Bacterial Pathogenesis

Dr Shyamal Kr Paul Associate. Professor
Microbiology, MMC

PATHOGENICITY & VIRULENCE

- **Pathogenicity** – the ability to cause disease by overcoming the defenses of the host

- **Virulence** – is a quantitative measure of the pathogenicity
- **Virulence factors** – **Any microbial product or strategy that contributes to disease** . These include- **adhesion, toxin production, any microbial product or strategy that contributes to disease resistance to antibiotics, ability to invade host tissues, enhanced intracellular survival and growth**

How to distinguish infection from colonization ~

colonization → disease = infection

vs.

colonization by normal flora ⊣ disease ≠ infection

colonization of an infectious agent → no disease = asymptomatic carrier

Asymptomatic colonization by pathogenic bacteria

Streptococcus pyogenes **…. 20-30% - nasopharynx**
(strep throat / rheumatic fever / "flesh-eating disease"/ scarlet fever)

Streptococcus pneumoniae **.... 20-50% - nasopharynx**
(pneumonia / septicemia / meningitis / ear infections)

Staphylococcus aureus **…. >40% - anterior nares**
(hospital infections, septicemia, pneumonia)

Group B streptococci …. >24% of females - vaginal
(neonatal septicemia / pneumonia / meningitis)

PORTALS OF ENTRY

- To cause disease, most pathogenic bacteria must gain access to the host
- Organisms must also be able to evade, compromise or take advantage of a compromised innate immune system including the primary barriers of **skin** and **mucus membranes**
- Any compromise in these barriers (cuts, ulcers, surgical procedures, catheters, etc) may allow bacteria entrance into the host
- Normal skin flora, including *Staphylococcus aureus* and *Staphylococcus epidermidis*, can enter through these compromised barriers and establish an infection

PORTALS OF ENTRY

- May enter through the mucus membranes of the respiratory tract, gastrointestinal tract and urogenital tract
- the innate immune system also is comprised of mucus and cilia in the upper respiratory tract, acid pH and bile in the GI tract, lysozyme in tears and mucus
- Bacteria that can withstand the stomach acid and cause disease include *Vibrio cholerae*, *Salmonella typhi* and *Campylobcter jejuni*

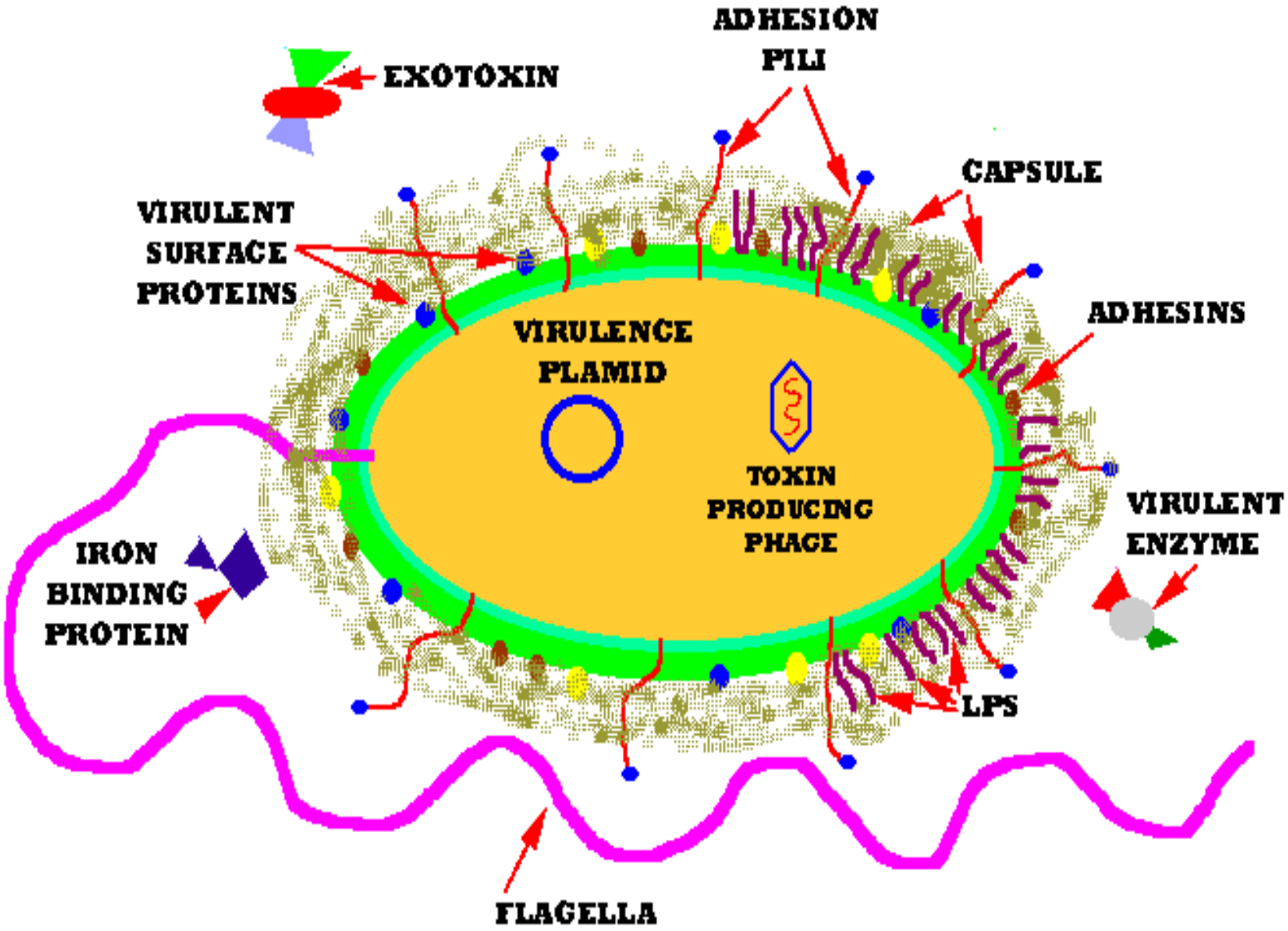
PORTALS OF ENTRY

- Many pathogens have **preferred portals of entry** that are necessary for disease production
- If they gain entrance via another portal, disease may not occur

  – *Bacillus anthracis* can initiate disease from more than one portal of entry (skin inoculation, GI, respiratory)

NUMBERS OF INVADING BACTERIA

- Generally speaking, entry of only a few or very small number of bacteria into the body will not result in infection. They will be overcome by host defenses
- One virulence factor is the number of bacteria required to institute an infection. This is called the ID_{50} or infectious dose for 50% of a sample population
  - Less than 100 *Shigella* organisms are required to induce dysentery whereas 10^6 – 10^9 *Salmonella* organisms are required for an infection



Virulence of pathogenic bacterial

ADHERENCE AND INVASION

- Most pathogenic bacteria have some mechanism of adherence for target cells
- Adherence is accomplished by **adhesins** on the organism binding with some degree of specificity to receptors on the target cells
- Most adhesins are either glycoproteins or lipoproteins and the receptors on target cells are usually some form of sugar such as mannose
- Gram negative bacteria have adhesins located at the ends of pili.

