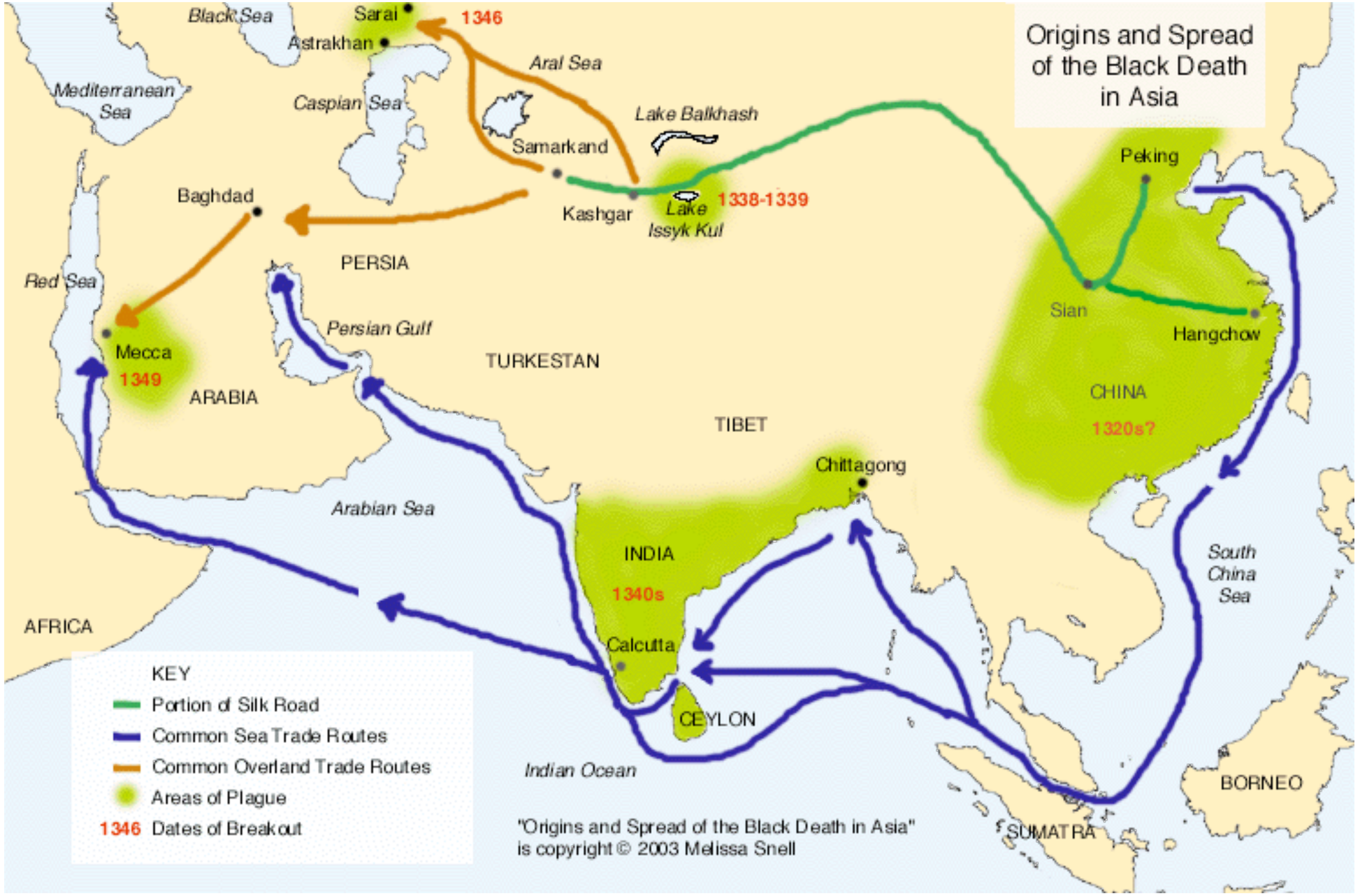
The Immune System

Some History

Plague

- Black death began in central Asia and spread to Europe by mid 1340s
- An estimated 75 million people died (20 – 30 million people)
  - between 1/3 – 2/3 of the European population


Origins and Spread of the Black Death in Asia
Black Sea
Sarai
1346
Astrakhan
Aral Sea
Mediterranean Sea
Caspian Sea
Lake Balkhash
Samarkand
Peking
Baghdad
Kashgar
Lake Issyk Kul
1338-1339
PERSIA
Red Sea
Sian
Hangchow
Persian Gulf
Mecca
1349
TURKESTAN
ARABIA
CHINA
1320s?
TIBET
Chittagong
Arabian Sea
INDIA
1340s
South China Sea
AFRICA
Calcutta
CEYLON
Indian Ocean
BORNEO
SUMATRA
KEY
Portion of Silk Road
Common Sea Trade Routes
Common Overland Trade Routes
Areas of Plague
1346 Dates of Breakout
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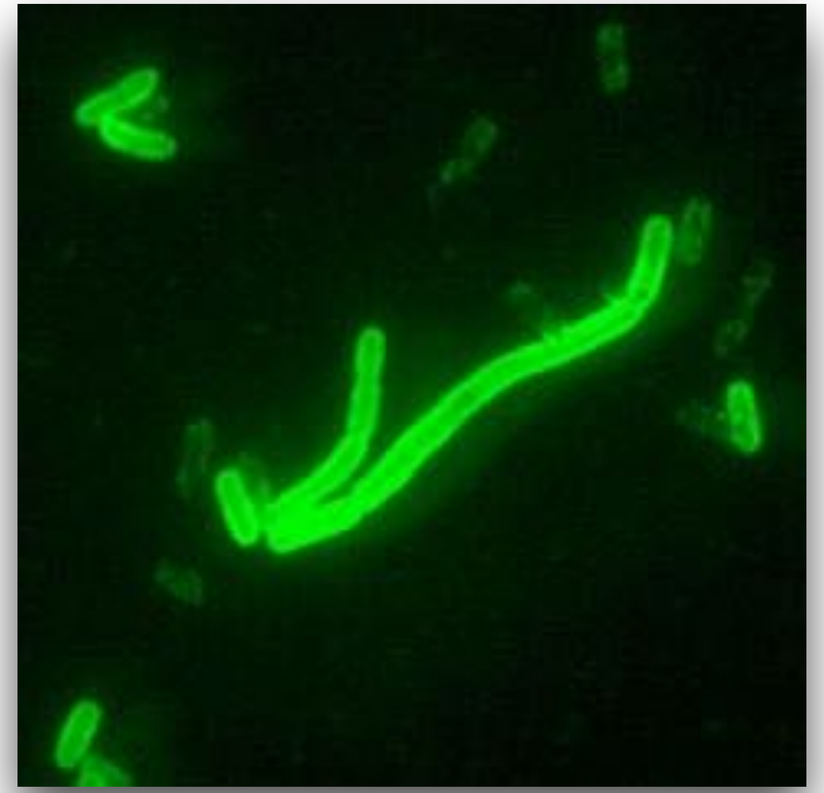
1347
Jan. 1348
June 1348
1349
1350
1351 and later
Few or no plague deaths
Center of urban revolt
Rural uprisings
N
W
E
S
NORWAY
SWEDEN
SCOTLAND
North Sea
Baltic Sea
IRELAND
DENMARK
Novgorod
RUSSIAN STATES
ENGLAND
Lübeck
Hamburg
Brunswick
LITHUANIA
Bruges
London
Ghent
Liège
Calais
POLAND
ATLANTIC OCEAN
Rouen
Ypres
Rhine R.
HOLY ROMAN EMPIRE
Paris
Strasbourg
Vienna
FRANCE
Alsace
Zürich
HUNGARY
Savoy
Milan
Venice
Caffa
Po R.
Genoa
VENICE
Danube R.
Black Sea
Ebro R.
Marseille
Florence
PORTUGAL
CASTILE
ARAGON
Barcelona
PAPAL STATES
Corsica
Rome
Constantinople
Thessalonika
Sardinia
Naples
OTTOMAN EMPIRE
Seville
Sicily
Mediterranean Sea
Crete
Cyprus
0 200 400 miles
0 200 400 kilometers

Questions

- What causes disease?
- Why do animals get sick?
- Why do some recover and some die?
- How does the environment influence the virulence and spread of disease-causing agents?

Yersinia pestis

This is the cause of plague (viewed with fluorescent staining techniques)



(2000x)

History of Immunology

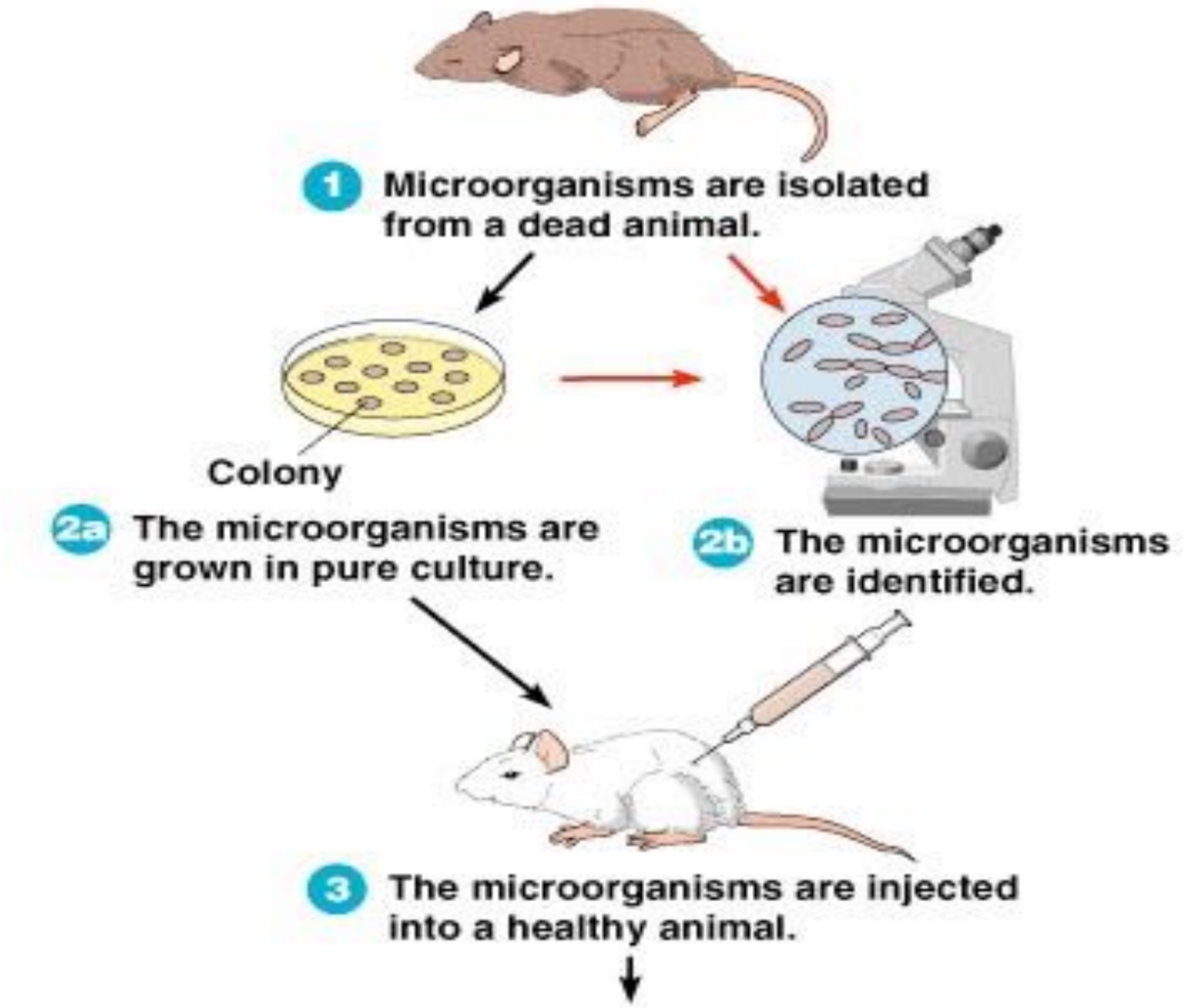
430 BC - Thucydides (Greece) observes "immunity" to the plague

