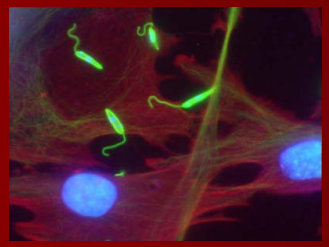
Bacterial Pathogenesis



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To cause disease, an organism must:

1. Maintain a reservoir before and after infection (humans, animals, environment, etc.),
2. Leave the reservoir and gain access to the new host.
3. Colonize the body.
4. Harm the body.

Pathogenicity and Virulence

Pathogenicity and virulence are terms that refer to an organism's ability to cause disease.

- **Pathogenicity** is used with respect to differences between microbial species whereas
- **Virulence** denotes differences between strains of the same species. In practice they are often used interchangeably.

Host-Parasite relationship

- Host specific or broad range
  - *Streptococcus equi, Brachyspira hyodysenteriae, Pythium insidiosum* , Yersinia pestis, Coccidioides immitis
  - *B. pilosicoli, Salmonella spp.*
- Tissue specific in the same host
  - *E. coli* : commensal in intestine → active pathogen in urinary tract, peritoneal cavity.

How commensal parasite convert into active pathogen?

- Transfer to new host or tissue
- A change in host resistance

Evolution of Pathogenic Concent

Commensalism

Most stable form of parasitic existence

Parasitism

Active disease → Active immune → Killing host

Milder strain of pathogen

- Best pathogen and best for ancestor
- Chronic infection (eg. tuberculosis, syphilis)
- Longer survive in host
- Favors a resistant host

Unsatisfied ideal of Koch's postulates

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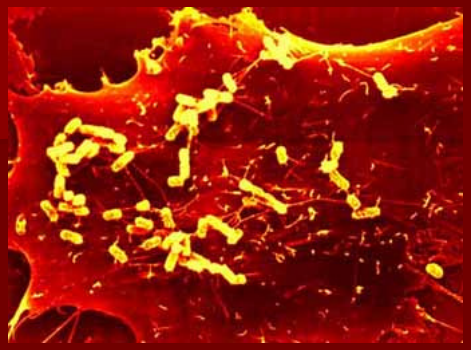


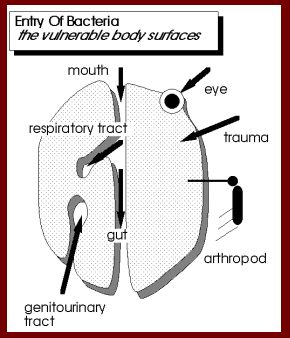
Infection is distinguished from disease, a morbid process that does not necessarily involve infection

Type of Bacterial Infection

Type of Infection	Description	Examples
Inapparent (subclinical)	No detectable clinical symptoms of infection	Asymptomic gonorrhea in women and men
Dormant (latent)	Carrier state	Typhoid carrier
Accidental	Zoonosis or environmental or inadvertent exposures	Anthrax, cryptococcal infection, and laboratory exposure, respectively
Opportunistic	Infection caused by normal flora or transient bacteria when normal host defenses are compromised	*Serratl* or *Candida* infection of the genitourinary tract
Primary	Clinically apparent (e.g., invasion and multiplication of microbes in body tissues, causing local tissue injury)	*Shigella* dysentery
Secondary	Microbial invasion subsequent to primary infection	Bacterial pneumonia following viral lung infection
Mixed	Two or more microbes infecting the same tissue	Anaerobic abscess (*E coli* and *Bacteroides fragilis*)
Acute	Rapid onset (hours or days); brief duration (days or weeks)	Diphtheria
Chronic	Prolonged duration (months or years)	Mycobacterial diseases (tuberculosis and leprosy)
Localized	Confined to a small area or to an organ	Staphylococcal boil
Generalized	Disseminated to many body regions (gonococcemia)	Gram-negative bacteremia
Pyogenic	Pus-forming	Staphyloccal and streptococcal infection
Retrograde	Microbes ascending in a duct or tube against the flow of secretions or excretions	*E coli* urinary tract infection
Fulminant	Infections that occur suddenly and intensely	Airborne *Yersinia pestis* (pneumonic plague)

How Bacteria Cause Disease

Stages in Microbial Infection
- Attachment to and/or entry into the body
- Local or general spread in the body
- Multiplication
- Evasion of host defenses
- Shedding (exit) from the body
- Damage to the host



Pathogenic Mechanisms

- Host Susceptibility and Resistance
- Host-Mediated Pathogenesis
- Bacterial Infectivity
  - Genetic and Molecular Basis for Virulence

Host Susceptibility

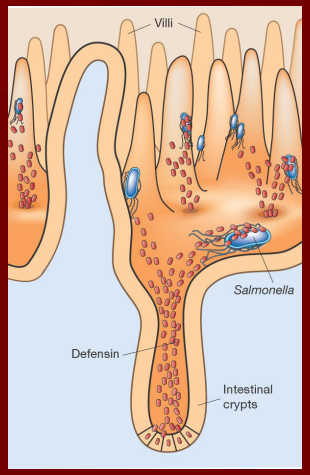
Initial resistance: physiologic and immunologic condition of the host

Susceptibility:eery young, very old and in immunosuppressed patients.

Virulence of the bacteria

Host Resistance

Physical and chemical attributes
- **antibacterial factors in secretions covering mucosal surfaces lysozyme, lactoferrin, lactoperoxidase, IgA**
- **rapid rate of replacement of skin and mucosal epithelial cells**
- **"nonspecific" mechanisms of host resistance**
- **effective specific immunity**

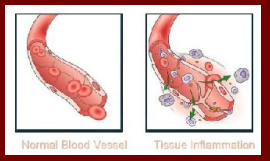


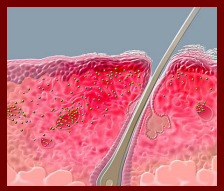
Ability of the organism to cause disease despite host resistance mechanisms

- The number of infecting bacteria
- Route of entry into the body
- Virulence factors of the bacterium

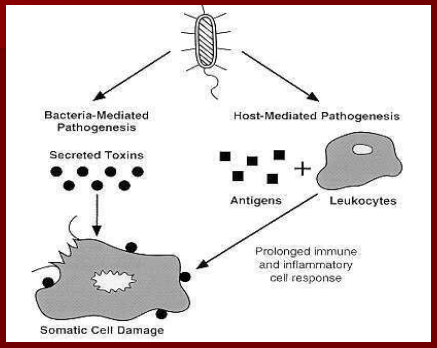
Host-Mediated Pathogenesis

- Tissue damage results from the toxic mediators released by lymphoid cells rather than from bacterial toxins eg. TB, HP





Host-Mediated Pathogenesis



Generalized mechanisms of bacterial pathogenesis: bacteria-induced toxicity or host-mediated damage.

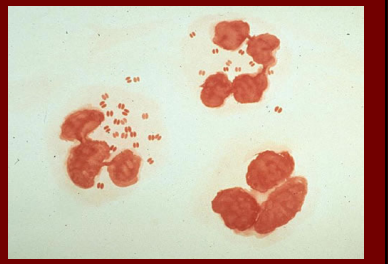
Bacterial Infectivity

- Bacterial infectivity results from a disturbance in the balance between bacterial virulence and host resistance.

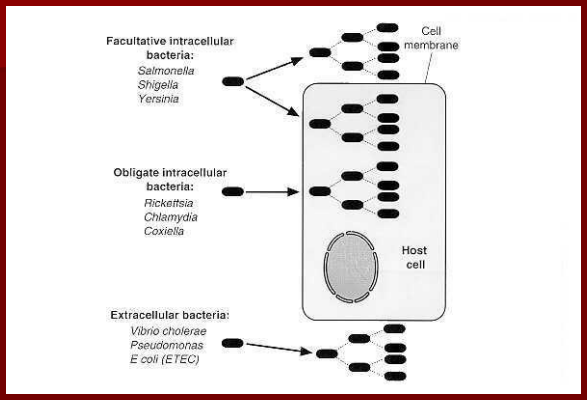
The "objective" of bacteria is to multiply rather than to cause disease; it is in the best interest of the bacteria not to kill the host

Intracellular Growth

- Some bacteria can grow only within eukaryotic cells, whereas others (e.g., *Salmonella* species) invade cells but do not require them for growth. Most pathogenic bacteria multiply in tissue fluids and not in host cells.



