regulator (AIRE)**, which results in the production of T cells reactive against a number of tissues in the body. Also known as **autoimmune polyglandular disease (APD)**.

Autoimmune response an adaptive immune response directed at an antigenic component of the individual's own body.

Autoimmunity adaptive immunity specific for an antigenic component of the individual's own body.

Autologous describes cells, HLA molecules, and so on that derive from the individual in question.

Autologous bone marrow transplant a bone marrow transplant in which the donor and recipient are the same person.

Azathioprine an immunosuppressive drug that kills dividing cells. It is used in transplantation.

β_2 -microglobulin (β_2m) the invariant polypeptide that is common to all MHC class I molecules. Also called the light chain of MHC class I molecules.

B cells lymphocytes that are dedicated to making immunoglobulins and antibodies.

B-cell receptor the antigen receptor on B cells. Each B cell is programmed to make a single type of immunoglobulin. The cell-surface form of this immunoglobulin serves as the B-cell receptor for specific antigen. Associated in the membrane with the immunoglobulin are the signal transduction molecules $Ig\alpha$ and $Ig\beta$.

B-cell co-receptor a complex of the CD19, TAPA-1, and CR2 polypeptides that associates with the B-cell receptor and augments its response to specific antigen.

B-1 cells the minority population of B cells. They express the CD5 glycoprotein and make antibodies of broad specificities. They are also known as CD5 B cells.

B-2 cells the majority population of B cells. They do not express the CD5 glycoprotein and make antibodies of narrow specificities.

B7 molecules the **B7.1** and **B7.2** proteins, which are co-stimulatory molecules present on the surface of professional antigen-presenting cells.

B lymphocytes *see* **B cells**

Bacteria diverse prokaryotic microorganisms that are responsible for many infectious diseases of humans and other animals.

Balancing selection type of evolutionary selection that acts to maintain a variety of phenotypes (for example MHC isoforms) in a population.

BALT *see* **bronchial-associated lymphoid tissue**

Bare lymphocyte syndromes genetically determined diseases in which MHC class I or II molecules are not expressed on cells. They can be caused by various different regulatory gene defects, and their effect is severe immunodeficiency.

Basophil white blood cell present in small numbers in the blood; it is one of the three types of granulocyte. Basophils contain granules that stain with basic dyes.

Benign tumor a growth due to abnormal proliferation of cells that is localized and contained by epithelial barriers.

Bone marrow the tissue in the center of certain bones that is the major site of generation of all the cellular elements of blood (hematopoiesis).

Brambell receptor (FcRB) an Fc receptor that transports IgG across epithelia and has a structure resembling an MHC class I molecule.

Bronchial-associated lymphoid tissues (BALT) the lymphoid cells and organized lymphoid tissues in the respiratory tract.

Bronchiectasis chronic inflammation of the bronchioles of the lung.

C domain *see* **constant domain**

C region *see* **constant region**

C-reactive protein (CRP) an acute-phase protein that binds to phosphocholine, a surface constituent of various bacteria. CRP binds bacteria, opsonizing them for uptake by phagocytes.

C1 inhibitor (C1INH) a regulatory protein in plasma that inhibits the activity of activated complement component C1. C1INH deficiency causes the disease hereditary angioneurotic edema, in which spontaneous complement activation causes episodes of epiglottal swelling and suffocation.

C3 convertases proteolytic enzymes that are formed during complement activation and cleave complement component C3 to C3b and C3a, thereby enabling C3b to bond covalently to antigens. *See* **alternative C3 convertase**, **classical C3 convertase**.

C4-binding protein (C4BP) a regulatory protein in plasma that inactivates the classical C3 convertase by binding to C4b and displacing C2b.

C5 convertases proteolytic enzymes that are formed during complement activation and cleave complement component C5 to form C5a and C5b.

Calcineurin a cytosolic serine/threonine phosphatase that contributes to T-cell activation. The immunosuppressive drugs cyclosporin A and tacrolimus act by inhibiting calcineurin.

Calnexin a membrane protein in the endoplasmic reticulum that facilitates the folding of MHC molecules and other glycoproteins.

Calreticulin a soluble protein in the endoplasmic reticulum that is structurally related to calnexin and helps MHC molecules and other glycoproteins to fold properly.

CAM *see* **cell adhesion molecule**

Cancer diseases caused by abnormal and invasive cell proliferation.

Carcinogen chemical or physical agent that increases the risk of cancer.

Carcinoma cancer of epithelial cells.

Carrier foreign protein to which small non-immunogenic antigens, or haptens, can be coupled to render the hapten immunogenic. *In vivo*, self proteins can also serve as carriers if they are suitably modified by the hapten; this is important in allergy to drugs.

Caseation necrosis a form of necrosis seen in the center of some large granulomas. The term comes from the white cheesy appearance of the central necrotic area.

Catalytic antibody an antibody that binds an antigen, chemically changes it, and then releases it.

CCL2 a chemokine produced by activated T cells that attracts macrophages into a site of infection. Formerly known as macrophage chemotactic protein (MCP).

CCL21 a chemokine made by vascular endothelial cells and which is involved in extravasation of leukocytes. Formerly known as SLC.

CD2 an adhesion molecule of T cells that binds to the LFA-3 adhesion molecule of antigen-presenting cells. Also called LFA-2.

CD3 complex a complex of signaling molecules that associates with T-cell receptors. It consists of CD3 γ , δ , and ϵ chains, and ζ chains.

CD4 a cell-surface glycoprotein on some T cells that recognize antigens presented by MHC class II molecules. CD4 binds to MHC class II molecules on the antigen-presenting cell and acts as a co-receptor to augment the T cell's response to antigen.

CD4 T cells the subset of T cells that express the CD4 co-receptor and recognize peptide antigens presented by MHC class II molecules.

CD5 B cells *see* **B-1 cells**

CD8 a cell-surface glycoprotein on some T cells that recognize antigens presented by MHC class I molecules. CD8 binds to MHC class I molecules on the antigen-presenting cell and acts as a co-receptor to augment the T-cell's response to antigen.

CD8 T cells the subset of T cells that express the CD8 co-receptor and recognize peptide antigens presented by MHC class I molecules.

CD19 a component of the B-cell co-receptor.

CD21 another name for complement receptor 2 (CR2). It is a component of the B-cell receptor.

CD28 the low-affinity receptor on T cells that interacts with B7 co-stimulatory molecules to promote T-cell activation.

CD34 a vascular addressin expressed on high endothelial venules in lymph nodes, and which is involved in extravasation of white blood cells.

CD40 cell-surface glycoprotein on B cells whose interaction with **CD40 ligand** on T cells triggers B-cell proliferation.

CD81 a component of the B-cell receptor that is also a cellular receptor for hepatitis C virus. Also called TAPA-1.

CDR *see* **complementarity-determining regions**

Celiac disease inflammatory autoimmune disease of the gut mucosa caused by an immune response to the gluten proteins present in some cereals such as wheat.

Cell adhesion molecules (CAMs) cell-surface proteins that enable cells to bind to each other.

Cell-mediated immunity (cellular immunity) any adaptive immune response in which antigen-specific effector T cells dominate. It is defined operationally as all adaptive immunity that cannot be transferred to a naive recipient with serum antibody.

Central lymphoid tissues the anatomical sites of lymphocyte development. In humans, B lymphocytes develop in bone marrow, whereas T lymphocytes develop in the thymus. *See also* **primary lymphoid tissues**.

Central MHC the class III region of the MHC, located between the class I and II regions.

Centroblast large dividing B cell present in germinal centers. Somatic hypermutation occurs in centroblasts, and antibody-secreting and memory B cells derive from them.

Centrocyte nondividing B cell in germinal centers. Centrocytes have undergone isotype switching and somatic hypermutation.

Chediak-Higashi syndrome a genetic disease in which phagocytes malfunction. Their lysosomes fail to fuse properly with phagosomes, and killing of ingested bacteria is impaired.

Chemokines large group of small proteins involved in guiding white blood cells to sites where their functions are needed. They have a central role in inflammatory responses.

Chronic asthma a disease characterized by chronic inflammation of the airways and difficulty in breathing. Although probably initiated by exposure to an allergen, chronic asthma can be perpetuated in its absence.

Chronic granulomatous disease an immunodeficiency disease in which multiple granulomas form as a result of defective elimination of bacteria by phagocytic cells. It is caused by a defect in the NADPH oxidase system of enzymes, which generates the superoxide radical involved in bacterial killing.

Chronic rejection rejection of organ grafts that occurs years after

transplantation and is characterized by degeneration and occlusion of the blood vessels in the graft. It is caused by an antibody response to the HLA class I alloantigens of the graft.

Chronic thyroiditis an autoimmune disease that causes progressive destruction of the thyroid gland. Also called Hashimoto's thyroiditis or Hashimoto's disease.

Class I region the part of the major histocompatibility complex that contains the MHC class I heavy-chain genes.

Class II region the part of the major histocompatibility complex that contains the MHC class II α - and β -chain genes.

Class II-associated invariant chain peptide (CLIP) a peptide of variable length cleaved from the class II invariant chain by proteases in the endosomal pathway. It remains associated with the MHC class II molecule in an unstable form until it is removed by the HLA-DM protein.

Class III region a region of the major histocompatibility complex between the class I and II regions. Also known as the **central MHC**, it contains no genes for class I or II MHC molecules.

Class switching *see* **isotype switching****Class** *see* **isotype**

Classical C3 convertase a surface-associated serine protease of the classical pathway of complement activation. It is composed of the complement components C4b2a and cleaves C3 into C3a and C3b.

Classical C5 convertase C5-cleaving enzyme consisting of the complement fragments C4b, C2b, and C3b.

Classical pathway of complement activation one of three pathways of complement activation. It is activated by antibody bound to antigen, and involves complement components C1, C4, and C2 in the generation of the C3 and C5 convertases. *See also* **alternative pathway of complement activation**; **lectin pathway of complement activation**.

Clonal deletion the elimination of immature lymphocytes that bind to self antigens. Clonal deletion is the main mechanism that produces self-tolerance.

Clonal selection the central principle of adaptive immunity. It is the mechanism by which adaptive immune responses derive only from individual antigen-specific lymphocytes, which are stimulated by the antigen to proliferate and differentiate into antigen-specific effector cells.

Co-receptor a cell-surface protein that increases the sensitivity of an antigen receptor to its antigen. A co-receptor can accomplish this by increasing adhesive interactions between the interacting cells, and/or by enhancing signal transduction from the main receptor.

Co-stimulator molecule a molecule on an antigen-presenting cell that delivers signals to an interacting naive lymphocyte that are required in addition to the antigen-binding signal for the lymphocyte to respond. Co-stimulator molecules include the B7.1 and B7.2 proteins on professional antigen-presenting cells, which engage molecules CD28 and CTLA-4 on T cells. CD40 ligand serves a co-stimulatory role when it binds to CD40 on B cells.

Cognate interactions cell-cell interactions between B and T lymphocytes specific for the same antigen.

Collectins a family of calcium-dependent sugar-binding proteins or lectins containing collagen-like sequences. An example is mannose-binding lectin.

