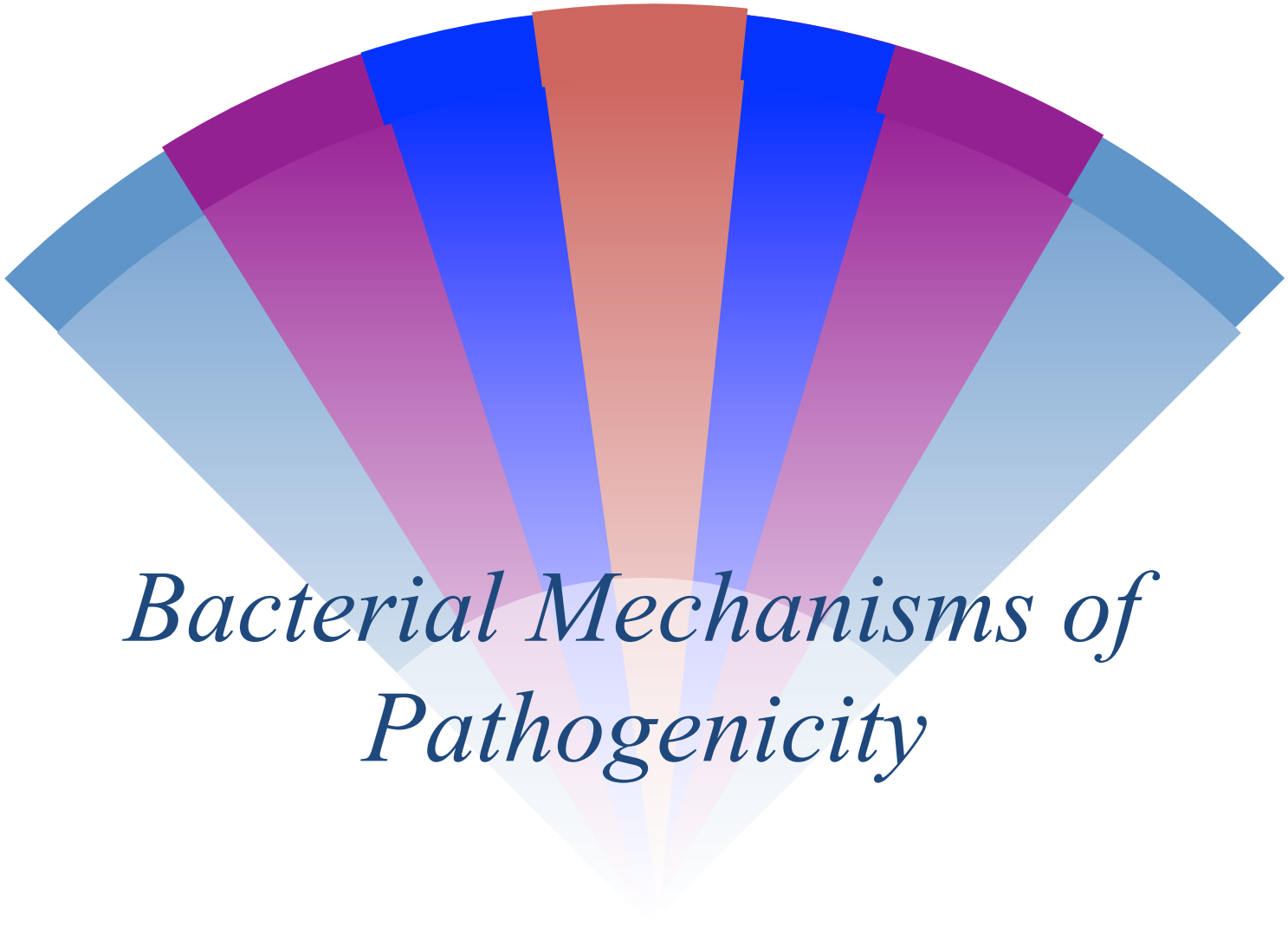
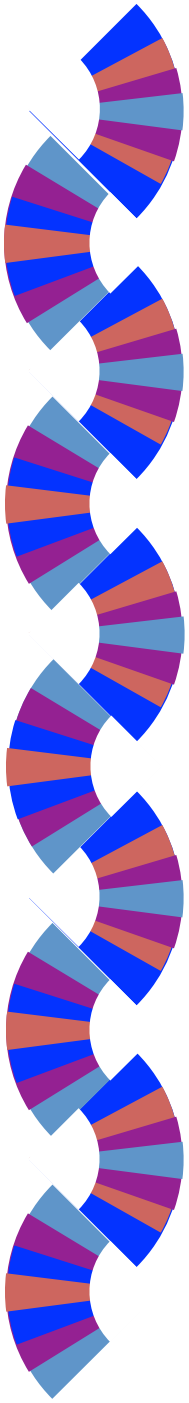