ADHERENCE AND INVASION

- The term **pili** (**pilus**) is also used to describe these projections for the tube-like projections that transfer genetic material from one bacterium to another in conjugation
- Gram positive organisms use other structures for adhesins (lipoproteins, etc). *Streptococcus pyogenes* uses lipoteichoic acid to bind to epithelial cells
- Once attached to target cells, many bacteria can then invade the cell

ADHERENCE AND INVASION

- Not all bacteria are invasive. Invasive organisms attach and enter host cells by a number of mechanisms:
  - Production of surface proteins called **invasins** that rearrange host cell actin filaments
  - Production of enzymes:
    - **collagenase** -breaks down collagen in connective tissue
    - **hyaluronidase** - breaks down hyaluronic acid that holds cells together
    - **Coagulase** - converts fibrinogen to fibrin producing a clot (may be protective against phagocytes)
    - **Kinases** - can break down clots decreasing the isolation of bacteria in clots (spreading effect)

TISSUE DAMAGE

- Most of the enzymes cause tissue destruction. Others include:
  - DNAase
  - Lipase
  - Phospholipase
  - Proteases
- Toxin production – toxins are bacterial products produced by certain microorganisms. They are byproducts of bacterial growth that are poisonous to host cells. Basically, there are exotoxins and endotoxins

TISSUE DAMAGE

- Exotoxins are generally released while the bacterium is actively growing but may also be released when the organism dies
- May be produced by both gram positive and gram negative bacteria
- Are protein in nature and many are enzymes that catalyze certain biochemical reactions.
- The genes for most exotoxins are carried on bacterial plasmids or bacteriophages

TISSUE DAMAGE

- Exotoxins are typically soluble in body fluids and can easily diffuse into the blood where they are rapidly transported systemically
- Many exotoxins are composed of A and B subunit and are called A-B toxins
  - The A subunit is the active or enzymatic component
  - The B subunit is the binding component
  - When the A-B toxin is released from the bacterium, the B subunit binds to a surface receptor on the host cell
  - Following binding, the toxin is transported across the plasma membrane where the two subunits separate. The A subunit then exerts its enzy activity

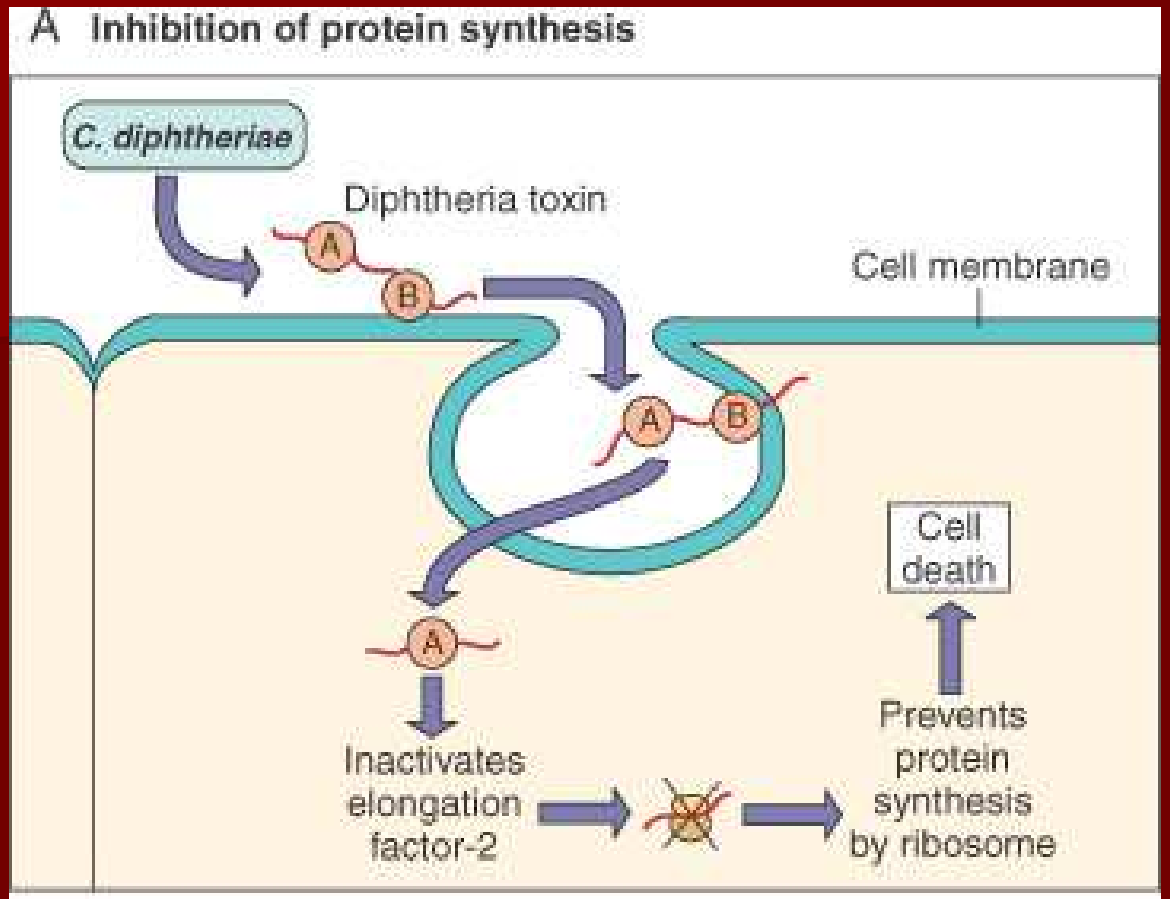


Figure 18–2A. The mode of action of dimeric A-B exotoxins. The bacterial A-B toxins often consist of a two-chain molecule. The B chain promotes entry of the bacteria into cells, and the A chain has inhibitory activity against some vital function. ACH, acetylcholine; cAMP, cyclic adenosine monophosphate.

(Redrawn from Mims C, et al: Medical Microbiology. London, Mosby-Wolfe, 1993.)

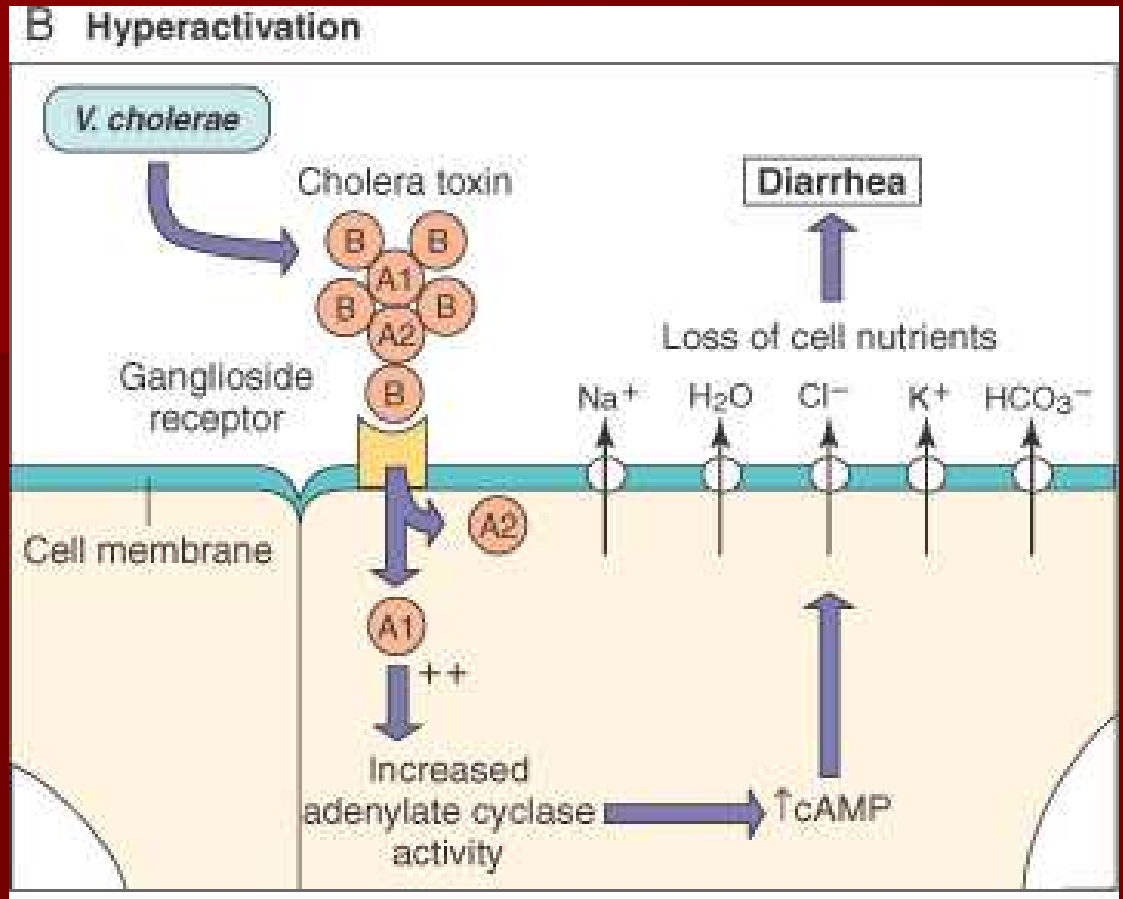


Figure 18–2B. The mode of action of dimeric A-B exotoxins. The bacterial A-B toxins often consist of a two-chain molecule. The B chain promotes entry of the bacteria into cells, and the A chain has inhibitory activity against some vital function. ACH, acetylcholine; cAMP, cyclic adenosine monophosphate.