15th Century – First attempts at immunization (China, Turkey)

1798 – Edward Jenner (England) used cowpox inoculum to immunize against smallpox

1880 – Louis Pasteur (France) immunizes against cholera, rabies, anthrax; coins term *vaccination*

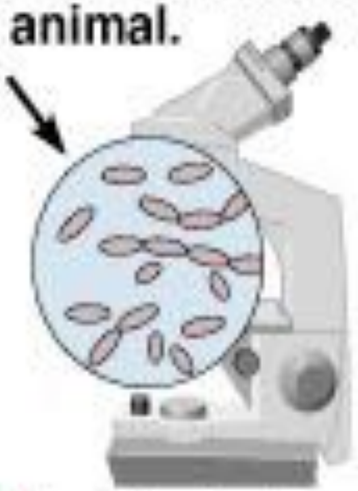
Koch’s Postulates (1890s)



Koch's Postulates

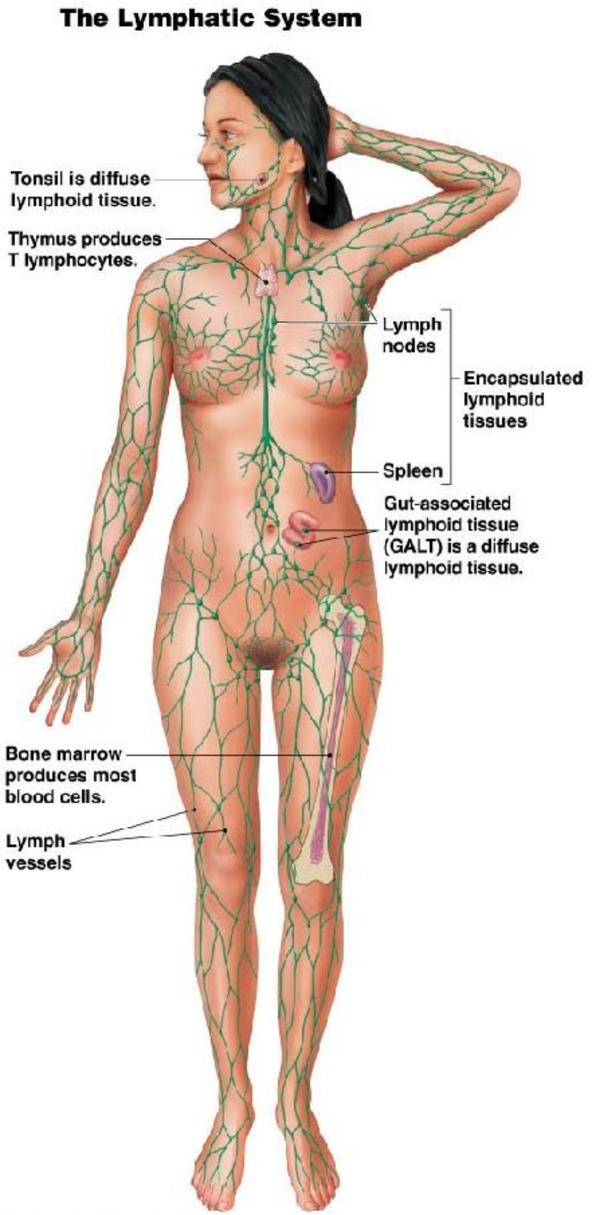
4 The disease is reproduced in the second animal; microorganisms are isolated from this animal.

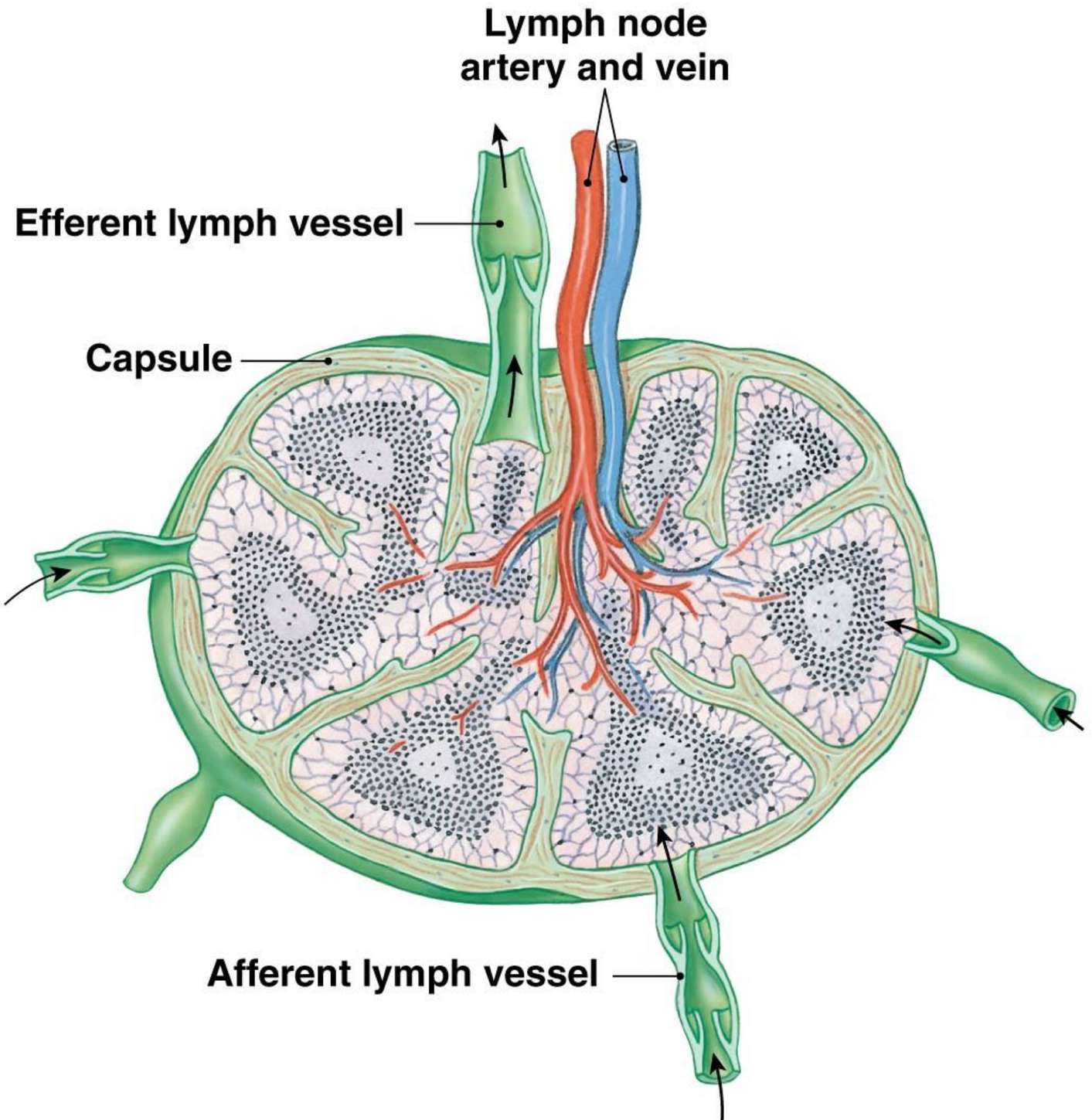
5a Pathogenic microorganisms are grown in pure culture.



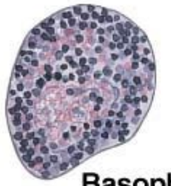
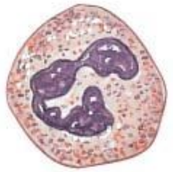
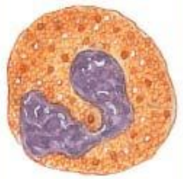
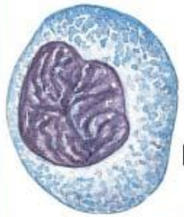
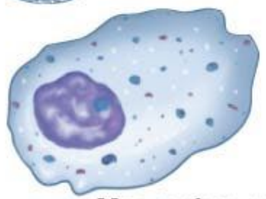
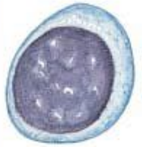
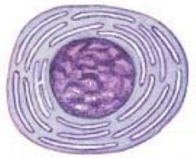
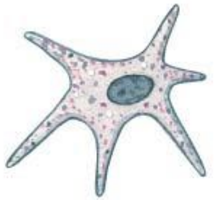
5b Identical microorganisms are identified.

Introduction




Lymph node
artery and vein
Efferent lymph vessel
Capsule
Afferent lymph vessel

CELLS OF THE IMMUNE SYSTEM Circulating leukocytes, tissue macrophages, and dendritic cells are the body's immunocytes.

