

# Microbes as Agents of Infectious Disease

- Normal Flora
- Virulence and Pathogenicity
- Toxicity vs. Invasiveness

# WE ARE NOT ALONE!

“We are outnumbered. The average human contains about 10 trillion cells. On that average human are about **10 times as many microorganisms**, or 100 trillion cells...As long as they stay in balance and where they belong, [they] do us no harm...In fact, many of them provide some important services to us. [But] most are opportunists, who if given the opportunity of increasing growth or invading new territory, will cause infection.”

- Sullivan (1989)

## Take Home Message:

Prokaryotic Cells  $\sim 10^{14}$  cells/body

Eukaryotic Cells  $\sim 10^{13}$  cells/body

Normal Flora helps maintain our health

- Provides vitamins & nutrients
- Detoxify many compounds
- Prevent colonization of pathogens

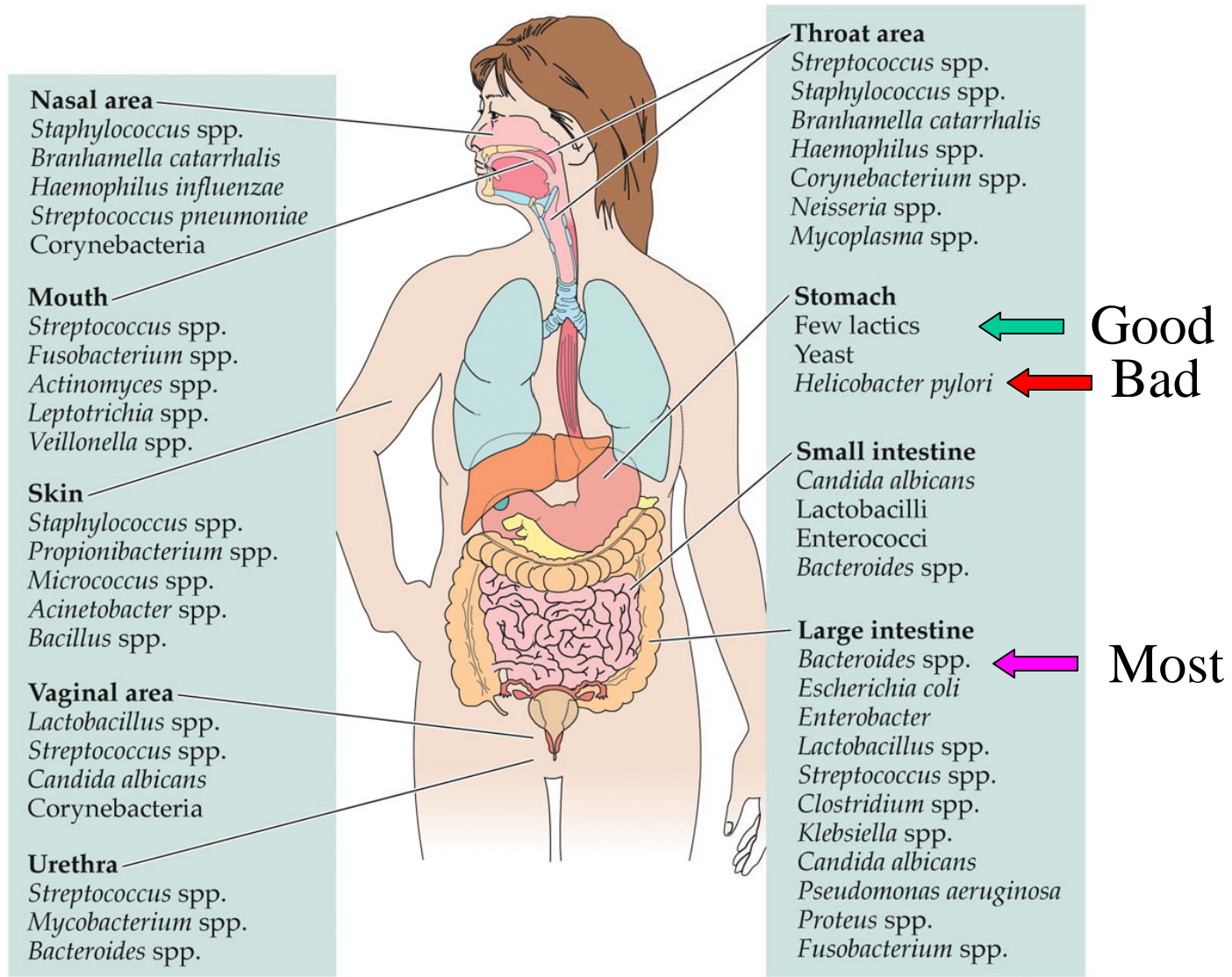
Table 21.1

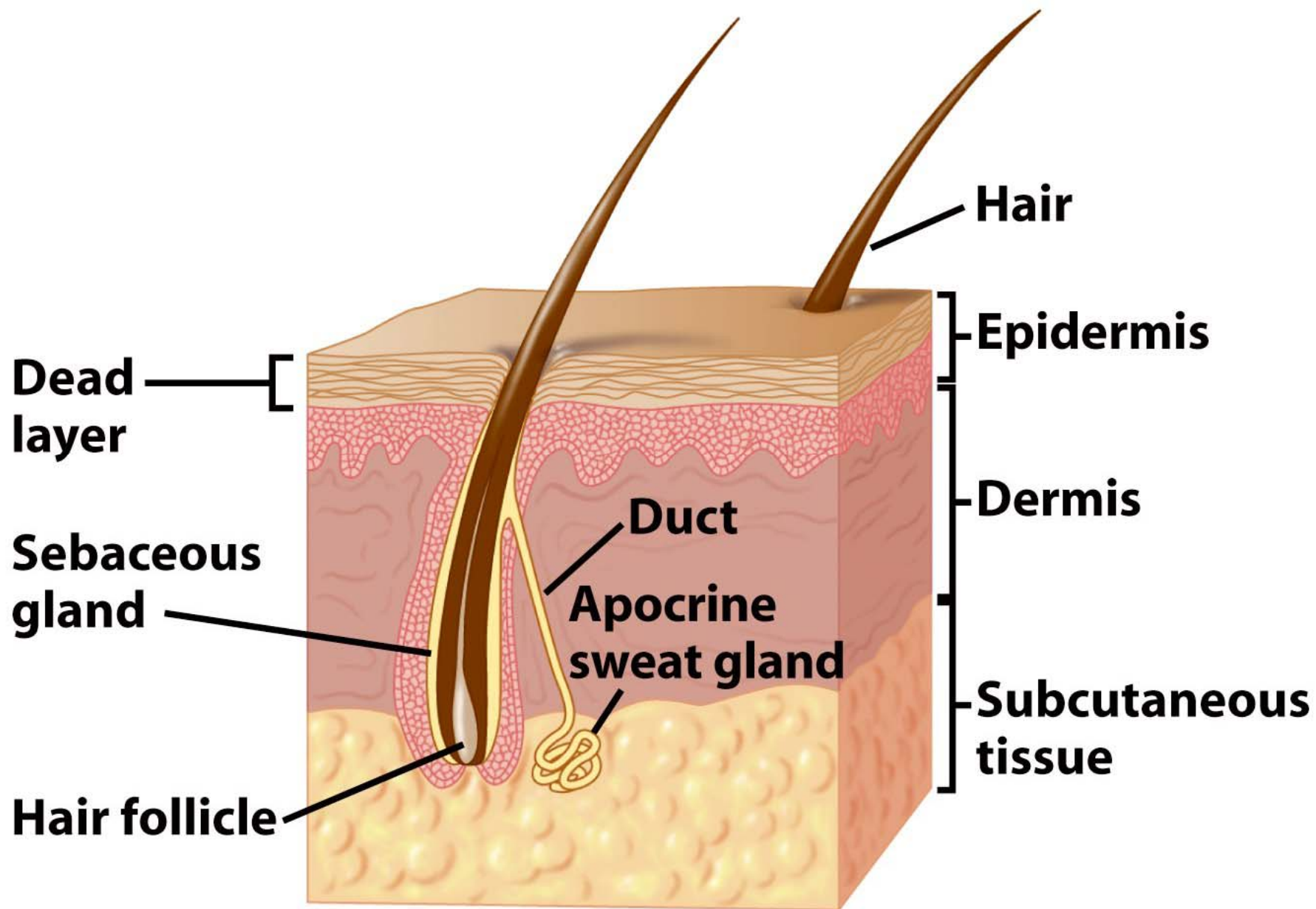
## Representative genera of microorganisms in the normal flora of humans