Bacterial Mechanisms of Pathogenicity

4th Lecture

4. Toxins

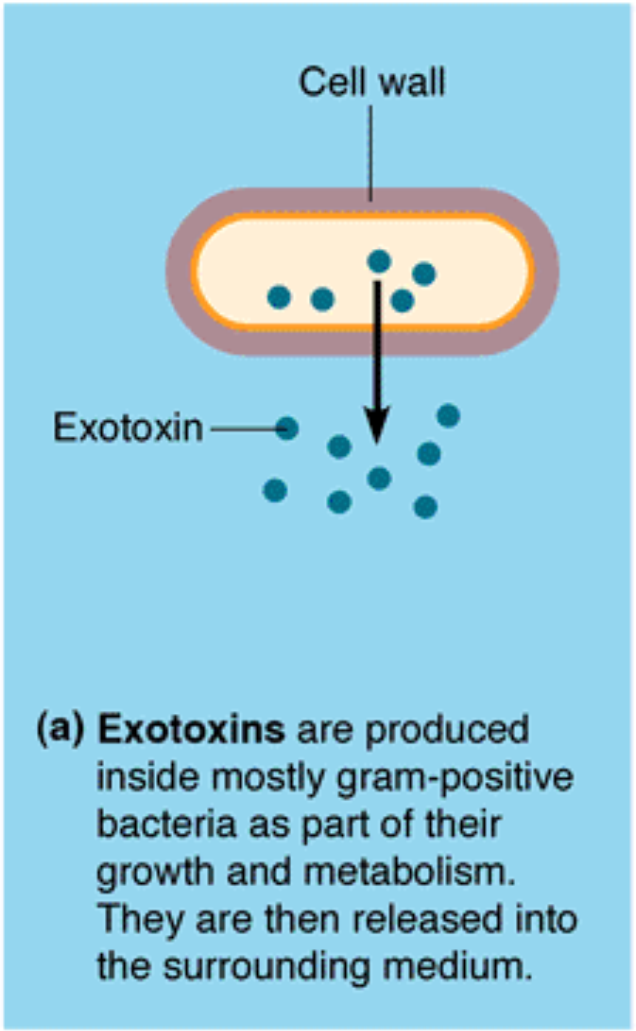
- Poisonous substances produced by microorganisms
- toxins - primary factor - pathogenicity
- 220 known bacterial toxins
  - 40% cause disease by damaging the Eukaryotic cell membrane
- Toxemia
  - Toxins in the bloodstream
  - Toxigenicity: Capacity of microorganisms to produce toxins.



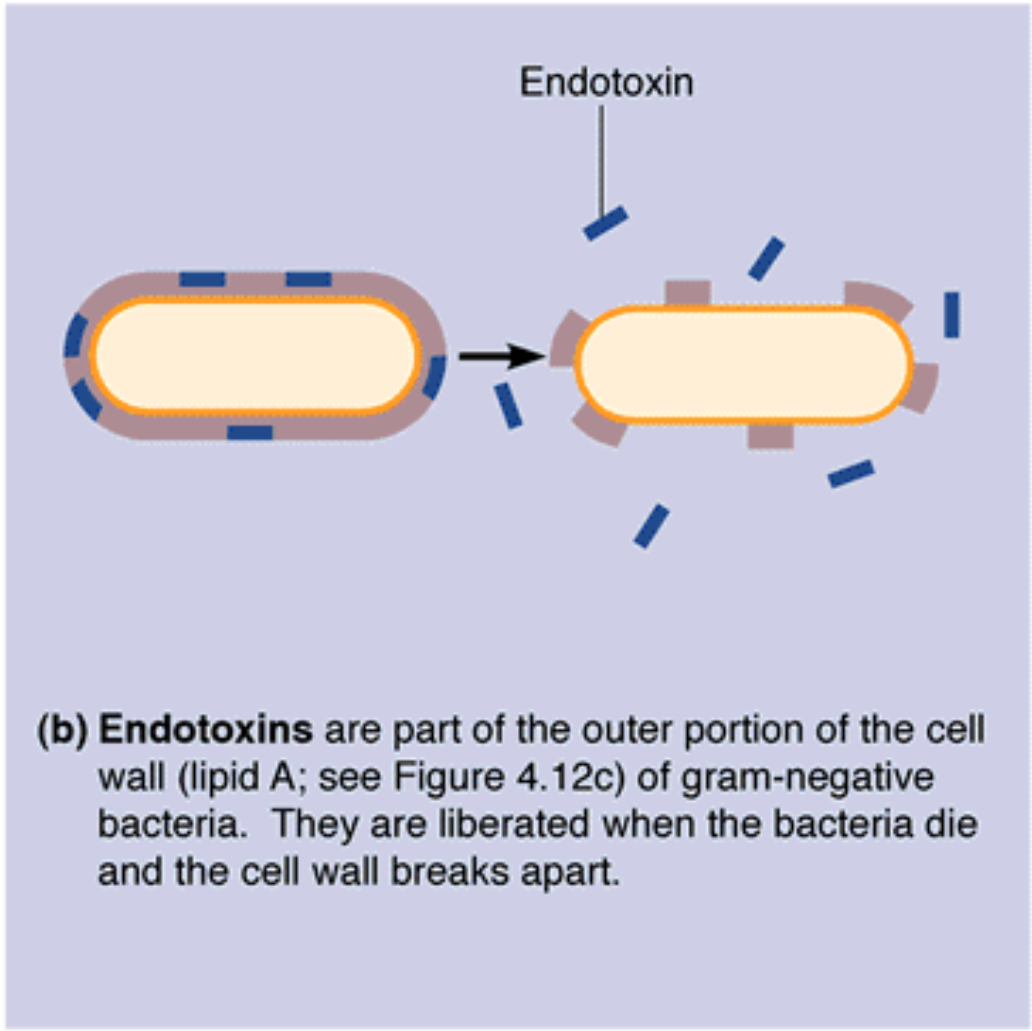
Two Types of Toxins

- 1. Exotoxins
  - secreted outside the bacterial cell
- 2. Endotoxins
  - part of the outer cell wall of Gram (-) bacteria. ??