Types of cells	 Basophils  Mast Cells	 Neutrophils	 Eosinophils	 Monocytes  Macrophages	 Lymphocytes  Plasma Cells	 Dendritic Cells
Classifications		Phagocytes				
	Granulocytes					
			Cytotoxic cells		Cytotoxic cells (some types)	
				Antigen-presenting cells		
% of WBCs in blood	Rare	50–70%	1–3%	1–6%	20–35%	N/A
Subtypes and nicknames		Called "polys" or "segs." Immature forms called "bands" or "stabs."		Called the mononuclear phagocyte system	B lymphocytes Plasma cells Memory cells T lymphocytes Cytotoxic T cells Helper T cells Natural killer cells	Also called Langerhans cells, veiled cells
Primary function(s)	Release chemicals that mediate inflammation and allergic responses	Ingest and destroy invaders	Destroy invaders, particularly antibody-coated parasites	Ingest and destroy invaders. Antigen presentation	Specific responses to invaders, including antibody production	Recognize pathogens and activate other immune cells by antigen presentation

Functions of the Immune System

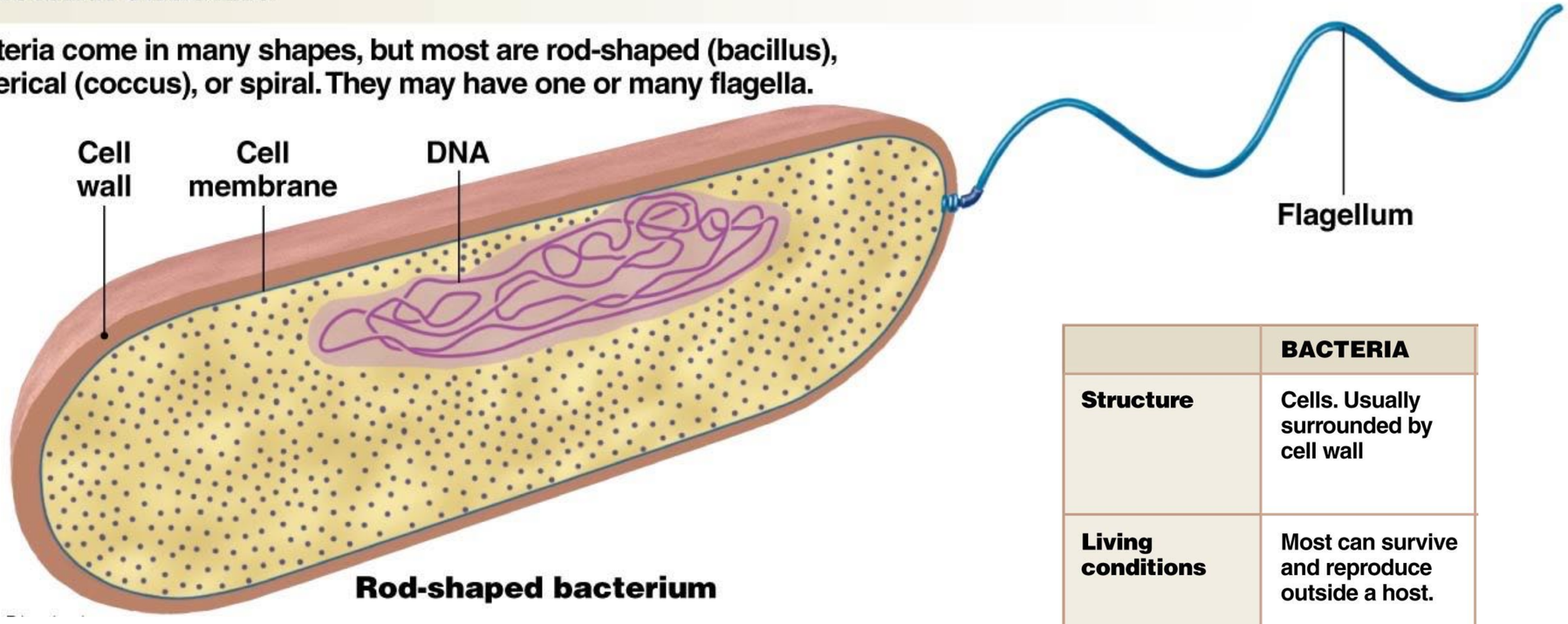
- Prevent pathogens from gaining entrance to our bodies
- Identifying and destroying pathogens which do enter
- Protect against foreign human cells and cancer cells

(c) Differences between bacteria and viruses

	BACTERIA	VIRUSES
Structure	Cells. Usually surrounded by cell wall	Not cells. Nucleic acid core with protein coat
Living conditions	Most can survive and reproduce outside a host.	Parasitic. Must have a host cell to reproduce.
Susceptibility to drugs	Most can be killed or inhibited by antibiotics.	Cannot be killed with antibiotics. Some can be inhibited with antiviral drugs.

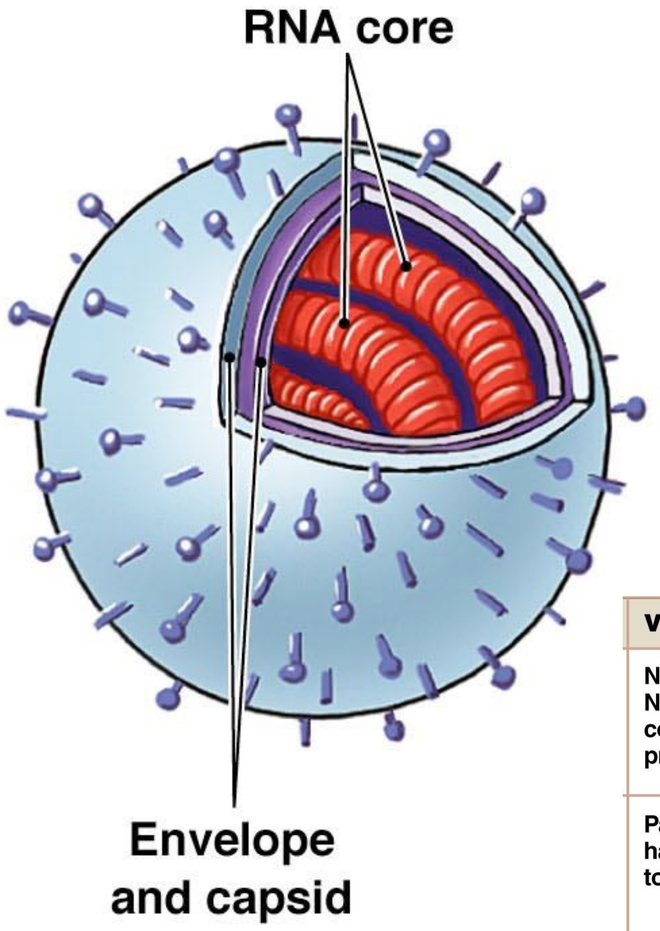
(a) Bacterial structure

Bacteria come in many shapes, but most are rod-shaped (bacillus), spherical (coccus), or spiral. They may have one or many flagella.



	BACTERIA
Structure	Cells. Usually surrounded by cell wall
Living conditions	Most can survive and reproduce outside a host.
Susceptibility to drugs	Most can be killed or inhibited by antibiotics.

(a) Influenza, an RNA virus



VIRUSES
Not cells. Nucleic acid core with protein coat
Parasitic. Must have a host cell to reproduce.
Cannot be killed with antibiotics. Some can be inhibited with antiviral drugs.

(b) General steps of viral replication

Viral invasion of host cell

↓

Synthesis of new viral nucleic acids and proteins

↓

Self-assembly of new viral macromolecules into new virus particles

↓

Virus particles released from host cell

Nonspecific Defenses

- Surface Membrane Barriers
  - Skin
    - Keratin, acidic pH
  - Mucous membranes
    - Vaginal secretions, stomach mucosa
    - Saliva and lacrimal fluid contain lysozymes
    - Mucous itself is sticky and traps particles

PHYSICAL AND CHEMICAL BARRIERS

Epithelium

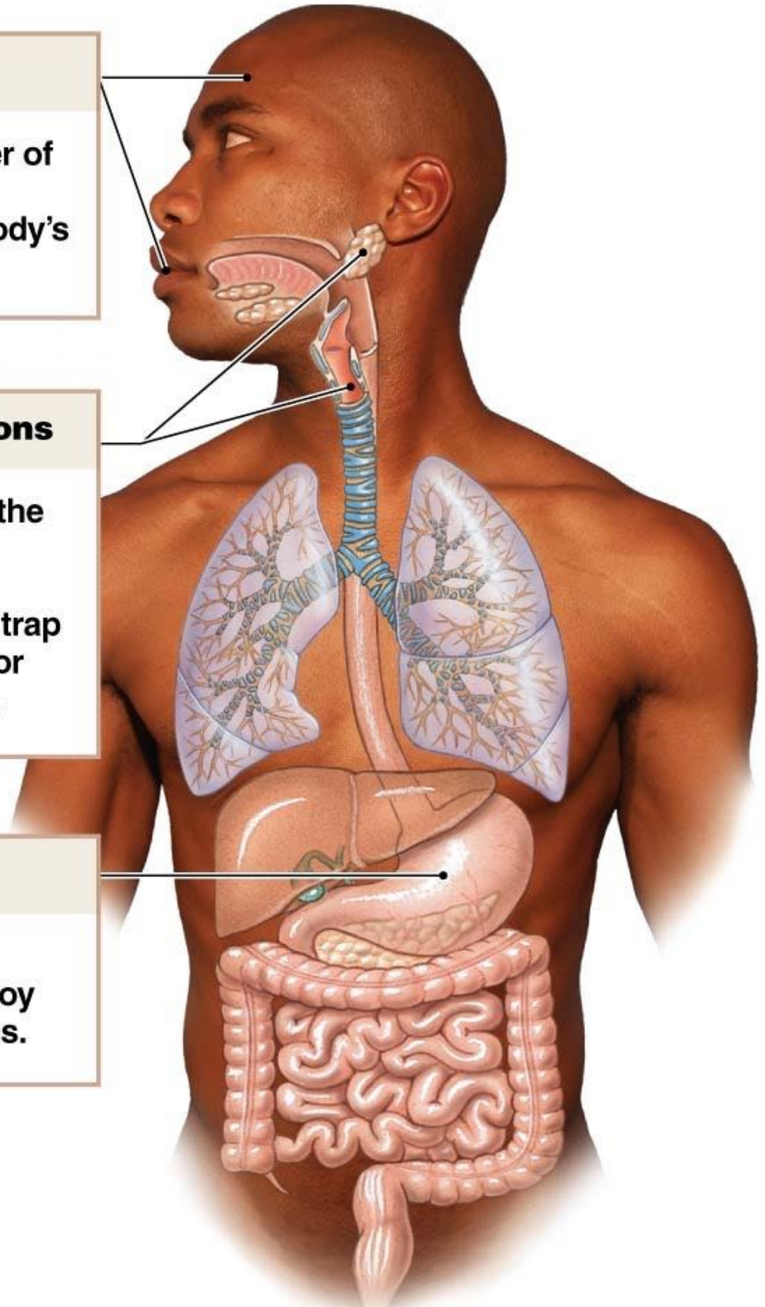
The protective barrier of skin and mucous membranes is the body's first line of defense.