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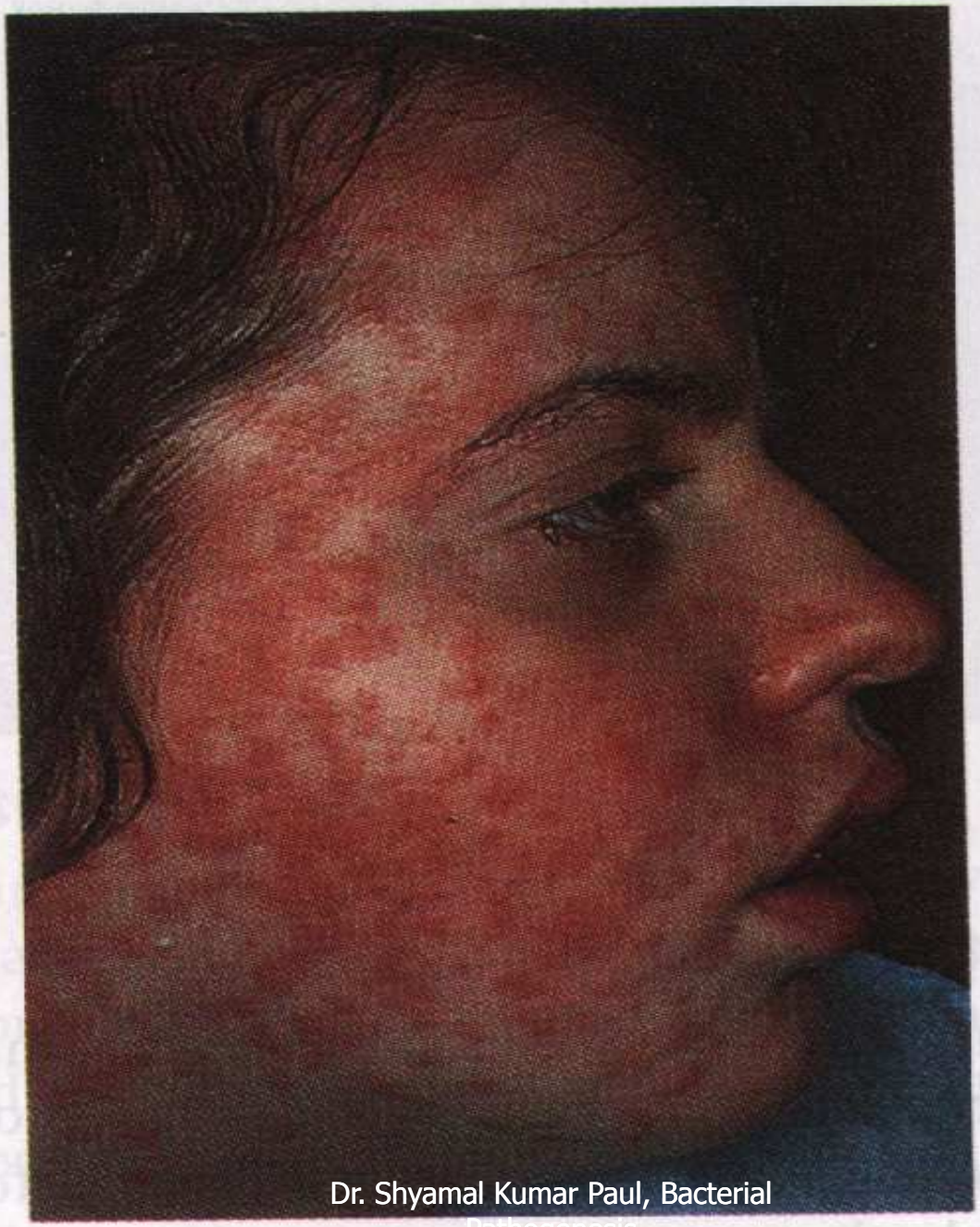
TISSUE DAMAGE

- Representative exotoxins:
  - Diphtheria toxin – inhibits protein synthesis
  - Erythrogenic toxins –*Streptococcus pyogenes* produces that damage plasma membranes of capillaries in the skin producing a red rash
  - Botulinum toxin – neurotoxin that inhibits acetylcholine LD_{50} for the botulism toxin is 10 nanograms/kg or 0.00001 mg/kg
  - Tetanus toxin – neurotoxin that inhibits the relaxation pathway resulting in uncontrollable muscle contractions
  - Vibrio enterotoxin – toxin increases intracellular cAMP resulting in prolonged hypersecretion of water and electrolytes



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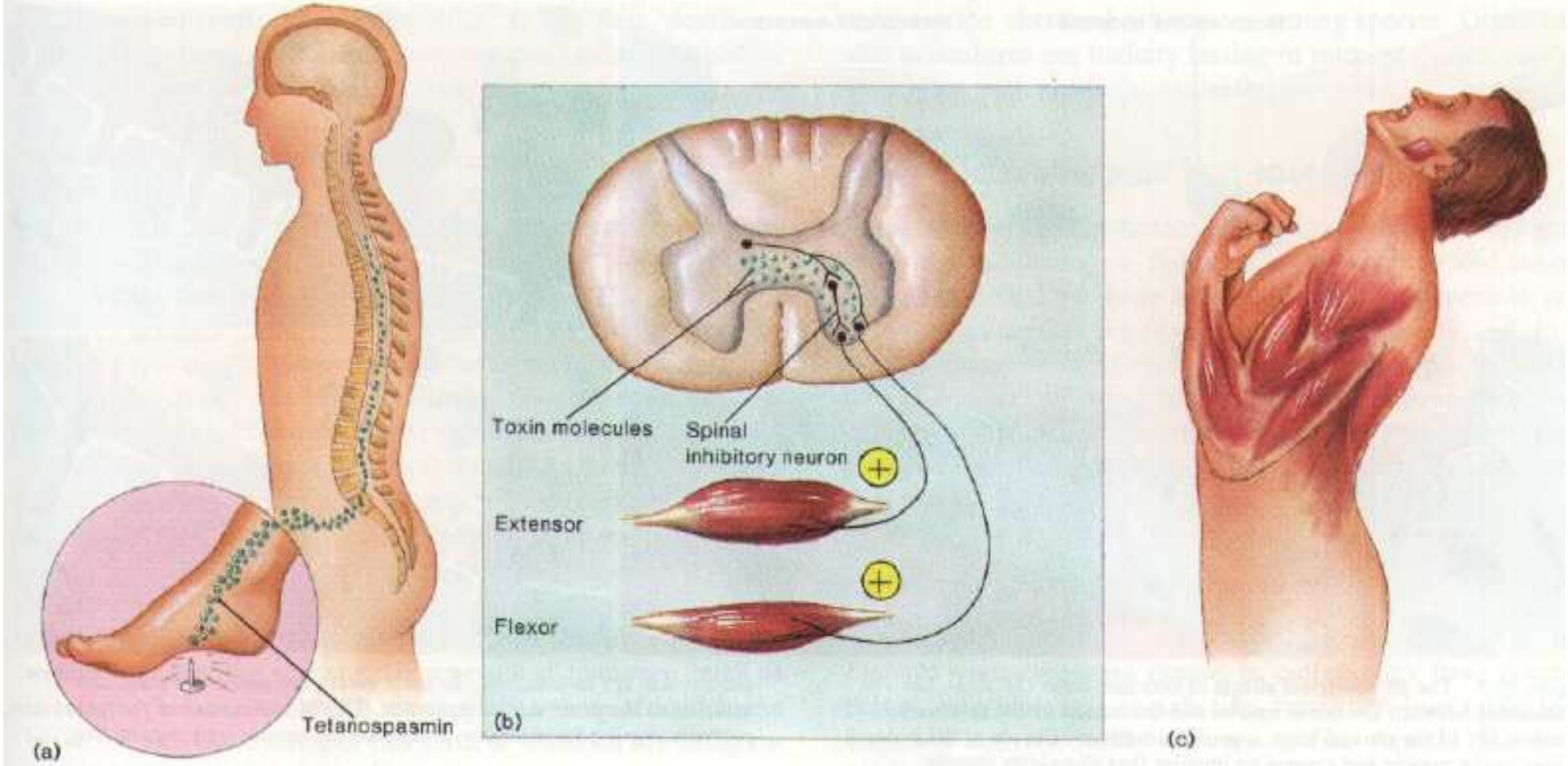

