Lecture 32

BT 206

25 April 2023

Mechanisms of Pathogenicity

- **Disease:** Abnormal condition that negatively affects the structure or function of part or all of an organism, that is not due to any external injury
- ✓ Four types: Infectious diseases, deficiency diseases, hereditary diseases and physiological or metabolic diseases
- **Pathogenicity**: the ability of an organism to cause disease
- **Virulence**: the extent of pathogenicity of an organism
- **Pathology**: The study of disease including etiology, or cause.

Figure 15.9 Microbial Mechanisms of Pathogenicity.

When the balance between host and microbe is tipped in favor of the microbe, an infection or disease results. Learning these mechanisms of microbial pathogenicity is fundamental to understanding how pathogens are able to overcome the host's defenses.

H1N1 flu virus

portals of entry

Mucous membranes
- Respiratory tract
- Gastrointestinal tract
- Genitourinary tract
- Conjunctiva

Skin
Parenteral route

Number of invading microbes

Adherence

penetration or evasion of host defenses

Capsules
Cell wall components
Enzymes
Antigenic variation
Invasins
Intracellular growth

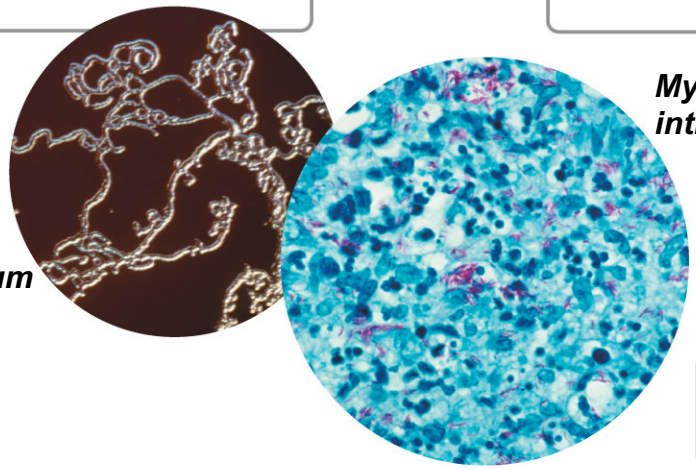
damage to host cells

Siderophores
Direct damage
Toxins
- Exotoxins
- Endotoxins

Lysogenic conversion
Cytopathic effects

portals of exit

Generally the same as the portals of entry for a given microbe:
- Mucous membranes
- Skin
- Parenteral route



Clostridium tetani

Mycobacterium intracellulare

Micrographs are not shown to scale.

Portals of Entry

- Mucous membranes
- Skin
- Parenteral route: skin punctures e.g bites, cuts, surgery etc

Microbes must enter preferred portal of entry eg *Salmonella typhi* (when swallowed), *Streptococci* (inhaled). But some can cause disease from many routes of entry eg. *Yersinia pestis, Bacillus anthracis*.

Numbers of Invading Microbes

Virulence of microbe can be expressed as:

- **ID_{50}**: infectious dose for 50% of the test population.
- Infectious dose differs with pathogens and route of entry.

Potency of a toxin or lethality of pathogen is expressed as:

- **LD_{50}**: lethal dose (of a toxin or microbe) to kill 50% of the test population in a particular time frame

Bacillus anthracis

Portal of Entry	**ID_{50}**
Skin	10–50 endospores
Inhalation	10,000–20,000 endospores
Ingestion	250,000–1,000,000 endospores

Toxins

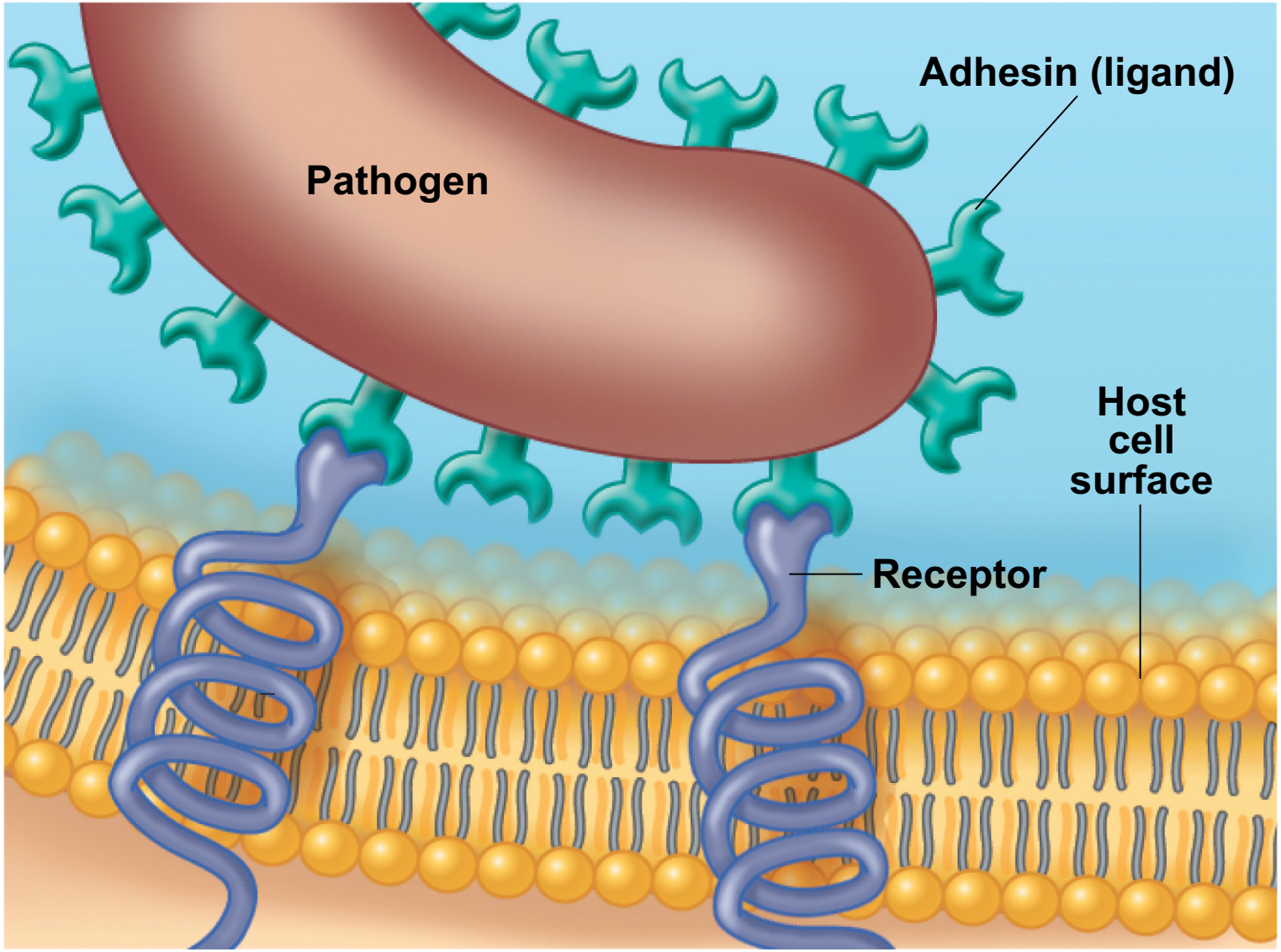
Potency of toxins in mice	LD_{50}
Botulinum	0.03 ng/kg
Shiga toxin	250 ng/kg
Staphylococcal enterotoxin	1350 ng/kg