Glandular secretions

Salivary glands and the glands in airways secrete mucus and immunoglobulins to trap and disable inhaled or ingested pathogens.

Stomach acidity

The low pH of the stomach helps destroy swallowed pathogens.



Chemicals of the Immune Response

Table 24.1

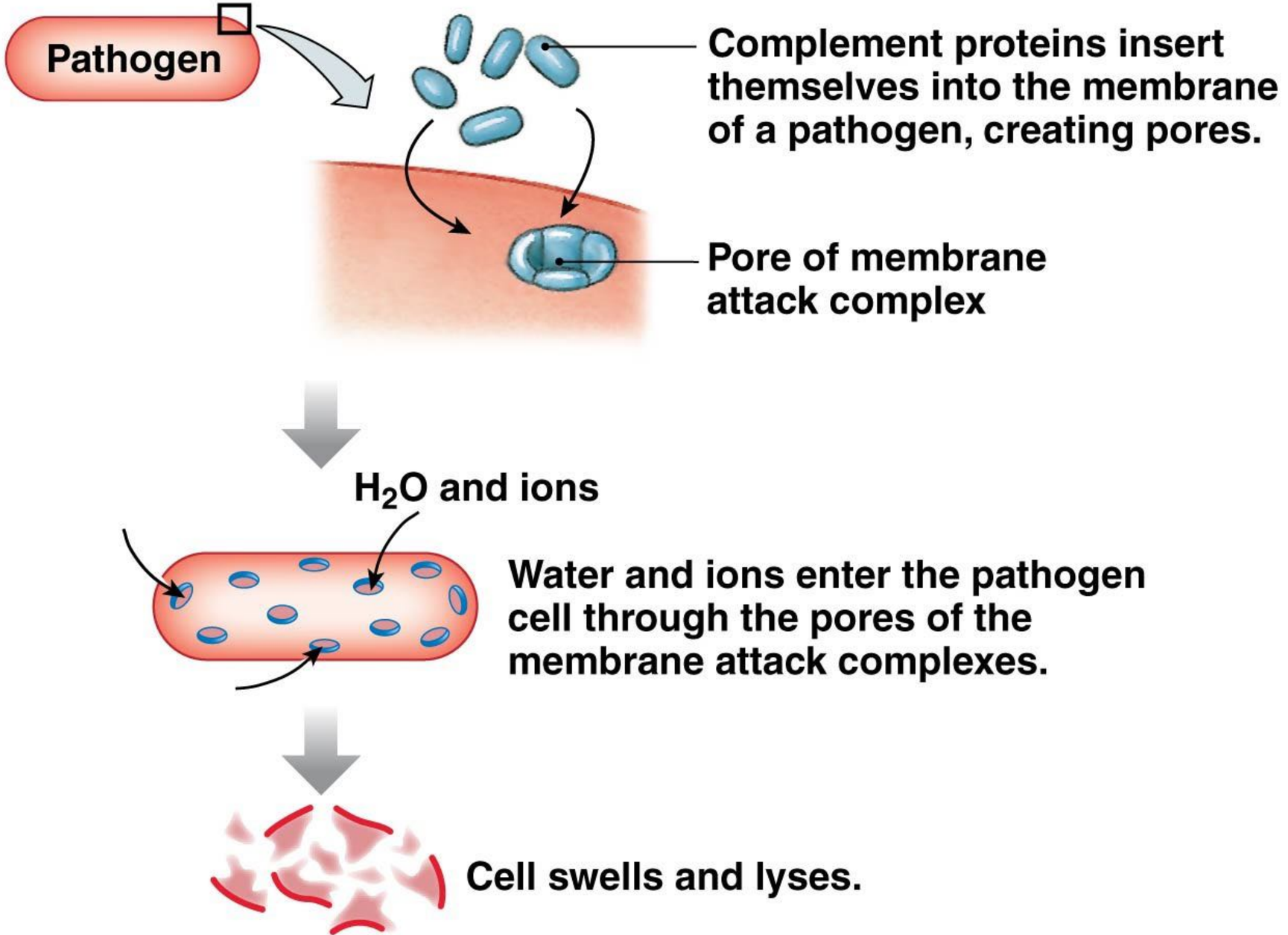
Functional Classes
Acute phase proteins: Liver proteins that act as opsonins and that enhance the inflammatory response
Chemotaxins: Molecules that attract phagocytes to a site of infection
Cytokines: Proteins released by one cell that affect growth or activity of another cell
Opsonins: Proteins that coat pathogens so that phagocytes recognize and ingest them
Pyrogens: Fever-producing substances

Chemicals of the Immune Response

Table 24.1

Specific Chemicals and Their Functions
Antibodies (immunoglobulins, gamma globulins): Proteins secreted by B lymphocytes that fight specific invaders
Bradykinin: Stimulates pain receptors; vasodilator
Complement: Plasma and cell membrane proteins that act as opsonins, cytolytic agents, and mediators of inflammation
C-reactive protein: Opsonin that activates complement cascade
Granzymes: Cytotoxic enzymes that initiate apoptosis
Heparin: An anticoagulant
Histamine: Vasodilator and bronchoconstrictor released by mast cells and basophils
Interferons (IFN): Cytokines that inhibit viral replication and modulate the immune response
Interleukins (IL): Cytokines secreted by leukocytes to act primarily on other leukocytes; IL-1 mediates inflammatory response and induces fever
Kinins: Plasma proteins that activate to form bradykinin
Lysozyme: An extracellular enzyme that attacks bacteria
Major histocompatibility complex (MHC): Membrane protein complexes involved in cell recognition
Membrane attack complex: A membrane pore protein made in the complement cascade
Perforin: A membrane pore protein that allows granzymes to enter the cell; made by NK and cytotoxic T cells
Superoxide anion (O_2^-): Powerful oxidant in phagocyte lysosomes
T-cell receptors: T lymphocyte receptors that recognize and bind antigen presented by MHC receptors
Tumor necrosis factor (TNF): Cytokines that promote inflammation and can cause cells to self-destruct through apoptosis

Membrane attack complex creates pores in pathogens.



Inflammation

- Inflammatory Response
- Function:
  - 1. Prevents the spread of damaging agents
  - 2. Disposes of cell debris and pathogens
  - 3. Sets the stage for repair
- Mechanism: Injured cells release histamine and kinins, causing a cascade effect

Fever

- Makes the host less comfortable for the pathogen
- Something else?

Specific Defenses

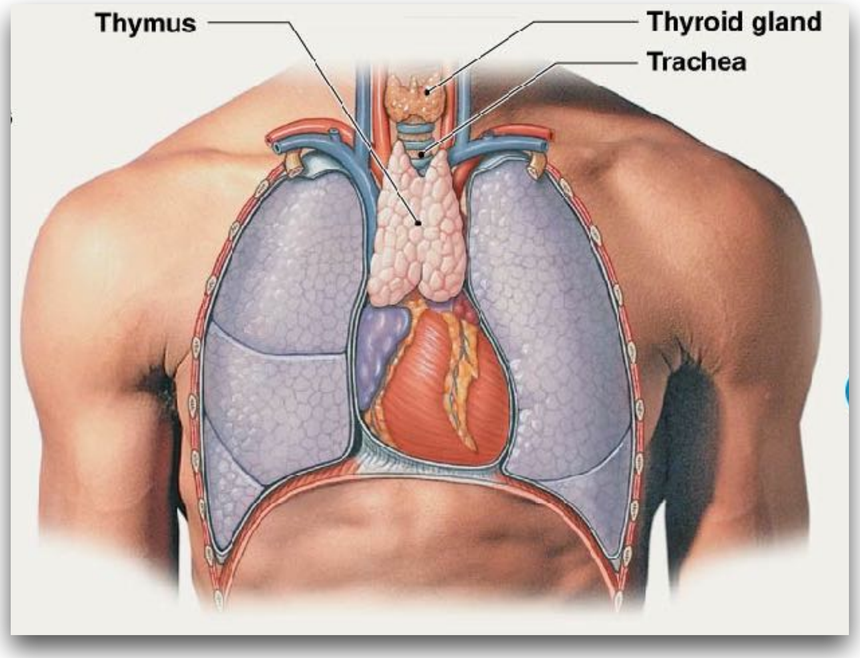
- Antigen-specific
- Systemic
- Memory is involved