(a)
Tetanospasmin
Toxin molecules
Spinal
inhibitory neuron
Extensor
Flexor
(b)
(c)

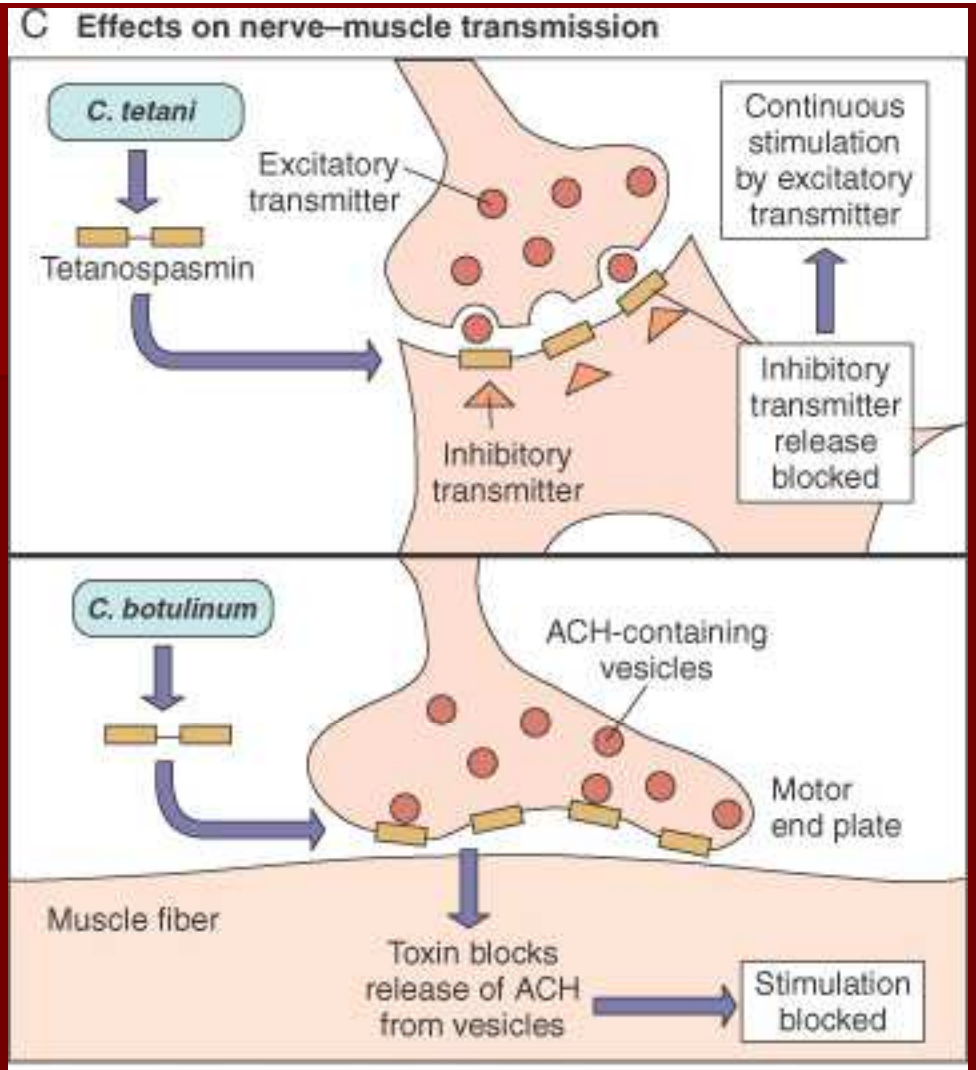


Figure 18–2C. The mode of action of dimeric A-B exotoxins. The bacterial A-B toxins often consist of a two-chain molecule. The B chain promotes entry of the bacteria into cells, and the A chain has inhibitory activity against some vital function. ACH, acetylcholine; cAMP, cyclic adenosine monophosphate.

(Redrawn from Mims C, et al: Medical Microbiology. London, Mosby-Wolfe, 1993.)

TISSUE DAMAGE

- Superantigens are a type of exotoxin that can bind to the outside of the T cell receptor and the major histocompatability complex receptor on antigen-presenting cells.
- This binding is not specific for a particular T cell and can result in production of large quantities of cytokines including interleukin 1 and tumor necrosis factor leading to systemic inflammatory responses
- Examples are staphylococcal toxic shock syndrome toxin, enterotoxins and erythrogenic toxins

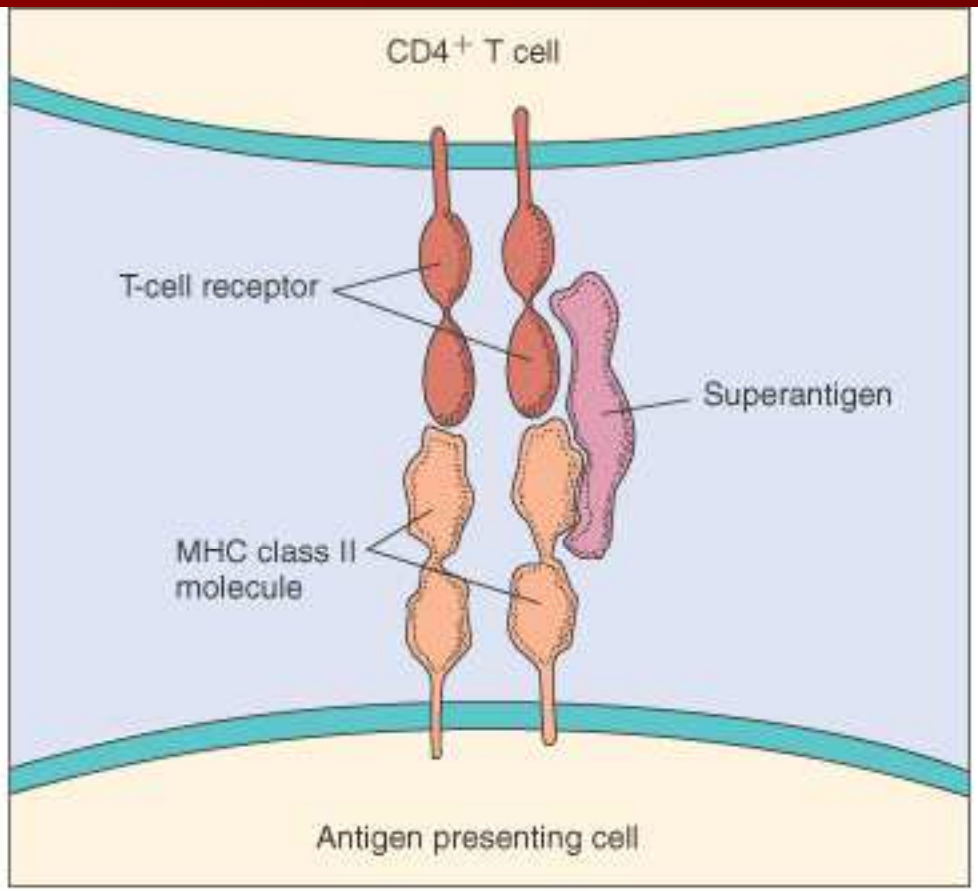


Figure 18–3. Superantigen binding to the external regions of the T-cell receptor and the major histocompatibility complex class II (MHC II) molecules.

