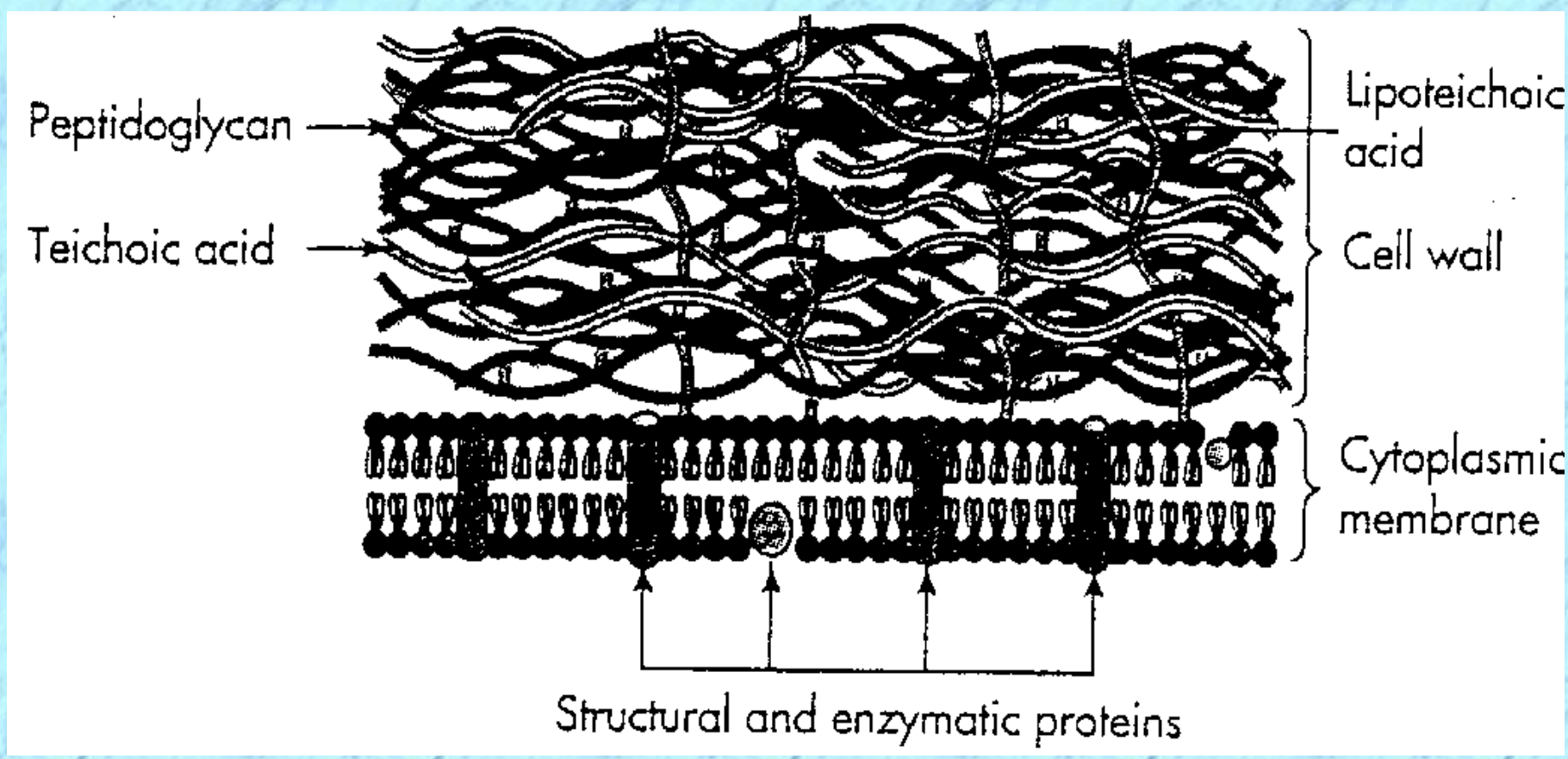
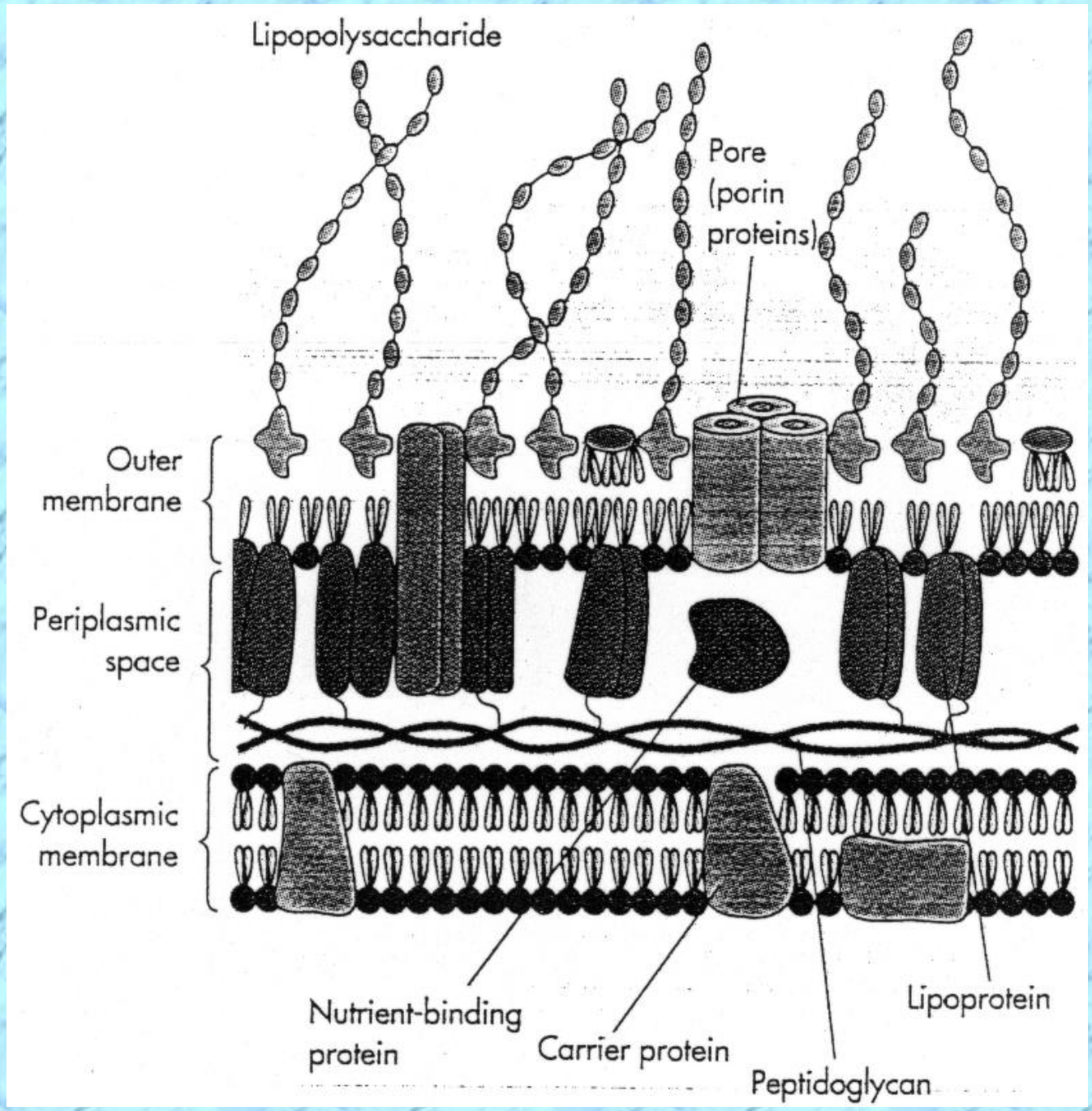
Lipopolysaccharide structure