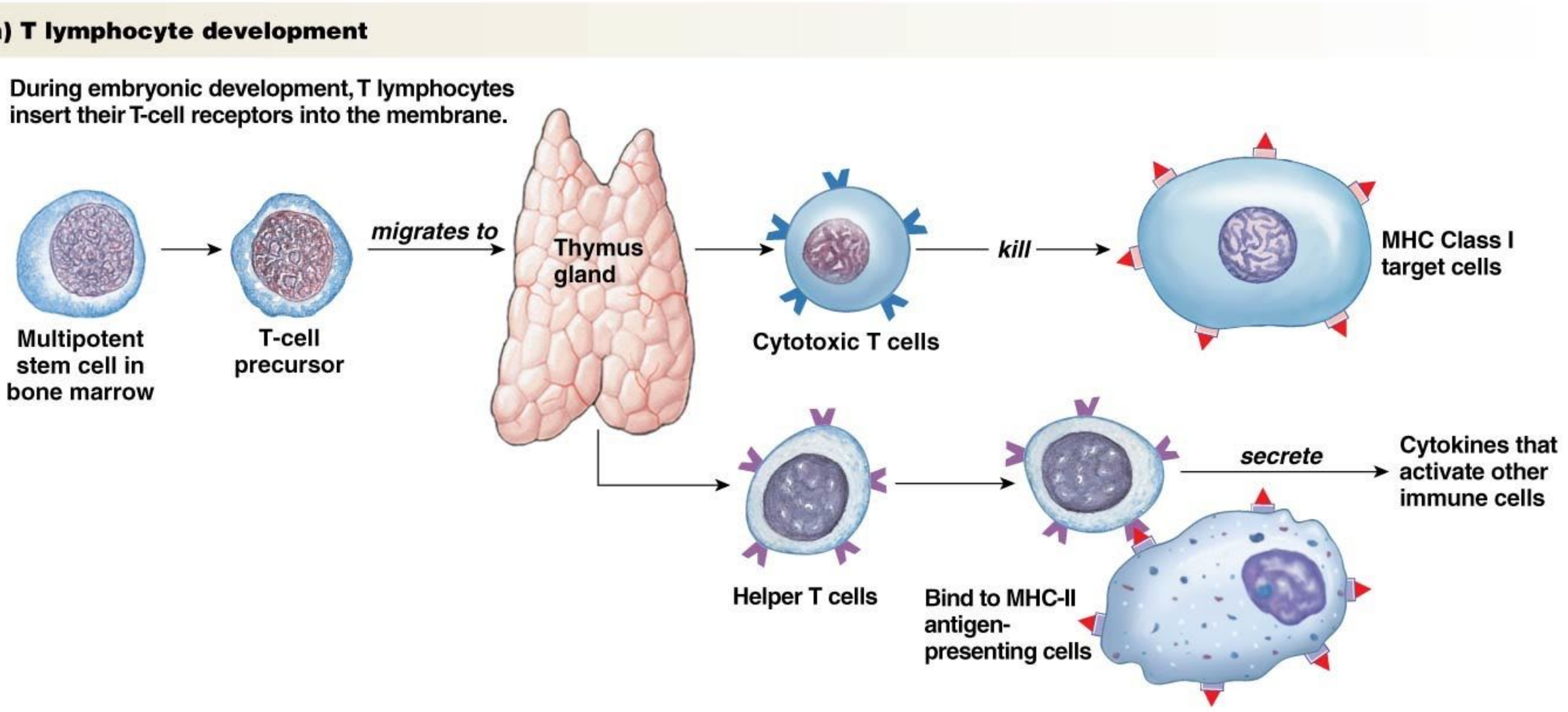
Some vocabulary:

- Foreign Antigen = any substance capable of exciting the immune system
- Antibodies = special molecules designed to fit the foreign antigen
- Immunocompetence = capability of recognizing a particular antigen (“sensitization”)

Lymphocytes

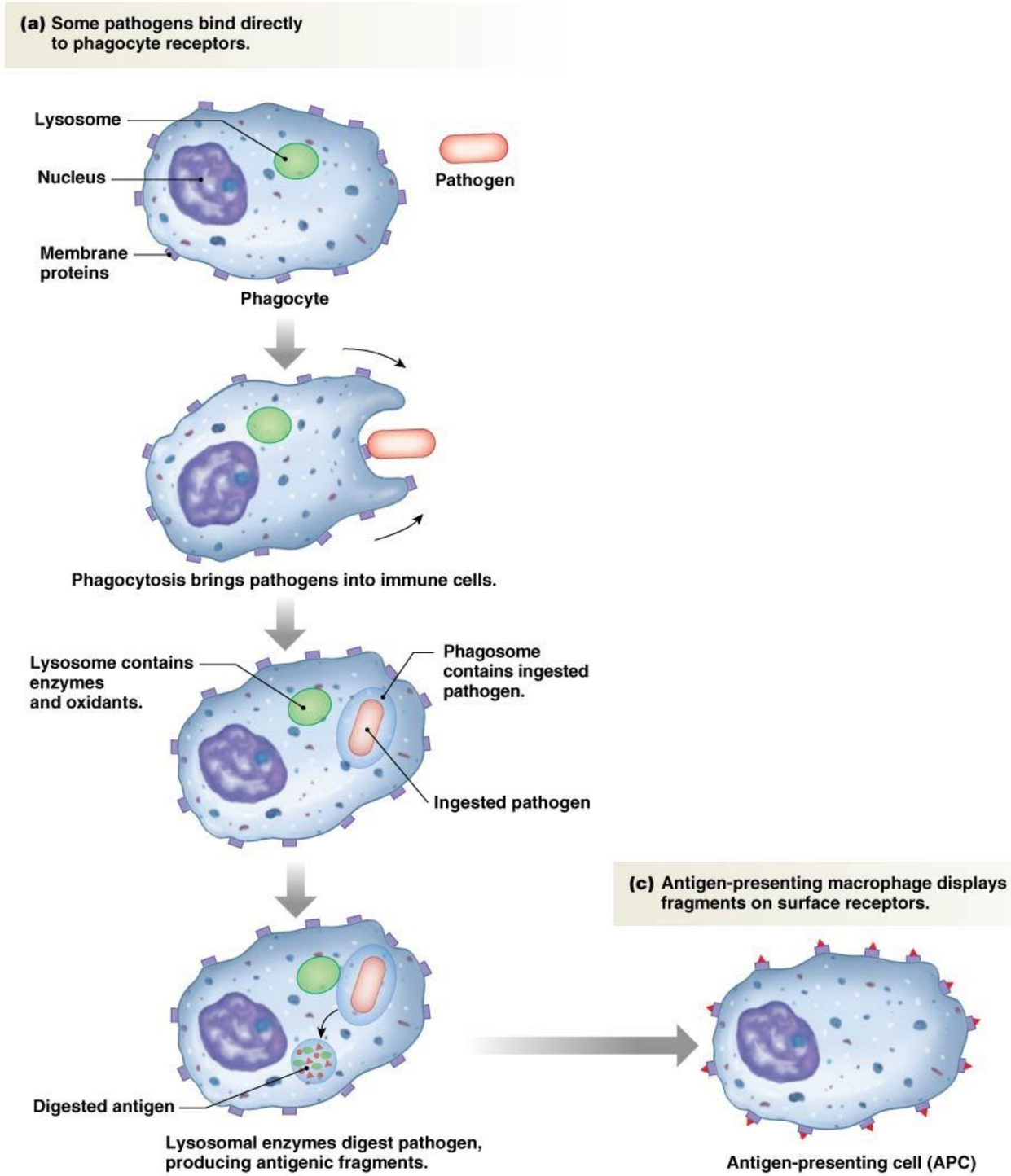
- Name depends on where in the body they go later in their development.
  - B cells: finish development in the bone marrow
  - T cells: migrate to the thymus




(a) T lymphocyte development
During embryonic development, T lymphocytes insert their T-cell receptors into the membrane.
Multipotent stem cell in bone marrow
T-cell precursor
migrates to
Thymus gland
Cytotoxic T cells
kill
MHC Class I target cells
Helper T cells
secrete
Cytokines that activate other immune cells
Bind to MHC-II antigen-presenting cells

Cell-Mediated Immunity

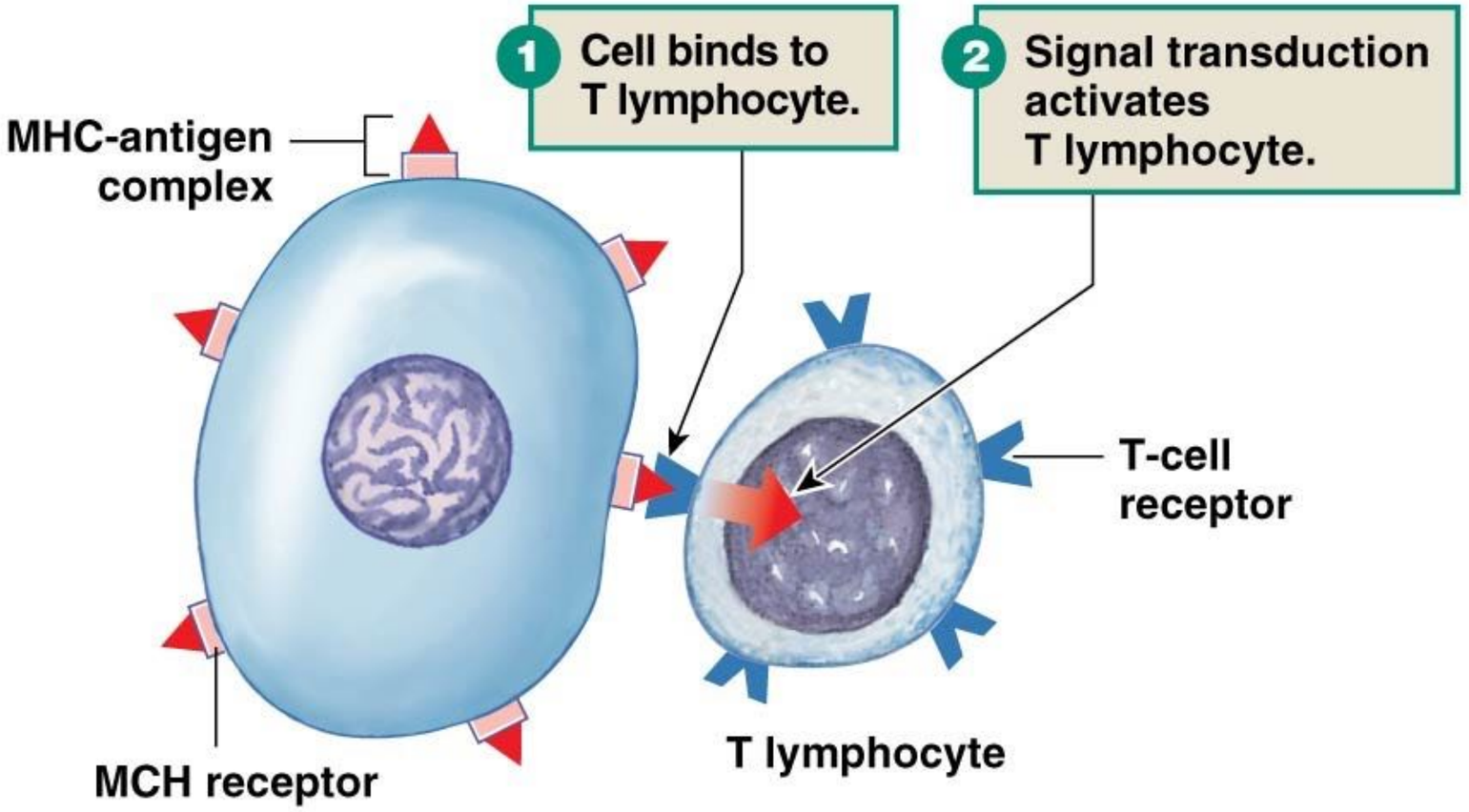
- Macrophages
  - They produce chemicals to enhance the immune response.
  - They can become super-charged (killer macrophages)
  - Can become APCs