Combination therapy antiviral therapy (for HIV, for example) in which several antiviral drugs are used together to try and avoid the rapid generation of mutant viruses resistant to one of the drugs alone.

Combination vaccine vaccine that contains antigens derived from more than one pathogen and is designed to provide protection against more than one disease.

Common lymphoid progenitor stem cell that gives rise to all lymphocytes and is derived from a pluripotent hematopoietic stem cell.

Complement a set of plasma proteins that act in a cascade of reactions to attack extracellular forms of pathogens. As a result of complement activation, pathogens become coated with complement components, which can either kill the pathogen directly or cause its engulfment and destruction by phagocytes.

Complement activation the initiation by pathogens of a series of reactions involving the complement components of plasma, leading to the death and elimination of the pathogen. *See also* **alternative pathway of complement activation**; **classical pathway of complement activation**; **lectin pathway of complement activation**.

Complement control protein (CCP) modules family of structurally similar protein modules found in many of the proteins that regulate complement activity.

Complement receptors (CR) cell-surface proteins on various cell types that recognize and bind complement proteins bound to antigens. Complement receptors on phagocytes facilitate the phagocytic engulfment of pathogens coated with complement. Complement receptors include **CR1**, **CR2**, **CR3**, **CR4**, and the receptor for **C1q**.

Complement system *see* **complement**

Complementarity-determining regions (CDRs) the localized regions of immunoglobulin and T-cell receptor chains that determine the antigenic specificity and bind to the antigen. The CDRs are the most variable parts of the variable domains and are also called hypervariable regions.

Conformational epitopes epitopes on a protein antigen that are formed from several separate regions in the primary sequence of a protein brought together by protein folding. Antibodies that bind conformational epitopes bind only to native folded proteins. Also called **discontinuous epitopes**.

Conjugate vaccine a vaccine made from capsular polysaccharides bound to an immunogenic protein such as tetanus toxoid. The protein provides peptide epitopes that stimulate CD4 T cells to help B cells specific for the polysaccharide.

Constant domains (C domains) the constituent domains of the constant regions of immunoglobulin and T-cell receptor polypeptides.

Constant region (C region) the part of an immunoglobulin or T-cell receptor (or of its constituent polypeptide chains) that is of identical amino-acid sequence in molecules of the same isotype but different antigen-binding specificities.

Contact sensitivity a form of delayed-type hypersensitivity in which T cells respond to antigens that are introduced into the body by contact with the skin.

Corticosteroids compounds related to the steroid hormones produced in the adrenal cortex, such as cortisone. They suppress immune responses and are widely used as anti-inflammatory and immunosuppressive agents in medicine.

CR, CR1, CR2, CR3, CR4 *see* **complement receptors**

Cross-match testing a test used in blood typing and histocompatibility testing to determine whether donor and recipient have antibodies against each other's cells that might interfere with successful transfusion or transplantation.

CRP *see* **C-reactive protein**

Cryptic epitope antigenic determinant on a molecule that is normally

hidden from the immune system but becomes revealed under conditions of infection or inflammation.

CTLA-4 a high-affinity inhibitory receptor on T cells that interacts with B7 co-stimulatory molecules.

Cutaneous T-cell lymphoma a malignant growth of T cells that home to the skin. Also known as mycosis fungoides.

CXCL8 a chemokine involved in the extravasation of neutrophils. Formerly known as IL-8.

Cyclophilins family of cytoplasmic proteins that bind to the immunosuppressive drugs cyclosporin A and tacrolimus. The complex of drug and cyclophilin binds calcineurin and this prevents T-cell activation.

Cyclophosphamide an alkylating agent used as an immunosuppressive drug. It acts by killing rapidly dividing cells, including lymphocytes proliferating in response to antigen.

Cyclosporin A an immunosuppressive drug that specifically prevents T-cell activation and effector function. Also called cyclosporine.

Cytokines proteins made by cells that affect the behavior of other cells. Cytokines made by lymphocytes are often called lymphokines or interleukins (abbreviated IL). Cytokines bind to specific receptors on their target cells.

Cytotoxic CD8 T cells the subset of T cells that express the CD8 co-receptor and recognize peptide antigen presented by MHC class I molecules.

Cytotoxic T cells T cells that can kill other cells. Almost all cytotoxic T cells are CD8 T cells. Cytotoxic T cells are important in host defense against viruses and other cytosolic pathogens, because they recognize and kill the infected cells.

Cytotoxins proteins made by cytotoxic T cells that participate in the destruction of target cells. Perforins, granzymes or fragmentins, and granulysin are examples of cytotoxins.

Dark zone the part of a germinal center in secondary lymphoid tissue that contains dividing centroblasts.

Decay-accelerating factor (DAF) a cell-surface protein that prevents complement activation on human cells. DAF binds to C3 convertases of both the alternative and classical pathways of complement activation and, by displacing Bb and C2b respectively, prevents their action.

Degenerate binding specificity the type of antigen-binding specificity exhibited by MHC class I and II molecules, in which each MHC allotype can bind numerous peptides of different amino acid sequences.

Delayed-type hypersensitivity (DTH) a form of cell-mediated immunity elicited by antigen in the skin and mediated by CD4 T_H1 cells. It is called delayed-type hypersensitivity because the reaction appears hours to days after antigen is injected.

Dendritic cells professional antigen-presenting cells with a branched, dendritic morphology. They are the most potent stimulators of T-cell responses. Also known as interdigitating reticular cells, they are derived from the bone marrow and are distinct from the follicular dendritic cell that presents antigen to B cells. **Immature dendritic cells** take up and process antigens but cannot yet stimulate T cells. **Mature or activated dendritic cells** are present in secondary lymphoid tissues and are able to stimulate T cells.

Dendritic epidermal T cells (dETC) a specialized class of $\gamma\delta$ T cells found in the skin of mice and some other species, but not humans. All dETCs have the same $\gamma\delta$ T-cell receptor; their function is unknown.

Desensitization a therapeutic procedure in which an allergic individual is exposed to increasing doses of allergen with the goal of inhibiting their allergic reactions. It probably works by shifting the balance between CD4 T_H1 and T_H2 cells and thus changing the antibody produced from IgE to IgG.

Diapedesis the movement of white blood cells from the blood across blood vessel walls into tissues.

DiGeorge syndrome a recessive genetic immunodeficiency disease in which thymic epithelium fails to develop.

Diphtheria toxin the toxin secreted by the bacterium *Corynebacterium diphtheriae*, the cause of diphtheria, which causes the disease symptoms. The diphtheria vaccine consists of an inactive form of the toxin called diphtheria toxoid.

Direct pathway of allorecognition type of alloreactive response in which T cells of the recipient of a transplant are stimulated by direct interaction of their receptors with the allogeneic HLA molecules expressed by dendritic cells from the donor, present in the transplant.

Directional selection type of natural selection that replaces older alleles with newer variants (for example in the MHC). Its characteristic outcome is change.

Discontinuous epitopes see conformational epitopes

Diversity (D) gene segments short DNA sequences present in immunoglobulin heavy-chain loci and in T-cell receptor β - and δ -chain loci. In the rearranged functional genes at these loci, a D region connects the V and J regions.

Double-negative thymocyte immature T cell within the thymus that expresses neither CD4 nor CD8.

Double-positive thymocyte T cell at an intermediate stage of development in the thymus. It expresses both CD4 and CD8.

Draining lymph node the lymph node to which extracellular fluid collected at a site of infection first travels.

DTH see delayed-type hypersensitivity

E-selectin see selectins

Early pro-B cell see pro-B cell

Eczema a common skin disease of children, appearing as scaly, red, itchy patches on the skin. Its etiology is poorly understood. Also called atopic dermatitis.

Edema abnormal accumulation of fluid in connective tissue, leading to swelling.

Effector cells lymphocytes that can mediate the removal of pathogens from the body without the need for further differentiation.

Effector mechanisms the physiological and cellular processes used by the immune system to destroy pathogens and remove them from the body.

Efferent lymphatic vessel the single vessel in which lymph and lymphocytes leave a lymph node en route to the blood.

Encapsulated bacteria bacteria that possess thick carbohydrate coats that protect them from phagocytosis. Encapsulated bacteria cause extracellular infections and can be dealt with by phagocytes only if the bacteria are first coated with antibody and complement.

Endocytic vesicle membrane vesicle that is pinched off from the plasma membrane and takes extracellular material into cells.

Endocytosis the uptake of extracellular material into cells by endocytic vesicles that form by pinching off pieces of plasma membrane.

Engraftment the time at which a bone marrow transplant is making new blood cells.

Eosinophil white blood cell that is one of the three types of granulocyte. It contains granules that stain with eosin and whose contents are secreted when the cell is stimulated. Eosinophils contribute chiefly to defense against parasitic infections.

Eotaxin-1 and **eotaxin-2** chemokines that act specifically on eosinophils. Now called CXCL11 and CXCL24, respectively.

Epidemic an outbreak of infectious disease that affects many individuals within a population.

Epitope the portion of an antigenic molecule that is bound by an antibody or gives rise to the MHC-binding peptide that is recognized by a T-cell receptor. Also called an antigenic determinant.

Erythrocyte red blood cell.

Extravasation the movement of cells or fluid from within blood vessels to the surrounding tissues.

F(ab')₂ a proteolytic fragment of IgG that consists of the two Fab arms held together by a disulfide bond. It is produced by digesting IgG with pepsin.

Fab fragment a proteolytic fragment of IgG that consists of the light chain and the amino-terminal half of the heavy chain held together by an interchain disulfide bond. It is called Fab because it is the Fragment with antigen binding specificity. In the intact IgG molecule the parts corresponding to the Fab fragment are often called Fab or Fab arms.

Factor B plasma protein that binds to C3(OH) or C3b and is cleaved to form part of the C3 convertases (C3(OH),Bb and C3b,Bb) in the alternative pathway of complement activation.

Factor D plasma protease that cleaves factor B to Bb and Ba in the alternative pathway of complement activation.

Factor H a complement regulatory protein of plasma that inactivates the C3 convertase of the alternative pathway and C5 convertases by binding to C3b and rendering it susceptible to cleavage by factor I to produce inactive iC3b.

Factor I a regulatory protease of complement that can cleave C3b and C4b into inactive forms.

Factor P see properdin

Farmer's lung a hypersensitivity disease caused by the interaction of IgG antibodies with large particles of inhaled allergen in the alveolar wall of the lung. The resulting inflammation compromises gas exchange by the lungs. The disease is caused by chronic exposure to large quantities of the allergen.

Fas a member of the TNF receptor family that is expressed on certain cells and makes them susceptible to killing by cells expressing **Fas ligand**, a cell-surface member of the TNF family of proteins. Binding of Fas ligand to Fas triggers apoptosis in the Fas-bearing cell.

Fc fragment a fragment of an antibody, resulting from proteolytic cleavage, that consists of the carboxy-terminal halves of the two heavy chains disulfide-bonded to each other by the residual hinge region. It is called Fc because it was the fragment that was most readily crystallized in early studies of IgG antibody structure. In an intact antibody the part corresponding to the Fc fragment is called **Fc**, **Fc region**, or **Fc piece**.