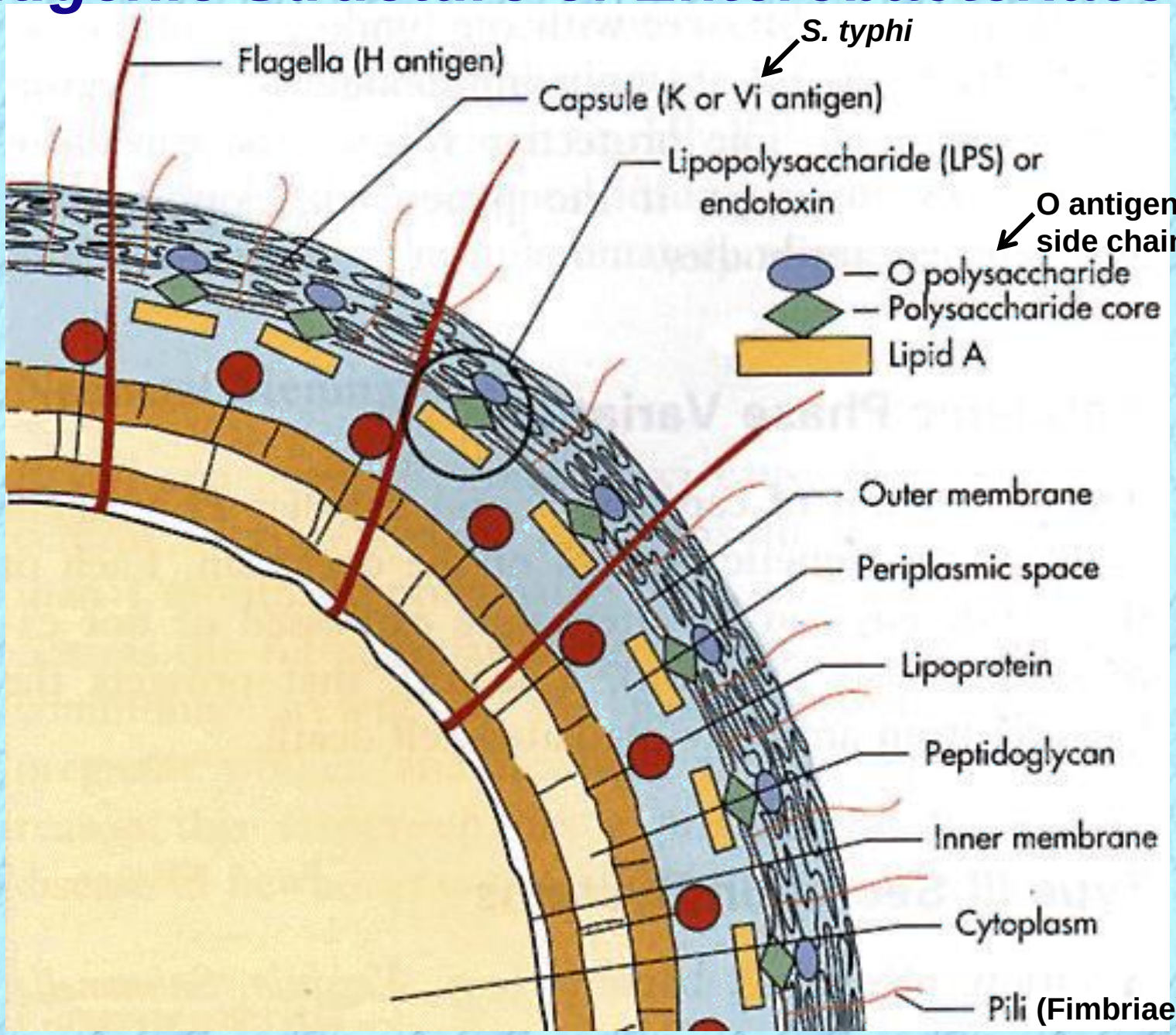
Gram-Positive Cell Wall

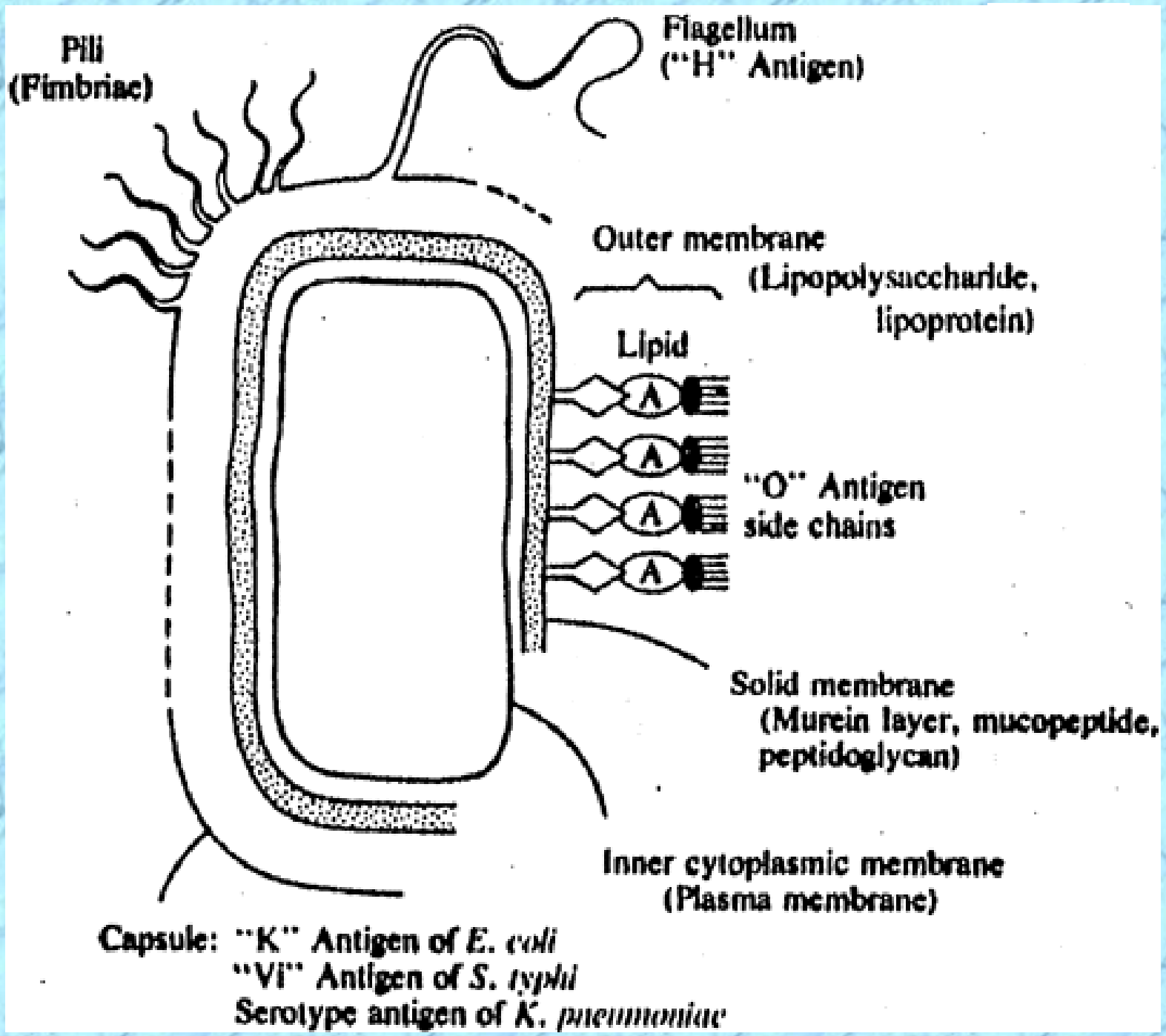


Gram-Negative Cell Wall

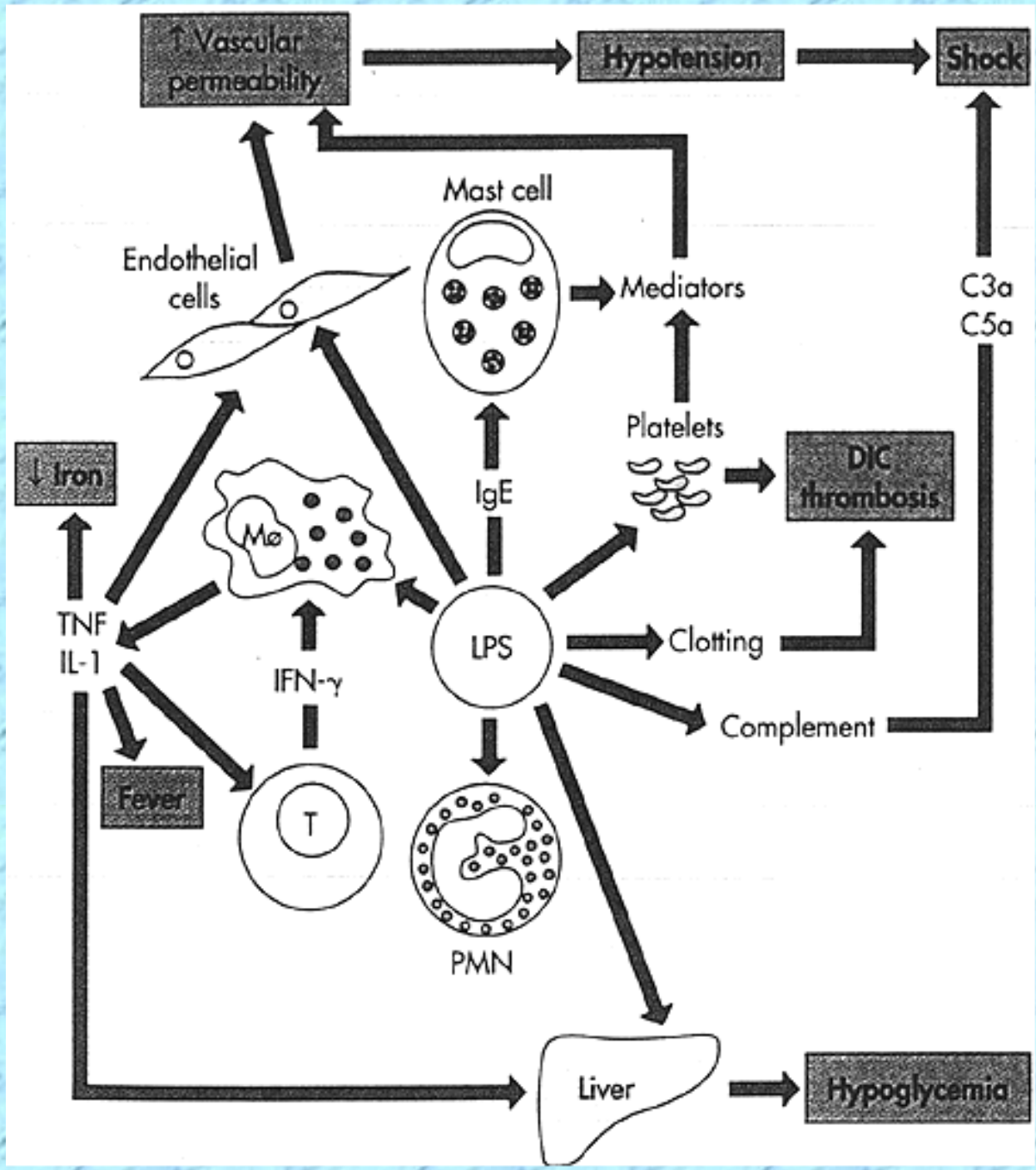


Antigenic Structure of Enterobacteriaceae



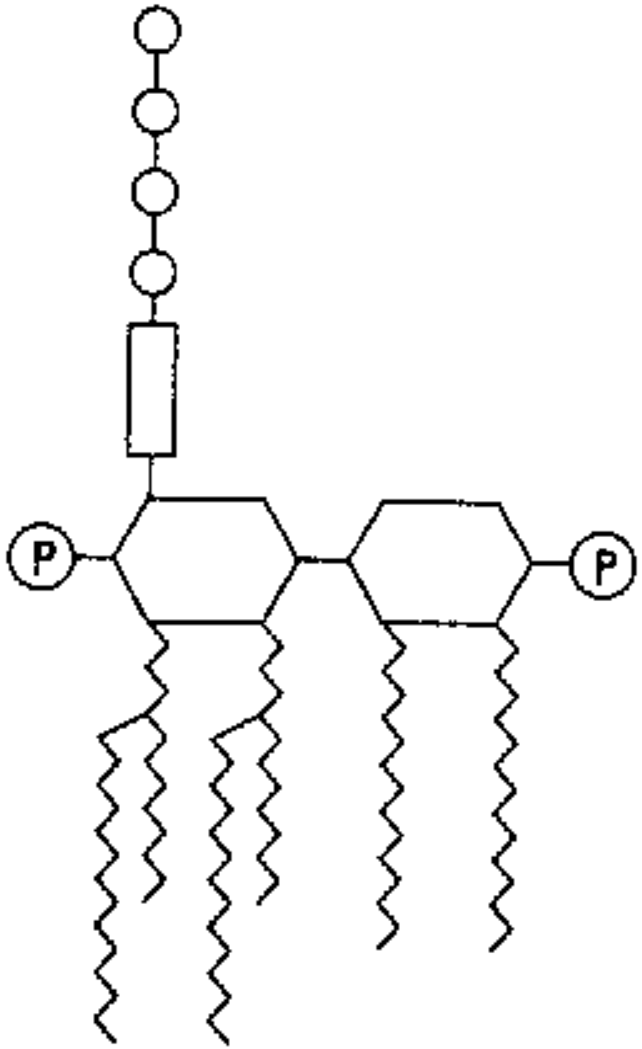

Pili
(Fimbriae)
Flagellum
("H" Antigen)
Outer membrane
(Lipopolysaccharide,
lipoprotein)
Lipid
"O" Antigen
side chains
Solid membrane
(Murein layer, mucopeptide,
peptidoglycan)
Inner cytoplasmic membrane
(Plasma membrane)
Capsule: "K" Antigen of E. coli
"Vi" Antigen of S. typhi
Serotype antigen of K. pneumoniae

Diversity of Activities Associated with LPS



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

Structure of Lipopolysaccharide



Repeat units (up to 40)