TISSUE DAMAGE

- **Endotoxin** is an integral part of the outer leaflet of the **gram negative** cell wall. Also called lipopolysaccharide or LPS
- The actual toxic component of endotoxin is **lipid A**
- Endotoxin is released as gram negative bacteria lyse
- Are lipopolysaccharides and relatively resistant to heat. Exotoxins are readily denatured by heat

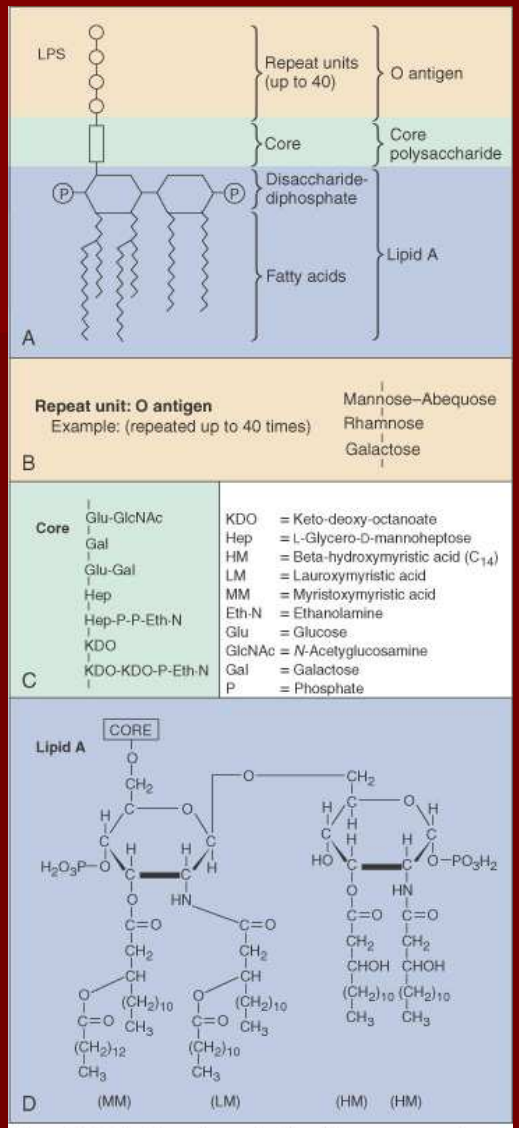


Figure 2–9. The lipopolysaccharide of the gram-negative cell envelope. **A,** Segment of the polymer showing the arrangements of the major constituents. Each LPS molecule has one Lipid A and one polysaccharide core unit but many repeats of O antigen. **B,** Structure of Lipid A of *Salmonella typhimurium*. **C,** Polysaccharide core. **D,** Typical O-antigen repeat unit *(S. typhimurium)*.

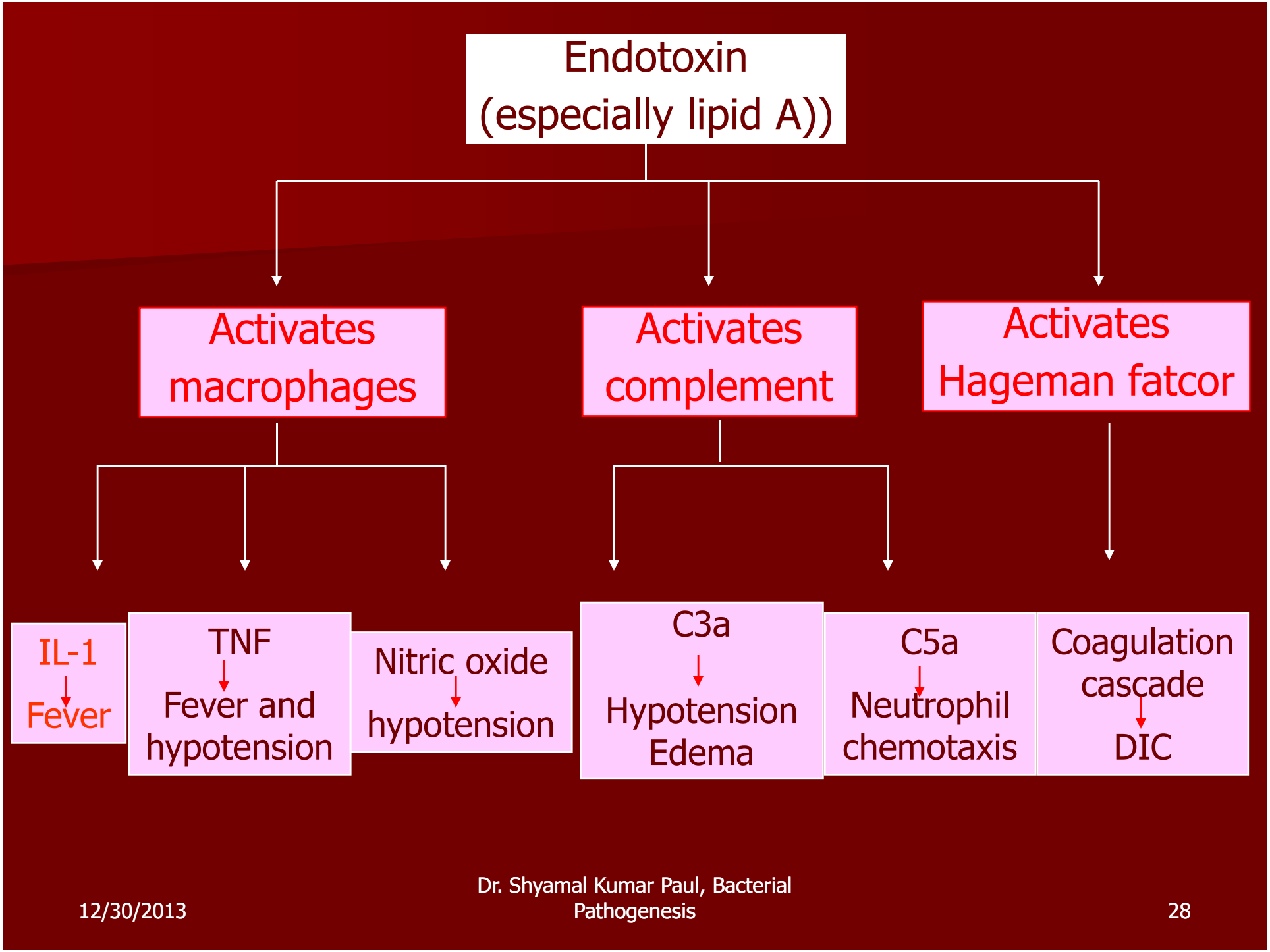
(Redrawn from Brooks GF, Butel JS, Ornston LN: Jawetz, Melnick and Aldenberg's Medical Microbiology, 19th ed. Norwalk, Connecticut: Appleton & Lange, 1991.)