Exotoxins versus Endotoxins



(a) **Exotoxins** are produced inside mostly gram-positive bacteria as part of their growth and metabolism. They are then released into the surrounding medium.



(b) **Endotoxins** are part of the outer portion of the cell wall (lipid A; see Figure 4.12c) of gram-negative bacteria. They are liberated when the bacteria die and the cell wall breaks apart.

ENDOTOXINS	EXOTOXINS
1. Integral part of cell wall	1. Released from the cell before or after lysis
2. Endotoxin is LPS; lipid A is toxic	2. Protein
3. Heat stable	3. Heat labile
4. Antigenic; questionable immunogenicity	4. Antigenic and immunogenic
5. Toxoids not be produced	5. Toxoids can be produced
6. Many effects on host	6. Specific in effect on host
7. Produced only by gram-negative organisms	7. Produced by gram-positive & gram-negative organisms

I- Exotoxins

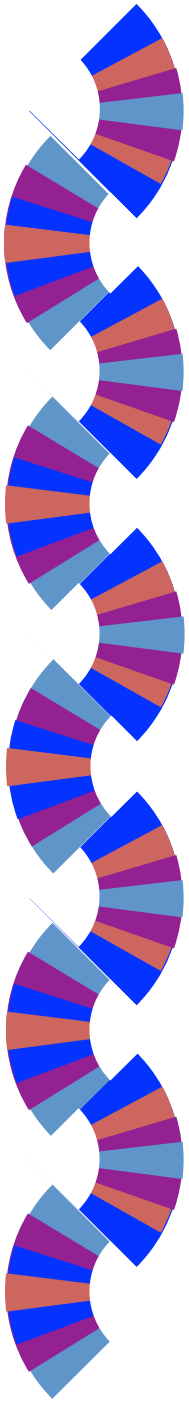
- Mostly seen in Gram (+) Bacteria
- Most gene that code for exotoxins are located on plasmids or phages

Three Types of Exotoxins

- 1. Cytotoxins
  - kill cells e.g. Diphtheria toxin
- 2. Neurotoxins
  - interfere with normal nerve impulses.e.g. Botulinum Toxin
- 3. Enterotoxins
  - effect cells lining the G.I. Tract. e.g. Cholera toxin or choleragen.

Response to Toxins

- If exposed to exotoxins: antibodies against the toxin (antitoxins)
- Exotoxins inactivated (heat, formalin or phenol) no longer cause disease, but stimulate the production of antitoxin
  - altered exotoxins - Toxoids
- Toxoids - modified toxin by heat, chemical, radiation, that have lost their toxicity. Injected to stimulate the production of antitoxins and provide immunity.



Example: DPT Vaccine

- D - Diphtheria
  - *Corynebacterium diphtheriae*
- P - Pertussis
  - *Bordetello pertussis*
- T - Tetanus
  - *Clostridium tetani*

DPT - Diphtheria Toxoid

Pertussis Antigen

Tetanus Toxoid

Required Immunizations

1. Diphtheria	*Corynebacterium diphtheriae*
2. Pertussis	*Bordetello pertussis*
3. Tetanus	*Clostridium tetani*
4. Measles	Measles virus
5. Mumps	Mumps virus
6. Rubella	Rubella virus
• German Measles	
7. Polio	Polio virus
9. Hepatitis B	Hepatitis B Virus

Most genes that code for exotoxins - plasmids or phages

- Lysogenic convergence
- Diphtheria
- Cytotoxin inhibits protein synthesis - resulting in cell death
- Pseudomembrane
  - fibrin, dead tissue, bacterial cells

Lysogenic Convergence

- Scarlet Fever
- *Streptococcus pyogenes*
  - lysogenic convergence
- cytotoxin - damages blood capillaries and results in a skin rash
  - Strep Thoat with a rash

Rash of Scarlet Fever Caused by Erythrogenic Toxins of *Streptococcus pyogenes*

Diseases Caused by Staphylococcal Toxins

Scalded Skin Syndrome

Toxic Shock Syndrome

Diseases caused by Neurotoxins

- Botulism
  - *Clostridium botulinum*
    - Gram (+), anaerobic, spore-forming rod, found in soil
  - works at the neuromuscular junction
  - prevents impulse from nerve cell to muscle cell
  - results in muscle paralysis

Tetanus (Lock Jaw)