Intracellular Growth



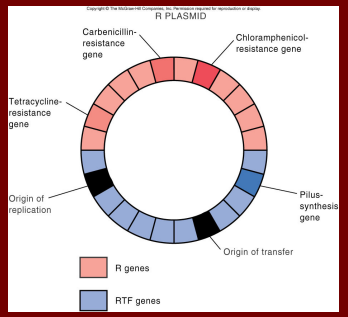
Examples of pathogenic bacteria, indicating their preferred growth phase within the host. (ETEC:enterotoxigenic *E coli*)

TABLE 7-3 Intracellular or Extracellular Growth Preference Relative to Eukaryotic Cells

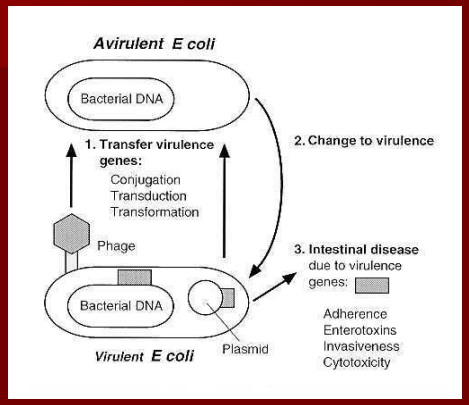
Category	Bacterial Pathogen
Obligate intracellular	*Rickettsia* spp *Coxiella burnetii* *Chlamydia* spp
Facultative intracellular	*Salmonella* spp *Shigella* spp *Legionella pneumophila* Invasive *Escherichia coli* *Neisseria* spp *Mycobacterium* spp *Listeria monocytogenes* *Bordetella pertussis*
Predominantly extracellular	*Mycoplasma* spp *Pseudomonas aeruginosa* Enterotoxigenic *Escherichia coli* *Vibrio cholerae* *Staphylococcus aureus* *Streptococcus pyogenes* *Haemophilus influenzae* *Bacillus anthracis*

Genetic and Molecular Basis for Virulence

- Bacterial virulence factors may be encoded on chromosomal, plasmid, transposon, or temperate bacteriophage DNA; virulence factor genes on transposons or temperate. Bacteriophage DNA may integrate into the bacterial chromosome.



Genetic and Molecular Basis for Virulence



Mechanisms of acquiring bacterial virulence genes.

TABLE 7-2 Genetic Basis for Virulence of Selected Bacterial Pathogens

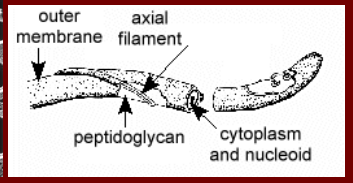
Gene(s) Encoded on	Bacterial Pathogen	Virulence Factor
Chromosome	*Vibrio cholerae*	Enterotoxin
	Salmonella typhimurium	Enterotoxin, invasion factors
	Shigella spp	Enterotoxin,invasion factors
	Aeromonas hydrophila	Enterotoxin, aerolysin
	Pseudomonas aeruginosa	Exotoxin A
	Staphylococcus aureus	Enterotoxin B
	Yersinia enterocolitica	Invasion factors
	Yersinia pseudotuberculosis	Invasion factors
	Escherichia coli	Enterotoxin (LTII)
Plasmid	*Shigella* spp	Invasion factors
	Escherichia coli	Invasion factors, colonization factor, and enterotoxin (LTI)
	Staphylococcus aureus	Exfoliative toxin
	Bacillus anthracis	Anthrax toxin
Bacteriophage	*Corynebacterium diphtheriae*	Diphtheria toxin
	Streptococcus pyogenes	Erythrogenic toxin
	Escherichia coli	Shiga-like enterotoxin
	Clostridium botulinum	Botulinum toxin (C,D)
Transposons*	*Escherichia coli*	Enterotoxins(STA and STB), iron acquisition,hemolysin

* Transposable genetic elements located on plasmids that often insert into the chromosome

Virulence factors that promote bacterial colonization of the host

1. Adhere to host cells and resist physical removal;
2. Invade host cells;
3. Contact host cells;
4. Resist innate immune defenses such as phagocytosis and complement;
5. Evade adaptive immune defenses;
6. Compete for iron and other nutrients.

Ability to Contact Host Cells



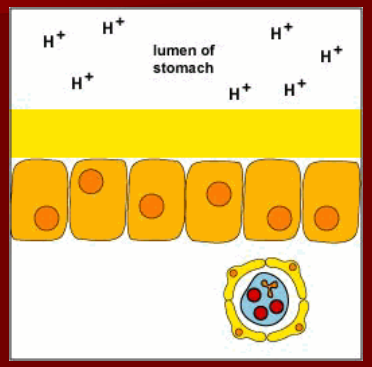
STRUCTURE

CHEMOTACTIC RESPONSE INHIBITORY PROTEIN

MOTILITY

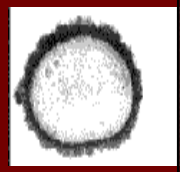
Enzyme eg. streptokinase, DNase

Helicobacter pylori-Induced Ulceration of the Stomach

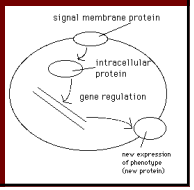


Ability to adhere to host cells and resist physical removal

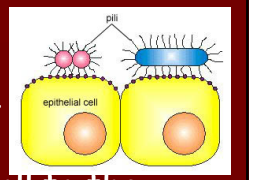
- Bacteria may resist this physical removal producing pili, cell wall adhesin proteins, and/or biofilm-producing capsules.



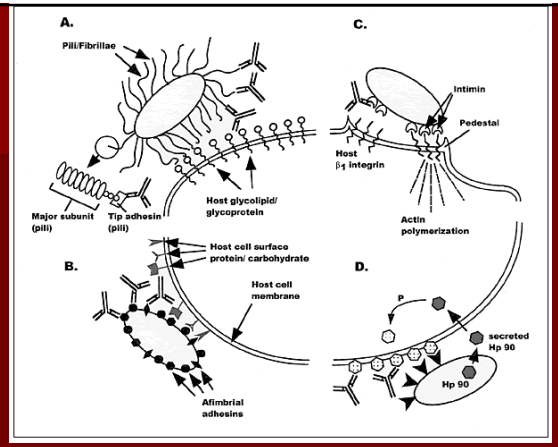
- A signal for the activation of genes involved in bacterial virulence called signal transduction.



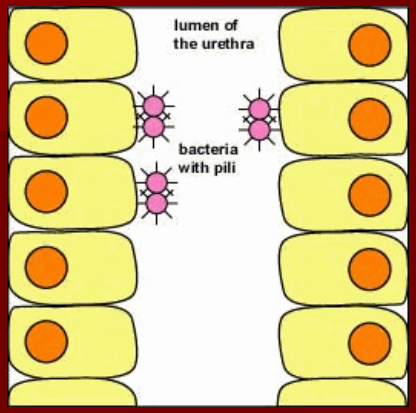
Pili or Fimbriae (H antigen)



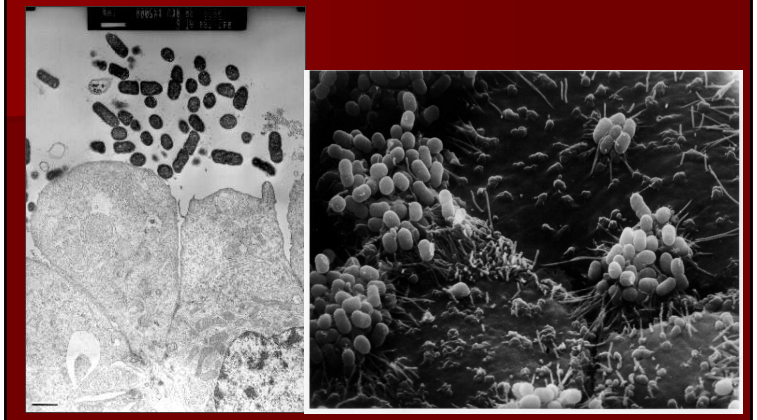
- Not considered part of the plasma membrane.
- Protrude through the cell wall to the outside of the cell.
- Enable some organisms to **adhere** to receptors on target host cells
- Termed **adhesins** because their major function is adhesion to other cells, both bacterial and animals.



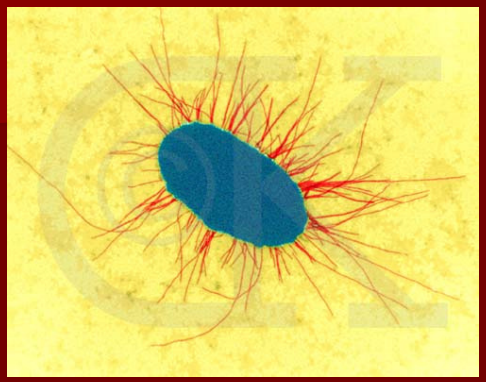
A shows pili or fibrillae protruding from the bacterial surface. B afimbrial adhesin proteins. C intimin proteins, resulting in cytoskeletal rearrangements. D bacteria secrete their own receptor protein.



- Bacteria such as *Neisseria gonorrhoeae* use pili to adhere to the mucous membranes of the urethra and thus resist the flushing action of the urine.



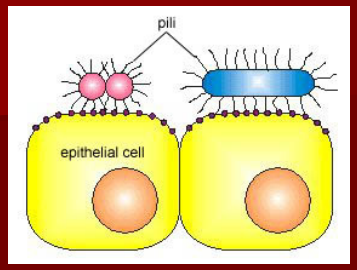
- Transmission electron microscopy reveals adherence of bacteria to the apical surface of the T84 cells without internalization. The apical brush border is effaced; cells are ballooning and will eventually be extruded from the monolayer.

