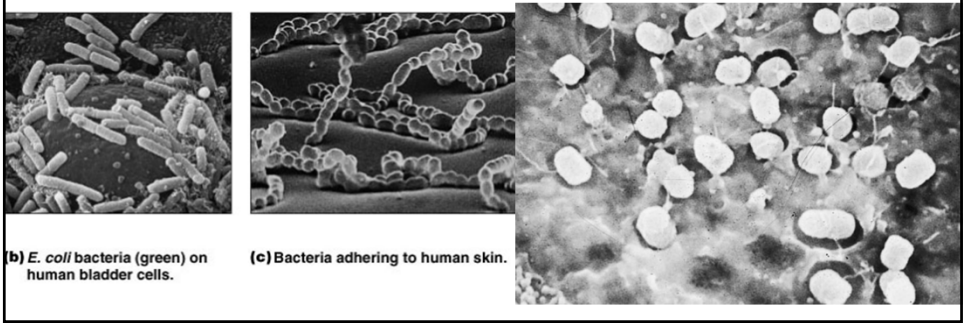
Ch. 15 OBJECTIVES:

Students should be able to ……

1. **Ch. 15:** **** Describe **Portals of Entry and Exit** for pathogens and give two examples of how entry through each portal is accomplished.
2. Describe and give examples of **4** different types of adhesion factors (**adhesins**), and the host target **receptors**, that pathogens use.
3. Diagram and compare the toxic mechanisms and effects of **Exotoxins** and **Endotoxins**. Provide **specific examples**.
4. **** Define, describe the mechanisms, and **give specific examples of at least 6 different types of Virulence factors** and how they enhance the severity of disease caused by the microorganisms that produce them.
5. **** Compare and contrast how Eukaryotic pathogens – Fungi, Protistans, Helminths – **damage** the host.

❖ ***Objectives & SGQ's are your HOMEWORK each week!!!***

Chapter 15
Microbial Mechanisms of Pathogenicity



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

(c) Bacteria adhering to human skin.

Microbial Mechanisms of Pathogenicity

- **Pathogenicity** = the ability to cause disease.
- **Virulence** = the extent of pathogenicity.
- **Opportunistic Pathogen** = microbe that does not normally cause disease, but can if the host is compromised or it reaches tissues it usually does not occupy.

- **Virulence Factors:** Promote infection, invasion, and/or survival of the pathogen inside the host organism. Eg:
  1) **Adhesins**
  2) **Invasins**
  3) **Colonization factors**
  4) **Nutrient acquisition factors**
  5) **Camouflage** & other **Immune Avoidance** factors
  6) **Toxins** – ***exotoxins***, ***endotoxins***
  7) ***** [**Many are **Enzymes**!– includes: invasins, toxins, camouflage…..**]**

15.1) Portals of Entry

1. **Mucous membranes**
   - many!
2. **Skin**
3. ***Parenteral*** route
   - entry into deeper tissues by unnatural means (puncture, trauma, bite, etc.)

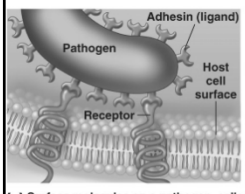
Numbers of Invading Microbes

- **ID_{50}:** Infectious dose for 50% of the test population.
- **LD_{50}:** Lethal dose (of a toxin or pathogen) for 50% of the test population.

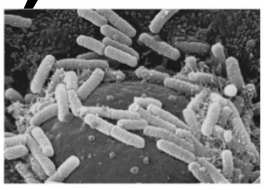
e.g.: Bacillus anthracis

Portal of entry	**ID_{50}**
Skin	10-50 endospores **!!!!!!**
Inhalation	10,000-20,000 endospores
Ingestion	250,000-1,000,000 endospores

15.2) Adherence

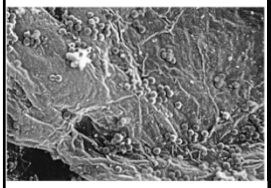


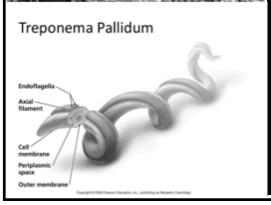
(a) Surface molecules on a pathogen, called adhesins or ligands, bind specifically to complementary surface receptors on cells of certain host tissues.



