

**Glossary of immunological terminology**

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(Please let me know of any errors! mchercl@uic.edu)

References:

- JT JANEWAY, Charles A., Paul TRAVERS, Mark WALPORT, and J. Donald CAPRA, *Immunobiology: The Immune System in Health and Disease*, 4th ed. New York: Garland Publishing, 1999.
- LJ LEVINSON, Warren, and Ernest JAWETZ, *Examination and Board Review: Medical Microbiology and Immunology*, 5th ed. Stamford, Connecticut: Appleton and Lange, 1998.
- SO SOMPAYRAC, Lauren, *How the Immune System Works*. Blackwell Science, 1999.

Reference to handouts from lecture are given by lecture number, followed by a colon and the page number of the handout (e.g. "3:10" means handout to lecture 3, page 10).

Lectures:

1-3	Introduction to immunology 1, 2, 3	Teodorescu
4	Microbial pathogenicity	Hendrickson
5	Viruses: structure and multiplication	Prabhakar
6-8	Diversity of immunoglobulin binding	Kenter
9-11	Antigen-antibody reactions	Cohen
12	Complement 1	Ucker
13	Complement 2	Ucker
14	Phagocytes and phagocytosis	Pittrak
15	Lymphoid organs and cell surface markers	Teodorescu
16	Major histocompatibility complex	Teodorescu
17	Lymphocyte activation and mitogens	Teodorescu
18	Lymphokines and cytokines	Teodorescu
19	Lymphocyte-target cell interactions	Teodorescu
20	Cell collaboration in antibody formation	Teodorescu
21	Origin and distribution of lymphocytes	Teodorescu
22	The humoral immune response	Teodorescu
23-24	Cell-mediated immunity 1 and 2	Teodorescu
25	Tolerance and manipulation of the immune response	Teodorescu
26	Immunity to protozoa and worms	Teodorescu
27	Immunodeficiencies	Rich
28	Blood groups	Sosler
29	Hypersensitivity reactions	Cohen
30	Type III hypersensitivity diseases	Cohen
31	Autoimmunity	Cohen

32	Tumor antigens and tumor immunity	Cohen
33	Tumor immunotherapy	Cohen

Also see the materials on the web page of the department of microbiology and immunology at <http://www.uic.edu/depts/mcmi/restricted/med/mim425>.

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**Activation of B cells.** CD45, present on all leukocytes, is involved in signal delivery at the surface Ig (17:9). CD40 is the critical molecule for the “send” (?) signal (17:8).

Proliferation of B cells is induced by IL-4 (17:8).

See JT 177 fig. 5.14 for a flowchart depicting B cell activation.

B cells can be activated either by T-cell dependent activation or by T-cell independent activation (SO 33). In T-cell dependent activation of B cells, two signals are required: (1) specific recognition of the cognate antigen by B cell receptors (BCRs) on the surface of the B cell (and clustering of the BCRs), and (2) a co-stimulatory signal provided by a T<sub>H</sub> cell. In contrast, T-cell independent activation of B cells does not require stimulation by T<sub>H</sub> cells. This type of activation is antigen specific; only those B cells whose receptors recognize the repeated epitope will be activated.

**Activation of B1 cells (CD5<sup>+</sup> B cells).** Cross linking of surface Ig delivers a signal to B cells, mostly to CD5<sup>+</sup> B cells (17:9). The process of activation involves NFκB (17:10).

**Activation of T cells.** Membrane binding for “signal 1” can involve antigens, mitogens, or superantigens (17:6). Other activation systems depend on the γ chain (17:7). The TCR-delivered signal 1 can be inhibited by cyclosporin A and FK562 (17:7).

Effective activation is dependent upon “signal 2,” which is received from CD28 (which has ligands B7.1 and B7.2) on the surface of T cells; this signal stabilizes the mRNA for IL-2 (17:8).

Proliferation of T cells is induced by IL-2 (17:8). Production of IL-2 can be blocked by glucocorticoids or rapamycin (17:8).

See JT 178 fig. 5.15 for a flowchart depicting T cell activation.

The sequence of early events in T cell activation is: non-specific adhesion, TCR recognition of the MHC-peptide complex, and stronger cell-cell adhesion (SO 54).

**Acute phase response.** The acute phase response is a change in the blood that occurs during early phases of an infection. It includes the production of acute phase proteins and also of cellular elements (JT 593). The acute phase response can be triggered by IL-1, IL-6 and TNFα, which induce effects in the liver, bone marrow endothelium, hypothalamus, adipose tissue, muscle, and dendritic cells (JT 383 ff.). Acute phase response produces molecules that bind bacteria but not host cells (JT 384 fig. 10.15).

**Adaptive immunity.** See “immunity, adaptive.”

**ADCC** (“antibody-dependent cellular cytotoxicity”). ADCC is the killing of antibody-coated target cells by cells with Fc receptors that recognize the Fc region of the bound

antibody. Most ADCC is mediated by NK cells that have the Fc receptor Fc $\gamma$ RIII or CD16 on their surface (JT 594, 335). First, IgG antibodies are formed against some surface antigens of the offending cell, including recently attached virus particles. The Fc of IgG present on the surface of the cell is recognized by NK cells and the killing mechanism is activated (19:12).

**Addressin.** The addressin family of molecules are a type of adhesion molecule. (An example is the GlyCAM-1 on tall endothelial cells of the post-capillary venule of lymph nodes.) Some addressins are inducible in inflammation for leukocyte penetration in chronic inflammatory sites. They play a role in lymphocyte traffic through capillaries. Interference with adhesion molecules may affect the function of cells involved in inflammation and the immune response (15:10-11).

**Adhesion molecule.** Adhesion molecules are essential for any cell interaction (15:10). They mediate the binding of cells to each other, or of a cell to extracellular matrix proteins. Integrins, selectins, members of the immunoglobulin gene superfamily, and CD44 and related proteins are all adhesion molecules important in the operation of the immune system (JT 593). Memory cells have adhesion molecules which enable them to attach to endothelial cells of blood vessels (1:21). Lymphocytes can adhere to the endothelial wall and cross it via diapedesis (JT 392 fig. 10.22).

There are four families of adhesion molecules (15:10-11; JT 267-9): **(1)** selectins, **(2)** addressins, **(3)** Ig superfamily, **(4)** integrins.

T cells use adhesion molecules to attach temporarily to cells. If antigen is not encountered, the cells signal to each other to detach, and the T cell moves on. However, if there are enough copies (at least 100) of a particular antigen on the surface of a cell, the TCR for MHC + fragment will bind, and the two cells form a conjugate via multiple bridges (19:7).

**Adjuvant.** Any substance which enhances the immune response to an antigen with which it is mixed (JT 593). Adjuvants function by stimulating antigen presenting cells to express B7 (25:7). Adjuvants are only employed in laboratory settings. There are several kinds (JT 38 fig. 2.4).

Aluminum hydroxide only induces antibody formation (22:5). It mainly activates T<sub>H</sub>2 cells (22:6).

Freund's complete adjuvant (containing dead mycobacteria) induces both antibody formation and cell-mediated immunity (22:6).

Freund's incomplete adjuvant (lacks mycobacteria) only induces antibody formation (22:6).

**Adoptive transfer.** Memory of any reaction mediated by T cells may be transferred in syngenic animals by a process called adoptive transfer (23:15).

**Affinity.** The strength of the association of the antibody to the binding site of the antigen (9:2; JT 39). The tightness of binding between antibody and antigen is given by the affinity constant,  $K = \frac{[Ag:Ab]}{[Ag][Ab]}$ . If K is large (i.e. affinity is high), it means that in a mix of antigen and antibody, most are complexed (i.e. few are free). Contrast with "avidity."

**Affinity maturation.** Towards the end of the primary response and in all subsequent responses, IgG antibodies of higher and higher affinity are produced; this is called affinity maturation (22:10; JT 593, 405 fig. 10.33 and p. 407 fig. 10.36). Affinity maturation depends upon the interaction of activated B cells with cells in the specialized microenvironment of the germinal center (JT 316).

**AIDS** (“autoimmune deficiency syndrome”). The lack of T<sub>H</sub>1 cells in AIDS can cause normally benign infectious agents (such as pneumocystis carinii or leishmania) to grow unchecked (18:10). The deficiency of T<sub>H</sub>1 cells is due not only to the cytopathic effect of the virus, but also to T<sub>C</sub> cells that are activated to kill T<sub>H</sub>1 cells (23:14). See also “HIV.”

**Allergen.** An antigen that elicits a hypersensitivity or allergic reaction (JT 593). Allergens selectively evoke T<sub>H</sub>2 cells that drive an IgE response (JT 463).

**Allergy.** See “hypersensitivity.”

**Alloantibody.** An antibody specific for an alloantigen.

**Alloantigen.** An antigen that occurs in some, but not in other members of the same species.

**Allotype.** Immunologic differences between homologous proteins within the same species are known as allotypes (9:6; LJ 343). An antigenic determinant which induces an immune response in a member of the same species is an allotype (Dr. Teodorescu).

**Anamnestic response.** Synonym for “secondary immune response” (Stedman’s medical dictionary). Used to refer to the more rapid immune response which is produced when memory cells recognize a previously encountered antigen (23:20).

**Anaphylaxis.** This term usually denotes the immediate, transient kind of immunologic (allergic) reaction (type I hypersensitivity; JT 463 fig. 12.2) characterized by contraction of smooth muscle and dilation of capillaries due to release of pharmacologically active substances, classically initiated by the combination of antigen (allergen) with mast-cell-fixed cytophilic antibody (chiefly IgE). Systemic or generalized anaphylaxis is a reaction involving the smooth muscles and capillaries throughout the body of a sensitized individual, and can lead to anaphylactic shock and death (Stedman’s medical dictionary). Anaphylaxis is usually a type I hypersensitivity reaction, but can sometimes be a type III hypersensitivity reaction (Dr. Teodorescu).

**Anaphylactic shock.** An allergic reaction to systemically administered antigen that causes circulatory collapse and suffocation due to tracheal swelling. It results from binding of antigen to IgE antibody on connective tissue mast cells throughout the body, leading to the disseminated release of inflammatory mediators (JT 594, 473).

**Anaphylatoxin.** Small fragments of complement proteins released by cleavage during complement activation that recruit fluid and inflammatory cells to sites of antigen deposition. The fragments C5a, C3a and C4a are all anaphylatoxins (JT 594).

**Anemia, autoimmune hemolytic.** Autoimmune hemolytic anemia can be caused by IgG or IgM responses to antigens located on the surface of blood cells. For instance,

antibodies against self antigens on red blood cells trigger red blood cell destruction (JT 496).

**Anergy.** A state of non-responsiveness to an antigen. T and B cells are said to be anergic when they cannot respond to their specific antigen under optimal conditions of stimulation (JT 594, 211). Anergic cells continue to live and are thought to acquire the role of protectors against an autoimmune response (25:7).

The antigen-specific clonal expansion of naive T cells requires a second or co-stimulatory signal which must be delivered by the same antigen-presenting cell on which the T cell recognizes its specific antigen (JT 270). Antigen binding to the T cell receptor in the absence of co-stimulation not only fails to activate the cell but also leads to anergy (JT 272, 279).

Anergy can also be induced in B cells (JT 528 fig. 13.36).

**Ankylosing spondylitis.** An arthritic condition involving the sacroiliac joints and the spine. Caused by the B27 specificity of MHC which favors an autoimmune response (16:11; 31:2; JT 492 fig. 13.2). Can result from infection by salmonella or shigella (23:18).

**Antibody** (or “Ab”). Antibodies are the antigen-specific products of B cells, and the production of antibody in response to infection is the main contribution of B cells to adaptive immunity (JT 79, 307). This production of antibodies by B cells usually requires stimulation by helper T cells (JT 308), except in the case of T-independent antigens (JT 310).

Antibodies are part of a larger class of molecules called immunoglobulins (JT 80). Antibodies constitute part of the “third line of defense,” i.e. the adaptive immune response (1:11). The primary function of antibodies is to protect against infectious agents or their products. They provide resistance by (1) neutralizing toxins and viruses, (2) opsonizing microorganisms (LJ 347), or (3) activating complement (JT 24).

Antibodies are selectively developed through a learning process. They bind specifically to a particular substance—an antigen. Antibodies are produced by plasma cells in response to infection or immunization, and then bind to and neutralize pathogens or prepare them for uptake and destruction by phagocytes (JT 594). Antibody and antigen reciprocally define each other (1:11).

In order for the immune system to produce antibodies, four things are required: (1) antigen-presenting cells must present the antigen to T<sub>H</sub> cells; (2) T<sub>H</sub> cells must recognize the presented antigen; (3) opsonized antigen must be displayed by follicular dendritic cells; (4) B cells with receptors must recognize the antigen (SO 68).

Antibody molecules have a “Y”-shaped structure, with each half of the Y being exactly symmetrical (at the molecular level) to the other. Thus, the basic antibody structure is bivalent (9:2). Each half of the Y contains a heavy chain and a light chain. The light chain contains a variable region and a constant region. The heavy chain has a different variable region and a different constant region. Disulfide bonds connect the two halves of the Y, and connect each light chain to its nearest heavy chain.

Part of the constant region of the heavy chain (viz. the “trunk” of the Y) is called the Fc (“fragment which is crystallizable”) fragment (JT 83). This region is what determines which effector mechanisms the antibody will induce (i.e. what response it

triggers when the Fc gets bound); in other words, it determines the isotype of the antibody (JT 21, 81, 325).

The branch-part of the heavy and light chains is called the **Fab** (“fragment which binds antibody”) fragment (JT 83). This region is what gives the antibody its specificity.

There are five isotypes (q.v.) of antibody: IgA, IgD, IgE, IgG, IgM (1:12-13; LJ 341-3; SO 39), each of which has a different structural organization (JT 102).

**IgA** is found in secretions (such as mucous and colostrum). It is dimeric in secretions (and thereby has four binding sites), monomeric in serum (LJ 341). IgA is found low concentration in the serum (2000 TLE #1, question 22), but is the most abundant antibody in the body as a whole because it protects mucosal surfaces (SO 36). Transforming growth factor  $\beta$  (TGF $\beta$ ) induces IgA production by B cells in the intestine (18:13).

**IgD** is monomeric, and is almost found attached to a B cell in association with IgM (15:13). It is present in small amounts in serum (LJ 342).

**IgE** is monomeric. It is involved in type I hypersensitivity reactions. It binds to mast cells and basophils. It is the main host defense against certain helminth infections (LJ 342). One of the functions of IL-6 is to induce B cells to produce IgE (18:12). IgE induces mast cells to produce more IgE; this “positive feedback” loop is involved in type I hypersensitivity reactions (JT 466 fig. 12.5).

**IgG** is monomeric, is expressed by memory cells, can cross the placenta, binds to macrophages and neutrophils, is involved in the secondary response, has the longest half life, and of all the antibodies is found in the greatest amount in the serum. IgG is the immunoglobulin that opsonizes (LJ 341). IgG is the most abundant antibody in the blood (SO 36), though it is not the most abundant antibody in the body as a whole. IgG is the predominant class of serum antibody elicited in the secondary immune response to a protein antigen (2000 tutorial #1, question 2). The **IgG1** isotype efficiently opsonizes invading pathogens, whereas the **IgG3** isotype is effective at fixing complement (SO 37).

**IgM** is a pentamer (and thus has ten binding sites), binds complement, and is involved in the primary response. It is the first antibody to be produced in an immune response (LJ 106, 341). It has the highest avidity of the immunoglobulins (LJ 341).

For the relative proportions of antibody populations see JT 67 fig. 2.34.

Immunoglobulins of all heavy chain isotypes can be produced either in secreted form or as a membrane-bound receptor (JT 109).

When antibody binds antigen, their attachment is mediated by non-covalent interactions (electrostatic forces, hydrogen bonds, Van der Waals forces, hydrophobic forces), and is thus reversible (9:2; JT 88-9).

The order in which the three major Ig classes develop in plasma during infancy and childhood are IgM, IgG and IgA (2000 tutorial #1, question 3; JT 432 fig. 11.11).

In a 1 month old infant, by far the dominant Ig in the plasma is IgG1 (2000 TLE #1, question 6). The two classes of Ig in the highest concentration in the serum of a normal 2 year old child are IgG and IgM (2000 tutorial #1, question 4).

Early in the immune response, the affinity of antibodies is relatively low, but increases as the immune response progresses (Dr. Teodorescu).

Approximately 90% of all immunoglobulins (and hence antibodies) are produced in the bone marrow (22:8).

**Antibody combining site.** See “paratope.”

**Antibody-dependent cellular cytotoxicity.** See “ADCC.”

**Antigen** (or “Ag”). Any molecule that can bind specifically to an antibody. Not all antigens induce antibody production. Those antigens which *do* induce antibody production are called immunogens (JT 594). Antigen and antibody reciprocally define each other (1:11).

Antigens which induce antibodies (from B cells) with the help of T cells are called T-dependent (TD antigens). Some antigens can stimulate B cells directly (i.e. without the help of T cells) and are thus called T-independent (TI antigens) (an example is E. coli) (1:20; JT 309 fig. 9.2).

Even after a successful immune response is mounted, antigen can still persist in the body. The degree of persistence depends on the nature of the antigen. For example, poly-D-amino acids and polysaccharides are poorly degraded by enzymes, so they tend to persist (22:5). Sometimes antigens can persist (at a low level) for years after the initial infection, and this may contribute to the maintenance of B memory cells (22:9) and memory T cells (JT 409).

**Antigenic determinant.** See “epitope.”

**Antigenic drift.** An antigenic variation strategy employed by some viruses (such as the influenza virus) to evade host defenses. In antigenic drift, the virus mutates in such a fashion as to render antibodies from a previous immunization ineffective (23:16; JT 419).

**Antigenic shift.** An antigenic variation strategy employed by some viruses (such as the influenza virus) to evade host defenses. In antigenic shift, the virus exchanges RNA segments with animal viruses, with the result that the antigenic structure is substantially modified (23:16; JT 419).

**Antigenic variation.** One way in which an infectious agent can evade immune surveillance is by altering its antigens. There are three ways in which antigenic variation can be accomplished. **(1)** antigenic drift (q.v.); **(2)** antigenic shift (q.v.); **(3)** programmed rearrangements in the DNA of the pathogen (JT 418-21, especially fig. 11.3). Antigenic variation can even be employed by some cancer cells (JT 554 fig. 14.13).

**Antiserum.** The fluid component of clotted blood from an immune individual that contains antibodies against the molecule used for immunization (9:3; JT 595). Antiserum is polyclonal since multiple B cells, each programmed to form a particular antibody, are

activated to secrete antibodies that react with the same antigen with greater or lesser affinity (9:4).

**Apoptosis.** Programmed cell death. Apoptosis is characterized by nuclear DNA degradation, nuclear degeneration and condensation, and phagocytosis of the residua (JT 595, 293). During the maturational process, those immune cells which fail the selection processes die by apoptosis and are ingested by macrophages (21:9, 12). During negative selection, self reactive cells are induced to undergo apoptosis by activating their Fas receptors (21:10). Apoptosis is a “neat” cell death, which prevents the dying cell from damaging adjacent cells or from releasing viruses. This contrasts with necrosis, a “messy” cell death which can cause damage to adjacent cells (SO 61).

**Armed effector T cells.** Can be either  $T_H1$  or  $T_H2$  cells (q.v.).

**Arthus reaction.** A skin reaction in which antigen is injected into the dermis and reacts with IgG antibodies in the extracellular spaces, activating complement and phagocytic cells to produce a local inflammatory response (JT 595, 480 fig. 12.16). This is a type III hypersensitivity reaction (30:1-2).

**Atopy.** The increased tendency seen in some people to produce immediate hypersensitivity reactions (usually mediated by IgE antibodies, i.e. type I hypersensitivity) against innocuous substances (JT 595; LJ 369).

**Autoimmunity.** Adaptive immunity specific for self antigens (JT 595). This is obviously bad, because the body mounts an immune response against itself. It is not known what triggers autoimmunity, but both environmental and genetic factors, especially MHC genotype, are important (JT 491), as well as the hormonal status of the patient (31:1; JT 494). Most autoimmune diseases are antibody-mediated (LJ 375), though some are T cell mediated (JT 490 fig. 13.1 and pp. 495-6).

The presence of an autoantibody by itself is not sufficient to cause autoimmune disease. For disease to occur, the autoantigen must be available for binding by the autoantibody (JT 500). The loss of tolerance to self tissues requires the co-expression of both a suitable target antigen and co-stimulatory molecules (JT 523). The mere existence in the body of some B lymphocytes with receptor specificities directed against self is not in itself harmful. Before an immune response can be initiated, they need to receive effective help, the B cell antigen receptors must be ligated, and their intracellular signaling machinery must be set to respond normally (JT 528).

Autoimmune disease caused by antibodies also requires autoreactive T cells (JT 505 fig. 13.16).

It is not clear how autoimmune diseases are initiated. However, there is evidence that infections can trigger autoimmune disease in genetically susceptible individuals (JT 529). See “mimicry, molecular.”

Certain HLA serotypes are associated with particular autoimmune diseases (JT 492 fig. 13.2).

