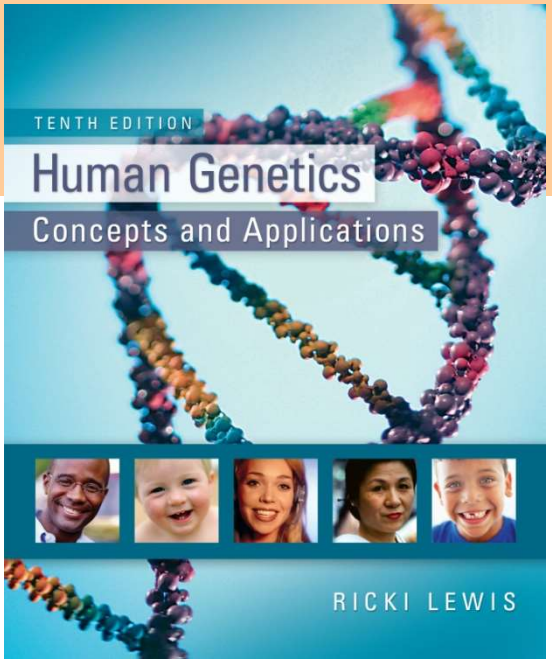
Human Genetics
Concepts and Applications

Tenth Edition

RICKI LEWIS



17 Genetics of Immunity

PowerPoint® Lecture Outlines
Prepared by Johnny El-Rady, University of South Florida

Foreign versus Self

Immune system protects organisms from foreign invaders

Protection from harmful organisms (pathogens) is based upon the ability to identify foreign molecules as “nonself”

Foreign may be bacteria, viruses, fungi, tumor, or transplanted cells

Molecules recognized by the immune system are called **antigens** and are usually protein fragments or carbohydrates

Foreign versus Self

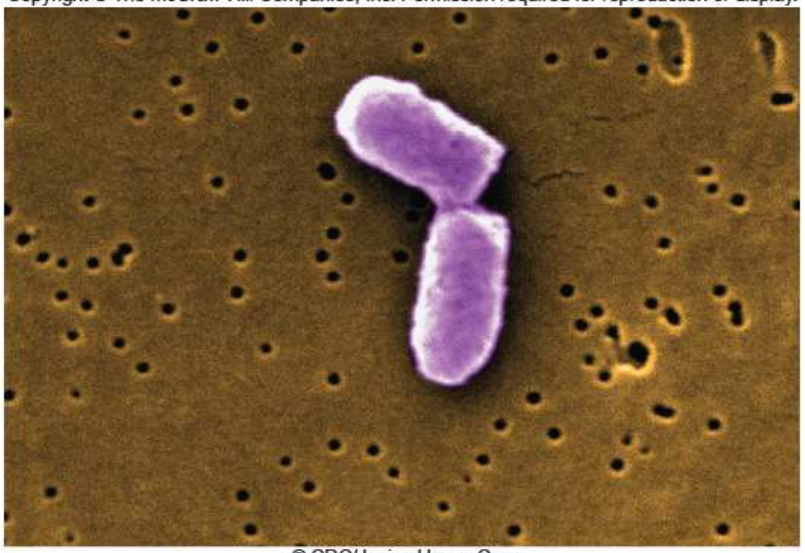


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Figure 17.1

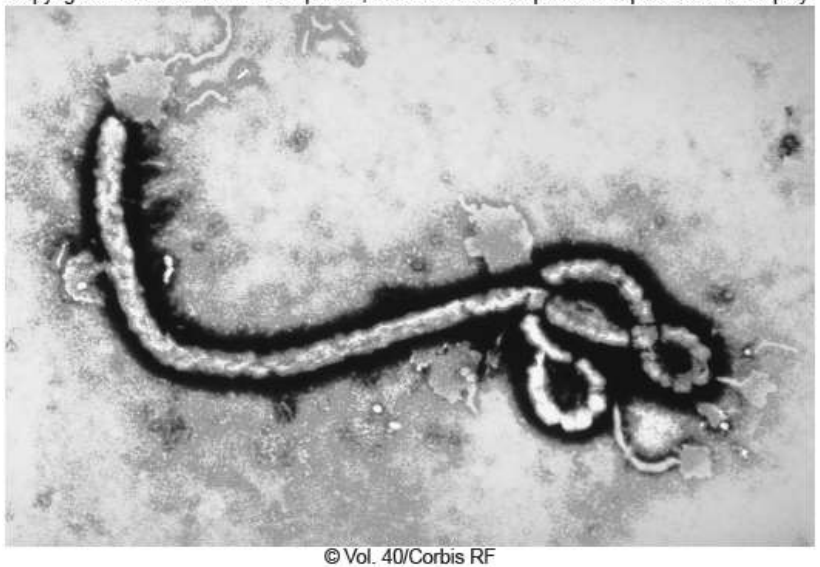

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Figure 1
Reading 17.1

Genetic Control of Immunity

Genes affect immunity by conferring susceptibility or resistance to infection

A few types of single genes encode **antibodies** and **cytokines** that directly attack foreign antigens

Genes also specify the cell surface antigens that mark the body's cells as "self"

Genetic Control of Immunity

Understanding how genes control immunity makes it possible to enhance or redirect the system's ability to fight disease

Mutations can impair immunity causing:

- Immune deficiencies
- Autoimmune disorders
- Allergies
- Cancer

Blood Groups

Some of the antigens that dot our cell surfaces determine blood types

We actually have 29 major blood types

For more than a century, serology typed blood according to the RBC antigens

A newer way to type blood is to identify the *instructions* (i.e. genes) for these antigens

- This approach, termed **genotyping**, uses a device called a BLOOD-chip

Table 17.1 Blood Groups

Blood Group (MIM)	Description
MN (111300)	Codominant alleles *M*, *N*, and *S* determine six genotypes and phenotypes. The antigens bind two glycoproteins.
Lewis (111100)	Allele *Le* encodes fucosyltransferase (FUT3) that adds an antigen to the sugar fucose, which the product of the *H* gene places on red blood cells. *H* gene expression is necessary for the ABO phenotype (see section 5.1). People with *LeLe* or *Lele* have the Lewis antigen on red blood cells and in saliva. People of genotype *lele* do not.
Secretor (182100)	People with *Se* allele secrete A, B, and H antigen in body fluids.

Major Histocompatibility Complex

Found on short arm of chromosome 6

Includes about 70 genes

Code for cell protein surface features

Classified into three functional groups

- Class III genes encode plasma proteins that carry out non-specific immune functions

- Class I and II genes encode **human leukocyte antigens (HLA)**

Human Leukocyte Antigens (HLA)

Link sugars to form branched glycoproteins that extend from cell surfaces

HLA glycoproteins can recognize bacterial and viral proteins, marking them for immune system to target

- A process called **antigen processing**

Class I are found on all cell types

Class II are found mostly on antigen-presenting cells

Antigen-Presenting Cells

Cells that bind antigens with HLA glycoproteins

Two main types of antigen-presenting cells are:

- Macrophages
- T-cells (or T-Lymphocytes)