Core

Disaccharide-diphosphate

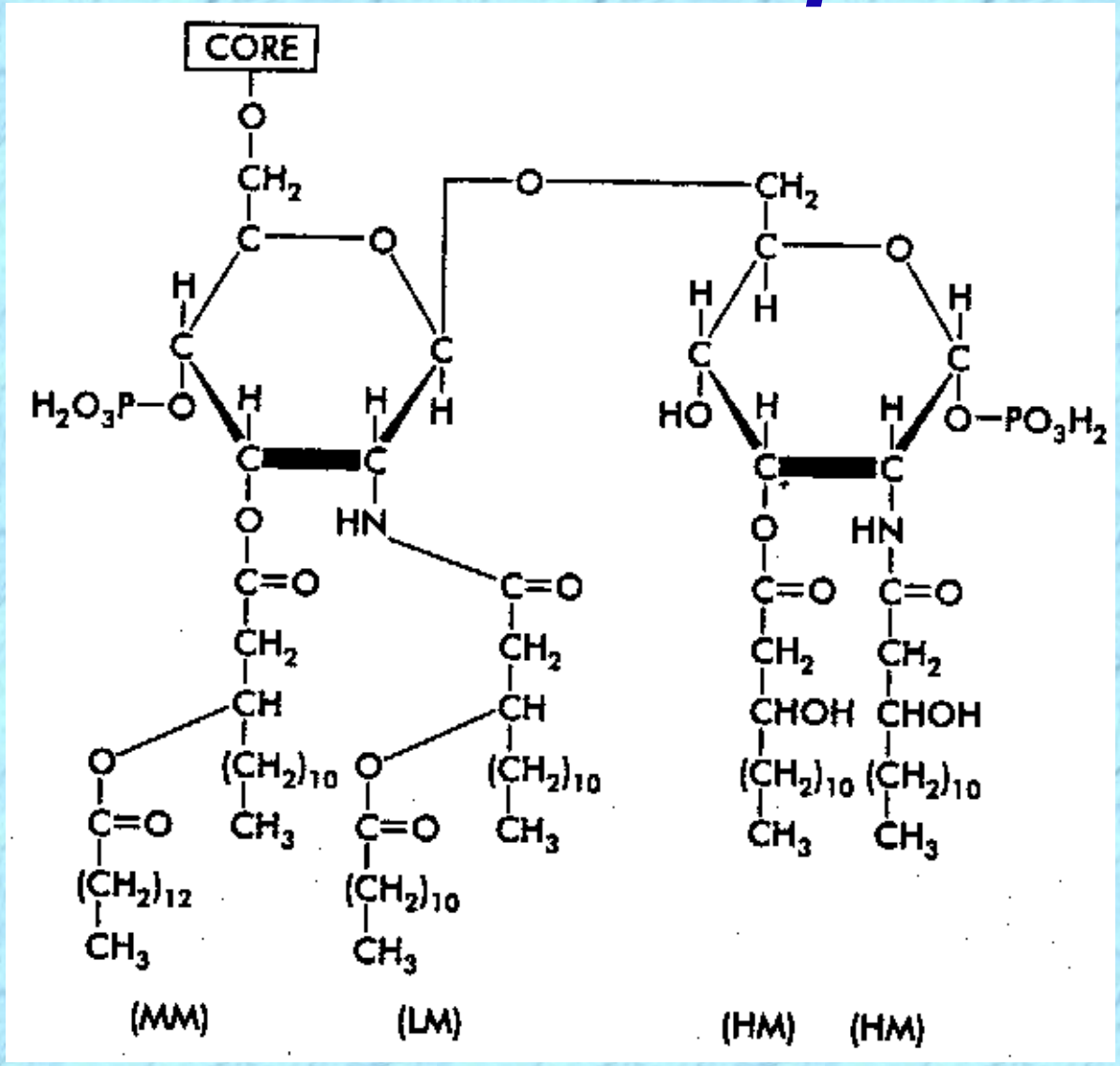
Fatty acids

O Antigen

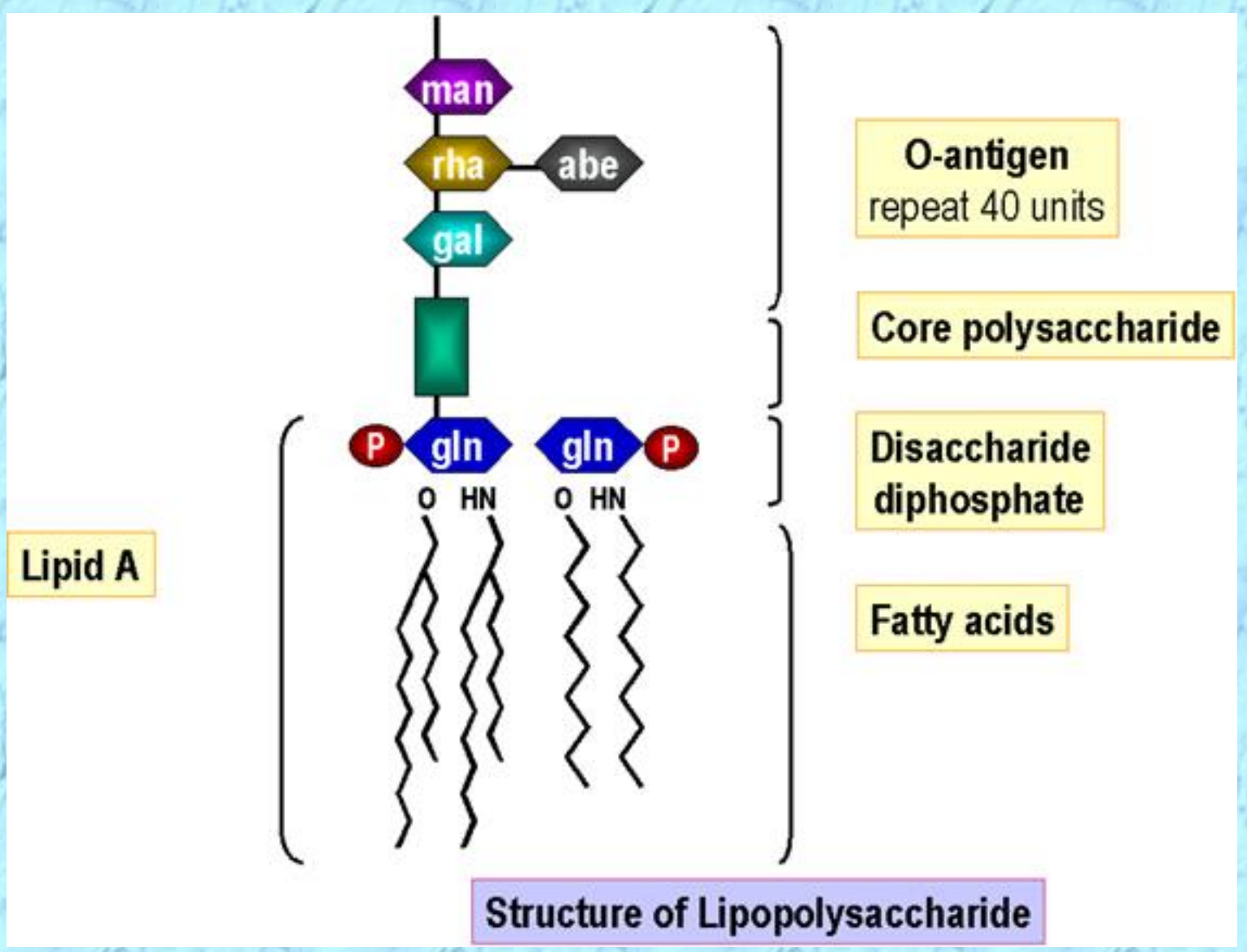
Core polysaccharide

Lipid A

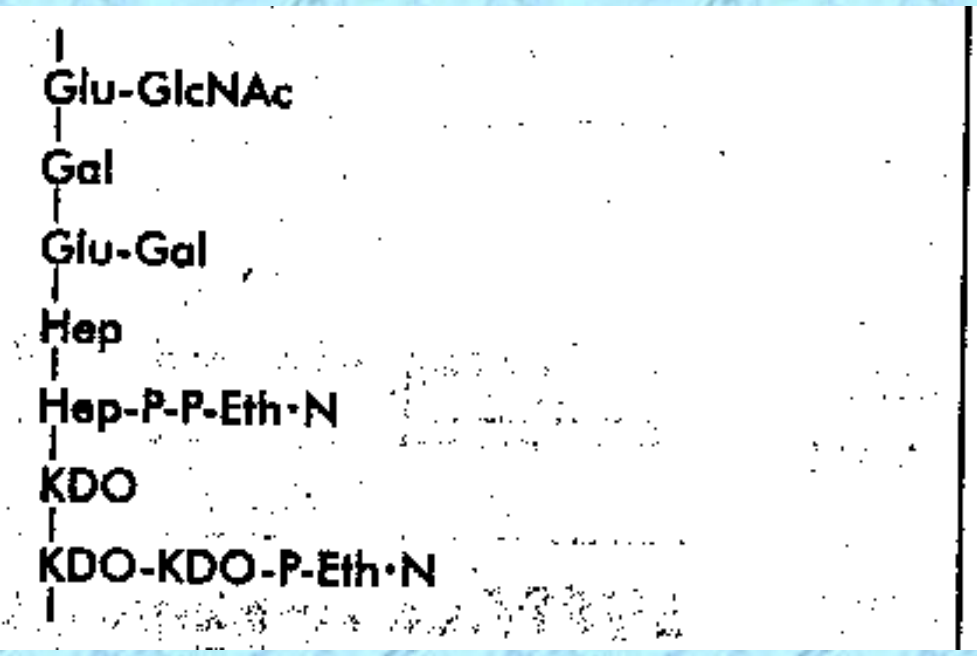
Structure of Lipid A



- **Hydrophobic** Lipid A is **endotoxic component**


man
rha
abe
gal
P
gln
gln
P
O HN
O HN
O-antigen
repeat 40 units
Core polysaccharide
Disaccharide
diphosphate
Fatty acids
Lipid A
Structure of Lipopolysaccharide

Structure of Core Polysaccharide

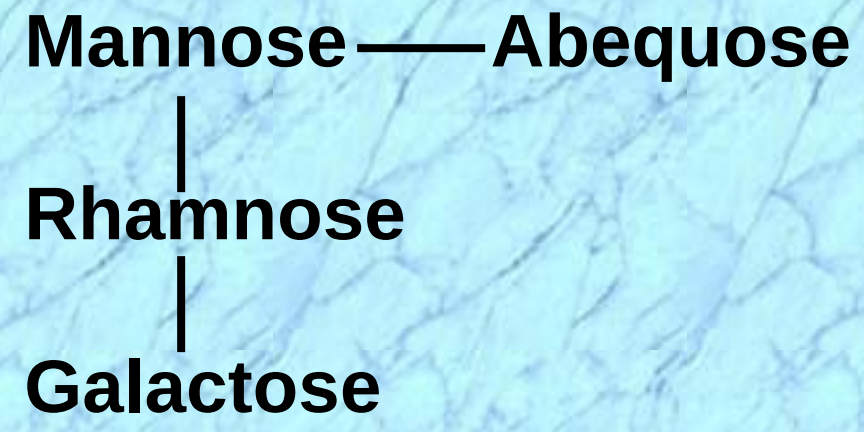


KDO = Keto-deoxy-octulonate
Hep = L-Glycero-D-mannoheptose
HM = β-Hydroxymyristic acid (C_{14})
LM = Lauroxymyristic acid
MM = Myristoxymyristic acid
Eth·N = Ethanolamine
Glu = Glucose
GlcNAc = N-Acetyglucosamine
Gal = Galactose

- **KDO** is **distinctive sugar** moiety in core polysaccharide

Repeat Units of O Antigen Side Chain

Example: (Repeated up to 40 times)



- **Heat stable** O antigen is often used to **serotype**

Lipooligosaccharide (LOS)

