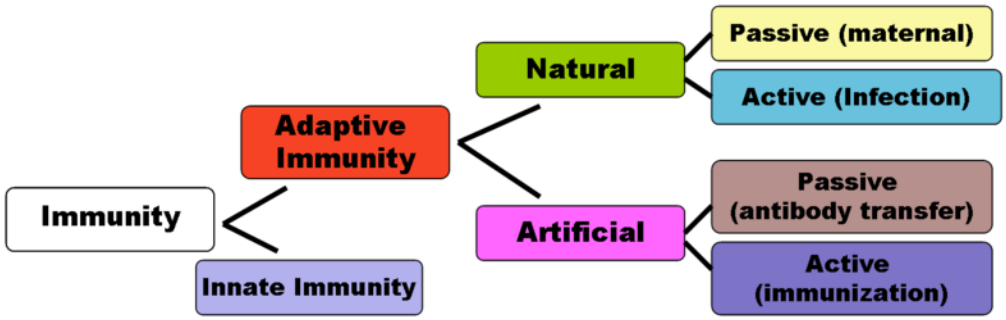
IMMUNITY



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Immunity is a biological term that describes a state of having sufficient biological defenses to avoid infection, disease, or other unwanted biological invasion. In other words, it is the capability of the body to resist harmful microbes from entering it. Immunity involves both specific and non-specific components. The non-specific components act either as barriers or as eliminators of wide range of pathogens irrespective of antigenic specificity. Other components of the immune system adapt themselves to each new disease encountered and are able to generate pathogen-specific immunity.

Innate immunity, or nonspecific, immunity is the natural resistance with which a person is born. It provides resistance through several physical, chemical, and cellular approaches. Microbes first encounter the epithelial layers, physical barriers that line our skin and mucous membranes. Subsequent general defences include secreted chemical signals (cytokines), antimicrobial substances, fever, and phagocytic activity associated with the inflammatory response. The phagocytes express cell surface receptors that can bind and respond to common molecular patterns expressed on the surface of invading microbes. Through these approaches, innate immunity can prevent the colonization, entry, and spread of microbes.

Adaptive immunity is often sub-divided into two major types depending on how the immunity was introduced.

- **Naturally acquired immunity** occurs through contact with a disease causing agent.
- **Artificially acquired immunity** develops only through deliberate actions such as vaccination.

Both naturally and artificially acquired immunity can be further subdivided depending on whether immunity is induced in the host or passively transferred from a immune host.

- **Passive immunity** is acquired through transfer of antibodies or activated T-cells from an immune host, and is short lived—usually lasting only a few months.
- **Active immunity** is induced in the host itself by antigen, and lasts much longer, sometimes lifelong. The diagram below summarizes these divisions of immunity

Species immunity: A pig injected with AIDS virus cannot get AIDS because pigs are immune to virus. The immunity of a species to a particular type of organism is called species immunity.

Autoimmunity: It is the development of an immune response to one's own tissue.

- Once a foreign organism has been recognized, the immune system recruits a variety of cells and molecules to mount an appropriate response, called an **effector response,** to eliminate or neutralize the organism.

- Later exposure to the same foreign organism induces a **memory response,** characterized by a more rapid and heightened immune reaction that serves to eliminate the pathogen and prevent disease.
- Immunity mediated by antibodies contained in body fluids (known at the time as humors), it was called humoral immunity.

- An effective immune response involves two major groups of cells

B LYMPHOCYTES

B cells are lymphocytes that play a large role in the humoral immune response. B cells are an essential component of the adaptive immune system. B cells, which are the precursors of plasma cells, are characterized by the presence of a B-cell receptor able to bind specifically an antigen.

Their principal functions are to make antibodies against antigens, perform the role of antigen-presenting cells (APCs) and eventually develop into memory B cells after activation by antigen interaction. Recently, a new, suppressive function of B cells has been discovered.

The abbreviation "B", in B cell, comes from the bursa of Fabricius in birds, where they mature. In mammals, immature B cells are formed in the bone marrow, which is used as a backronym for the cells' name.

B cell types

- **Plasma B cells** (also known as *plasma cells*, *plasmocytes*, and *effector B cells*) are large B cells that have been exposed to antigen and produce and secrete large amounts of antibodies, which assist in the destruction of microbes by

binding to them and making them easier targets for phagocytes and activation of the complement system.