Antigen-Presenting Cells

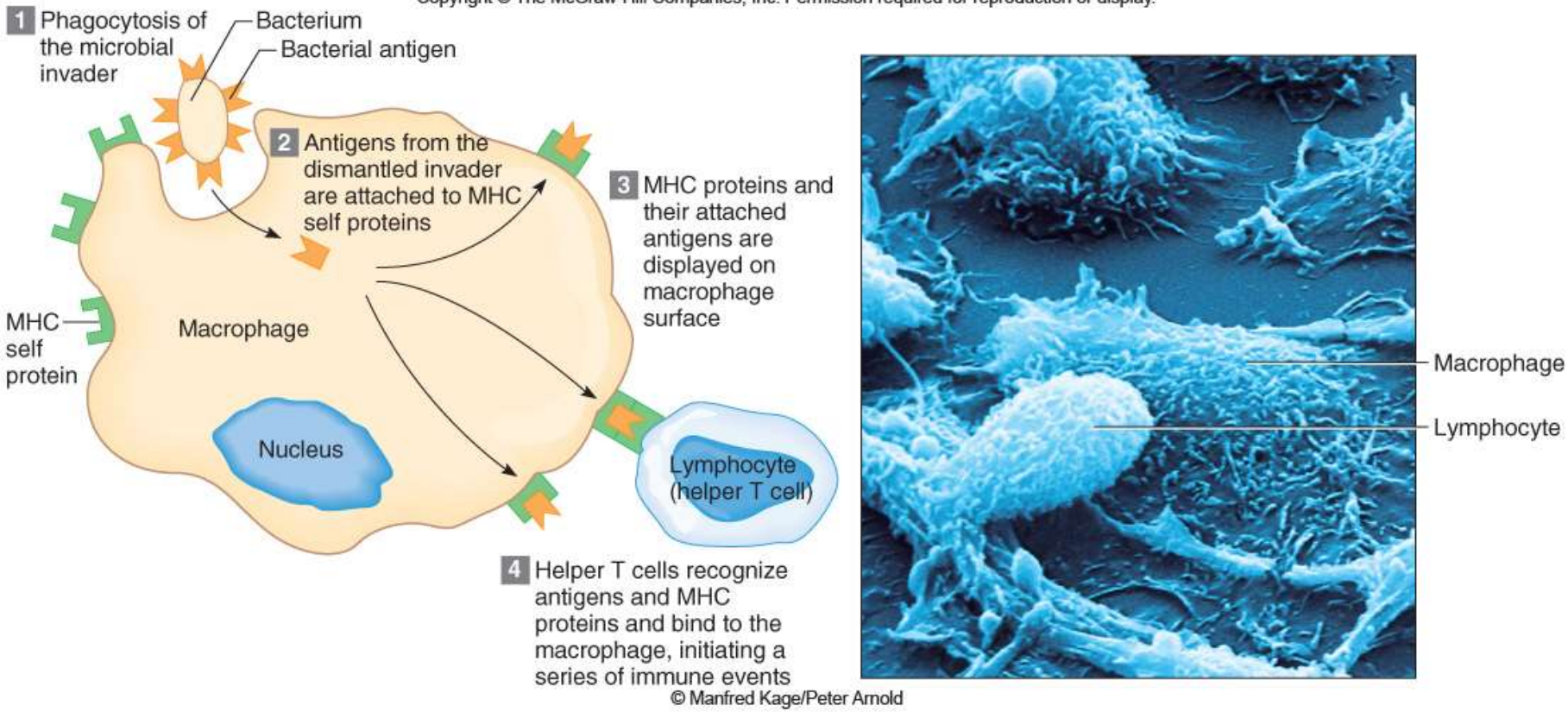


Figure 17.2

Antigen Processing Animation

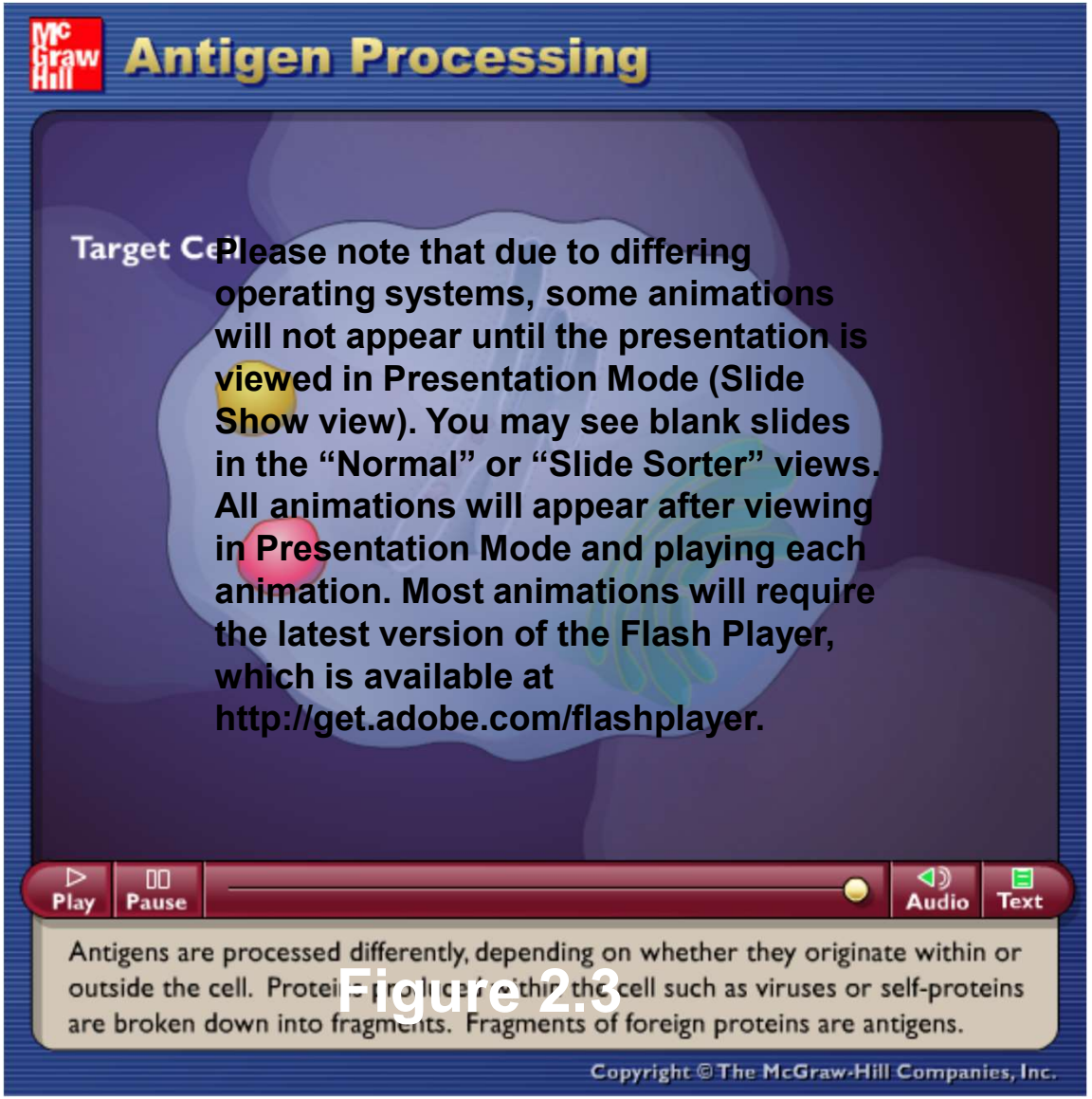


Figure 2.3

HLA Diversity

Several genes with multiple alleles determine an HLA type

Genetic diversity at HLA genes is large

Only 1 in 10,000 unrelated people will share an HLA type by chance at the six major HLA genes

Matching at least four major HLA genes is needed for most transplants to succeed.

HLA genes account for about 50% of the genetic impact on immunity

The Human Immune System

A network of vessels called lymphatics and bean-shaped structures called lymph nodes

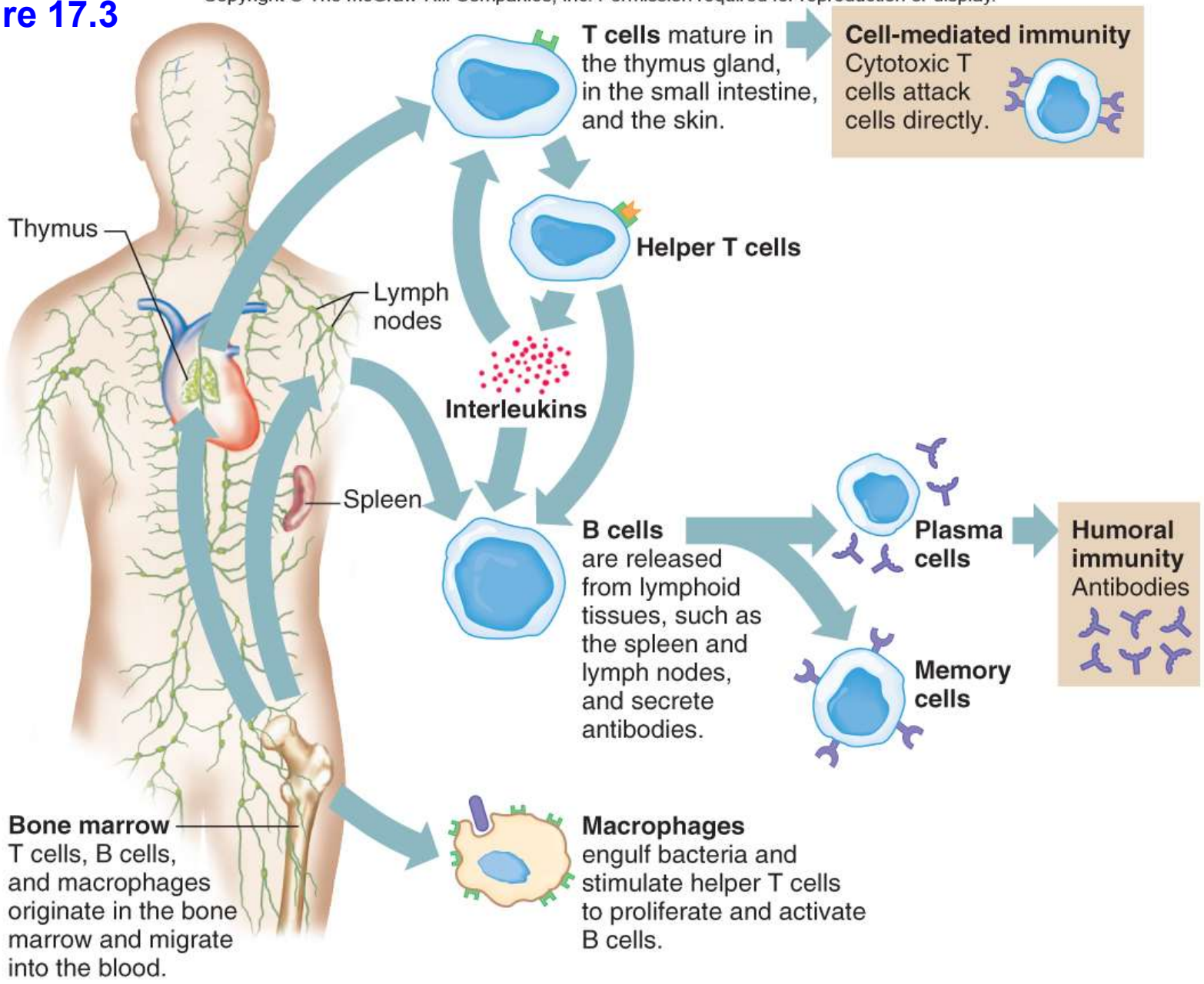
Lymph is the fluid filling the lymph ducts

- Carries macrophages and B- and T-lymphocytes

Organs involved in production or maturation of immune cells

- Spleen and Thymus
- Bone marrow

Figure 17.3



Immunity

The immune response attacks pathogens, cancer cells and transplanted cells with two lines of defense

- **Innate immunity** is immediate and generalized
- **Adaptive immunity** is specific and slower

These act after various physical barriers block pathogens

Levels of Protection

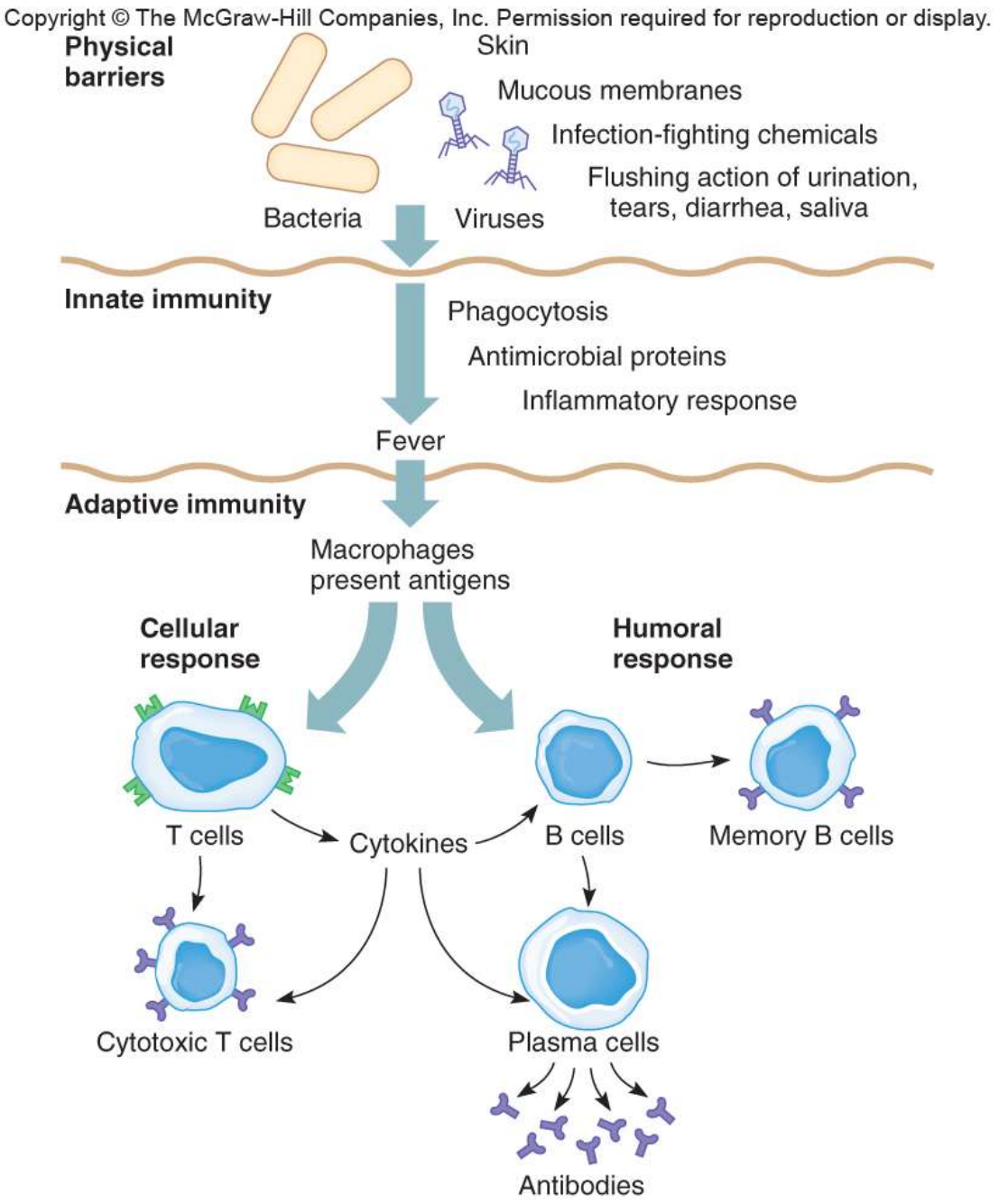


Figure 17.4

Physical Barriers

The first line of defense

Examples include:

- Unbroken skin
- Mucous membranes and secretions
- Waving cilia of the respiratory tract
- Flushing effect of tears, saliva, urination, and diarrhea

All of these are non-specific defenses

Innate Immune Response

General defenses found in the body

If pathogen breaches physical barriers produces a rapid broad response

Response time is in minutes

A central part is **inflammation**

- A process that creates a hostile environment for pathogens

- Sends in phagocytes that engulf and destroy pathogens via **phagocytosis**

Innate Immune Response

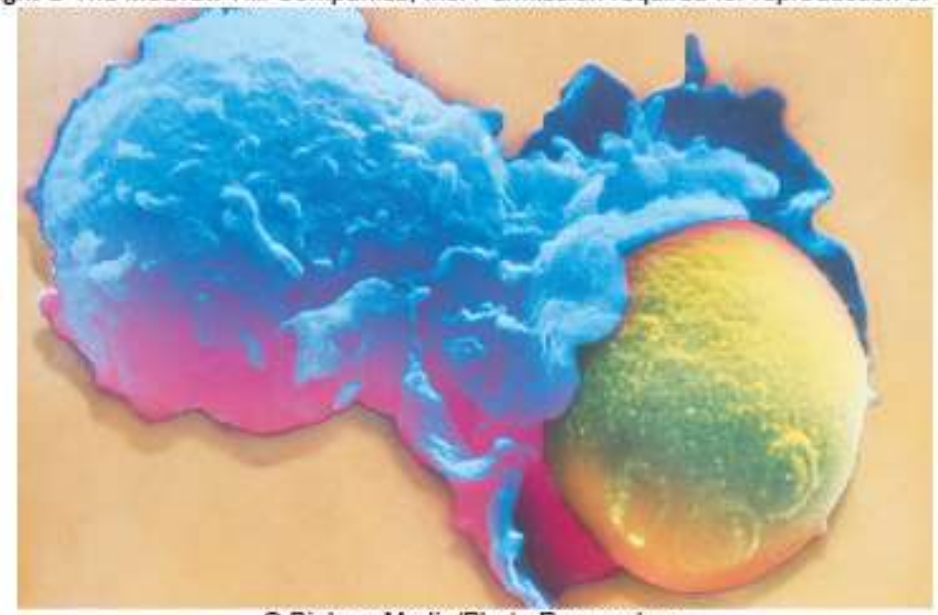


Figure 17.5

Innate Immune Response

Collectins

Cytokines

- Interferon = Anti-viral
- Interleukins = Fever-inducing
- Tumor necrosis factor α = Anti-cancer