10-100kda

e.g. Naiseria spp. **Causative agent for gornorroea**

Virulence factors/Mechanism of Disease

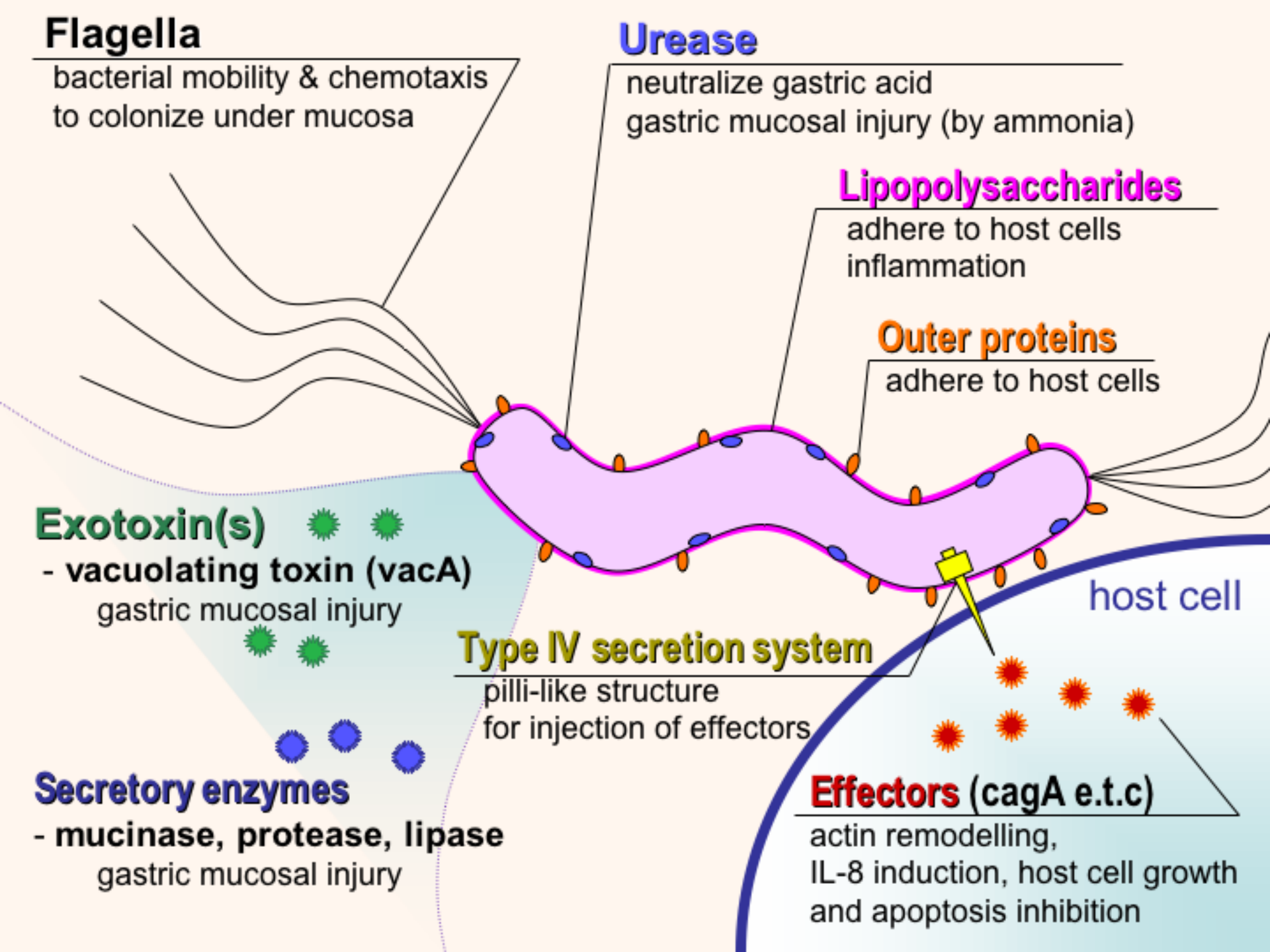
Consider an analogy of an INTRUDER (pathogen/microbe) breaking into a HOUSE (body) and either causing damage and or not

Pathogen- Microbe

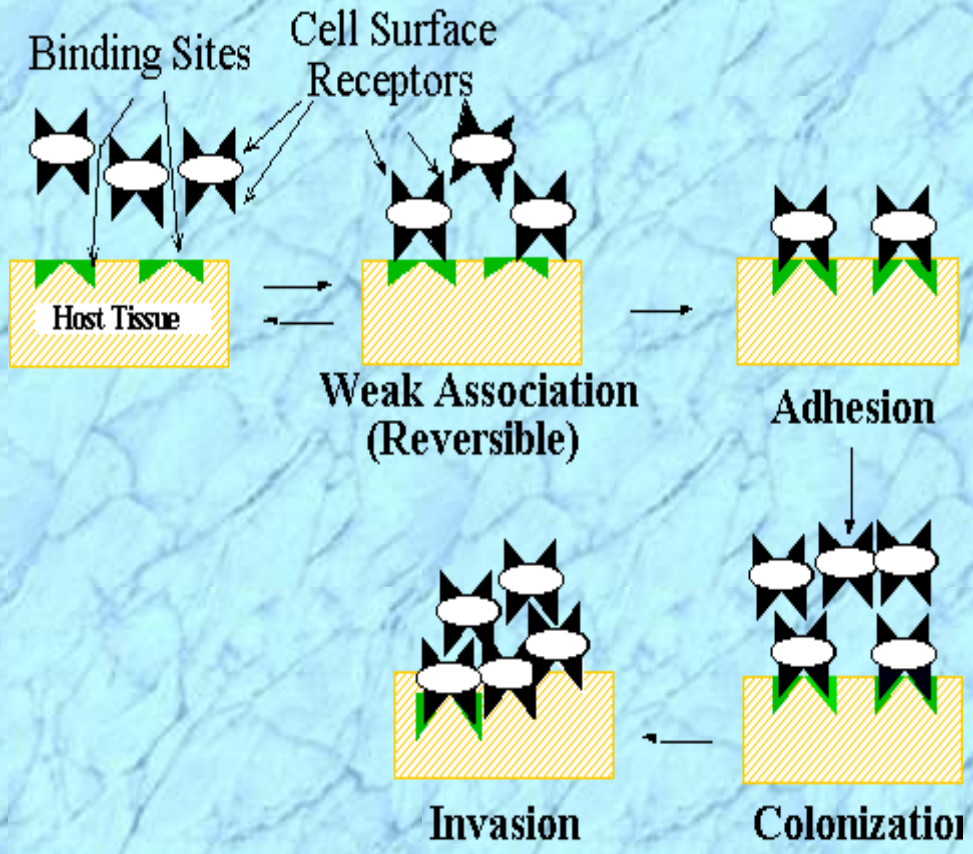
Pathogenicity- Ability to cause disease

Determinants of virulence

- Adhesion
- Evading host defense (phagocytosis)
- Damage- Cause damage to the cells


Flagella
bacterial mobility & chemotaxis
to colonize under mucosa
Urease
neutralize gastric acid
gastric mucosal injury (by ammonia)
Lipopolysaccharides
adhere to host cells
inflammation
Outer proteins
adhere to host cells
Exotoxin(s)
- vacuolating toxin (vacA)
gastric mucosal injury
Type IV secretion system
pilli-like structure
for injection of effectors
host cell
Secretory enzymes
- mucinase, protease, lipase
gastric mucosal injury
Effectors (cagA e.t.c)
actin remodelling,
IL-8 induction, host cell growth
and apoptosis inhibition

TheMechanisms of Bacterial Pathogenecity

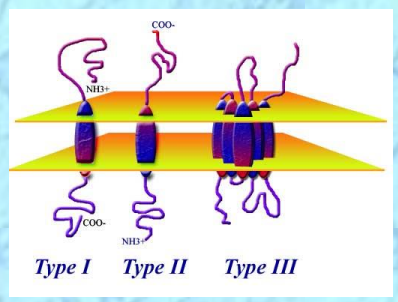


EXAMPLES OF SPECIFIC ATTACHMENTS OF BACTERIA TO HOST CELL OR TISSUE SURFACES

Bacterium	Adhesin	*Receptor*	*Attachment site*	*Disease*
Streptococcus pyogenes	*Protein F*	*Amino terminus of fibronectin*	*Pharyngeal epithelium*	*Sore throat*
Enterotoxigenic E. coli	*Type-1 fimbriae*	*Species-specific carbohydrate*	*Intestinal epithelium*	*Diarrhea*
Bordetella pertussis	*Fimbriae ("filamentous hemagglutinin*	*Galactoseon sulfated glycolipids*	*Respiratory epithelium*	*Whooping cough*

Bacterial VF can be divided into several groups on the basis of the mechanism of virulence and function:

Membrane Proteins

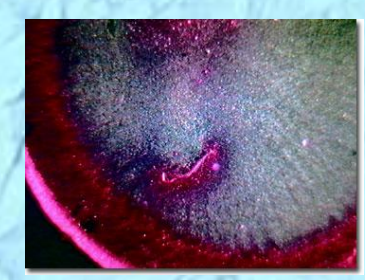


Adhesion, colonization and invasion

Promote adherence to the host cell surface

Responsible for resistance to antibiotics

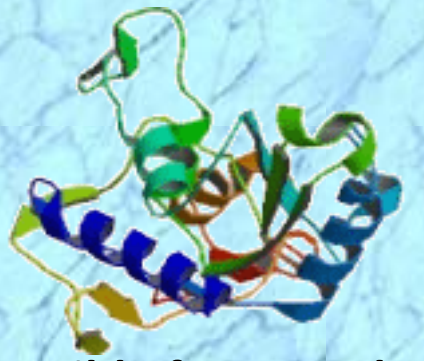
Promote intercellular communication



Polysaccharide Capsules

surround the bacterial cell and

have anti-phagocytic properties



Secretory Proteins

can be toxins

can modify the host cell environment and are responsible for some host cell-bacteria interactions

To understand HOW pathogenic bacteria interact with their host to produce clinical disease is fundamental

Discovering Virulence Factors **is the first step in understanding bacterial pathogenesis and their interactions with the host, which may also serve as a novel targets in drugs and vaccine development**