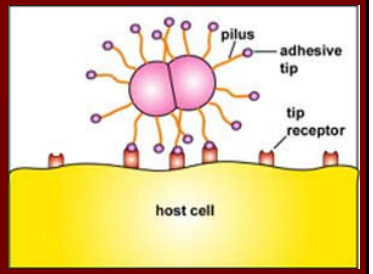


- The types of pili varies both among and between species. Pili are hair-like projections of the cell. Some are involved in sexual conjugation and others allow adhesion to host epithelial surfaces in infection.

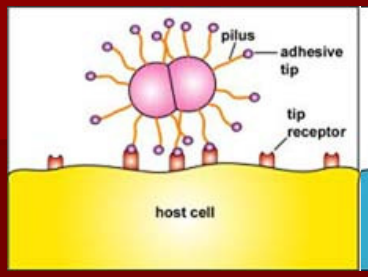
Function of Fimbria

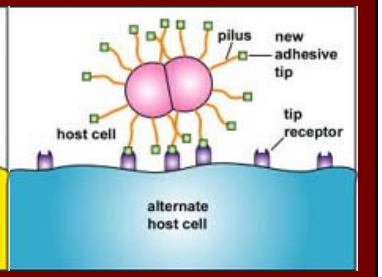
- F-pili are produced by male bacteria and allow them to bind to female bacteria to promote sexual conjugation.
- Pili promote adhesion to host cells
  a. Binding of platelets and fibrin around the bacterial cell to evade phagocytosis, promote fibrin deposition on heart valves and promote blood clots.
  b. Binding of bacterial cells to epithelial adhesion receptors which results in interactions which may kill the host cell.





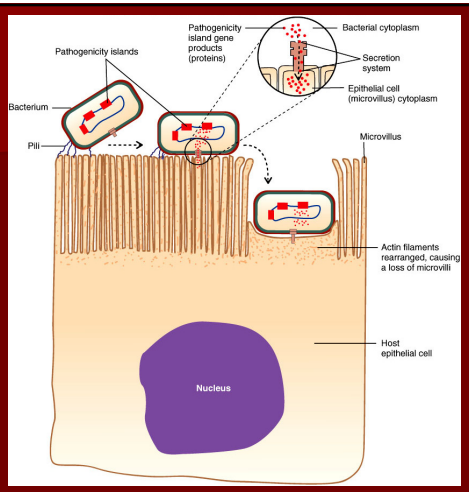
- **Adhesive tip structure having a shape corresponding to that of specific glycoprotein or glycolipid receptors on a host cell**



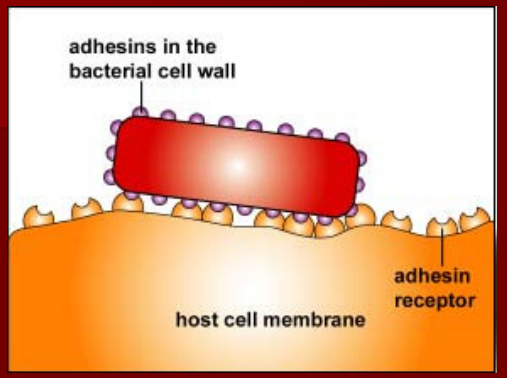


- By genetically altering the adhesive tips of their pili, certain bacteria are able to:

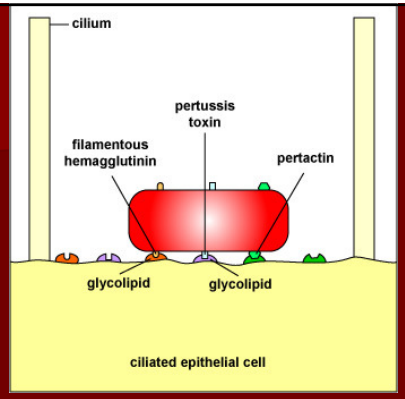
1) adhere to and colonize different cell types with different receptors, and
2) evade antibodies made against the previous pili



Secretions that produce cellular changes

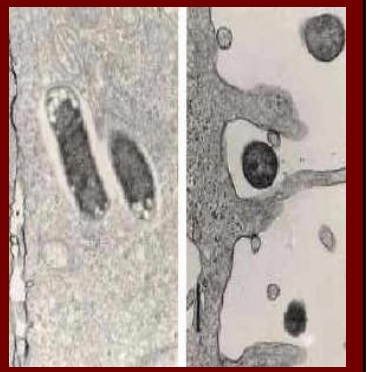


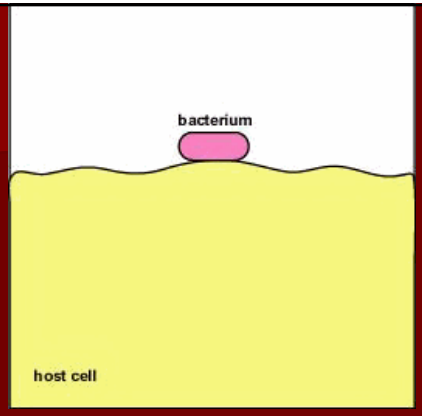
- Surface proteins called adhesins in the bacterial cell wall bind to receptor molecules on the surface of a susceptible host cell enabling the bacterium to make intamate contact with the host cell, adhere, colonize, and resist flushing.



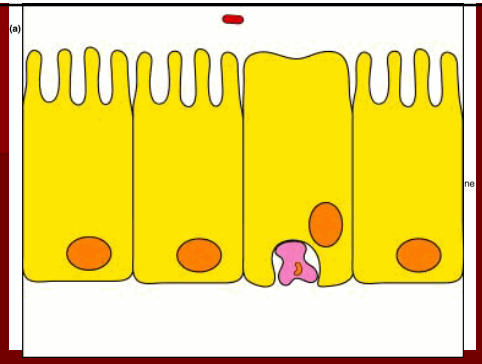
Ability to invade host cells

- To penetrate into nonphagocytic host cells. This ability may enable these microorganisms to reach deeper tissue or cross the blood brain barrier.
- To protect against the host's immune system and many antibiotics.

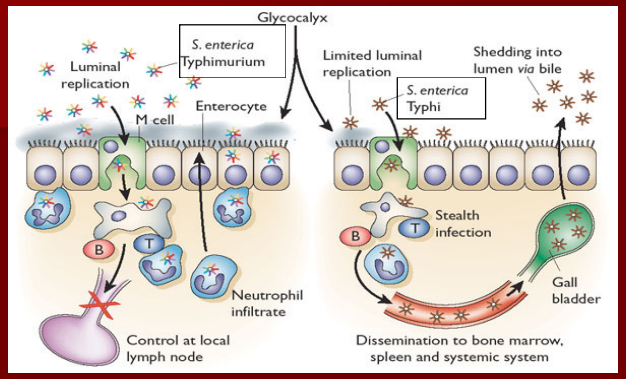




- Invasins activates the host cell's cytoskeletal machinery enabling bacterial entry into the cell by phagocytosis called type III secretion systems.



- The M cell passes the *Shigella* on to a macrophage.
- By its invasin, *Shigella* enter the mucosal epithelial cells and cause actin polymer rearrangements in the cell's cytoskeleton resulting in the bacterium being engulfed and placed in an endocytic vesicle.
- The *Shigella* are able to move through the host cell and spread to adjacent host cells.



- Invasins of *Salmonella* and *Yersinia enterocolitica* allow these bacteria to invade intestinal epithelial cells by **stimulating actin rearrangement.**

Abilty to compete for iron and other nutrients

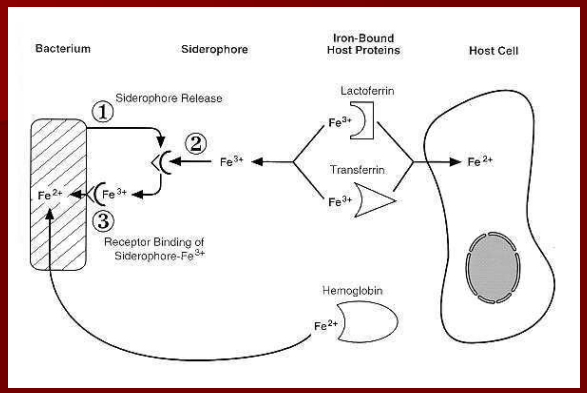
- **The ability to be pathogenic is directly related to the bacterium's ability to compete successfully with host tissue and normal flora for limited nutrients.**
- **Bacteria compete for nutrients by synthesizing specific transport systems or cell wall components capable of binding limiting substrates and transporting them into the cell.**
- **Iron is essential for both bacterial growth and human cell growth.**

Siderophores

- Siderophores are low molecular weight iron-chelating compound
- Corresponding membrane receptor protein
- Mechanisms of "withholding" iron from tissue fluids in an attempt to limit the growth of invading bacteria.
- Hemin, transferrin, hemoglobin, lactoferrin

Siderophores

- *Neisseria gonorrhoeae* are able to use iron bound to human transferrin and lactoferrin for their iron needs.
- Pathogenic *Yersinia* species are able to use transferrin and hemin as iron sources.
- *Borrelia burgdorferi* doesn't even use iron as a cofactor, but instead uses manganese. Furthermore, a number of bacteria are able to **produce exotoxins that kill host cells only when iron concentrations are low.**



Competition between host cells and bacterial pathogens for iron, illustrating the importance of siderophores. Since free iron is scarce in tissue fluids and blood, bacterial siderophores compete effectively for Fe3+ bound to lactoferrin and transferrin.