Cytokines also play a role in adaptive immunity

Innate Immune Response

Complement

- Plasma proteins that assist or complement other defense responses
- Roles of complement proteins include:
    - Puncture bacterial cells
    - Dismantle viruses
    - Trigger histamine release to dilate blood vessels
    - Attract phagocytes

Adaptive Immunity

Requires stimulation

Response time is in days

Has three basic characteristics:

- **Diversity**: many different pathogens recognized
- **Specificity:** distinguishes particular molecules
- **Memory**: responds faster with subsequent exposure
    - **Primary immune response**: reaction to first exposure
    - **Secondary immune response**: reaction to exposure using “memory” of first response

Adaptive Immunity

Two types of response:

- **Humoral immune response**
  - B cells produce antibodies in response to activation by T cells

- **Cellular immune response**
  - T cells produce cytokines and activate other cells

Humoral Immune Response

1. Antigen-presenting macrophage activates a helper T cell
2. Helper T cell activates a B cell with matching cell surface receptors
3. B cells divide to produce plasma cells and memory cells
4. Plasma cells secrete antibodies into blood that will recognize the antigen presented.
5. Memory cells remain dormant until second exposure when they respond faster and more effectively

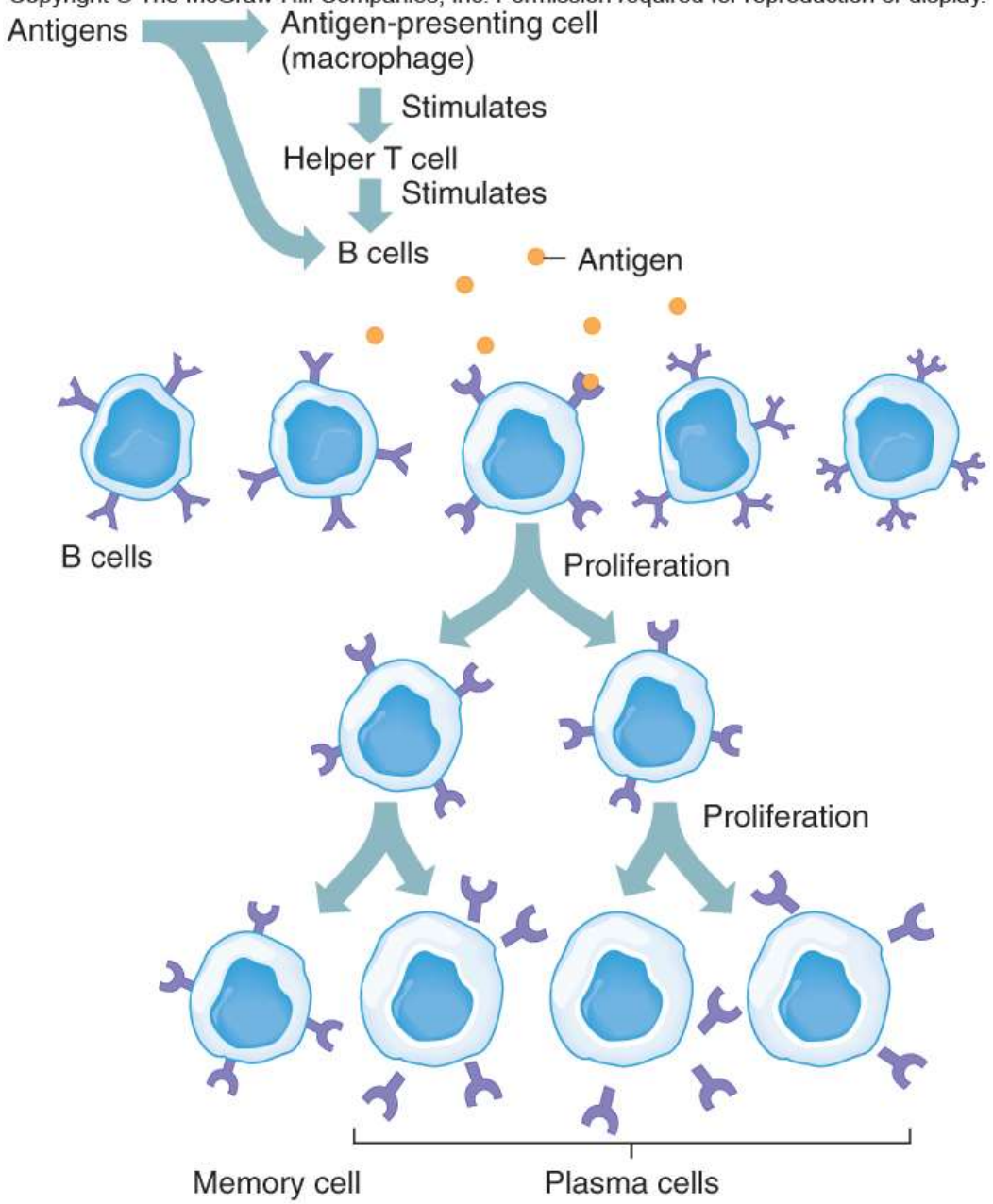


Figure 17.6

A humoral immune response is polyclonal

- Different antibody proteins recognize and bind to different features of foreign cells

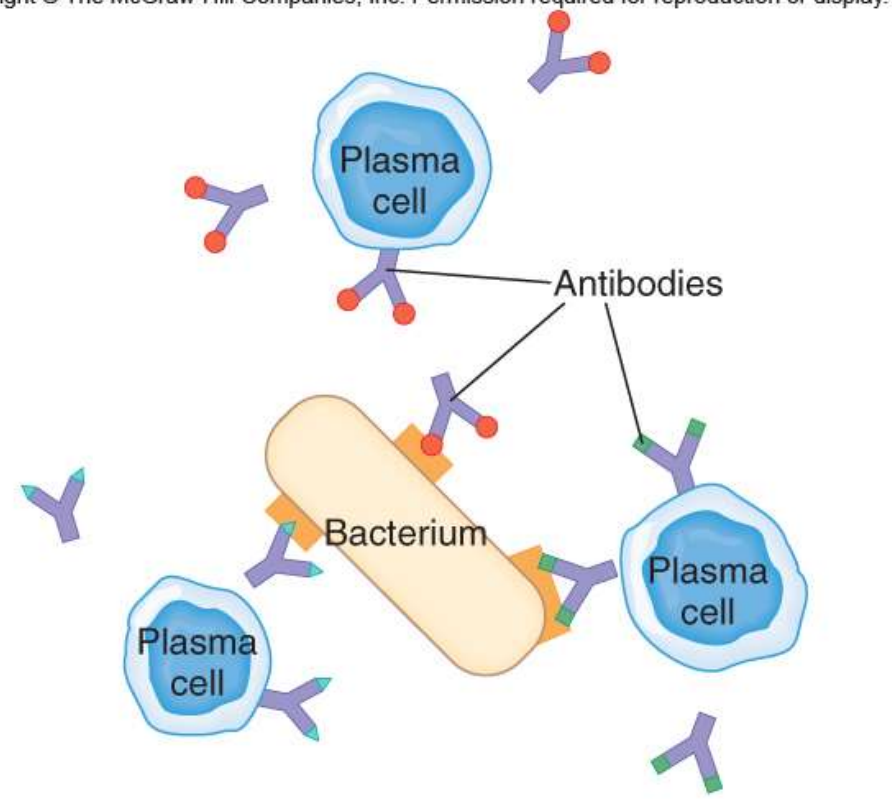


Figure 17.7

Antibody Structure

Minimally consist of four polypeptide chains

- Two long (heavy) chains
- Two shorter (light) chains

Constant region of each chain is similar

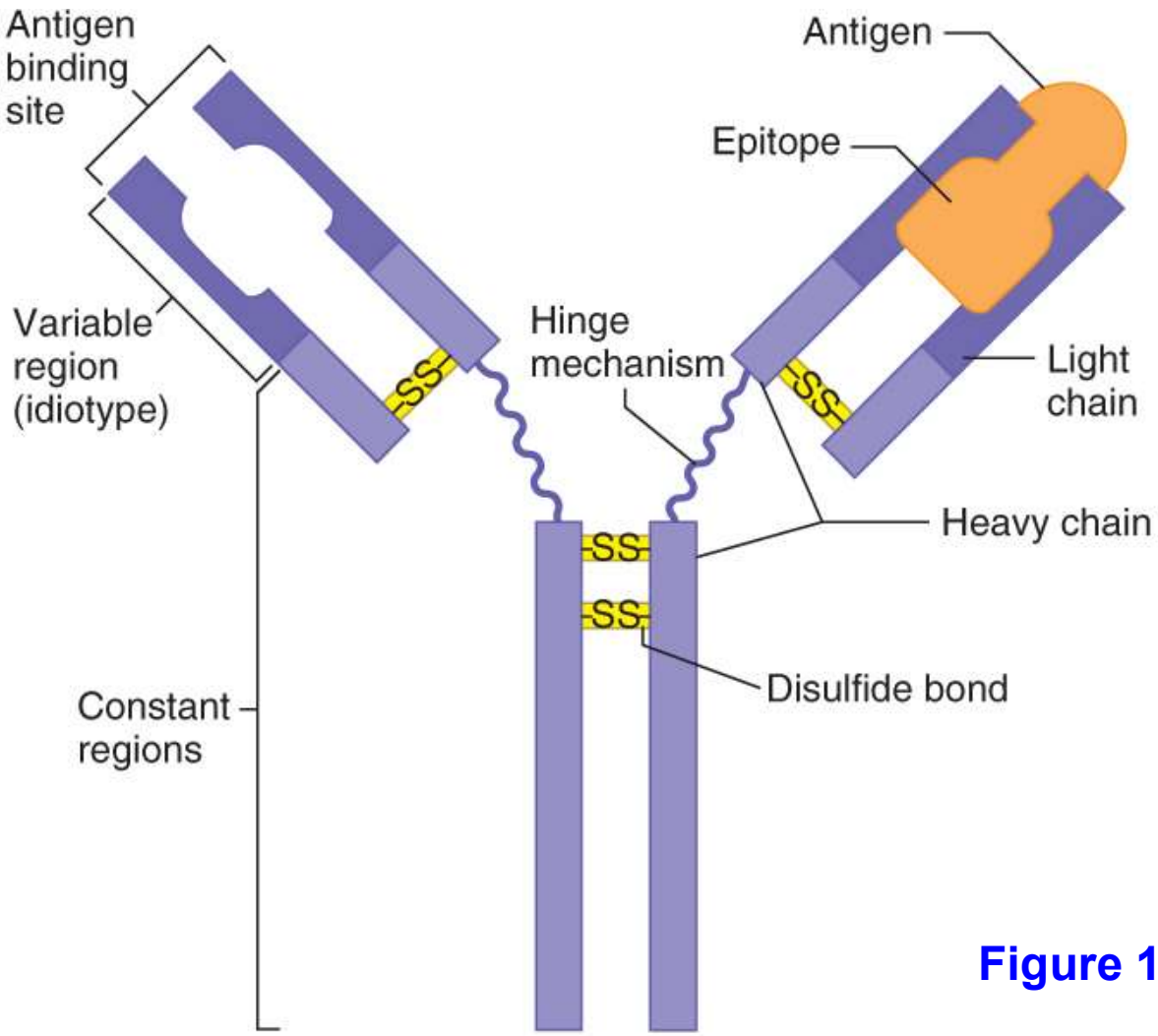
Variable region of each chain is diverse