Anatomical site	Genera <sup>a</sup>
Skin	<i>Acinetobacter</i> , <i>Corynebacterium</i> , <i>Enterobacter</i> , <i>Klebsiella</i> , <i>Malassezia</i> (f), <i>Micrococcus</i> , <i>Pityrosporum</i> (f), <i>Propionibacterium</i> , <i>Proteus</i> , <i>Pseudomonas</i> , <i>Staphylococcus</i>
Mouth	<i>Streptococcus</i> , <i>Lactobacillus</i> , <i>Fusobacterium</i> , <i>Veillonella</i> , <i>Corynebacterium</i> , <i>Neisseria</i> , <i>Actinomyces</i> , <i>Geotrichum</i> (f), <i>Candida</i> (f), <i>Capnocytophaga</i> , <i>Eikenella</i> , <i>Prevotella</i> , spirochetes (several genera)
Respiratory tract	<i>Streptococcus</i> , <i>Staphylococcus</i> , <i>Corynebacterium</i> , <i>Neisseria</i> , <i>Haemophilus</i>
Gastrointestinal tract	<i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Eubacterium</i> , <i>Peptococcus</i> , <i>Peptostreptococcus</i> , <i>Ruminococcus</i> , <i>Clostridium</i> , <i>Escherichia</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Enterococcus</i> , <i>Staphylococcus</i>
Urogenital tract	<i>Escherichia</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>Neisseria</i> , <i>Lactobacillus</i> , <i>Corynebacterium</i> , <i>Staphylococcus</i> , <i>Candida</i> (f), <i>Prevotella</i> , <i>Clostridium</i> , <i>Peptostreptococcus</i> , <i>Ureaplasma</i> , <i>Mycoplasma</i> , <i>Mycobacterium</i> , <i>Streptococcus</i> , <i>Torulopsis</i> (f)

<sup>a</sup> This list is not meant to be exhaustive, and not all of these organisms are found in every individual. Some organisms are more prevalent at certain ages (adults vs. children). Distribution may also vary between sexes. Most of these organisms can be opportunistic pathogens under certain conditions. Several genera can be found in more than one body area. (f)–fungi.

# Normal human microflora





**Skin:**

**Resident Microbes:**

Most are Gram (+)

*Staphylococcus*

*Micrococcus*

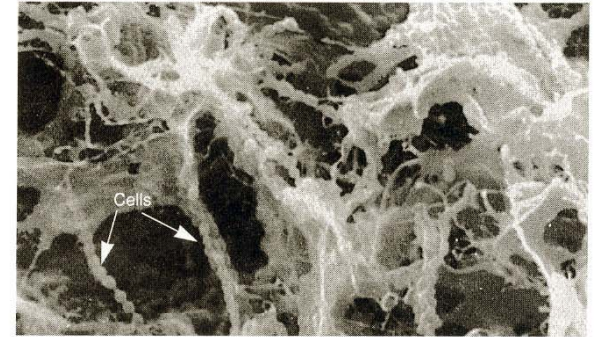
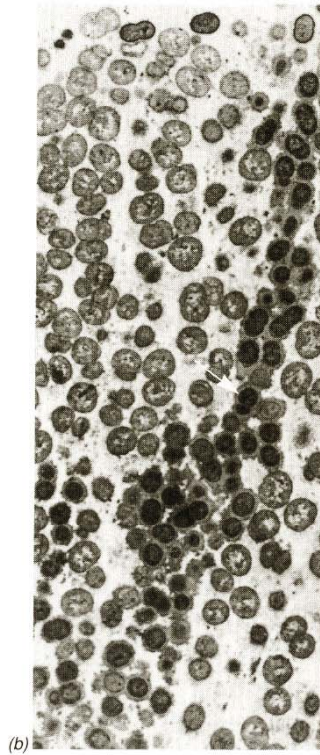
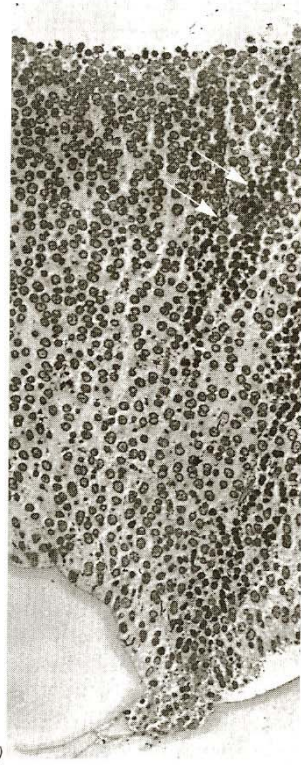
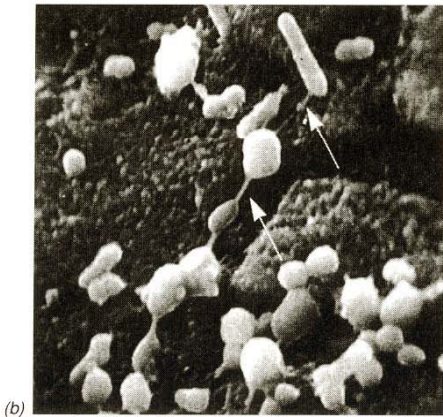
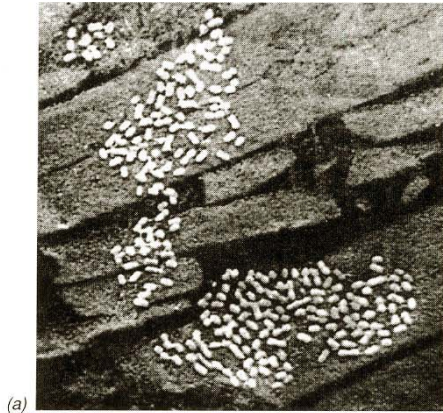
Few G (-) & fungi