"food in a mustache"

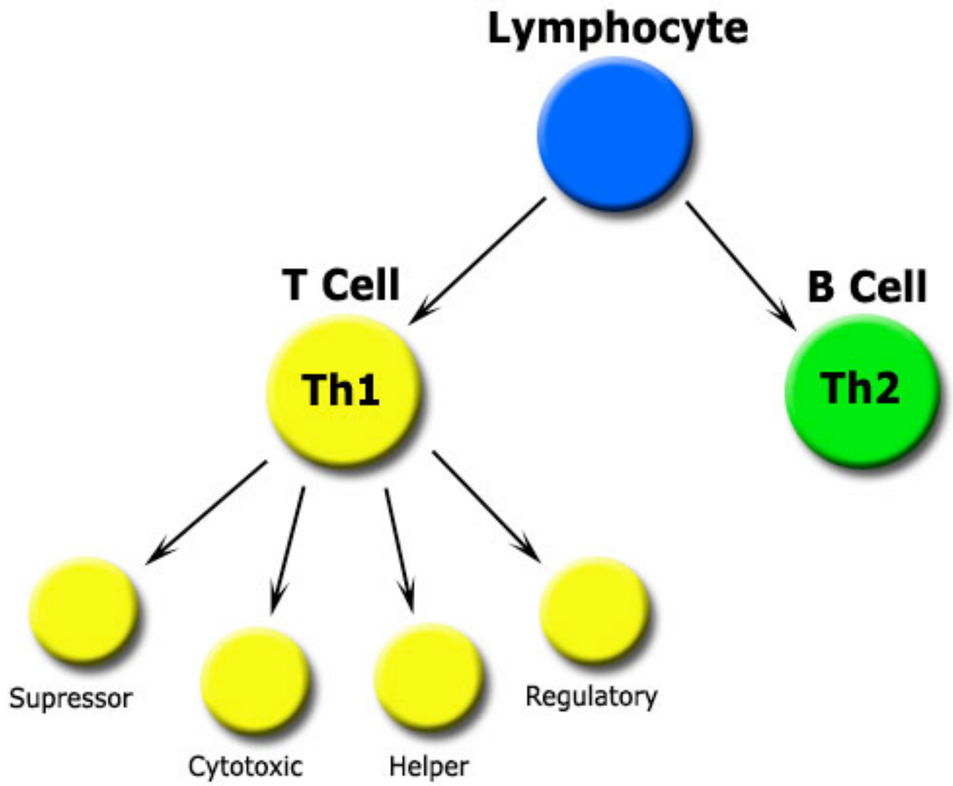
(b) T lymphocyte activation

When T-cell receptors bind to antigen presented on MHC receptors.



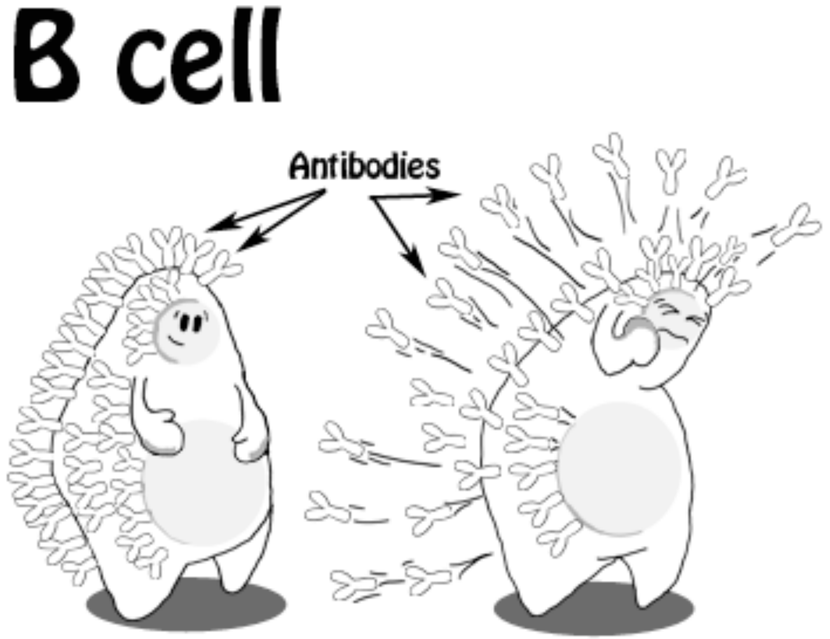
Cell-Mediated Immunity

- Antigen presentation and 'double recognition' by the T cell toward a macrophage
- Killer T Cells
  - Kill pathogens
- Helper T Cells
  - Manager cells
  - Release lymphokines
- Suppressor T Cells
  - Suppress T and B cells
- Memory T Cell



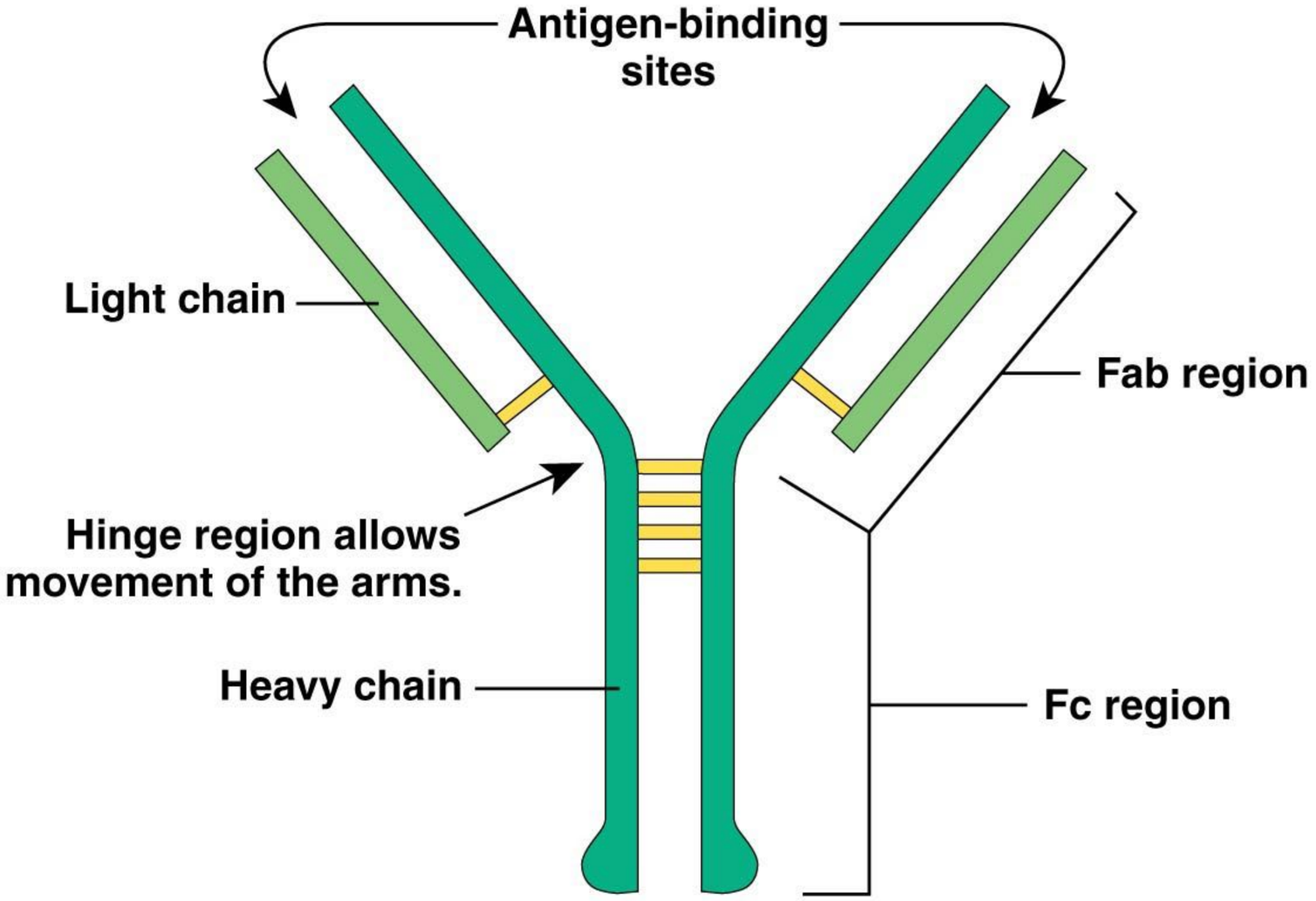
Humoral Immunity

- All about the B cells and antibodies
  - What are antibodies?
  - What do they do?