(b) *E. coli* bacteria (yellow-green) on human urinary bladder cells. SEM 1 μm

*** A major theme in pathogenesis (and in symbiosis!) is ***CoEvolution!*** .....



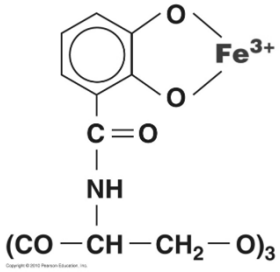


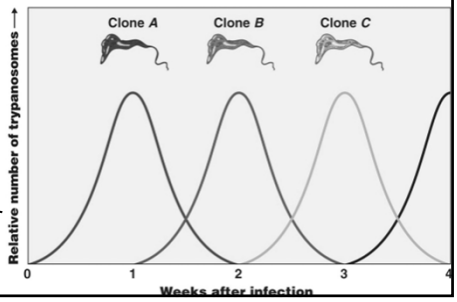
- ***Adhesins/ligands*** bind to receptors on host cells *(=1 type of "virulence factor"!)*:
  - **Glycocalyx =** ***Streptococcus mutans***
  - **Fimbriae =** ***Escherichia coli***
  - **M protein =** ***Streptococcus pyogenes***
  - **Opa protein =** *Neisseria gonorrhoeae*
  - **Tapered end =** *Treponema pallidum (syphilis)*
- Form ***biofilms***

opa = opacity

More Virulence Factors:
Enzymes, Invasins, Nutrient acquisition, Immune Avoidance

1. **Coagulase** = Coagulate blood
2. **Kinases** = Digest fibrin clots
3. **Hyaluronidase** = Hydrolyses hyaluronic acid
4. **Collagenase** = Hydrolyzes collagen
5. **IgA proteases** = Destroy IgA antibodies
6. **<u>Siderophores</u>** = Take iron from host iron-binding proteins
7. **Antigenic Variation/Shift** = Alter surface proteins (eg: African Sleeping Sickness)



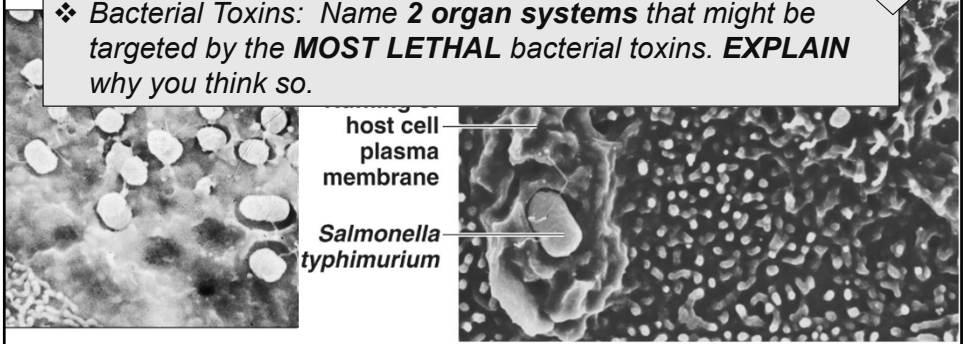


Penetration into the Host Cell: <u>Invasins</u>, Membrane Ruffling

BB

<u>CLASS JOURNAL QUESTION (Blue Book):</u>

- *Bacterial Toxins: Name **2 organ systems** that might be targeted by the **MOST LETHAL** bacterial toxins. **EXPLAIN** why you think so.*



Salmonella enterica, sv. typhimurium

Figure 15.2

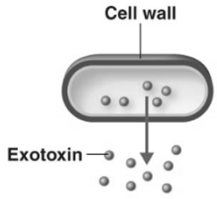
<u>http://www.med.yale.edu/micropath/galan/Pages/galan_movies.html</u>

15.3) Toxins

1. ***Toxin*** = Substances that contribute to pathogenicity and are deadly to the host or host cells
2. ***Toxigenicity*** = Ability to produce a toxin
3. ***Toxemia*** = Presence of toxin the host's blood
4. ***Toxoid*** = Inactivated toxin used in a vaccine
5. ***Antitoxin*** = Antibodies against a specific toxin

Exotoxin	**LD_{50}**
Botulinum	0.03 ng/kg
Shiga toxin	250 ng/kg
Staphylococcal enterotoxin	1350 ng/kg