Adherence

Essential for progression of infection and disease.

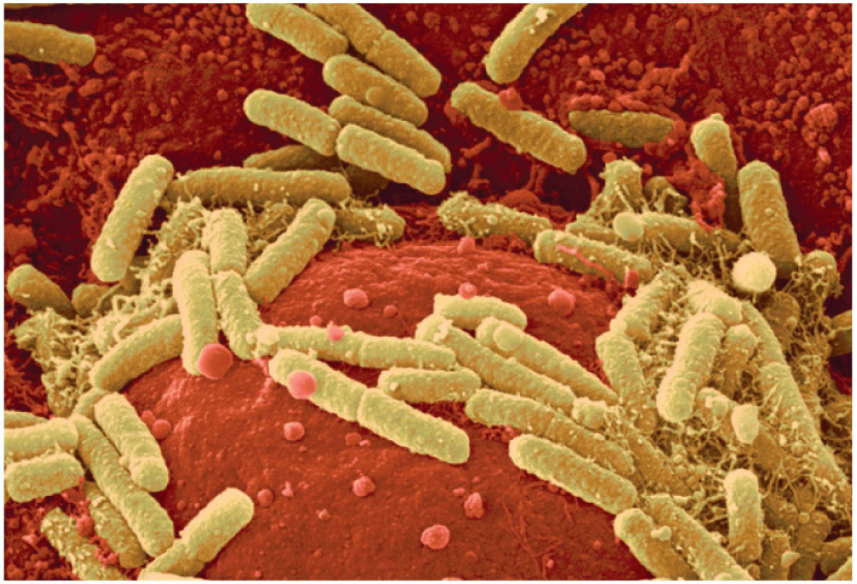
- **Adhesins/ligands** bind to **receptors** on host cells
  - Glycocalyx: *Streptococcus mutans*
  - Fimbriae: *Escherichia coli*
  - M protein: *Streptococcus pyogenes*
- Form **biofilms**

Figure 15.1a Adherence.



(a) Surface molecules on a pathogen, called adhesins or ligands, bind specifically to complementary surface receptors on cells of certain host tissues.

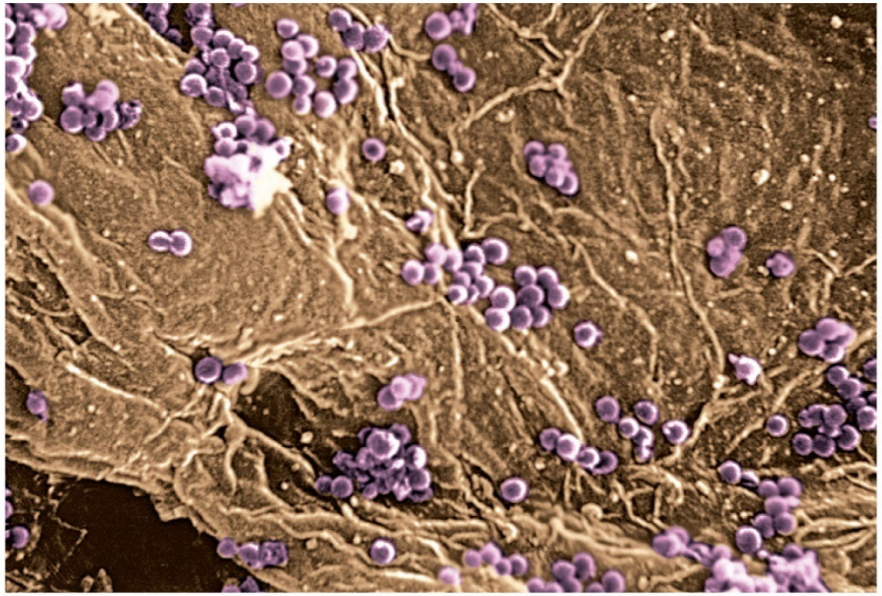
Figure 15.1b-c Adherence.