There is no known way to inhibit the immune response against a specific antigen (31:2). Consequently, there is no definitive cure for autoimmune disease; the treatment aims to control symptoms, using a variety of anti-inflammatory agents (31:3).

**Avidity.** The avidity of the antibodies that react with different epitopes on a pathogen is the net sum of the affinity of the individual combining sites (9:3; JT 50). Contrast with “affinity.”

**B7.** The major T cell co-stimulatory molecules are B7.1 and B7.2 (JT 270), closely related members of the immunoglobulin gene superfamily. They are expressed differentially on various antigen presenting cell types, and they may have different consequences for the responding T cells (JT 595). Adjuvants function by stimulating antigen presenting cells to express B7 (25:7). B cells do not constitutively express co-stimulatory activity but they can be induced (by various microbial constituents) to express B7.1 and especially B7.2 (JT 276).

**B27.** Having B27 specificity in the MHC predisposes a person to having an autoimmune response which can result in ankylosing spondylitis (16:11; 31: 2; JT 492 fig. 13.2).

**Bacteria.** Many infectious diseases are caused by bacteria, which are prokaryotic microorganisms that exist as many different species and strains. Bacteria can live on body surfaces, in extracellular spaces, in cellular vesicles, or in the cytosol, and different bacterial species cause distinctive infectious diseases (JT 595).

Bacteria can thwart or escape host defenses by shifting their expression of surface antigens (JT 421 fig. 11.3), by expressing a capsule that inhibits or retards phagocytosis, by taking up residence inside the host cell, and by synthesizing IgA-degrading protease (2000 TLE #1, question 15; JT 423 fig. 11.5).

Defense against parasitic bacteria, fungi and protozoa is carried out as follows. These parasites get ingested by macrophages and appear (fragmented or intact) in endosomal vesicles. The macrophages must be activated. In the induction phase, antigens of the invader are presented (by the infected macrophages) in association with MHC II to  $T_H1$  cells, and (due to leakage from the endosome into the cytosol) in association with MHC I to  $T_C$  cells. The infected macrophages are also presenting B7. The macrophages also secrete IL-12, which causes  $T_H0$  cells to differentiate into  $T_H1$  cells (23:16). In the effector phase, armed effector  $T_H1$  cells develop and migrate to the site of infection (23:17).

Some intracellular parasites evade host defenses by various means (23:18).

**BALT** (“bronchial-associated lymphoid tissues”). The lymphoid cells and organized lymphoid tissues in the respiratory tract (JT 596).

**Bare lymphocyte syndrome.** A condition in which either class I or class II MHC is congenitally absent (LJ 382). If MHC I is missing, then there are no  $CD8^+$  T cells. If MHC II is missing, then there are no  $CD4^+$  T cells (21:9).

**B cell** (or “B lymphocyte”). One of the two major types of lymphocyte (the other being T cells). There are actually two subsets of B cells. The more common ones are B-2 cells, usually just called B cells, which respond to T-dependent antigens. In contrast,  $CD5^+$  B-1 cells respond to T-independent antigens such as lipopolysaccharides (15:14; JT 217, 389).

**B1 cell** (or “ $CD5^+$  B cell”). This “unconventional” lineage of B cells arises early in ontogeny and has a distinctive receptor repertoire and functional properties (JT 217). (See JT 217 fig. 6.16 for a comparison of B1 and B2 cells.) These cells do not require T

cells for activation by antigens. They can be activated by the crosslinking between surface Ig and lipopolysaccharide (LPS) complexes present on gram negative bacteria (JT 389). The signal for activation is transmitted through NF $\kappa$ B, which in turn acts on the nucleus (20:5, 13).

B1 cells are more primitive and appear first in ontogeny (21:13; JT 218). They have no terminal deoxynucleotidyl transferase (TdT), so they are not continuously produced in the bone marrow (unlike B2 cells). They produce much of the serum IgM as well as IgG. The antibodies which they produce tend to be polyspecific or promiscuous (21:14), and are described as polyreactive (JT 218).

**B2 cell** (also called “conventional B cell” or simply “B cell”). Precursors of B cells (1:24) develop in the bone marrow (15:8) and are then distributed to the periphery (1:22). The antigen receptor on B lymphocytes, sometimes called the B cell receptor, is a cell-surface immunoglobulin. When activated by antigen, B cells differentiate into cells producing antibody molecules of the same antigen-specificity as this receptor (1:18; JT 595). An activated B cell expresses high levels of B7 and MHC II (SO 50). Each B cell expresses immunoglobulin of a single antigen specificity (JT 195). B cells can differentiate into memory cells (1:20).

The stages of B cell development are as follows: stem cell → early pro-B cell → late pro-B cell → large pre-B cell → small pre-B cell → immature B cell → mature naive B cell → lymphoblast → plasma cell (JT 197, 223; Dr. Kenter). When B cells differentiate to plasma cells, they lose their surface Ig and do not respond to antigen stimulation (15:13). See 21:11 concerning B cell differentiation.

B7.1 and B7.2 are critical surface molecules which are not present on resting B cells, but are present only after the B cells have been activated. Their ligand is CD28 on T cells (15:14).

T cells can ingest relatively large pathogens and present their antigens. However, if the pathogen is relatively small, B cells can also participate in this function (20:6).

B cells require two signals for activation. The first is a signal through antigen receptors. The second is a signal delivered usually through a T cell (JT 18).

B cells are usually activated by T<sub>H</sub>2 cells which have previously been activated (armed) by interaction with another antigen-presenting cell (such as a macrophage or a dendritic cell) (20:8). Two additional signals are essential for activating the B cell. Signal 1 is delivered to MHC II by the interaction with TCR. Signal 2 comes from the CD40 on B cells, which binds to the CD40 ligand on T<sub>H</sub>2 cells. For conjugate formation to occur, both B and T cells must recognize the same antigen, a process called “linked recognition” (20:9).

During the second phase of the B cell response, B cells are activated again at the germinal centers. Antigen:antibody complexes which have been formed now become attached to the follicular dendritic cells. Here B cells find the antigen and bind with their surface Ig. This binding would normally be inefficient, but is facilitated by a co-receptor complex composed of three molecules: CR2, CD19 and TAPA-1 (20:11).

Distribution of B cells: B cells are found in lymphoid tissue (specifically in primary follicles, germinal centers and medullary cords), in blood, and in bone marrow as plasma cells (21:14). B cells at different developmental stages are found in different anatomical sites (JT 219).

B cells are produced continuously throughout life (21:14).

Immature B cells become tolerant to self antigens and are most likely deleted (by being cross linked to the surface of tingible body macrophages) at the stage of immature B cells, before they develop IgD. They also interact with antigens in free form and become anergic in the absence of any help from T cells (25:10).

Mature B cells have both IgM and IgD and can encounter antigen in the periphery during recirculation. However, tolerance develops in the periphery because of subsequent loss of IgM receptors (the  $\mu$  chains remain sequestered in the cytoplasm), rendering the mature B cells anergic or tolerant. Peripheral tolerance can also operate during maturation in the germinal centers (25:10).

**B cell receptor.** See “BCR.”

**BCG** (“bacille Calmette-Guérin”). An attenuated form of mycobacterium bovis used in the preparation of BCG vaccine that is used for immunization against tuberculosis (23:20; Stedman’s medical dictionary).

**Bcl-X<sub>L</sub>**. A “death-inhibiting gene” (JT 188-9), also called a proto-oncogene. This gene is activated as part of a “survival signal” for cells (JT 319 fig. 9.11). It is also continually expressed in malignant B cells (22:7).

**BCR** (“B cell receptor”). The complete B cell receptor is generally considered as a complex of eight chains: two identical light chains, two identical heavy chains, and two each of the Ig $\alpha$  and Ig $\beta$  chains (JT 171; SO 31). Signaling from the B cell receptor complex depends on the presence (in the Ig $\alpha$  and Ig $\beta$  amino acid sequences) of immunoreceptor tyrosine-based activation motifs (ITAMs) (JT 172). Phosphorylation of the tyrosines in the ITAMs serves as the first intracellular signal indicating that the lymphocyte has detected its specific antigen (JT 173).

Note that a BCR recognizes antigen in its natural, unprocessed state. This contrasts with a TCR, which only recognizes antigen that has been “processed” and presented by a MHC molecule (SO 64).

**Bence Jones protein.** Proteins with unusual thermosolubility found in the urine of patients with multiple myeloma, consisting of monoclonal immunoglobulin light chains (Stedman’s medical dictionary), specifically  $\kappa$  and  $\lambda$  light chains (21:14). Bence Jones proteins are present in urine and plasma, and are composed of free light chains (Dr. Teodorescu).

**Blast transformation.** Antigenic stimulation transforms a small resting lymphocyte (in the G<sub>0</sub> phase of the cell cycle) into a blastic cell which may lead to clonal proliferation and expansion (i.e. enters G<sub>1</sub>, S and mitosis phases of the cell cycle) (JT 186). Within 24-48 hours of this initial stimulation (19:8), the lymphocyte expands up to 40-fold in volume (17:4). It also undergoes a variety of morphological changes; light microscopy reveals the cells to be intensely basophilic with visible nuclei (17:4); electron microscopy reveals euchromatic structure with visible Golgi, mitochondria and free polyribosomes (17:5). T<sub>C</sub> cells appear granular, while T<sub>H</sub> cells appear agranular (17:5).

There are several ways of measuring the degree of lymphocyte activation (17:5), such as the use of radiolabeled precursors (which get incorporated into newly synthesized DNA and RNA), or monitoring the increase in protein and uridine incorporation.

**Bruton's agammaglobulinemia** (or "X-linked hypogammaglobulinemia"). An immunodeficiency in which there is an abnormality of Bruton's tyrosine kinase (Btk) (21:11). Female carriers are normal. Young boys display very low levels of all immunoglobulins (IgG, IgA, IgM, IgD, IgE) and a virtual absence of B cells (LJ 380).

**Cachectin.** A synonym for TNF $\alpha$ .

**Calcineurin.** A cytosolic serine/threonine phosphatase which has a crucial but undefined role in signaling via the T cell receptor. The immunosuppressive drugs cyclosporin A and FK506 form complexes with cellular proteins called immunophilins that bind and inactivate calcineurin, thereby suppressing T cell responses (JT 596).

When a cell (usually a T cell) is stimulated, there is an increase in cytosolic Ca<sup>2+</sup> which causes calcineurin to dephosphorylate (and thereby activate) NFAT, which moves from the cytosol to the nucleus and acts as a transcriptional regulatory protein in combination with AP-1 factors (JT 180).

**Cancer.** Immune surveillance against cancer cells is generally carried out by macrophages and NK cells (SO 100).

**Candida albicans.** The most important species of candida. It is an opportunistic fungus which normally does not induce disease in healthy individuals, but may do so in a patient with impaired host defenses (LJ 271). Skin tests with candida antigens are uniformly positive in normal adults and are used as an indicator of competent cellular immunity. A person who does not respond to candida antigens in the skin test is presumed to have deficient cell-mediated immunity (LJ 272).

**Caspase.** Caspases are a family of closely related cysteine proteases that cleave proteins at aspartic acid residues (JT 596). They play an important role in apoptosis (JT 187).

**CD marker** (or "cluster of differentiation"). Groups of monoclonal antibodies that identify the same cell-surface molecule (JT 597; 15:10). There is an enormous number of different CD markers; see JT 579-87. Below are listed some CD markers which figure prominently in Dr. Teodorescu's handouts.

- CD 1** An MHC I-type molecule, controlled outside the MHC (on chromosome 1) which has the ability to bind lipid antigens from bacteria (16:7; JT 138).
- CD 2** T cells and thymocytes, most NK cells (15:11).
- CD 3** T cells, in close association with the TCR (15:12).
- CD 4** T cells, in association with MHC II (15:13).
- CD 5** T cells and B-1 cells (15:10).
- CD 7** T cells and thymocytes (15:11).
- CD 8** T cells, in association with MHC I (15:13).
- CD 10** Early pro-B cells. Also called CALLA (21:11).
- CD 19** B cells. Acts as a co-receptor (along with CD40) on B cells when they get activated (by T cells) to differentiate (21:11).

- CD 20** B cells (21:12).
- CD 28** T cells (15:12). Its ligands are B7.1, B7.2 (15:14, 16). The CD28 is involved in “signal 2” in the activation of T cells (17:8).
- CD 40** Helps in the interaction between B cells and T cells (20:8-9), and between T cells and macrophages (15:13-14).
- CD 45** Naive lymphocytes, memory cells, hematopoietic cells (15:10). Present on all leukocytes; involved in B cell activation (17:9).
- CD 59** See “protectin.”

**Cell-mediated immunity.** See “immunity, cell-mediated.”

**Centroblast.** Centroblasts are large, rapidly dividing cells found in germinal centers, and are the cells in which somatic hypermutation is believed to occur. Antibody-secreting and memory B cells derive from these cells (JT 597).

**Centrocyte.** Centrocytes are the small, non-proliferating B cells in germinal centers that derive from centroblasts. They may mature into antibody-secreting plasma cells or memory B cells, or may undergo apoptosis, depending on their receptor’s interaction with antigen (JT 597, 319 fig. 9.11).

**CGD** (“chronic granulomatous disease”). A defect wherein phagocytic cells’ ability to kill intracellular and/or ingested extracellular bacteria is compromised because the phagocytic cells cannot produce the superoxide radical and their antibacterial activity is thereby severely impaired (JT 435; LJ 382).

**Chain.** Each immunoglobulin chain consists of a distinct variable (V) and constant (C) region. For each type of immunoglobulin chain there is a separate pool of gene segments located on different chromosomes. Each pool contains a set of different V gene segments widely separated from the D (diversity), J (joining) and C gene segments (LJ 343). See also “gene.”

**Chemokine.** There are many types of chemokines (see table in JT 381). They constitute a specialized class of small proteins with a variety of functions in the attraction and activation of various types of leukocytes. Chemokines are produced by T cells, B cells and macrophages. They are classified on the basis of the position of their unpaired cysteine residues. Chemokines play an important role in inflammation. Some important chemokines include interleukin-8 (IL-8) and RANTES (18:11).

**Chemotaxis.** The directed movement of neutrophils to a particular endothelial location. Mediated by chemoattractants (14:3). (This is in contrast to chemokinesis, which is random movement.) Factors which are chemotactic for neutrophils include C5a and IL-8 (2000 TLE #1, question 34).

**Class switching** (or “isotype switching”). In class switching, the same assembled  $V_H$  (variable region of heavy chain) gene can sequentially associate with different  $C_H$  (constant region of heavy chain) genes so that the immunoglobulins produced later (IgG, IgA, or IgE) are specific for the same antigen as the original IgM but have different biological characteristics (LJ 344). Class switching occurs only with heavy chains; light chains do not undergo class switching (LJ 345).

Isotype switching requires expression of CD40 ligand by the helper T cell and is directed by cytokines (JT 314).

When isotype switching occurs, the active heavy-chain V-region exon undergoes somatic recombination with a 3' constant-region gene at a switch region of DNA. These DNA joints do not need to occur at precise sites, because they occur in intronic DNA. Thus, all switch recombinations are productive (JT 612).

Class-switching of cells involves changing production of some of its molecules. T cell collaboration is essential for any class switch (20:9).

T<sub>H</sub>2 cells can signal (via cytokines) to B cells for the B cells to switch the C (constant region) genes and thereby change antibody class. A particular cytokine promotes a particular antibody class (20:10), as summarized in the following table (from 20:11; also see JT 315 fig. 9.8).

Cytokine secreted by T <sub>H</sub> 2 cell	Ig class promoted in B cell
IL-2, 4	IgM
IFN $\gamma$	IgG2a
IL-4	IgG1 and IgE
IL-2 and TGF $\beta$	IgA

During B cell differentiation, T cells can stimulate B cells to switch by activating the CD40 receptors (and CD19 co-receptor) on the B cell (21:11; JT 105, 107).

Class switching takes place during the formation of the primary focus, when T and B cells interact and proliferate (22:6).

**Clonal deletion.** During development, T cells capable of reacting to antigens present in abundance in the thymus (including MHC and their peptides) are deleted (25:6). Clonal deletion is the main mechanism of central tolerance and can also occur in peripheral tolerance (JT 597). Antigen-induced loss from the B cell population is known as clonal deletion (JT 211).

**Clonal expansion.** The proliferation of antigen-specific lymphocytes in response to antigenic stimulation. This precedes their differentiation into effector cells. It is an essential step in adaptive immunity, allowing rare antigen-specific cells to increase in number so that they can effectively combat the pathogen that elicited the response (JT 597). One naive lymphocyte gives rise to a clone of around 1000 daughter cells of identical specificity (JT 16). This expansion requires approximately one week (SO 9). Immunological memory is the most important biological consequence of the development of adaptive immunity based on clonal selection (JT 17).

The antigen-specific clonal expansion of naive T cells requires a second or co-stimulatory signal which must be delivered by the same antigen-presenting cell on which the T cell recognizes its specific antigen (JT 270). Antigen binding to the T cell receptor in the absence of co-stimulation not only fails to activate the cell but also leads to anergy (JT 272, 279).

**Clonal ignorance** (or “immunological ignorance”). In order for a T cell to recognize an antigen, at least 100 copies of the same peptide for each antigen presenting cell (APC) must be present. Moreover, the APC must express B7; if this does not occur (as is the

case with immunization), the clone of T cells may be deleted or may become anergic (25:6). (See also JT 520 and SO 79.)

**Clonal selection.** When receptors on T or B cells recognize their cognate antigen, these cells are triggered (selected) to proliferate. As a result, a clone of B or T cells with identical antigen specificities is produced (SO 9, 105). Immunological memory is the most important biological consequence of the development of adaptive immunity based on clonal selection (JT 17).

**Clone.** A population of cells all derived from a single progenitor cell (JT 597). Each clone of lymphocytes is specific for one antigen (1:15). The number of different clones in an individual is estimated to be over one billion (1:15).

Each clone is trained to recognize only a certain (MHC II):(antigen fragment) combination. This is true for all types of T cell-APC interactions (20:12).

**Clustering.** Clustering (and sometimes also cross-linking) of some sort of surface receptor molecules is a frequently employed mechanism for initiating signal transmission within a cell. Some examples include the clustering of B cell receptors (SO 31-4), Fc receptors (SO 38), TCR/CD3 receptor complexes (SO 57).

**Clusters of differentiation.** See “CD markers.”

**CMI.** See “immunity, cell-mediated.”

**C-myc.** A proto-oncogene which plays a significant role in the initiation and maintenance of proliferation. When its product accumulates, cell proliferation stops and the lymphocyte reverts to its G0 (resting) state. Reciprocal translocation of c-myc close to H (heavy chain) or L (light chain) genes of Ig leads to B cell lymphoma (17:11).

**Cognate.** An antibody is specific for a particular antigen, and that antigen is said to be the “cognate” of the antibody (SO 9).

**Combinatorial diversity.** The ability to create many different specificities by making many different combinations of a (relatively) small number of gene segments is known as combinatorial diversity (JT 96).

**Complement.** A component of the innate immune response. The complement system is made up of a large number of distinct plasma proteins (JT 339) which are produced mainly in the liver (SO 17). There is a series of complement molecules which trigger each other in a domino-like cascade (1:10, 13) which operates very rapidly (SO 19). See LJ 355 and JT 341 for good flowcharts depicting complement activation. Complement is an amplificatory protease cascade which is tightly regulated and is self-limiting (12:1).

The regulation of complement by various proteins protects host cells from accidental damage (JT 356 fig. 9.51). Activated complement components can sometimes erroneously bind proteins on host cells, which can potentially destroy the host cell. Host cells are protected from such inadvertent damage by a series of complement-regulatory proteins. These proteins protect host cells from accidental complement activation, thereby confining these reactions to the surfaces of pathogens (JT 355). Certain proteins on the surface of cells (such as decay accelerating factor and protectin) prevent self cells from being coated by complement and attacked (SO 19).

The presence of complement makes the B cell response  $10^2$  to  $10^4$  times more effective than in the absence of complement (22:8).

The main effect of complement activation is to deposit large quantities of C3b on the surface of the initiating pathogen, where it can signal the ultimate destruction of the pathogen by phagocytes (JT 346). The most important action of complement is to facilitate the uptake and destruction of pathogens by phagocytic cells. This occurs by the specific recognition of bound complement components by CRs on phagocytes (JT 348).

The effector functions of complement can be activated through three pathways: the classical pathway, the mannan-binding lectin pathway, and the alternative pathway (JT 339 ff., see also the summary chart in JT 373 fig. 10.8).

The alternative pathway is more important for the first exposure to an infectious agent (LJ 354). The alternative pathway of complement is stimulated by bacterial cell walls, especially lipopolysaccharides (2000 TLE #1, question 24).

The mannan-binding lectin pathway involves binding between a MBL complex (mannan-binding lectin) and a MASP (MBL-associated serine protease) (JT 373), which converts C3 into C3b and initiates the complement cascade. This pathway is effective at targeting carbohydrate on the surface of an invading pathogen (SO 19).

Complement is necessary to mount a host response against encapsulated bacteria (2000 TLE #1, question 16).

Complement is heat labile (Dr. Teodorescu), and will not function well at temperatures far from normal body temperature.