A. Exotoxin



Source	**Mostly Gram +**
Metabolic product	By-products of growing cell
Chemistry	**Protein**
Fever?	No
Neutralized by antitoxin	Yes
LD_{50}	**Small**

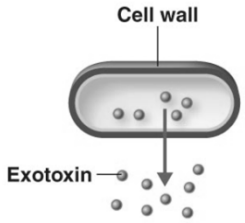
http://highered.mcgraw-hill.com/sites/0072556781/student_view0/chapter34/animation_quiz.html

http://www.sumanasinc.com/webcontent/anisamples/microbiology/diphtheria.html

Exotoxins

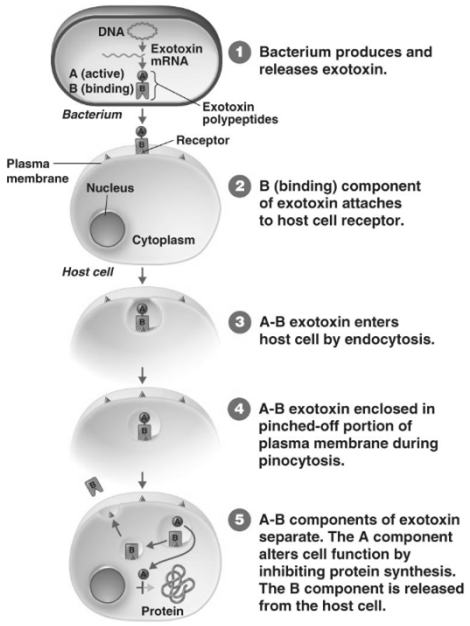
Figure 15.5

1. **A-B toxins** or *type III toxins*



(a) Exotoxins are proteins produced inside pathogenic bacteria, most commonly gram-positive bacteria, as part of their growth and metabolism. The exotoxins are then secreted or released into the surrounding medium following lysis.

Figure 15.4a



Exotoxins

2. **Superantigens** or *type I toxins*
   - ***Nonspecifically hyperstimulate T-Cell Receptors!!!!!***
   - Cause an intense immune response due to release of cytokines from host cells
   - Fever, nausea, vomiting, diarrhea, shock, death

3. **Membrane-disrupting toxins** or *type II toxins*
   - Lyse host's cells by:
     - Making protein channels in the plasma membrane (e.g., leukocidins, hemolysins)
     - Disrupting phospholipid bilayer

Exotoxins

	Exotoxin	Lysogenic conversion
• ***Corynebacterium diphtheriae***	A-B toxin. Inhibits protein synthesis.	+
• ***Streptococcus pyogenes***	Membrane-disrupting. Erythrogenic.	+
• ***Clostridium botulinum***	A-B toxin. Neurotoxin	+
• ***Clostridium tetani***	A-B toxin. Neurotoxin	--
• ***Vibrio cholerae***	A-B toxin. Enterotoxin	+
• ***Staphylococcus aureus***	Superantigen. Enterotoxin.	+

Table 15.2 Diseases Caused by Exotoxins

Disease	Bacterium	Type of Exotoxin	Mechanism
Botulism	*Clostridium botulinum*	A-B	Neurotoxin prevents the transmission of nerve impulses; flaccid paralysis results.
Tetanus	*Clostridium tetani*	A-B	Neurotoxin blocks nerve impulses to muscle relaxation pathway; results in uncontrollable muscle contractions.
Diphtheria	*Corynebacterium diphtheriae*	A-B	Cytotoxin inhibits protein synthesis, especially in nerve, heart, and kidney cells.
Scalded skin syndrome	*Staphylococcus aureus*	A-B	One exotoxin causes skin layers to separate and slough off (scalded skin).
Cholera	*Vibrio cholerae*	A-B	Enterotoxin causes secretion of large amounts of fluids and electrolytes that result in diarrhea.
Traveler's diarrhea	Enterotoxigenic *Escherichia coli* and *Shigella* spp.	A-B	Enterotoxin causes secretion of large amounts of fluids and electrolytes that result in diarrhea.
Anthrax	*Bacillus anthracis*	A-B	Two A components enter the cell via the same B. The A proteins cause shock and reduce the immune response.
Gas gangrene and food poisoning	*Clostridium perfringens* and other species of *Clostridium*	Membrane-disrupting	One exotoxin (cytotoxin) causes massive red blood cell destruction (hemolysis); another exotoxin (enterotoxin) is related to food poisoning and causes diarrhea.
Antibiotic-associated diarrhea	*Clostridium difficile*	Membrane-disrupting	Enterotoxin causes secretion of fluids and electrolytes that results in diarrhea; cytotoxin disrupts host cytoskeleton.
Food poisoning	*Staphylococcus aureus*	Superantigen	Enterotoxin causes secretion of fluids and electrolytes that results in diarrhea.
Toxic shock syndrome (TSS)	*Staphylococcus aureus*	Superantigen	Toxin causes secretion of fluids and electrolytes from capillaries that decreases blood volume and lowers blood pressure.