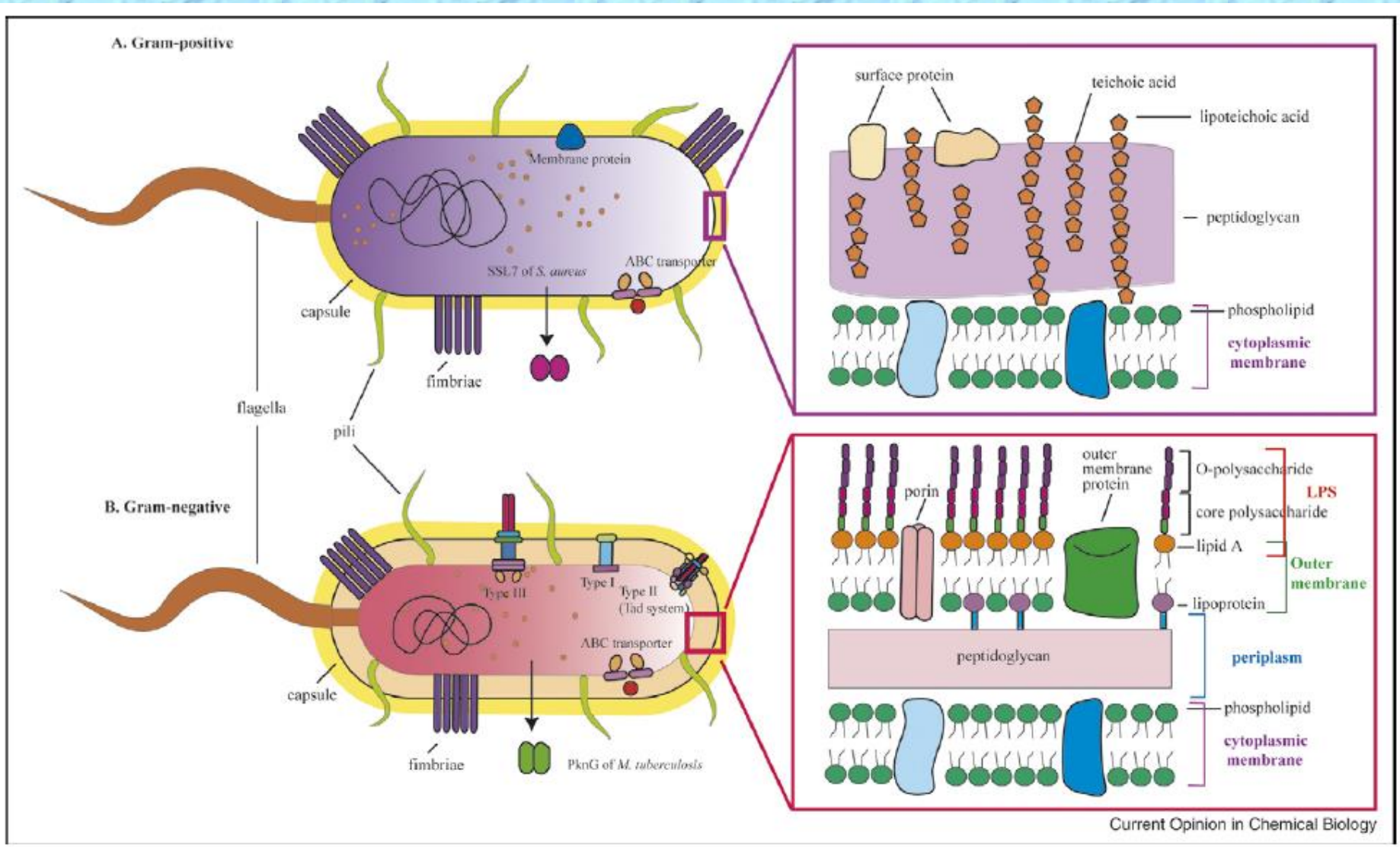
Comparative Genomics

& Transcriptomics

Proteomics

Important Tools in discovering VF in bacterial pathogens

Major Virulence Factors of Pathogenic Bacteria



Evading host immune system

Avoid phagocytosis

Capsule- Most pathogens have capsule

Enzyme synthesis e.g. Coagulase in S. aureus (boils, abscess, cellulitis).

Waxy cell wall

e.g. Mycobacterium- prevents phagocytosis and destruction

Calming signal

Signals the immune system not to produce Abs against the invading pathogen

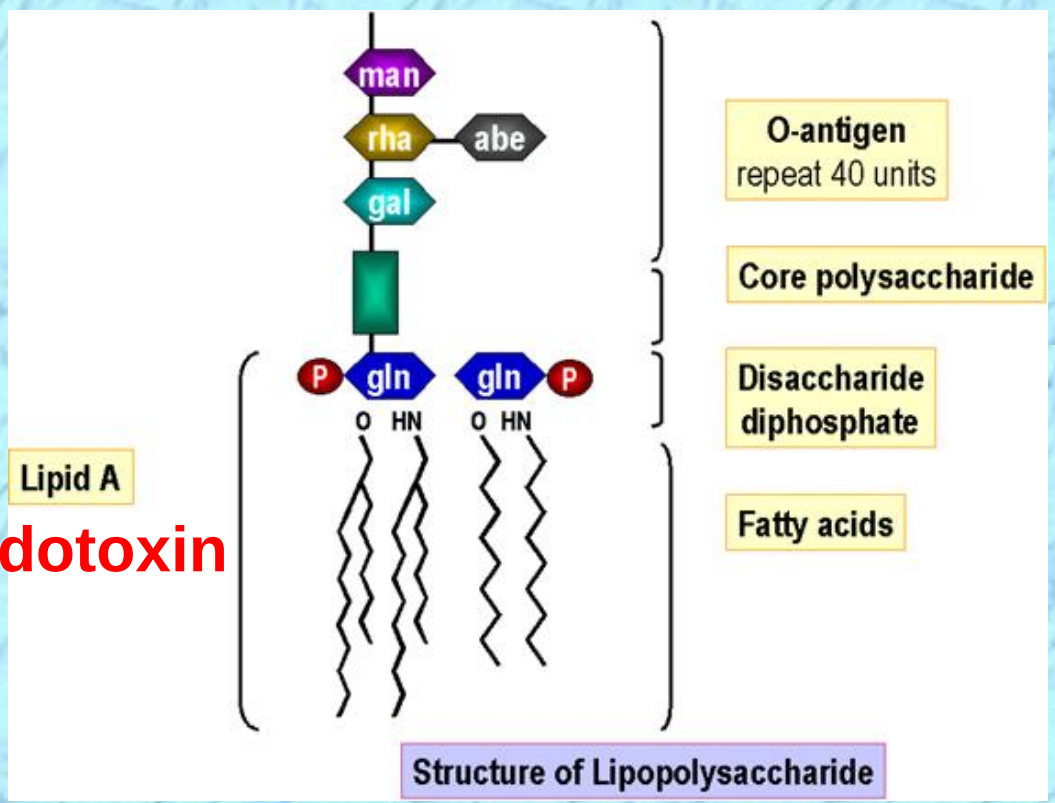
Antigenic variation

Most common factors used by many pathogens

Cause Damage

Endotoxin- Found within the bacteria

Exotoxin- Secreted outside of the cell



Endotoxin

1. Only found in G-ve bacteria
2. Known to stimulate cytokines- (super-antigen)
   - Cytokines storm
   - Fever
   - Body aches
   - Leaky blood vessels
   - Reduced blood pressure- Septic shock
   - Organ failure
   - DIC- Disseminated Intravascular Clotting