**Complement receptors.** See “CR.”

**Concanavalin A** (or “Con A”). A commonly employed polyclonal mitogen which activates T cells (17:4; JT 60 fig. 2.26). The receptors for concanavalin A are glucosyl and manosyl residues on glycoproteins (17:6).

**Conjugate.** A conjugate is formed when a T cell recognizes enough copies (at least 100) of an antigen on the surface of another cell and binds to that cell via multiple bridges. Various antibodies can interfere with any of the molecules participating in these bridges, resulting in clonal anergy (19:7).

During the formation of a conjugate, the binding of the TCR induces a conformational change in the LFA-1, whose affinity for ICAMs is significantly increased (19:7). With signaling help from the CD4 or CD8 co-receptor molecules, the TCR/CD3 gives signal 1 to T cells to become activated (19:7). Infected dendritic cells induce the expression of B7.1 and B7.2 on the surface of APCs, and B7 interacts with CD28 on T cells to deliver signal 2 (19:8).

**Contact dermatitis.** A type IV hypersensitivity reaction. An example is the reaction to pentadecacatechol, the compound found in poison ivy (JT 483).

**Corticosteroid.** Corticosteroid drugs are powerful anti-inflammatory agents that are used widely to suppress the harmful effects of immune responses of autoimmune or allergic origin, as well as those induced by graft rejection (JT 538). Corticosteroid therapy induces a number of effects (JT 539 fig. 14.3).

**Cortisone.** Treatment with cortisone (as an anti-inflammatory agent) can deplete the cells in the cortical region of the thymus by approximately 65% (21:7).

**CR** (“complement receptor”). Specific receptors for complement components elicit specific cellular responses by the host (13:3). The most important action of complement is to facilitate the uptake and destruction of pathogens by phagocytic cells. This occurs by the specific recognition of bound complement components by CRs on phagocytes (JT 348). CRs are found mostly on B cells and macrophages, as well as on follicular dendritic cells in germinal centers (15:10).

**Crosslinking.** The crucial effect of ligand binding to antigen receptors is to cause them to cluster together on the cell surface (JT 164). Antigen receptor clustering (q.v.) occurs when the receptors are crosslinked (JT 165; also see JT 176-7).

**Crossreactive.** Antibodies that can bind more than one type of antigen are said to be crossreactive (9:3).

**Cyclophosphamide.** A powerful immunosuppressant which causes cross-linking of DNA strands in proliferating cells (23:14). This mainly kills cells which are in the proliferative state. When antigen stimulation is induced and cyclophosphamide is injected during the phase of B cell proliferation, the clone may be eliminated and tolerance induced, though this tolerance is only transient since new clones of B cells will develop (25:11).

**Cyclosporin A.** A powerful immunosuppressive drug that inhibits signaling from the T cell receptor, thereby preventing T cell activation and effector function. It binds to cyclophilin, and this complex binds to and inactivates the serine/threonine phosphatase calcineurin (17:7; JT 598). Cyclosporin A has a variety of effects (JT 541-2).

**Cytokine.** Intercellular messenger molecules which constitute part of the innate immune response (1:10). This term covers several subcategories, including factors, interferons, growth factors, lymphokines and interleukins (18:6; JT 288 ff.). Most cytokines are very short lived in circulation (1-5 minutes) (18:7). Due to their low concentration in fluids, a sensitive assay (such as sandwich ELISA) must be employed to detect their presence (18:7).

The general mechanism of activation is similar for almost all cytokines. When a cytokine gets bound by its receptor, the receptors form associations (homodimers or heterodimers) with some signal-transducing domain and with Janus kinases (JAKs). The result of the association is the tyrosine phosphorylation (and activation) of the JAKs, which in turn causes the phosphorylation (and activation) of STATs, thereby transmitting the activation signal to the nucleus (18:14).

**Cytokine antagonism.** The subsets of T cells regulate each other through an antagonistic effect.  $\text{IFN}\gamma$  made by type 1 cells ( $T_H1$  and  $T_C1$ ) inhibits type 2 cells ( $T_H2$  and  $T_C2$ ) by acting on their interferon receptors. Conversely, type 2 cells act on macrophages through IL-10 and make them deliver a negative signal to  $T_H1$  cells (18:15).

**Cytokine receptor.** See “IL receptor.”

**Cytotoxic T cell.** See “ $T_C$  cell.”

**DAF** (“decay accelerating factor”). A protein found on the surface of human cells which accelerates the breakdown of the convertase, C3bBb by other proteins in the blood. The purpose is to prevent self cells from being coated with complement and attacked (SO 19).

**Decay accelerating factor.** See “DAF.”

**Delayed type hypersensitivity (DTH).** See type IV under “hypersensitivity.”

**Dendritic cell** (or “interdigitating reticular cell,” JT 266). Dendritic cells are not phagocytic, but they are easily infected by most viruses, which makes them very effective professional antigen-presenting cells (PAPC) in the response to viral infections (19:6; JT 263). In fact, the only known function of dendritic cells is to present antigen to T cells (JT 272). Dendritic cells are actually Langerhans cells which have migrated to the deep cortex (paracortex) of a regional lymph node (23:19). As the Langerhans cells are migrating towards the lymph node, they upregulate their surface expression of B7 and MHC II (SO 49). Langerhans cells can ingest antigen but have no co-stimulatory activity. However, once they have migrated to lymph nodes and differentiate into dendritic cells, they no longer ingest antigen but do have co-stimulatory activity (JT 274 fig. 8.14). Dendritic cells can activate naive T cells (SO 49) and can re-stimulate experienced T cells (SO 50).

**Dendritic cell, follicular.** Follicular dendritic cells are unrelated to plain old “dendritic cells” (SO 65). The follicular dendritic cells of lymphoid follicles are cells of uncertain origin with long branching processes that make intimate contact with many different B cells and present antigen to those B cells. They have Fc receptors that are not internalized by receptor-mediated endocytosis and thus hold antigen:antibody complexes on the surface for long periods. These cells are crucial in selecting antigen-binding B cells during antibody responses (JT 600).

**Diabetes.** Insulin-dependent diabetes mellitus (IDDM) has been linked to certain HLA serologies, particularly DR3/DR4 (JT 492-5). It often manifests as an autoimmune disease in which antibodies are produced against antigens of the  $\beta$  cells in the islets of Langerhans (JT 508 fig. 13.19). The autoimmunity responsible for IDDM can sometimes be triggered by viral infection (JT 530 fig. 13.38).

**Diapedesis.** The movement of blood cells, particularly leukocytes, from the blood across blood vessel walls into tissues (JT 599, 378).

**Diffuse intravascular coagulation.** Caused mainly by the action of TNF $\alpha$  produced during an infection with gram negative bacteria which release LPS. Presents as a shock with drop in blood pressure due mainly to increased vascular permeability (18:9-10).

**DiGeorge syndrome.** An autosomal dominant condition arising from developmental failure of the 3rd and 4th pharyngeal pouches, resulting in the absence or underdevelopment of the thymus and parathyroid gland. The immunologically related sequelae include a deficiency in T cell immunity (21:7; LJ 380; Stedman’s medical dictionary).

**Distribution of lymphoid cells in transit.** The thoracic duct contains B cells and T cells. The peripheral blood contains mainly T cells (80-85%), some B cells (10%), some NK cells (5-10%) and some  $\gamma\delta$  TCR cells (1-5%) (15:7).

**Diversity of receptors.** During development, receptor diversity in B and T lymphocytes is provided by different strategies. B cell receptors can diversify by mutation, but cannot use combinations of D genes (in the VDJ complex). T cell receptors cannot diversify by mutation, but are capable of using different combinations of D genes (2000 tutorial #1, question 8).

**Double negative cell.** Double negative thymocytes are immature T cells within the thymus that lack expression of the two co-receptors, CD4 and CD8 (JT 599, 232).

**Double positive cell.** Double positive thymocytes are an intermediate stage in T cell development in the thymus and are characterized by expression of both the CD4 and CD8 co-receptor proteins (JT 599, 233).

After the rearrangement of genes for the  $\beta$  chains, thymocytes express TCR with a surrogate  $\alpha$  chain (called pT $\alpha$ ) together with the CD3 receptor complex. In addition, they acquire CD4 and CD8, and thereby become double positive cells (21:8).

**DTH** (“delayed type hypersensitivity”). See type IV under “hypersensitivity.”

**EAE** (“experimental allergic encephalomyelitis”). An inflammatory disease of the central nervous system that develops after mice are immunized with neural antigens in a strong adjuvant (JT 600). This condition resembles multiple sclerosis (25:7).

**Eczema.** Accumulation of fluid, cell proliferation, and formation of vesicles. May be a clinical manifestation of contact hypersensitivity (23:20).

**Effector mechanism.** Effector mechanisms are those processes by which pathogens are destroyed and cleared from the body. Innate and adaptive immune responses use most of the same effector mechanisms to eliminate pathogens (JT 599). Also see JT 400-1.

**Effector phase.** See “phase, effector.”

**Eosinophil.** A type of polymorphonuclear leukocyte which plays an important role in the defense against parasites such as helminths (JT 5, 335). Eosinophils secrete a range of products (JT 470 fig. 12.8).

**Epitope** (or “antigenic determinant”). The sequence of amino acids on an antigen to which the corresponding shape of the variable region of the antibody (i.e. the paratope) attaches. An epitope comprises about 8 or 9 amino acids (9:3; JT 594 s.v. “antigenic determinant”). An epitope is recognized as foreign by the host’s immune system if the host does not express that epitope (9:4).

**Erythema.** Redness due to capillary dilation (Stedman’s medical dictionary).

**Erythroblastosis fetalis** (or “hemolytic disease of the newborn”). A severe form of Rh hemolytic disease in which maternal anti-Rh<sup>+</sup> antibody enters the fetus through the placenta and produces a hemolytic anemia so severe that the fetus has mainly immature erythroblasts in the peripheral blood (JT 600; LJ 366).

This effect (which occurs during a second pregnancy with an Rh<sup>+</sup> fetus) can be avoided if, during the first pregnancy with an Rh<sup>+</sup> fetus, IgG anti-Rh antibody is administered to the mother during the delivery. (Dr. Cohen says that the drug Rogan is commonly used, which is an anti-Rh<sup>+</sup> serum.) The IgG forms immune complexes with the Rh antigen and cross links the FcγRII on the naive B cells with their surface Ig, resulting in clonal inactivation of naive B cells (25:11).

**Experimental allergic encephalomyelitis.** See “EAE.”

**Fas.** A member of the TNF (tumor necrosis factor) family of receptors. It 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 (JT 600, 186 fig. 5.22).

**Fc receptor.** The Fc receptors are a family of molecules that can bind to the Fc portion of immunoglobulin molecules. Each member of the family recognizes immunoglobulin of one or a few closely related isotypes through a recognition domain on the α chain of the Fc receptor. Fc receptors are themselves members of the immunoglobulin gene superfamily of proteins (JT 332).

The Fc receptors on phagocytes must be able to distinguish antibody molecules bound to a pathogen from the majority of free antibody molecules that are not bound to anything. This condition is met by the aggregation or multimerization of antibodies that occurs when antibodies bind to multimeric antigens or to particles such as viruses and bacteria (JT 333).

**Fcγ receptor.** A family of cell surface receptors (including FcγRI, II and III) which bind the Fc portion of IgG molecules. Most Fcγ receptors bind only aggregated IgG, allowing them to discriminate bound antibody from free IgG. They are expressed on phagocytes, B lymphocytes, NK cells and follicular dendritic cells. They have a key role in humoral immunity, linking antibody binding to effector cell functions (JT 600).

FcγRII receptors are involved in negative signaling for B cells (17:10).

**FK506** (or “tacrolimus”). An immunosuppressive polypeptide drug that inactivates T cells by inhibiting signal transduction from the T cell receptor. FK506 and cyclosporin A are the most commonly immunosuppressive drugs in organ transplantation (JT 600). FK506 has a variety of effects (JT 541-2).

**FK562.** An immunosuppressive drug which (similarly to cyclosporin A) complexes with cytophilin, blocking calcineurin from binding Ca<sup>2+</sup> and thereby blocking the transmission of “signal 1” (17:7).

**Follicle.** Lymphoid tissues contain lymphoid follicles made up of follicular dendritic cells and B lymphocytes. The primary follicles contain resting B lymphocytes and are the site at which germinal centers form when they are entered by activated B cells, forming secondary follicles (1:24; 15:6; JT 609).

**Follicular dendritic cell.** See “dendritic cell, follicular.”

**Frustrated phagocytosis.** See “phagocytosis, frustrated.”

**Fungi.** Fungi are single-celled and multicellular eukaryotic organisms, including the yeasts and molds, that can cause a variety of diseases. Immunity to fungi is complex and involves both humoral and cell-mediated responses (JT 600). Concerning defense against fungi, see “bacteria.”

**GALT** (“gut-associated lymphoid tissue”). Lymphoid tissues closely associated with the gastrointestinal tract, including the palatine tonsils, Peyer’s patches, and intraepithelial lymphocytes (JT 601).

**Gamma/delta TCR cells** (“ $\gamma/\delta$  TCR cells”). These are primitive defense cells, similar to NK cells. They have dendritic morphology, are functionally very homogeneous and are found under mucosal epithelium. They appear to act non-specifically and kill cells that are induced to make heat shock proteins. They become able to kill these cells simply because they appear abnormal (19:12).

$\gamma/\delta$  TCR thymocytes are double negative (21:7), meaning that they express neither CD4 nor CD8.

**Gene.** The functional gene segments are organized into three clusters: H,  $\kappa$  and  $\lambda$ . The H cluster codes for the heavy chain, while the  $\kappa$  and  $\lambda$  clusters code for the light chains. Each cluster contains many segments (JT 92-3). The ability to create many different specificities by making many different combinations of a (relatively) small number of gene segments is known as combinatorial diversity (JT 96). Gene rearrangement is both a powerful mechanism for regulating gene expression, as well as for generating receptor diversity (JT 203-4). The production of the very large number of different immunoglobulin molecules ( $10^6$ - $10^9$ ) is made possible by DNA rearrangement and RNA splicing (LJ 343). See also “chain.”

Concerning the sequence of gene rearrangement, RNA processing and expression of antibody see JT 92 fig. 3.13 and p. 110 fig. 3.28. Concerning gene rearrangement in B cell development see JT 199 fig. 6.5 and p. 224 fig. 6.23. Concerning gene rearrangement in thymocyte development see JT 237 fig. 7.10.

**Germinal center.** Germinal centers in secondary lymphoid tissues are sites of intense B cell proliferation, selection, maturation, and death during antibody responses. Germinal centers form around follicular dendritic cell networks when activated B cells migrate into lymphoid tissues (1:24; 15:6; 22:7; JT 601, 219; SO 66).

When B cells (at this stage called “centroblasts”) migrate to the germinal centers, they proliferate in the “dark zone” of the germinal center. Gradually the cells become smaller and migrate from the dark zone through the basal light zone and apical light zone towards the periphery where there are follicular dendritic cells. During this phase of development the B cells exhibit a high rate of mutation (somatic hypermutation) and thereby develop receptors with varying degrees of “fit” for a particular antigen (22:7).

Affinity maturation depends upon the interaction of activated B cells with cells in the specialized microenvironment of the germinal center (JT 316).

**GM-CSF** (“granulocyte-macrophage colony-stimulating factor”). GM-CSF (and IL-3) activate the bone marrow to produce more macrophages and PMNs (18:12, 15-16; 26:7).

**Goodpasture's syndrome.** An autoimmune disease in which autoantibodies against basement membrane or type IV collagen are produced and cause extensive vasculitis (JT 500-1, 601).

**Graft.** Transplantation of tissue. See "transplantation."

**Graft versus host disease.** See "GvHD."

**Gram stain.** A method for differential staining of bacteria which is useful in bacterial taxonomy and identification. Gram positive bacteria have thicker, multi-layered cell walls which contain teichoic acids and stain blue, while gram negative bacteria have thinner, single-layer cell walls which contain lipopolysaccharide and stain red (LJ 6-7).

**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 (23:17; JT 303, 601). A granuloma forms when an intracellular pathogen or its constituents cannot be totally eliminated (JT 303 fig. 8.42).

**Graves' disease.** An autoimmune disease in which antibodies against the thyroid-stimulating receptor cause overproduction of thyroid hormone and thus hyperthyroidism (31:3; JT 601, 498 fig. 13.7; LJ 377).

**Growth factor.** Cytokines which can induce cell proliferation (18:6). Some are called "colony stimulating factors (CSF)" (18:7).

**GvHD** ("graft versus host disease"). If lymphoid tissue containing T cells is grafted to an immunoincompetent host, the result is graft versus host disease (JT 516; LJ 353). This means that the graft essentially mounts an immune response against the recipient. The recipient tolerates the grafted lymphoid tissue (23:12), but T cells from the graft recognize allogenic MHC I and II of the host and initiate an immune response. Initially all types of T cells (viz.  $T_C$ ,  $T_{H1}$ ,  $T_{H2}$ ) are involved. These secrete various cytokines (IL-1,  $IFN\gamma$ , IL-3) and in turn activate NK cells. The armed effector  $T_{H2}$  cells activate B cells through MHC II, CD40 and production of IL-4. Clinical symptoms of GvHD include splenomegaly, hepatomegaly, anemia, weight loss, low complement, diarrhea, skin rash (23:13).

GvHD is substantially suppressed by injection of monoclonal antibodies against  $TNF\alpha$  or by injection of the hybrid protein construct with TNF receptor and Fc of IgG. Administration of corticosteroids also helps (23:13).

**Haplotype.** In immunogenetics, this term refers to that portion of the phenotype determined by a set of closely linked genes inherited from one parent (Stedman's medical dictionary).

**Hapten.** A small molecule which, on its own, will not provoke an immune response. However, when bound to another molecule (such as a carrier; JT 35), the complex becomes immunogenic.

**Helminth.** A parasitic worm. (The other type of parasite is a protozoa.) See under "parasite."

**Helper T cells.** See “T<sub>H</sub>1 cells” and “T<sub>H</sub>2 cells.”

**Hemolytic disease of the newborn.** See “erythroblastosis fetalis.”

**Hereditary angioedema** (see 2000 TLE #1 question 26). An inherited deficiency of C1 esterase inhibitor results in angioedema (LJ 357). In the absence of the C1 esterase inhibitor, complement C1 continues to act on C4 to perpetuate the complement cascade, leading to capillary permeability and edema in several organs (LJ 362).

**Herpes virus.** The herpes virus evades the host defense by inhibiting the function of TAP (a protein that transports a peptide from the cytoplasm into the lumen of the endoplasmic reticulum), which results in less MHC I being expressed (23:15).

**Herpes zoster.** Varicella virus remaining from a childhood episode of “chickenpox” travels through a sensory neuron and develops a painful skin infection in the territory of that neuron. This condition is called herpes zoster (23:14-15).

**HEV** (“high endothelial venule”). Naive T cells and B cells enter lymphoid tissue by crossing the walls of specialized venules known as high endothelial venules (SO 66; JT 265).

**High endothelial venule.** See “HEV.”

**Histamine.** A vasoactive amine stored in mast cell granules. Histamine release triggered by antigen binding to IgE molecules on mast cells causes dilation of local blood vessels and smooth muscle contraction, producing some of the symptoms of immediate hypersensitivity reactions (JT 602; SO 37-8, 88-9).

**Histocompatibility antigens.** See “MHC antigens.”

**HIV** (“human immunodeficiency virus”). An enveloped retrovirus (JT 443). There are at least two types of HIV viruses. The HIV virus is carried in infected CD4 T cells, dendritic cells, and macrophages, and as a free virus in blood (JT 441). The cytokine receptor MIP-1 $\beta$  is a receptor for HIV, together with CD4 (18:14). HIV destroys CD4 cells, which are crucial for mounting a cell-mediated immune response (23:15-16). As the HIV infection runs its course there is a gradual decline in the function and numbers of CD4 T cells, and eventually patients have few CD4 T cells left. At this point, opportunistic infections begin to appear (JT 442, 452 fig. 11.27), and the condition is known as AIDS (q.v.). The HIV virus mutates rapidly, and thus quickly develops resistance to anti-viral drugs (JT 449). See JT 446-7 fig. 11.21 for a diagram of the HIV infective cycle.

**HLA** (“human leukocyte antigens”). The genetic designation for the human MHC. MHC I consists of HLA-A, HLA-B and HLA-C (SO 44). HLA-G is a non-polymorphic MHC I molecule expressed by trophoblast cells which protects the embryo from rejection by inhibiting activation of maternal NK cells (25:7).

**Hodgkin’s disease.** A malignancy which can develop from antigen presenting cells (21:11; JT 256 fig. 7.24).

**Homeostasis.** In the absence of infection, lymphocyte populations are kept remarkably constant in numbers. This homeostasis is achieved by a host of extracellular factors (JT 183, 289). The pool of B cells seems to remain constant (JT 214).

**Host versus graft reaction.** When an organ, tissue or even lymphoid tissue or bone marrow cells are transplanted, the result is host versus graft reaction (23:12). The recipient mounts an immune response against the transplant and rejects it.

**Hyper-IgM syndrome.** See “immunodeficiency with hyper IgM.”

**Hypersensitivity.** The state of heightened reactivity to antigen is called hypersensitivity. Immune responses to innocuous antigens that lead to symptomatic reactions upon re-exposure are called hypersensitivity reactions (JT 602; LJ 367-73).