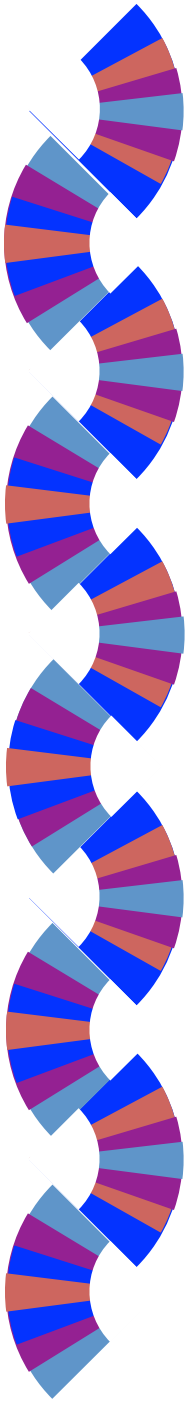
- *Clostridium tetani*
- Gram (+), spore-forming, anaerobic rod
- neurotoxin acts on nerves, resulting in the inhibition of muscle relaxation
- tetanospasmin - “spasms” or “Lock Jaw”

Muscle Spasms of Tetanus are Caused by Neurotoxin of *Clostridium tetani*

Neonatal Tetanus (Wrinkled brow and risus sardonicus)
Source: Color Guide to Infectious Diseases, 1992

Diseases caused by Enterotoxins

- Cholera
  - *Vibrio cholerae*
  - Gram (-) comma shaped rods



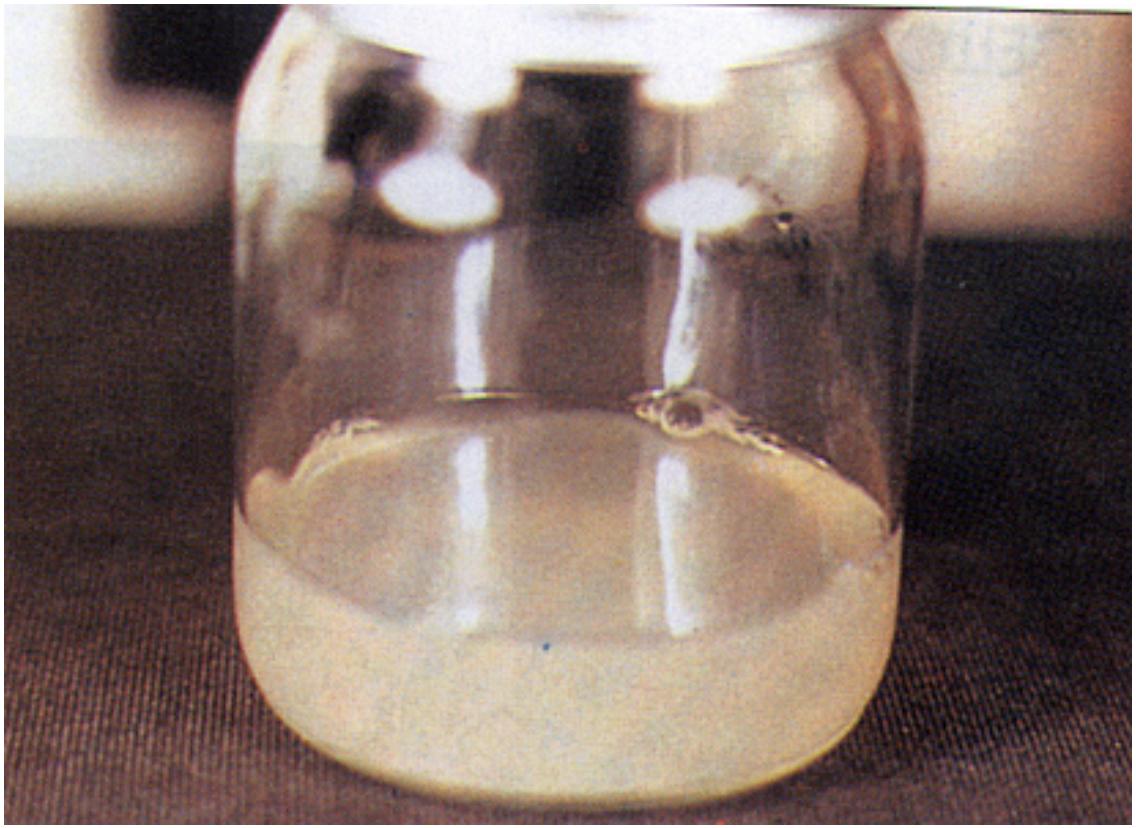
Cholera toxin

- Converts ATP into cAMP
- causes cells to excrete Cl^- ions and inhibits absorption of Na^+ ions
- Electrolyte imbalance
- H_2O leaves by osmosis
- H_2O Loss (Diarrhea)
- **Two polypeptides: A (active) and B (binding). The A subunit of enterotoxin causes epithelial cells to discharge large amounts of fluids and electrolytes.**

Severe cases, 12 - 20 liters of liquid lost in a day

- Untreated cases - Mortality Rate about 50%
- Mortality may be reduced to about 1%
  - administering fluids and electrolytes

Vibrio Enterotoxin Causes Profuse Watery Diarrhea



Rice-water stool of cholera. The A subunit of enterotoxin causes epithelial cells to discharge large amounts of fluids and electrolytes.
Source: Tropical Medicine and Parasitology, 1995

EHEC (Enterohemorrhagic E. coli)