(b) *E. coli* bacteria (yellow-green) on human urinary bladder cells

SEM

1 μm



(c) Bacteria (purple) adhering to human skin

SEM

9 μm

How Bacterial pathogens penetrate host defenses

Capsules: related to virulence

- Prevent phagocytosis
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Bacillus anthracis*

Cell Wall Components

- **M protein** resists phagocytosis
  - *Streptococcus pyogenes*
- **Opa (opaque) protein** inhibits immune cells of body
  - *Neisseria gonorrhoeae* has many variety of *opa* gene
- **Mycolic acid** (waxy lipid) resists digestion
  - *Mycobacterium tuberculosis*

Enzymes

- **Coagulase**: coagulates fibrinogen
- **Kinases**: digest fibrin clots eg. Streptokinase
- **Hyaluronidase**: hydrolyzes hyaluronic acid eg. *Clostridium* species.
- **Collagenase**: hydrolyzes collagen eg. *Clostridium* species.
- **IgA proteases**: destroy IgA antibodies eg *Neisseria* species.

Antigenic variation: ***opa*** **gene of** ***Neisseria*****, surface antigen of** ***Trypanosoma*****, influenza virus**

Lecture 33

BT 206

28 April 2023

Chapter 15, unnumbered figure C, p. 434.

Mechanism of streptokinase

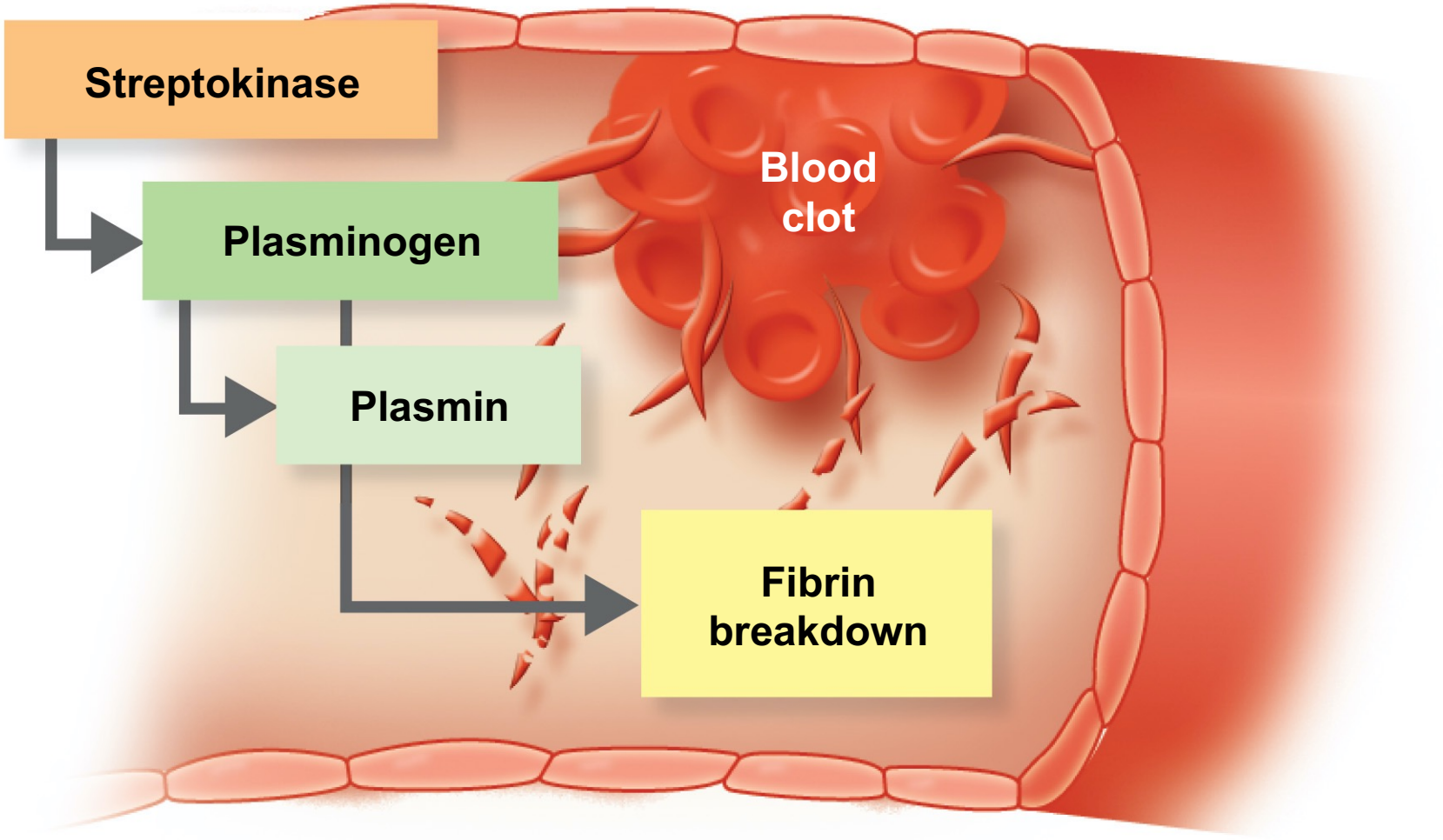
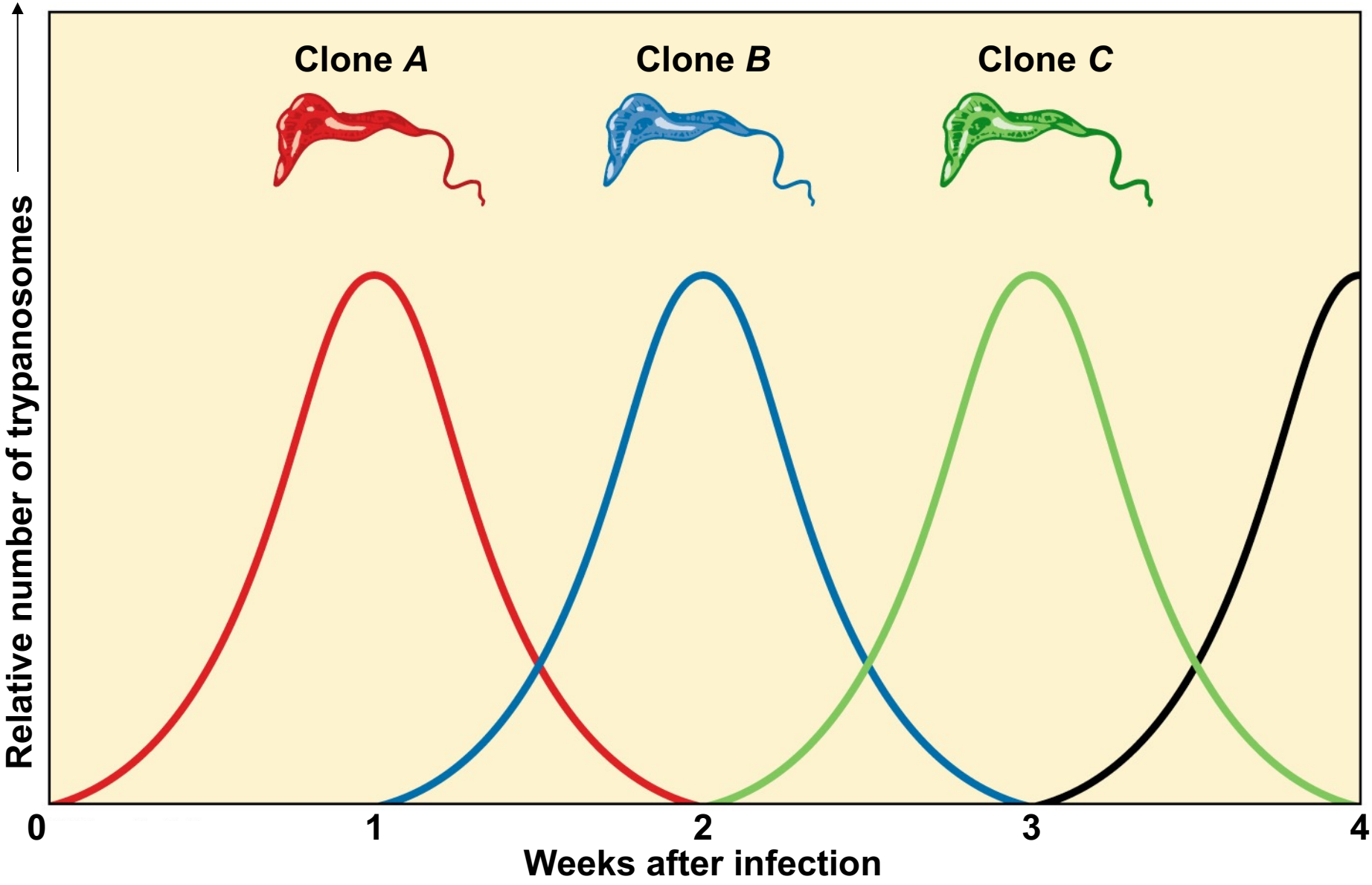