The tendency to mount hypersensitivity reactions is called atopy (q.v.). There is a genetic component to atopy; in other words, the tendency to develop allergies can be inherited. However, the specific substances to which a person is allergic is something which is not inherited; rather, it is determined by the antigens present in the environment (29:4). See table in JT 463 fig. 12.2 and the following:

Hypersensitivity reaction	Mediators	Comments	Examples
<b>Type I</b> ("allergy")	IgE (synthesized by B cells) triggers mast cells.	Divided into two phases. The <b>immediate reaction</b> occurs within minutes, and follows from the activity of histamine, prostaglandins and other mediators (JT 471). The <b>late-phase reaction</b> occurs within hours, and is caused by the induced synthesis and release of mediators including leukotrienes, chemokines and cytokines from activated mast cells (JT 472).	Allergic rhinitis (hay fever), asthma (29:1; JT 463 fig. 12.2). Allergic reaction to the soluble derivatives of ragweed pollen (Dr. Teodorescu). Anaphylactic reaction.
<b>Type II</b>	IgG antibodies against cell-surface or matrix antigens (JT 479).		Thrombocytopenic purpura, pemphigus (31:2). Chronic urticaria (JT 463 fig. 12.2). Erythroblastosis fetalis, myasthenia gravis, Goodpasture's syndrome.
<b>Type III</b>	Antigen:antibody complexes form and get deposited in tissues (30:1). Mediated by IgG or IgM and complement (LJ 370).	Such reactions can arise when the antigen is soluble (JT 479).	Arthus reaction (30:1), serum sickness (30:2; JT 463 fig. 12.2), lupus erythematosus (30:2; 31:3).
<b>Type IV</b> ("delayed type hypersensitivity reaction")	T cell-mediated (JT 481). Primarily mediated by T <sub>C</sub> cells (29:2).	The following three forms are mediated by antibodies (23:19): (1) contact hypersensitivity (2) tuberculin type hypersensitivity (3) granulomatous hypersensitivity	Tuberculin (JT 482). Contact dermatitis (JT 483).

Concerning type I hypersensitivity: At an earlier stage of evolution, allergies (type I hypersensitivity) probably served as a protective mechanism against infestation by intestinal parasites (29:1). When an allergen passes through the membrane, it selectively stimulates T<sub>H</sub>2 cells to switch the antibody isotype in B cells from IgM to IgE (29:3), thereby triggering the allergic reaction. An allergic reaction recruits mast cells, but can additionally recruit basophils and eosinophils (29:3).

The following are more detailed descriptions of the three subtypes of type IV hypersensitivity. Also see JT 481 ff.

**Contact hypersensitivity** can be induced by chemicals in the environment or by natural products (such as poison ivy and poison oak). In the induction phase, these antigens enter Langerhans cells and become attached to proteins. The Langerhans cells migrate to the deep cortex (paracortex) of the regional lymph nodes, at which point they are known as dendritic cells. The antigens also cause these cells to express B7 and to present antigen (via MHC I and II) to type 1 T cells. Armed effector T cells develop. In

the effector phase the armed effector T cells home into the dermis (via chemotactic factors) and produce inflammatory cytokines and chemokines (23:19). Clinically this may manifest as eczema (23:20).

**Tuberculin type hypersensitivity.** The induction phase may result from any of the cell-mediated immune reactions. Bacterial, fungal and viral infections which induce activation of T<sub>H</sub>1 cells lead to the establishment of memory T cells. (This is called “tuberculin type” hypersensitivity because infection with mycobacterium tuberculosis or BCG (bacille Calmette-Guérin).) Elicitation refers to testing for the existence of memory T cells with inflammatory character, and is employed for diagnostic purposes. It involves intradermal injection of tuberculin (also called PPD) and induces a characteristic skin reaction (consisting of erythema and induration) detectable after 48-72 hours (23:20). This is useful as a positive control for establishing that an individual can mount an immune response (23:21). A very similar reaction can be elicited by administering the supernatant of lymphocytes activated with PHA (phytohemagglutinin) (23:21).

**Granulomatous hypersensitivity.** See “granuloma.”

**Hyposensitization therapy** (or “desensitization”). The reduction or abolition of allergic sensitivity or reactions to the specific antigen (allergen) (Stedman’s medical dictionary).

**ICAM** (“intercellular adhesion molecule”). The intercellular adhesion molecules (ICAM-1, ICAM-2, ICAM-3) are cell-surface ligands for the leukocyte integrins and are crucial in the binding of lymphocytes and other leukocytes to certain cells, including antigen presenting cells and endothelial cells. The ICAMs are members of the immunoglobulin superfamily (JT 604).

**Iccosome.** A small fragment of membrane coated with immune complexes that fragment off the processes of follicular dendritic cells in lymphoid follicles early in a secondary or subsequent antibody response (JT 602-3, 406). Antibodies produced in the primary focus form complexes with antigen; these complexes are called iccosomes (22:7).

**Idiotope.** An antigenic determinant formed by an idio type (20:13).

**Idiotype.** Each immunoglobulin molecule has the potential of binding a variety of antibodies directed at its unique features or its idiotype. An idiotype is made up of a series of idiotopes (JT 603; LJ 343).

**IFN** (“interferon”). Produced as a result of viral infections. Interferons activate specialized proteins in cells in order to defend against multiplication of viruses. Almost all nucleated cells can produce interferons (1:10). Interferons inhibit the growth of viruses by blocking the translation of viral proteins (LJ 176). There are three interferons (JT 589, 385).

**IFN $\alpha$**  Inhibits viral multiplication (18:10).

**IFN $\beta$**  Inhibits viral multiplication (18:10).

**IFN $\gamma$**  Produced by T<sub>H</sub>1 cells, but also by T<sub>C</sub> and NK cells (18:10). Has several functions:

- Activates macrophages during an infection. It makes macrophages very sensitive to a membrane form of TNF $\alpha$  on the surface of T<sub>H</sub>1 cells. It is delivered at close range (18:10).
- Inhibits viral replication (though less than IFN $\alpha$  and IFN $\beta$ ) (18:10).
- Suppresses B cell proliferation and forces them to differentiate to antibody-forming cells, and to switch to making IgG (18:10).
- Has an antiproliferative effect on tumor cells (18:10).
- Increases MHC expression (16:8, 9)—or, in humans, HLA expression—in antigen-presenting cells, thereby making them more visible for interaction with T cells in an anti-infection response (18:10).

Another general effect of all interferons is to increase the expression of MHC I molecules (JT 386). Interferons have *no direct effect* on extracellular virus particles (LJ 177).

**Ig** (“immunoglobulin”). A family of plasma proteins (JT 603). A certain subset of immunoglobulins (*viz.* IgA, IgD, IgE, IgG, IgM) are called antibodies (*q.v.*).

**Ig superfamily**. A family of molecules which are a type of adhesion molecule. They are genetically related to immunoglobulins and have the characteristic domain structure. Examples are ICAM-1, 2 and 3, which are present mainly on the vascular endothelium, macrophages and on antigen-presenting cells. Their ligands are usually the integrins or other Ig superfamily molecules (15:11).

**IL** (“interleukin”). Interleukins are cytokines with specialized functions in the interactions between leukocytes. However, some “interleukins” are made by cells other than leukocytes (18:6). There are many interleukins (see JT 588, 289; LJ 334-5). Those which appear frequently in Dr. Teodorescu’s handouts are listed below.

- IL-1** Produced by activated macrophages. Appears in two forms: secreted (IL-1 $\beta$ ) and insoluble on membranes (IL-1 $\alpha$ ). Potentiates the response of B and T cells to antigens and mitogens. Ingestion of bacteria and toxins stimulates the activation of macrophages and produces IL-1. This interleukin has multiple biological effects (18:8), including:
- It is a “competence inducing” factor in lymphocyte activation.
  - It can act as an autocrine or paracrine, stimulating cells to produce more IL-1.
  - It can induce the production of TNF $\alpha$  by macrophages.
  - It can activate macrophages to produce prostaglandins and to become cytotoxic and to have increased sensitivity to chemotaxis.
  - It can activate collagenase production in synovial cells, contributing to inflammation and cartilage destruction (as in arthritis).
  - It can activate osteoclasts, leading to bone resorption.
  - It induces endothelial cells to express adhesion molecules (such as ICAM-1), which makes leukocytes adhere to endothelial cells. This contributes to the inflammatory effect.
  - Its effects on the brain include inducing sleep, fever and anorexia.

IL-1 can be inhibited by IL-1RA (IL-1 receptor antagonist) and by corticosteroids (18:8). IL-1 is part of a “competence signal” (18:11).

IL-1 is a “competence factor” produced by APCs in the early stages of B cell activation (20:10).

**IL-2** Produced by B cells when stimulated by IL-6 (18:9). Also called T cell growth factor, and can be produced by  $T_H0$ ,  $T_H1$  and memory T cells. It tends to be produced mainly by  $CD4^+$  T cells, but  $CD8^+$  T cells will produce it when stimulated by dendritic cells. IL-2 It is considered a “progression signal” for cell proliferation. Like most cytokines, IL-2 has a short half life (3-4 minutes) (18:11). It has several actions:

- Acts as a proliferative agent for other cells, including NK cells (18:11).
- Causes conventional B cells (B2 cells) to proliferate (18:12).
- Activates  $T_C$  cells (19:8).

**IL-3** Also called “panspecific hemopoietin.” Produced by  $T_H$  cells. Unlike most cytokines, IL-3 (along with GM-CSF) acts at a distance on the bone marrow (18:12). IL-3 has several functions:

- Induces increased production of new polymorphonuclear cells and macrophages to be exported to the site of infection (18:12).
- Induces colony formation in vitro (18:12).
- Stimulates bone marrow to produce leukocytes (26:7).

**IL-4** Also called “B cell growth factor” (18:12). Produced by T cells when stimulated by IL-6 (18:9), specifically by  $T_H2$  cells (18:12). It can also be produced by basophils. IL-4 has several functions:

- Acts on receptors on blastic B cells to help them to proliferate (18:12).
- Pushes B cells towards the production of IgE (18:12).
- Induces  $T_H0$  cells to differentiate into  $T_H2$  cells (25:9-10).

**IL-6** Has many actions in common with IL-1 (JT 383 fig. 10.14). Produced mainly by macrophages and fibroblasts. Potentiates the response of B and T cells to generate IL-2 and IL-4, respectively. IL-6 and IL-1 induce each other’s expression. IL-6 activates liver cells to produce acute phase reactants, which includes (18:9):

- C reactive protein and mannose binding protein, which bind to some bacteria and prepare them for phagocytosis.
- Serum amyloid A is induced under chronic conditions, and gets deposited in muscles, kidneys and other tissues, causing amyloidosis.
- Fibrinogen production increases, causing an increase in the erythrocyte sedimentation rate in inflammation and infections.

IL-6 is a “competence factor” produced by APCs in the early stages of B cell activation (20:10).

**IL-7** A type of hemopoietin. Produced mainly by stromal cells in the bone marrow and by epithelial cells of the thymus where precursor cells grow (18:12). IL-7 stimulates B cells to differentiate (21:11).

- IL-8** A chemokine which is involved in attracting polymorphonuclear cells (PMN). It is produced by  $T_H1$  cells during the response to antigens on the surface of macrophages (18:11).
- IL-10** A cytokine produced by type 2 cells ( $T_H2$  and  $T_C2$ ) which inhibits  $T_H1$  cells (18:15; 25:10). This seems to play a role in preventing rejection of the fetus by the mother (25:7).
- IL-12** Produced by macrophages and  $T_H1$  cells. Has several functions (18:10):
- Helps the differentiation of  $CD4^+$  T cells into inflammatory T cells ( $T_H1$ ).
  - Activates NK cells, which participate in tumor cell killing and chronic inflammation.
  - Involved in the antagonism between  $T_H1$  and  $T_H2$  cells.
  - Induces  $T_H0$  cells to differentiate into  $T_H1$  cells (23:16; 25:9).

**IL receptor.** May have two chains for intermediate affinity or three chains ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) for high affinity. Cytokines are mainly effective on high affinity receptors. The  $\alpha$  and  $\beta$  chains are used for interaction with the cytokine, while the  $\gamma$  chain is involved in delivering signals to activate the cell (18:13). There are four main families of receptors:

- Ig superfamily, such as the IL-1 receptor.
- Hemopoietin family, such as the IL-2 receptor  $\beta$  and  $\gamma$  chains, IL-3, IL-4 (18:13).
- TNF family, including the Fas receptors (18:14).
- Chemokine family, such as the IL-8 receptor (18:14).

**Immune deviation** (or “split tolerance”). Reaction to one antigen (or more) on a cell surface but no reaction to others (Stedman’s medical dictionary). Animals injected with protein plus Freund’s *incomplete* adjuvant will develop antibodies against the protein. Subsequent injection of the protein plus Freund’s *complete* adjuvant will fail to induce delayed type hypersensitivity (type IV hypersensitivity). The mechanism is similar to that of oral tolerance, specifically: the initial injection activates  $T_H2$  cells, and in the subsequent injection those  $T_H2$  cells suppress  $T_H1$  cells (25:9).

**Immune response.** The magnitude of the immune response depends on the dose of immunogen administered. Below a certain threshold dose, most proteins do not elicit any immune response. As most infectious agents enter the body in small numbers, immune responses are generally elicited only by pathogens that multiply to a level sufficient to exceed the antigen dose threshold (JT 37).

There are several phases of antibody formation: lag phase (in which there is no antibody production), log phase (in which antibody production increases logarithmically), plateau, and decrease (22:9-10).

An immune response can be classified as primary (the body’s first encounter with an antigen) or secondary (all subsequent encounters with that same antigen). The differences between these responses is shown in the following table (from 22:10):

Characteristic	Primary response (to initial exposure)	Secondary response (to all subsequent exposures)
Latent period	long	short
Peak of antibody titer	low	high
Affinity of antibody	low	high
Avidity of antibody	low	high
Specificity	high	low
Number of reacting cells	low	high
Dose of antigen required to elicit a response	high	low
Antibody class which is primarily produced	IgM	IgG

IgM antibodies produced in the early phase have relatively poor affinity but high avidity (due to multiple combining sites; remember it is pentameric). Towards the end of the primary response and in all subsequent responses, IgG antibodies of higher and higher affinity are produced; this is called affinity maturation (22:10).

For phases of the immune response see JT 364 fig. 10.1; p. 390 fig. 10.20; p. 402 fig. 10.31; p. 412 fig. 10.42.

**Immunity, adaptive** (or “acquired immunity”). Adaptive immunity is triggered when an infection eludes the innate defense mechanisms and generates a threshold dose of antigen (JT 391). Adaptive immunity is the response of antigen-specific lymphocytes to antigen, including the development of immunological memory. Adaptive immune responses are generated by clonal selection of lymphocytes. Adaptive immune responses are distinct from innate and non-adaptive phases of immunity, which are not mediated by clonal selection of antigen-specific lymphocytes (JT 593).

**Immunity, cell-mediated.** Cell-mediated immunity (CMI) is carried out by  $T_C$  and  $T_H1$  cells. Antibodies which can provoke CMI include histocompatibility antigens, tumor antigens, viruses, chemicals or proteins on the skin, and microorganisms that cause chronic infection of macrophages (23:8).

**Immunity, innate.** The early phases of the host response to infection depend on innate immunity, in which a variety of innate resistance mechanisms recognize and respond to the presence of a pathogen. Innate immunity is present in all individuals at all times, does not increase with repeated exposure to a given pathogen, and does not discriminate between pathogens (JT 604). Compare with “adaptive immunity.”

**Immunization.** The deliberate provocation of an adaptive immune response by introducing antigen into the body (JT 603). Immunization can be induced by a natural route (such as infections) or through an artificial route (e.g. via vaccines) (22:5).

With repeated immunizations the overall specificity of the antibody population decreases. This is advantageous to the host, since an antibody directed against one infectious agent may fit well enough with another agent to provide some protection until a more specific response is mounted (22:11).

**Immunoassay.** A method of detecting substances by serological (immunological) methods. Some common assays (or at least those to which Dr. Teodorescu has made reference) are the following:

Coombs test. An anti-human globulin test for detecting antibodies. Specifically, it can be used to test whether a baby's red blood cells are coated with antibodies from the mother, and can thereby be used in prevention of erythroblastosis fetalis. In the direct Coombs test maternal IgG antibodies bound to the fetal red blood cells can be detected after washing the cells to remove unbound immunoglobulin that is present in the fetal serum. Adding anti-human immunoglobulin antibodies to the washed fetal red blood cells agglutinates any cells to which maternal antibodies are bound. This test is called "direct" because it directly detects antibody bound to the surface of the fetal red blood cells. The indirect Coombs test is used to detect non-agglutinating anti-Rh antibody in maternal serum; the serum is first incubated with Rh<sup>+</sup> red blood cells, which bind the anti-Rh antibody, after which the antibody-coated cells are washed to remove unbound immunoglobulin and are then agglutinated with anti-immunoglobulin antibody. This test is "indirect" because you are testing whether the mother's serum contains anti-Rh antibodies (not whether such antibodies have bound to fetal red blood cells). This test allows Rh incompatibilities that might lead to erythroblastosis fetalis to be detected (JT 45).

Enzyme-linked immunosorbent assay (ELISA). An enzyme is chemically linked to an antibody or antigen (for this example, let us assume that it is an antibody). The unlabeled component (i.e. that which has not been chemically linked to an enzyme; for this example let us assume that it is the antigen) is attached to a solid support which will adsorb a certain amount of any protein. The labeled antibody is allowed to bind to the unlabeled antigen under conditions where non-specific adsorption is blocked, and any unbound antibody and other proteins are washed away. Antibody binding is then detected by a reaction that converts a colorless substrate into a colored reaction product (JT 41; LJ 361). ELISA is an extremely sensitive assay (Dr. Teodorescu).

Hemagglutination inhibition. An agglutination reaction is based on an antibody's ability to alter the physical state of the antigen to which it binds (specifically, it induces agglutination of the antigen particles). In a hemagglutination reaction the target antigens are on the surface of the erythrocytes, and hemagglutination is the clumping which is induced by the antibody (JT 43; LJ 363).

Jerne plaque assay. An assay which enumerates individual antibody-forming cells (Stedman's medical dictionary).

Radial immunodiffusion (RID). Immunodiffusion is a technique used to study antigen-antibody reactions by observing precipitates formed by antigen-antibody complexes, which are formed by combination of specific antigen and antibodies which have diffused in a gel in which they have been separately placed. In radial immunodiffusion, antigen solution and antibody incorporated in agar are layered in tubes, permitting effective diffusion in the vertical dimension; the antibody-containing agar may be overlaid directly with antigen solution (Stedman's medical dictionary). Radial immunodiffusion is a quantitative assay (2000 TLE #1, question 35; LJ 358).

Radioallergosorbent test (RAST). A radioimmunoassay used to detect specific IgE antibodies responsible for hypersensitivity (Stedman's medical dictionary; see 2000 TLE #1, question 27). Radioallergosorbent test is a quantitative assay (2000 TLE #1, question 35).

**Radioimmunoassay (RIA).** An antibody or antigen (for this example, let us assume that it is an antibody) is radioactively labeled, usually with  $^{125}\text{I}$ . The unlabeled component (i.e. that which has not been radioactively labeled; for this example let us assume that it is the antigen) is attached to a solid support which will adsorb a certain amount of any protein. The labeled antibody is allowed to bind to the unlabeled antigen under conditions where non-specific adsorption is blocked, and any unbound antibody and other proteins are washed away. Antibody binding is measured directly in terms of the amount of radioactivity retained by the coated wells (JT 41; LJ 361). In a **competitive inhibition** radioimmunoassay, the presence and amount of a particular antigen in an unknown sample is determined by its ability to compete with a labeled reference antigen for binding to an antibody attached to a plastic well (JT 41).

**Rocket immunoelectrophoresis.** Immunoelectrophoresis is a kind of precipitin test in which the components of one group of immunological reactants (usually a mixture of antigens) are first separated on the basis of electrophoretic mobility in agar or other medium, the separated components then being identified (by means of the technique of double diffusion) on the basis of precipitates formed by reaction with components of the other group of reactants (viz. antibodies). Rocket immunoelectrophoresis is a quantitative method for serum proteins that involves electrophoresis of antigen into a gel containing antibody. The technique is restricted to detection of antigens that move to the positive pole on electrophoresis (Stedman's medical dictionary). Rocket immunoelectrophoresis is a quantitative assay (2000 TLE #1, question 35).

**Serum immunoelectrophoresis.** An assay which is **qualitative**, not quantitative. In other words, it detects the presence of a protein, but not its quantity (2000 TLE #1, question 35).

**Immunodeficiency.** A group of inherited or acquired disorders in which some aspect or aspects of the host defense are absent or functionally defective (JT 603). Immunodeficiencies can result from a variety of defects (JT 428 fig. 11.8). For instance, these disorders can result from lack of development of those cells which are local to the thymus, or from lack of development of those cells which mature in the thymus (21:11). Most of the gene defects that cause inherited immunodeficiencies are recessive (JT 429). Immunodeficiency can occur in any of the four major components of the immune system: **(1) B cells (antibody), (2) T cells, (3) complement, (4) phagocytes** (LJ 380).