TISSUE DAMAGE

- Endotoxin is one of many molecular patterns on bacteria termed **pathogen-associated molecular patterns** or PAMPs
- Upon release, endotoxin binds receptors (toll-like receptors or TLRs) on various cells including macrophages and B lymphocytes
- This binding leads to the stimulation of various cytokines including the pro-inflammatory cytokines Interleukin or IL-1, IL-6 and Tumor Necrosis factor or TNFα.
- At low concentrations inflammatory and immune responses occur

TISSUE DAMAGE

- At higher concentrations, endotoxin can induce what is known as gram negative shock, septic shock or endotoxic shock
- Due to activation of the complement pathway with the production of C3a and C5a (anaphylotoxins)
- These anaphylotoxins, along with inflammatory cytokines can lead to fluid loss from the vasculature and result in hypotension and shock
- Fever also results as IL-1 and TNFα stimulate the hypothalamus to adjust body temperature
- Disseminated intravascular coagulation (DIC) can also result from activation of the clotting mechanism


Endotoxin
(especially lipid A))
Activates macrophages
Activates complement
Activates Hageman fatcor
IL-1
Fever
TNF
Fever and hypotension
Nitric oxide
hypotension
C3a
Hypotension
Edema
C5a
Neutrophil chemotaxis
Coagulation cascade
DIC

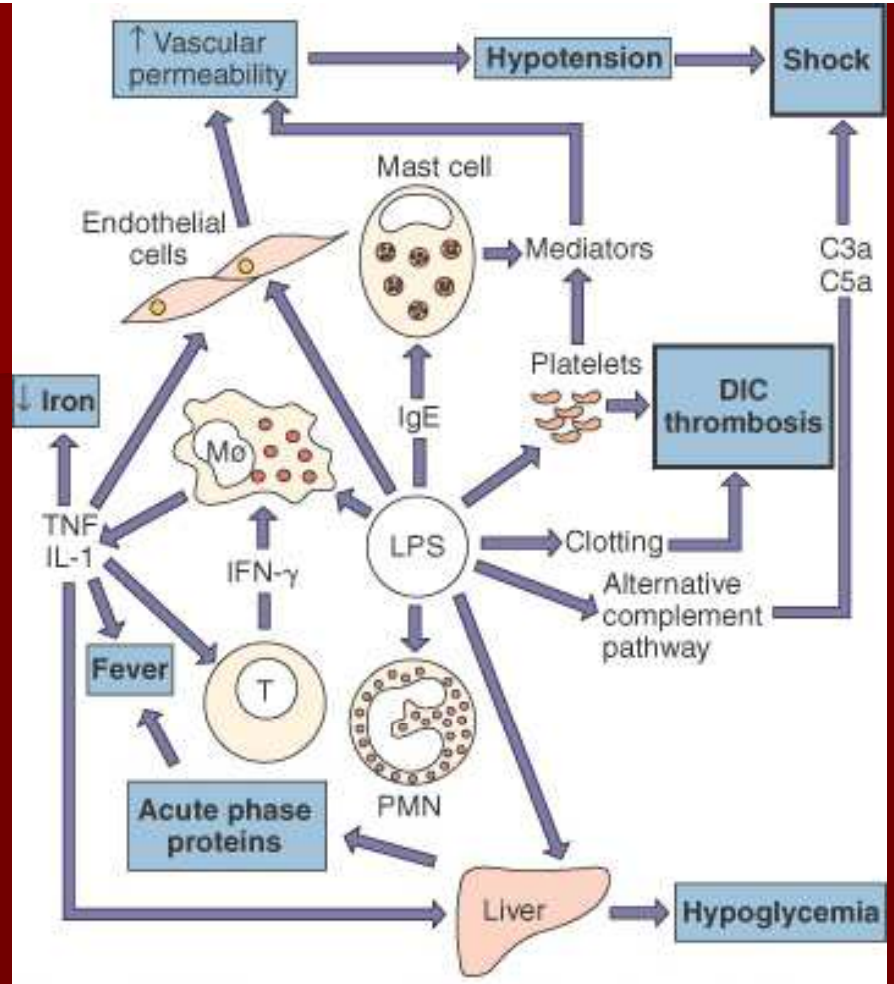


Figure 18–4. The many activities of lipopolysaccharide (LPS). This bacterial endotoxin activates almost every immune mechanism, as well as the clotting pathway, which together make LPS one of the most powerful immune stimuli known. DIC, disseminated intravascular coagulation; IFN-γ, interferon-γ; IgE, immunoglobulin E; IL-1, interleukin-1; PMN, polymorphonuclear (neutrophil) leukocytes; TNF, tumor necrosis factor.

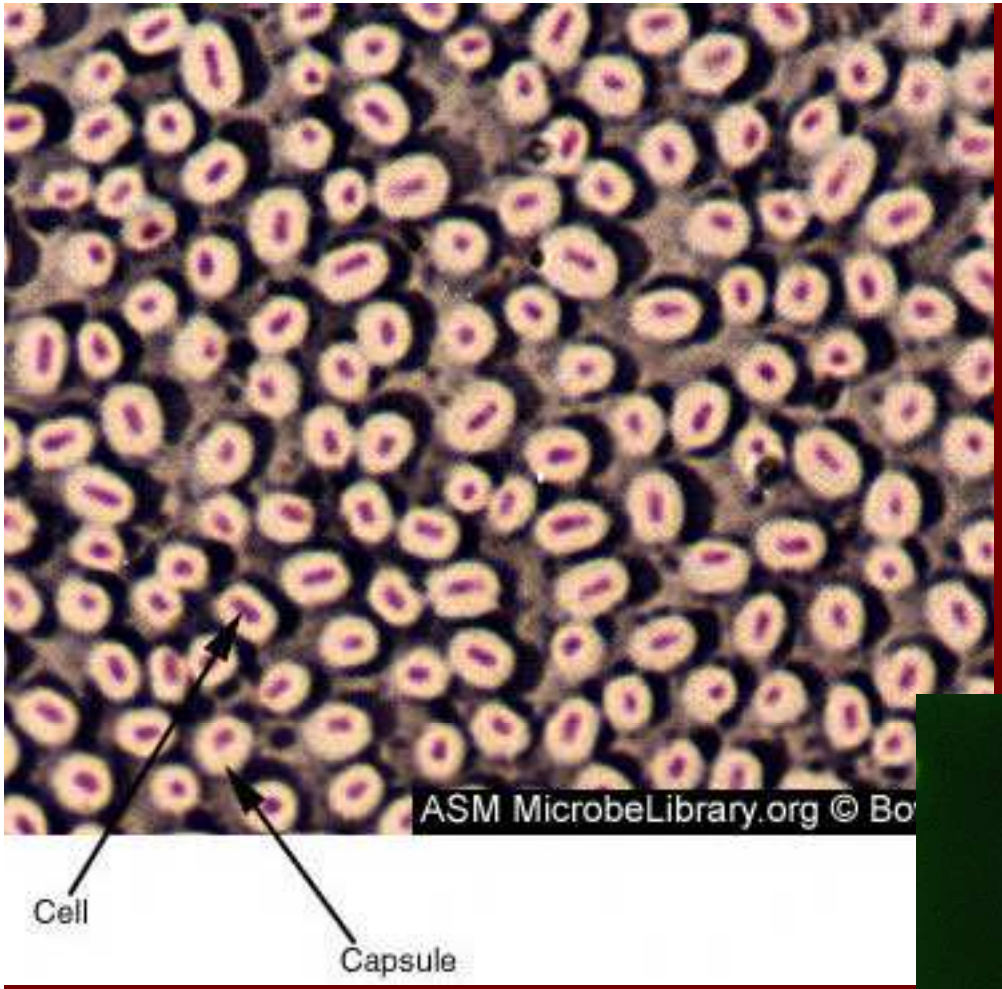
(Redrawn from Mims C, et al: Medical Microbiology. London, Mosby-Wolfe, 1993.)