- **Memory B cells** are formed from activated B cells that are specific to the antigen encountered during the primary immune response. These cells are able to live for a long time, and can respond quickly following a second exposure to the same antigen.

T LYMPHOCYTES

T cells or **T lymphocytes** belong to a group of white blood cells known as lymphocytes, and play a central role in cell-mediated immunity. They can be distinguished from other lymphocytes, such as B cells and natural killer cells (NK cells), by the presence of a *T cell receptor* (TCR) on the cell surface. They are called *T* cells because they mature in the thymus. There are several subsets of T cells, each with a distinct function.

T cell Types

- **Helper**

T helper cell (T_H cells) assist other white blood cells in immunologic processes, including maturation of B cells into plasma cells and memory B cells, and activation of cytotoxic T cells and macrophages. These cells are also known as **$CD4^+$ T cells** because they express the CD4 protein on their surface. Helper T cells become activated when they are presented with peptide antigens by MHC class II molecules, which are expressed on the surface of antigen presenting cells (APCs). Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or assist in the active immune response.

- **Cytotoxic**

Cytotoxic T cells (T_C cells, or CTLs) destroy virally infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as **$CD8^+$ T cells** since they express the CD8 glycoprotein at their surface. These cells recognize their targets by binding to antigen associated with MHC class I, which is present on the surface of nearly every cell of the body.

- **Memory**

Memory T cells are a subset of antigen-specific T cells that persist long-term after an infection has resolved. They quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen, thus providing the immune system with "memory" against past infections. Memory T cells comprise two subtypes: central memory T cells (T_{CM} cells) and effector memory T cells (T_{EM} cells). Memory cells may be either $CD4^+$ or $CD8^+$.

- **Regulatory**

Regulatory T cells (T_{reg} cells), formerly known as **suppressor T cells**, are crucial for the maintenance of immunological tolerance. Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress auto-reactive T cells that escaped the process of negative selection in the thymus.

- **Natural killer**

Natural killer T cells (NKT cells – not to be confused with natural killer cells of the innate immune system) bridge the adaptive immune system with the innate immune system. Unlike conventional T cells that recognize peptide antigens presented by major histocompatibility complex (MHC) molecules, NKT cells recognize glycolipid antigen presented by a molecule called CD1d. Once activated, these cells can perform functions ascribed to both T_h and T_c cells (i.e., cytokine production and release of cytolytic/cell killing molecules). They are also able to recognize and eliminate some tumor cells and cells infected with herpes viruses.

Type	Acquired through
Passive immunity	Natural maternal antibody
	Immune globulin*
	Humanized monoclonal antibody
	Antitoxin†
Active immunity	Natural infection
	Vaccines‡
	Attenuated organisms
	Inactivated organisms
	Purified microbial macromolecules
	Cloned microbial antigens
	Expressed as recombinant protein
	As cloned DNA alone or in virus vectors
	Multivalent complexes
	Toxoid§

*An antibody-containing solution derived from human blood, obtained by cold ethanol fractionation of large pools of plasma; available in intramuscular and intravenous preparations.

†An antibody derived from the serum of animals that have been stimulated with specific antigens.

‡A suspension of attenuated live or killed microorganisms, or antigenic portions of them, presented to a potential host to induce immunity and prevent disease.

§A bacterial toxin that has been modified to be nontoxic but retains the capacity to stimulate the formation of antitoxin.

Location of antigen

Antigen	Location
H-antigen	Associated with the flagella and are therefore only found on motile bacteria
O-antigen	Associated with the surface of the bacterial cell wall and are often referred to as somatic antigens
K-antigen	Associated with capsule

Types of Antibodies:

No.	Immunoglobulin	Function
1.	IgG	Major line of defense infection during the first few weeks of a body's life; neutralizes bacterial toxins; binds to microorganisms to enhance their phagocytosis and lysis.
2.	IgM	Efficient agglutinating and cytolytic agent; effective first line of defense in cases of bacteremia(bacteria in blood)
3.	IgA	Protects mucosal surfaces from inversion by pathogenic microbes.
4.	IgD	Regulator for the synthesis of other immunoglobulins; fetal antigen receptor.
5.	IgE	Responsible for severe acute and accasionally fatal allergic reactions; combats parasitic infections.