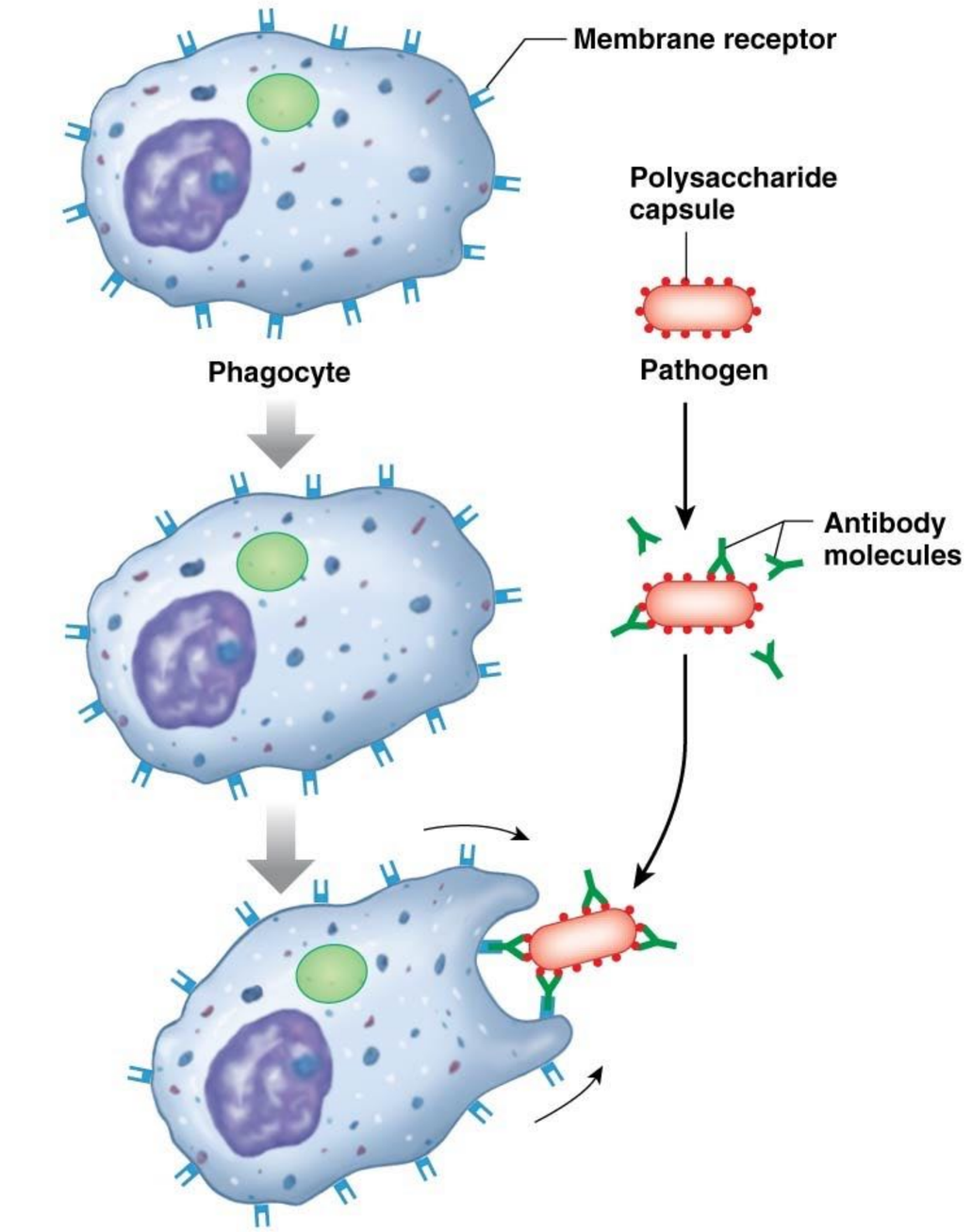


(a) Antibody structure

An antibody molecule is composed of two identical light chains and two identical heavy chains, linked by disulfide bonds.

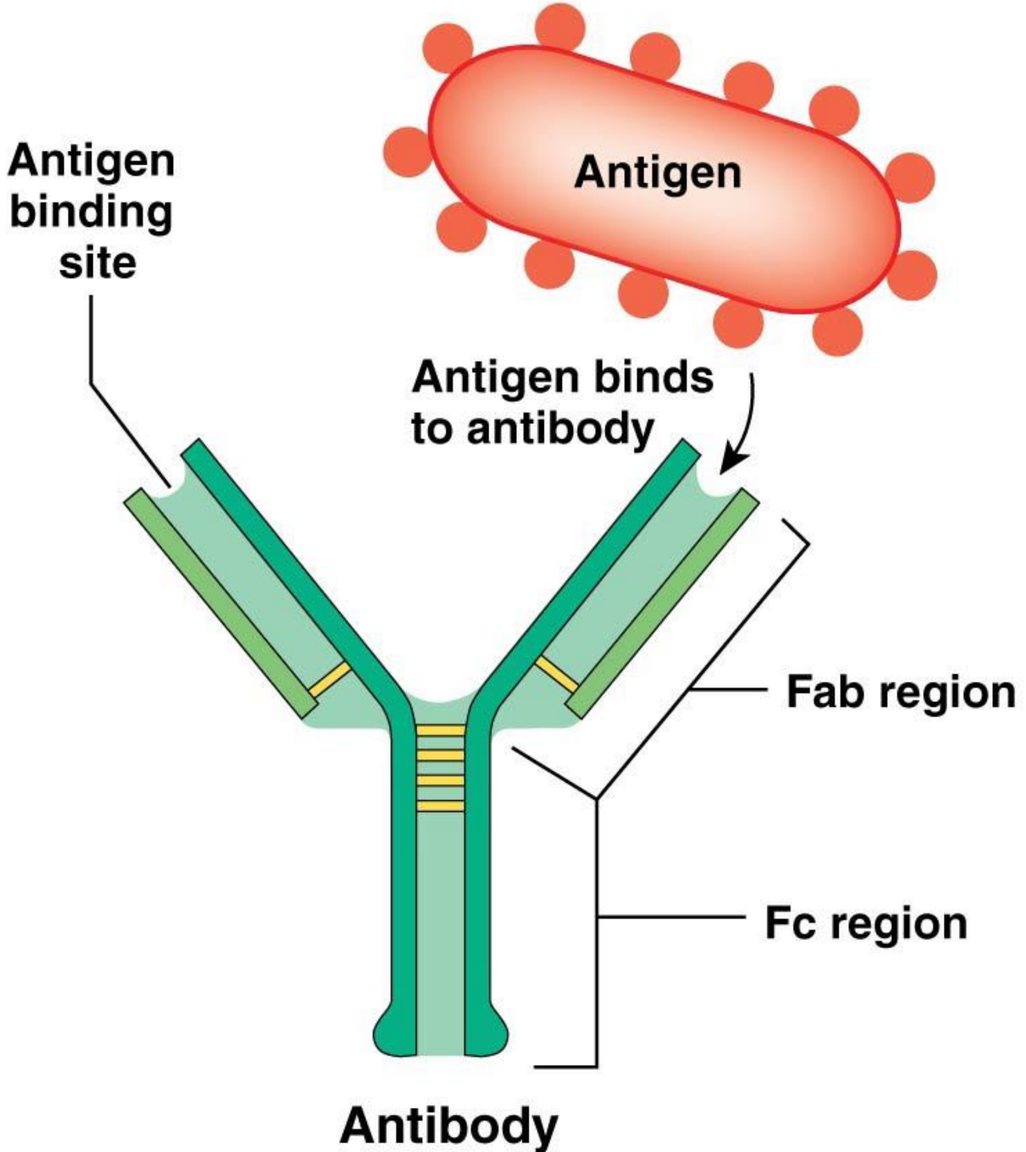


(b) Bacteria with capsules must be coated with antibody before phagocytes can recognize and ingest them.



(b) Antigen binding

Antibodies have antigen-binding sites on the Fab regions.



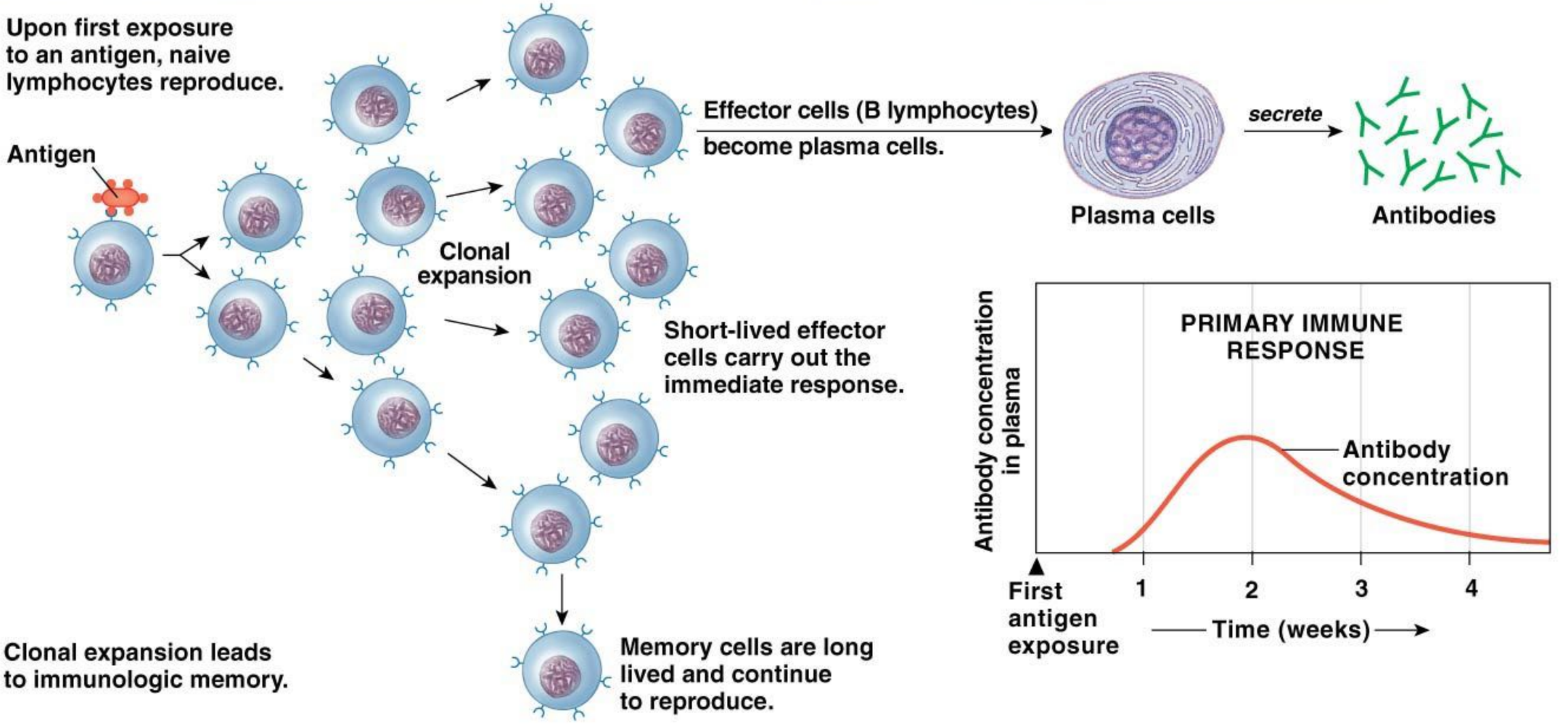
Humoral Immunity

- Primary Response:
  - Clonal selection: production of effector (plasma) cells and memory cells
- Secondary Response:
  - Memory cells, exposed to the antigen during a subsequent attack, respond more quickly and more strongly.

PRIMARY IMMUNE RESPONSE

(b) Exposure to an antigen triggers clonal expansion and the immune response.

(c) B lymphocytes secrete antibodies.