**Immunodeficiency with hyper IgM.** Caused by a genetic defect in the CD40 ligand. In this syndrome, only T-independent antigens induce antibody formation, and the only antibody produced is IgM (LJ 380-1).

**Immunogen.** An antigen which induces antibody production (JT 594 s.v. "antigen"). Most antigens are also immunogens. However, not all antigens are immunogens; i.e. there are some antigens (e.g. haptens) which get bound by antibodies and yet do not provoke an immune response (LJ 319).

**Immunogenicity.** The ability of an antigen to provoke an immune response. There are five features which determine immunogenicity: **(1) foreignness, (2) size, (3) chemical or structural complexity, (4) epitopes, (5) dosage, route and timing of antigen administration** (LJ 319-20; JT 36).

**Immunological ignorance.** See “clonal ignorance.”

**Immunologically privileged sites.** See “privileged sites.”

**Immunosuppressant.** Immunosuppressive drugs are compounds that inhibit adaptive immune responses. They are used mainly in the treatment of graft rejection and severe autoimmune disease (JT 604). Some immunosuppressants discussed in class include: cyclophosphamide, cyclosporin A, FK506 (tacrolimus), FK562, rapamycin.

**Induction phase.** See “phase, induction.”

**Inflammation.** Generally consists of redness, heat (vasodilation), swelling (increased vascular permeability) and pain (irritation of nerve endings) (18:7; JT 376). A variety of cytokines are involved, including migration inhibitory factor (MIF), interleukin-1 (IL-1), interleukin-6, interleukin-12, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interferon gamma (IFN $\gamma$ ). Some chemokines are also involved, including interleukin-8 and RANTES.

**Innate immunity.** See “immunity, innate.”

**In situ activation of memory T cells.** In a second set reaction (i.e. a second attempt at grafting from the same donor) the graft is rejected very rapidly by an in situ activation of memory T cells (23:10).

**Integrin.** The integrin family of molecules are a type of adhesion molecule (15:11; JT 266-7). They are heterodimeric cell-surface proteins involved in cell-cell and cell-matrix interactions. They are important in adhesive interactions between lymphocytes and antigen-presenting cells and in lymphocyte and leukocyte migration into tissues (JT 604). Firm adhesion requires neutrophil activation to associate the integrins with cytoskeletal proteins (14:3). Integrins have Ig superfamily molecules as ligands (15:11). Genetic defect can result in conditions such as leukocyte adhesion deficiency (q.v.).

**Intercellular adhesion molecule.** See “ICAM.”

**Interdigitating cells.** See “dendritic cells.”

**Interferon.** See “IFN.”

**Interleukin.** See “IL.”

**Isotype.** Isotypes are defined by antigenic (amino acid) differences in their constant regions. IgG, IgM, IgA, IgD and IgE are different isotypes. Within a given isotype there are several subtypes. For instance, the IgG isotype has four subtypes: IgG1, IgG2, IgG3 and IgG4 (LJ 343), while the IgA isotype has two subtypes, IgA1 and IgA2 (JT 102). The isotype of an antibody depends on its C region locus.

**Isotype switching.** See “class switching.”

**ITAM** (“immunoreceptor tyrosine-based activation motif”). T and B cell antigen receptors are associated with transmembrane molecules with ITAMs in their cytoplasmic domains. These tyrosine-containing motifs are sites of tyrosine phosphorylation and of association with tyrosine kinases and other phosphotyrosine-binding moieties involved in receptor signaling (JT 604).

**ITIM** (“immune tyrosine-based inhibitory motif”). ITIMs oppose the actions of ITAMs; specifically, ITIMs recruit phosphatases to the receptor site that remove the phosphate groups added by tyrosine kinases (JT 604). A motif on the cytoplasmic end of B and T cell surface receptors which are involved in negative signaling (q.v.; JT 182).

**Janus kinase.** See “JAK.”

**JAK** (or “Janus kinase”). Cytokine receptors signal via Janus kinases, which are tyrosine kinases that are activated by the aggregation of cytokine receptors. These kinases phosphorylate proteins known as STATs (signal transducers and activators of transcription). STATs are normally found in the cytosol, but move to the nucleus upon phosphorylation and activate a variety of genes (17:9; JT 605).

**Killer inhibitory receptor.** See “KIR.”

**KIR** (“killer inhibitory receptor”). Involved in negative signaling for NK cells (17:10). Specifically, they inhibit the release of cytotoxic granules when the NK cell recognizes a healthy uninfected cell (JT 182).

**Langerhans cell.** A phagocytic cell found in the epidermis. Langerhans cells can migrate from the epidermis to regional lymph nodes via the lymphatics. In the lymph node they differentiate into dendritic cells (JT 605). Langerhans cells can ingest antigen but have no co-stimulatory activity. However, once they have migrated to lymph nodes and differentiate into dendritic cells, they no longer ingest antigen but do have co-stimulatory activity (JT 274 fig. 8.14).

TNF $\alpha$  and IFN $\gamma$  (secreted by NK cells) constitute the signals which, in skin infections, cause Langerhans cells to migrate to lymph nodes (23:16).

**Latency.** Some viruses can enter a state of latency in which the virus is not being replicated. In the latent state, the virus does not cause disease but, because there are no viral peptides to flag its presence, the virus cannot be eliminated. Such latent infections can be reactivated and this results in recurrent illness (JT 421).

**Lck.** A kinase of the Src family. Lck is involved in the initial events in T cell receptor signaling (JT 173).

**LCMV** (“lymphocytic choriomeningitis virus”). See 23:14.

**Lectin.** Any of a group of glycoproteins of primarily plant (usually seed) origin that binds to glycoproteins on the surface of cells causing agglutination, precipitation, or other phenomena resembling the action of specific antibody (Stedman’s medical dictionary).

**Leprosy.** See “mycobacterium leprae.”

**Leukocyte adhesion deficiency (LAD).** Autosomal recessive disease. Clinical syndrome characterized by poor umbilical vein stump healing at birth, omphalitis, skin and soft tissue infections. One type of LAD is due to deficiency of integrin proteins (CD11/CD18); other types also exist (14:10).

**Leukemia, acute lymphoblastic.** A malignancy which can develop from early T cells (21:11; JT 256 fig. 7.24).

**Leukemia, chronic lymphocytic.** A malignancy which can develop from mature T cells (21:11). It can also develop from B1 cells (21:14; JT 256 fig. 7.24).

**Leukemia, common acute lymphoblastic.** Malignancies derived from stem cells and progenitor cells. These cells contain terminal deoxynucleotidyl transferase (TdT) (21:6).

**LFA** (“lymphocyte function-associated antigen”).

LFA-1 is one of the leukocyte integrins, which are heterodimeric molecules involved in the interaction of leukocytes with other cells, such as endothelial cells and antigen-presenting cells. LFA-1 is particularly important in T cell adhesion to these cells (JT 606).

LFA-3 is a molecule found on many cells that is the ligand for CD2 (also known as LFA-2). It is a member of the immunoglobulin superfamily (JT 606).

**Lines of defense.** Dr. Teodorescu likes to use the term “first line of defense” for the anatomical (keratinized layer of skin, mucous slime), mechanical (passage of urine, lysozyme in tears, biliary fluid) and chemical (low pH of stomach and vagina) mechanisms (JT 370 fig. 10.6); “second line of defense” for the phagocytic cells; and “third line of defense” for the lymphocytes and antibodies (1:7).

**Linkage disequilibrium.** Alleles at linked loci within the major histocompatibility complex are said to be in linkage disequilibrium if they are inherited together more frequently than predicted from their individual frequencies (JT 605). The presence of linkage disequilibrium may be explained by its conferring a survival advantage in certain instances (as is found in the HLA-B53, an unusual MHC I gene which seems to confer some protection against malaria) (16:11).

**Linked recognition.** In order for B cells to be activated by  $T_H2$  cells, it is necessary that both the B cell and the  $T_H2$  cell recognize the same antigen. This process is called linked recognition. The B cells recognize mainly conformational determinants of the antigen, whereas the T cells recognize sequential determinants of the fragmented antigen (20:9; JT 310-11).

**Lipopolysaccharide.** See “LPS.”

**LPS** (“lipopolysaccharide”). A component of the cell wall of many gram negative bacteria (JT 389; LJ 6-7). Lipopolysaccharide serves as a polyclonal mitogen for activating only B cells (17:4; JT 60 fig. 2.26).  $CD5^+$  B-1 cells respond to T-independent antigens such as lipopolysaccharides (15:14; JT 217, 389). The alternative pathway of complement is stimulated by bacterial cell walls, especially lipopolysaccharides (2000 TLE #1, question 24).

**Lymphadenopathy.** Increase in lymph node size during an immune response (22:6).

**Lymph node.** Highly organized lymphoid structures that are the sites of convergence of an extensive system of vessels that collect the extracellular fluid from the tissues and return it to the blood. This extracellular fluid is produced continuously by filtration from the blood, and is called lymph, and the vessels which carry it are called lymphatic vessels. Cells bearing antigens from sites of infection in most parts of the body are brought to the lymph nodes, where they get trapped (JT 7-8).

Lymph nodes are composed of cortex, paracortex and medulla (15:7). In the lymph nodes, B cells are localized in follicles, while T cells are more diffusely distributed in the surrounding paracortical areas (15:7; JT 8).

Lymphocytes (both T cells and B cells) enter the lymph nodes (1) from the afferent lymphatics which bring fluid from tissues during an inflammatory reaction, and (2) through the postcapillary venules of lymph nodes, where they attach to adhesion molecules on specialized tall endothelial cells. Subsequently they cross into the cortex (15:7).

**Lymphocyte.** Lymphocytes (descended from common lymphoid progenitor cells) are part of the adaptive immune system. They comprise T cells, B cells and NK cells. Lymphocytes (both T cells and B cells) can differentiate into memory cells (1:20). Lymphocytes do not adhere to glass (15:8, 16), in contrast to macrophages. There are approximately  $2 \times 10^{12}$  lymphocytes in humans. Of those cells, about  $10^9$  are short lived cells which are produced and destroyed daily (21:15). An individual lymphocyte is equipped with receptors that will recognize only one particular antigen (JT 6).

Lymphocytes require two signals for activation. The first signal is delivered through antigen receptors. For B cells, the second signal is usually delivered by a T cell, whereas for T cells, the second signal is delivered by a professional antigen presenting cell (such as a dendritic cell) (JT 18).

For the relative proportions of lymphocyte populations see JT 57 fig. 2.23 and p. 67 fig. 2.34.

**Lymphocytic choriomeningitis virus.** See “LCMV.”

**Lymphoid tissue.** All lymphoid tissue (lymph nodes, spleen, mucosal-associated lymphoid tissues) all share the same basic architecture. Each of these tissues operates on the same principle, trapping antigen from sites of infection and presenting it to migratory small lymphocytes (T and B cells), thus inducing adaptive immune responses (JT 10; SO 65).

**Lymphoma, Burkitt's.** A malignancy in the spleen deriving from mature B cells (21:14).

**Lymphoma, follicular center.** A malignancy in the lymph node deriving from mature B cells (21:14).

**Lymphokine.** A cytokine made by a lymphocyte (1:18).

**Lysosome.** A vacuole within a phagocyte that contains pathogen-degrading enzymes. The lysosome fuses with a phagosome in order to degrade any pathogen which the phagosome has ingested (1:9).

**MAC** (“membrane attack complex”). The complement system can mediate the assembly of a membrane attack complex on the surface of an offending cell; this complex will facilitate the puncturing of the pathogen's membrane (SO 18).

**Macrophage** (also “Mph” or “MΦ”). A type of PMN in the innate immune system which is derived from monocytes (JT 4). These are large phagocytic cells which can ingest large particles. They can also release toxic mediators in order to attack

extracellular pathogens which are too large to ingest (JT 300). They recognize (non-specifically) pathogens from polysaccharides and proteins on the surface of the pathogen (1:8-9). Macrophages appear in a variety of morphologies (monocytes, bone marrow tingibile macrophages, lung, spleen and lymph node macrophages) (15:15). Macrophages adhere to glass (15:8, 16), unlike lymphocytes.

There are two types of macrophages, each with different functions. Professional phagocytes remove particles. Antigen-presenting cells (APCs) process and present antigen to T cells (14:13; 15:15; JT 263).

Macrophages require two signals for activation. The first signal is IFN $\gamma$ . The second signal can be provided by a variety of means (JT 299). Once activated, macrophages undergo changes that greatly enhance their antimicrobial effectiveness and amplify the immune response (JT 300 fig. 8.40).

Macrophages secrete a variety of cytokines (JT 376 fig. 10.10).

**Major histocompatibility complex.** See “MHC.”

**Malignant cell.** May derive from stem cells and progenitor cells, and may be located in the bone marrow and peripheral blood. Such malignancies are called common acute lymphoblastic leukemias, and their cells contain terminal deoxynucleotidyl transferase (TdT) (21:6).

Malignant cells may develop from T cells at various stages of differentiation (JT 256 fig. 7.24). However, they represent cells that are either very early or very late in development, since most of the cells in intermediate stages are eliminated in the process of thymus selection (21:10-11).

Malignant cells can develop from B cells at any stage (21:14; JT 220 fig. 6.19). Some malignant B cells continuously express the bcl-X<sub>L</sub> “death-inhibiting” gene (22:7).

**MALT** (“mucosal-associated lymphoid tissue”). Comprises all lymphoid cells in epithelia and in the lamina propria lying below the body’s mucosal surfaces (JT 607).

**Mast cell.** Large cells found in connective tissues throughout the body, most abundantly in the submucosal tissues and the dermis. Mast cells contain large granules that store a variety of mediator molecules including the vasoactive amine histamine. Mast cells have high-affinity Fc $\epsilon$  receptors (Fc $\epsilon$ RI) that allow them to bind IgE monomers. Antigen binding to this IgE triggers mast cell degranulation and mast cell activation, producing a local or systemic immediate hypersensitivity reaction. Mast cells have a crucial role in allergic reaction (JT 606). Mast cell products have different effects on different tissues (JT 468 fig. 12.6).

**MBP** (“myelin basic protein”). Tolerance to myelin basic protein (in the mouse model involving experimental allergic encephalomyelitis) may be induced by interfering with MHC presentation with a monoclonal antibody, though this is only temporary (25:9).

**Membrane attack complex.** See “MAC.”

**Memory cell.** Immunological memory is the ability of the immune system to respond more rapidly and effectively to pathogens that have been encountered previously, and reflects the pre-existence of a clonally expanded population of antigen-specific lymphocytes. Memory responses differ qualitatively (JT 402) and quantitatively (JT 404)

from primary responses. How immunological memory is maintained is poorly understood (JT 402-3).

Lymphocytes (both T cells and B cells) can differentiate into memory cells (1:20; 22:8; JT 410). Memory cells have adhesion molecules which enable them to attach to endothelial cells of blood vessels (1:21). Memory cells arise after a pathogen has been cleared from the body. Memory cells represent a “dormant” state of lymphocytes (1:22). Long-lived cells are responsible for immunological memory (21:15). Immunological memory is the most important biological consequence of the development of adaptive immunity based on clonal selection (JT 17).

Memory B cells require very little antigen when a secondary immune response is induced (22:7).

Memory T cells have the same surface characteristics and properties as those involved in cell-mediated immunity (22:8). Memory T cells do not change their affinity for antigen, because there is no mutation in the genes that control the V domains of TCR (22:9).

The maximum number of memory cells is found at approximately 30 days after the primary response (22:8).

When T and B cells become memory cells, they change their CD45 from CD45RA to CD45RO through alternative RNA splicing during reactivation. These memory cells have an improved ability to participate in the immune response; they will have a higher density of adhesion molecules. B cells will have a higher density of MHC II, which makes them more effective in presenting antigen (22:9).

Memory cells recirculate and redistribute in all lymphoid organs, so that an infection at a new site (i.e. other than the site of the first exposure) will still generate an improved immune response (22:9).

Memory of a virus is preserved by long lived memory T<sub>C</sub> cells. These cells can become immediately reactivated by antigen presenting cells bearing B7 (23:15).

Memory of any reaction mediated by T cells may be transferred in syngenic animals by a process called adoptive transfer (23:15).

**MHC** (“major histocompatibility complex”). A cluster of genes on chromosome 6 in humans (16:7) (or on chromosome 17 in mice). It encodes a set of membrane glycoproteins called the MHC molecules. MHC class I molecules present peptides generated in the cytosol to CD8 T cells, and MHC class II molecules present peptides degraded in intracellular vesicles to CD4 T cells (JT 606, 117).

The MHC is codominantly expressed (16:8; LJ 350; JT 140 fig. 4.22), which means that all class I and class II genes which are inherited from both parents get expressed on the membrane. There is no allelic exclusion, unlike that found in surface Ig or T cell receptor (16:7). MHC genes are polygenic (there are several genes) and polymorphic (there are multiple alleles of each gene) (JT 116, 135, 609).

A human typically expresses six different MHC I molecules and eight different MHC II molecules on his or her cells (JT 141).

MHC loci respond to the action of interferon  $\gamma$ , which increases MHC expression (16:8, 9).

MHC I consists of HLA A, HLA B and HLA C (SO 44).

The self antigens displayed by MHC I molecules are transported from the cell's own endoplasmic reticulum in conjunction with TAP molecules (SO 45).

There are three sets of MHC:

MHC I encodes for a set of membrane glycoproteins which present peptides generated in the *cytosol* to CD8 T cells (JT 606). They are like billboards that "advertise" the inside contents of the cell (16:10). These molecules are expressed on the surface of cells (16:4), specifically on the surface of all nucleated cells and on platelets (16:9). MHC I molecules are "serologically defined," which means that their typing is determined with antibody and complement (16:5). Its light chain is composed of an  $\alpha$  chain (consisting of  $\alpha 1$ ,  $\alpha 2$  and  $\alpha 3$  outside domains) and  $\beta 2$  microglobulin (16:5-6). (Concerning  $\beta 2$  microglobulin see JT 127 fig. 4.13 and SO 13, 44.) The  $\alpha 1$  and  $\alpha 2$  domains form the alloantigenic determinants; the  $\alpha 3$  domain is Ig-like and has a transmembrane portion and a cytoplasmic portion (16:6). Human MHC I genes (called A, B and C) are found to the right of MHC II and III genes (16:7; JT 136 fig. 4.19). Humans have MHC I molecules on all nucleated cells (16:8). Class I antigens are called K and D and are controlled by genes at the opposite ends of the MHC gene (16:8). MHC I molecules cannot achieve diversity through combinatorial association (2000 TLE #1, question 31). The antigenic fragments presented to MHC I are nonapeptides (nine peptides in length) and have anchor residues for the groove of MHC antigens (19:5; JT 121).

MHC II encodes a set of membrane glycoproteins which present peptides degraded in *intracellular vesicles* to CD4 T cells (JT 606). They are like billboards that "advertise" the outside of the cell (16:10), in the sense that intracellular vesicles are topologically outside of the cell (in the same way that the lumen of the gastrointestinal tract is "outside" the body). These molecules are expressed on the surface of cells (16:4) involved in antigen presentation to  $T_H$  cells (i.e. they are found on the surface of professional antigen-presenting cells) (16:9). MHC II molecules are "cell defined," which means that in culture they can induce a response in lymphocytes from an unrelated individual. Their typing is done by one-way mixed leukocyte culture. Each MHC II molecule is composed of an  $\alpha$  chain (consisting of  $\alpha 1$  and  $\alpha 2$  domains) and a  $\beta$  chain (consisting of  $\beta 1$  and  $\beta 2$  domains) (16:6) and the Ii (or "invariant") chain (16:10). (Concerning the invariant chain see JT 130 fig. 4.15) The  $\alpha 1$  and  $\beta 1$  domains are the alloantigenic determinants; the  $\alpha 2$  and  $\beta 2$  domains are Ig-like and have transmembrane and cytoplasmic domains (16:6). Human MHC II genes (called DP, DQ and DR) are found to the left (16:7-8; JT 136 fig. 4.19). Class II antigens are called I antigens (e.g. I-A and I-E, for "immune response") and are located in the middle area of the MHC gene (16:8). Small resting T cells do not express MHC II molecules, but activated T cells (blastic cells) do (16:9). MHC II molecules can achieve diversity through combinatorial association; they can have an  $\alpha$  chain from one parent and a  $\beta$  chain from the other parent (2000 TLE #1, question 31). MHC II molecules are restricted to professional antigen-presenting cells (PAPC) (16:9). MHC II presents antigens that are larger than those presented by MHC I (19:6-7), typically over 13 residues (20:7; JT 123). Characteristic amino acids in position 4 and 9 usually make a difference as to whether a peptide is accepted or not (20:7).

MHC III molecules are complement molecules present in the serum (16:4).