Fc receptors cell-surface receptors for the Fc portion of some immunoglobulin isotypes. They include the Fc γ and Fc ϵ receptors.

Fc region see Fc fragment

Fc ϵ receptor (Fc ϵ RI) a receptor present on the surface of mast cells, basophils and activated eosinophils that binds free IgE with very

high affinity. When antigen binds to IgE and cross-links FcεRI it causes cellular activation and degranulation.

Fcγ receptors receptors present on various cell types that are specific for the Fc regions of IgG antibodies. There are different receptors for different subclasses of IgG.

FDC *see* **follicular dendritic cells**

Fever a rise of body temperature above the normal. It is caused by cytokines produced in response to infection.

FK-binding proteins another name for the cyclophilins that bind tacrolimus (FK506). *See also* **cyclophilins**.

FK506 *see* **tacrolimus**

Follicular center cell lymphoma a malignancy of mature B cells.

Follicular dendritic cells (FDCs) characteristic nonlymphoid cells of follicles in secondary lymphoid tissues. They have long branching processes that make intimate contact with B cells and have Fc and complement receptors that hold antigen:antibody:complement complexes on their surfaces for long periods. These cells are crucial in selecting antigen-binding B cells during antibody responses.

Framework regions relatively invariant regions within the variable domains of immunoglobulins and T-cell receptors that provide a protein scaffold for the hypervariable regions.

Freund's complete adjuvant an adjuvant consisting of an emulsion of mineral oil and water containing killed mycobacteria.

Fungi single-celled and multicellular eukaryotic organisms, including the yeasts and molds, that can cause a variety of diseases. Immunity to fungi involves both humoral and cell-mediated responses.

γδ T cells a minority population of T cells that express receptors made up of γ and δ chains. The antigen specificities and functions of these cells are uncertain.

GALT *see* **gut-associated lymphoid tissues**

Gene family a set of genes encoding proteins of similar structure, and often of similar function, such as the MHC class I genes.

Gene segments multiple short DNA sequences in the immunoglobulin and T-cell receptor genes. These can be rearranged in many different combinations to produce the vast diversity of immunoglobulin or T-cell receptor polypeptide chains. *See also* **D gene segments**; **J gene segments**; **V gene segments**.

Genetic polymorphism variation in a population due to the existence of two or more alleles of a gene.

Germinal center area in secondary lymphoid tissue that is a site of intense B-cell proliferation, selection, maturation, and death. Germinal centers form around follicular dendritic cell networks when activated B cells migrate into lymphoid follicles.

Germline configuration the organization of the immunoglobulin and T-cell receptor genes in the DNA of germ cells and in the vast majority of somatic cells that do not undergo somatic recombination.

GlyCAM-1 a vascular addressin found on the high endothelial venules of lymphoid tissues. It is an important ligand for the L-selectin molecule on naive lymphocytes and directs these cells to leave the blood and enter the lymphoid tissues.

GM-CSF *see* **granulocyte-macrophage colony-stimulating factor**

Goodpasture's syndrome an autoimmune disease in which autoantibodies against type IV collagen of the basement membrane of blood vessel endothelium cause extensive vasculitis.

Graft-versus-host disease (GVHD) pathological condition caused

by the **graft-versus-host reaction (GVHR)**, which is the response of mature donor-derived T cells in transplanted bone marrow against the alloantigens of the recipient's tissues.

Graft-versus-leukemia (GVL) effect an effect in bone marrow transplantation as therapy for leukemia where some degree of genetic incompatibility between donor and recipient is thought to help T cells or NK cells from the transplant to eliminate residual leukemia cells in the recipient. Also known as a **graft-versus-tumor effect**.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) a cytokine involved in the growth and differentiation of cells in the granulocyte and monocyte lineages.

Granulocytes white blood cells with irregularly shaped, multilobed nuclei and cytoplasmic granules. There are three types of granulocyte: neutrophils, eosinophils, and basophils. They are also known as polymorphonuclear leukocytes.

Granuloma a site of chronic inflammation usually triggered by persistent infectious agents such as mycobacteria, or by a non-degradable foreign body. Granulomas have a central area of macrophages, often fused into multinucleate giant cells, surrounded by T lymphocytes.

Granulysin a membrane-perturbing protein present in the granules of cytotoxic T cells. With perforin it is thought to make pores in the target cell's membrane.

Granzymes serine esterases present in the granules of cytotoxic T cells and NK cells. On entering the cytosol of a target cell, granzymes induce apoptosis of the target. Also called fragmentins.

Graves' disease an autoimmune disease in which antibodies against the thyroid-stimulating hormone receptor cause the overproduction of thyroid hormone and the symptoms of hyperthyroidism.

Gut-associated lymphoid tissues (GALT) lymphoid tissues closely associated with the gastrointestinal tract, including the palatine tonsils, Peyer's patches in the intestine, and layers of intraepithelial lymphocytes.

H chain *see* **heavy chain**

HAART *see* **highly active anti-retroviral therapy**

HANE *see* **hereditary angioneurotic edema**

Haploidentical transplant a transplant from a donor who shares one HLA haplotype with the patient but differs in the second.

Haplotype in respect of a linked cluster of polymorphic genes, the set of alleles carried on a single chromosome is called a haplotype. Every person inherits two haplotypes, one from each parent. The term was first used in connection with the genes of the major histocompatibility complex.

Hashimoto's disease *see* **Hashimoto's thyroiditis**

Hashimoto's thyroiditis an autoimmune disease characterized by persistent high levels of antibodies against thyroid-specific antigens. These antibodies recruit NK cells to the thyroid, leading to damage and inflammation.

Heavy chain (H chain) the larger of the two component polypeptides of an immunoglobulin molecule. Heavy chains come in a variety of heavy-chain classes or isotypes, each of which confers a distinctive effector function on the antibody molecule.

Helper CD4 T cells CD4 T cells are sometimes generally known as helper cells because their function is to help other cell types to perform their functions. The term helper T cell sometimes refers to T_H2 cells only, the cells that help B cells to produce antibody.

Hematopoiesis the generation of the cellular elements of blood, including the red blood cells, white blood cells, and platelets. These

cells all originate from pluripotent **hematopoietic stem cells** whose differentiated progeny divide under the influence of various **hematopoietic growth factors**.

Hematopoietic stem cell transplantation any transplantation in which the role of the graft is to replace the hematopoietic system. Sources of hematopoietic stem cells include bone marrow and umbilical cord blood.

Hemolytic anemia of the newborn a potentially fatal disease caused by maternal IgG antibodies directed towards paternal antigens expressed on fetal red blood cells. The usual target of this response is the Rh blood group antigen. Maternal anti-Rh IgG antibodies cross the placenta to attack the fetal red blood cells. Also called erythroblastosis fetalis.

Herd immunity the phenomenon whereby those people in a population who have no protective immunity against a pathogen are largely protected from infection when the majority of the population is resistant to the pathogen.

Hereditary angioneurotic edema (HANE) a genetic disease due to deficiency of the C1 inhibitor of the complement system. In the absence of C1 inhibitor, spontaneous activation of the complement system causes diffuse fluid leakage from blood vessels, the most serious consequence of which is epiglottal swelling leading to suffocation.

Heterozygous describes an individual who has inherited different forms (alleles) of a given gene from their two parents.

Highly active anti-retroviral therapy (HAART) combination therapy for HIV infection, in which several antiviral drugs are used together to try and avoid the rapid generation of drug-resistant mutant viruses that occurs when one of the drugs is used alone.

Highly polymorphic genes that have many alleles and for which most individuals in a population are heterozygotes.

Histamine a vasoactive amine stored in mast cell granules. Histamine is released when antigen binds to IgE molecules on mast cells and causes dilation of local blood vessels and contraction of smooth muscle, producing some of the symptoms of immediate hypersensitivity reactions. Anti-histamines are drugs that counter histamine action.

Histocompatibility literally, the ability of tissues (Greek *histo*) to get along with each other. The term is used in immunology to describe the genetic systems that determine the rejection of tissue and organ grafts as a result of the immunological recognition of alloantigens (known in this context as **histocompatibility antigens**).

HIV *see* **human immunodeficiency virus**

Hives itchy red swellings in the skin caused by IgE-mediated reactions. Also called urticaria or nettle rash.

HLA the acronym for Human Leukocyte Antigen. It is the genetic designation for the human MHC. Individual loci are designated by capital letters, as in HLA-A, and alleles are designated by numbers, as in HLA-A*0201.

HLA class I molecules the name for the human version of the **MHC class I molecules**.

HLA class II molecules the name for the human version of the **MHC class II molecules**.

HLA-A, HLA-B, and HLA-C the highly polymorphic human MHC class I genes.

HLA-DM an invariant MHC class II molecule in humans that is involved in the intracellular loading of MHC class II molecules with peptides.

HLA-DO a relatively invariant human MHC class II molecule.

Although not precisely defined, the function of HLA-DO is thought to modify that of HLA-DM.

HLA-DP, HLA-DQ, and HLA-DR the highly polymorphic human MHC class II molecules. Each class II molecule is made from α and β chains encoded by A and B genes respectively. For example, the HLA-DP α and HLA-DP β chains are encoded by the HLA-DPA and HLA-DPB genes respectively. All the genes are in the MHC.

HLA-E, HLA-G relatively invariant human MHC class I molecules that form ligands for NK-cell receptors.

HLA-F a monomorphic human MHC class I molecule of unknown function.

HLA type the combination of HLA class I and class II allotypes that a person expresses.

Hodgkin's disease a malignant disease caused by transformed germinal center B cells.

Homing the movement of naive T cells into secondary lymphoid tissues, or of effector T cells to an effector site.

Homozygous describes an individual who has inherited the same form (allele) of a given gene from both parents.

Human immunodeficiency virus (HIV) the causative agent of the acquired immune deficiency syndrome (AIDS). HIV is a retrovirus of the lentivirus family that infects CD4 T cells, leading to their slow depletion, which eventually results in immunodeficiency.

Human leukocyte antigen (HLA) complex the human major histocompatibility complex (MHC).

Humanize to replace, by means of genetic engineering, the CDR loops in a human antibody with the corresponding CDR sequences of a desired specificity from a mouse antibody.

Humoral immunity immunity that is mediated by antibodies and can therefore be transferred to a non-immune recipient by serum.

HV regions *see* **hypervariable regions**

Hybridomas hybrid cell lines that make monoclonal antibodies of defined specificity. They are formed by fusing a specific antibody-producing B lymphocyte with a myeloma cell that grows in tissue culture and does not make any immunoglobulin chains of its own.

Hygiene hypothesis hypothesis advanced to explain the increasing incidence of hypersensitivity and autoimmune diseases in developed countries, in which the increase is proposed to be due to widespread hygiene, vaccination, and antibiotic therapy, preventing children's immune systems from becoming used to dealing correctly with infections.

Hyperacute rejection rejection of an allogeneic tissue graft as a result of preformed antibodies that react against A,B,O blood group antigens or HLA class I antigens on the graft. The antibodies bind to endothelium and trigger the blood clotting cascade, leading to ischemia and death of the transplanted organ or tissue.

Hyper-IgM syndrome a genetically determined X-linked immunodeficiency disease in which B cells cannot switch their immunoglobulin heavy-chain isotype. It arises from the absence of CD40 ligand.