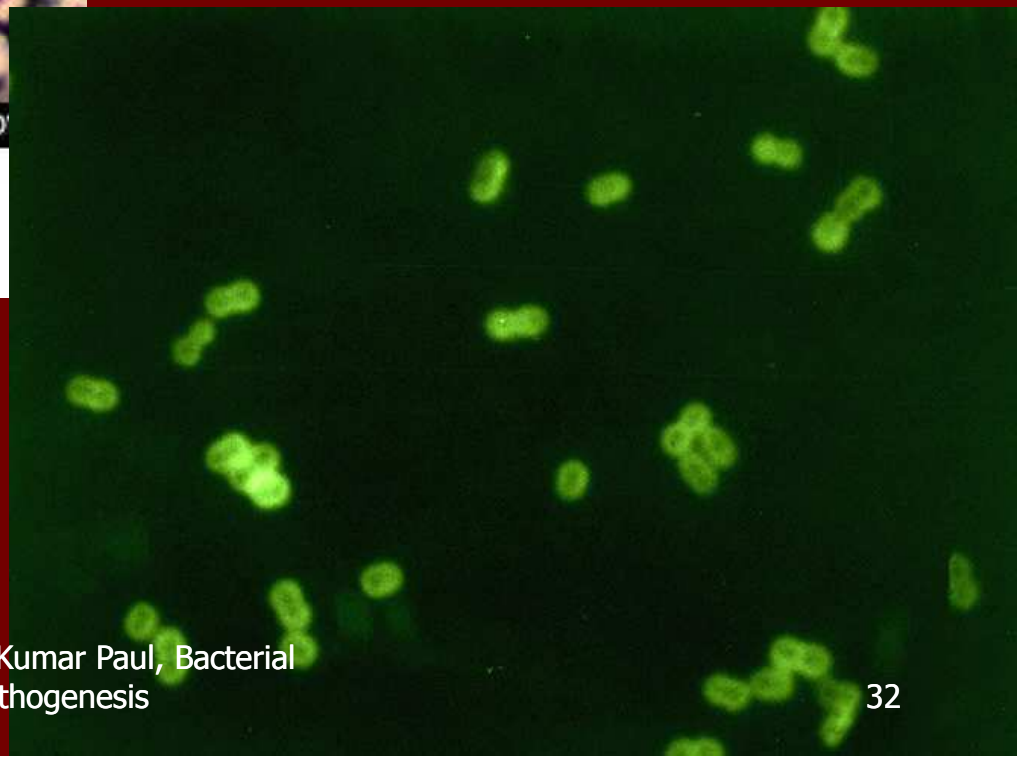
The different between indotoxin and exotoxin

kinds	exotoxin	indotoxin
source	**G +9ve) or a few G – (ve)**	**G – (ve)**
component	**protein**	**LPS**
stebility	**Short of**	**good、160℃ 2-4h destroyed**
virulence	**strong**	**weak**
antigenicity	**strong**	**weak**

MECHANISMS OF EVADING HOST DEFENSES

- Capsules – the chemical nature of the capsule appears to prevent phagocytic cells from adhering to the organism
  - Capsules are often polysaccharide in nature but may be amino acid (*Bacillus anthracis*)
- Cell wall components
  - M protein in *Streptococcus pyogenes* – mediates attachment and inhibits phagocytosis
- Intracellular growth
  - *Neisseria gonorrhoeae*
  - *Mycobacterium tuberculosis* – mycolic acid


ASM MicrobeLibrary.org © Bo
Cell
Capsule



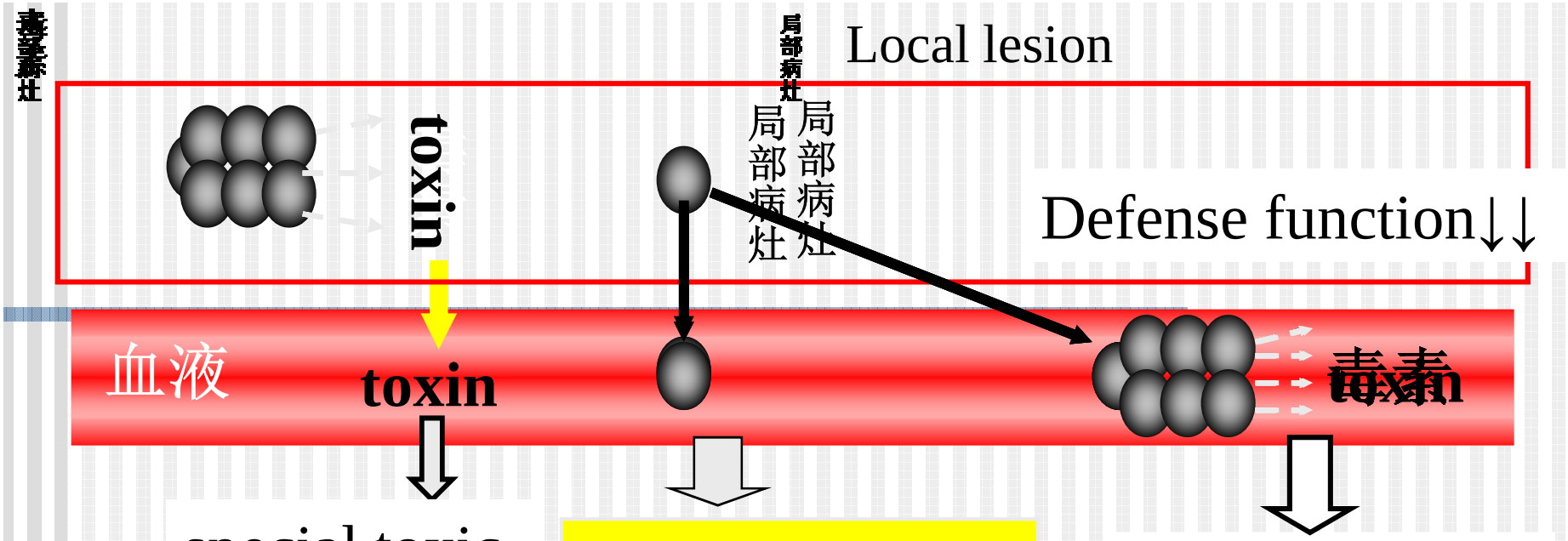
MECHANISMS OF EVADING HOST DEFENSES

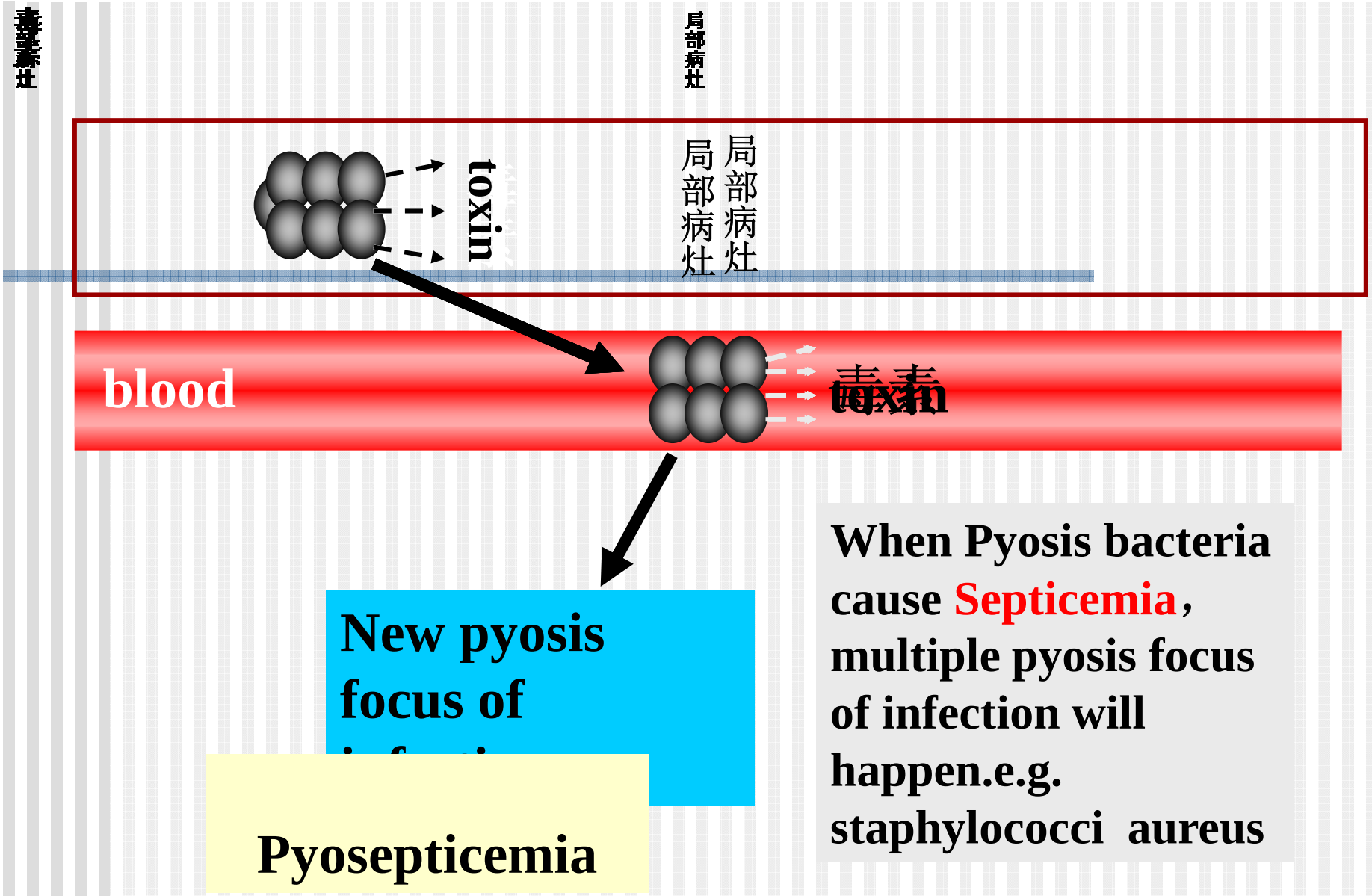
- Antigenic variation occurs when the organism has the genetic ability to produce different structural compositions for a particular bacterial structure which is recognized as an antigen by the immune system
- An example is *Neisseria gonorrhoeae* with multiple copies of the gene that codes for Opa protein (a protein that mediates binding of the organism with cells