Characteristic	MHC class I	MHC class II
Found on which types of cells	All nucleated cells (16:8).	Professional antigen presenting cells (16:9).
Presents peptides from	Cytosol (JT 606).	Intracellular vesicles (JT 606).
Presents peptides to	CD8 T cells (JT 606), i.e. T <sub>C</sub> cells.	CD4 T cells (JT 606), i.e. T <sub>H</sub> cells.
Size of peptide which is presented	Nonapeptides (nine peptides in length) (19:5; JT 121; SO 44).	Typically over 13 residues (20:7; JT 123; SO 45).
Important points of binding	Have anchor residues for the groove of MHC antigens (19:5). The peptides are bound by their termini (JT 121; SO 45).	Characteristic amino acids in position 4 and 9 usually make a difference as to whether a peptide is accepted or not (20:7).
MHC molecules are defined	“Serologically,” i.e. their typing is determined with antibody and complement (16:5).	“Cellularly,” which means that in culture they can induce a response in lymphocytes from an unrelated individual (16:10).
Chain composition	Light chain is composed of an $\alpha$ chain (consisting of $\alpha$ 1, $\alpha$ 2 and $\alpha$ 3 outside domains) and $\beta$ 2 microglobulin (16:5-6). The $\alpha$ 1 and $\alpha$ 2 domains form the alloantigenic determinants; the $\alpha$ 3 domain is Ig-like and has a transmembrane portion and a cytoplasmic portion (16:6).	Composed of an $\alpha$ chain (consisting of $\alpha$ 1 and $\alpha$ 2 domains) and a $\beta$ chain (consisting of $\beta$ 1 and $\beta$ 2 domains) (16:6) and the Ii (or “invariant”) chain (16:10).
Location of MHC genes	MHC I genes (A, B and C) are found to the “right” of MHC II and III genes (16:7; JT 136 fig. 4.19), i.e. farther from the centromere.*	MHC II genes (called DP, DQ and DR) are found to the “left” of MHC I genes (16:7-8; JT 136 fig. 4.19), i.e. closer to the centromere.*
Antigens	MHC I antigens are called K and D and are controlled by genes at the opposite ends of the MHC gene (16:8).	MHC II antigens are called I antigens (e.g. I-A and I-E, for “immune response”) and are located in the middle area of the MHC gene (16:8).
Diversity is achieved by	Cannot achieve diversity through combinatorial association (2000 TLE #1, question 31).	Can achieve diversity through combinatorial association; they can have an $\alpha$ chain from one parent and a $\beta$ chain from the other parent (2000 TLE #1, question 31).

\* See Thomas D. GELEHRTER, Francis S. COLLINS and David GINSBURG, *Principles of Medical Genetics*, 2nd ed. Baltimore: Williams & Wilkins, 1998, p. 207.

**MHC antigen** (or “histocompatibility antigen”). See 1:19.

**MHC molecule.** MHC molecules are a set of glycoproteins (encoded for by the MHC). MHC class I molecules present peptides generated in the cytosol to CD8 T cells, and MHC class II molecules present peptides degraded in intracellular vesicles to CD4 T cells (JT 606).

MHC molecules always present some protein. A non-infected cell has fragments of self-protein derived from its own cytosol attached to the MHC molecules on the surface (1:22), and it is the presentation of these molecules which indicates the “self”-ness of this cell to components of the immune system.

In contrast, when a cell is infected, some of the MHC molecules on its surface will be presenting protein fragments from the pathogen, and it is the presentation of these molecules which enables components of the immune system to recognize that this cell is infected.

**MHC restriction.** When a  $T_C$  clone develops for recognition of MHC + Ag fragment, that particular clone can only kill if it is presented with the same exact combination of MHC and antigen fragment. This restriction has a selective advantage, in that it avoids collateral damage (19:10; LJ 326, 351; JT 143 fig. 4.25). It turns out that only MHC I is critical in MHC restriction (19:10).

**MIF** (“migration inhibitory factor”). A cytokine involved in inflammation (18:7). This cytokine inhibits migration of macrophages in order to cause them to remain at sites of infection. This is critical for the accumulation of macrophages and lymphocytes at the inflammatory site, where T cells are activated by antigen (18:8).

**Migration inhibitory factor.** See “MIF.”

**Mimicry, molecular.** Molecular mimicry has been proposed as a hypothesis explaining why infection can sometimes induce an autoimmune response. According to the hypothesis, T and B cells whose receptors recognize certain microbial antigens will be activated in the normal course of an immune reaction to the microbial invasion. If, however, these receptors happen to cross react with self antigens, an autoimmune response to the self antigens can result (SO 91).

**Minor histocompatibility.** The minor histocompatibility complex is present on the Y chromosome, and is thus restricted to males (19:4).

**Minor histocompatibility antigen.** Formed as a result of allelic variance (heterogeneity) in other proteins. These antigens are involved in transplant rejection (23:9; JT 511; LJ 350).

**Mitogen.** A polyclonal mitogen induces proliferation of lymphocytes of many different specificities or clonal origins (17:4; JT 60 fig. 2.26). The most frequently used mitogens for stimulating only T cells are concanavalin A and phytohemagglutinin. Pokeweed mitogen stimulates proliferation of both T cells and B cells. Mitogens used for stimulating only B cells are anti-Ig light chain antibodies and lipopolysaccharide from the wall of gram negative bacteria (17:4). Mitogens are effective in stimulating blast transformation because they involve multiple molecular bridges (17:6).

**Mixed leukocyte reaction.** See “MLR.”

**MLR** (“mixed leukocyte reaction”). An experimental procedure for inducing  $T_H$  and  $T_C$  cells in culture (19:10). MLR can be used to detect histoincompatibility (JT 516 fig. 13.26).

**Monoclonal.** Monoclonal antibodies are antibodies produced by a single clone of B lymphocytes (JT 607; LJ 337). Monoclonal antibodies bind a single specific antigen. Compare with “polyclonal.”

**Monocyte.** The precursor cell of a macrophage (JT 4; SO 7).

**Multiple sclerosis.** A neurological disease characterized by focal demyelination in the central nervous system, lymphocytic infiltration in the brain, and a chronic progressive course. It is believed to be an autoimmune disease (JT 607). It is classified as a type IV T cell-mediated autoimmune disease (JT 490 fig. 13.1).

**Myasthenia gravis.** An autoimmune disease in which the immune system erroneously produces antibodies against the acetylcholine receptors which are crucial for muscle contraction (1:14; JT 498 fig. 13.8).

**Mycobacteria.** Usually live pathogens are required to provoke an immune response, but mycobacteria constitute an exception in this regard, as even dead micobacteria can provoke an immune response. This is one of the reasons why dead mycobacteria constitute a component of Freund's complete adjuvant.

**Mycobacterium leprae.** The bacterium responsible for leprosy. Leprosy appears in two forms: tuberculoid and lepromatous. In lepromatous leprosy, cell-mediated immunity is profoundly depressed, *M. leprae* proliferate dramatically. In tuberculoid leprosy there is potent cell-mediated immunity with macrophage activation (which can produce a granuloma) and  $T_H1$  inflammation, which controls but does not eradicate the infection (23:18; JT 424-5).

**Myelin basic protein.** See "MBP."

**Myeloma, multiple.** Malignancy in the bone marrow deriving from plasma cells (21:14; 22:8).

**Natural killer cell.** See "NK cell."

**Necrosis.** Death of cells or tissues due to chemical or physical injury (as opposed to apoptosis, which is a biologically programmed form of cell death). Necrosis leaves extensive cellular debris that needs to be removed by phagocytes, whereas apoptosis does not (JT 607, 293).

**Negative selection.** See "selection, negative."

**Negative signaling.** Both B and T cells receive signals that can counteract and modify the activation signals delivered through antigen receptors and co-receptors. These inhibitory signals usually block the response by raising the threshold for signal transduction to occur. Most of these modifying signals are received through receptors that bear a distinct motif called an immunoreceptor tyrosine-based inhibitory motif (ITIM) in their cytoplasmic tails (JT 182). The ITIMs bind and activate inhibitory phosphatases (SHP-1 and SHIP) (17:10).

On B cells the most important ITIM is Fc $\gamma$ RII which, when cross linked to surface Ig, delivers a negative signal, thereby blocking the activation of naive B cells.

For T cells, CTLA-4 has B7 as a ligand (just as CD28 has B7 as a ligand). However, instead of activation, CTL-4 delivers an inhibitory signal.

For NK cells the KIR (killer inhibitory receptor) binds MHC I and delivers a negative signal, so that normal cells that have enough MHC molecules are not killed.

**Neutralization.** Antibodies can inhibit the activity of a virus or the toxicity of a toxin molecule by coating the virus or toxin, thereby preventing the pathogen's ability to interact with host cells (1:13; JT 607).

**Neutropenia.** Reduction in the number of circulating neutrophils (14:8).

**Neutrophil.** A type of polymorphonuclear leukocyte which is relatively short-lived (about 5 days) (SO 21). Neutrophils phagocytose antibody-coated pathogens. They are able to phagocytose bacteria even in the absence of specific antibodies. They can also phagocytose microorganisms coated with complement component C3b and its inactive derivative iC3b. Neutrophils are short-lived (JT 382-3). They do not present antigens to T cells (SO 21; 2000 TLE #1, question 32). Factors which are chemotactic for neutrophils include C5a, IL-8 (2000 TLE #1, question 34) and LPS (SO 22).

In order for a neutrophil to home in on a pathogen, several sets of molecules are involved. The neutrophil "rolling" along the endothelium is mediated by binding between the selectin and the selectin-ligand. The rolling is stopped by interactions between integrins and ICAMs. The neutrophil's exit from the vessel and entry into the tissues is mediated by chemoattractants and their receptors (SO 23).

**NFAT** ("nuclear factor activated T cells, cytoplasmic"). A transcription factor. Its name is misleading because it is also found in B cells, NK cells, mast cells, monocytes, and some non-hematopoietic cells. NFAT contains a nuclear localization signal which allows it to be translocated into the nucleus. When the cell is unstimulated, NFAT is kept phosphorylated and inactive. When the cell is stimulated, there is an increase in cytosolic  $Ca^{2+}$  which causes calcineurin to dephosphorylate (and thereby activate) NFAT, which moves from the cytosol to the nucleus and acts as a transcriptional regulatory protein in combination with AP-1 factors (JT 180).

**NFκB.** A transcription factor (JT 183-4).

**NK cell** ("natural killer cell"). A type of cell (descended from a common lymphoid progenitor) which constitutes part of the adaptive immune system. It is distinct from lymphocytes (i.e. it is distinct from T cells and B cells). NK cells bear no known antigen-specific receptors but are nevertheless able to recognize and kill a limited range of abnormal cells. The destruction of antibody-coated target cells by NK cells is called antibody dependent cell-mediated cytotoxicity (ADCC), and is triggered when antibody bound to the surface of a cell interacts with Fc receptors on the NK cell (JT 335).

NK cells are also involved in innate immunity (JT 335). They serve as an early defense against certain intracellular infections, such as viruses (JT 386-8).

CD2 is present on the surface of most NK cells (15:11, 14).

NK cells are not MHC restricted (Dr. Teodorescu).

NK cells kill by several mechanisms, including their ability to produce granzymes, TNFs and  $IFN\gamma$ , Fas, perforin (19:11, 12; SO 24). NK cells have receptors which induce killing and other receptors which block killing. NK cells mainly kill cells that exhibit abnormal expression of MHC I. NK cells are also sensitive to the density of MHC I expression on the cell surface; therefore, if a cell is infected with a virus, most of its MHC I molecules will be displaying viral antigens, and the NK cell will recognize that

the number of MHC I molecules displaying self antigens is abnormally low, so it will kill this offending cell (19:11; SO 24-5).

**Nude mice.** Lack of development of the thymus (resulting in the absence of functional T cells) can be due to the lack of differentiation of the thymic anlage, resulting in “nude mice” (21:6-7). (Apparently these mice are called “nude” because one of the characteristics of this condition is that the mice are hairless; JT 608, 230).

**Opportunistic infection.** Opportunistic pathogens are those that rarely if ever cause disease in immunocompetent people, but can cause serious infections in immunocompromised patients (LJ 25).

**Opsonization.** The alteration of the surface of a pathogen or other particle so that it can be ingested by phagocytes (LJ 347; JT 333). Antibody and complement opsonize extracellular bacteria for destruction by neutrophils and macrophages (JT 608). IgG is the antibody that opsonizes (LJ 341).

**Original antigenic sin.** A phrase used to describe the tendency of humans to make antibody responses to those epitopes shared between the original strain of a virus and subsequent related viruses, while ignoring other highly immunogenic epitopes on the second and subsequent viruses (25:11; JT 608, 411).

**PAPC** (“professional antigen-presenting cell”). These cells are specialized for presenting antigen to T<sub>H</sub> cells. Among PAPCs are activated macrophages, activated B cells (16:9; 20:7) and dendritic cells (SO 49). MHC II molecules are restricted to professional antigen-presenting cells (16:9). These are the only cells which have B7 (Dr. Teodorescu). The antigen-specific clonal expansion of naive T cells requires a second or co-stimulatory signal which must be delivered by the same antigen-presenting cell on which the T cell recognizes its specific antigen (JT 270). The requirement for simultaneous delivery of antigen-specific and co-stimulatory signals by one cell in the activation of naive T cells means that only professional antigen-presenting cells can initiate T cell responses (JT 271). Antigen binding to the T cell receptor in the absence of co-stimulation not only fails to activate the cell but also leads to anergy (JT 272).

**Parasite.** An organism that obtains sustenance from a live host. In medicine the term is restricted to helminths (worms) and protozoa (JT 608; LJ 276).

After a parasite penetrates the skin and mucosa, almost all of the host’s immunological defense mechanisms are invoked. Malarial parasites get ingested by macrophages in the spleen, liver or tissues. This ingestion triggers production of IL-1, IL-6, IL-12 and TNF $\alpha$ , and leads to inflammation and limitation of spreading of the parasite. Parasites are killed by reactive oxygen intermediates, and by nitric oxide (NO), which is released from macrophages (stimulated by TNF $\alpha$  [which is secreted by other macrophages] and by IFN $\gamma$  [which is released by T cells]) (26:6). The process of macrophage activation is a major manifestation of parasitic infections, with production of chronic inflammation due to TNF $\alpha$  (26:7).

Neutrophils kill extracellular parasites by secreting hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and NO. They kill intracellular parasites by granular cytoplasmic components. They also become involved in ADCC through their high affinity Fc $\gamma$  receptors (26:7).

Eosinophils are also involved in defense against parasites. Mast cells with IgE on their surface are triggered by parasite antigens to produce various mediators (such as histamine) which attract eosinophils. Eosinophils are not very useful for phagocytosis, but they are effective in ADCC (26:7).

Platelets are cytotoxic mainly by ADCC with IgE receptors (26:7). This is one of the few roles which platelets play in the immune system (Dr. Teodorescu).

T cells also participate in the defense against parasites. Both CD8<sup>+</sup> cells (T<sub>C</sub> cells) and CD4<sup>+</sup> cells (T<sub>H</sub>1 and T<sub>H</sub>2 cells) are involved in cell-mediated and antibody responses. Intracellular trypanosomes or leishmanias are killed by T<sub>H</sub>1 cells which are stimulated by IFN $\gamma$  and TNF $\alpha$  (26:7). CD8<sup>+</sup> cells produce inflammatory cytokines (such as IFN $\gamma$ , TNF $\alpha$ , TNF $\beta$ ) and cause granuloma formation around parasite eggs. The CD8<sup>+</sup> cells can also induce apoptosis in affected cells (26:8).

The T cell response to a parasitic infection depends on the life cycle phase of the parasite, and in a given phase, a T<sub>H</sub>1 or a T<sub>H</sub>2 cell response may predominate. In any case, effective defense against parasites depends upon IgE (26:8).

Antibodies are involved in defense against parasites in several ways. (1) Direct inhibitory effect through neutralization. (2) Direct damage caused by the antibodies' perturbing the membrane function in the parasite. (3) IgG and IgE help in ADCC by macrophages, neutrophils and platelets. However, the antibody response to parasites can also cause various pathologies, such as anemia, splenomegaly and other problems. In particular, IgE can cause an anaphylactic reaction (26:9).

See 26:9-10 for examples of defense against parasitic infections.

Parasites invoke various mechanisms for escaping the host defense. (1) Some parasites can exploit the antagonism between T<sub>H</sub>1 and T<sub>H</sub>2 cells. For instance, leishmania can deviate the immune response by producing IL-4 (which causes an ineffective antibody response). (2) Some parasites can hide inside macrophages. (3) Some parasites can avoid recognition by changing antigens, by acquiring antigens from the host, or by shedding antigens. Some parasites also have superoxide dismutase which protects them from the action of oxygen radicals (26:10). (4) Some parasites can interfere with the immune system response through several mechanisms, such as by activating polyclonal lymphocytes, by activating macrophages to produce suppressive prostaglandins, by overloading macrophages with polysaccharides, by inhibiting T<sub>H</sub>1 cells, by inducing clonal anergy, or by blocking antibody forming cells (26:11).

**Paratope** (or "antibody combining site"). The portion of an antibody which binds to the epitope of the antigen.

**Passenger cell.** Dr. Teodorescu seems to use this term to refer to Langerhans cells and macrophages (23:9).

**Phagocyte.** Phagocytes (neutrophils, monocytes, macrophages) are part of the cell-mediated (adaptive) immune response and ingest pathogens opsonized with specific antibody (14:1). Phagocytes have a variety of receptors (JT 374 fig. 10.9). Microorganisms that are destroyed by phagocytes without additional help from T cells do not cause disease and do not require an adaptive immune response (JT 274).

**Phagocytosis.** The internalization of particulate matter by cells. Usually the phagocytic cells are macrophages or neutrophils, and the particles are bacteria that are taken up and destroyed. The ingested material is contained in a vesicle contained a phagosome, which then fuses with one or more lysosomes to form a phagolysosome. The lysosomal enzymes are important in pathogen destruction and degradation to small molecules (JT 608).

**Phagocytosis, frustrated.** In type III (or type II?) hypersensitivity reactions, antigen:antibody complexes form, get deposited in critical tissues (such as the glomerulus in lupus) and attract phagocytic cells. When the leukocytes engulf the complexes, there is collateral tissue damage. Dr. Cohen calls this process “frustrated phagocytosis” (30:1).

**Phagosome.** A vacuole within a phagocyte that contains ingested pathogen (1:9).

**Phase, effector** (or “efferent phase,” 19:6). In the effector phase (which follows the induction phase), T<sub>C</sub> cells secrete the contents of their toxic granules onto any cells on whose surface is displayed the antigen for which the T cell has been programmed to attack (1:22).

**Phase, induction** (or “afferent phase,” 19:6). The induction phase (which precedes the effector phase) is the period of the immune response in which MHC molecules present antigen on the surface of a cell. This presentation induces a clone of T cells to proliferate (1:22). CD27 is necessary for the induction phase (Dr. Teodorescu).

**Phytohemagglutinin** (or “PHA”). A commonly employed polyclonal mitogen for activating only T cells (17:4; JT 60 fig. 2.26). Phytohemagglutinin binds to monosaccharides (17:6).

**Plasmablasts.** Precursors of plasma cells. Plasmablasts which synthesize IgA are generated in the mesenteric lymph nodes and home in the lamina propria where they secrete IgA for external delivery (22:8).

**Plasma cell.** Terminally differentiated B cells which are the main antibody-secreting cells of the body (JT 308 fig. 9.1 and p. 314 fig. 9.7). They are found in the medulla of lymph nodes, in splenic red pulp, and in bone marrow (JT 609).

Plasma cells lose surface Ig and MHC II and are no longer activated by any cellular interaction (22:8); they no longer respond to antigen or helper T cells (JT 320 fig. 9.12). Most plasma cells live for about one month and produce antibodies (22:8).

**Platelet.** Platelets can be invoked in the immune system response to certain parasites (q.v.). They are cytotoxic mainly by ADCC with IgE receptors (26:7). This is one of the few roles which platelets play in the immune system (Dr. Teodorescu).

**Pleiotropy.** When a single molecule can serve multiple functions it is said to exhibit pleiotropy. For example, a given cytokine may act on a variety of cell types because the different cell types all have common receptor structures (18:14).

**PMN cell** (“polymorphonuclear leukocyte”). Part of the “second line of defense” (i.e. the phagocytic cells). PMNs consist of neutrophils, eosinophils, basophils, mast cells and macrophages (JT 4), and thus constitute the cells providing innate immunity.

**Pokeweed mitogen** (or “PWM”). A polyclonal mitogen which stimulates proliferation of both T and B cells (17:4; JT 60 fig. 2.26). Pokeweed mitogen binds to monosaccharides (17:6).

**Polyclonal.** Antibodies that arise in an animal in response to typical antigens are heterogeneous, because they are formed by several different clones of plasma cells, i.e. they are polyclonal (LJ 337). Antiserum is polyclonal since multiple B cells, each programmed to form a particular antibody, are activated to secrete antibodies that react with the same antigen with greater or lesser affinity (9:4).

**Polygenic.** Containing several loci encoding proteins of identical function. The MHC complex is described as polygenic (JT 116, 135, 609).

**Polymorphic.** Having multiple alleles at each locus. The MHC complex is described as polymorphic (JT 116, 135, 139, 609).

**Polymorphonuclear leukocyte.** See “PMN cell.”

**Positive selection.** See “selection, positive.”

**PPD** (“purified protein derivative”). A purified protein derivative of tuberculin employed in elicitation of tuberculin type hypersensitivity (see type IV under “hypersensitivity”).