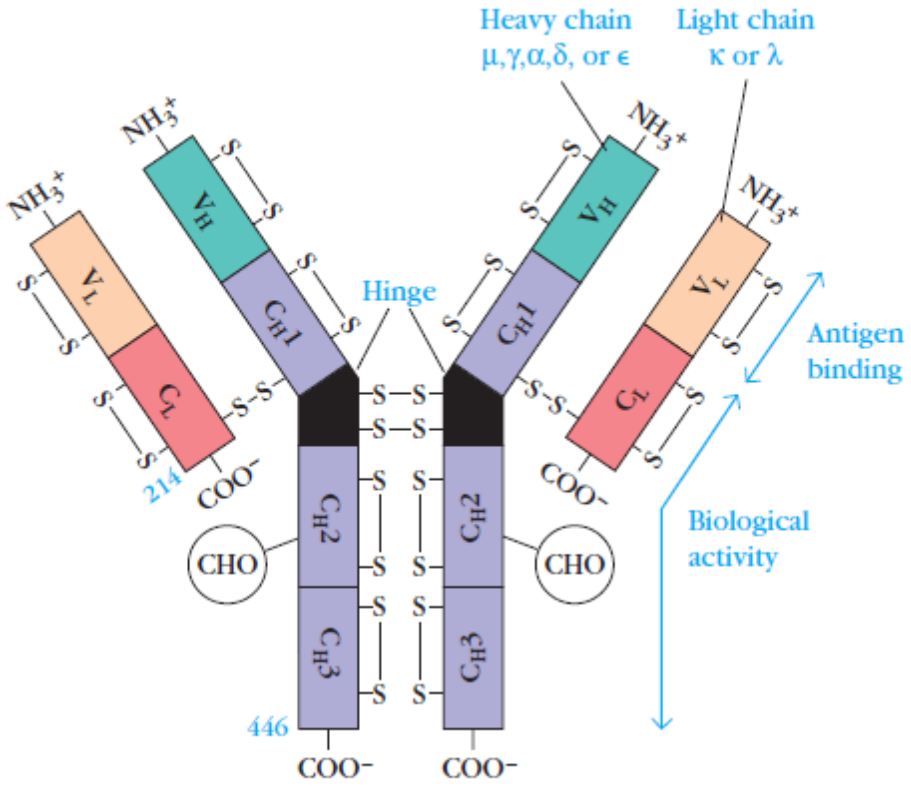

FIGURE 4-2 Schematic diagram of structure of immunoglobulins derived from amino acid sequencing studies. Each heavy and light chain in an immunoglobulin molecule contains an amino-terminal variable (V) region (aqua and tan, respectively) that consists of 100–110 amino acids and differs from one antibody to the next. The remainder of each chain in the molecule—the constant (C) regions (purple and red)—exhibits limited variation that defines the two light-chain subtypes and the five heavy-chain subclasses. Some heavy chains (γ, δ, and α) also contain a proline-rich hinge region (black). The amino-terminal portions, corresponding to the V regions, bind to antigen; effector functions are mediated by the other domains. The μ and ε heavy chains, which lack a hinge region, contain an additional domain in the middle of the molecule.

Vaccine

A **vaccine** is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Vaccines can be prophylactic (example: to prevent the effects of a future infection by any natural or "wild" pathogen), or therapeutic (e.g. vaccines against cancer are also being investigated e.g cancer vaccine). The incidence of diseases such as diphtheria, measles, mumps, pertussis (whooping cough), rubella (German measles), poliomyelitis, and tetanus has declined dramatically as vaccination has become more common.
Clearly, vaccination is a cost-effective weapon for disease prevention.
Genetic engineering techniques can be used to develop vaccines to maximize the immune response to selected epitopes and to simplify delivery of the vaccines.

Whole-Organism Vaccines

- Many of the common vaccines currently in use consist of inactivated (killed) or live but attenuated (avirulent) bacterial cells or viral particles.
- In some cases, microorganisms can be attenuated so that they lose their ability to cause significant disease (pathogenicity) but retain their capacity for transient growth within an inoculated host.
- Attenuation often can be achieved by growing a pathogenic bacterium or virus for prolonged periods under abnormal culture conditions.

- Attenuated vaccines have advantages and disadvantages. Because of their capacity for transient growth, such vaccines provide prolonged immune-system exposure to the individual epitopes on the attenuated organisms, resulting in increased immunogenicity and production of memory cells.
- As a consequence, these vaccines often require only a single immunization, eliminating the need for repeated boosters.
- A major disadvantage of attenuated vaccines is the possibility that they will revert to a virulent form. Attenuated vaccines also may be associated with complications similar to those seen in the natural disease.