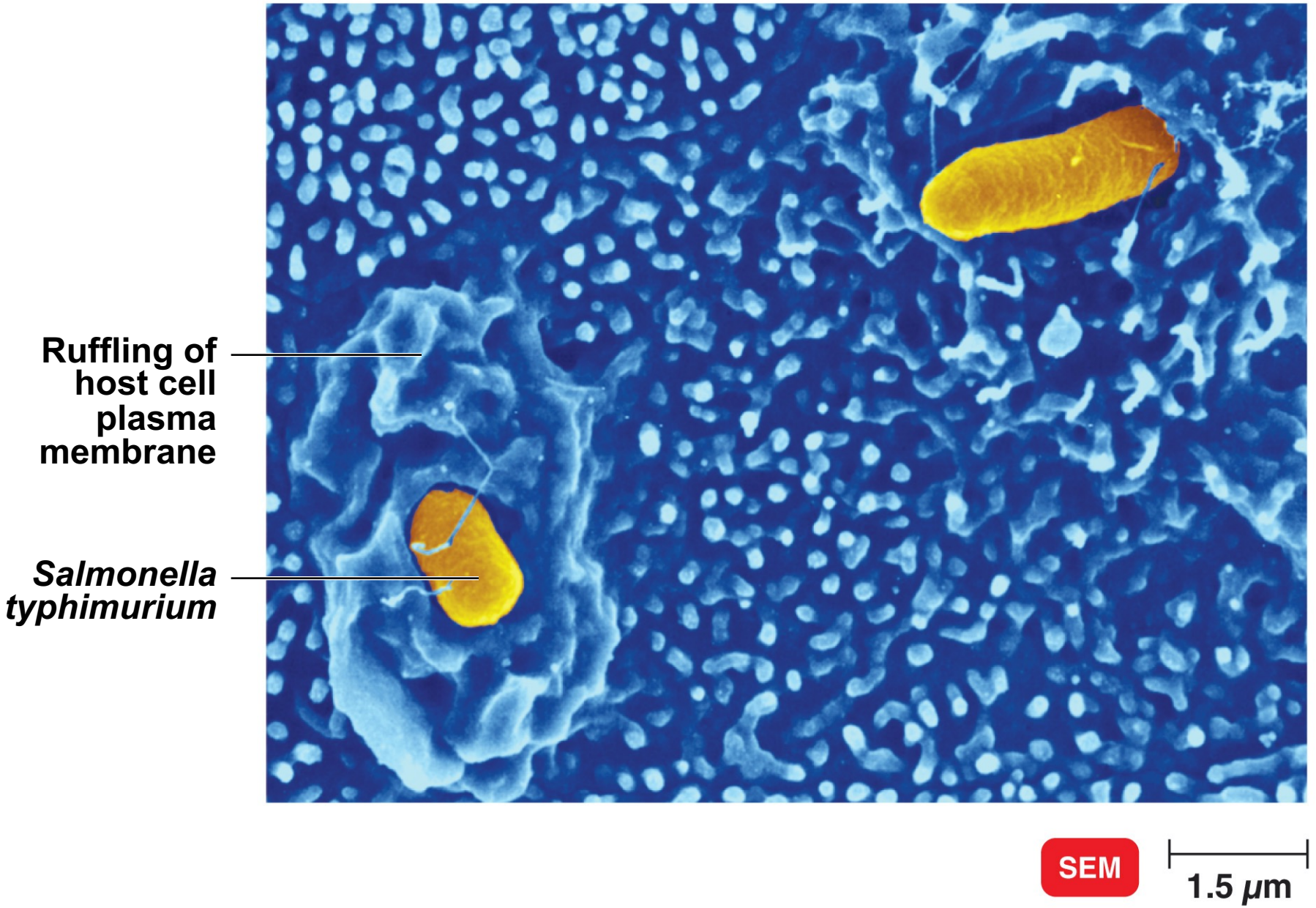
Figure 22.16 How trypanosomes evade the immune system.