Table 15.2

B. Endotoxin

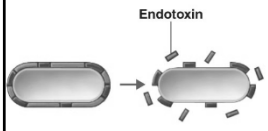


Figure 15.4b

(b) Endotoxins are the lipid portions of lipopolysaccharides (LPSs) that are part of the outer membrane of the cell wall of gram-negative bacteria (lipid A; see Figure 4.13c). The endotoxins are liberated when the bacteria die and the cell wall breaks apart.

Endotoxins → Pyrogenic

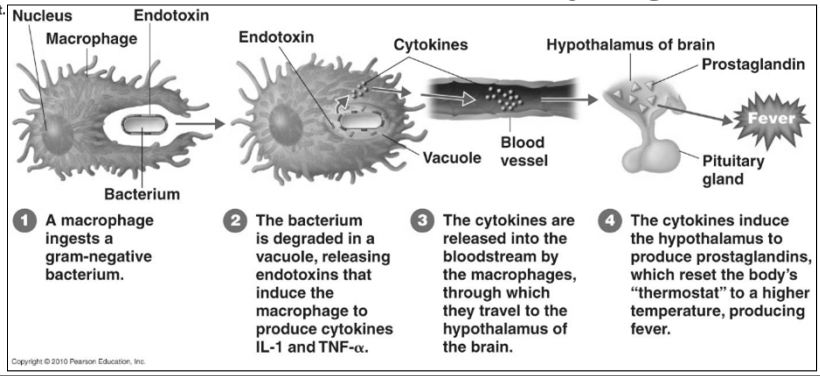
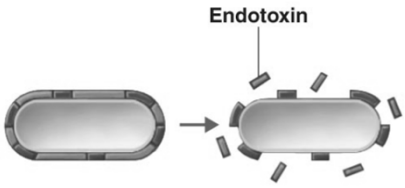


Figure 15.6

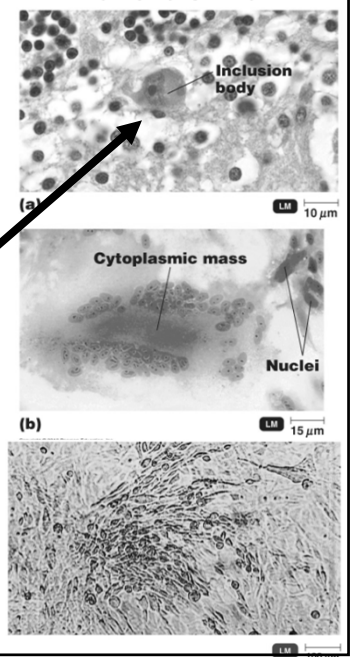
Endotoxins

	
Source	**Gram–**
Metabolic product	Present in LPS of outer membrane (Lipid A)
Chemistry	**Lipid**
Fever?	Yes
Neutralized by antitoxin	No
LD_{50}	**Relatively large**

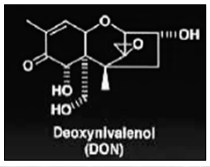
15.4) Cytopathic Effects of Viruses

Table 15.4

Table 15.4	Cytopathic Effects of Selected Viruses
Virus (Genus)	**Cytopathic Effect**
Poliovirus (*Enterovirus*)	Cytocidal (cell death)
Papovavirus (family Papovaviridae)	Acidophilic inclusion bodies in nucleus
Adenovirus (*Mastadenovirus*)	Basophilic inclusion bodies in nucleus
Rhabdovirus (family Rhabdoviridae)	Acidophilic inclusion bodies in cytoplasm
Cytomegalovirus	Acidophilic inclusion bodies in nucleus and cytoplasm
Measles virus (*Morbillivirus*)	Cell fusion
Polyomavirus	Transformation
HIV (*Lentivirus*)	Destruction of T cells