Ability to resist innate immune defenses such as phagocytosis and complement.

- Ability to resist phagocytic engulfment (attachment and ingestion)
- Ability to resist phagocytic destruction and serum lysis

Capsules (K-antigen)

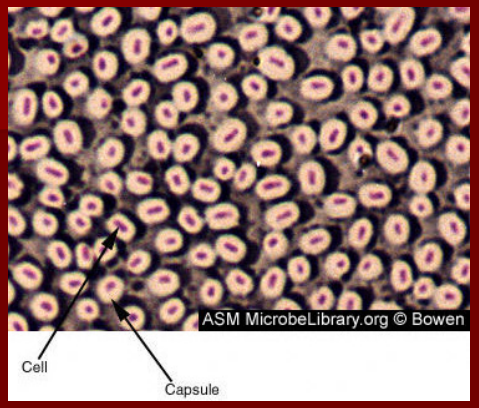
- polysaccharide capsules: repeating oligosaccharide units of two to four monosaccharides
- protein capsules: *Bacillus anthracis* (pure D-glutamic acid) and *Yersinia pestis* (mixed amino acids).
- *Haemophilus influenzae, Neisseria meningitidis, Escherichia coli, Streptococcus pneumoniae, Klebsiella pneumoniae* and group B streptococci
- Nonencapsulated mutants of these organisms are avirulent.
- it may serve a diversity of functions

Diversity of functions of **K-antigen**

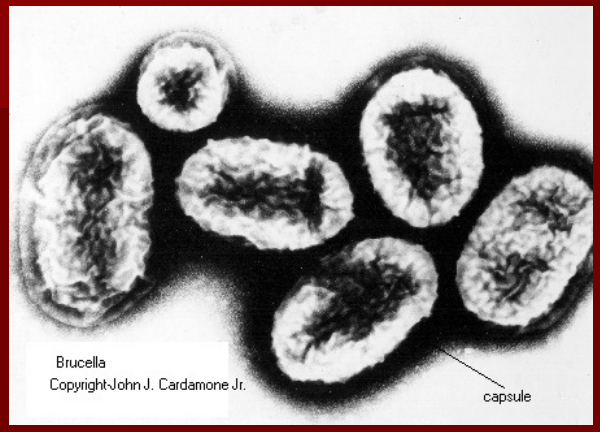
1. Antiphagocytosis - the smooth nature of the capsule, opsonins.
2. Prevention of neutrophil killing of engulfed bacteria
3. Prevention of complement-mediated bacterial cell lysis.
4. Prevention of PMN migration - *Bacteroides fragilis*; Succinic acid is released from the capsule and paralyzes the PMN
5. Toxicity to the host cell- the capsule of *B. fragilis* induces abscess formation.

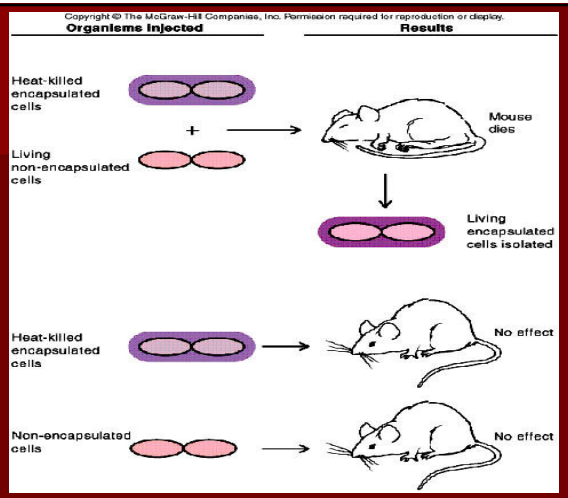
Diversity of functions of **K-antigen**

6. Adhesion to the host cell.
7. Protection of anaerobes from oxygen toxicity.
8. Determination of colonial type (**S-R variation**)
   capsules + form smooth (S) colonies
   capsules - form rough (R) colonies.
9. Enhancement of the pathogenicity of other species in a mixed infection.
10. Receptors for bacteriophage.
11. Induction of antibody synthesis - this is the basis for:
    a. Serological diagnosis.
    b. Vaccine production.



Capsule-producing bacillus-shaped bacteria. The capsule is composed of polysaccharides and polyproteins. Capsules have a role in adherence, virulence, protection, securing nutrients, and cell-to-cell recognition.

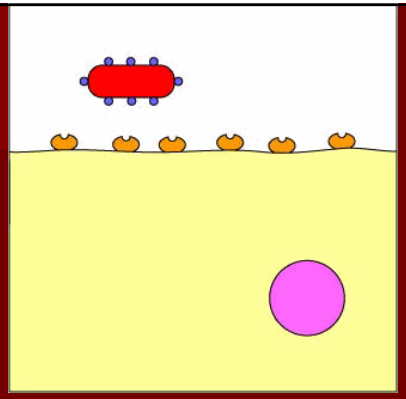




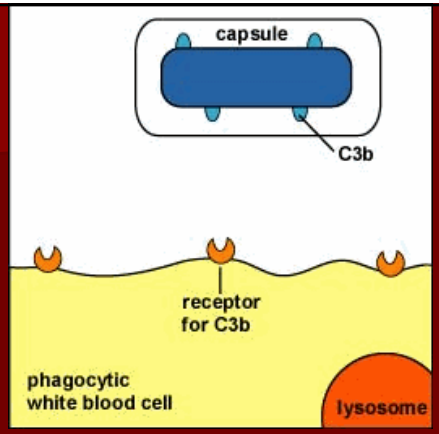
What does this tell us about the virulence factor added by the capsule?

Phagocytosis and bacterial pathogen

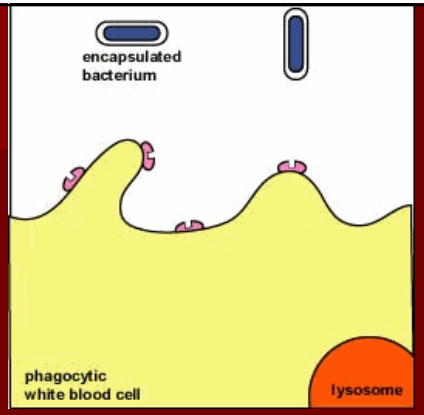
Phago.swf



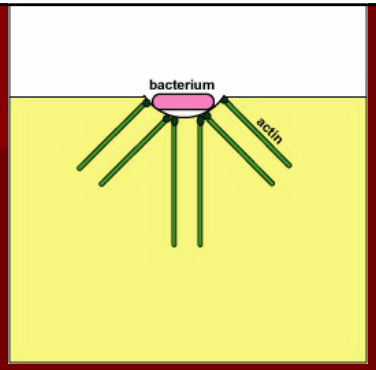
- Glycoprotein molecules; endocytic pattern-recognition receptors are found on the surface of phagocytes. These include bacterial molecules such as peptidoglycan, lipoteichoic acids, and lipopolysaccharide (LPS). These receptors enable the phagocyte to attach to the cell wall of the microorganism so it can be engulfed and destroyed by lysosomes.



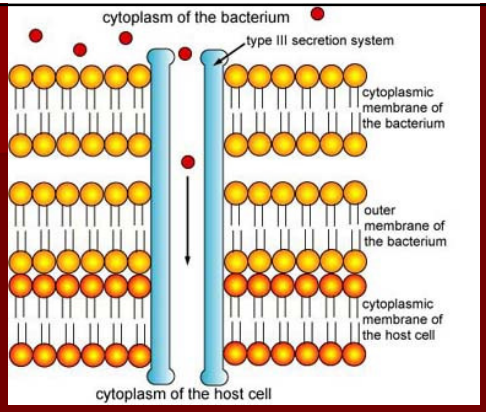
- Bacterial Capsule Preventing C3b Receptors on Phagocytes from Binding to C3b Attached to a Bacterial Cell Wall



The Fab portion of IgG binds to epitopes of a capsule. The Fc portion can now attach the capsule to Fc receptors on phagocytes for enhanced attachment. Once attached to the phagocyte by way of IgG, the encapsulated bacterium can be engulfed more efficiently and placed in a phagosome.



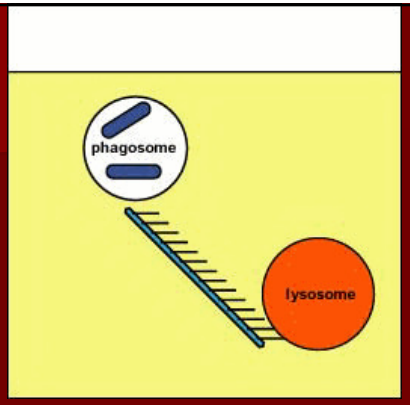
Molecules of some bacteria, through a type III secretion system, deliver proteins that depolymerize the phagocyte's actin microfilaments used for phagocytic engulfment.