Penetration into the Host Cell Cytoskeleton

- **Invasins**
  - *Salmonella* alters host actin to enter a host cell
- Use actin to move from one cell to the next
  - *Listeria*

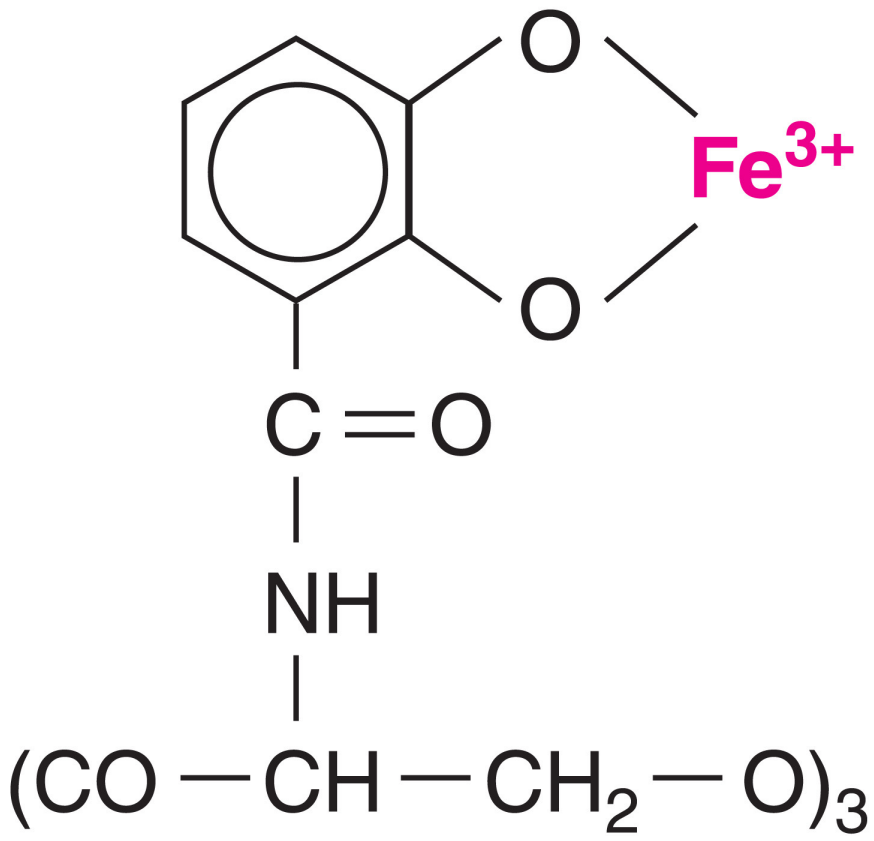
Figure 15.2 *Salmonella* entering intestinal epithelial cells as a result of ruffling.



How Bacterial pathogens damage host cells

- Using host nutrients
- Causing direct damage
- Producing toxins
- Inducing hypersensitivity: immune response

Figure 15.3 Structure of enterobactin, one type of bacterial siderophore.



Direct Damage

- Disrupt host cell function
- Produce waste products
- Toxins

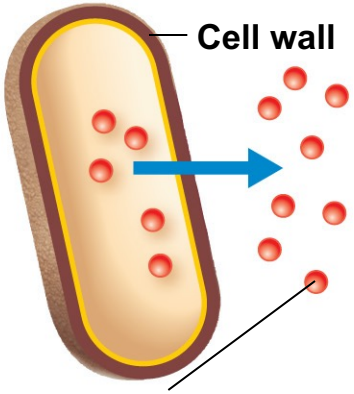
The Production of Toxins

- **Toxin**: substance that contributes to pathogenicity
- **Toxigenicity**: ability to produce a toxin
- **Toxemia**: presence of toxin in the host's blood
- **Toxoid**: inactivated toxin used in a vaccine
- **Antitoxin**: antibodies against a specific toxin

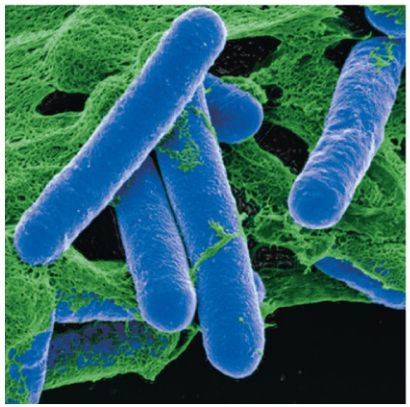
Figure 15.4 Mechanisms of Exotoxins and Endotoxins.

exotoxins

Exotoxins are proteins produced inside pathogenic bacteria, most commonly gram-positive bacteria, as part of their growth and metabolism. The exotoxins are then secreted into the surrounding medium during log phase.