- E. coli (0157:H7)
- enterotoxin causes a hemolytic inflammation of the intestines
- results in bloody diarrhea
  - Toxin
    - alters the 60S ribosomal subunit
    - inhibits Protein Synthesis
    - Results in cell death
    - lining of intestine is “shed”
    - Bloody Diarrhea (Dysentary)

More on Toxins

Toxin	Bacteria	Effect
Endotoxin	Gram-negative lipopolysaccharide	Fever and inflammatory cell stimulation
Exotoxins		
Neurotoxins	*Clostridium tetani* *Clostridium botulinum*	Disordered neuromuscular transmission (tetanus and botulism)
Enterotoxins (infectious diarrhoea)	*Vibrio cholera, E. coli* *Bacillus cereus*	Diarrhoea
Enterotoxins (food poisoning)	*Staphylococcus aureus* *Bacillus cereus*	Diarrhoea and vomiting
Tissue-invasive toxins	*Staphylococcus aureus* *Streptococcus pyogenes* *Clostridium perfringens*	Tissue destruction by enzymes
Pyrogenic toxins	*Staphylococcus aureus* *Streptococcus pyogenes*	Toxic shock syndrome Scarlet fever
Verotoxins	*E. coli* (O157:H7)	Haemolytic uraemic syndrome
Miscellaneous	*Bordetella pertussis* *Corynebacterium diphtheria* *Clostridium difficile*	Whooping cough Diphtheria (heart and nerve damage) Pseudomembranous colitis

II- Endotoxins

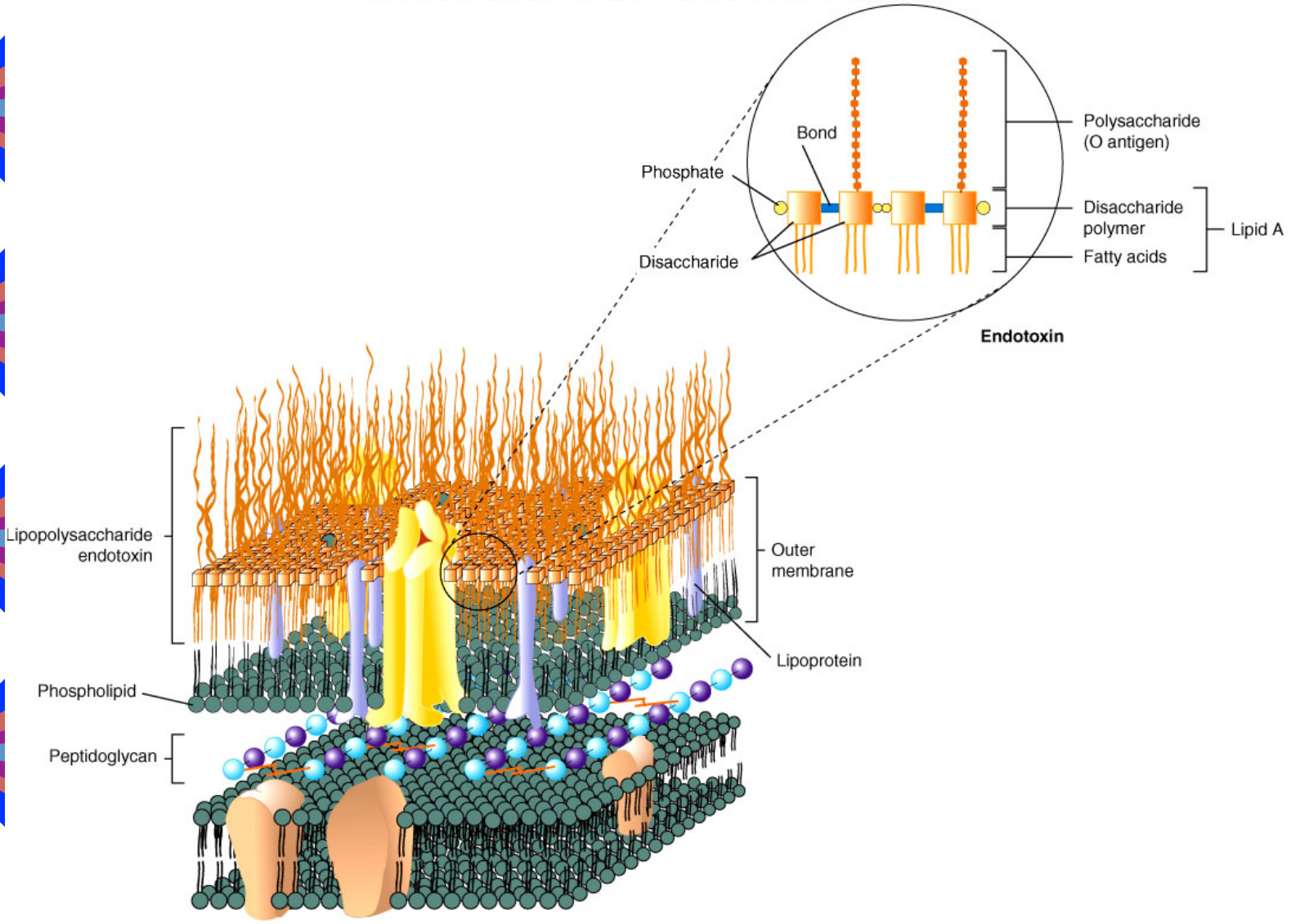
- **Part of outer membrane surrounding gram-negative bacteria.**
- **Endotoxin is lipid portion of lipopolysaccharides (LPS), called lipid A.**
- **Effect exerted when gram-negative cells die and cell walls undergo lysis, liberating endotoxin.**
- **All produce the same signs and symptoms:**
  - **Chills, fever, weakness, general aches, blood clotting and tissue death, shock, and even death. Can also induce miscarriage.**
  - **Fever: Pyrogenic response is caused by endotoxins.**