**Environmental Conditions: Hostile**

- High Salt
- Low pH
- Dry



# Dental Plaque Bacteria



*Streptococcus mutans*

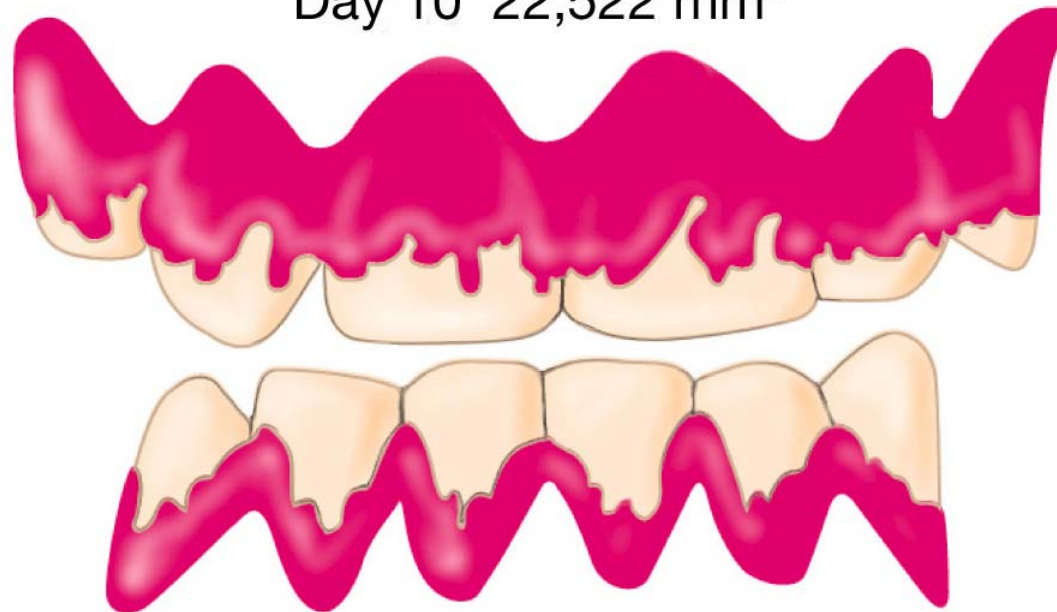
Tooth Colonies    Plaque Cross Section



Day 1 1436 mm<sup>2</sup>



Day 10 22,522 mm<sup>2</sup>



## Mouth:

### Resident Microbes:

Gram (+): *Streptococcus* & *Lactobacilli*

Gram (-): obligate anaerobes

Spirochetes: *Borrelia*

### Environmental Conditions: More Favorable

- Moist, though contains lysozyme
- Lots of polysaccharides
- Lots of amylase & protease

**Upper  
respiratory  
tract**

**Nasopharynx**

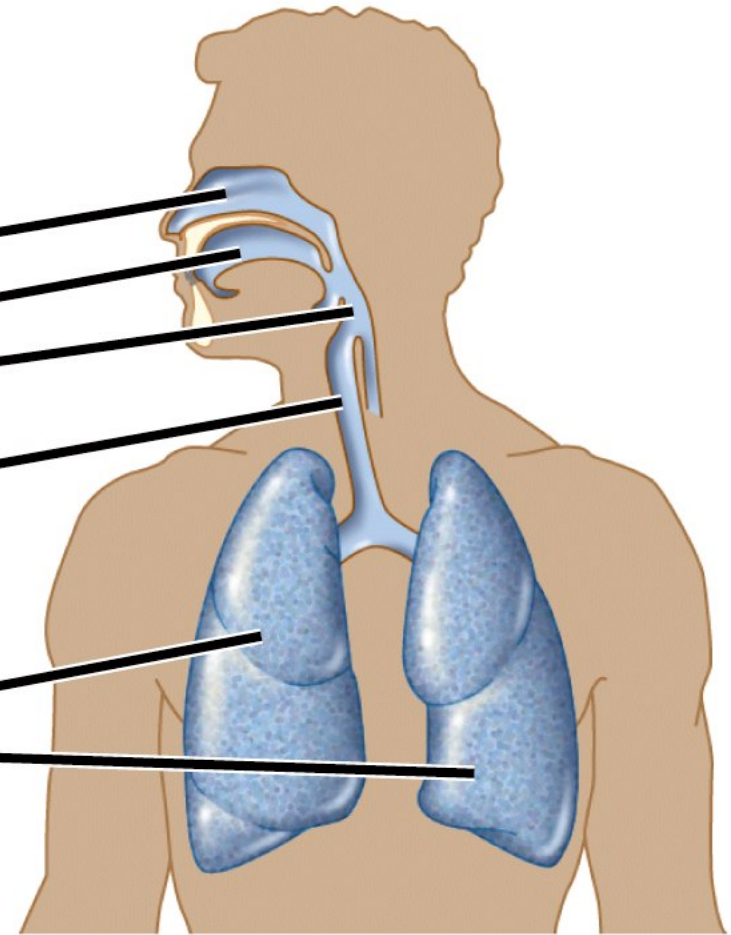
**Oral cavity**

**Throat**

**Lower  
respiratory  
tract**

**Trachea**

**Lungs**



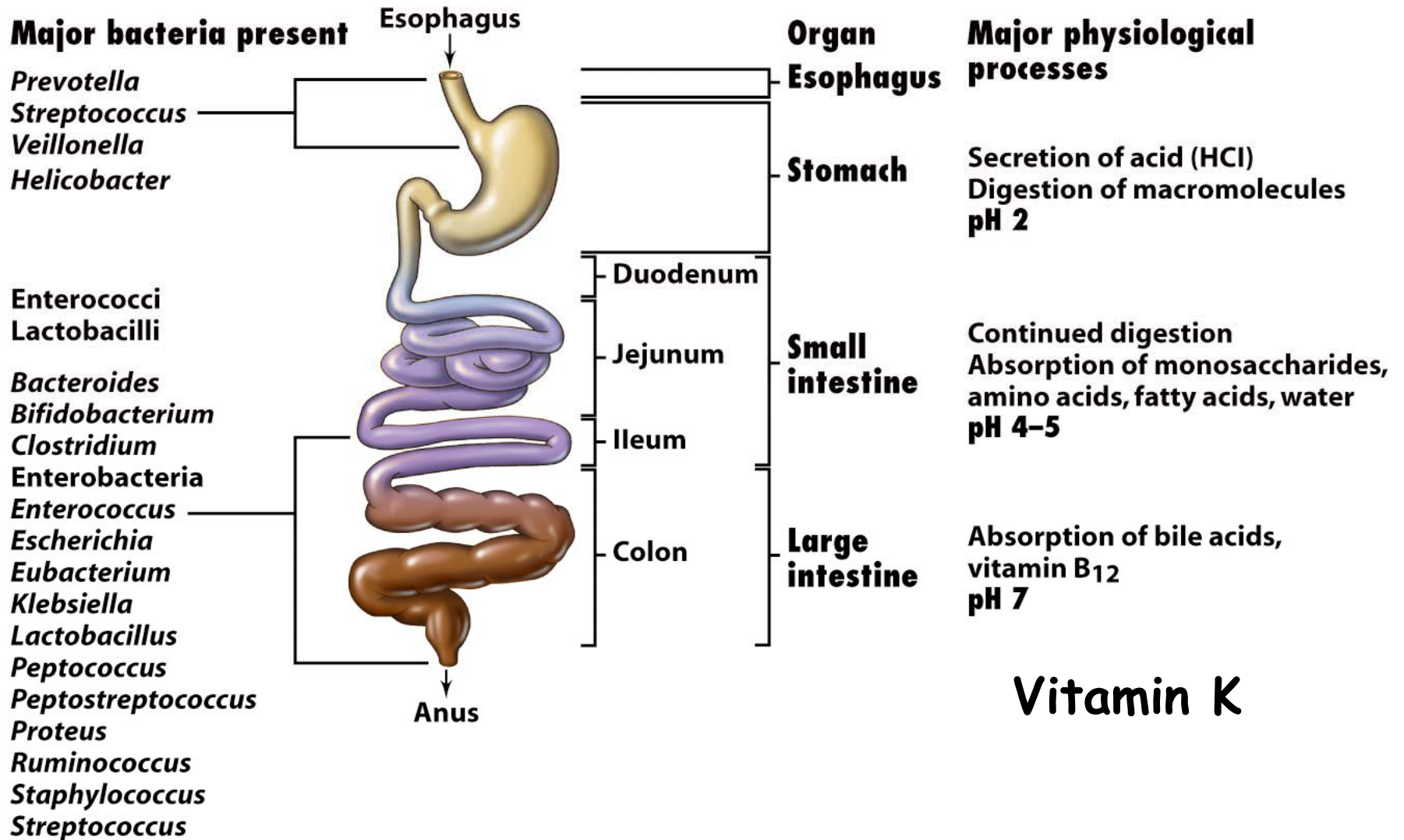
## Respiratory Tract:

Resident Microbes: Upper Only

Gram (+): *Streptococcus* & *Staphylococcus*

Environmental Conditions:

- Mucous membranes
- Others compete with potential pathogens





## G.I. Tract:

Stomach: Hostile, pH ~2

Gram (+): *Lactobacilli* & *Streptococcus*

Gram (-): *Helicobacter pylori*

Small Intestine: Gradient in pH

low pH: *Lactobacilli*

neutral: *Enterococcus*

Large Intestine: Moist and pH ~7

$10^{11}$  to  $10^{12}$  bacteria/g wet wt feces

#1 is *Bacteroides vulgatus* at ~15%

*E. coli* is only ~0.03%

# Physical, chemical, & anatomical barriers to infection

Lysozyme in tears and other secretions dissolves cell walls

Normal flora compete with pathogens

Skin is a physical barrier, produces antimicrobial fatty acids, and its normal flora inhibit pathogen colonization

Rapid pH change inhibits microbial growth

Flushing of urinary tract prevents colonization

Removal of particles including microorganisms by rapid passage of air over cilia in nasopharynx

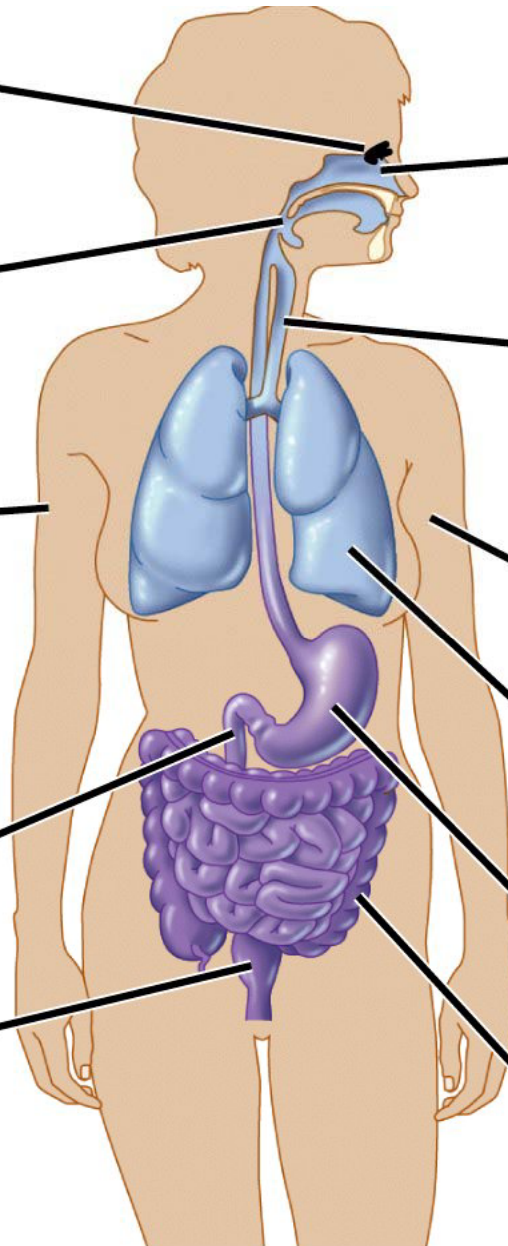
Mucus, cilia lining trachea suspend and move microorganisms out of the body

Blood proteins inhibit microbial growth

Mucus and phagocytes in lungs prevent colonization

Stomach acidity (pH 2) inhibits microbial growth

Normal flora compete with pathogens



## Virulence and Pathogenicity

**Pathogen:** A parasitic organism that causes damage to, or disease in its host.

**Pathogenicity:** The ability to cause disease.

**Virulence:** The relative degree or intensity of pathogenicity.

Virulence is determined by the five following characteristics of the pathogen →

**Invasiveness:** The ability of the organism to spread to adjacent tissues or other tissues.

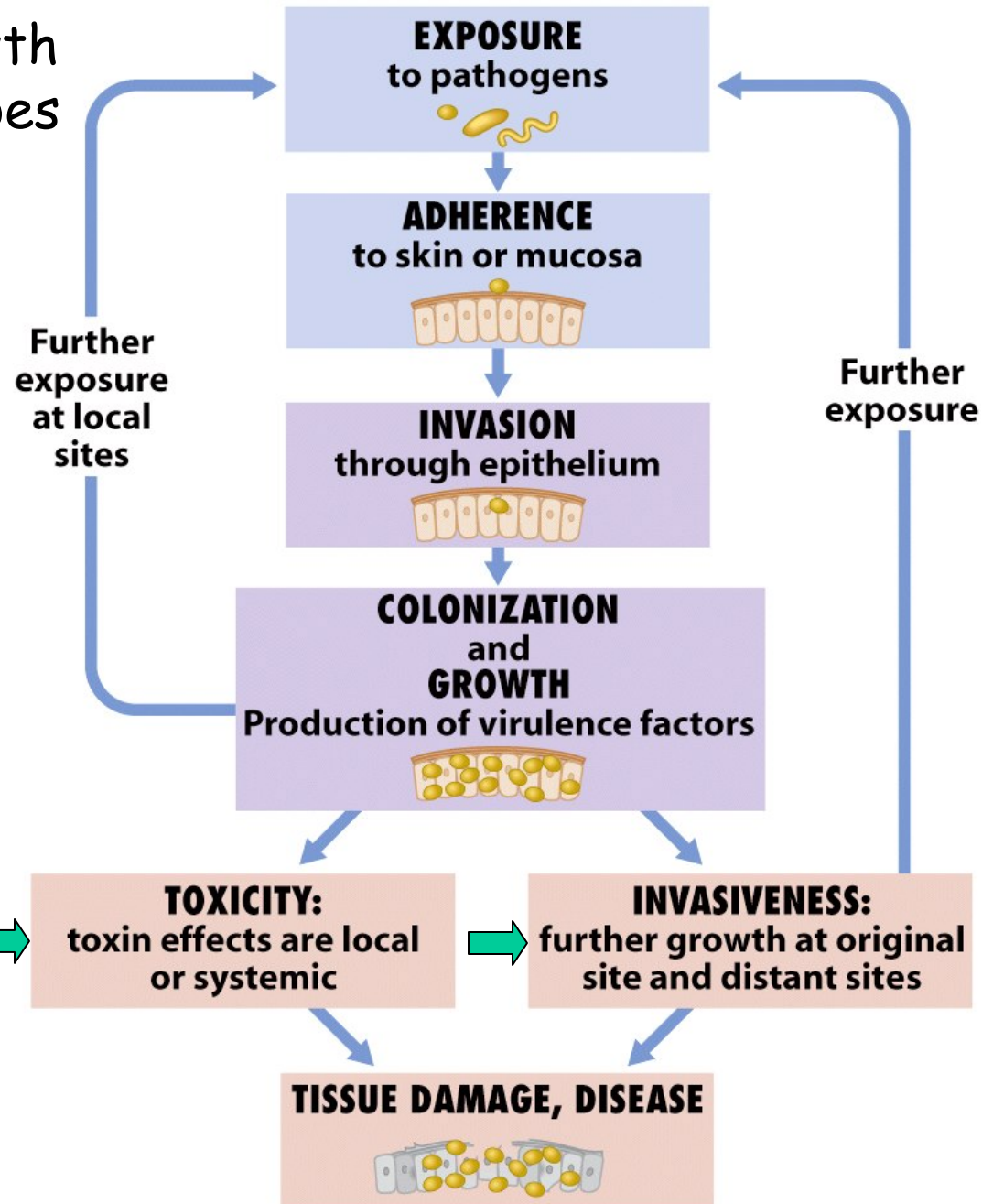
**Toxigenicity:** The ability of the organism to produce toxic products that cause disease and/or damage in the host.