Hypereosinophilia abnormally high numbers of eosinophils in the blood.

Hypersensitivity reactions immune responses to innocuous antigens that lead to symptomatic reactions on reexposure. These can cause **hypersensitivity diseases** if they occur repetitively. This state of heightened reactivity to an antigen is called **hypersensitivity**. Hypersensitivity reactions are classified by mechanism: type I hypersensitivity reactions involve the triggering of mast cells by IgE antibodies; type II hypersensitivity reactions involve IgG antibodies

against cell-surface or matrix antigens; type III hypersensitivity reactions involve antigen:antibody complexes; and type IV hypersensitivity reactions are mediated by effector T cells.

Hyperthyroid refers to an abnormally high production of thyroid hormones by the thyroid gland.

Hypervariable regions (HV regions) small regions of high amino-acid sequence diversity within the variable regions of immunoglobulin and T-cell receptors. They correspond to the complementarity-determining regions.

Hypothyroid refers to an abnormally low production of thyroid hormone by the thyroid gland.

ICAM-1, ICAM-2, ICAM-3 the three different types of ICAM. *See also* **intercellular adhesion molecules**.

Iccosomes immune-complex coated bodies. Small fragments of membrane coated with immune complexes that bud off from the processes of follicular dendritic cells in lymphoid follicles.

IDDM *see* **insulin-dependent diabetes mellitus**

IFN- α , IFN- β , IFN- γ *see* **interferons**

Ig domain *see* **immunoglobulin domains**

Ig α , Ig β *see* **B-cell antigen receptor**

IgA the class of immunoglobulin having α heavy chains. IgA antibodies in dimeric form are the antibodies present in mucosal secretions. IgA in monomeric form is present in the blood.

IgD the class of immunoglobulin having δ heavy chains. It appears as surface immunoglobulin on mature naive B cells but its function is unknown.

IgE the class of immunoglobulin having ϵ heavy chains. It is involved in allergic reactions.

IgG the class of immunoglobulin having γ heavy chains. It is the most abundant class of immunoglobulin in plasma.

IgM the class of immunoglobulin having μ heavy chains. It is the first immunoglobulin to appear on the surface of B cells and the first antibody secreted during an immune response. It is secreted in pentameric form.

Ii *see* **invariant chain**

IL-1 (interleukin-1) a cytokine released by macrophages, which with IL-6 and TNF- α induces a wide range of inflammatory responses at early times in infection.

IL-2 (interleukin-2) a cytokine produced by activated T cells, which is essential for the development of adaptive immune responses.

IL-3 (interleukin-3) a growth factor for hematopoietic progenitor cells.

IL-4 (interleukin-4) a cytokine secreted by CD4 T_H2 cells, which helps to initiate the proliferation and clonal expansion of B cells.

IL-6 (interleukin-6) a cytokine released by macrophages, which with IL-1 and TNF- α induces a wide range of inflammatory responses at early times in infection.

IL-10 (interleukin-10) a cytokine released by CD4 T_H2 cells.

IL-12 (interleukin-12) a cytokine released by macrophages, which activates NK cells.

IL-13 (interleukin-13) a cytokine secreted by CD4 T_H2 cells.

Immature B cells B cells that have rearranged a heavy- and a light-chain variable-region gene and express surface IgM but not IgD.

Immature dendritic cells dendritic cells present in tissues, which

take up antigen but do not express co-stimulatory molecules and cannot yet act as professional antigen-presenting cells to naive T cells.

Immediate reactions reactions occurring within minutes of exposure to antigen. They are mediated by preexisting antibodies in the circulation. Also called immediate hypersensitivity reactions.

Immune resistant to infection.

Immune complex the protein complex formed from the binding of antibodies to soluble antigens. The size of the immune complexes formed depends on the relative concentrations of antigen and antibody. Large immune complexes are cleared by phagocytes bearing Fc and complement receptors. Small soluble immune complexes tend to be deposited on the walls of small blood vessels, where they can activate complement and cause damage.

Immune-complex coated bodies *see* **iccosomes**

Immune stimulatory complexes (ISCOMs) lipid carriers that act as adjuvants.

Immune system the tissues, cells, and molecules involved in host defense mechanisms, primarily against infectious agents.

Immunity the ability to resist infection.

Immunization the deliberate provocation of an adaptive immune response by introducing antigen into the body.

Immunodeficiency diseases a group of inherited or acquired disorders in which some part or parts of host defense are either absent or defective.

Immunogenetics a subfield of immunology that was originally concerned with the analysis of genetic traits by means of antibodies against genetically polymorphic molecules such as blood group antigens and MHC proteins. Immunogenetics now encompasses the genetic analysis, by any technique, of molecules that are of specific importance to the immune system.

Immunoglobulin A *see* **IgA**

Immunoglobulin D *see* **IgD**

Immunoglobulin domains (Ig domains) components of protein structure consisting of about 100 amino acids that fold into a sandwich of two β sheets held together by a disulfide bond. Immunoglobulin heavy and light chains are made up of a series of immunoglobulin domains. Similar domains are present in many other proteins.

Immunoglobulin E *see* **IgE**

Immunoglobulin G *see* **IgG**

Immunoglobulin M *see* **IgM**

Immunoglobulin superfamily (Ig superfamily) the name given to all the proteins that contain one or more immunoglobulin or immunoglobulin-like domains.

Immunoglobulin-like domains protein domains that resemble the immunoglobulin domain in structure but are present in a variety of other proteins.

Immunoglobulins (Ig) the antigen-binding molecules of B cells.

Immunological memory the capacity of the immune system to make quicker and stronger adaptive immune responses to successive encounters with an antigen. Immunological memory is specific for a particular antigen and is long-lived.

Immunophilins intracellular proteins with peptidyl-prolyl *cis-trans* isomerase activity that bind the immunosuppressive drugs cyclosporin A, tacrolimus, and sirolimus (rapamycin).

Immunoreceptor tyrosine-based activation motifs (ITAMs) sequences in the cytoplasmic domains of membrane receptors that are sites of tyrosine phosphorylation and of association with tyrosine kinases and phosphotyrosine-binding proteins involved in signal transduction. Related motifs with opposing effects are **immunoreceptor tyrosine-based inhibitory motifs (ITIMs)**, which recruit phosphatases that remove the phosphate groups added by tyrosine kinases.

Immunosuppressive drugs compounds that inhibit adaptive immune responses.

Immunotoxins conjugates made of a specific antibody that is chemically coupled to a toxic protein usually derived from a plant or microbe. The antibody delivers the toxin moiety to the surface of the target cells.

Inactivated virus vaccines *see* **killed virus vaccines**

Indirect pathway of allorecognition one means by which alloreactive T cells in a transplant recipient can be stimulated to react against the transplant. The alloreactive T cells do not directly recognize the transplanted cells but recognize subcellular material that has been processed and presented by autologous antigen-presenting cells.

Inflammation a general term for the local accumulation of fluid, plasma proteins, and white blood cells that is initiated by physical injury, infection, or a local immune response. This is also known as an **inflammatory response**. The cells that invade tissues undergoing inflammatory responses are often called **inflammatory cells** or an **inflammatory infiltrate**.

Inflammatory mediators a variety of substances released by various cell types that contribute to the production of inflammation at a site of infection or trauma.

Influenza hemagglutinin a glycoprotein of the influenza virus coat that binds to certain carbohydrates on human cells, the first step in viral infection. Changes in the hemagglutinin are the major source of antigenic shift.

Innate immunity the host defense mechanisms that act from the start of an infection and do not adapt to a particular pathogen. Also called the **innate immune response**.

Insulin-dependent diabetes mellitus (IDDM) an autoimmune disease in which insulin-secreting β cells of the pancreatic islets of Langerhans are gradually destroyed.

Insulinitis an infiltration of the pancreatic islets of Langerhans with lymphocytes and other leukocytes. This is a symptom of incipient diabetes.

Integrins a class of cell-surface glycoproteins that mediate adhesive interactions between cells and the extracellular matrix.

Interallelic conversion a mechanism of genetic recombination between two alleles of a locus in which a segment of one allele is replaced with the homologous segment from the other. This mechanism is used to generate new HLA class I and II alleles.

Intercellular adhesion molecules (ICAMs) ligands for the leukocyte integrins that enable lymphocytes and other leukocytes to bind to other cells, including antigen-presenting cells and endothelial cells.

Interdigitating reticular cells *see* **dendritic cells**

Interferons cytokines that help cells to resist viral infection. **Interferon- α** (IFN- α) and **interferon- β** (IFN- β) are produced by leukocytes and fibroblasts respectively, as well as by other cells, whereas **interferon- γ** (IFN- γ) is a product of CD4 T_H1 cells, CD8 T cells, and NK cells. IFN- γ acts principally to activate macrophages.

Interferon response changes in the expression of a variety of human genes in cells exposed to interferon.

Interferon-producing cells (IPCs) specialized lymphocyte-like cells in the blood that secrete up to 1000-fold more type I interferon than other cells. *See also* **plasmacytoid dendritic cells**.

Interleukin (IL) a generic term used for many of the cytokines produced by leukocytes. *See also* **IL-1**, **IL-2**, **IL-3**, etc.

Intermolecular epitope spreading the process by which the immune response initially reacts against an epitope of one antigenic molecule and then progresses to epitopes on different proteins.

Intramolecular epitope spreading the process by which the immune response initially reacts against epitopes in one part of an antigenic molecule and then progresses to other, non-cross-reactive, epitopes of the same molecule.

Invariant chain (Ii) polypeptide that associates with major histocompatibility complex (MHC) class II proteins in the endoplasmic reticulum and prevents them from binding peptides there. It guides the MHC class II molecules to endosomes where Ii is degraded, enabling MHC class II molecules to bind peptides present in the endosomes.

Ischemia deficient blood supply due to obstructed blood vessels.

ISCOMs *see* **immune stimulatory complexes**

Islets of Langerhans the endocrine hormone-producing tissue of the pancreas, which includes the β cells that produce insulin.

Isoforms the different forms of a protein that are encoded by the alleles of a gene or by different but closely related genes.

Isograft a tissue or organ graft from one genetically identical individual to another.

Isotype switching the process by which a B cell changes the class of immunoglobulin made while preserving the antigenic specificity of the immunoglobulin. Isotype switching involves somatic recombination that attaches a different heavy-chain constant-region gene to the variable-region exon.

Isotypes classes of immunoglobulin—IgM, IgG, IgD, IgA, and IgE—each of which has a distinct heavy-chain constant region encoded by a different constant-region gene. The heavy-chain constant region determines the effector properties of each antibody class.

ITAMs *see* **immunoreceptor tyrosine-based activation motifs**

ITIMs immunoreceptor tyrosine-based inhibitory motifs. *See also* **immunoreceptor tyrosine-based activation motifs**.

J gene segments *see* **joining (J) gene segments**

Janus kinases (JAKs) a family of tyrosine kinases that transduce activating signals from cytokine receptors.

Joining (J) gene segments one of the types of gene segment in immunoglobulin and T-cell receptor genes that is rearranged to make functional variable-region exons.