Superantigens

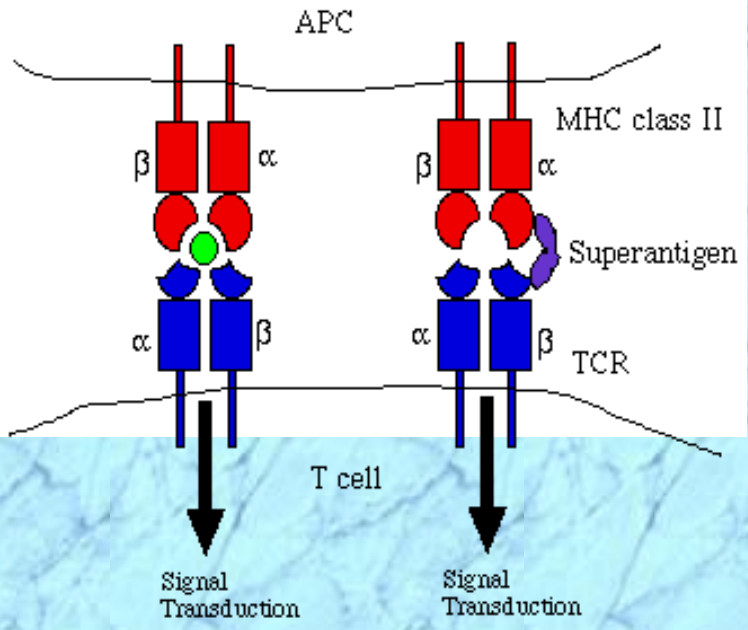
Special type of Exotoxin

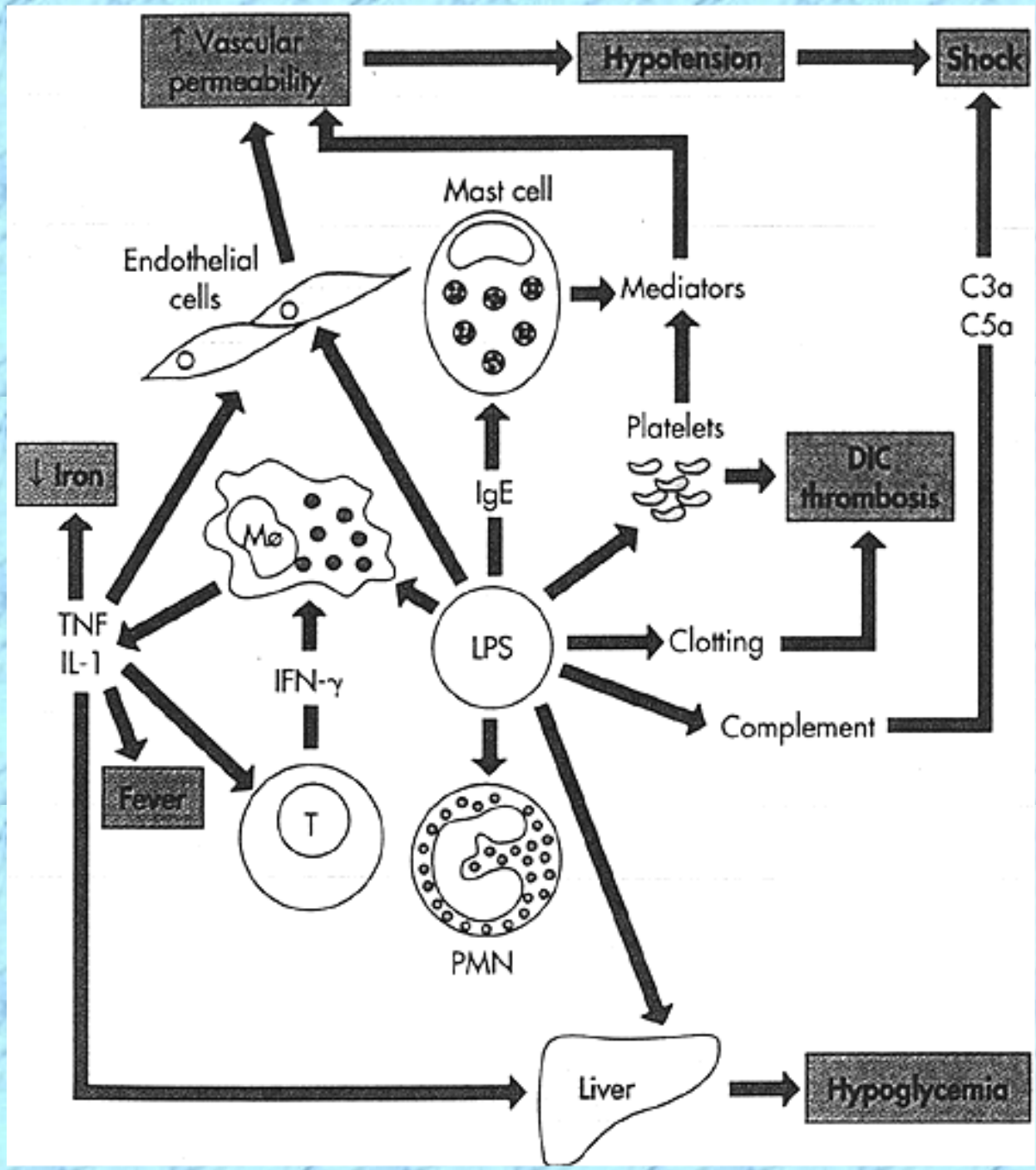
Nonspecifically stimulate T-cells.

Cause intense immune response due to release of cytokines from host cells.

Fever, nausea, vomiting,

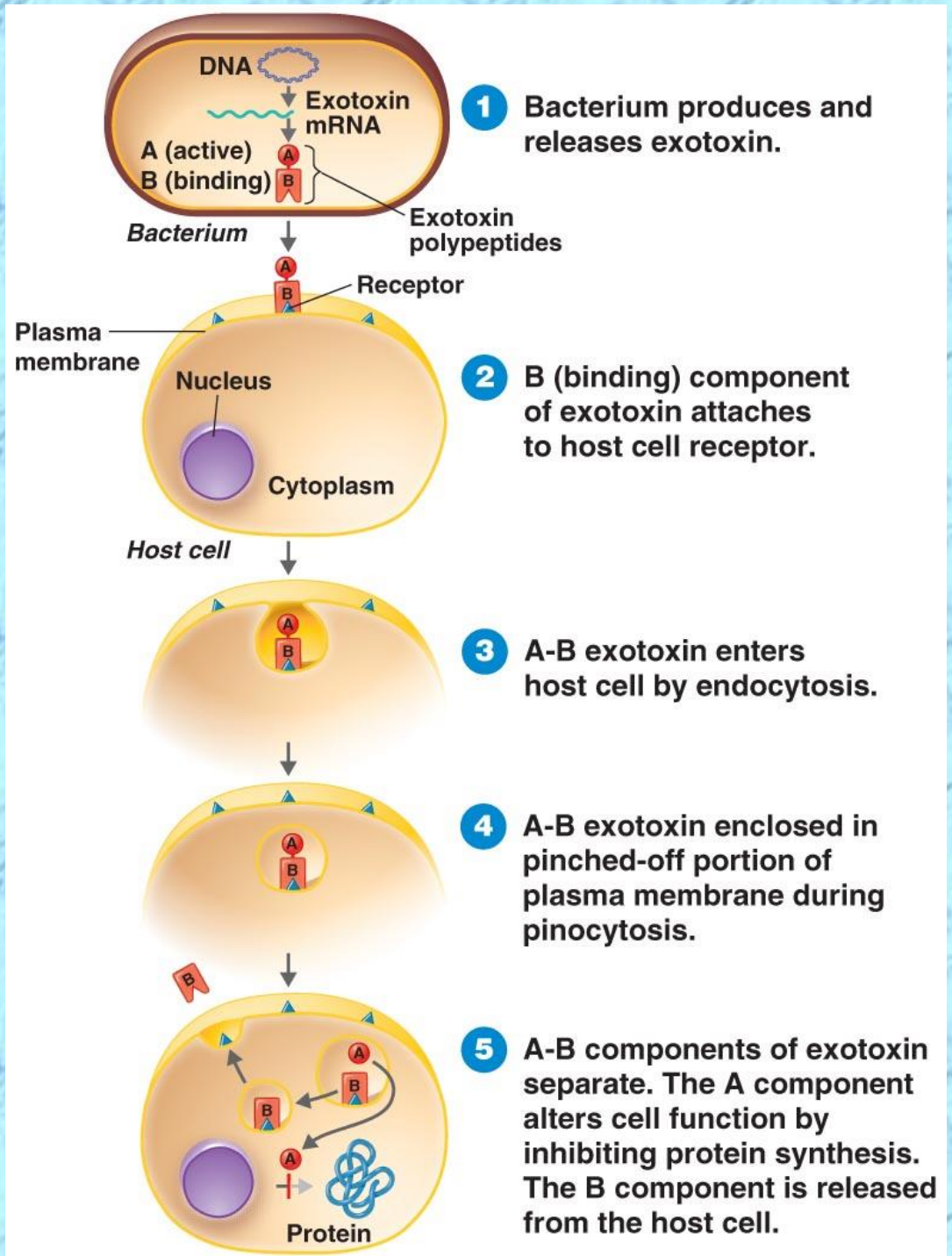
diarrhea, shock,
and death.




↑ Vascular permeability
Hypotension
Shock
Mast cell
Endothelial cells
Mediators
C3a
C5a
Platelets
↓ Iron
IgE
DIC thrombosis
Mø
TNF
IL-1
LPS
Clotting
IFN-γ
Complement
Fever
T
PMN
Liver
Hypoglycemia

Type of Exotoxins:

A-B Exotoxins



Exotoxin

Commonly found in G+ve bacteria

Cytotoxin

- Destroy RBC and sometimes WBC
- e.g. *S. pyogenes* is beta-hemolytic

Neurotoxin

- Blocks the transmission of chemical across the synaptic cleft E.g. *C. botulinum (*Flaccid paralysis)
- Stimulates the transmission leading to increased contraction. E.g. C. tetani (Spastic paralysis)

Enterotoxin

Promote leakage of potassium into the GIT and influx of water leading to Diarrhea and Dehydration

Streptococcus Mechanism of disease

Alpha-hemolytic

S. pneumoniae- otitis media, sinusitis, pneumonia

S. mutans- Caries/cavities (Plaque), Atherosclerotic plaque

Beta- hemolytic (Group A&B)

Group A- *S. pyogenes*

Strep throat

Otitis media

Scarlet fever

Beta- hemolytic (Group B)