**Infectivity:** The ability of the organism to establish a focal point of infection through growth.

**Pathogenic potential:** The degree that the pathogen causes morbid symptoms.

**Hypersensitivity:** Host's innate sensitivity to pathogen.

The presence or even growth of microbes on the host does not always lead to disease.



These two are key factors to the success or failure of a potential pathogen to cause disease!

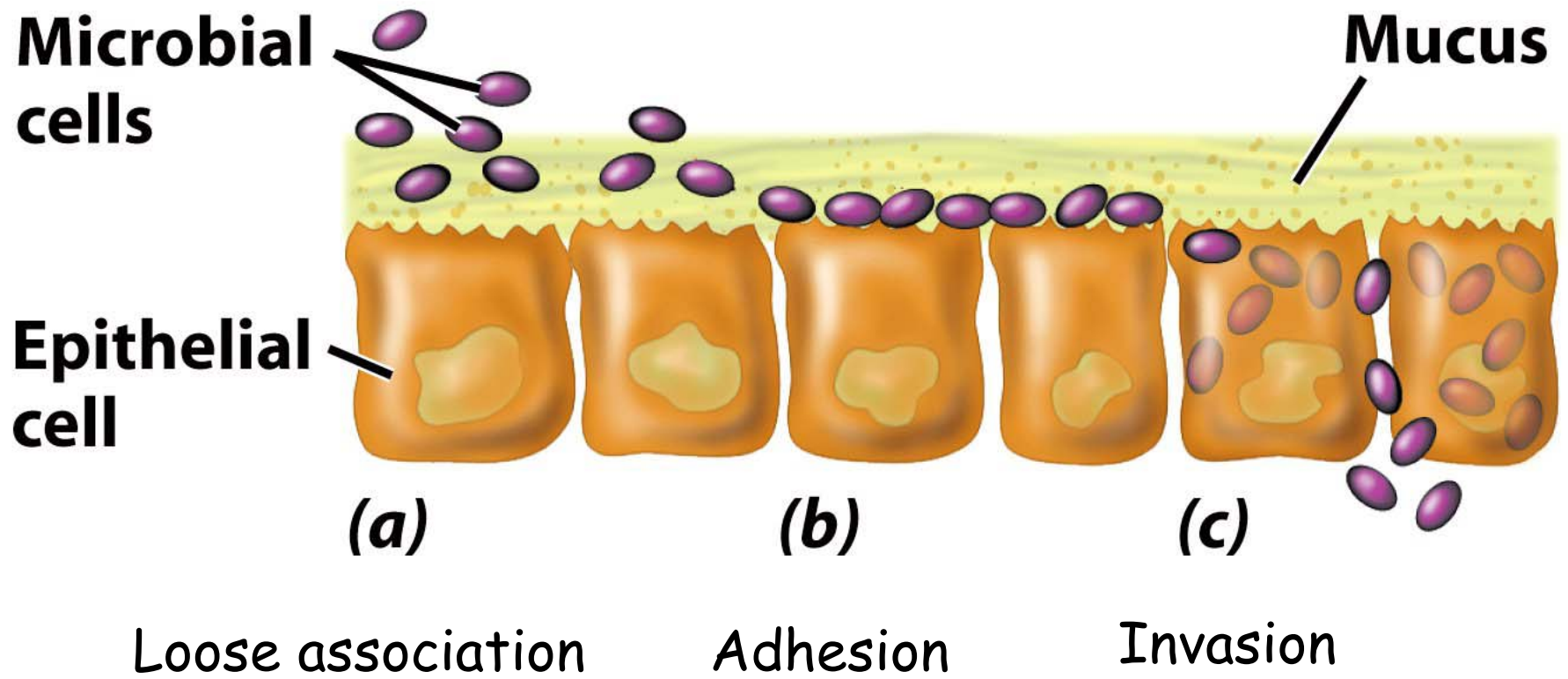


## Determinants of Infectious Disease

To produce an infectious disease, a pathogen must be able to:

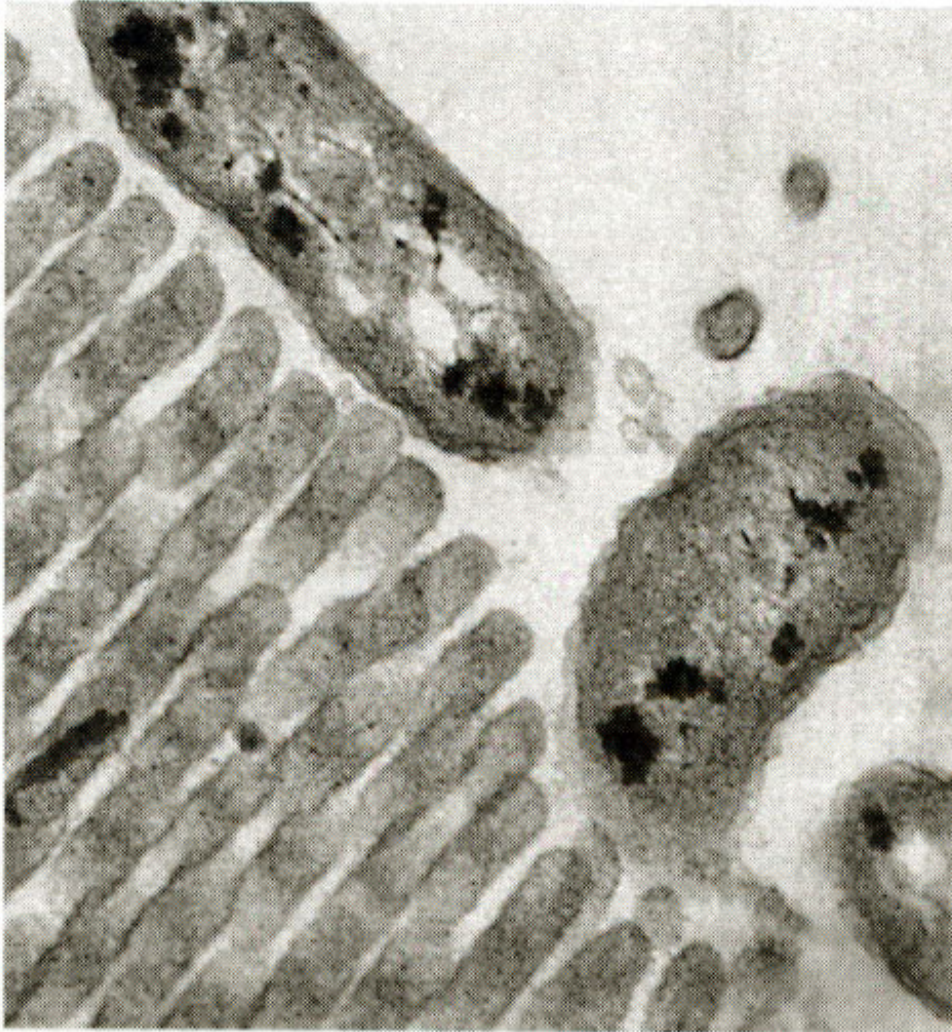
1. initially be transported to the host
2. adhere to, colonize or invade the host
3. grow, multiply, or complete its life cycle in the host
4. initially evade host defense mechanisms
5. damage the host by mechanical and/or chemical means