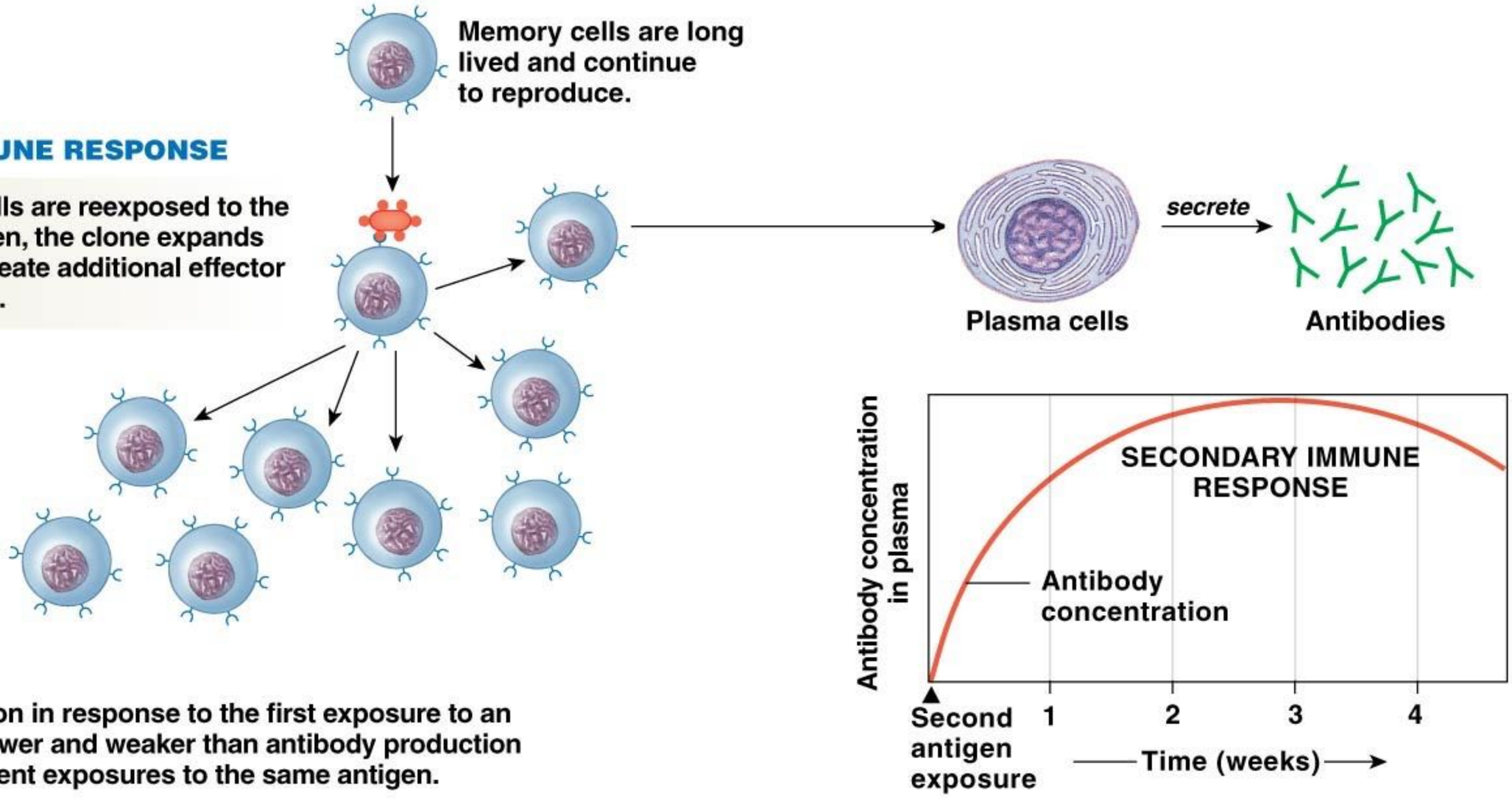


Humoral Immunity

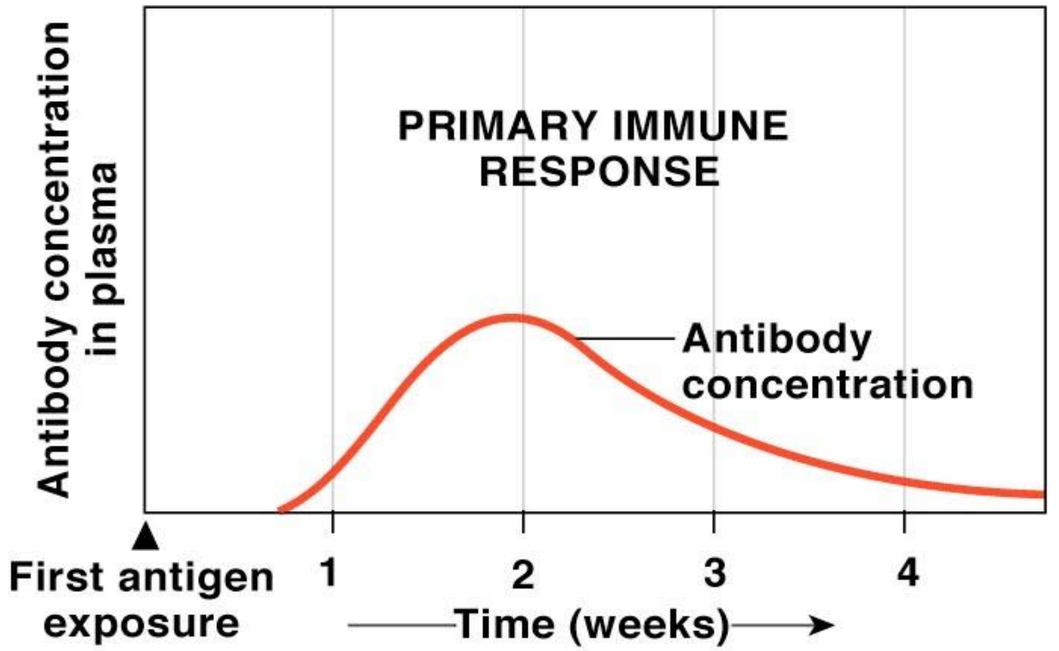
- Primary Response:
  - Clonal selection: production of effector (plasma) cells and memory cells
- Secondary Response (if you survive the first exposure and are are exposed to the same antigens at a later time):
  - Memory cells, exposed to the antigen during a subsequent attack, respond more quickly and more strongly.

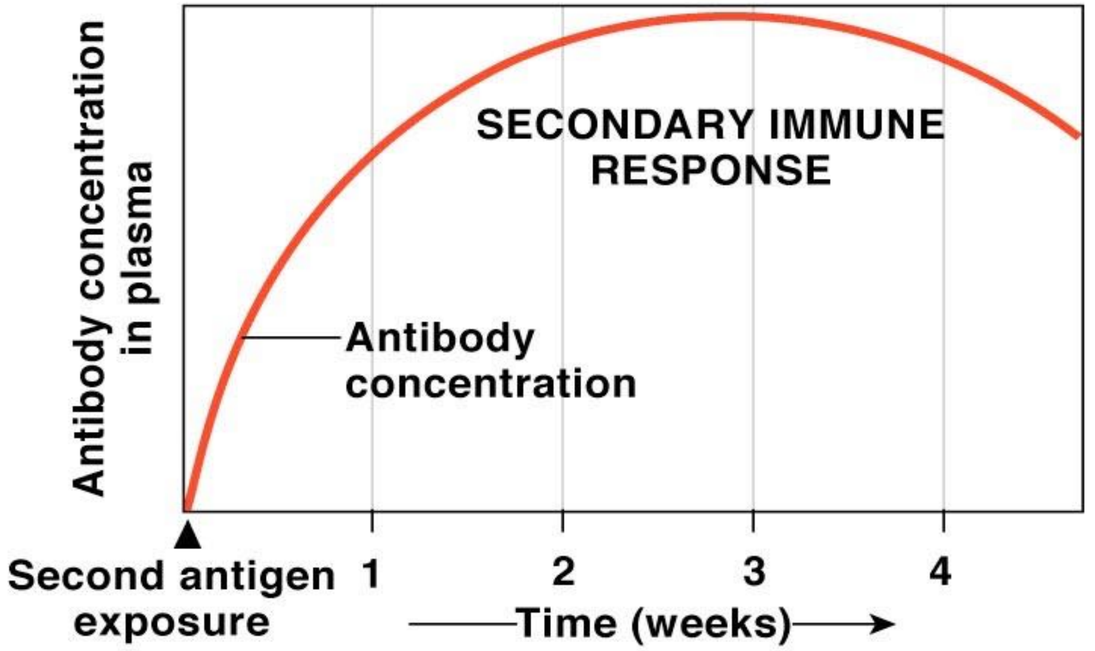
SECONDARY IMMUNE RESPONSE

(d) When memory cells are reexposed to the appropriate antigen, the clone expands more rapidly to create additional effector and memory cells.



Antibody production in response to the first exposure to an antigen is both slower and weaker than antibody production following subsequent exposures to the same antigen.


PRIMARY IMMUNE RESPONSE
Antibody concentration in plasma
Antibody concentration
First antigen exposure
1
2
3
4
Time (weeks)


SECONDARY IMMUNE RESPONSE
Antibody concentration in plasma
Antibody concentration
Second antigen exposure
1
2
3
4
Time (weeks)

Two Types of Humoral Immunity:

1. Active Immunity

    - Lymphocytes are challenged by antigens and produce antibodies against them.

    - Naturally acquired during bacterial and viral infections.

    - Artificially acquired when we receive a vaccine

Two Types of Humoral Immunity:

2. Passive Immunity

   - Antibodies are acquired, but B cells are not challenged by antigens
   - Naturally acquired = mother to baby across placenta and in milk
   - Artificially acquired = receiving serum from an immune animal or donor

Special Topics

Organ Transplants

Autografts = on the same person.

Isografts = identical twins

Allografts = grafts from someone else

Xenografts = tissues harvested from a different species.

Immune Dysfunction

- Immunodeficiencies
  - Production of immune cells or complement is abnormal
  - Congenital or acquired

David, “Bubble Boy”

Immune Dysfunction

- Autoimmune Diseases
  - Ability to recognize self from non-self is impaired.

Some Common Autoimmune Diseases in Humans

Table 24.3

Disease	Antibodies Produced Against
Graves' disease (hyperthyroidism)	TSH receptor on thyroid cells
Insulin-dependent diabetes mellitus	Pancreatic beta cell antigens
Multiple sclerosis	Myelin of CNS neurons
Myasthenia gravis	Acetylcholine receptor of motor endplate
Rheumatoid arthritis	Collagen
Systemic lupus erythematosus	Intracellular nucleic acid protein complexes (antinuclear antibodies)
Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy)	Myelin of peripheral nerves