Exotoxins vs. Endotoxins

Table 19.3 Comparison of Exotoxins and Endotoxin

Property	Exotoxins	Endotoxin
Bacterial source	Gram-positive and Gram-negative species	Gram-negative species only
Location in the bacterium	Synthesized in the cytoplasm; may or may not be secreted	Component of the outer membrane
Chemical nature	Protein	Lipopolysaccharide (the lipid A component)
Ability to form a toxoid	Generally	No
Heat stability	Generally inactivated by heat	Heat-stable
Mechanism	A distinct toxic mechanism for each	Innate immune response; a systemic response leads to fever, a dramatic drop in blood pressure, and disseminated intravascular coagulation.
Toxicity	Generally very potent; some are among the most potent toxins known.	Not very toxic; small amounts lead to an appropriate response that helps clear an infection.

Endotoxin is LPS



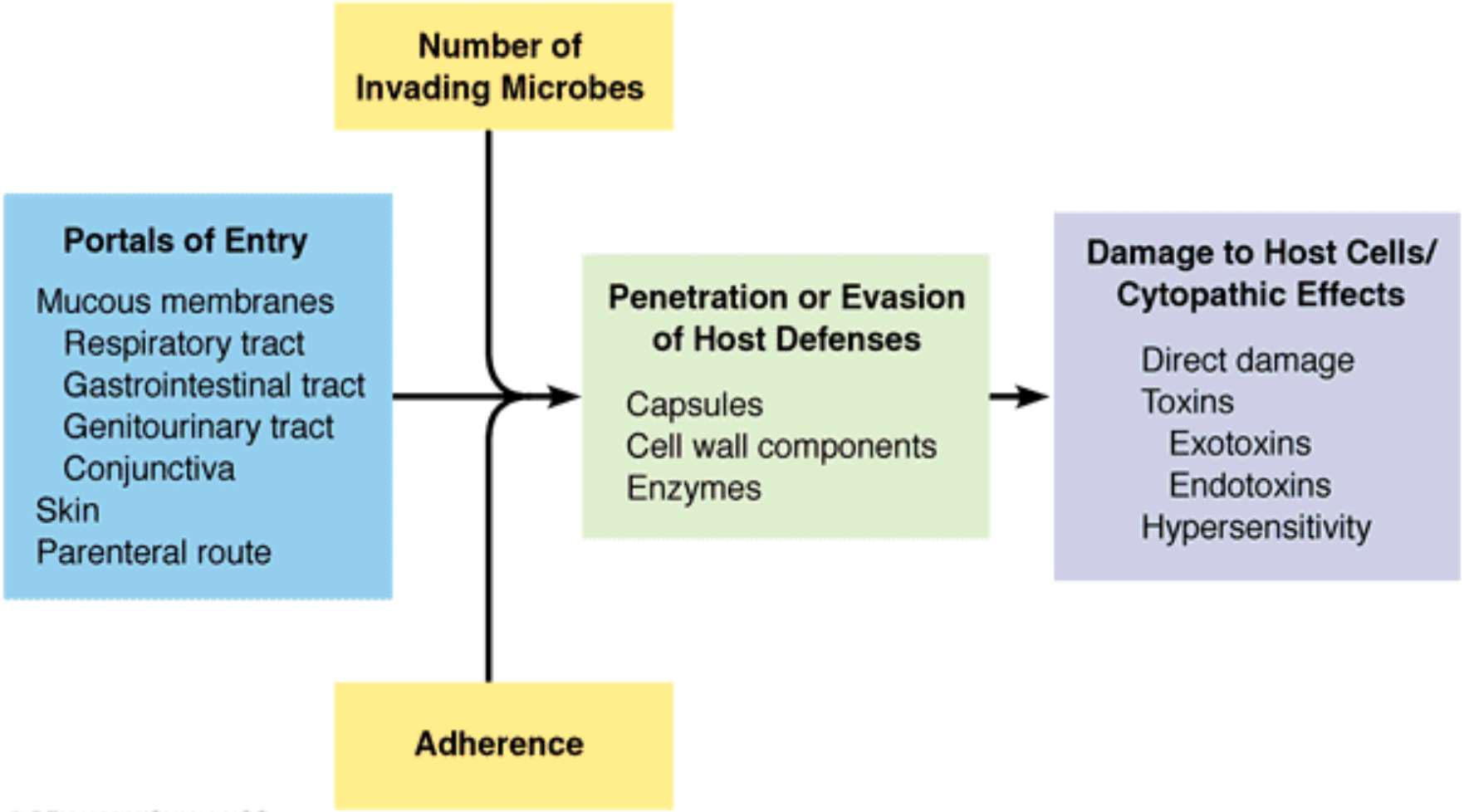
Endotoxins (Continued)