**In the end it is - Numbers (of bacteria) that make you sick!**

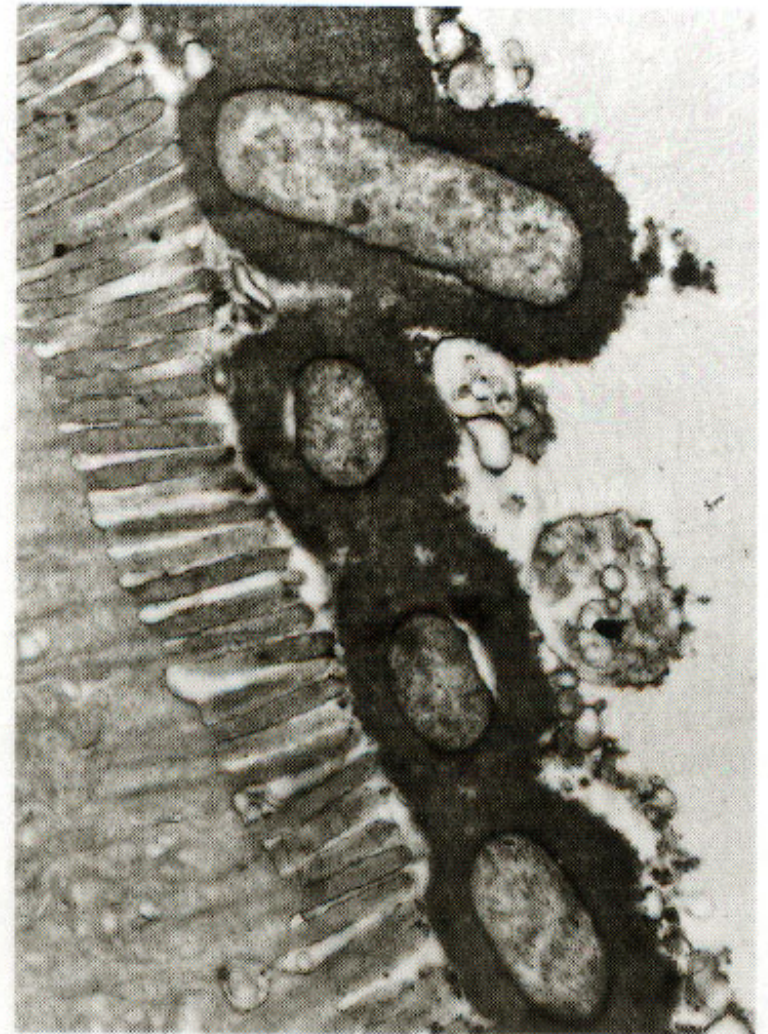




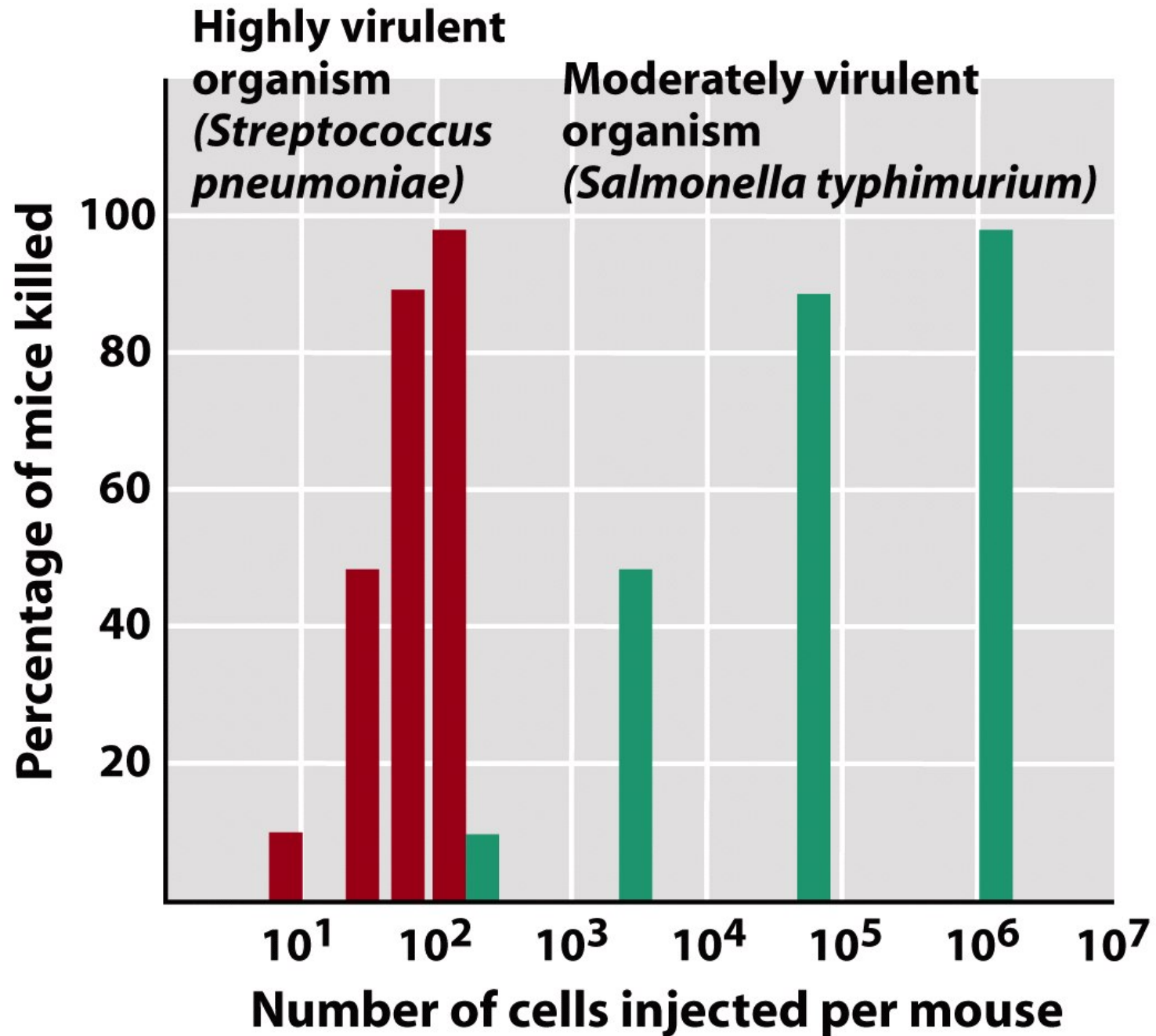
# Adherence of microorganisms



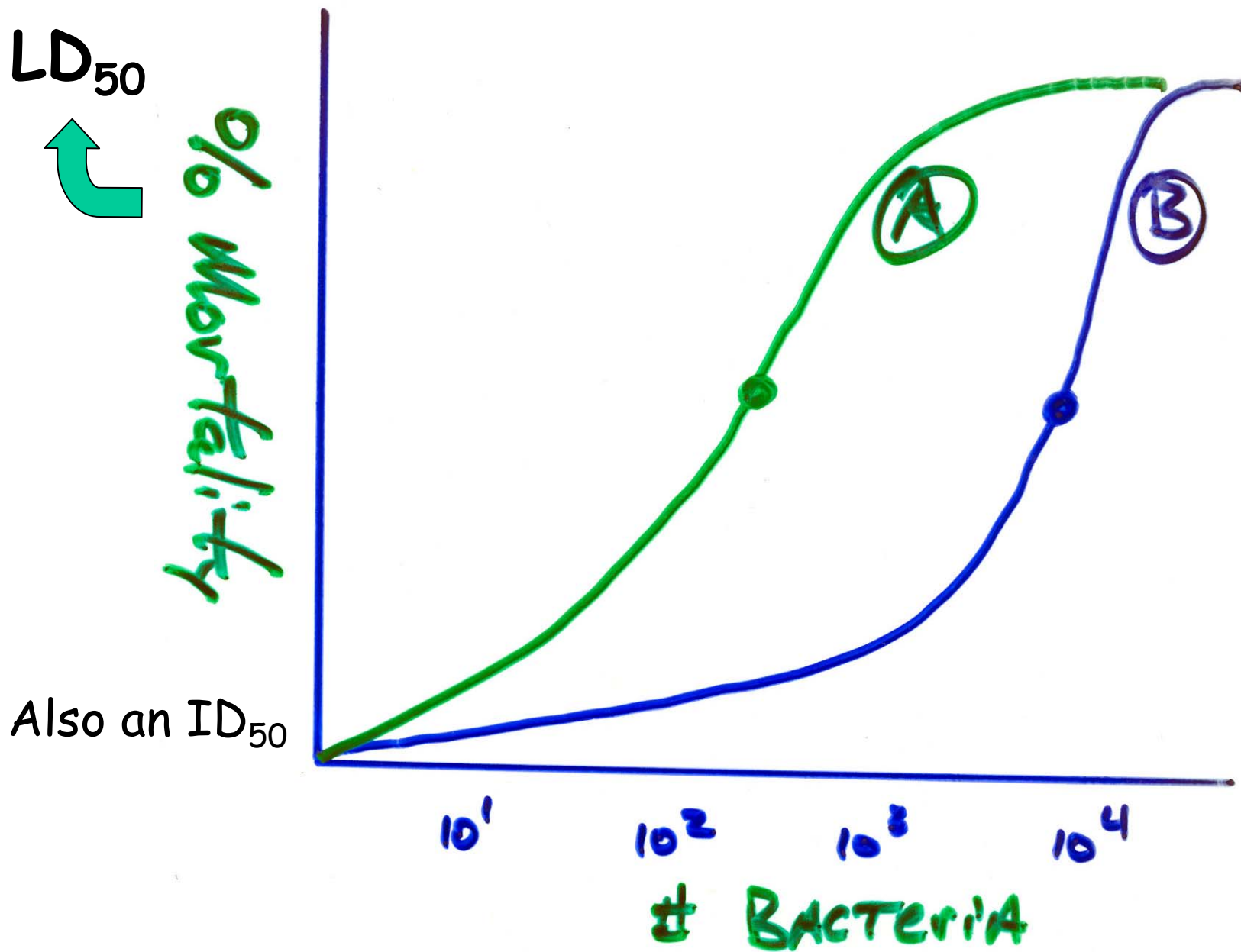
(a) Entero-toxic *Vibrio cholerae*



(b) Entero-invasive *E. coli*



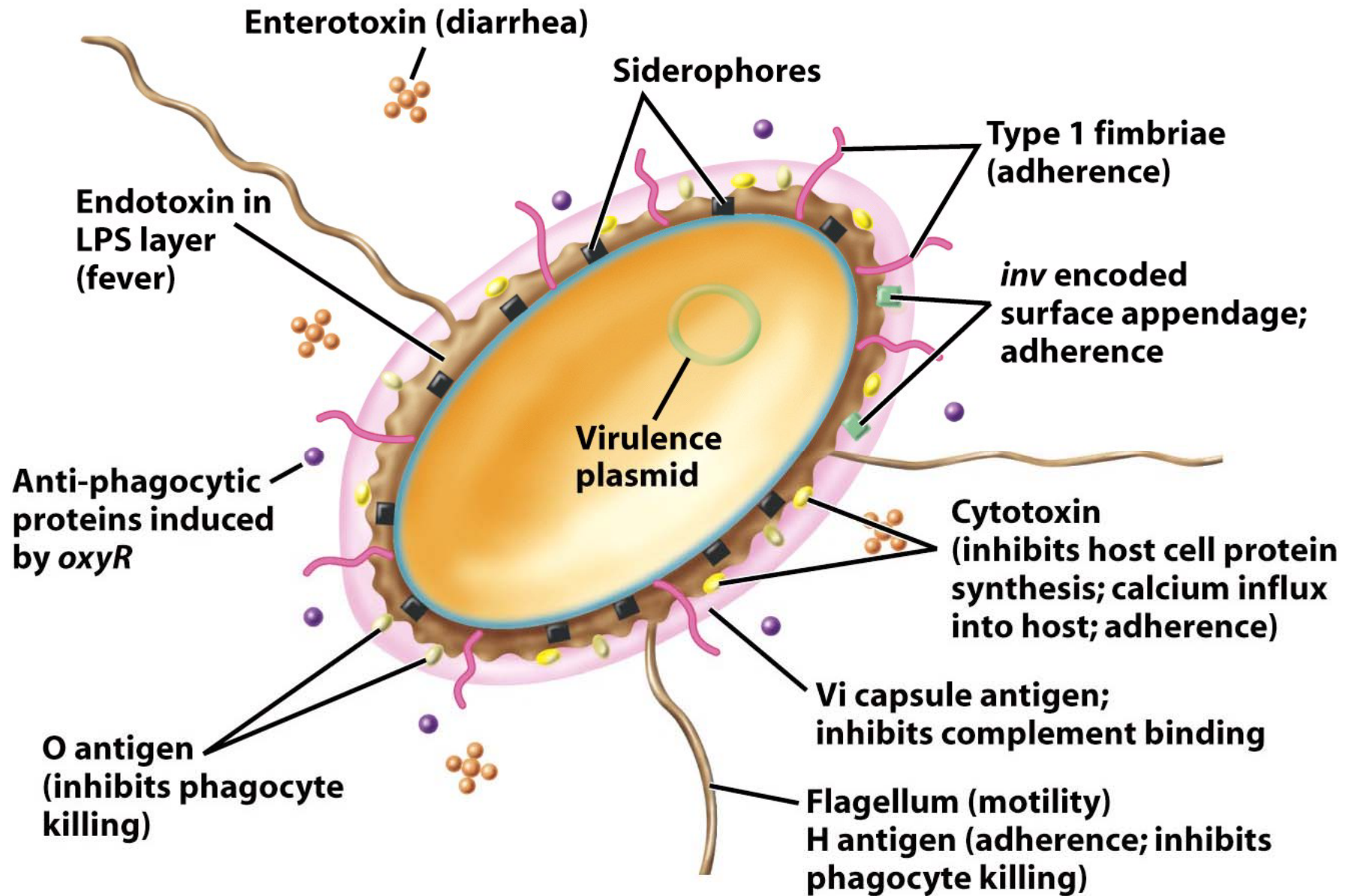




Bacterium A is more virulent than bacterium B



# Virulence factors in *Salmonella*



# Adherence Factors:

**Table 26.2**

**Adherence factors involved in attachment of organisms to host cells**

Adherence Factor	Example
Fimbriae (adhesion proteins)	<i>Proteus mirabilis</i> —urinary tract infections <i>Neisseria gonorrhoeae</i> —attach to urinary epithelia <i>Salmonella</i> —attach to intestinal epithelia <i>Streptococcus pyogenes</i> —M protein attaches to epithelia
Capsule (glycocalyx)	<i>Streptococcus mutans</i> —dextrans attach to teeth <i>Streptococcus salivarius</i> and <i>S. sanguis</i> —attach to tongue epithelia
Teichoic acids Lipoteichoic acids	<i>Staphylococcus aureus</i> —attach to nasal epithelia

# Virulent Factors: Invasiveness

**Table 26.3**

Some enzymes produced by pathogenic bacteria that promote invasion of the host

Enzyme	Organism	Function
Collagenase	<i>Clostridia</i>	Breaks down collagen in connective tissue
Coagulase	<i>Staphylococcus aureus</i>	Clot formation around point of entry protects from host defenses
→ Elastase	<i>Pseudomonas aeruginosa</i>	Disrupts membranes