Pathogenic Organisms Are Inactivated by Heat or Chemical Treatment

- Another common approach in vaccine production is inactivation of the pathogen by heat or by chemical means so that it is no longer capable of replication in the host. It is critically important to maintain the structure of epitopes on surface antigens during inactivation.
- Heat inactivation is generally unsatisfactory because it causes extensive denaturation of proteins; thus, any epitopes that depend on higher orders of protein structure are likely to be altered significantly.
- Chemical inactivation with formaldehyde or various alkylating agents has been successful.
- Killed vaccines often require repeated boosters to maintain the immune status of the host. In addition, killed vaccines induce a predominantly humoral antibody response.

Purified Macromolecules as Vaccines

Some of the risks associated with attenuated or killed whole organism vaccines can be avoided with vaccines that consist of specific, purified macromolecules derived from pathogens.

Three general forms of such vaccines are in current use: inactivated exotoxins, capsular polysaccharides, and recombinant microbial antigens.

Bacterial Polysaccharide Capsules Are Used as Vaccines

The virulence of some pathogenic bacteria depends primarily on the antiphagocytic properties of their hydrophilic polysaccharide capsule. Coating of the capsule with antibodies and/ or complement greatly increases the ability of macrophages and neutrophils to phagocytose such pathogens. These findings provide the rationale for vaccines consisting of purified capsular polysaccharides. The current vaccine for *Streptococcus pneumoniae*, which causes pneumococcal pneumonia, consists of 23 antigenically different capsular polysaccharides.

Toxoids Are Manufactured from Bacterial Toxins

Some bacterial pathogens, including those that cause diphtheria and tetanus, produce exotoxins. These exotoxins produce many of the disease symptoms that result from infection. Diphtheria and tetanus vaccines, for example, can be made by purifying the bacterial exotoxin and then inactivating the toxin with formaldehyde to form a **toxoid**. Vaccination with the toxoid induces anti-toxoid antibodies, which are also capable of binding to the toxin and neutralizing its effects. Conditions for the production of toxoid vaccines must be closely controlled to achieve detoxification without excessive modification of the epitope structure.

Recombinant-Vector Vaccines

Genes that encode major antigens of especially virulent pathogens can be introduced into attenuated viruses or bacteria. The attenuated organism serves as a vector, replicating within the host and expressing the gene product of the pathogen. A number of organisms have been used for vector vaccines, including vaccinia virus, the canarypox virus, attenuated poliovirus, adenoviruses, attenuated strains of *Salmonella*, the BCG strain of *Mycobacterium bovis.* Vaccinia virus, the attenuated vaccine used to eradicate smallpox, has been widely employed as a vector vaccine.

DNA Vaccines

In a recently developed vaccination strategy, plasmid DNA encoding antigenic proteins are injected directly into the muscle of the recipient. Muscle cells take up the DNA and the encoded protein antigen is expressed, leading to both a humoral antibody response and a cell-mediated response. The DNA appears either to integrate into the chromosomal DNA or to be maintained for long periods in an episomal form.

DNA vaccines offer advantages over many of the existing vaccines. For example, the encoded protein is expressed in the host in its natural form—there is no denaturation or modification.

The immune response is therefore directed to the antigen exactly as it is expressed by the pathogen. DNA vaccines cause prolonged expression of the antigen, which generates significant immunological memory.

Refrigeration is not required for the handling and storage of the plasmid DNA, a feature that greatly lowers the cost and complexity of delivery.

The same plasmid vector can be custom tailored to make a variety of proteins, so that the same manufacturing techniques can be used for different DNA vaccines, each encoding an antigen from a different pathogen.

An improved method for administering these vaccines entails coating microscopic gold beads with the plasmid DNA and then delivering the coated particles through the skin into the underlying muscle with an air gun (called a *gene gun*).

This will allow rapid delivery of a vaccine to large populations without the requirement for huge supplies of needles and syringes.

Disadvantage- only protein antigens can be encoded—certain vaccines, such as those for pneumococcal and meningococcal infections, use protective polysaccharide antigens.