Junctional diversity diversity present in immunoglobulin and T-cell receptor polypeptides that is created during the process of gene rearrangement by the addition of nucleotides into the junctions between gene segments.

kappa (κ) one of the two types of immunoglobulin light chain.

Killed virus vaccines vaccines that contain viral particles that have been deliberately killed by heat, chemicals, or radiation.

Killer cell immunoglobulin-like receptors (KIRs) receptors on NK cells that bind to MHC class I molecules and can send either activating or inhibitory signals to the NK cell.

Kupffer cells phagocytic cells of the liver that line the hepatic sinusoids.

$\lambda 5$ *see* pre-B-cell receptor

L chain *see* light chain

L-selectin an adhesion molecule of the selectin family found on lymphocytes. It binds to CD34 and GlyCAM-1 on high endothelial venules to initiate the migration of naive lymphocytes into secondary lymphoid tissue.

lambda (λ) one of the two types of immunoglobulin light chain.

Langerhans' cells phagocytic dendritic cells found in the epidermis. They can migrate in lymph from the epidermis to lymph nodes, where they differentiate into dendritic cells.

Large granular lymphocytes *see* natural killer cells

Large pre-B cells immature B cells that have a cell-surface pre-B-cell receptor.

Late pro-B cell *see* pro-B cell

Late-phase reaction that part of a type 1 immediate hypersensitivity reaction that occurs 7–12 hours after contact with antigen and is resistant to treatment with anti-histamine.

Latency a state adopted by some viruses in which they have entered cells but do not replicate.

Lck a protein tyrosine kinase associated with the CD4 and CD8 coreceptors of T cells.

Lectin pathway of complement activation one of the three pathways of complement activation. It is activated by the binding of a mannose-binding lectin present in blood plasma to mannose-containing peptidoglycans on bacterial surfaces. *See also* **alternative pathway of complement activation**; **classical pathway of complement activation**.

Lentiviruses group of slow retroviruses that includes the human immunodeficiency virus (HIV). They have a long incubation period and disease can take years to become apparent.

Leukemia the unrestrained proliferation of a malignant white blood cell characterized by abnormally high numbers of white cells in the blood. A leukemia can be lymphocytic, myelocytic, or monocytic depending on the type of white blood cell that became malignant.

Leukocyte a general term for a white blood cell. Lymphocytes, granulocytes, and monocytes are all leukocytes.

Leukocyte adhesion deficiency an immunodeficiency disease in which the common β chain of the leukocyte integrins is absent. This mainly affects the ability of leukocytes to enter sites infected with extracellular pathogens, so such infections cannot be effectively eradicated.

Leukocytosis increased numbers of leukocytes in the blood. It is commonly seen in acute infection.

LFA-1 *see* lymphocyte function-associated antigen-1

LFA-3 *see* lymphocyte function-associated antigen-3

Light chain (L chain) the smaller of the two types of polypeptide chain that make up immunoglobulins. It consists of one variable and one constant domain, and in the immunoglobulin molecule it is disulfide-bonded to a heavy chain. There are two classes of light chain, known as κ and λ .

Light zone the part of a germinal center in secondary lymphoid tissue that contains non-dividing centrocytes interacting with follicular dendritic cells.

Linear epitope epitope of a protein recognized by antibody that consists of a linear sequence of amino acids within the protein's primary structure.

Linkage disequilibrium (LD) the situation when particular alleles of two or more polymorphic genes (for example those comprising an

HLA haplotype) are inherited together at frequencies higher than expected by chance.

Live-attenuated viral vaccines vaccines composed of live viruses that have an accumulation of mutations that impedes their growth in human cells and their capacity to cause disease.

LPS-binding protein plasma protein that binds bacterial lipopolysaccharide (LPS) and delivers it to LPS receptors on neutrophils and macrophages.

LT *see* lymphotoxin

Lymph mixture of extracellular fluid and cells that is carried by the lymphatic system.

Lymph nodes a type of secondary lymphoid tissue found at many sites in the body where lymphatic vessels converge. Antigens are delivered by the lymph and presented to lymphocytes within the lymph node where adaptive immune responses are initiated.

Lymphatic vessels (lymphatics) thin-walled vessels that carry lymph from tissues to secondary lymphoid tissues (with the exception of the spleen) and from secondary lymphoid tissues to the thoracic duct.

Lymphocyte function-associated antigen-1 (LFA-1) one of the leukocyte integrins that mediate the adhesion of lymphocytes, especially T cells, to endothelial cells and antigen-presenting cells.

Lymphocyte function-associated antigen-3 (LFA-3) cell adhesion molecule of the immunoglobulin superfamily that is expressed on antigen-presenting cells (and other types of cell) and mediates their adhesion to T cells.

Lymphocytes a class of white blood cells that consist of small and large lymphocytes. The small lymphocytes bear variable cell-surface receptors for antigen and are responsible for adaptive immune responses. There are two main classes of small lymphocyte—B lymphocytes (B cells) and T lymphocytes (T cells). Large granular lymphocytes are natural killer (NK) cells, lymphocytes of innate immunity.

Lymphoid containing lymphocytes, or pertaining to lymphocytes.

Lymphoid lineage all types of lymphocyte, and the bone marrow cells that give rise to them.

Lymphoid organs (lymphoid tissues) organized tissues that contain very large numbers of lymphocytes held in a non-lymphoid stroma. The primary lymphoid organs, where lymphocytes are generated, are the thymus and bone marrow. The main secondary lymphoid tissues, in which adaptive immune responses are initiated, are the lymph nodes, spleen, and mucosa-associated lymphoid tissues such as tonsils, Peyer's patches, and the appendix.

Lymphoid progenitor stem cell in bone marrow cell that gives rise to all lymphocytes.

Lymphokines cytokines produced by lymphocytes.

Lymphomas tumors of lymphocytes that grow in lymphoid and other tissues but do not enter the blood in large numbers.

Lymphotoxin (LT) a cytotoxic cytokine secreted by some CD4 T cells. Also known as tumor necrosis factor- β (TNF- β).

Lytic granules intracellular storage granules of cytotoxic T cells and NK cells that contain perforin and granzymes.

M cells specialized cells in intestinal epithelium through which antigens and pathogens enter gut-associated lymphoid tissue from the intestines. Short for microfold cells.

Macrophage activation stimulation of macrophages, which increases their phagocytic, antigen-presenting, and bacterial killing functions. It occurs in the course of infection.

Macrophages large mononuclear phagocytic cells resident in most tissues. They are derived from blood monocytes and contribute to innate immunity and early nonadaptive phases of host defense. They function as professional antigen-presenting cells and as effector cells in humoral and cell-mediated immunity.

MAdCAM-1 mucosal cell adhesion molecule-1, a mucosal addressin that is recognized by the lymphocyte surface proteins L-selectin and VLA-4. This interaction mediates the specific homing of lymphocytes to mucosal tissues.

Major basic protein a constituent of eosinophil granules that is released on eosinophil activation. It acts on mast cells to cause their degranulation.

Major histocompatibility complex (MHC) a cluster of genes on the short arm of human chromosome 6 that encodes a set of polymorphic membrane glycoproteins called the MHC molecules, which are involved in presenting peptide antigens to T cells.

Major histocompatibility complex (MHC) molecules *see* MHC molecules

Malignant transformation the changes that occur in a cell to make it cancerous.

Malignant tumors tumors that are capable of uncontrolled and invasive growth.

MALT *see* mucosa-associated lymphoid tissues

Mannose-binding lectin (MBL) an acute-phase protein in the blood that binds to mannose residues on pathogen surfaces and when bound activates the complement system. It is also known as **mannose-binding protein (MBP)** and **mannan-binding lectin**.

Mannose-binding protein pathway *see* lectin-mediated pathway

Mantle zone in lymphoid follicles, a rim of B lymphocytes that surrounds a follicle.

Mast cells large bone marrow derived cells found resident in connective tissues throughout the body. They contain large granules that store a variety of chemical mediators including histamine. Mast cells have high-affinity Fcε receptors (FcεRI) that bind free IgE. Antigen binding to mast cell associated IgE triggers mast cell activation and degranulation, producing a local or systemic immediate hypersensitivity reaction. Mast cells have a crucial role in allergic reactions.

Mature B cells B cells that have IgM and IgD on their surface and are able to respond to antigen.

Mature dendritic cells dendritic cells in secondary lymphoid tissues that express co-stimulatory molecules and other cell-surface molecules that enable them to present antigen to naive T cells and activate them.

Megakaryocytes large cells of the erythroid lineage, produced in the bone marrow and resident there. They produce platelets.

Membrane co-factor protein (MCP) complement regulatory protein on human cells that promotes the inactivation of C3b and C4b by factor I.

Membrane-attack complex the complex of terminal complement components that forms a pore in the membrane of the target cell, damaging the membrane and leading to cell lysis.

Memory B cells long-lived antigen-specific B cells that are produced from activated naive B cells during the primary immune response to an antigen. On subsequent exposure to their specific antigen they are reactivated to differentiate into plasma cells as part of the secondary and subsequent immune responses.

Memory cells general term for lymphocytes that are responsible

for the phenomenon of immunological memory and protective immunity.

Memory T cells long-lived antigen-specific T cells that are activated in secondary and subsequent immune responses to an antigen.

Metastasis the spread of a tumor from its site of origin to other tissues. Some cells from the primary tumor invade other tissues and grow and divide to become secondary tumors.

Methotrexate cytotoxic drug used to inhibit graft-versus-host reactions in bone marrow transplant recipients.

MHC *see* major histocompatibility complex

MHC class I molecules the class of MHC molecules that present peptides generated in the cytosol to CD8 T cells. They consist of a heterodimer of a class I heavy chain associated with β₂-microglobulin.

MHC class II molecules the class of MHC molecules that present peptides generated in intracellular vesicles to CD4 T cells. They consist of a heterodimer of class II α and β chains.

MHC class II transactivator (CIITA) a transcriptional activator of MHC class II genes. When defective it causes a type of bare lymphocyte syndrome.

MHC molecules major histocompatibility complex molecules. Highly polymorphic glycoproteins encoded by the major histocompatibility complex (MHC). They form complexes with peptides and present peptide antigens to T cells. There are two classes—MHC class I and MHC class II molecules—with different roles in the immune response. They are also known as major histocompatibility antigens because they are the main alloantigens involved in the rejection of transplanted tissues.

MHC restriction the fact that a given T-cell receptor will recognize its peptide antigen only when the peptide is bound to a particular form of MHC molecule.

Microfold cells *see* M cells

Minor histocompatibility antigens (minor H antigens) peptides of polymorphic cellular proteins that can lead to graft rejection when they are bound by MHC molecules and recognized by T cells.

Minor histocompatibility loci the genes encoding proteins that can act as minor histocompatibility antigens.

Mixed lymphocyte reaction cellular assay for detecting MHC differences between two individuals. The T cells from one individual proliferate in response to allogeneic MHC molecules on the cells of the other individual.

Molecular mimicry antigenic similarity between a pathogen antigen and a cellular antigen, which results in the induction of antibodies or T cells that act against the pathogen but also cross-react with the self antigen.

Monoclonal antibodies antibodies produced by a single clone of B lymphocytes and that are therefore identical in structure and antigen specificity.