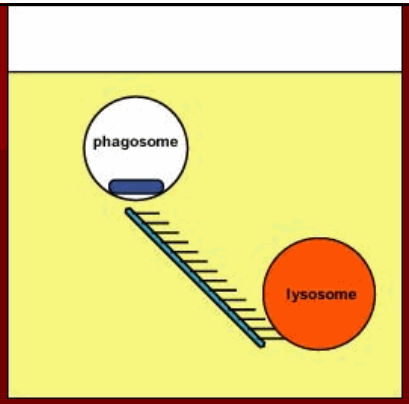
- A type III secretion system is one in which the bacterium produces pore-forming proteins that create a pore spanning not only the bacterium's cytoplasmic membrane and outer membrane, but also the plasma membrane of the host cell. This allows the bacterium to deliver proteins directly from its cytoplasm into the cytoplasm of the host cell.)

Ability to resist innate immune defenses such as phagocytosis and complement.

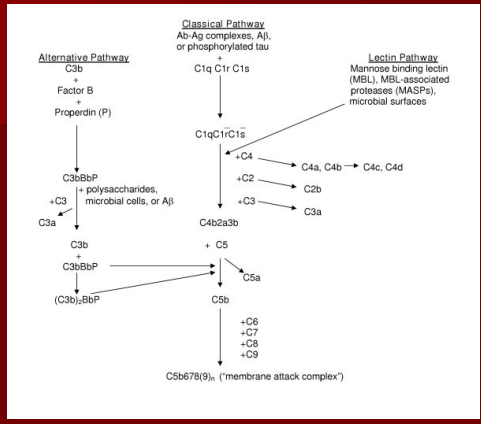
- Ability to resist phagocytic engulfment (attachment and ingestion)
- Ability to resist phagocytic destruction and serum lysis



- Some bacteria resist phagocytosis by escaping from the phagosome prior to its fusing with a lysosome. *Shigella flexneri*



- Some bacteria alter the phagocyte's vesicular transport machinery and block the fusion of the lysosomes with the phagosome. *Salmonella*, *Mycobacterium*, *Legionella*, and *Chlamydia*.



Schematic diagram of classical, alternative, and lectin complement activation pathways. There is evidence for activation of the classical and alternative pathways

Preventing of serum lysis

- **Membrane Attack Complex or MAC**.
- The LPS of the cell wall is the principle target for complement in gram-negative bacteria by activating the alternative complement pathway and serving as a binding site for C3b as well as the site for formation of MAC.
- **Some gram-negative bacteria attach sialic acid to the LPS O antigen and this prevents the formation of the complement enzyme C3 convertase** that is needed for the eventual formation of all the beneficial complement proteins such as C3b, C5a, nd MAC.

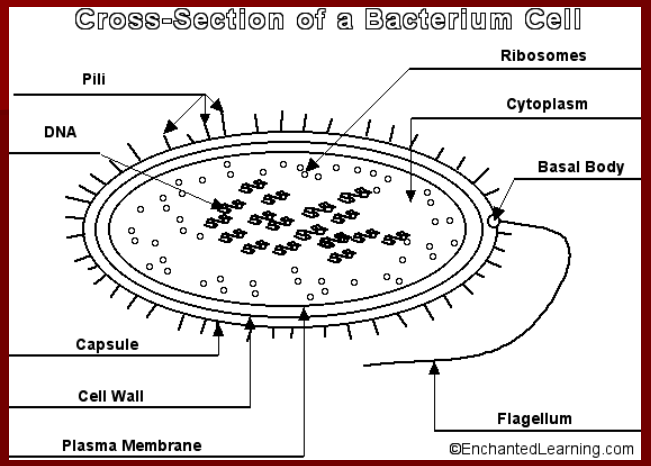
  Bordetella pertussis and *Haemophilus influenzae*.

Virulence Factors that Damage the Host

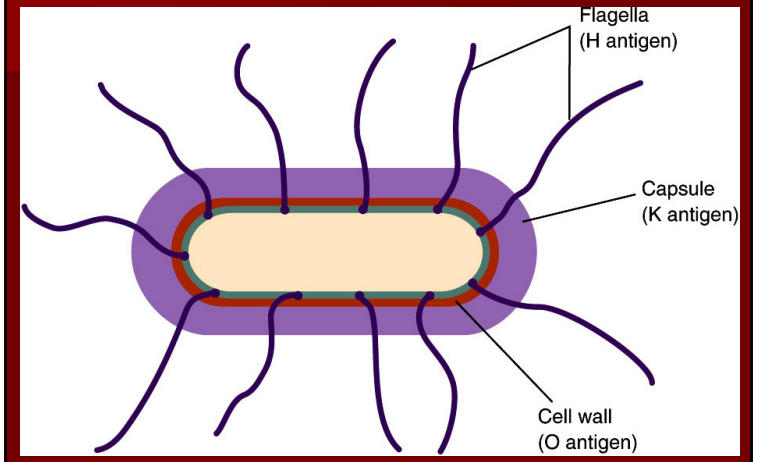
1. The ability to produce cell wall components that bind to host cells causing them to synthesize and secrete inflammatory cytokines and chemokines;
2. The ability to produce harmful exotoxins.
3. The ability to induce autoimmune responses.

Ability to produce cell wall components that bind to host cells

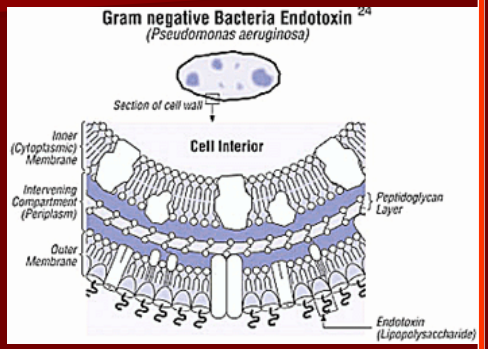
- Peptidoglycan monomers, teichoic acids, LPS, mycolic acid, and mannose bind to **pattern-recognition receptors** on a variety of defense cells causing **synthesize and secrete a variety of proteins called cytokines**.

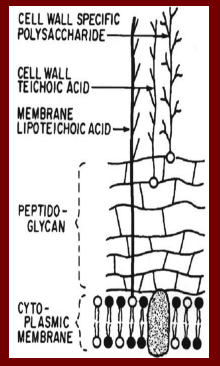


Bacterial antigenicities



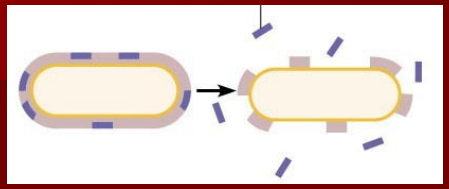
Structure of Bacterial cell wall





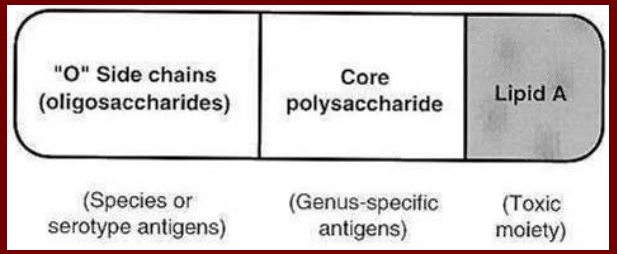
GRAM NEGATIVE GRAM POSITIVE

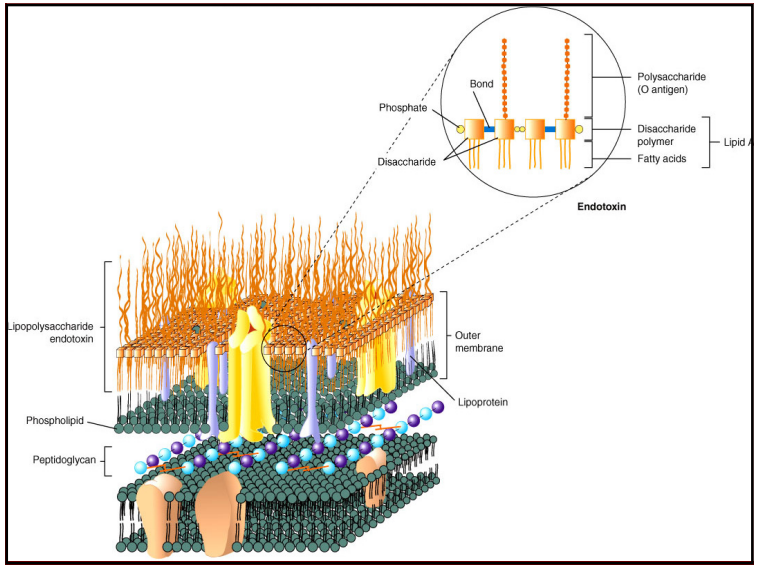
Endotoxin



- Endotoxin is released by Gram-negative bacteria, such as Pseudomonas.
- Shed by the bacterial cell during normal cell growth and division, and large amounts of it are liberated when the cell dies and undergoes lysis (bursts).
- Cell lysis can be rapidly induced by exposing the bacteria to some types of antibiotic or disinfectant such as sodium hypochlorite (bleach).

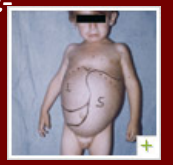
- LPS is an amphiphile composed of three regions: O-polysaccharide (the **O- or somatic-antigen**), the core polysaccharide and lipid A. Lipid A is anchored in the outer membrane. LPS is also known as **endotoxin**.