Antigen binding sites: where antigen binds

Idiotypes: sites in direct contact with antigen

Epitope: portion of the antigen contacting the antibody

Antibody Structure

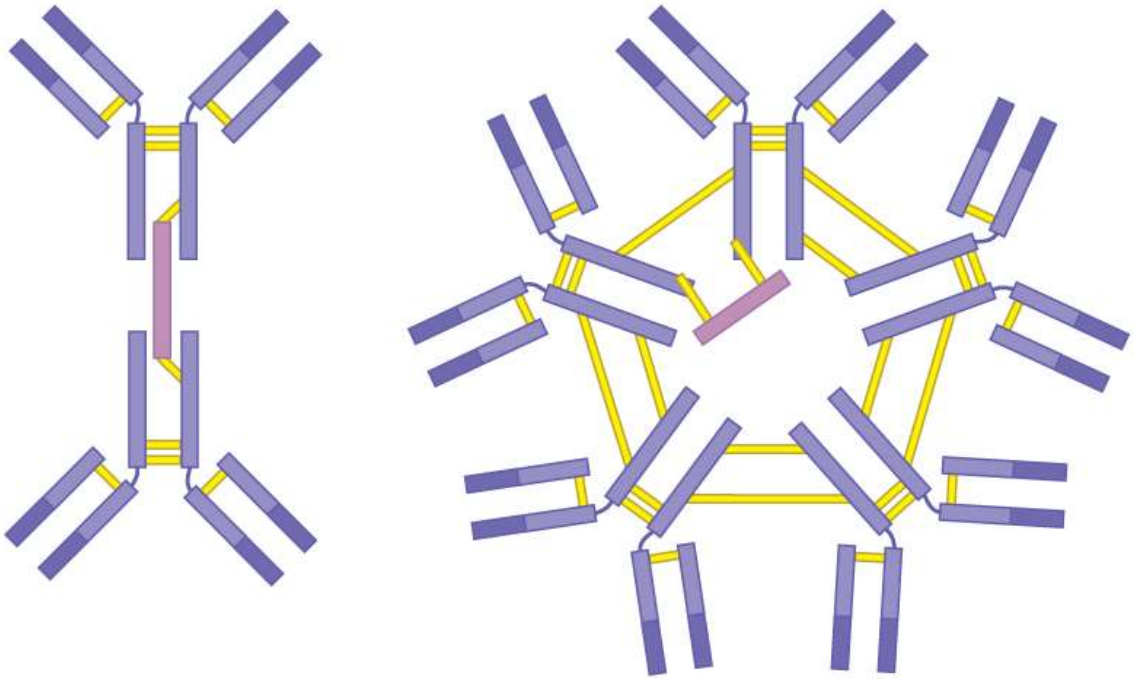


a. An antibody subunit

Figure 17.8

Antibody Structure

Large antibody molecules might consist of two or five Y-shaped subunits



IgA

b.

IgM

c.

Figure 17.8

Antigenic Determinants Animation

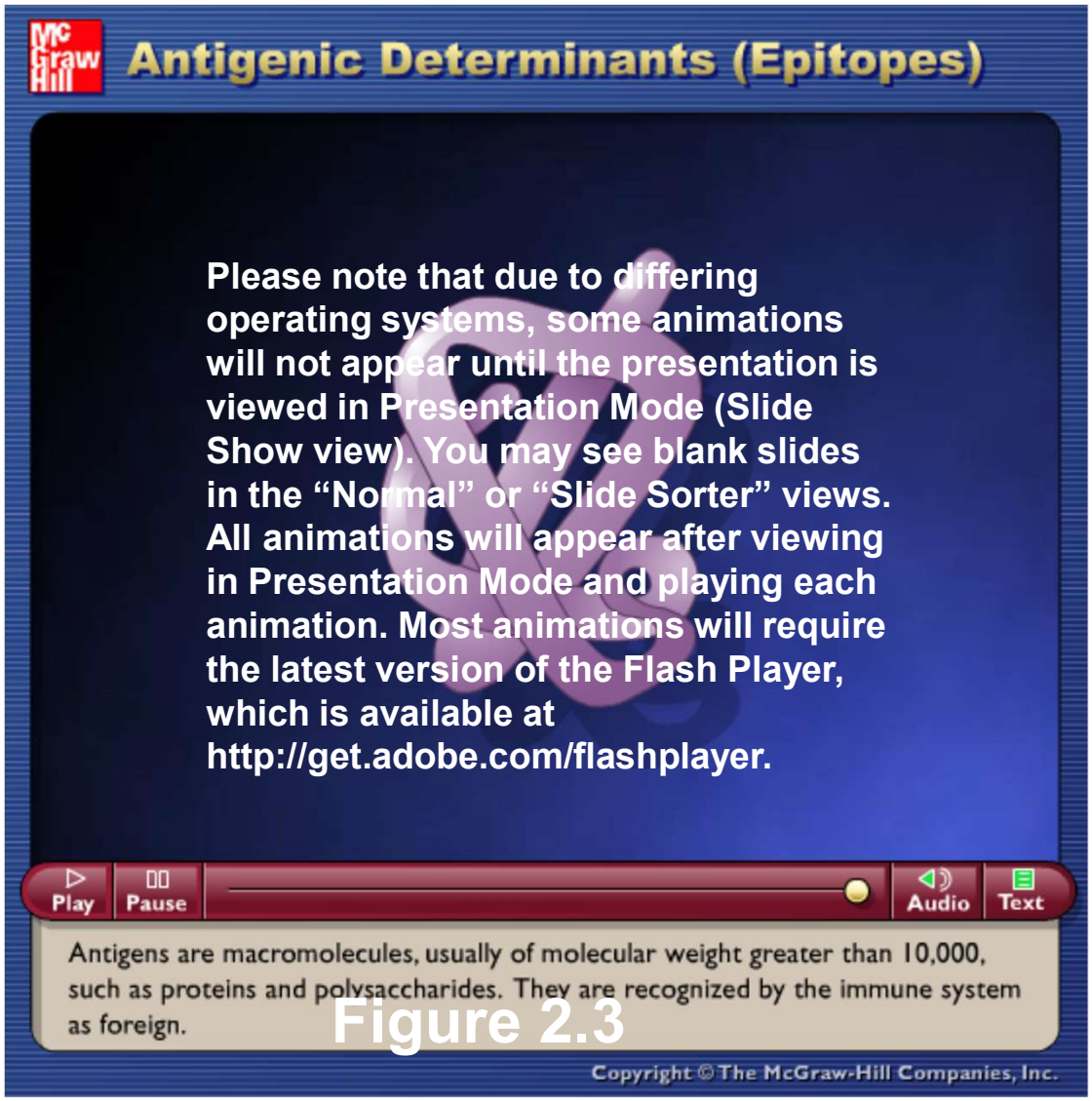


Figure 2.3

Function of Antibodies

Bind pathogen protein or toxin and inactivates or neutralizes them

Can clump pathogens making them more visible for macrophages

Activate the complement system boosting the innate immune response

In some situations, the antibody response can be harmful

Types of Antibodies

Also called **immunoglobulins**

Five major types distinguished by location and function

Different antibody types predominate in different stages of an infection

Table 17.2 Types of Antibodies

Type*	Location	Functions
IgA	Milk, saliva, urine, and tears; respiratory and digestive secretions	Protects against pathogens at points of entry into body
IgD	On B cells in blood	Stimulates B cells to make other types of antibodies, particularly in infants
IgE	In secretions with IgA and in mast cells in tissues	Acts as receptor for antigens that cause mast cells to secrete allergy mediators
IgG	Blood plasma and tissue fluid; passes to fetus	Protects against bacteria, viruses, and toxins, especially in secondary immune response
IgM	Blood plasma	Fights bacteria in primary immune response; includes anti-A and anti-B antibodies of ABO blood groups

*The letters *A, D, E, G,* and *M* refer to the specific conformation of heavy chains characteristic of each class of antibody.

Creation of Antibody Diversity

The genome has a limited number of antibody genes

- However, the human body can shuffle these in many different ways to make a seemingly limitless variety of antibodies

During early development of B cells, sections of the antibody genes are rearranged along their chromosome

Rearrangement due to enzymes cutting and pasting different combinations of V (Variable), D (Diversity), and J (Joining) genes creates new versions of the antibody proteins

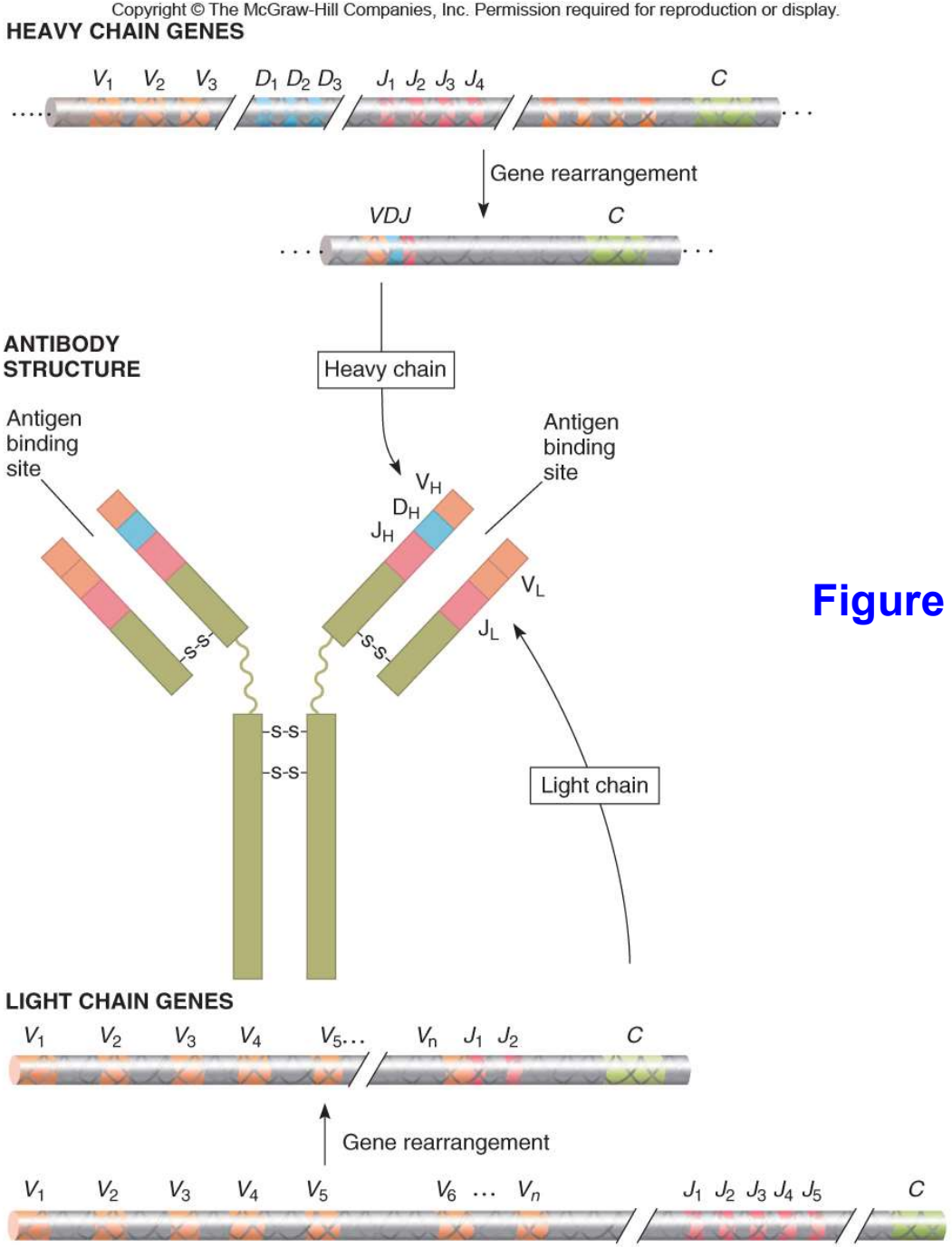


Figure 17.9

Cellular Immune Response
Maturation of T Cells

T cells must recognize foreign antigens and not recognize self antigens

Immature T cells, called thymocytes, travel to the thymus and display their cell surface receptors