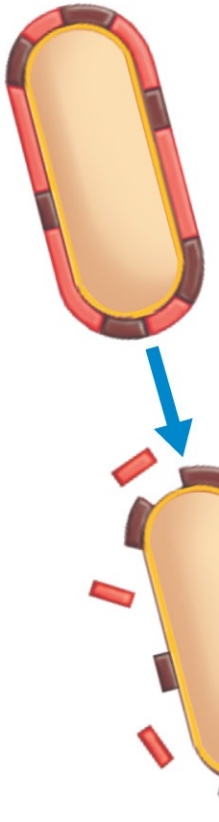
Exotoxin: toxic substances released outside the cell

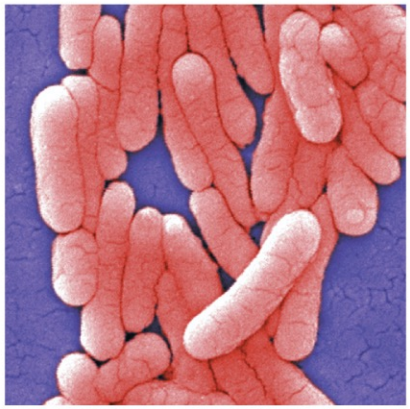


Clostridium botulinum, an example of a gram-positive bacterium that produces exotoxins

endotoxins

Endotoxins are the lipid portions of lipopolysaccharides (LPS) that are part of the outer membrane of the cell wall of gram-negative bacteria. The endotoxins are liberated when the bacteria die and the cell wall breaks apart.





Salmonella typhimurium, an example of a gram-negative bacterium that produces endotoxins

Endotoxins: toxins composed of lipids that are part of the cell membrane

Exotoxins

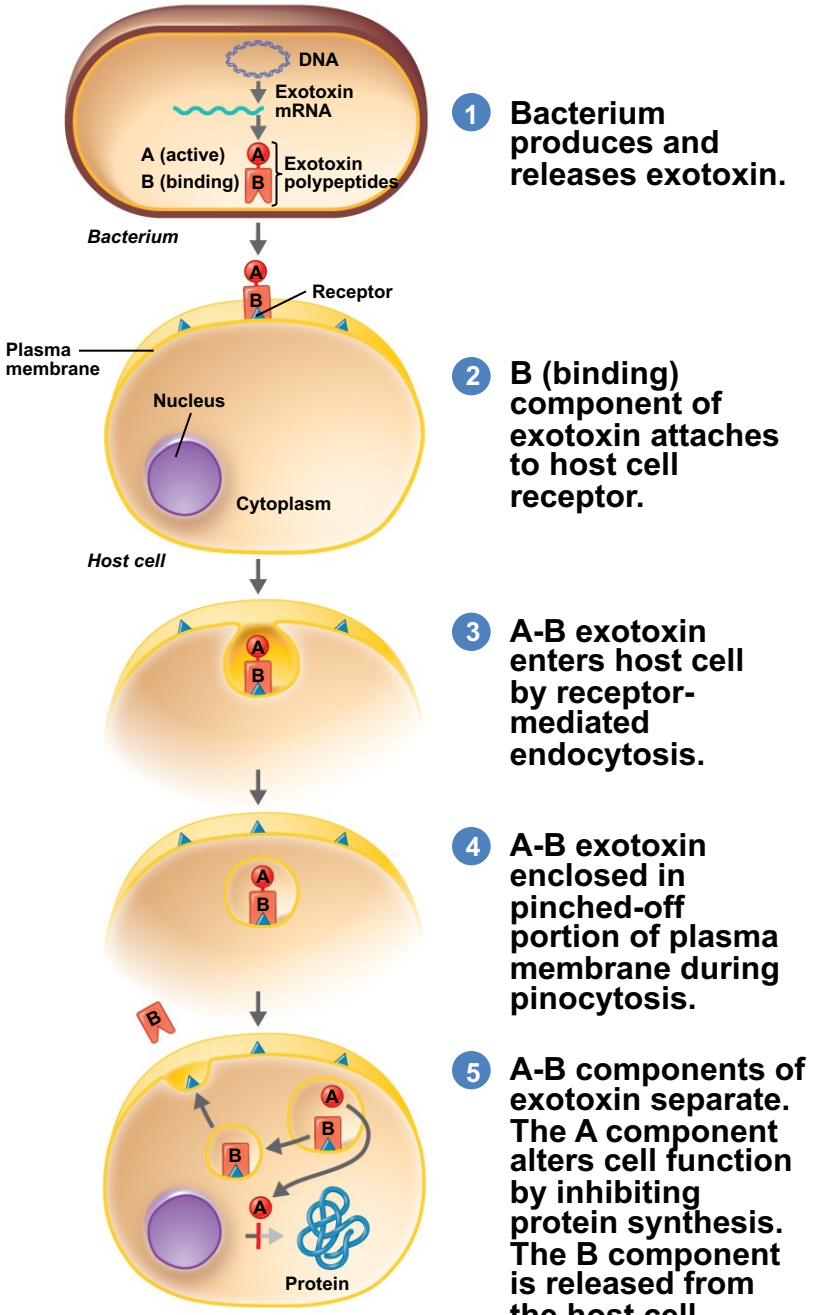
- Specific for a structure or function in host cell
- Three types of exotoxins:

a. **A-B toxins**: Example. botulinum and tetanus toxin.

b. **Membrane disrupting toxins**. Example. leukocidins, hemolysins.

c. **Superantigens**: Staphylococcus enterotoxins

Figure 15.5 The action of an A-B exotoxin.