Monocytes white blood cells with a bean-shaped nucleus. They are the precursors of tissue macrophages.

Monocyte chemoattractant protein (MCP-1) *see* CCL2

Monomorphic having only one form. The term is used, for example, for genes that have only one allele.

Mucosa the mucus-secreting epithelia that line the respiratory, intestinal, and urogenital tracts. The conjunctiva of the eye and the mammary glands are also in this category.

Mucosa-associated lymphoid tissue (MALT) aggregations of lymphoid cells in mucosal epithelia and in the lamina propria beneath.

The main mucosa-associated lymphoid tissues are the gut-associated lymphoid tissues (GALT) and the bronchial-associated lymphoid tissues (BALT).

Mucosal surfaces *see* **mucosa**

Mucus slimy protective secretion produced by many internal epithelia.

Multiple sclerosis a chronic progressive neurological disease characterized by patches of demyelination in the central nervous system and lymphocyte infiltration into the brain. It is believed to be an autoimmune disease.

Multivalent having more than one binding site for the same or different ligands.

Mutagen any agent, such as a chemical or radiation, that can cause a mutation.

Mutation an alteration in the DNA sequence of a gene.

Myasthenia gravis an autoimmune disease in which autoantibodies against the acetylcholine receptor on skeletal muscle cells cause a block of signal transmission from nerve to muscle at neuromuscular junctions, leading to progressive muscle weakness and eventually to death.

Myeloablative therapy a conditioning regime used before a bone marrow transplant. The recipient's immune system is destroyed with a combination of cytotoxic drugs and irradiation.

Myeloid lineage a subset of bone-marrow derived cells comprising granulocytes, monocytes, and macrophages.

Myeloid progenitors stem cells in the bone marrow that give rise to granulocytes, monocytes, and macrophages.

Myelomas tumors of plasma cells resident in bone marrow.

Myelopoiesis the production of monocytes and granulocytes in the bone marrow.

N-nucleotides nucleotides added at the junctions between gene segments of T-cell receptor and immunoglobulin heavy-chain variable-region sequences during somatic recombination, which contribute to the diversity of these molecules. They are not encoded in the gene segments but are inserted by the enzyme terminal deoxynucleotidyltransferase (TdT).

Naive B cell a mature B cell that has left the bone marrow but has not yet encountered its specific antigen.

Naive T cell a mature T cell that has left the thymus but not yet encountered its specific antigen.

Natural cytotoxicity receptors (NCRs) a group of activating NK-cell receptors of the immunoglobulin superfamily.

Natural interferon-producing cells (NIPCs) *see* **interferon-producing cells**

Natural killer cells (NK cells) large, granular, cytotoxic lymphocytes that circulate in the blood. NK cells are important in innate immunity to viruses and other intracellular pathogens and also kill certain tumor cells. They are the cytotoxic cells in antibody-dependent cell-mediated cytotoxicity (ADCC).

NCR *see* **natural cytotoxicity receptor**

Necrosis the death of cells by lysis that results from chemical or physical injury. It leaves extensive cellular debris that must be removed by phagocytes. Neighboring tissue is also damaged by the molecules released from necrotic cells.

Negative selection process in the thymus whereby developing T cells that recognize self antigens are induced to die by apoptosis.

Neoplasm a tumor, which may be benign or malignant.

Neutralization the mechanism by which antibodies binding to sites on pathogens prevent growth of the pathogen and/or its entry into cells. The toxicity of bacterial toxins can similarly be **neutralized** by bound antibody.

Neutropenia a deficiency of neutrophils in the blood.

Neutrophils phagocytic white blood cells that enter infected tissues in large numbers. They contain granules that stain with neutral dyes. After their entry into infected tissues, neutrophils engulf and kill extracellular pathogens in large numbers. They are also known as neutrophilic polymorphonuclear leukocytes and are a type of granulocyte. The most abundant white blood cell.

NFAT (nuclear factor of activated T cells) a transcription factor that is activated as a result of signaling from the T-cell receptor. It functions as a complex of the NFAT protein with the dimer of Fos and Jun proteins known as AP-1.

NFκB nuclear factor κB, a transcription factor that helps turn on the expression of many immune system genes.

NIPC *see* **interferon-producing cell**

NK cells *see* **natural killer cells**

NK-cell lectin-like receptors one of the two main structural classes of NK-cell receptors. They include both activating and inhibitory receptors.

Non-obese diabetic (NOD) mice a strain of mice in which diabetes arises spontaneously and has clinical and immunological characteristics similar to those in human insulin-dependent diabetes mellitus.

Oligomorphic describes genes that have only a small number of different alleles in the population.

Oncogenes genes involved in the control of cell growth. When these genes are defective in either structure or expression, they can cause cells to proliferate abnormally and form a tumor.

Oncogenic viruses viruses that are involved in causing cancer.

Oncology the clinical discipline that deals with the study, diagnosis, and treatment of cancer.

Opportunistic pathogen a microorganism that causes disease only in individuals whose immune systems are in some way compromised.

Opsonins antibodies and complement components that bind to pathogens and facilitate their phagocytosis by neutrophils or macrophages.

Opsonization the coating of the surface of a pathogen or other particle with any molecule that makes it more readily ingested by phagocytes. Antibody and complement opsonize extracellular bacteria for phagocytosis by neutrophils and macrophages because the phagocytic cells carry receptors for these molecules.

Oral tolerance the fact that harmless antigens, such as those in food, taken into the body by mouth do not usually cause an immune response.

Organ-specific autoimmune diseases autoimmune diseases targeted at a particular organ, such as the thyroid in Graves' disease.

Original antigenic sin a bias seen in successive immune responses to structurally related antigens such as those on different strains of influenza virus. On infection for the second time with influenza, the antibody response is restricted to epitopes that the second strain shares with the first strain to which the person was exposed. Other highly immunogenic epitopes on the second and subsequent viruses are ignored.

P-nucleotides nucleotides added into the junctions between gene segments during the somatic recombination that generates a rearranged variable-region sequence. They are an inverse repeat (a palindrome) of the nucleotide sequence at the end of the adjacent gene segment, which gives them their name of palindromic or P-nucleotides.

P-selectin *see* **selectins**

Pandemic outbreak of an infectious disease that spreads worldwide.

Panel reactive antibody (PRA) a measure of the likelihood that a patient seeking a transplant is sensitized to potential donors. The patient's serum is tested against tissue from a representative panel of individuals for antibodies that would cause immediate hyperacute rejection of a graft. The PRA is the percentage of individuals in the panel whose cells react with the patient's antibodies.

Paracrine term applied to a cytokine that is released from one type of cell and acts on other cells nearby.

Parasites the unicellular protozoa and multicellular worms that infect animals and humans and live within them.

Paroxysmal nocturnal hemoglobinuria (PNH) a disease in which the complement regulatory proteins CD59 and DAF are defective, so that complement activation leads to episodes of spontaneous hemolysis. The defect is in the attachment of CD59 and DAF to cell membranes via a glycolipid anchor.

Passive immunization the injection of specific antibodies to provide protection against a pathogen or toxin. The administered antibodies may derive from human blood donors, immunized animals or hybridoma cell lines.

Passive transfer of immunity transfer of immunity to a non-immune individual by the injection of specific antibody, immune serum, or T cells.

Pathogen an organism, most commonly a microorganism, that can cause disease.

Pathology the scientific study of disease or detectable damage to tissue caused by disease.

Pemphigus foliaceus and **pemphigus vulgaris** autoimmune diseases involving blistering of the skin.

Pentraxins a family of acute-phase proteins to which C-reactive protein belongs. They are formed of five identical subunits.

Peptide-binding motif of an MHC isoform, the combination of anchor residues that are common to the amino-acid sequences of peptides that bind to the isoform.

Perforin one of the proteins released by cytotoxic T cells on contact with their target cells. It forms pores in the target cell membrane that contribute to cell killing.

Peripheral lymphoid tissues *see* **secondary lymphoid tissues**

Peyer's patches gut-associated lymphoid tissue present in the wall of the small intestine, especially the ileum.

Phagocyte a cell specialized to perform phagocytosis. The principal phagocytic cells in mammals are neutrophils and macrophages.

Phagocytosis cellular internalization of particulate matter, such as bacteria, by means of endocytosis. Cells specialized in phagocytosis are known as phagocytes.

Phagolysosome intracellular vesicle formed by fusion of a phagosome with a lysosome, in which the phagocytosed material is broken down by degradative lysosomal enzymes.

Phagosome intracellular vesicle containing material taken up by phagocytosis.

Plasma cells terminally differentiated B lymphocytes that secrete antibody.

Plasmablast an activated B cell differentiating within a lymphoid follicle at the stage at which it shows some features of a plasma cell.

Plasmacytoid dendritic cells (PDCs) dendritic-like cells derived from interferon-producing cells cultured with microbial products and inflammatory cytokines.

Pluripotent hematopoietic stem cell stem cell in bone marrow that gives rise to all the cellular elements of the blood.

PNH *see* **paroxysmal nocturnal hemoglobinuria**

Poly-Ig receptor a receptor present on the basolateral membrane of epithelial cells that binds polymeric immunoglobulins, especially dimeric IgA, and transports them across the epithelium by transcytosis.

Polymorphism the existence of different variants of a gene or trait in the population. Genetic polymorphism is defined as the existence of two or more forms (alleles) of a given gene within the population, with the variant alleles each occurring at a frequency greater than 1%.

Polymorphonuclear leukocytes *see* **granulocytes**

Polyspecificity the ability to bind to many different antigens, a property shown by some antibodies. It is also known as polyreactivity.

Positive selection a process in the thymus that selects immature T cells with receptors that recognize peptide antigens presented by self-MHC molecules. Only cells that are positively selected are allowed to continue their maturation.

PRA *see* **panel reactive antibody**

Pre-B cells a stage in B-cell development at which the B cells have rearranged their heavy-chain genes but not their light-chain genes.

Pre-B-cell receptor immunoglobulin-like receptor that is expressed on the surface of pre-B cells. It consists of μ heavy chains in association with surrogate light chains. Its appearance signals the cessation of heavy-chain gene rearrangement.

Pre-T-cell receptor receptor that is present on the surface of some immature thymocytes. It consists of a T-cell receptor β chain associated with a surrogate α chain called pT α .

Prednisolone the biologically active compound to which the immunosuppressive drug prednisone is converted *in vivo*.

Prednisone a synthetic steroid drug with potent anti-inflammatory and immunosuppressive activity. Prescribed to patients who have had organ transplants.

Present cells carrying cell-surface complexes of peptide antigens and MHC molecules are said to present these antigens to T lymphocytes.

Primary immune response or **primary response** the adaptive immune response that follows a person's first exposure to an antigen.

Primary lymphoid follicles the name given to the B-cell areas of secondary lymphoid tissues in the absence of an immune response. They contain resting B lymphocytes.

Primary lymphoid tissues anatomical sites of lymphocyte development. The bone marrow and the thymus gland.

Pro-B cells an early stage in B-cell development at which B-cell precursors express B-cell marker proteins and rearrange their heavy-chain genes. D $_H$ to J $_H$ joining occurs at the **early pro-B cell** stage, followed by V $_H$ to D $_H$ joining at the **late pro-B cell** stage.