S. agalactiae

Meningitis, Pneumoniae

S. pyogenes Mechanism of disease

Exotoxins

Invasins

Help bacteria move through tissues

Streptolysins

Hemolytic to RBC

Streptokinase

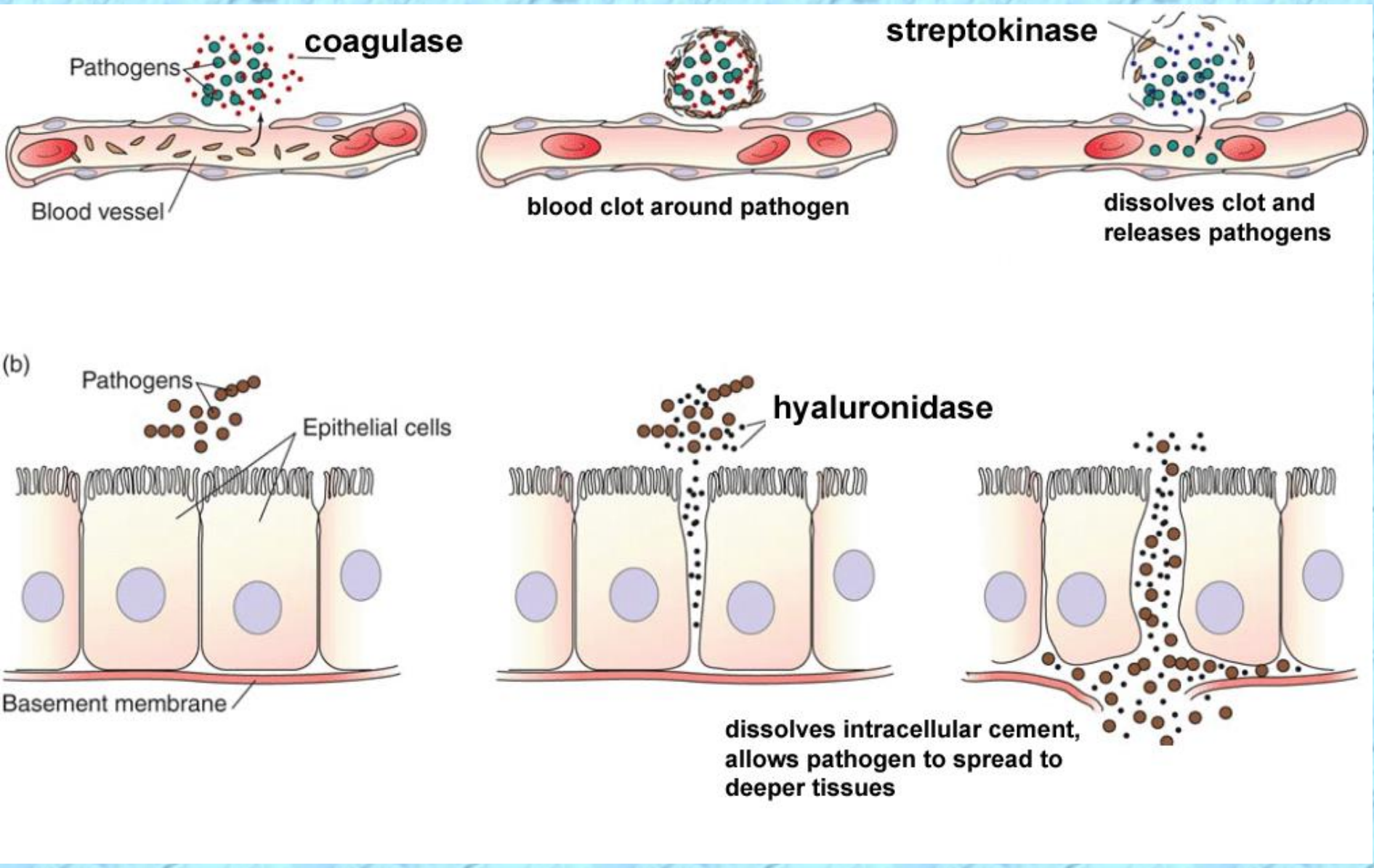
Digest blood clot and move through tissues

Pyogenic exotoxins

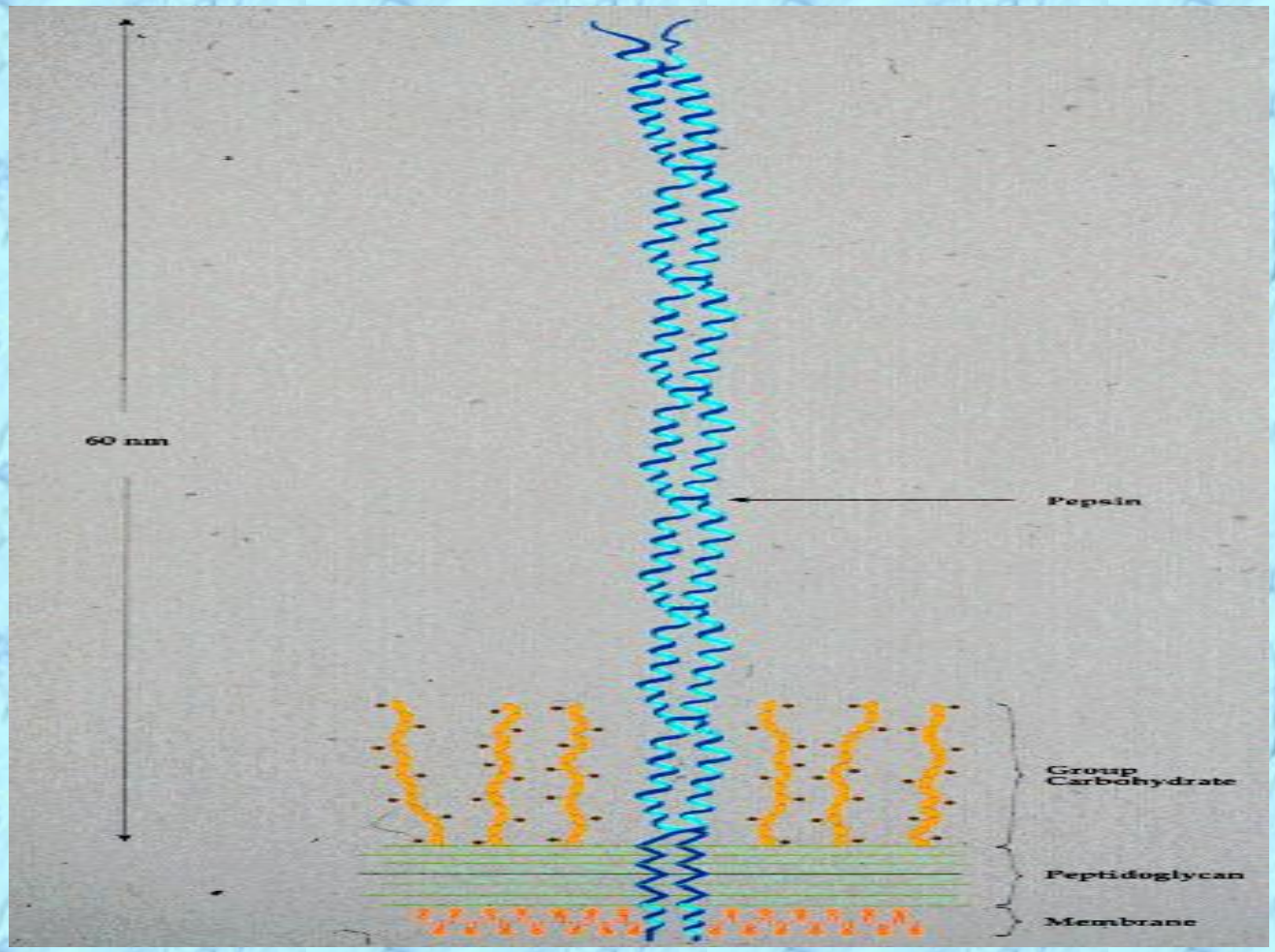
Inflammatory response

M proteins

Attacks Abs (Ig)


coagulase
Pathogens
Blood vessel
blood clot around pathogen
streptokinase
dissolves clot and
releases pathogens
(b)
Pathogens
Epithelial cells
Basement membrane
hyaluronidase
dissolves intracellular cement,
allows pathogen to spread to
deeper tissues

M PROTEIN STRUCTURE



✯Apoptosis as Bacterial virulense factor

programmed cell death: activation of apoptosis to destroy cells,

- ***utilization of apoptosis to initiate inflammation***

- ***The induction of apoptosis by Bordetella pertussis adenylate cyclase hemolysin***

•P. aeruginosa can induce apoptosis by producing exotoxin

Quorum Sensing as a virulence factor

- ***An important factor in the pathogenesis of some infections is a bacterial cell-to-cell signaling mechanism, referred to as "quorum sensing", which enables bacteria to coordinately turn on and off specific virulence genes through the production of autoinducer molecules.***

- ***Interference or blocking of quorum-sensing systems lead to inhibition of a variety of virulence factors.***

Genomics and Bacterial Pathogenesis

- ***Complete knowledge of an organism's genetic makeup allows exhaustive identification for virulence genes, vaccine and antimicrobial targets, and diagnostics.***

- ***Understanding the genomes of pathogenic bacteria is the solution.***