- **Endotoxins do not promote the formation of effective antibodies.**
- **Organisms that produce endotoxins include:**
  - ***Salmonella typhi***
  - ***Proteus spp.***
  - ***Pseudomonas spp.***
  - ***Neisseria spp.***
- **Medical equipment that has been sterilized may still contain endotoxins.**
  - ***Limulus* amoebocyte assay (LAL) is a test used to detect tiny amounts of endotoxin.**

Events leading to fever:

- Gram-negative bacteria are digested by phagocytes.
- LPS is released by digestion in vacuoles, causing macrophages to release interleukin-1 (IL-1).
- IL-1 is carried via blood to hypothalamus, which controls body temperature.
- IL-1 induces hypothalamus to release prostaglandins, which reset the body's thermostat to higher temperature.

Microbial Mechanisms of Pathogenicity: How Microorganisms Cause Disease



III. B. The Normal Flora of Humans

Types of Symbiosis

- Mutualism
  - A symbiotic relationship in which both species benefit
- Commensalism
  - A symbiotic relationship in which one species benefits, and the other species is neither helped nor harmed

III. B. The Normal Flora of Humans

Types of Symbiosis (cont.)

- Parasitism
  - A symbiotic relationship in which one species benefits, and the other species is harmed
  - Generally, the species that benefits (the parasite) is much smaller than the species that is harmed (the host)

III. B. The Normal Flora of Humans

Normal flora is present in

- skin
- upper respiratory tract
- oral cavity
- intestine, especially large intestine
- vaginal tract

Very little normal flora in eyes & stomach

III. B. The Normal Flora of Humans

- Notably absent in most all internal organs
  - Absent in:
    - lower respiratory tract
    - muscle tissue
    - blood & tissue fluid
    - cerebrospinal fluid
    - peritoneum
    - pericardium
    - meninges

III. B. The Normal Flora of Humans

- Benefits of the normal flora
  - Nutrient production/processing
    eg Vitamin K production by *E. coli*
  - Competition with pathogenic microbes
  - Normal development of the immune system
- Normal flora and opportunistic infections

III. C. Generalized Stages of Infection

1. Entry of Pathogen
   - Portal of Entry
2. Colonization
   - Usually at the site of entry
3. Incubation Period
   - Asymptomatic period
   - Between the initial contact with the microbe and the appearance of the first symptoms

III. C. Generalized Stages of Infection

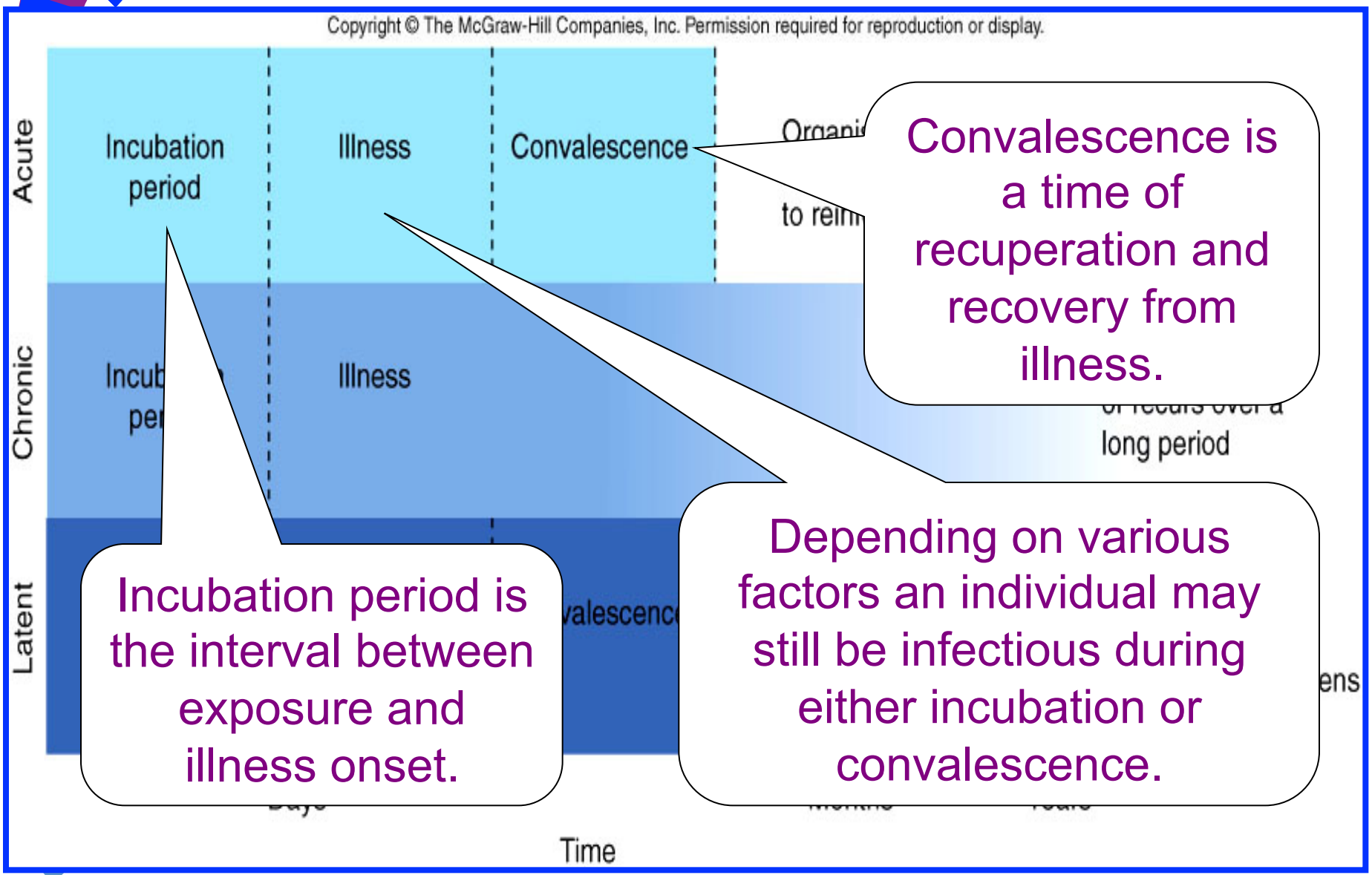
4. Prodromal Symptoms
   - Initial Symptoms
5. Invasive period
   - Increasing Severity of Symptoms
   - Fever
   - Inflammation and Swelling
   - Tissue Damage
   - Infection May Spread to Other Sites