Pro-drug biologically inactive compound that is metabolized in the body to produce an active drug.

Productive rearrangements DNA rearrangements within immunoglobulin and T-cell receptor genes that lead to a gene that can direct the synthesis of a functional polypeptide chain.

Professional antigen-presenting cells cells that can present antigen to naive T cells and activate them. A professional antigen-presenting cell not only displays peptide antigens bound to appropriate MHC molecules but also has co-stimulatory molecules on its surface that are needed to activate the T cell. Only dendritic cells, macrophages, and B cells can be professional antigen-presenting cells.

Programmed cell death *see* apoptosis

Properdin a blood protein that helps to activate the alternative pathway of complement activation. It binds to and stabilizes the alternative pathway C3 and C5 convertases on the surfaces of bacterial cells. It is also known as factor P.

Proteasome large multisubunit protease present in the cytosol of all cells that degrades cytoplasmic proteins. It generates the peptides presented by MHC class I molecules.

Protective immunity the specific immunological resistance to a pathogen that follows either from specific vaccination or recovery from an infection with the pathogen.

Protein tyrosine kinases enzymes that phosphorylate tyrosine residues on proteins. They are involved in signal transduction from many types of cell-surface receptor, including the antigen receptors on B cells and T cells.

Proto-oncogenes cellular genes that regulate the control of cell growth and division. When mutated or aberrantly expressed, they contribute to the malignant transformation of cells, which leads to cancer.

Provirus the DNA form of a retrovirus when it is integrated into the host cell genome. In this state it can remain transcriptionally inactive for a long time.

pTα *see* pre-T-cell receptor

Purine nucleotide phosphorylase (PNP) enzyme involved in purine metabolism. Its deficiency results in the accumulation of purine nucleosides, which are toxic for developing T cells. This leads to severe combined immunodeficiency.

Pus thick yellowish-white fluid that is formed in infected wounds. It is composed of dead and dying white blood cells (principally neutrophils), tissue debris, and dead microorganisms.

Pyogenic bacteria extracellular encapsulated bacteria that cause the formation of pus at sites of infection.

RAG-1, RAG-2 *see* recombination activation genes

Rapamycin *see* sirolimus

Receptor editing a process in developing B cells that have generated a self-reactive receptor by which further rounds of light-chain gene rearrangement can produce a new light chain to replace the self-reactive one.

Recirculation of lymphocytes, their continual movement from blood to secondary lymphoid tissues to lymph and back to the blood. An exception to this pattern is traffic to the spleen; lymphocytes both enter and leave the spleen in the blood.

Recombination activation genes (RAG-1, RAG-2) two genes whose expression is required for immunoglobulin and T-cell receptor gene rearrangement in B cells and T cells.

Recombination signal sequences (RSSs) short stretches of DNA that flank the gene segments that are rearranged to generate V-region exons. They are the sites at which somatic recombination occurs.

Regulators of complement activation (RCA) proteins that regulate

the activity of complement and contain a particular structural motif called the CCP motif.

Regulatory CD4 T cells (T_R) antigen-specific CD4 T cells whose actions can suppress immune responses.

Respiratory burst metabolic change accompanied by a transient increase in oxygen consumption that occurs in neutrophils and macrophages when they have taken up opsonized particles. It leads to the generation of toxic oxygen metabolites and other anti-bacterial substances that attack the phagocytosed material.

Respiratory syncytial virus (RSV) a paramyxovirus that is a common cause of severe chest infection in young children. Often associated with wheezing.

Rev protein product of the rev gene of the human immunodeficiency virus (HIV). The protein promotes the passage of viral RNA from nucleus to cytoplasm during HIV replication.

Rheumatic fever autoimmune disease involving inflammation of the heart, joints, and kidneys, which can follow 2–3 weeks after a throat infection with certain strains of *Streptococcus pyogenes*. It is due to antibodies made against bacterial antigens cross-reacting with components of heart tissue, and the continued deposition of immune complexes.

Rheumatoid arthritis a common inflammatory disease of joints that is due to an autoimmune response.

Rheumatoid factor an IgM antibody with specificity for human IgG that is produced in some people with rheumatoid arthritis.

RSS *see* recombination signal sequences

RSV *see* respiratory syncytial virus

Sarcoma a tumor that arises from a cell of connective tissue.

SCID, scid *see* severe combined immunodeficiency

SE *see* staphylococcal enterotoxins

Secondary immune response or **secondary response** the adaptive immune response provoked by a second exposure to an antigen. It differs from the primary response by starting sooner and building more quickly.

Secondary lymphoid follicle the name given to the B-cell areas of secondary lymphoid tissues that are responding to antigen. They contain proliferating B cells.

Secondary lymphoid tissues the lymph nodes, spleen and mucosa-associated lymphoid tissues. These are the tissues in which immune responses are initiated. The more highly organized tissues such as lymph nodes and spleen are also often known as **secondary lymphoid organs**.

Secretory component (secretory piece) fragment of the poly-Ig receptor left attached to dimeric IgA after its transport across epithelial cells.

Segmental exchange *see* gene conversion

Selectins family of adhesion molecules present on the surfaces of leukocytes and endothelial cells. They are lectins and bind to sugar moieties on certain mucin-like glycoproteins.

Self antigens a term used to describe all the normal constituents of the body to which the immune system would respond were it not for the mechanisms of tolerance that destroy or inactivate self-reactive B and T cells.

Self-MHC a person's own MHC molecules.

Self peptides peptides produced from the body's own proteins. In the absence of infection these peptides occupy the peptide-binding sites of MHC molecules on cell surfaces.

Self-renewal the ability of a population of cells to renew itself.

Self-tolerance the normal situation whereby a person's immune system does not respond to constituents of the person's body.

Sensitization in connection with allergy, the first exposure to an allergen that elicits an IgE response. Allergic reactions occur only in individuals who have already been **sensitized**.

Sepsis the toxic effects of infection of the bloodstream. Usually caused by Gram-negative bacteria. *See also septic shock*.

Septic shock shock syndrome that is frequently fatal, caused by the systemic release of the cytokine TNF- α after bacterial infection of the bloodstream, usually with Gram-negative bacteria.

Septicemia bacterial invasion of the blood.

Seroconversion the phase of an infection when antibodies against the infecting agent are first detectable in the blood.

Serotypes antigenically different strains of a bacterium or other pathogen that can be distinguished by immunological means, for example by antibody-based detection tests. Also used to describe human alloantigens such as HLA and blood group antigens.

Serum sickness the collection of symptoms that follow the injection of large amounts of a foreign molecule (such as a serum protein) into a person. It is caused by the immune complexes formed between the injected protein and the antibodies that are made against it. Characterized by fever, arthralgias, and nephritis.

Severe combined immune deficiency (SCID) immune deficiency disease in which neither antibody nor T-cell responses are made. It is usually the result of genetic defects that lead to T-cell deficiencies, and is fatal in childhood if not treated.

Single-positive thymocytes a late stage of T-cell development in the thymus characterized by the expression of either the CD4 or the CD8 co-receptor on the cell surface.

Sirolimus the proprietary name for the immunosuppressive drug rapamycin. Both names are in common use.

SLE *see* **systemic lupus erythematosus**

Small lymphocytes the general name for resting T and B lymphocytes as they recirculate.

Small pre-B cells pre-B cells in which light-chain gene rearrangements are being made.

Somatic gene therapy a possible therapy for curing inherited immunodeficiency diseases. Stem cells isolated from the patient are transfected with a normal copy of the gene that is defective in the patient. The stem cells, which now express a good copy of the formerly defective gene, are reinfused into the patient's circulation.

Somatic hypermutation mutation that occurs at high frequency in the rearranged variable-region DNA of immunoglobulin genes in activated B cells, resulting in the production of variant antibodies, some of which have a higher affinity for the antigen.

Somatic recombination DNA recombination that occurs between gene segments in the immunoglobulin genes and T-cell receptor genes in developing B cells and T cells respectively. It generates a complete exon that encodes the variable region of an immunoglobulin or T-cell receptor polypeptide chain.

Specificity the property of antibodies and other antigen-binding molecules for selective interaction with only one or a few types of molecule or cell.

Spleen organ situated adjacent to the cardiac end of the stomach. One function of the spleen is to remove old or damaged red blood cells from the circulation; the other is as a secondary lymphoid organ that responds to blood-borne pathogens and antigens.

Staphylococcal enterotoxins (SEs) toxins secreted by strains of staphylococcus that act on the gut and cause the symptoms of food poisoning. They are also superantigens.

STATs signal transducers and activators of transcription. Proteins that are activated to become transcription factors through the Janus kinase signaling pathway from cytokine receptors.

Stromal cells cells that provide the supporting framework of a tissue or organ.

Subunit vaccines vaccines composed only of isolated antigenic components of a pathogen and not the pathogen itself, either alive or dead.

Superantigens molecules that, by binding non-specifically to MHC class II molecules and T-cell receptors, stimulate the polyclonal activation of T cells.

Suppressor CD4 T cells *see* **regulatory CD4 T cells**.

Surrogate light chain a protein that mimics an immunoglobulin light chain and made up of two subunits, VpreB and $\lambda 5$. It is produced by pro-B cells and together with μ heavy chain forms the pre-B-cell receptor.

Switch regions (switch sequences) DNA sequences preceding heavy-chain constant-region genes at which somatic recombination occurs when B cells switch from producing one immunoglobulin isotype to another.

Sympathetic ophthalmia an autoimmune response that sometimes follows damage to an eye and affects both the damaged eye and the healthy eye.

Syngeneic genetically identical. A syngeneic tissue graft is one made between two genetically identical individuals. It does not provoke an immune response or a rejection reaction.

Systemic anaphylaxis a rapid-onset and potentially fatal form of IgE-mediated allergic reaction, in which antigen in the bloodstream triggers the activation of mast cells throughout the body, causing circulatory collapse and suffocation due to tracheal swelling.

Systemic autoimmune disease (systemic autoimmunity) autoimmunity that involves reactions to common components of the body and whose effects are not confined to one particular organ.

Systemic lupus erythematosus a systemic autoimmune disease in which autoantibodies made against DNA, RNA, and nucleoprotein particles form immune complexes that damage small blood vessels.

T cells (T lymphocytes) lymphocytes that develop in the thymus and are responsible for cell-mediated immunity. Their cell-surface antigen receptor is called the T-cell receptor.

T-cell activation the stimulation of mature naive T cells by antigen presented to them by professional antigen-presenting cells. It leads to their proliferation and differentiation into effector T cells.

T-cell areas parts of secondary lymphoid tissues where the lymphocytes are predominantly T cells.

T-cell priming the activation of mature naive T cells by antigen presented to them by professional antigen-presenting cells.

T-cell receptor α chain (TCR α) one of the two polypeptide chains that make up the most common form of T-cell receptor.

T-cell receptor β chain (TCR β) one of the two polypeptide chains that make up the most common form of T-cell receptor.

T-cell receptor complex the complex of T-cell receptor α and β chains and the invariant CD3 and ζ chains that makes up a functional antigen receptor on the T-cell surface.