The thymus lining displays self antigens

T cells that bind these self antigens die by apoptosis

T cells that do not bind the self antigens survive and mature

Types of T cells

Several types of T cells are distinguished by the types and patterns of receptors on their surface and by their function

- **Helper T cells**
  - Have CD4 antigens
- **Cytotoxic T cells**
  - Have CD8 antigens
- **Regulatory T cells**

Role of Helper T cells

In humoral immune response:

- Recognize antigens presented by macrophages
- Stimulate B cells to produce antibodies

In cellular immune response:

- Secrete cytokines
- Activate cytotoxic T cell

Table 17.3 Types of Cytokines

Cytokine	Function
Colony stimulating factors	Stimulate bone marrow to produce lymphocytes
Interferons	Block viral replication, stimulate macrophages to engulf viruses, stimulate B cells to produce antibodies, attack cancer cells
Interleukins	Control lymphocyte differentiation and growth, cause fever that accompanies bacterial infection
Tumor necrosis factor	Stops tumor growth, releases growth factors, stimulates lymphocyte differentiation, dismantles bacterial toxins

Cytotoxic T cells

Continuously monitor body cells, recognizing and eliminating virus-infected and tumor cells

Figure 17.10

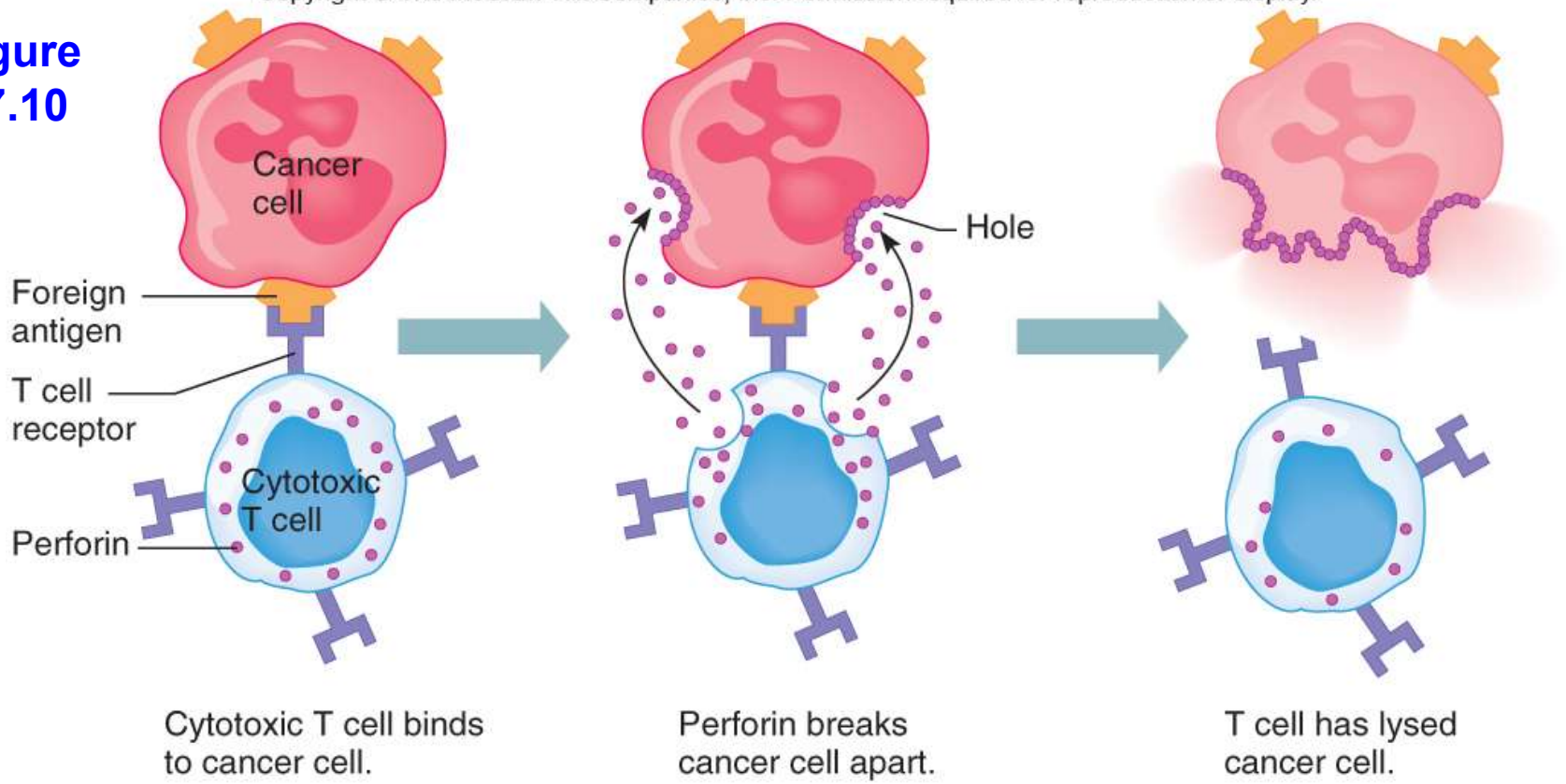


Table 17.4 Types of Immune System Cells

Cell Type	Function
Macrophage	Presents antigens
	Performs phagocytosis
Dendritic cell	Presents antigens
Mast cell	Releases histamine in inflammation
	Releases allergy mediators
B cell	Matures into antibody-producing plasma cell or into memory cell
T cells	
Helper	Recognizes nonself antigens presented on macrophages
	Stimulates B cells to produce antibodies
	Secretes cytokines
	Activates cytotoxic T cells
Cytotoxic	Attacks cancer cells and cells infected with viruses upon recognizing antigens
Natural killer	Attacks cancer cells and cells infected with viruses without recognizing antigens; activates other white blood cells
Suppressor	Inhibits antibody production

Table 17.4

Abnormal Immunity

Immune system malfunction may be inherited or acquired

In addition, immunity may be too weak, too strong, or misdirected

Abnormal immune responses may be multifactorial or caused by a mutation in a single gene

Inherited Immune Deficiencies

At least 20 types

Affect innate and adaptive immunity

Examples

- **Chronic granulomatous disease**: Mutation of oxidase enzyme results in neutrophils that cannot kill bacteria

- **Severe combined immune deficiency (SCID)**: Impacts both humoral and cellular immunity due to lack of mature B cells and/or T cells

Inherited Immune Deficiencies

David Vetter had an autosomal recessive form of SCID

- He was born without a thymus gland
- His T cells could not mature and activate B cells

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Figure 17.11

Table 17.5 Inherited Immune Deficiencies

Disease	MIM	Inheritance*	Defect
Chronic granulomatous disease	306400	ar, AD, Xlr	Abnormal phagocytes can't kill engulfed bacteria
Immune defect due to absence of thymus	242700	ar	No thymus, no T cells
Neutrophil immuno-deficiency syndrome	608203	ar	Deficiencies of T cells, B cells, and neutrophils
SCID			
Adenosine deaminase deficiency	102700	ar	No T or B cells
Adenosine deaminase deficiency with sensitivity to ionizing radiation	602450	ar	No T, B, or natural killer cells
IL-2 receptor mutation	300400	Xlr	No T, B, or natural killer cells
X-linked lymphoproliferative disease	308240	Xlr	Absence of protein that enables T cells to bind B cells

*ar = autosomal recessive
AD = autosomal dominant
Xlr = X-linked recessive
SCID = severe combined immune deficiency

Human Immunodeficiency Virus (HIV)

An infectious virus enters the body with direct contact of bodily fluids

Infects macrophages, and later, helper T cells

Virus replicates and bursts out of the helper T cell, killing it

Loss of helper T-cells prevents B-cell activation

Infections occur because the immune system not functional

Replicates rapidly, mutates easily, and can hide

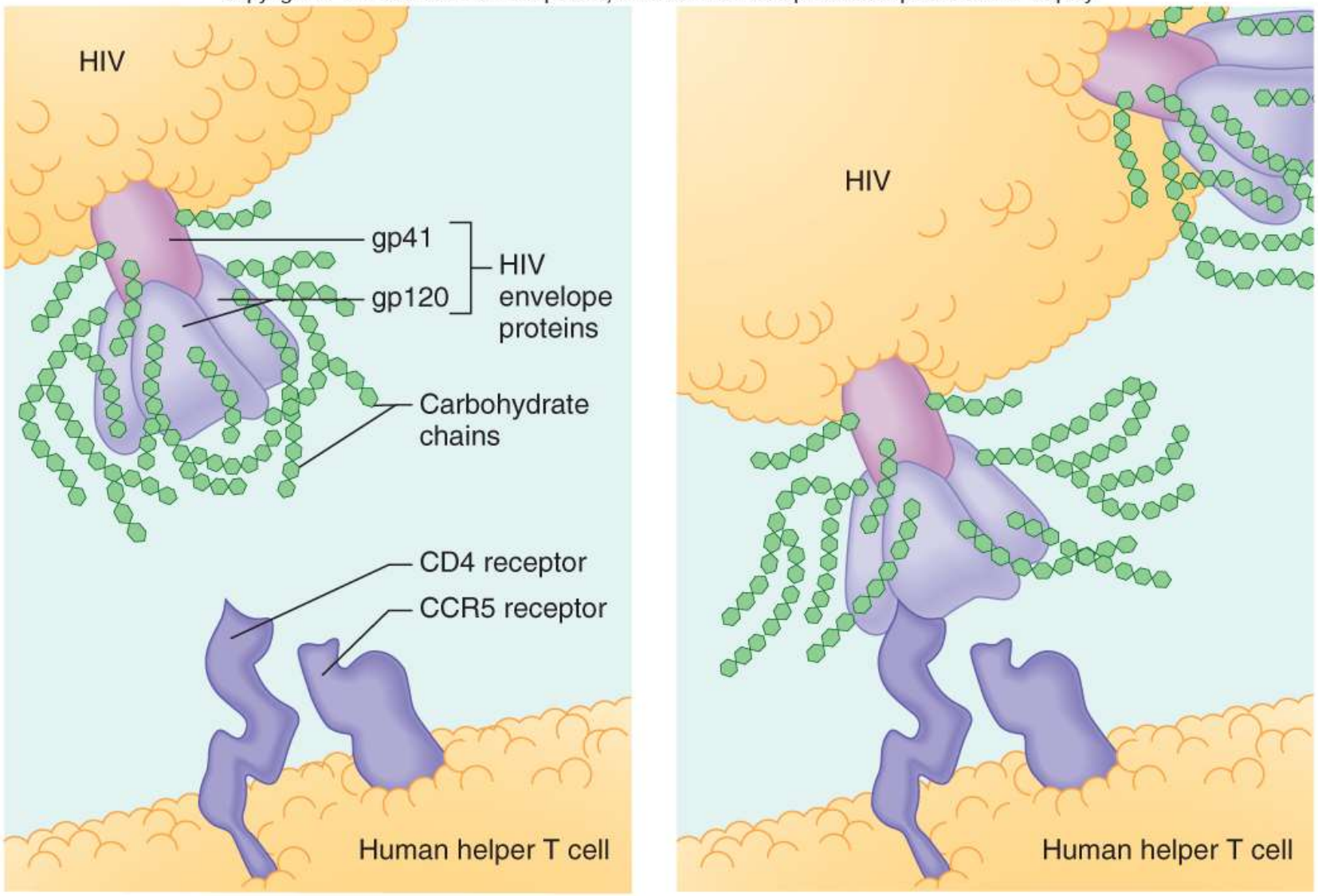
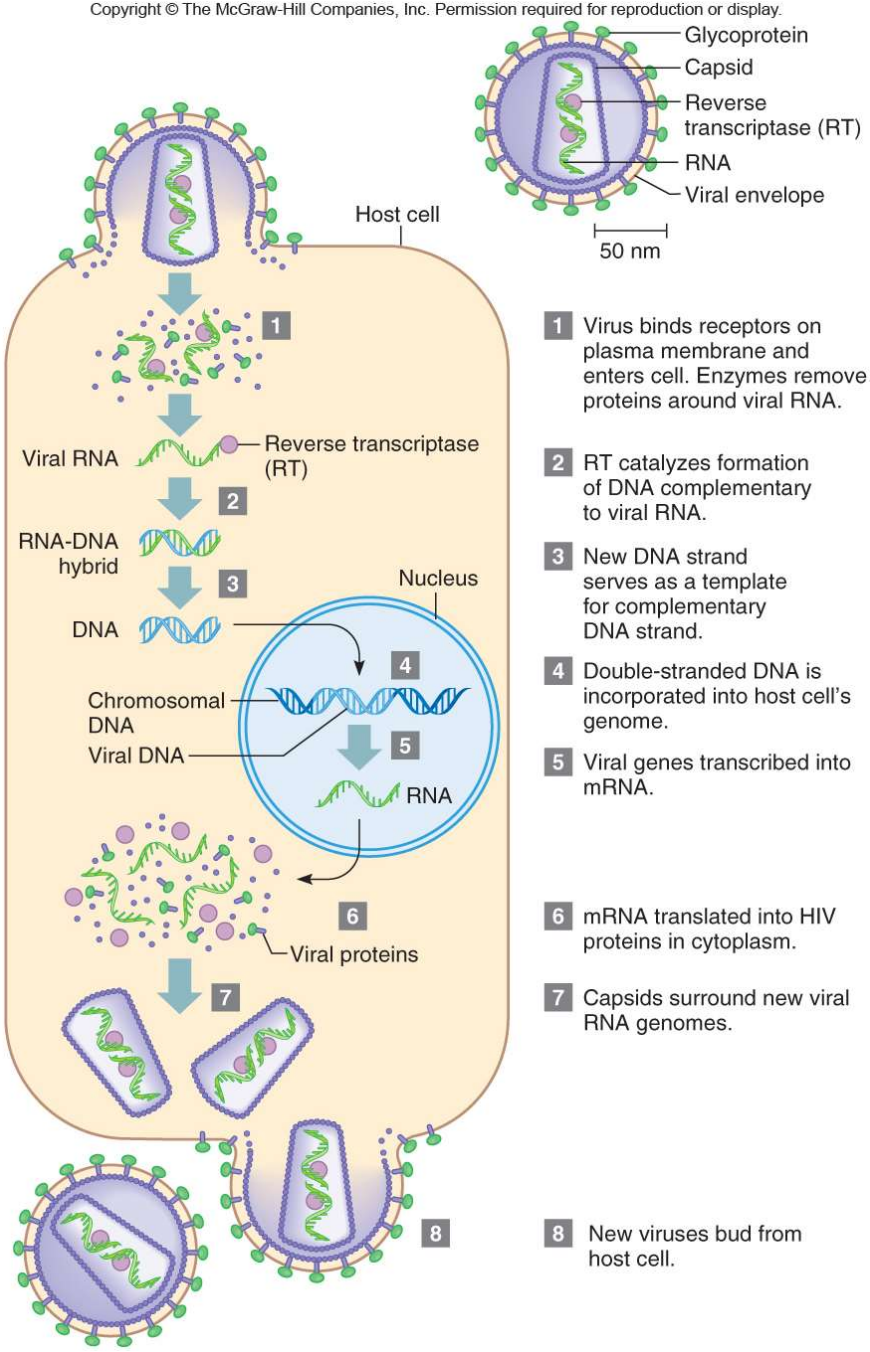