Systemic Inflammatory Response Syndrome (SIRS): The Shock Cascade

- **Excessive inflammatory response triggered by overproduction of cytokines such as TNF-alpha, IL-1, IL-6, IL-8, and PAF** often occurs. This leads to the following sequence of cytokine-induced events:



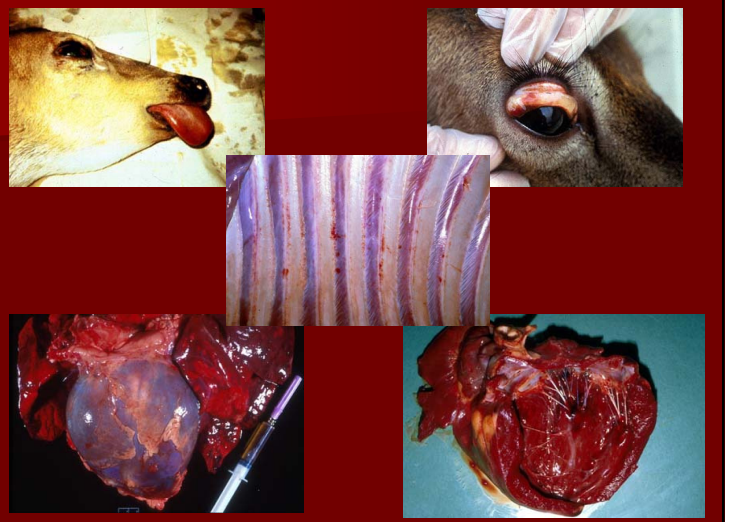
- **Neutrophils adhere to capillary walls in massive amounts.** Chemokines such as IL-8 activate neutrophils causing **release proteases and toxic oxygen radicals** results in **damage to the capillary walls and leakage of blood.**

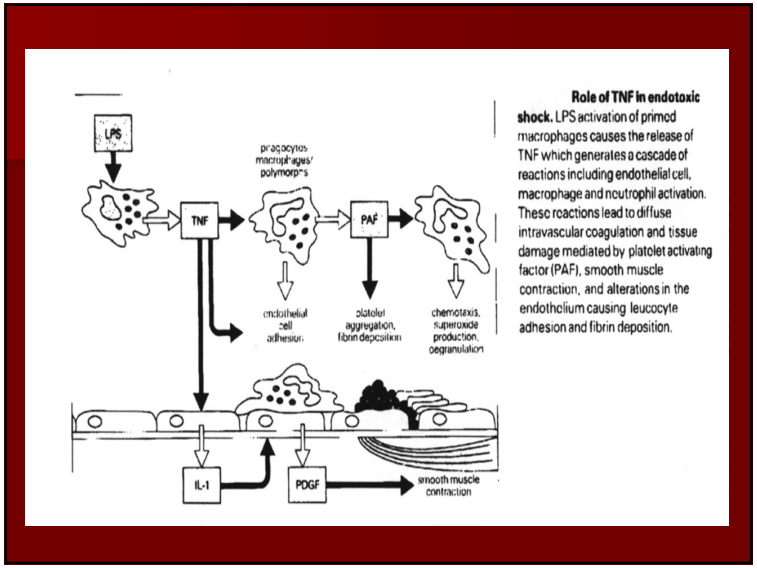
- **Hypotension: Prolonged vasodilation** and increased capillary permeability **causes plasma to leave the bloodstream** and enter the tissue.
- **Hypovolemia : Damage to the capillaries and prolonged vasodilation** result in **blood and plasma leaving the bloodstream** and entering the tissue. This can lead to a **decreased volume of circulating blood.**
- **Activation of the blood coagulation pathway and concurrent down-regulation of anticoagulation mechanisms** cause **clots to form within the blood vessels throughout the body.** This is called **disseminated intravascular coagulation (DIC).** This further limits the perfusion of blood and oxygen through tissues and organs

- The **increased capillary permeability** and **injury to capillaries in the alveoli of the lungs** results in **acute inflammation, pulmonary edema, and loss of gas exchange.**

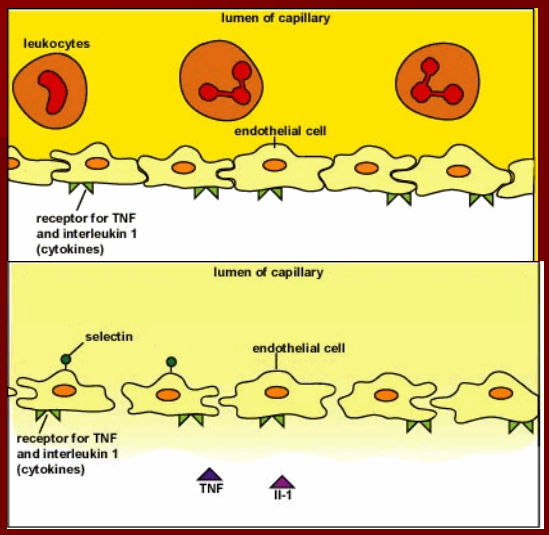
Acute Respiratory Distress Syndrome (ARDS).

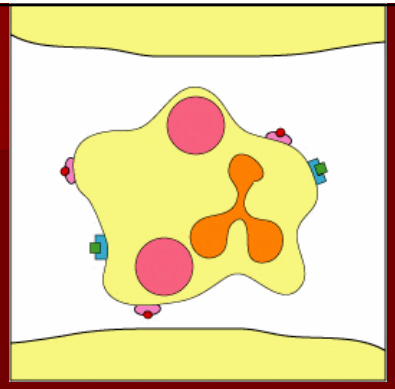
- **Reduced perfusion and capillary damage in the liver** results in **impaired liver function and a failure to maintain normal blood glucose levels. Reduced perfusion also leads to kidney and bowel injury.**
- All evidences leads to **acidosis** and decreased cardiac output. Cytokine-induced overproduction of nitric oxide (NO) by cardiac muscle cells leads to **heart failure**. Collectively, this cascade of events results in **irreversible septic shock, multiple system organ failure (MSOF)**, and **death**.





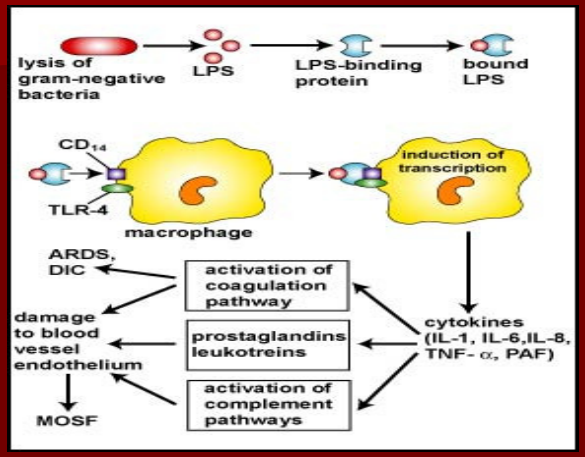
Role of TNF in endotoxic shock. LPS activation of primed macrophages causes the release of TNF which generates a cascade of reactions including endothelial cell, macrophage and neutrophil activation. These reactions lead to diffuse intravascular coagulation and tissue damage mediated by platelet activating factor (PAF), smooth muscle contraction, and alterations in the endothelium causing leucocyte adhesion and fibrin deposition.





- The binding of LPS to the LPS receptors and IL-8 to IL-8 receptors on the surface of neutrophils stimulates them to release proteases and toxic oxygen radicals for extracellular killing. These toxic agents not only kill bacteria in the vicinity but also kill surrounding host cells and tissues.

Harmful Effects of Lipopolysaccharide (LPS; Endotoxin) Released from the Gram-Negative Cell Wall



Virulence Factors that Damage the Host

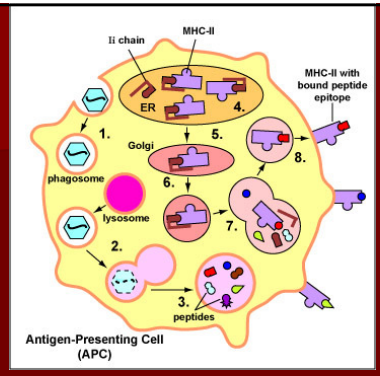
1. The ability to produce cell wall components that bind to host cells causing them to synthesize and secrete inflammatory cytokines and chemokines;
2. The ability to produce harmful exotoxins.
3. The ability to induce autoimmune responses.

Exotoxins : protein toxins usually secreted from a living bacterium but also **released upon bacterial lysis** and **sometimes injected directly into host cells** by bacteria.