Membrane-Disrupting Toxins

- Lyse host's cells by
  - Making protein channels in the plasma membrane
    - **Leukocidins**
    - **Hemolysins**
    - **Streptolysins**
  - Disrupting phospholipid bilayer

Superantigens

- Cause an **intense immune response** due to release of **cytokines** from host cells
- Symptoms: fever, nausea, vomiting, diarrhea, shock, and death

Exotoxin

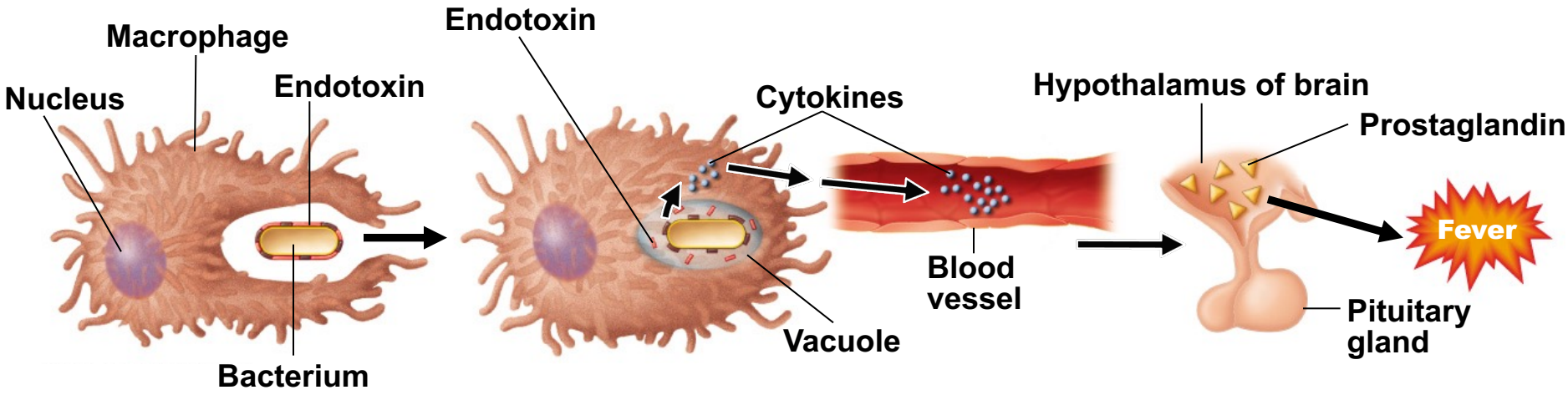
Source	Mostly gram-positive
Relation to microbe	By-products of growing cell
Chemistry	Protein
Fever?	No
Neutralized by antitoxin?	Yes
LD_{50}	Small

Endotoxins:

is part of outer membrane portion of cell wall of gram negative bacteria or Lipopolysaccharide component (LPS)

Source	Gram-negative
Relation to Microbe	Outer membrane
Chemistry	Lipid A
Fever?	Yes
Neutralized by Antitoxin?	No
LD_{50}	Relatively large

Figure 15.6 Endotoxins and the pyrogenic response.



1. A macrophage ingests a gram-negative bacterium.
2. The bacterium is degraded in a vacuole, releasing endotoxins that induce the macrophage to produce cytokines IL-1 and TNF-α.
3. The cytokines are released into the bloodstream by the macrophages, through which they travel to the hypothalamus of the brain.
4. The cytokines induce the hypothalamus to produce prostaglandins, which reset the body's "thermostat" to a higher temperature, producing fever.

LAL Assay

- **Limulus amebocyte lysate assay**
- Amebocyte lysis produces a clot
- Endotoxin causes lysis

Pathogenic properties of virus

- Viruses have mechanism to evade host defences as viruses grow inside host cell
- Kill immune cells eg. HIV –Th cells
- Cytopathic effects: The visible effects of viral infection on host cell.
- Viruses stop DNA, RNA and/ or protein synthesis eg Herpes block mitosis.
- Lysosomal autolysis of host cells eg. Influenza: bronchiolar epithelium
- Production of inclusion bodies (visible viral parts inside the cell) can identify a particular virus eg. Rabies virus: Negri bodies
- Syncytium formation (Neighbouring cells fuse together) eg. Varicella Zoster virus.
- Change in cell function eg. Measles, production of interferons by host cell (triggers host immune response), induces antigenic changes on host cell surface (triggers destruction of infected cell by host immune response.

Figure 15.7 Some cytopathic effects of viruses.