TABLE 18-5 Comparison of attenuated (live), inactivated (killed), and DNA vaccines

Characteristic	Attenuated vaccine	Inactivated vaccine	DNA vaccine
Production	Selection for avirulent organisms: virulent pathogen is grown under adverse culture conditions or prolonged passage of a virulent human pathogen through different hosts	Virulent pathogen is inactivated by chemicals or irradiation with γ-rays	Easily manufactured and purified
Booster requirement	Generally requires only a single booster	Requires multiple boosters	Single injection may suffice
Relative stability	Less stable	More stable	Highly stable
Type of immunity induced	Humoral and cell-mediated	Mainly humoral	Humoral and cell-mediated
Reversion tendency	May revert to virulent form	Cannot revert to virulent form	Cannot revert

Monoclonal Antibodies

Hybrid Lymphoid Cell Lines

In somatic-cell hybridization, immunologists fuse normal B or T lymphocytes with tumor cells, obtaining hybrid cells, or heterokaryons, containing nuclei from both parent cells. Random loss of some chromosomes and subsequent cell proliferation yield a clone of cells that contain a single nucleus with chromosomes from each of the fused cells; such a clone is called a **hybridoma.**

Historically, cell fusion was promoted with Sendai virus, but now it is generally done with polyethylene glycol.

Normal antigen-primed B cells can be fused with cancerous plasma cells, called **myeloma cells** .

The hybridoma thus formed continues to express the antibody genes of the normal B lymphocyte but is capable of unlimited growth, a characteristic of the myeloma cell.

B-cell hybridomas that secrete antibody with a single antigenic specificity, called monoclonal antibody, in reference to its derivation from a single clone, have revolutionized not only immunology but biomedical research as well as the clinical laboratory.