Figure 17.12

Figure 17.13



Acquired Immune Deficiency Syndrome (AIDS)

The disease resulting from HIV infection

The immune system impact of HIV infection has progressed to impairment of immune function

Due to genetically diverse population of HIV in a human host, treatment requires combination of medication with different actions

Drugs block/inhibit different points of infection

- Entry of virus into T cells
- Replication of viral genetic material
- Processing of viral proteins

Table 17.6 Anti-HIV Drugs

Drug Type	Mechanism
Reverse transcriptase inhibitor	Blocks copying of viral RNA into DNA
Protease inhibitor	Blocks shortening of certain viral proteins
Fusion inhibitor	Blocks ability of HIV to bind a cell
Entry inhibitor	Blocks ability of HIV to enter a cell

CCR5 Gene

- Encodes for a receptor protein on the cell membrane (co-receptor for HIV)
- Individuals homozygous for a 32-base deletion of CCR5 are resistant to infection
- Heterozygous individuals become infected but stay healthy for several years longer than people that do not have the mutation
- Same mutation may have enabled people to survive the plague in Europe during the Middle Ages

Autoimmunity

Immune system attacks the tissues of an individual's own body

Autoantibodies recognize "self" proteins

About 5% of the population has an autoimmune disorder

The signs and symptoms reflect the cell types under attack

Autoimmunity

Autoimmunity may arise in several ways:

- Viruses use host proteins on the viral cell surface. These proteins become the target of the immune system, which responds as if they were viral proteins

- Thymocytes that recognize “self” antigens survive instead of self-destructing

- Nonself antigen may coincidentally resemble “self” antigens

- Skewed X inactivation

Table 17.7 Autoimmune Disorders

Disorder	Symptoms	Autoantibodies against
Diabetes mellitus (type 1)	Thirst, hunger, weakness, weight loss	Pancreatic beta cells
Graves disease	Restlessness, weight loss, irritability, increased heart rate and blood pressure	Thyroid gland cells
Hemolytic anemia	Fatigue, weakness	Red blood cells
Multiple sclerosis	Weakness, poor coordination, failing vision, disturbed speech	Myelin in the white matter of the central nervous system
Myasthenia gravis	Muscle weakness	Neurotransmitter receptors on skeletal muscle cells
Rheumatic fever	Weakness, shortness of breath	Heart valve cells
Rheumatoid arthritis	Joint pain and deformity	Cells lining joints
Systemic lupus erythematosus	Red facial rash, fever, weakness, joint pain	Connective tissue
Ulcerative colitis	Lower abdominal pain	Colon cells

Rh Incompatibility

Occurs when an Rh^- (no Rh antigen) mother has an Rh^+ (has Rh antigen) child

First Rh incompatible pregnancy – Fetal cells recognized as foreign; Mother's immune system attacks fetal cells; Produces a mild reaction, few antibodies present

Second Rh incompatible pregnancy – Large response, plentiful antibodies; Destruction of fetal blood cells, much damage

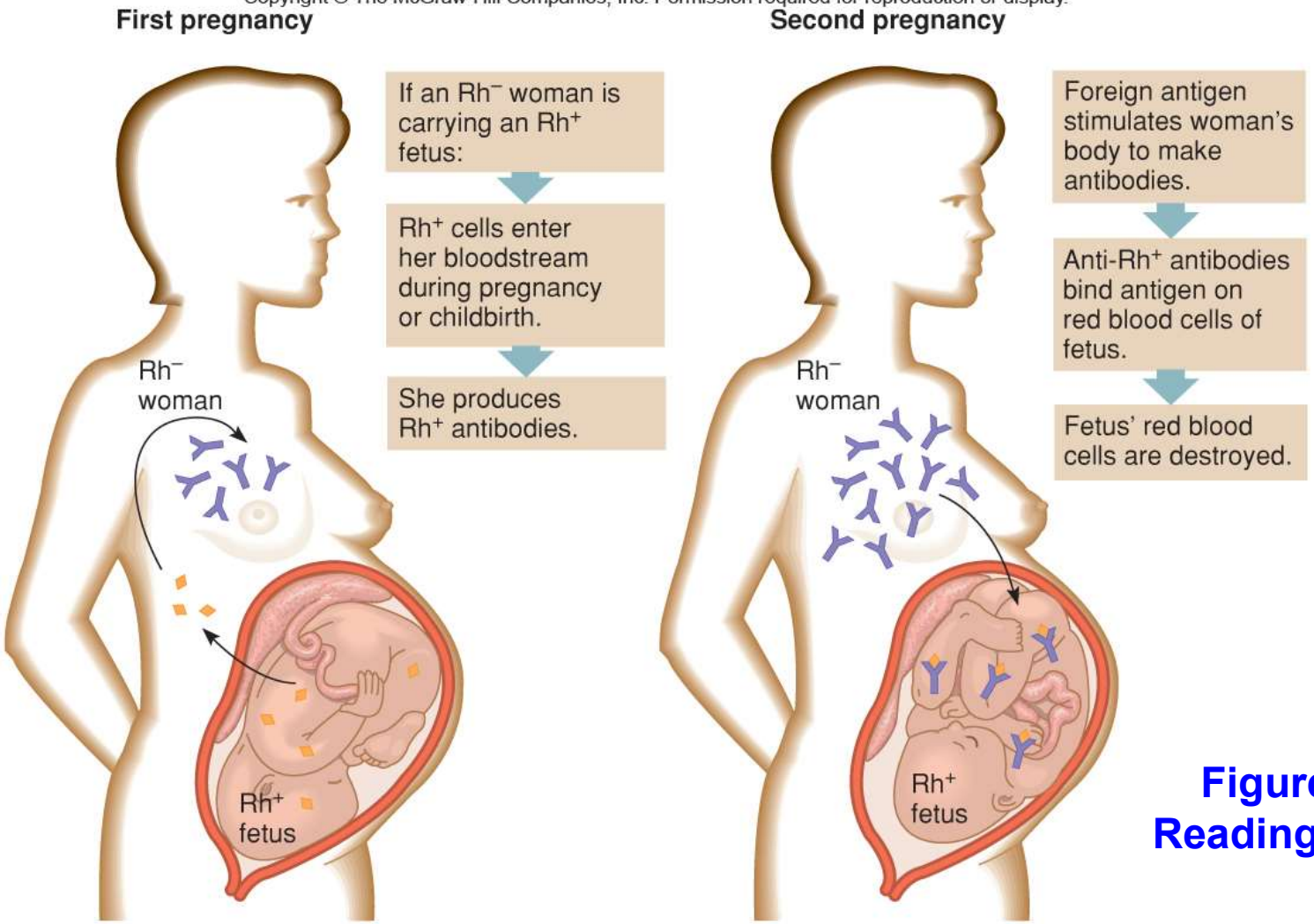


Figure 2
Reading 17.2

RhoGAM prevents formation of anti-Rh antibodies

Allergy

Immune response to a non-threatening foreign substance called an **allergen**

Size of allergens may determine type of allergic response

- Larger (e.g., grass pollen) produces hay fever
- Smaller (e.g., cat dander, dust mites) trigger asthma

Asthma is a chronic disease

- Contraction of the airways, inflammation and mucus production block air flow

Allergic Response

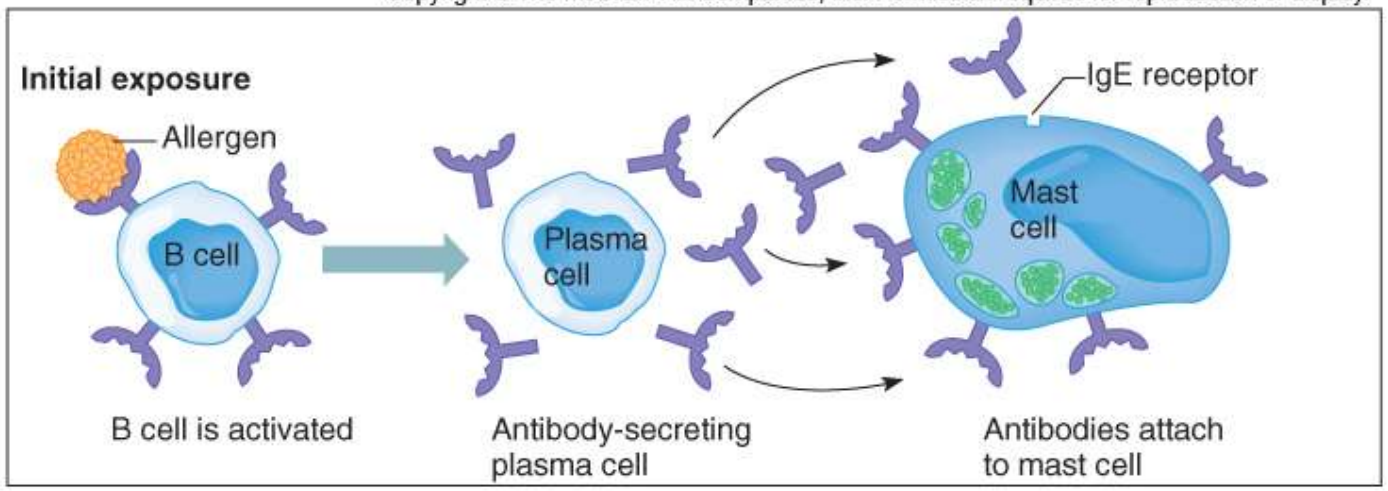
Humoral and cellular immunity are involved