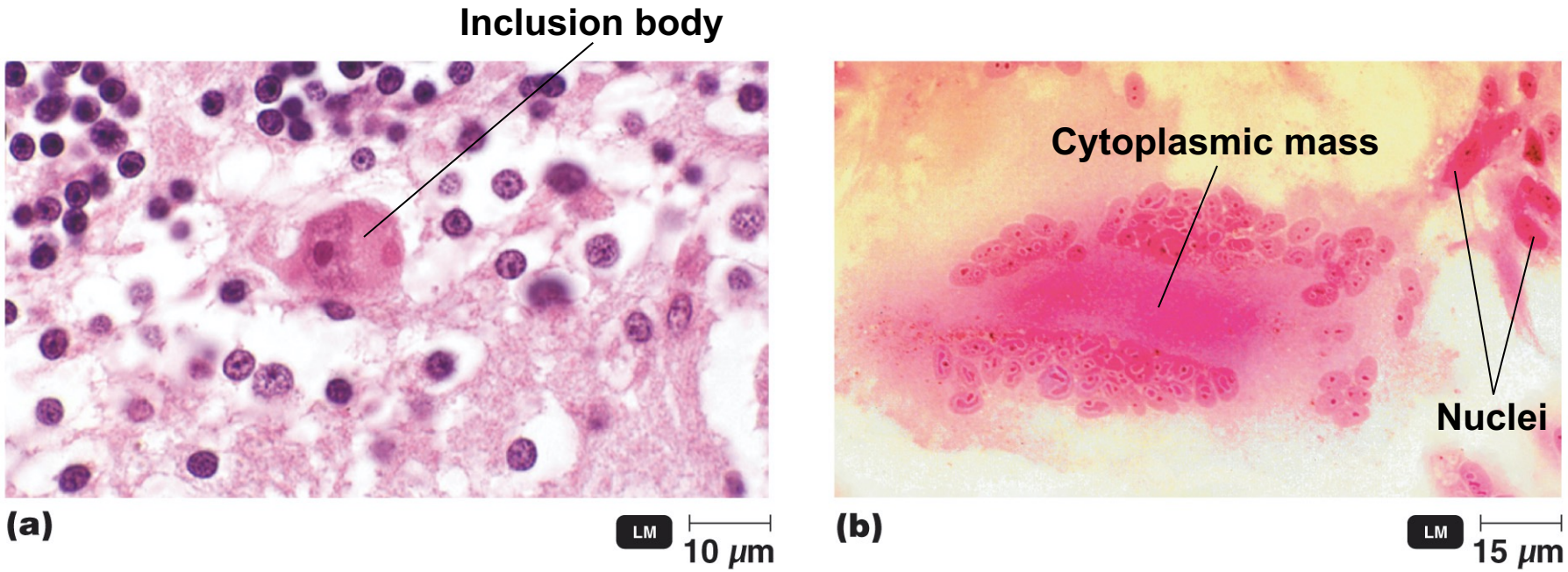
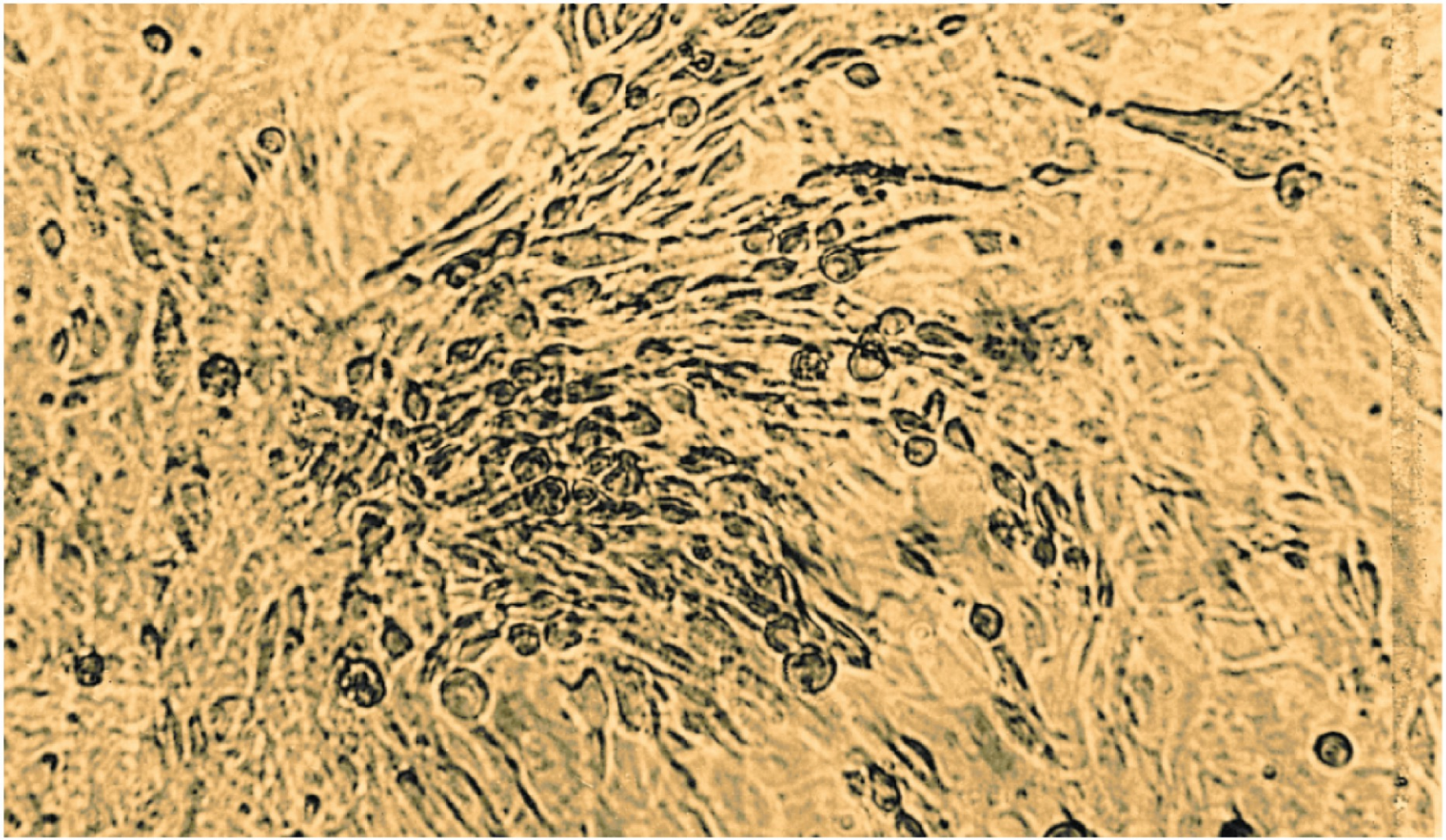


Figure 15.8 Transformed cells in culture.



Pathogenic Properties of Fungi

- Fungal waste products may cause symptoms
- Chronic infections provoke an allergic response
- Trichothecene toxins inhibit protein synthesis
  - *Fusarium*
- Proteases
  - *Candida, Trichophyton*
- Capsule prevents phagocytosis
  - *Cryptococcus*

Pathogenic Properties of Fungi

- **Ergot toxin**
  - *Claviceps*
- **Aflatoxin**
  - *Aspergillus*
- **Mycotoxins**
  - Neurotoxins: **phalloidin**, **amanitin**
    - *Amanita*

Pathogenic Properties of Protozoa

- Presence of protozoa
- Protozoan waste products may cause symptoms
- Avoid host defenses by
  - Growing in phagocytes
  - Antigenic variation

Pathogenic Properties of Helminths

- Use host tissue
- Presence of parasite interferes with host function
- Parasite's metabolic waste can cause symptoms

Pathogenic Properties of Algae

- Paralytic shellfish poisoning
  - Dinoflagellates
  - **Saxitoxin**

Portals of Exit

- Respiratory tract
  - Coughing and sneezing
- Gastrointestinal tract
  - Feces and saliva
- Genitourinary tract
  - Urine and vaginal secretions
- Skin
- Blood
  - Arthropods that bite; needles or syringes