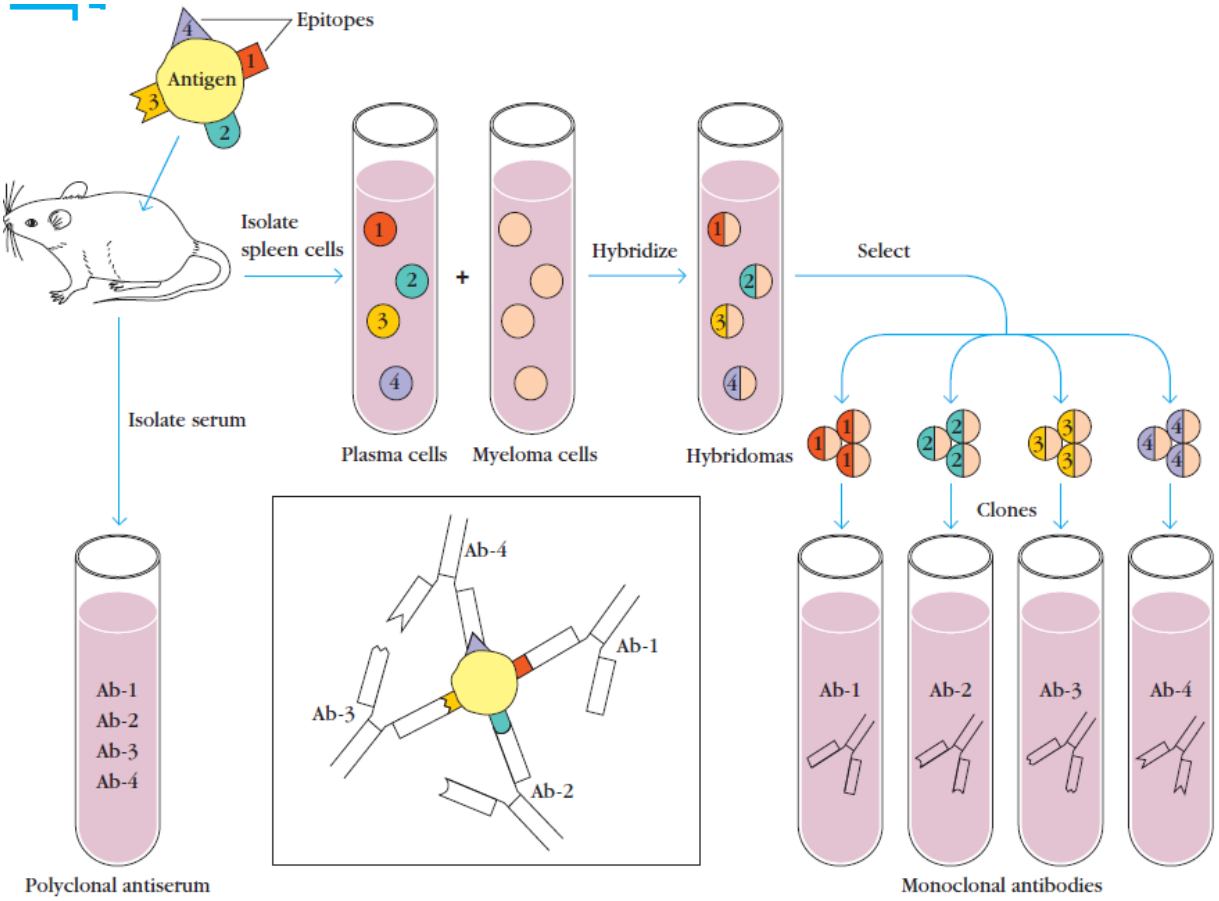

FIGURE 4-21 The conventional polyclonal antiserum produced in response to a complex antigen contains a mixture of monoclonal antibodies, each specific for one of the four epitopes shown on the antigen (inset). In contrast, a monoclonal antibody, which is derived from a single plasma cell, is specific for one epitope on a complex antigen. The outline of the basic method for obtaining a monoclonal antibody is illustrated here.

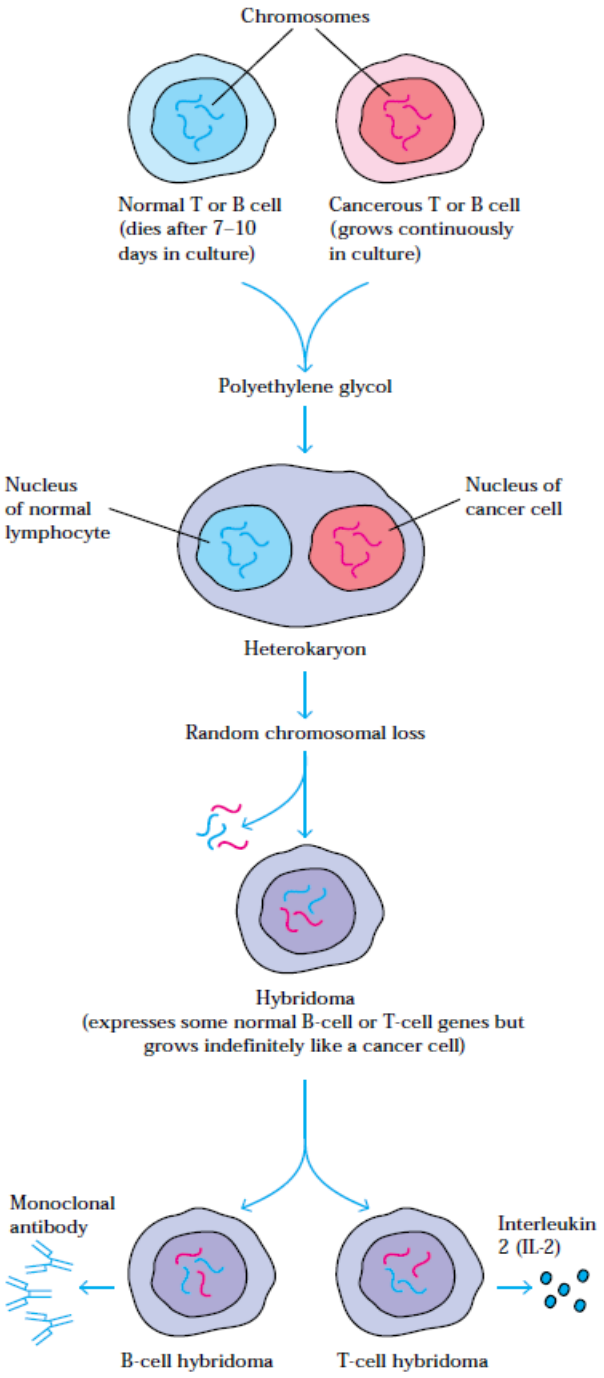

FIGURE 23-2 Production of B-cell and T-cell hybridomas by somatic-cell hybridization. The resulting hybridomas express some of the genes of the original normal B or T cell but also exhibit the immortal-growth properties of the tumor cell. This procedure is used to produce B-cell hybridomas that secrete monoclonal antibody and T-cell hybridomas that secrete various growth factors.