15.5) Pathogenic Properties of Fungi



1. Fungal waste products may cause symptoms

2. Chronic infections provoke an **allergic response**

3. Tichothecene toxins inhibit protein synthesis
- *Fusarium* – grows on grains
  - headaches, chills, nausea, vision loss

4. Proteases
- *Candida albicans, Trichophyton*
  - allow attachment to host PM, skin infections

5. Capsule prevents phagocytosis
- *Cryptococcus neoformans* – meningitis

6. Ergot toxin
- *Claviceps purpurea* – hallucinations/LSD, gangrene

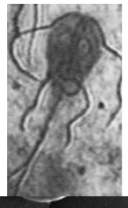
Barley

Pathogenic Properties of Fungi

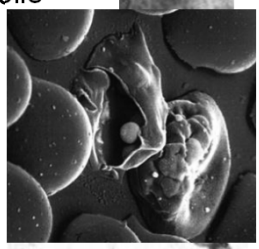
7. **Aflatoxin**
   - *Aspergillus flavus*
     - grain/peanut mold
     - carcinogenic mutagen – PB recalls!

8. **Mycotoxins –** mushrooms/toadstools
   - Neurotoxins: Phalloidin, Amanitin
     - *Amanita phalloides (death angel/ Death Cap)* –
       - Deadly by ingestion;
       - Phall. binds F-actin

15.6) Pathogenic Properties of Protozoa

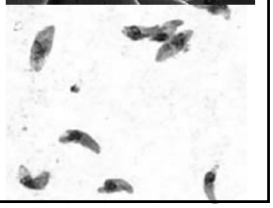


1. Presence of protozoa – irritant!?
- ***Giardia*** – attaches and digests cells & fluids
- ***Plasmodium*** – intracellular, ruptures cells



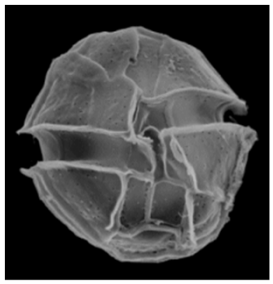
2. Protozoan waste products may cause symptoms

3. Avoid host defenses by
   - **a) Growing in phagocytes**
     - ***Toxoplasma***
       - prevents acidif'n, digest'n (no lysozome)
   - **b) Antigenic variation**

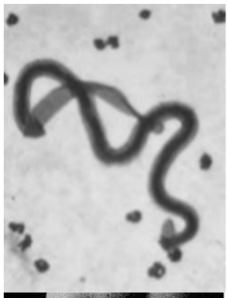


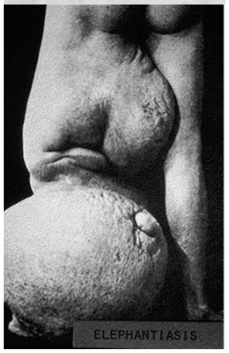
15.7) Pathogenic Properties of Algae

- Neurotoxins produced by dinoflagellates *(~Alexandrium)*
  - ***Saxitoxin***
    - eaten by mollusks → humans
    - **Paralytic shellfish poisoning**
      - Similar to botulism!!!
      - Don't eat during Red Tides!!!



15.8) Pathogenic Properties of Helminths





- Use host tissue – attach & feed on
  - → damage
- Presence of parasite interferes with host function
  - blockage, weakness of tissue
  - ***Wuchereria bancrofti*** (nematode)
    - **Elephantiasis** – blocks lymphatic circulation; wastes….
- Parasite's metabolic waste can cause symptoms

15.9) Portals of Exit
(often same as the portal of entry!)

1. **Respiratory tract**
   - Coughing, sneezing
2. **Gastrointestinal tract**
   - Feces, saliva
3. **Genitourinary tract**
   - Urine, vaginal secretions
4. **Skin**
5. **Blood**
   - Biting arthropods, needles/syringes

- → wait on ***FOMITES***….

Mechanisms of Pathogenicity (Review)

Figure 15.9