Generalized infection

- Bacteremia
  - Definition: a transitory disease in which bacteria present in the blood are usually cleared from the vascular system with no harmful effects.
- Septicemia
  - Definition: a disease in which the blood serves as a site of bacterial multiplication as well as a means of transfer of the infectious agent from one site to another.

- Toxemia
  - Definition: the presence of microbial toxins in the blood
- Pyemia
  - Definition: the presence of pyogenic bacteria in the blood as they are being spread from one site to another in the body


Local lesion
toxin
局部病灶
Defense function↓↓
血液
toxin
toxin
special toxic symptom
pathogenic bacterium can grow in blood
Organism is seriously dadamaged, toxic symptom all over the body。
Toxemia
Bacteremia
Septicemia
e.g.tetanus



When Pyosis bacteria cause Septicemia, multiple pyosis focus of infection will happen.e.g. staphylococci aureus

Host resistance mechanisms

- Nonspecific host defenses
- Anatomical defenses
- Skin and mucosal membrane
  - Mechanical barriers
  - Secretions
  - Normal flora

- Blood-brain barrier
- Placenta barrier

- Cellular defenses: the reticuloendothelial system
- Molecular defenses: complements, lysozymes, etc

Innate immunity

Skin & mucous membranes

Intact skin

Fatty acids sebaceous glands

Mucous membrane of respiratory tract

1. ciliary action
2. traps many microorganisms

Lysozyme

Normal flora

Innate immunity

Inflammatory response & phagocytosis

(early host responses to bacteria infection)

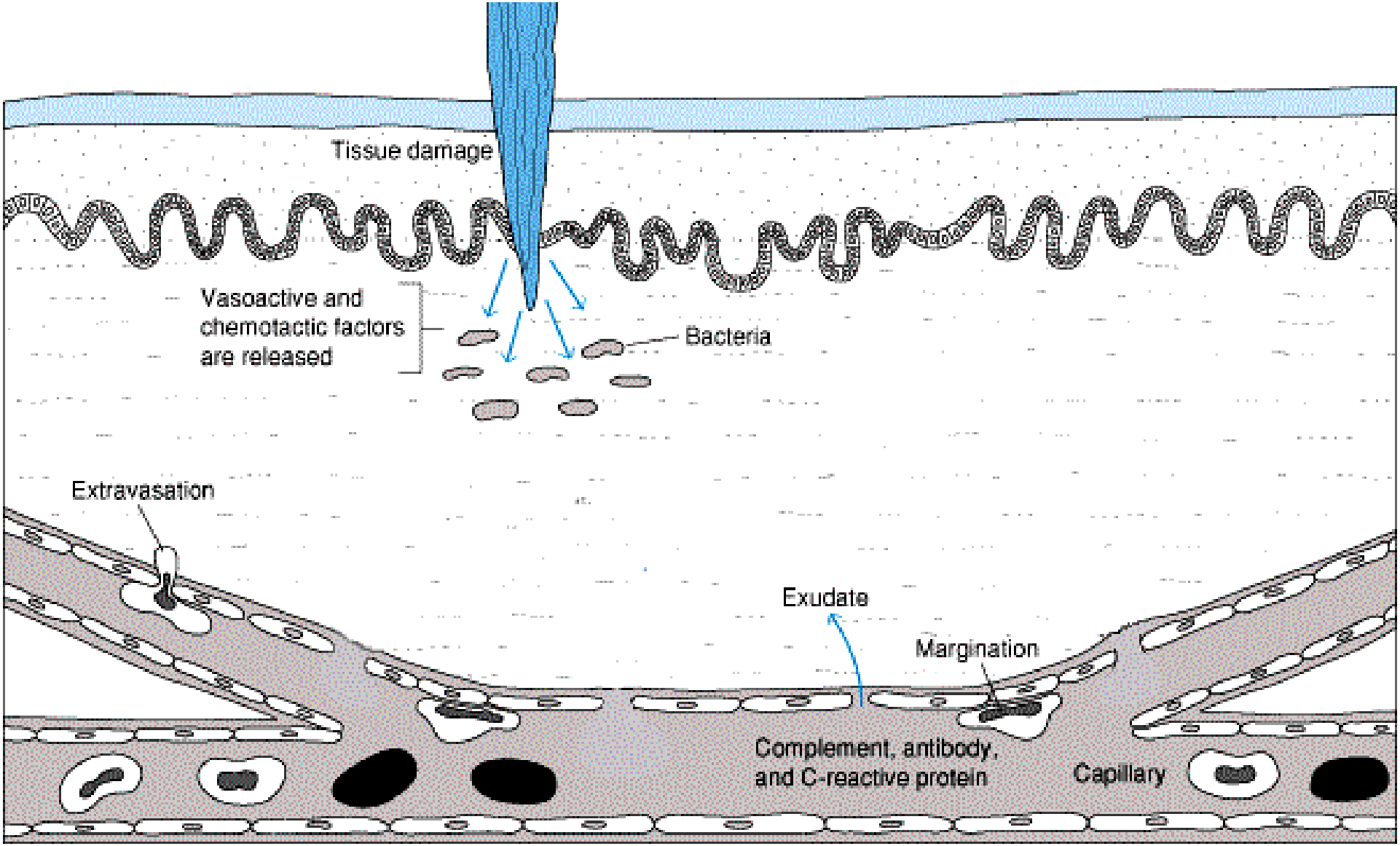
Bacteria infection→vasoactive factors → the increased permeability

Chemokines → Neutrophils and macrophages

Host resistance mechanisms

- Specific host of defenses
- Humoral immunity: antibody-mediated immunity
- Cellular immunity: cell-mediated immunity

Inflammatory response & phagocytosis


Tissue damage
Vasoactive and
chemotactic factors
are released
Bacteria
Extravasation
Exudate
Margination
Complement, antibody,
and C-reactive protein
Capillary

Acquired immunity

Humoral immunity

antibody to aggressin

antibody to toxin

Cell-mediated immunity

T cells

lymphokines (IFN- γ)

macrophages