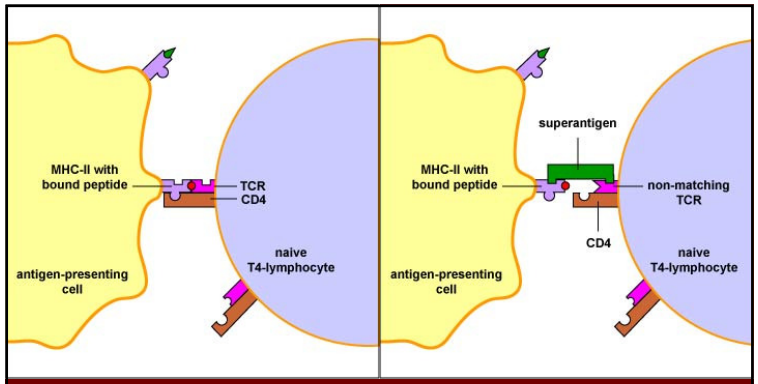
- **Superantigens (Type I toxins),**
- **A-B toxins and other toxin that interfere with host cell function (Type III toxins)**, and
- **Exotoxins that damage host cell membranes (Type II toxins).**

Superantigens

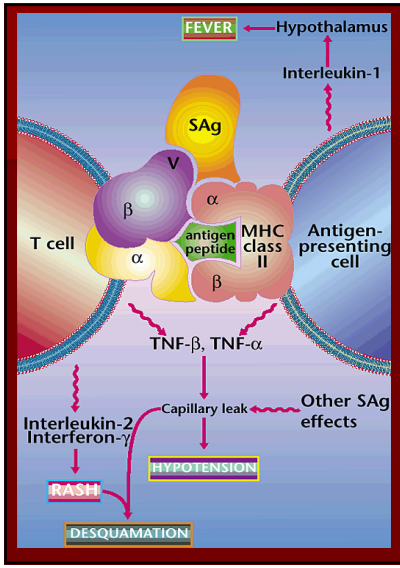
- An unusual bacterial toxins that interact with exceedingly large numbers of T4-lymphocytes.



The microbes are engulfed and placed in a phagosome. After lysosomes fuse with the phagosome, protein antigens are degraded by proteases into a series of peptides. These peptides eventually bind to grooves in MHC-II milecules and are transported to the surface of the APC.



Superantigens, on the other hand, bind directly to the outside of MHC-II molecules and the TCRs and activate many T4-lymphocytes. A specific TCR is not required for activation.



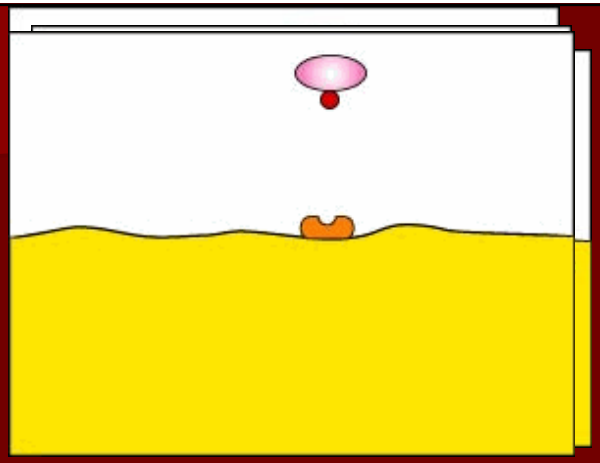
Endothelial damage, acute respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiple organ system failure seen above with LPS and other bacterial cell wall factors. Activation of self-reactive T-lymphocytes can also lead to autoimmune attack.

The following are examples of superantigens.

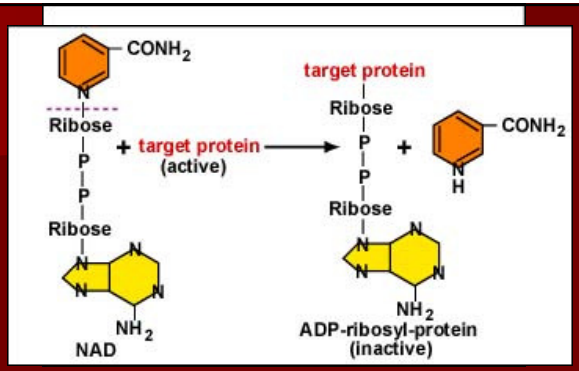
- **Toxic shock syndrome toxin-1 (TSST-1)**, *Staphylococcus aureus.*
- **Streptococcal pyrogenic exotoxin (Spe)**, *Streptococcus pyogenes* (group A beta streptococci).
- **Staphylococcal enterotoxins (SE)**, *Staphylococcus aureus.*

A-B toxins and other toxins that interfere with host cell function

(Type III toxins)



A-B toxins consist of two parts, an A (active) component and a B (binding) component.



After binding to the host cell receptor, the A component of this A-B toxin enters the host cell by directly passing through the host cell's membrane. It subsequently causes harm by the ADP-ribosylatior of a target host cell protein.

Cholera exotoxin (choleragen)

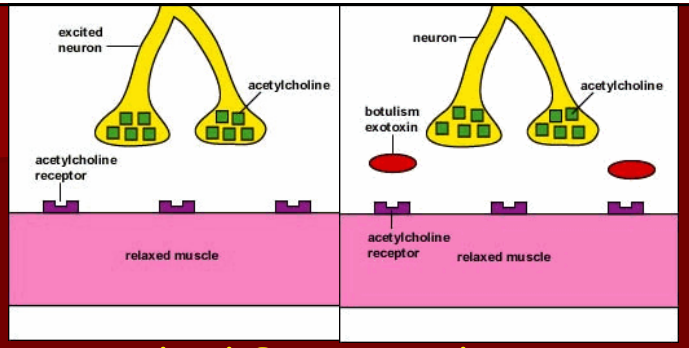
- This exotoxin turns the synthesis of a metabolic regulator molecule called cyclic AMP (cAMP) on. High levels of cAMP **block intestinal epithelial cells from taking in sodium from the lumen of the intestines and stimulates them to secrete large quantities of chloride. Water and other electrolytes osmotically follow.**
- This causes **loss of fluids, diarrhea, and severe dehydration.**

Enterotoxins

- Bind to the cells of the small intestines.
- Turn the synthesis of the metabolic regulator molecules cyclic AMP (cAMP) or cyclic GMP on in intestinal mucosal cells.
- High levels of cAMP and cGMP **cause loss of electrolytes and water that results in diarrhea.**
- *Clostridium perfringens* and *Bacillus cereus*

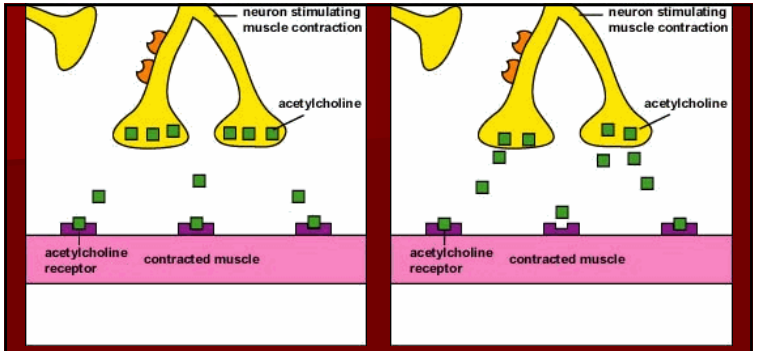
Shiga toxin

- Produced by species of *Shigella* and enterohemorrhagic *Escherichia coli* (EHEC) such as such as *E. coli* O157:H7.
- This toxin is an A-B toxin that **cleaves host cell rRNA** and prevents the attachment of charged tRNAs thus stopping host cell protein synthesis.
- The shiga toxin also enhances the LPS-mediated release of cytokines such as Il-1 and TNF-alpha and appears to be responsible for hemolytic uremic syndrome (HUS), probably by causing **blood vessel damage**.



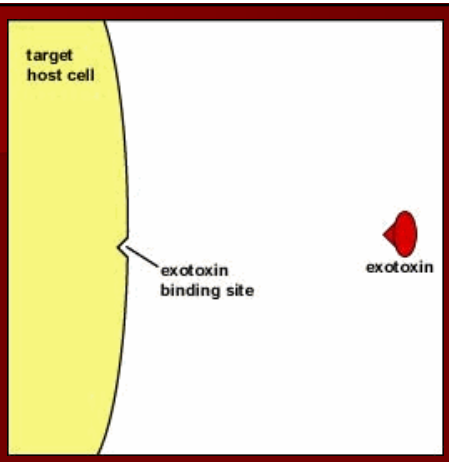
Botulinal Exotoxin Blocking Acetylcholine Release

- The botulism exotoxin binds to the presynaptic neuron and blocks its release of acetylcholine. This causes a flaccid paralysis, a weakening of the involved muscles.



Tetanus exotoxin

- Binds to inhibitory interneurons of the spinal cord and blocks their release of inhibitors. The toxin blocks the release of inhibitors, keeps the involved muscles in a state of contraction and leads to spastic paralysis.



The body's major **defense against exotoxins** is the production of **antitoxin antibodies**.

Toxins that Damage Host Cell Membranes (Type II Toxins)

- **Alpha toxin** (lecithinase): **increases the permeability of capillaries and muscle cells by breaking down lecithin in cytoplasmic membranes.** This results in the gross **edema** of gas gangrene.
- **Kappa toxin** (collagenase): **breaks down supportive connective tissue** (collagen) resulting in the mushy lesions of gas gangrene.
- **Mu toxin** (hyaluronidase): **breaks down the tissue cement** that holds cells together in tissue.