III. C. Generalized Stages of Infection

6. Decline of Infection

5. Convalescence

Course of Infectious Disease

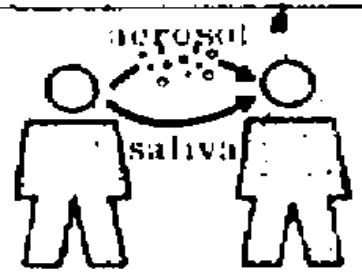


Convalescence is a time of recuperation and recovery from illness.

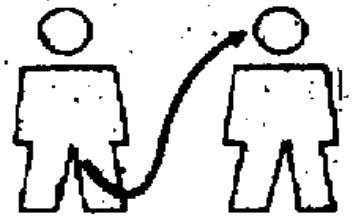
Incubation period is the interval between exposure and illness onset.

Depending on various factors an individual may still be infectious during either incubation or convalescence.

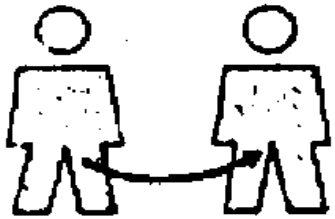
Pathogenesis of Infectious Disease



Respiratory or salivary spread



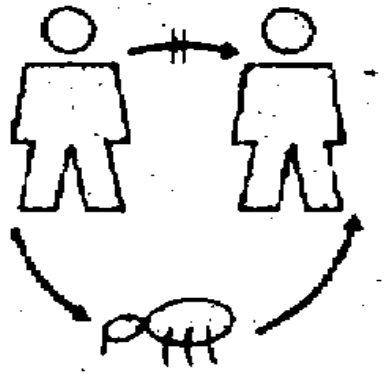
Faecal-oral spread



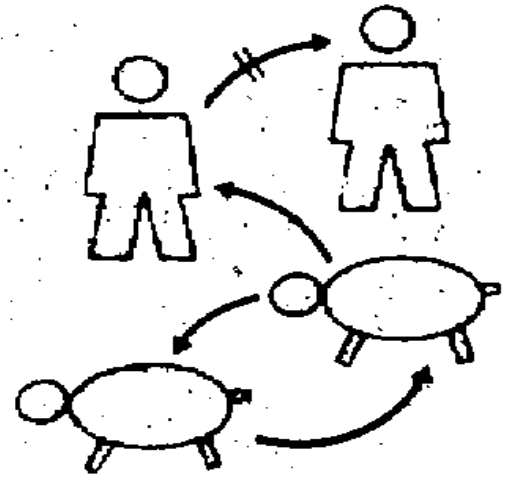
Venereal spread

ZOONOSES

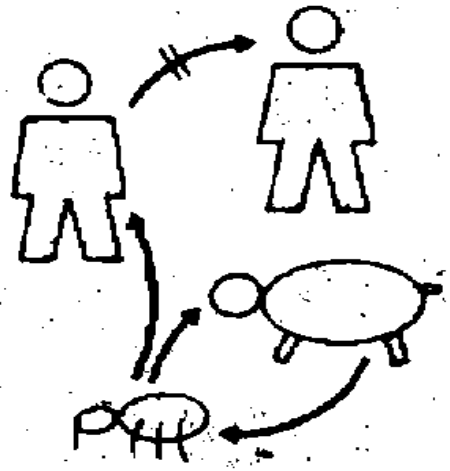
Infections acquired from animals (arthropods, vertebrates).
Human infection controlled by controlling animal infection.



Vector (biting arthropod)



Vertebrate reservoir



Vector-vertebrate reservoir