IgE antibodies are made and bind mast cells

Mast cells release allergy mediators like histamine and heparin that cause inflammation, runny eyes and nose, rashes and asthma

Allergens activate a class of helper T cells that release cytokines

Severe allergic reaction throughout the body is called **anaphylatic shock**



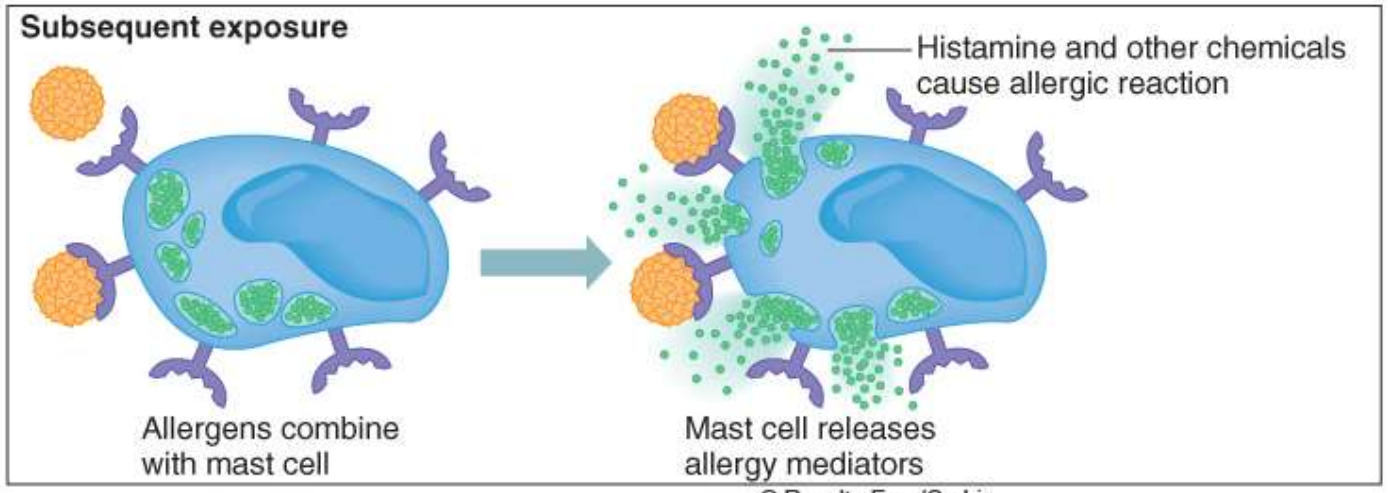


Figure 17.14

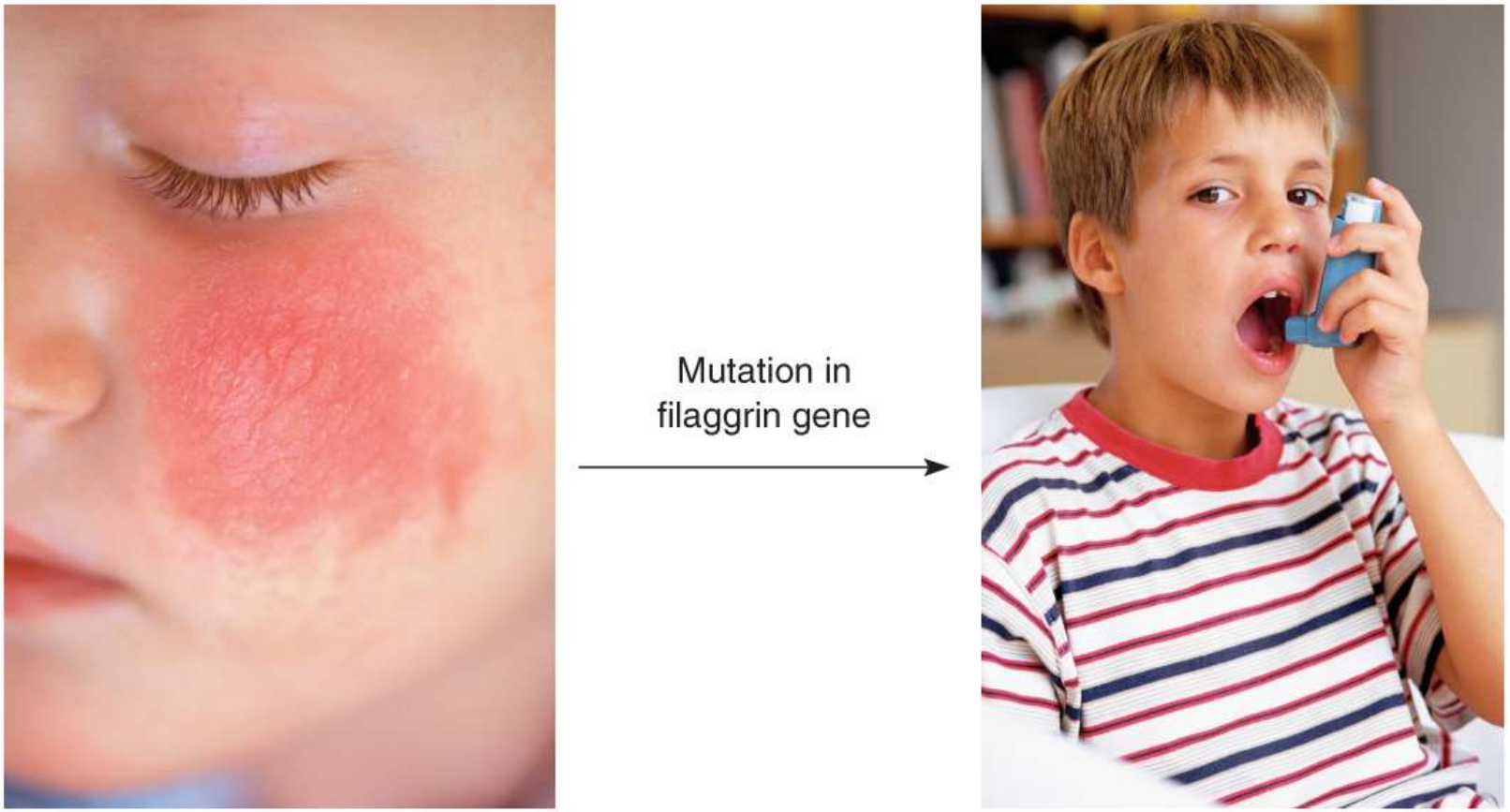


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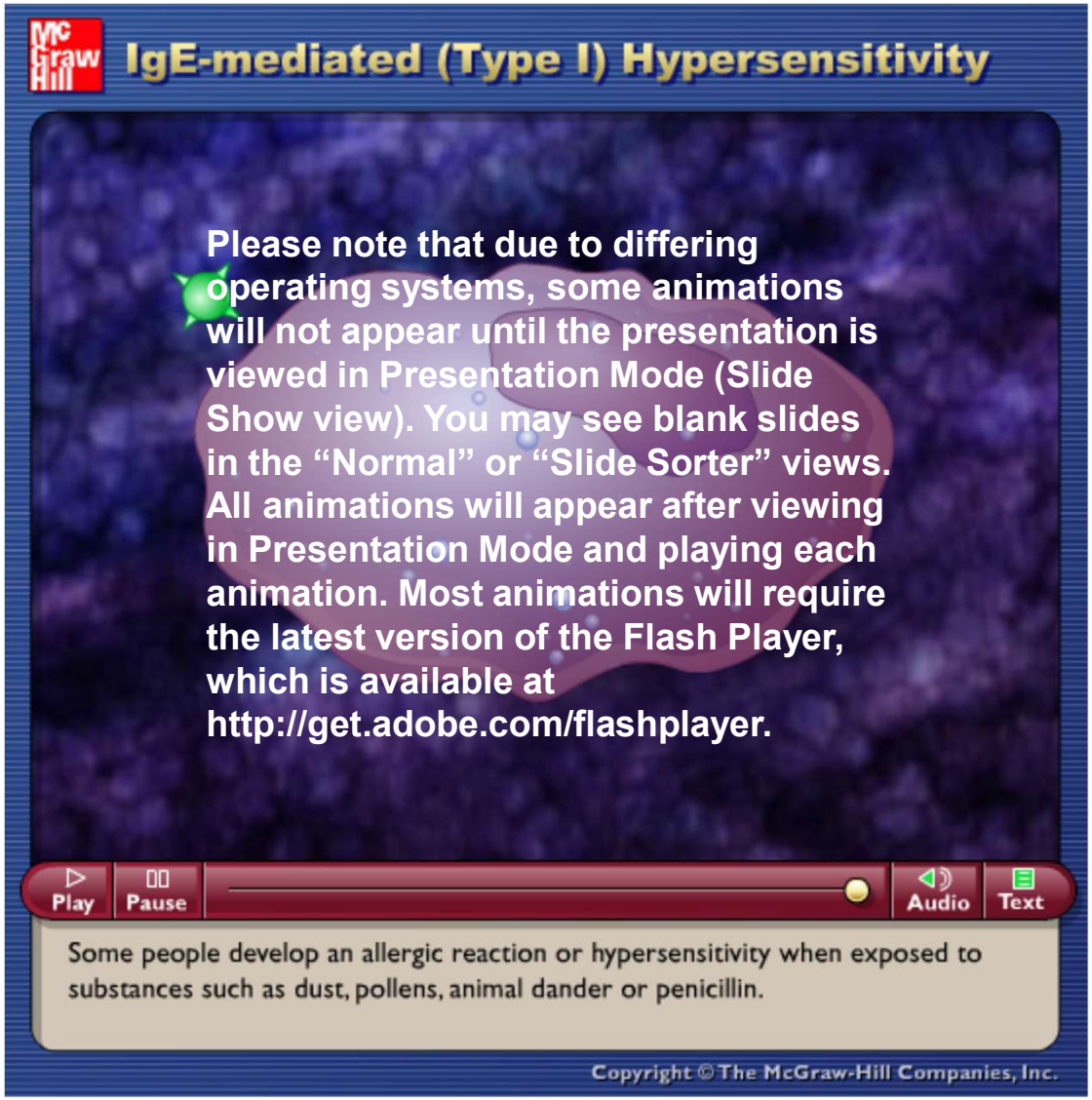
Figure 17.15

Allergies Animation



Vaccination

A vaccine uses antigens from a pathogen to invoke immunity before an individual has been exposed to the pathogen

Antigens are chosen to be harmless alone

Ability to respond rapidly to subsequent exposure prevents infection to a degree that would cause disease

Vaccine technology dates back to 11th century China

Edward Jenner used cowpox as a vaccine for smallpox

Vaccination

Smallpox has not naturally infected a human since 1977

- So vaccination are now unnecessary

Figure 17.16

New Methods

Most vaccines are injections

New delivery methods include nasal sprays and genetically modified fruits and vegetables

A banana can become a vaccine

- Foreign antigens stimulate phagocytes to "present" antigens to nearby T cells
- T cells stimulate B cells to make IgA antibodies
- They coat the small intestine and protect against food-borne pathogens

Immunotherapy

Medical treatment used to amplify or redirect the immune response

Monoclonal antibodies (MAb)

- Useful for detecting and targeting one particular antigen
- In 1975, British researchers devised a technology which mass-produces a single B cell
- Thus, preserving its specificity and amplifying its antibody type