ORGANISM AND DISEASE??

ORGANISM??

- Exotoxin A and Exotoxin S: inhibits host cell protein synthesis causing tissue damage; is immunosuppressive.
- Phospholipase C: Causes tissue damage; stimulates inflammation.
- Pyocyanin: a green to blue water-soluble pigment that catalyzes the formation of tissue-damaging toxic oxygen radicles; impairs ciliary function, stimulates inflammation.
- Alkaline protease: leads to tissue damage.Cytotoxin: Damages cell membranes of leukocytes causes microvascular damage.
- Elastase: Destroys elastin, a protein that is a component of lung tissue.

Bacterial Toxins

Bacterium	Toxin	Pathology
Bacillus anthracis	Anthrax toxin	edema, hemorrhage, circulatory collapse
Bordetella pertussis	Pertussigen	whooping cough
Clostridium botulinum *C. tetani*	Neurotoxin Tetanus toxin	paralysis muscle spasm
Corynebacterium diphtheriae	Diphtheria toxin	epithelial necrosis heart damage nerve paralysis
Escherichia coli	Vero toxin (shiga-like toxin)	diarrhea, cramping
Pseudomonas aeruginosa	Exotoxin A proteases, elastases	various
Shigella spp.	Shiga toxin	diarrhea, dysentery neurological effects
Staphylococcus aureus	Exfoliative Toxin TSST-1 Enterotoxin	scalded skin syndrome toxic shock diarrhea, vomiting
Streptococcus pneumoniae	Pneumolysin	bacteremia deafness
Streptococcus pyogenes	Erythrogenic toxin	scarlet fever
Vibrio cholerae	Cholera toxin	diarrhea
Gram negative bacteria	Endotoxin (LPS)	septic shock

Exotoxins produced by variuos primary pathogens

Toxins	Name of Disease; Name of Toxin	Characteristics of the Disease	Mechanism
A-B TOXINS—Composed of two subunits, A and B. The A subunit is the toxic, or active, part; the B subunit binds to the target cell.			
Neurotoxins			
Clostridium botulinum	Botulism; botulinum toxin	Flaccid paralysis	Blocks transmission of nerve signals to the muscles by preventing the release of acetylcholine.
Clostridium tetani	Tetanus; tetanospasmin	Spastic paralysis	Blocks the action of inhibitory neurons by preventing the release of neurotransmitters.
Enterotoxins			
Enterotoxigenic *E. coli*	Traveler's diarrhea; heat-labile enterotoxin (cholera-like toxin)	Severe watery diarrhea	Modifies a regulatory protein in intestinal cells, causing those cells to continuously secrete electrolytes and water.
Vibrio cholerae	Cholera; cholera toxin	Severe watery diarrhea	Modifies a regulatory protein in intestinal cells, causing those cells to continuously secrete electrolytes and water.
Cytotoxins			
Bacillus anthracis	Anthrax; edema factor, lethal factor	Inhaled form—septic shock; cutaneous form—skin lesions	Edema factor modifies a regulatory protein in cells, causing those cells to overproduce fluids. Lethal factor inactivates proteins involved in cell signaling functions.
Bordetella pertussis	Pertussis (whooping cough); pertussis toxin	Sudden bouts of violent coughing	Modifies a regulatory protein in respiratory cells, causing those cells to overproduce respiratory secretions and mucus. Other factors also contribute to the symptoms.
Corynebacterium diphtheriae	Diphtheria; diphtheria toxin	Pseudomembrane in the throat; heart, kidney damage.	Inhibits protein synthesis by inactivating an elongation factor of eukaryotic cells. Kills local cells (in the throat) but can also be carried in the bloodstream to various organs.
E. coli O157:H7	Bloody diarrhea, hemolytic uremic syndrome; shiga toxin	Diarrhea that may be bloody; kidney damage	Inactivates the 60S subunit of eukaryotic ribosomes, halting protein synthesis.
Shigella dysenteriae	Dysentery, hemolytic uremic syndrome; shiga toxin	Diarrhea that contains blood, pus, and mucus; kidney damage	Inactivates the 60S subunit of eukaryotic ribosomes, halting protein synthesis

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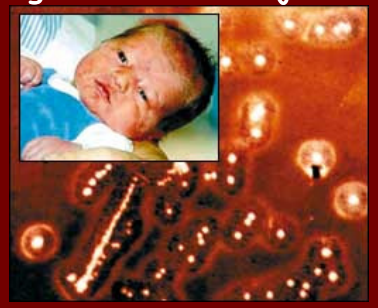
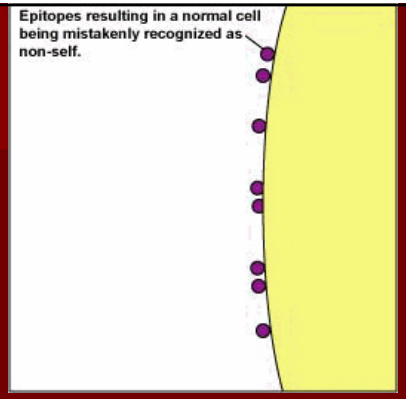
2. The ability to produce harmful exotoxins.
3. The ability to induce autoimmune responses.

Ability to Induce Autoimmune Responses

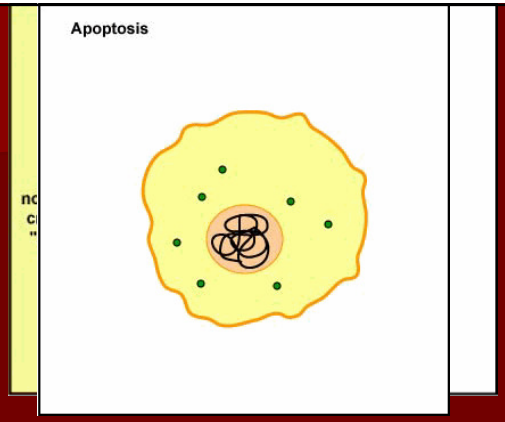
- Autoimmunity is when the body's immune defenses mistakenly attack the body and sometimes certain bacteria can serve as a trigger for this response.
- Inducing the production of cross-reacting antibodies and possibly auto-reactive cytotoxic T-lymphocytes or CTLs

- **Rheumatic fever** triggered by rheumatogenic strains of *Streptococcus pyogenes*. Antibodies and CTLs stimulated by antigens of *S. pyogenes* cross-react with heart and joint tissues damaging the heart and joints

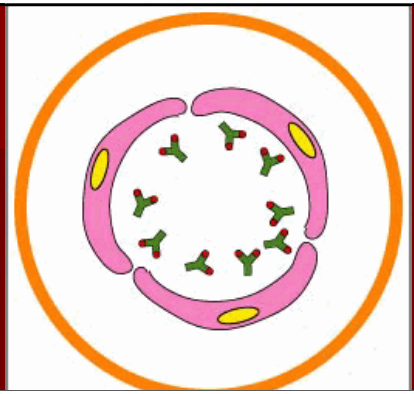




MAC Lysis During Type-II Hypersensitivity



ADCC Lysis During Type-II Hypersensitivity



Acute glomerulonephritis: *Streptococcus pyogenes*

- Type-III Hypersensitivity: Immune Complex: The antigen/antibody complex then activates the complement pathway

Measure of the pathogenicity of an organism.

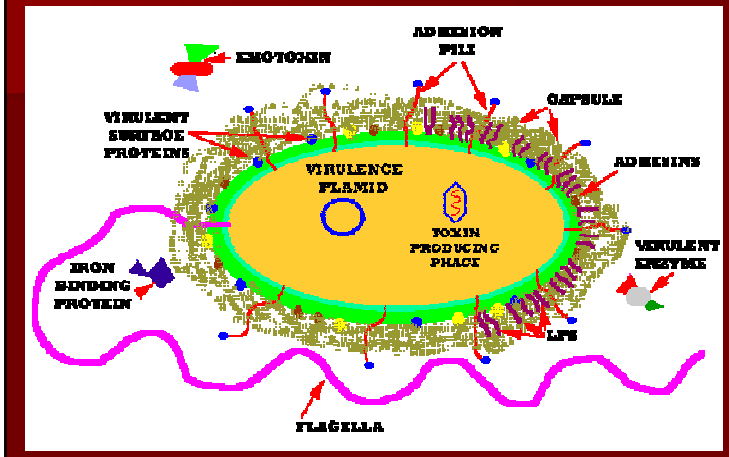
Measure experimentally by determining the number of bacteria required to cause animal death, illness, or lesions in a defined period.

LD50:

Calculations of Lethal dose affecting 50 percent of a population of animals

ED50:

Effective dose causing a disease symptom in 50 percent of a population of animals



- จงอธิบายกระบวนการก่อโรคเชิงมหภาพและระดับโมเลกุล ตาม Concepts ที่ท่านเรียนมาทั้งหมด ของเชื้อแบคทีเรียตัวที่ท่านสนใจ มา 1 ชนิด
  (ต้องไม่ซ้ำกัน)

ไม่ต่ำกว่า 2 หน้า A4 ส่งวันศุกร์ที่ 5 สิงหาคม 2548