T-cell receptor the highly variable antigen receptor of T lymphocytes. On most T cells it is composed of a variable α chain and β

chain and is known as the $\alpha\beta$ T-cell receptor. On a minority of T cells, the variable chains are γ and δ chains, and this receptor is known as the $\gamma\delta$ T-cell receptor. Both types of receptor are present at the cell surface in association with the complex of invariant CD3 chains and ζ chains, which have a signaling function.

T lymphocyte *see* T cells

Tacrolimus immunosuppressive polypeptide drug that inactivates T cells by inhibiting signal transduction from the T-cell receptor. It is widely used to suppress transplant rejection. It is also known as FK506.

TAP *see* transporter of antigen processing

Tapasin TAP-associated protein, a chaperone protein involved in the assembly of peptide-MHC class I molecule complexes in the endoplasmic reticulum.

Target cell any cell that is acted on directly by effector T cells, effector cells or molecules. For example, virus-infected cells are the targets of cytotoxic T cells, which kill them, and naive B cells are the targets of effector CD4 T cells, which help to stimulate them to produce antibodies.

Tat protein product of the tat gene of the human immunodeficiency virus (HIV), which enhances the rate of transcription of viral RNA.

TD antigens *see* thymus-dependent antigens

Terminal deoxynucleotidyltransferase (TdT) enzyme that inserts nontemplated nucleotides (N-nucleotides) into the junctions between gene segments during the rearrangement of T-cell receptor and immunoglobulin heavy-chain genes.

Tetanus toxin protein neurotoxin produced by the bacterium *Clostridium tetani*. The cause of the disease tetanus.

TGF- β *see* transforming growth factor- β

T_H1 cells a subset of CD4 T cells that are characterized by the cytokines they produce. They are involved mainly in activating macrophages. Also called inflammatory T cells.

T_H2 cells a subset of CD4 T cells that are characterized by the cytokines they produce. They are involved mainly in stimulating B cells to produce antibody. Also called helper T cells.

Thymectomy the surgical removal of the thymus gland.

Thymic anlage the tissue from which the thymic stroma develops during embryogenesis.

Thymic stroma the reticular epithelial cells and connective tissue of the thymus, which form the essential microenvironment for T-cell development.

Thymocytes developing T cells in the thymus.

Thymus a lymphoepithelial organ in the upper part of the middle of the chest, just behind the breastbone. It is the site of T-cell development.

Thymus-dependent antigens (TD antigens) antigens for which the elicitation of an antibody response on immunization or vaccination is dependent upon help provided by antigen-specific T cells. Most protein antigens are of this type.

Thymus-dependent lymphocyte *see* T cells

Thymus-independent antigens (TI antigens) antigens that can elicit antibody production in the absence of T cells. There are two types of TI antigen: TI-1 antigens, which have intrinsic B-cell activating activity, and TI-2 antigens, which have multiple identical epitopes that cross-link B-cell receptors.

TI-1 antigens, TI-2 antigens *see* thymus-independent antigens

Tingible body macrophages phagocytic cells that are seen in histological sections engulfing apoptotic B cells in germinal centers.

TNF- α *see* tumor necrosis factor- α

TNF- β *see* lymphotoxin

Tolerance when the immune system of a person does not or cannot respond to an antigen. In such cases the individual is said to be **tolerant** of the antigen.

Tonsils large aggregates of lymphoid cells lying on each side of the pharynx.

Toxic shock syndrome a systemic toxic reaction caused by the overproduction of cytokines by CD4 T cells activated by the bacterial superantigen **toxic shock syndrome toxin-1 (TSST-1)**, which is secreted by *Staphylococcus aureus*.

Toxoids toxins that have been deliberately inactivated by heat or chemical treatment so that they are no longer toxic but can still provoke a protective immune response on vaccination.

Toxoplasmosis the disease caused by the protozoan parasite *Toxoplasma gondii*.

Transcytosis the transport of molecules from one side of an epithelium to the other by endocytosis into vesicles within the epithelial cells at one face of the epithelium and release of the vesicles at the other.

Transforming growth factor- β (TGF- β) a multifunctional cytokine produced by T_H2 cells and other cell types.

Transfusion effect improved outcome of transplantation if the recipient has been given prior blood transfusions from people who share an HLA-DR allotype with the organ with which the patient is subsequently transplanted.

Translocation a chromosomal abnormality in which a piece of one chromosome has become joined to another chromosome. The rearranging genes of B and T cells are often the sites of translocation in B-cell and T-cell tumors.

Transplant rejection immune reaction that is directed towards transplanted tissue and leads to death of the graft.

Transplantation the grafting of organs or tissues from one individual to another.

Transporter associated with antigen processing (TAP) an ATP-binding protein in the endoplasmic reticulum membrane that transports peptides from the cytosol to the endoplasmic reticulum lumen. It is composed of two subunits, TAP-1 and TAP-2. It supplies MHC class I molecules with peptides.

Tuberculin test clinical test to detect exposure to *Mycobacterium tuberculosis*, the causal agent of tuberculosis. Subcutaneous injection of purified protein derivative (PPD) of *M. tuberculosis* elicits a delayed-type hypersensitivity reaction in individuals who have had tuberculosis or have been immunized against it.

Tumor a growth arising from uncontrolled cell proliferation. It may be benign and self-limiting, or malignant and invasive.

Tumor antigens cell-surface components of tumor cells that can elicit an immune response in the affected individuals. *See also* tumor-associated antigens; tumor-specific antigens.

Tumor-associated antigens antigens characteristic of certain tumor cells that are also present on some types of normal cells.

Tumor necrosis factor- α (TNF- α) a cytokine produced by macrophages and T cells that has several functions in the immune response and is the prototype of the TNF family of cytokines. These cytokines function as cell-associated or secreted proteins that interact with receptors of the tumor necrosis factor receptor (TNFR) family.

Tumor-specific antigens antigens that are characteristic of tumor cells and are not expressed by normal cells.

Tumor suppressor genes genes for cellular proteins that function to prevent cells from becoming cancerous.

Type I, type II, type III, type IV hypersensitivity reactions *see* **hypersensitivity reactions**

Type I Interferon cytokines (interferons- α and - β) produced by virus-infected cells that interfere with viral replication by the infected cell, and also signal neighboring uninfected cells to prepare for infection.

Unproductive rearrangements DNA rearrangements of immunoglobulin and T-cell receptor genes that produce a gene that cannot make a functional polypeptide chain.

Urticaria the technical term for hives, which are red, itchy skin welts usually brought on by an allergic reaction.

V domain *see* **variable domain**

V gene segment *see* **variable (V) gene segment**

V(D)J recombinase the set of enzymes needed to recombine V, D, and J segments.

V region *see* **variable region**.

Vaccination the deliberate induction of protective immunity to a pathogen by the administration of killed or non-pathogenic forms of the pathogen, or its antigens, to induce an immune response.

Vaccine any preparation made from a pathogen that is used for vaccination and provides protective immunity against infection with the pathogen.

Vaccinia the cowpox virus. It causes a limited infection in humans that leads to immunity to the human smallpox virus. Was used as a vaccine against smallpox.

Variable domain (V domain) the amino-terminal domain of immunoglobulin and T-cell receptor polypeptide chains. Paired variable domains make up the antigen-binding site.

Variable (V) gene segment DNA sequence in the immunoglobulin or T-cell receptor genes that encodes the first 95 or so amino acids of the V domain. There are multiple different V gene segments in the germline genome. To produce a complete exon encoding a V domain, one V gene segment must be rearranged to join up with a J or a rearranged DJ gene segment.

Variable region (V region) the part of an immunoglobulin or T-cell receptor, or of its constituent polypeptide chains, that varies in amino acid sequence between isoforms having different antigenic specificities. It is responsible for determining antigen specificity.

Variable surface glycoproteins (VSGs) glycoproteins that form the surface coat of African trypanosomes. The trypanosome can repeatedly change its glycoprotein coat by expressing different glycoprotein genes using a process akin to gene conversion.

Variola name given to both the smallpox virus and the disease it causes: smallpox.

Variolation historical procedure for immunization against smallpox in which a small amount of live smallpox virus was introduced through scarification of the skin.

Vascular addressins mucin-like cell adhesion molecules on endothelial cells to which some leukocyte adhesion molecules bind. They determine the selective homing of leukocytes to particular sites in the body.

Viruses submicroscopic pathogens composed of a nucleic acid genome enclosed in a protein coat. They replicate only in a living cell because they do not possess all the metabolic machinery required for independent life. A viral particle is called a virion.

VLA-4 integrin present on the surface of T lymphocytes that binds to mucosal cell adhesion molecules.

VpreB *see* **pre-B-cell receptor**

Weibel-Palade bodies granules containing P-selectin, which are present inside endothelial cells.

Wheal-and-flare reaction the reaction observed when small amounts of allergen are injected into the dermis of an individual who is allergic to the antigen. It consists of a raised area of skin containing fluid (the wheal) with a spreading, red, itchy reaction around it (the flare).

Wiskott-Aldrich syndrome a genetic disease in which interactions of T cells and B cells are defective. Antibody responses against polysaccharide antigens are deficient, and patients are susceptible to infection with pyogenic bacteria.

X-linked agammaglobulinemia (XLA) a genetic disorder in which B-cell development is arrested at the pre-B-cell stage and neither mature B cells or antibodies are formed. The disease is due to a defect in the gene encoding the protein tyrosine kinase Btk.

X-linked hyper-IgM syndrome *see* **hyper IgM syndrome**

X-linked lymphoproliferative syndrome immunodeficiency due to a defect in the SH2D1A gene on the X chromosome, resulting in an inability to control EBV infections.

Xenoantibodies antibodies produced in one species against the antigens of another species.

Xenoantigens antigens on the tissues of one species that provoke an immune response in members of another species.

Xenogeneic coming from a different species.

Xenograft an organ from one species transplanted into another species.

Xenotransplantation the transplantation of organs from one species into another. It is being explored as a possible solution to the shortage of human organs for clinical transplantation.

ZAP-70 a cytoplasmic tyrosine kinase in T cells that forms part of the signal transduction pathway from T-cell receptors.

Zymogen the inactive form in which some enzymes are synthesized. Active enzyme is usually produced by proteolytic cleavage of the zymogen.

Figure Acknowledgments

Chapter 1

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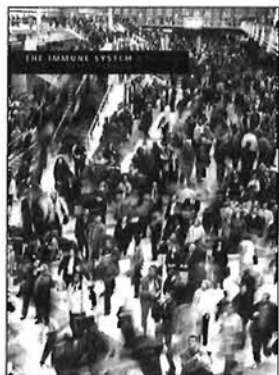
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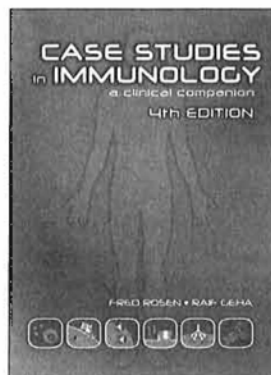
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Peter Parham is on the faculty at Stanford University where he is a Professor in the Departments of Structural Biology, and Microbiology and Immunology.

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