Monoclonal Antibody Production

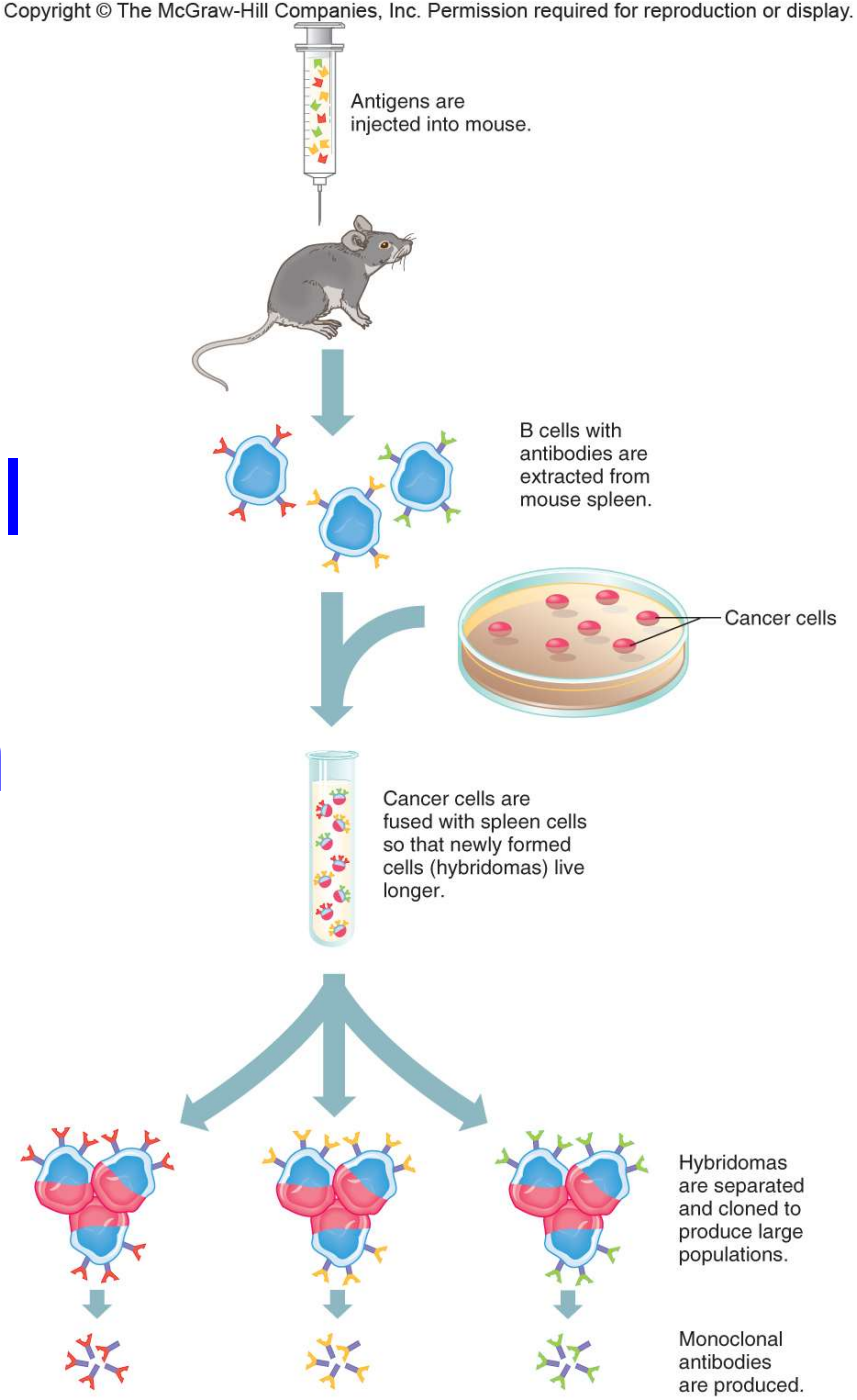
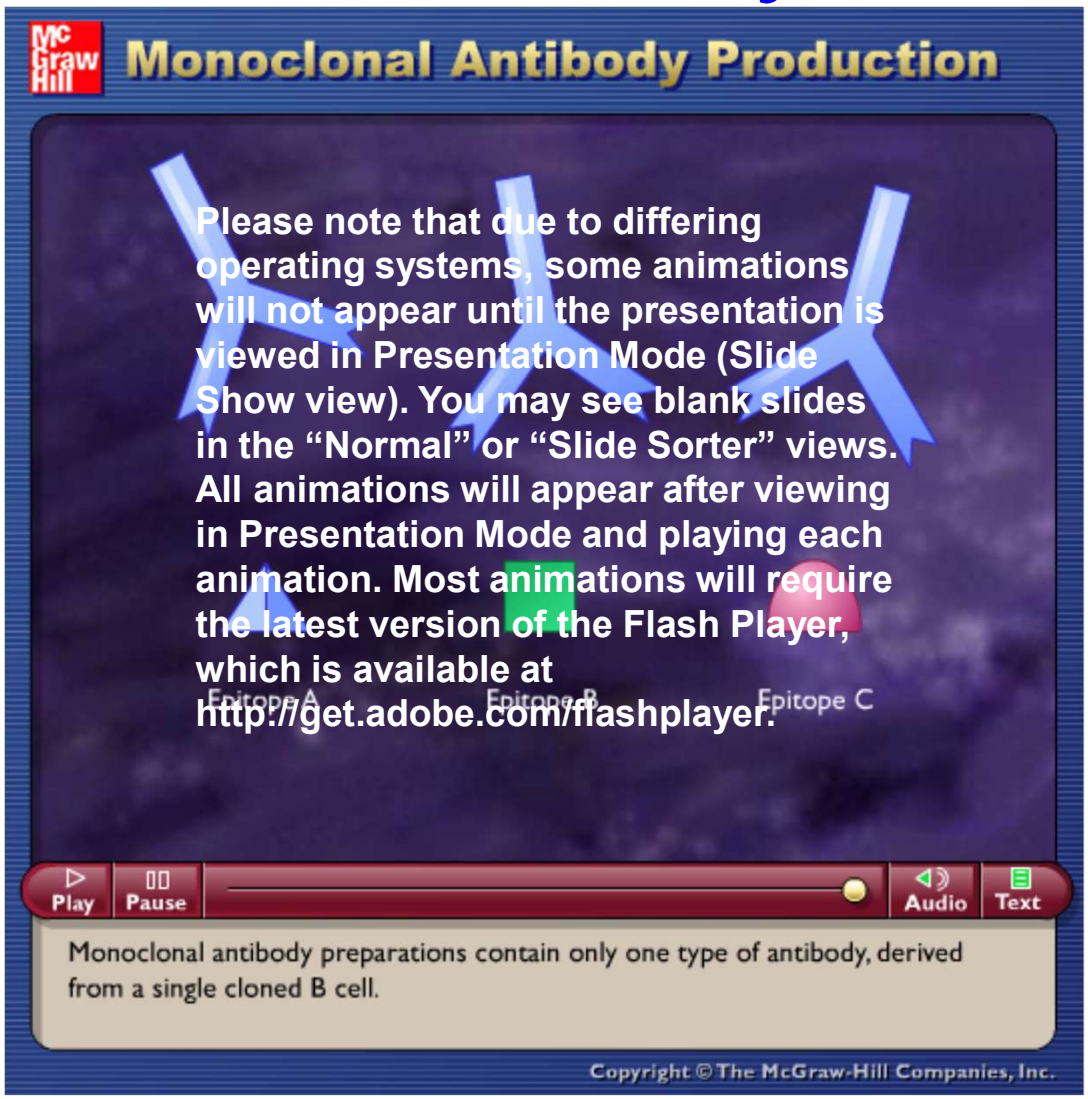


Figure 17.17

Monoclonal Antibody Animation



Uses of Monoclonal Antibodies

Basic research and disease diagnosis

Home pregnancy test strips

- Contain anti-hCG monoclonal antibody
- If hCG is present in the urine it binds and changes the color of the test strip

Herceptin

- A monoclonal antibody-based drug
- Blocks receptors on breast cancer cells
- Prevents reception of cell-division signal

Cytokines Boost Cellular Immunity

Cytokines are used to treat a variety of conditions

Examples

- Interferon: Cancer and multiple sclerosis
- Interleukin-2: Kidney cancer recurrence
- Colony stimulating factor: Boosts WBC levels in individuals with AIDS

Transplantation

Organs are moved from one individual to another

Hearts, kidneys, livers, lungs, corneas, pancreases, skin, and bone marrow are routinely transplanted

- Sometimes, several organs at a time

Today, thousands of transplants are performed annually and recipients gain years of life

Successful transplants lie in genetics

Transplantation

Types of transplantation are defined by the relationship between the donor and recipient:

- **Autograft:** from one person to self
- **Isograft**: from identical twin
- **Allograft**: members of same species
- **Xenograft**: from another species

Transplantation

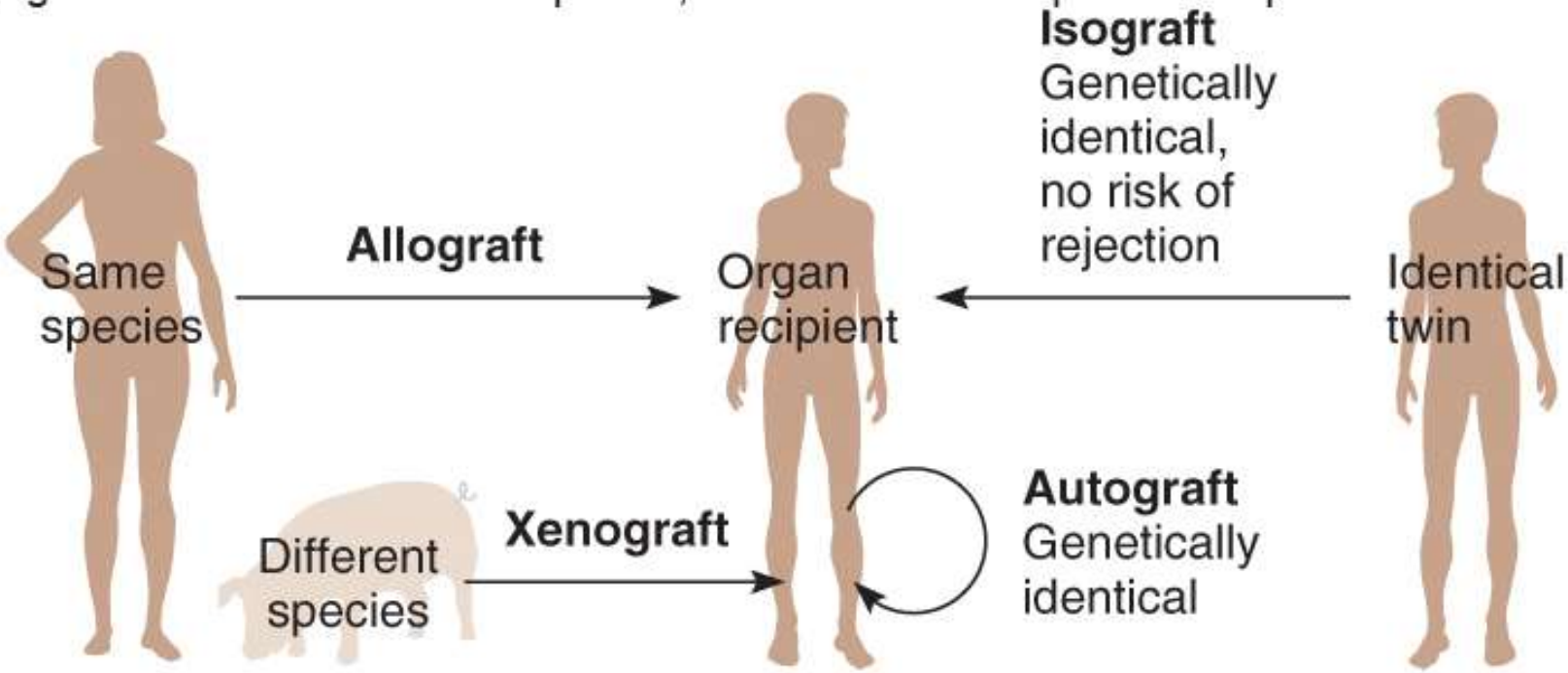


Figure 17.18

Graft Rejection

The immune system reacts to grafted tissue recognized as foreign by trying to destroy it

Hyperacute rejection reaction

- A severe form of graft reaction in which the blood supply to the graft tissue is cut off

Graft versus host disease

- Occurs in bone marrow transplants

- Immune cells of the grafted bone marrow recognize host body as foreign and attack it

Genomic View of Immunity

Sequencing genomes of pathogens

- Can help us understand how they infect, and aid in development of treatments

Crowd diseases

- Spread rapidly through unexposed populations
- Examples: smallpox, measles, pertussis, typhus, influenza, and SARS

Bioweapons

- Bacteria and viruses have been used throughout history as weapons
- In their natural state or genetically-manipulated