**Primary focus.** During T dependent antibody responses, a primary focus of B cell activation forms in the vicinity of the margin between T and B cell areas of lymphoid tissue. Here, the T and B cells interact and B cells can differentiate directly into antibody-forming cells or migrate to lymphoid follicles for further proliferation and differentiation (JT 609, 313). The primary focus develops approximately five days after the introduction of antigen (22:6).

During formation of the primary focus, T and B cells interact, and both proliferate (22:6). Activated B cells which are generated here can proceed to two places: (1) some migrate to medullary cords where they become plasma cells and produce the early antibodies; (2) others migrate (together with the T cells that activated them) to the germinal centers where clonal expansion occurs (22:7).

**Privileged site.** Allogenic tissue placed in certain sites in the body does not elicit graft rejection. Such sites are called immunologically privileged sites. Immunological privilege results from the effects of both physical barriers to cell and antigen migration, and soluble immunosuppressive mediators such as certain cytokines (JT 604).

Immunologically privileged sites include the brain, eye, testis, and uterus (specifically, the fetus) (JT 526). The antigens in these sites are “sequestered” from the immune system and therefore do not provoke immune responses. However, if the antigens are accidentally released into circulation (e.g. due to an injury), they can elicit humoral and cellular responses (LJ 376; JT 526).

**Professional antigen-presenting cell.** See “PAPC.”

**Proteasome.** Proteasomes are intracellular enzyme complexes which degrade proteins into short peptide chains. In most somatic cells the proteasomes chop up proteins into random lengths. However, MHC presenting cells contain proteasomes which are more selective in the manner in which they chop up proteins (SO 46).

**Protectin** (or “CD59”). A protein on the surface of human cells that can repulse membrane attack complexes. This is one of the body’s methods of insuring that its own cells do not get damaged by a complement-mediated attack (SO 19).

**Protozoa.** An organism consisting of a single functional cell unit or aggregation of nondifferentiated cells (Stedman’s medical dictionary). Concerning defense against protozoa, see under “bacteria.”

Protozoa are usually much larger than bacteria. They have different stages in their development, and the immune response may be different at each stage (e.g. plasmodium malariae). They tend to cause chronic infections (e.g. granuloma in the liver or lungs) and do not kill the host. Rather, they try to adapt and establish an equilibrium with the host (26:5).

Protozoa may employ several mechanisms for evading host defenses (26:6). See under “parasite.”

**Pus.** Consists of degraded pathogen and dead or dying neutrophils (JT 383).

**RANTES** (“regulated on activation, normal T expressed and secreted”). A member of the interleukin-8 superfamily of cytokines. It is a selective chemoattractant for memory T lymphocytes and monocytes (18:11; 23:13; Stedman’s medical dictionary).

**Rapamycin** (or “sirolimus”). An immunosuppressive drug which inhibits the production of IL-2 and thereby inhibits proliferation of T cells (17:8; JT 543).

**RAG** (“recombination activating genes”). The RAG genes (RAG-1 and RAG-2) encode the proteins RAG-1 and RAG-2, which are critical to receptor gene rearrangement (JT 610).

**Recombination activating genes.** See “RAG.”

**Respiratory burst.** When neutrophils and macrophages take up opsonized particles, this triggers a metabolic change in the cell called the respiratory burst. It leads to a production of a number of mediators (JT 610), including hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), the superoxide anion (O<sub>2</sub><sup>-</sup>), and nitric oxide (NO), which are directly toxic to bacteria. Production of these metabolites is induced by the binding of aggregated antibodies to Fcγ receptors (JT 334-5).

**Rheumatoid arthritis.** A generalized inflammatory disease affecting multiple joints with symmetrical distribution. Mutations to amino acids 70-74 on the β chains of MHC II are implicated in this disease (20:6). Can appear as synovitis, a clinical manifestation of parasitic infection (23:17).

**Sarcoidosis.** A systematic granulomatous disease of unknown cause. It may appear as an autoimmune process. It may also be a clinical manifestation of a parasitic infection. Activated macrophages may produce angiotensin converting enzyme and may convert pro-vitamin D into vitamin D, resulting in hypercalcemia (23:17).

**SCID** (“severe combined immunodeficiency syndrome”). Can be caused by a mutation in the γ chain of cytokine receptors (18:13), or by a lack of functional precursors (21:6).

**Selectin.** The selectin family of molecules are a type of adhesion molecule (15:10). They mediate rolling adhesion (JT 378 fig. 10.11). The major selectins on the surface of the neutrophil are LAM-1 or L-selectin. The major selectins on the surface of endothelial cells are ELAM-1 (E-selectin) and CD62 (P-selectin) (14:2). They recognize carbohydrates (as the suffix “-lectin” indicates), and play an essential role in homing to lymph nodes, spleen, or MALT. Their ligands are usually the addressins (15:10).

**Selection.** During the maturational process of immune cells, thymocytes initially undergo positive selection (first producing double positive T cells, then single positive T cells), and then undergo negative selection (to eliminate self-reactive cells). T cells undergo positive and negative selection in the thymus (JT 241, 242 fig. 7.13).

B cells undergo positive and negative selection in the bone marrow. Approximately 75% of the cells die in the bone marrow in the process of positive and negative selection (21:13).

**Selection, negative.** Clones of lymphocytes that react with self antigens on cell surfaces or in solutions are deleted. The process of elimination of self reactive clones is called negative selection (1:23-4).

T cells must undergo negative selection (JT 250 ff.). Following positive selection (producing first double positive and then single positive cells), thymocytes undergo negative selection, during which self-reacting cells are eliminated (21:9).

B cells must undergo negative selection. Following positive selection, B cells undergo negative selection. Immature B cells develop functional surface IgM with both H and L chains rearranged, and with all B cell surface markers (including CD19 and CD20). Before they develop to maturity, B cells are very sensitive to negative selection (21:12). Some additional negative selection of B cells occurs in the periphery (21:13).

**Selection, positive.** The entire process of growth and development of lymphocytes is called positive selection (1:23). Positive selection determines co-receptor specificity (JT 246 fig. 7.16).

T cells must undergo positive selection (JT 244 ff.). Positive selection is designed to select for the survival of cells that are functional. Double positive thymocytes interact with stromal cells in the cortex of the thymus (mainly with nurse cells); if the genes for the TCR were not correctly rearranged (i.e. if CD3, CD4 and CD8 are not correctly expressed) then they have failed the process of positive selection and they die by apoptosis. The signal for survival requires expression of an intact Lck gene (21:8).

For MHC I, a “weakly fitting” self peptide on thymic epithelial cells can deliver a positive selection signal (permitting the cell to be positively selected), while a strong, “perfect fitting” signal leads to apoptosis (21:10; JT 254 fig. 7.23).

B cells must undergo positive selection. During the pro-B through immature B cell stage, interactions with stromal cells are essential for positively selecting B cells via survival signals. Those B cells which fail to rearrange their immunoglobulin genes (even after repeated attempts) die by apoptosis and are engulfed by tingible body macrophages (21:12).

**Sepsis.** The symptoms resulting from a systemic infection. Sepsis is usually caused when large quantities of bacteria penetrate the first line of defense (the physical barriers). This can occur when bacteria escape from an abscess (SO 87).

**Serum sickness.** A type III hypersensitivity reaction (JT 463 fig. 12.2). Occurs when foreign serum or serum proteins are injected into a person. It is caused by the formation of immune complexes between the injected protein and the antibodies formed against it. It is characterized by fever, arthralgias, and nephritis (JT 611). Immune complexes are formed whenever there is an antibody response to a soluble antigen; normally these complexes are cleared efficiently by red blood cells (JT 499), but if the dose of antigen is large enough, the system may be unable to eliminate the complexes rapidly enough, and serum sickness ensues, though this is transient and only lasts until the complexes finally are cleared (JT 500).

**Severe combined immunodeficiency syndrome.** See “SCID.”

**Sézary syndrome.** A malignancy which can develop from mature T cells (21:11; JT 254 fig. 7.24).

**Single positive cells.** During T cell maturation in the thymus, mature T cells are detected by the expression of either the CD4 or the CD8 co-receptor (but not both), and are therefore called single positive thymocytes (JT 611). When the receptor of a thymocyte best fits to a MHC I, it will use its CD8 and after division the expression of CD4 is silenced (21:9).

**Sirolimus.** See “rapamycin.”

**SLE** (“systemic lupus erythematosus”). An autoimmune disease in which antibodies are formed against DNA, histones, nucleolar proteins and other components of the cell nucleus. Complexes of antigen:antibody form, consume complement and deposit in the kidneys (20:10; JT 499; LJ 377).

**Somatic hypermutation.** During B cell responses to antigen, the V region DNA sequence undergoes somatic hypermutation, resulting in the generation of variant immunoglobulins, some of which bind antigen with a higher affinity. This allows the affinity of the antibody response to increase. These mutations affect only somatic cells, and are not inherited through germline transmission (JT 611, 318; SO 39-40). Somatic hypermutation occurs in dividing centroblasts (JT 318, 597). Somatic hypermutation does *not* occur in T cell receptor genes (JT 154).

**Spleen.** A secondary lymphoid organ which is special because unlike the other secondary lymphoid organs, the spleen has no incoming lymphatics nor any high endothelial venules. Rather, T cells and B cells can only enter the spleen through the bloodstream. In effect, the spleen functions as a blood filter (SO 69) which is ideal for intercepting blood-borne pathogens (SO 74).

**STAT** (“signal transducer and activator of transcription”). See “JAK.”

**Stem cell.** Stem cells have the ability to regenerate themselves. Stem cells first appear in the blood islands of the yolk sac and then in the fetal liver. They may also be found circulating in the blood of 5-8 week fetuses. In the adult, stem cells are located in the

bone marrow (21:5). See JT 4 for an arboreal diagram depicting the cells descending from stem cells.

**Superantigen.** Superantigens are molecules that stimulate a subset of T cells by binding directly to MHC II molecules and V $\beta$  domains of T cell receptors, stimulating the activation of T cells expressing particular V $\beta$  V gene segments (JT 611, 155 fig. 4.36). They also bind to the  $\alpha$  chains of MHC II molecules (17:6). Thus, the superantigen effectively “clamps together” the MHC II molecule and the TCR (SO 74-5). Superantigens are effective at stimulating blast transformation because they involve multiple molecular bridges (17:6). Superantigens can induce the production of cytokines in overwhelming quantities, resulting in generalized inflammation (18:16; JT 154).

**Survival.** An ability to signal through surface immunoglobulin is required for the continued survival and recirculation of mature peripheral B cells (JT 207; SO 81). As naive T cells migrate through lymphoid tissue, they receive specific survival signals through their interactions with dendritic cells (JT 265). Activation of the bcl-X<sub>L</sub> “death-inhibiting gene” (JT 188-9) also serves as a survival signal for cells (22:7; JT 319 fig. 9.11).

**Switch.** See “class switching.”

**Synovitis.** Inflammation of a synovial membrane, especially that of a joint. Results from activation of T<sub>H</sub>1 cells. Can be a clinical manifestation of parasitic infection (23:17).

**Systemic lupus erythematosus.** See “SLE.”

**Tacrolimus.** See “FK506.”

**TAP** (“transporter associated with antigen processing”). TAP-1 and TAP-2 are ATP-binding cassette proteins involved in transporting short peptides from the cytosol into the lumen of the endoplasmic reticulum, where they associate with MHC I molecules (JT 612, 125, 127 fig. 4.13; SO 46).

**Target cell.** A cell on which an armed effector T cell acts (JT 263).

**T cell** (or “T lymphocyte”). One of the two major types of lymphocyte (the other being B cells). Precursors of T cells (1:24) originate in the bone marrow but mature in the thymus (15:8), after which they are distributed to the periphery (1:22). There are several types (T<sub>C</sub>, T<sub>H</sub>1, T<sub>H</sub>2). T cells constitute a component of the adaptive immune response. When activated, T cells produce lymphokines (1:20).

T cells can differentiate into memory cells (1:20).

Small resting T cells do not express MHC II molecules, but activated T cells (blastic cells) do (16:9).

T cells always have CD2 and CD3 on their surface (2000 TLE #1, question 20).

CD4<sup>+</sup> T cells (i.e. T<sub>H</sub>1 and T<sub>H</sub>2 cells) are found in the greatest proportion in the peripheral blood (2000 TLE #1, question 25).

T cells can ingest relatively large pathogens and present their antigens. However, if the pathogen is relatively small, B cells can also participate in this function (20:6).

Distribution of T cells: T cells are found in the deep cortex, the medullary cords of lymphoid tissue, the periarteriolar area of the spleen, the blood, and the thoracic duct (21:14).

The supply of T cells is substantially reduced after 35 years of age (21:14; JT 229).

CD8<sup>+</sup> cells (i.e. T<sub>C</sub> cells) can suppress the activity of T<sub>H</sub>1 cells by secreting TGFβ and IL-10 (25:10).

T cells require two signals for activation. The first signal is transmitted through antigen receptors. The second signal is delivered by a professional antigen presenting cell, such as a dendritic cell (JT 18).

The antigen-specific clonal expansion of naive T cells requires a second or co-stimulatory signal which must be delivered by the same antigen-presenting cell on which the T cell recognizes its specific antigen (JT 270). The requirement for simultaneous delivery of antigen-specific and co-stimulatory signals by one cell in the activation of naive T cells means that only professional antigen-presenting cells can initiate T cell responses (JT 271). Antigen binding to the T cell receptor in the absence of co-stimulation not only fails to activate the cell but also leads to anergy (JT 272).

**T cell receptor.** See “TCR.”

**T cell, suppressor.** Investigators have posited (but not yet proved) the existence of suppressor T cells, whose alleged function is to “turn off” the immune system once the infectious pathogen has been eliminated from the body (SO 11).

**T<sub>C</sub> cell** (or “cytotoxic T cell”). Cytotoxic T cells can kill other cells by inducing apoptosis (JT 293-4). Most cytotoxic T cells are MHC class I restricted CD8 T cells (though CD4 T cells can also kill in some cases). Cytotoxic T cells are important in host defenses against cytosolic pathogens (JT 598).

CD7 is present on T cells (15:11).

T<sub>C</sub> cells can differentiate into T<sub>C</sub>1 and T<sub>C</sub>2 cells in much the same fashion as T<sub>H</sub>0 cells can differentiate into T<sub>H</sub>1 and T<sub>H</sub>2 cells (18:15).

T<sub>C</sub> cells are activated by IL-2 (19:8; SO 60).

When T<sub>C</sub> cells pass from circulation to the lymph nodes they have L-selectin. When activated, they lose this molecule, and are thereby “granted permission” to leave the lymph node. They simultaneously acquire increased expression of LFA-1 and VLA-4, which are used to home on endothelial cells where there is infection and inflammation (19:8).

When a T<sub>C</sub> cell finds a cell displaying adequate amounts of antigen and bind to it, the T<sub>C</sub> cell orients its microtubule organizing center towards the offending cell in order to direct its attack (JT 286 fig. 8.28); in this fashion, the T<sub>C</sub> cell avoids harming adjacent cells, so the process is said to be selective. Once a T cell is activated, the B7-CD28 interaction is no longer needed. The T<sub>C</sub> cell kills its target through a variety of mechanisms, including granzymes (which induce caspase to chop up the target cell’s DNA), perforin polymerases, engaging the Fas receptor, and TNFα and TNFβ (19:9).

After the T<sub>C</sub> cell kills its target, it can move on to kill other cells (19:9; JT 297 fig. 8.37).

When a  $T_C$  clone develops for recognition of MHC + Ag fragment, that particular clone can only kill if it is presented with the same exact combination of MHC and antigen fragment (19:10).

Activated  $T_C$  cells may become able to kill target cells of unrelated genetic background if the recognition is replaced with a lectin, such as PHA or concanavalin A (19:12).

$CD8^+$  cells (i.e.  $T_C$  cells) can suppress the activity of  $T_H1$  cells by secreting  $TGF\beta$  and IL-10 (25:10).

**$T_H0$  cell** (“naive” or “uncommitted” T cell). Differentiate into  $T_H1$  or  $T_H2$  cells depending upon the needs dictated by multiple factors in their environment (18:16). The differential capacity of pathogens to interact with dendritic cells, macrophages, NK cells and  $CD4$  T cells can influence the overall balance of cytokines present early in the immune response and thus determine whether  $T_H1$  or  $T_H2$  cells develop preferentially (JT 394). When one type of  $T_H$  cell begins to predominate, it secretes cytokines which inhibit the activation of the other type of  $T_H$  cell (JT 394-5). IL-4 and IL-6 promote differentiation into  $T_H2$  cells, while IL-12 and  $IFN\gamma$  promote differentiation into  $T_H1$  cells (18:14, 16; 23:16).  $T_H0$  cells can produce a variety of cytokines (18:15). The balance between  $T_H1$  and  $T_H2$  cells is important in, for instance, the response to parasitic infections (26:8).

**$T_H1$  cell** (or “ $CD4$  T cell”). A subset of  $CD4$  T cells (the other subset being  $T_H2$ ) which are characterized by the cytokines they produce. They are mainly involved in activating macrophages (JT 612). IL-12 and  $IFN\gamma$  promote differentiation of  $T_H0$  cells into  $T_H1$  cells (18:14, 16).

$T_H1$  cells are crucial for activating macrophages (JT 394).

$T_H1$  cells can become “armed effector T cells,” e.g. in parasitic infections (23:16-17).

$CD8^+$  cells (i.e.  $T_C$  cells) can suppress the activity of  $T_H1$  cells by secreting  $TGF\beta$  and IL-10 (25:10).

**$T_H2$  cell** (or “helper  $CD4$  cell”). A subset of  $CD4$  T cells (the other subset being  $T_H1$ ) which are characterized by the cytokines they produce. They are mainly involved in stimulating B cells to produce antibody (JT 612), which is why they are called “helper” T cells (1:20). IL-4 and IL-6 promote differentiation of  $T_H0$  cells into  $T_H2$  cells (18:14, 16).

When macrophages present antigen and display B7, the  $T_H2$  cells recognize this processed antigen and become activated. Activation is the result of recognition at TCR/ $CD3$ / $CD4$  for signal 1, and at B7- $CD28$  for signal 2. Other adhesion molecules are also important for this initial conjugate formation (20:7), as shown in the table below (from 20:8):

On $T_H2$ cells	On B cells or macrophages
TCR/ $CD3$	MHC II plus antigen fragment
$CD4$ ( $p56^{lck}$ )	MHC II
LFA-1	ICAM-1, 2, 3
$CD2$	LFA-3
$CD5$	$CD72$
$CD27$	B7.1 and B7.2

After conjugate formation, T cells are activated and become “armed effector T cells” with several new characteristics (20:8):

- They are blastic cells, no longer in the G<sub>0</sub> phase of the cell cycle.
- They overexpress the integrin LFA-1.
- They begin to express the integrin VLA-4.
- They no longer require B7-CD28 interaction for proper function when they encounter a naive B cell.

T<sub>H</sub>2 cells are the most effective activators of B cells (JT 394), and tend to induce B cells to “class switch” to producing IgE antibodies (JT 465 fig. 12.4). During their interaction with B cells, T<sub>H</sub>2 cells orient their microtubule organizing center, cytoskeleton and secretory apparatus towards the B cell that has the MHC + Ag fragment (JT 313 fig. 9.6). In this manner the cytokines are delivered at close range and at a critical concentration. These cytokines (such as IL-4) are necessary to drive B cells into proliferation and to signal B cells to switch the C genes and change antibody class (20:10).

Armed effector T<sub>H</sub>2 cells are over 1000 times more effective than naive T cells in their collaboration with B cells (22:6).

**T<sub>H</sub>3 cell.** Produce transforming growth factor  $\beta$  (TGF $\beta$ ) (18:13).

**TCR** (“T cell receptor”). Approximately 95% of TCRs are of the “ $\alpha\beta$ ” type, i.e. they consist of a disulfide-linked  $\alpha\beta$  heterodimer (15:12; SO 54) of the highly variable  $\alpha$  and  $\beta$  chains expressed at the cell membrane as a complex with the invariant CD3 chains. T cells carrying this type of receptor are often called  $\alpha:\beta$  T cells. The remaining 5% of TCRs are of the “ $\gamma\delta$ ” type, in which variable  $\gamma$  and  $\delta$  chains are expressed with CD3 (JT 612).

Whatever the external configuration of the TCR (i.e. be it either of the “ $\alpha\beta$ ” type or of the “ $\gamma\delta$ ” type), the internal part of the TCR is a complex called CD3, which consists of  $\gamma$ ,  $\delta$ ,  $\epsilon$  and  $\zeta$  proteins which are responsible for signal transmission. (Note that the  $\gamma$  and  $\delta$  proteins are not the same as those molecules comprising the “ $\gamma\delta$ ” type receptor.) (See SO 55.)

Note that a TCR only recognizes “processed” antigen which is presented by a MHC molecule. This contrasts with a BCR which recognizes antigen in its natural, unprocessed state (SO 64.)

A T cell receptor is monovalent, whereas Ig is bivalent. A T cell receptor is never secreted, whereas Ig is secreted (JT 148). T cell receptor gene segments rearrange during development to form complete V-domain exons. The mechanics of gene rearrangement are similar for T and B cells (JT 150), and the structural diversity of T cell receptors is due entirely to combinatorial and junctional diversity generated during the process of gene rearrangement (JT 152). The three-dimensional structure of the antigen recognition site of a T cell receptor looks much like that of an antibody molecule (JT 151). Somatic hypermutation does not occur in T cell receptor genes (JT 154).

**TdT** (“terminal deoxynucleotidyl transferase”). Most immature progenitor cells and early thymocytes have TdT (JT 218 fig. 6.17). Malignant cells deriving from stem cells and progenitor cells also have TdT (21:6). TdT is also present on apoptotic cells (JT 187 fig. 5.23)

**Terminal deoxynucleotidyl transferase.** See “TdT.”

**TGF $\beta$**  (“transforming growth factor  $\beta$ ”). Produced primarily by T<sub>H</sub>3 cells (18:13), though it can also be produced by T<sub>H</sub>2 cells (18:14). It has several functions:

- It is a strong inhibitor of T<sub>H</sub>1 cells and inflammatory T cells (18:13; 25:10). This is its main function (LJ 335).
- In culture, TGF $\beta$  induces normal fibroblasts to behave as malignant cells (18:12).
- It is involved in the repair process by causing fibroblast proliferation and the deposition of collagen (18:12).
- It also plays a role in some pathological processes such as fibrosis and scleroderma (18:12).
- It induces IgA production by B cells in the intestinal tract (18:13).

**Thymic anlage.** The tissue from which the thymic stroma develops during embryogenesis (JT 612), specifically the 3rd and 4th pharyngeal pouches and the 3rd and 4th branchial clefts (21:6).

**Thymic stroma.** Consists of epithelial cells and connective tissue that form the essential microenvironment for T cell development (JT 612).

**Thymocyte.** Thymocytes are lymphoid cells found in the thymus. They consist mainly of developing T cells, although a few thymocytes have achieved functional maturity (JT 612).

CD7 is present on thymocytes (15:11).

The precursor cells of thymocytes are pluripotential. Early cortical thymocytes have terminal deoxynucleotidyl transferase (TdT). Cortisone treatment of stress depletes the cortical region of the thymus of approximately 65% of the cells (21:7).

After the rearrangement of genes for the  $\beta$  chains, thymocytes express TCR with a surrogate  $\alpha$  chain (called pT $\alpha$ ) together with the CD3 receptor complex. In addition, they acquire CD4 and CD8, and thereby become double positive cells. If the rearrangement is initially unsuccessful, these cells are permitted another attempt to rearrange their  $\alpha$  chains because the RAG genes are still active (21:8; JT 201, 238-9).

Thymocytes with a mature T cell phenotype are found in the medulla of the thymus (21:8).

Thymocytes generate a very large repertoire of receptors to fit all sorts of MHC specificities (21:9).

**Thymoma.** A malignancy which can develop from thymic stromal cells (21:11; JT 256 fig. 7.24).

**Thymus.** The site of T cell development. The thymus is a lymphoepithelial organ in the upper part of the middle of the chest, just posterior to the sternum (JT 612). It originates embryonically from the 3rd and 4th pharyngeal pouches and 3rd and 4th branchial clefts, which together form the thymic anlage (21:6).

Since the 3rd pharyngeal pouch is also the embryonic origin of the parathyroid glands, parathyroid deficiency in a newborn (resulting in hypocalcemic convulsions) may be correlated with thymic aplasia (21:6).

Lack of development of the thymus leads to the absence of functional T cells. The lack of development of the thymus may be due to either of two factors: (1) Lack of functional precursors, resulting in SCID, in which neither T nor B cells develop. (2) Lack of differentiation of the thymic anlage, resulting in DiGeorge Syndrome in humans (or “nude mice” in mice) (21:6-7).

The thymus is composed (from superficial to deep) of a capsule, subcapsular area, outer cortex, deep cortex, cortico-medullary junction, and medulla (21:6).

The cells in the thymus can be of “local” origin or can be “imported.”

The local cells include epithelial cells and nurse cells. There is a network of epithelial cells extending from the cortex to the cortico-medullary junction. Some of these epithelial cells in the subcortex are “nurse cells” which are involved in the development of thymocytes through their maturational stages.

The imported cells include dendritic cells, macrophages, and stem cells which generate thymocytes.

Approximately 95% of the cells generated in the thymus die there by apoptosis (21:6).

Thymocytes with a mature T cell phenotype are found in the medulla of the thymus (21:8).

Thymectomy in neonatal humans has almost no consequences in later life (21:10).

**TI antigen** (“T cell independent antigen”). Some antigens can stimulate B cells directly (i.e. without the help of T cells) and are thus called T-independent antigens (an example is *E. coli*) (1:20). Certain bacterial polysaccharides, polymeric proteins and lipopolysaccharides are examples of TI antigens (JT 321). There are several classes of TI antigens.

TI-1 antigens contain an intrinsic activity that can induce the proliferation of B cells (JT 321).

TI-2 antigens. Polysaccharide antigens (typical of bacteria) are mainly TI-2 antigens (20:6) These contain no intrinsic B cell stimulating activity (JT 321).

TI responses are important components of the humoral immune response to non-protein antigens that are unable to recruit peptide-specific T cell help (JT 323).

**Tingible body macrophage.** During the process of germinal center formation, tingible body macrophages appear. These are phagocytic cells engulfing apoptotic B cells, which are produced in large numbers during the height of the germinal center response (21:9, 12; JT 613, 318).

**TNF** (“tumor necrosis factor”). TNFs function as cell-associated or secreted proteins that interact with receptors of the tumor necrosis factor receptor (TNFR) family, which in turn communicates with the interior of the cell via components known as TRAFs (tumor necrosis factor receptor-associated factors) (JT 613). There are several TNFs (JT 589). Those which figure prominently in Dr. Teodorescu’s handouts are listed below:

**TNF $\alpha$**  A cytokine produced by macrophages and T cells that has multiple functions in the immune response. It is the defining member of the TNF family of cytokines (JT 613). Shares some properties of IL-1. Can act on Fas receptors to induce apoptosis of tumor cells and cells infected by viruses (18:9). TNF $\alpha$  has a potent activating effect for killing bacteria (23:17). TNF $\alpha$  is also called cachectin because in certain conditions its oversecretion can cause wasting (26:7).

**TNF $\beta$**  A cytokine produced by T<sub>C</sub> and T<sub>H1</sub> cells (18:9; 23:14). Acts on Fas receptors (18:9).

**Tolerance.** Failure to respond to an antigen. The healthy immune system is said to be tolerant to self antigens. Tolerance to self antigens is an essential feature of the immune system; when tolerance is lost, the immune system can destroy self tissues, as happens in autoimmune diseases (JT 613). Tolerance is as specific as the immune response for which it is the counterpart, meaning that tolerance towards a given antigen is developed with the same high degree of specificity as antibodies (which are extremely specific for particular antigens). Tolerance may be complete or may be limited to a particular type of response; it may hold for both humoral and cell-mediated immunity (25:6). The following is a summary of the general features of immunological tolerance (25:12):

- Tolerance is specific for the inducing antigen.
- Tolerance may be the result of either clonal deletion or inactivation.
- Tolerance is learned or acquired either to self antigens or to foreign antigens.
- Tolerance can be more easily induced in immature lymphocytes.
- Tolerance is mainly due to non-fulfillment of the requirement for antigen + a second signal during the exposure to antigen.
- Tolerance may be terminated by foreign cross reacting antigen by providing T cell help for a different determinant on the antigen.
- Tolerance by T cells lasts longer than tolerance by B cells.

Tolerance is of two sorts: central and peripheral (LJ 373). The way that these types of tolerance are induced is somewhat different for T cells versus B cells (SO 80-1).

Central tolerance. B cell clones that arise through genetic rearrangements that have the capacity to make antibodies to one's own epitopes are deleted in the thymus; this is known as central tolerance (9:5). Central tolerance of T cells involves two processes, the relative order of which is uncertain (SO 76-8):

Phase of central tolerance	Type of selection	Which cells are permitted to survive
MHC restriction	Positive selection	Cells which <i>do</i> recognize an empty T cell receptor.
Tolerance induction	Negative selection	Cells which do <i>not</i> recognize a T cell receptor bearing a self-antigen.

Only about 3% of thymocytes survive the tests of central tolerance; the rest die by apoptosis (SO 77).

Peripheral tolerance. Inhibition or deletion of self-reactive B cells in lymph nodes and spleen is known as peripheral tolerance (9:5), which can be demonstrated experimentally (25:8). T cells also are made to exhibit peripheral tolerance (SO 79).

The development of tolerance relies on several mechanisms, including clonal deletion and clonal ignorance (25:6).

Self proteins, or proteins injected in a deaggregated, free form, induce tolerance. (In general, free soluble antigen is much more likely to induce tolerance than aggregated antigen because aggregated antigen has a greater opportunity to be ingested by macrophages and presented; 25:12.) Apparently this tolerance is due to the following mechanisms. Macrophages ingest numerous self proteins, but do not get activated to produce B7. However, they do present (in association with MHC II) the peptides derived from these antigens. T<sub>H</sub>1 cells with receptors for the non-self proteins will recognize them on the surface of macrophages in an inappropriate fashion and will become clonally inactivated (25:8).

If the specific antigen signal is present but there is no co-stimulatory signal, the T cell is rendered anergic. Conversely, if the co-stimulatory signal is present but there is no specific antigen signal, there is no effect on the T cell (JT 279 fig. 8.20).

Tolerance can also be induced by interfering with co-receptors. For instance, tolerance to myelin basic protein (in the mouse model involving experimental allergic encephalomyelitis) may be induced by interfering with MHC presentation with a monoclonal antibody, though this is only temporary (25:9).

Tolerance by B cells may be drug-induced. For instance, when antigen stimulation is induced and cyclophosphamide is injected during the phase of B cell proliferation, the clone may be eliminated and tolerance induced, though this tolerance is only transient since new clones of B cells will develop (25:11).

Immature B cells become tolerant to self antigens and are most likely deleted (by being cross linked to the surface of tingibile body macrophages) at the stage of immature B cells, before they develop IgD. They also interact with antigens in free form and become anergic in the absence of any help from T cells (25:10).

Mature B cells have both IgM and IgD and can encounter antigen in the periphery during recirculation. However, tolerance develops in the periphery because of subsequent loss of IgM receptors (the  $\mu$  chains remain sequestered in the cytoplasm), rendering the mature B cells anergic or tolerant. Peripheral tolerance can also operate during maturation in the germinal centers (25:10).

Tolerance can be induced through manipulation of the antigen dose. When antigen is inoculated initially in a very high dose, tolerance may develop. This is probably because the antigen in the free form interacts directly with B cell receptors; moreover, the free antigen probably causes T cells to become anergic because they are exposed to antigen presenting cells without B7. Inoculation of antigen in a low dose can also induce tolerance. This is probably because the low dose of antigen may be sufficient to be recognized by T cell receptors, but it is not enough antigen to trigger activation with production of IL-2; the result is clonal anergy of the T cells (25:12).

Self-tolerance can be disrupted by a variety of infectious agents (JT 530 fig. 13.39).

**Tolerance, oral.** Oral tolerance can be induced by feeding an experimental animal with antigen or chemicals.  $T_H2$  cells in the gastrointestinal tract get activated. If the animal is subsequently injected with the antigen, a T cell response takes place, but the  $T_H2$  cells (previously induced in the gut) suppress new activation of  $T_H1$  cells (25:9).

**Tolerance, relative.** Relative tolerance refers to the antagonism between  $T_H1$  and  $T_H2$  cells (25:9). The balance of  $T_H1$  versus  $T_H2$  response can actually be shifted (artificially) by injecting various cytokines. For instance, IL-12 promotes activation of  $T_H1$  cells (25:9), while IL-4 induces  $T_H0$  cells to differentiate into  $T_H2$  cells (25:10).

**Toxin.** A major means by which bacteria cause disease is by producing toxins. (The other major means is invasion and inflammation; LJ 25). There are two types of toxins: exotoxins and endotoxins (LJ 29, 35; 2000 TLE #1, question 3).

	<b>Exotoxin</b>	<b>Endotoxin</b>
Produced by which bacteria?	Both gram+ and gram-.	Only gram-.
Consists of	Protein excreted by the bacterial cell into its surroundings.	Lipopolysaccharide component of the bacterial cell wall.
Effect of heating	Heat labile. Gets converted into toxoid.	Heat stable.
Toxicity	Extremely toxic.	Relatively low toxicity.
Antigenicity (or immunogenicity)	Highly antigenic.	Weakly antigenic.

High-affinity IgG and IgA antibodies can neutralize bacterial toxins (JT 328-9).

**Toxoid.** A toxin that has been treated so as to destroy its toxic property but retain its antigenicity. In other words, a toxoid remains capable of stimulating the production of antitoxin antibodies and thus of producing an active immunity (Stedman's medical dictionary). Toxoids are therefore employed in immunization (JT 613).

**Trafficking of lymphocytes.** This is Sompayrac's (SO 70) term describing where in the body lymphocytes (T and B cells) may or may not go at various phases during their development.

Naive T cells can travel to all secondary lymphoid organs, but cannot travel to sites of inflammation. Experienced T cells tend to return to the same type of secondary lymphoid organ as the one in which they gained their experience (SO 71).

Naive B cells can travel to all secondary lymphoid organs. Experienced B cells are more sedentary than experienced T cells; experienced B cells remain in secondary lymphoid organs or bone marrow and produce antibodies (SO 71).

**Transforming growth factor.** See "TGF."

**Transplantation.** Transplantation can involve an organ (in which case it is simply called a "transplant") or it can involve a tissue (in which case it is called a "graft"). An allograft (or allotransplant) is performed between individuals of the same species. An isograft (or isotransplant) is performed between individuals with the same genetic makeup (i.e. identical twins). A xenograft (or xenotransplant) is performed between members of

different species (e.g. porcine heart valve transplant into a human). An autograft is performed on a single individual, taking tissue from one area of the body and transplanting it to another part of the body (23:9).

Four laws of transplantation have been established based on inheritance of MHC: (1) Transplant from an allogenic individual is rejected; (2) Transplant from a parent into an F1 hybrid (i.e. a child) is accepted, provided that the two parents are homozygous and the F1 has both of their genetic makeup, including the MHC for which the F1 is tolerant; (3) Transplant from F1 into either of the parents is always rejected because the parent reacts to the MHC which the F1 has from the other parent; (4) Transplanting lymphoid tissue from a parent into an F1 or into an allogenic immunoincompetent host results in graft versus host disease (23:9).

**Skin allografts** can induce graft rejection. In the induction phase of the reaction, Langerhans cells and macrophages are activated (23:9). Necrotic damage can ensue because these cells do not express B7 (23:10). In the effector phase, the graft becomes vascularized. However, armed effector T cells attack the graft and cut off its blood supply. In a second set reaction (i.e. a second attempt at grafting from the same donor) the graft is rejected very rapidly by an in situ activation of memory T cells (23:10).

**Organ transplantation.** Certain organs (e.g. kidneys, liver, heart) have no constitutive expression of MHC II and therefore cannot express B7. This facilitates transplantation. In the induction phase of such transplants, vascular connection is immediately established, though  $T_H1$  and  $T_C$  cells are activated. In the effector phase these activated cells travel to the transplanted organ and initiate an inflammatory process which can cut off the blood supply and result in transplant rejection. The probability of rejection can be reduced by (1) removing the spleen, (2) purging the transplant organ of passenger cells; (3) seeking as good a match as possible for the MHC; (4) using immunosuppressants (23:11).

The **fetus** can be viewed as a type of allograft. There are several reasons why the fetus is not rejected (23:11-12), though the process is not entirely understood (JT 518-19). Two probable reasons are: (1) there is no expression of B7 in the fetal tissue; (2) trophoblast cells which constitute the embryo's outer layer (which is in contact with maternal tissue) does not express classical MHC antigens; moreover, these trophoblast cells produce IL-10, which inhibits  $T_H1$  cell development, and they have HLA-G (non-polymorphic class I molecules) which inhibit NK cell activation (25:7).

**Tumor.** Any neoplasm. Tumors arise due to mutagens (e.g. UV light, X radiation, certain chemicals, irritating agents such as asbestos) which damage DNA. If the mutation changes a proto-oncogene (e.g. *bcl-X<sub>L</sub>*, *c-myc*) into an oncogene (JT 221), or interferes with a tumor-suppressor gene (e.g. *p53*), or damages the DNA proofreading or repair mechanisms, then the cell is likely to become cancerous.

Tumor cells tend to be genetically unstable (JT 554-5).

Tumors express antigenic peptides that can become targets of a tumor-specific T cell response (JT 551). Some tumor antigens are the products of mutated genes. Others are normal proteins which are overexpressed. Some tumor antigens elicit humoral (antibody-mediated) responses; others elicit cell-mediated immune responses (32:1).

Tumor cells can escape immune surveillance in a variety of ways (JT 554 fig. 14.13). For instance, some tumor cells can invoke antigenic variation (JT 554 fig. 14.13).

**Tumor necrosis factor.** See “TNF.”

**Urticaria** (or “hives”). Chronic urticaria, a type II hypersensitivity reaction (JT 463 fig. 12.2), is a disseminated form of the wheal-and-flare reaction which sometimes appears when ingested allergens enter the bloodstream and reach the skin. Histamine release triggered by mast cells activated by allergen in the skin causes large, itchy red swellings beneath the skin (JT 476).

**Vaccination.** The deliberate induction of adaptive immunity to a pathogen by injecting a vaccine, a dead or attenuated (non-pathogenic) form of the pathogen (JT 613). There are several requirements for an effective vaccine (JT 562-3).

DNA vaccination involves injecting DNA which encodes a viral immunogen directly into muscle. It is not clear why this works (JT 571).

**Valence.** The valence of an antibody or antigen is the number of different molecules that it can combine with at one time (JT 613). An antibody must be minimally bivalent in order to cause aggregation of antigen.

**Varicella virus.** The virus which is responsible for “chickenpox” in childhood. After this initial infection, the virus lies dormant, but can become active again in adulthood, in which case it is called herpes zoster (23:14-15).

**Virus.** All enveloped viruses are sensitive to antibody and complement (23:14; 2000 TLE #1, question 4). Exit of virions from a host cell may occur by lysis of the host cell, by budding from the host cell, or by direct entry into a neighboring host cell through connecting pores (2000 TLE #1, question 10).

The cellular response to viral infection consists of two phases: (1) an afferent or inductive phase, and (2) an efferent or effector phase. For some viral infections the development of T<sub>C</sub> cells is critical for an effective defense; these cells engage any nucleated cell (which will have MHC I molecules) that has virus antigen fragment attached to its surface. For other viruses the immune system relies mainly on antibody production (chiefly IgG and IgA) to neutralize the virus before it can attach to any cells (19:6; 23:14; JT 330 fig. 9.22). Some viruses will activate type 1 T cells (both T<sub>H1</sub> and T<sub>C</sub> cells), which produce cytokines (IL-2, IFN $\gamma$ , TNF $\alpha$ , TNF $\beta$ ) that activate NK cells (23:14).

Viral antigens are frequently presented by both MHC I and MHC II (19:6). Normally they are presented by MHC I, since MHC I presents antigens from the cell's cytoplasm. However, sometimes virus particles are also endocytosed, fragmented, and displayed by MHC II molecules (SO 101).

Some viruses evade host immune responses by retreating into a state of latent, non-manifesting infection of neurons. An example is the varicella virus which remains after a childhood episode of “chickenpox” (23:14).

Memory of a virus is preserved by long lived memory T<sub>C</sub> cells. These cells can become immediately reactivated by antigen presenting cells bearing B7 (23:15).

Viruses can evade host defenses through several mechanisms. Some viruses encode the synthesis of molecules which impair the functioning of various molecules needed for the host defense (such as complement control molecules, cytokine receptors, adhesion molecules). Some viruses inhibit the function of TAP (a protein that transports

a peptide from the cytoplasm into the lumen of the endoplasmic reticulum), which results in less MHC I being expressed (23:15). The influenza virus employs antigenic drift and antigenic shift to evade host defenses (23:16).

Viruses can be classified by several criteria (LJ 157-9). They can be DNA or RNA based, can be single-stranded or double-stranded, can be of positive or negative polarity. (A virus exhibiting positive polarity has RNA with the same base sequence as the mRNA; a virus exhibiting negative polarity has a base sequence that is complementary to the mRNA.)

**Waldenstrom macroglobulinemia.** Caused by malignant B cells which produce IgM (21:14).

**Wheal-and-flare reaction** (or “wheal and erythema reaction”). When small amounts of allergen are injected into the dermis of an allergic individual, and wheal-and-flare reaction is observed. This consists of a raised area of skin containing fluid and a spreading, red, itchy circular reaction (JT 614). This immediate reaction follows the IgE-mediated mast cell activation and results from the activity of histamine, prostaglandins and other mediators which cause a rapid increase in vascular permeability and the contraction of smooth muscle (JT 471-2). The mast cell activation also stimulates a nerve axon reflex, causing the vasodilation of surrounding cutaneous blood vessels (JT 476).

**X-linked hypogammaglobulinemia.** See “Bruton’s agammaglobulinemia.”