→ Hyaluronidase	<i>Streptococcus</i>	Hydrolyzes hyaluronic acid–intercellular cement
	<i>Staphylococcus</i>	
	<i>Clostridium</i>	
→ Lecithinase	<i>Clostridia</i>	Disrupts phosphatidylcholine in membranes
	<i>Staphylococcus</i>	
	<i>Streptococcus</i>	

→ Also considered cytolytic toxins!

# Virulent Factors: Plasmids

**Table 26.4**

Virulence factors that are generally encoded in plasmids

Organism	Factor	Disease
<i>Escherichia coli</i>	Enterotoxin	Diarrhea
<i>Clostridium tetani</i>	Neurotoxin	Tetanus
<i>Staphylococcus aureus</i>	Coagulase enterotoxin	Boils / skin infections, food poisoning
<i>Streptococcus mutans</i>	Dextranucrase	Tooth decay
<i>Agrobacterium tumefaciens</i>	Tumor	Crown gall
<i>Staphylococcus</i> spp.	Antibiotic resistance	Various



# Virulent Factors: Antiphagocytic

**Table 26.5**

**Antiphagocytic factors produced by bacteria and their mode of action**

Factor	Action
→ Leukocidins	Specific lytic agent for leukocytes including phagocytes
→ Hemolysins	Form pores in host cells including macrophages. Streptolysin O affects sterols in membranes. Streptolysin S is a phospholipase
Capsules (glycocalyx)	Long polymers of carbohydrate—physically prevents engulfment
Fimbriae	(1) Bind to surface components of phagocytes, prevent close contact, and phagocytosis may not occur (2) Phase variation—a change in the antigenic composition

→ Also considered cytolytic toxins!

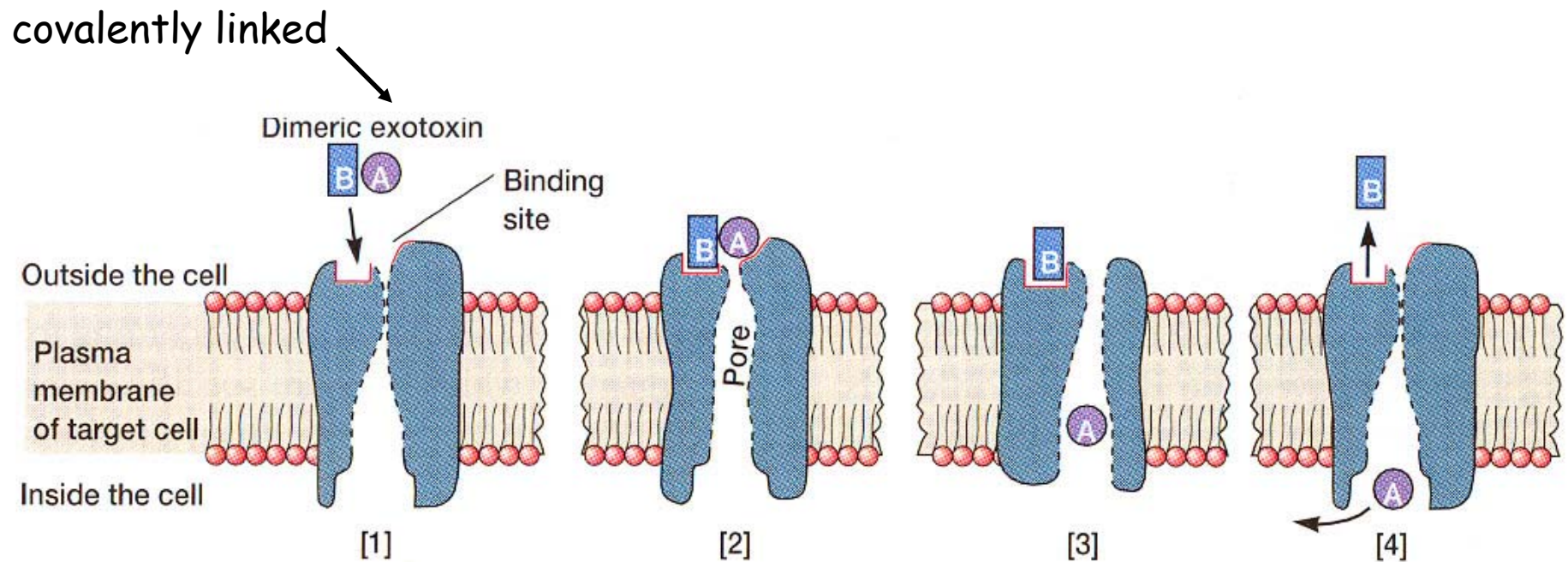


# Exotoxins:

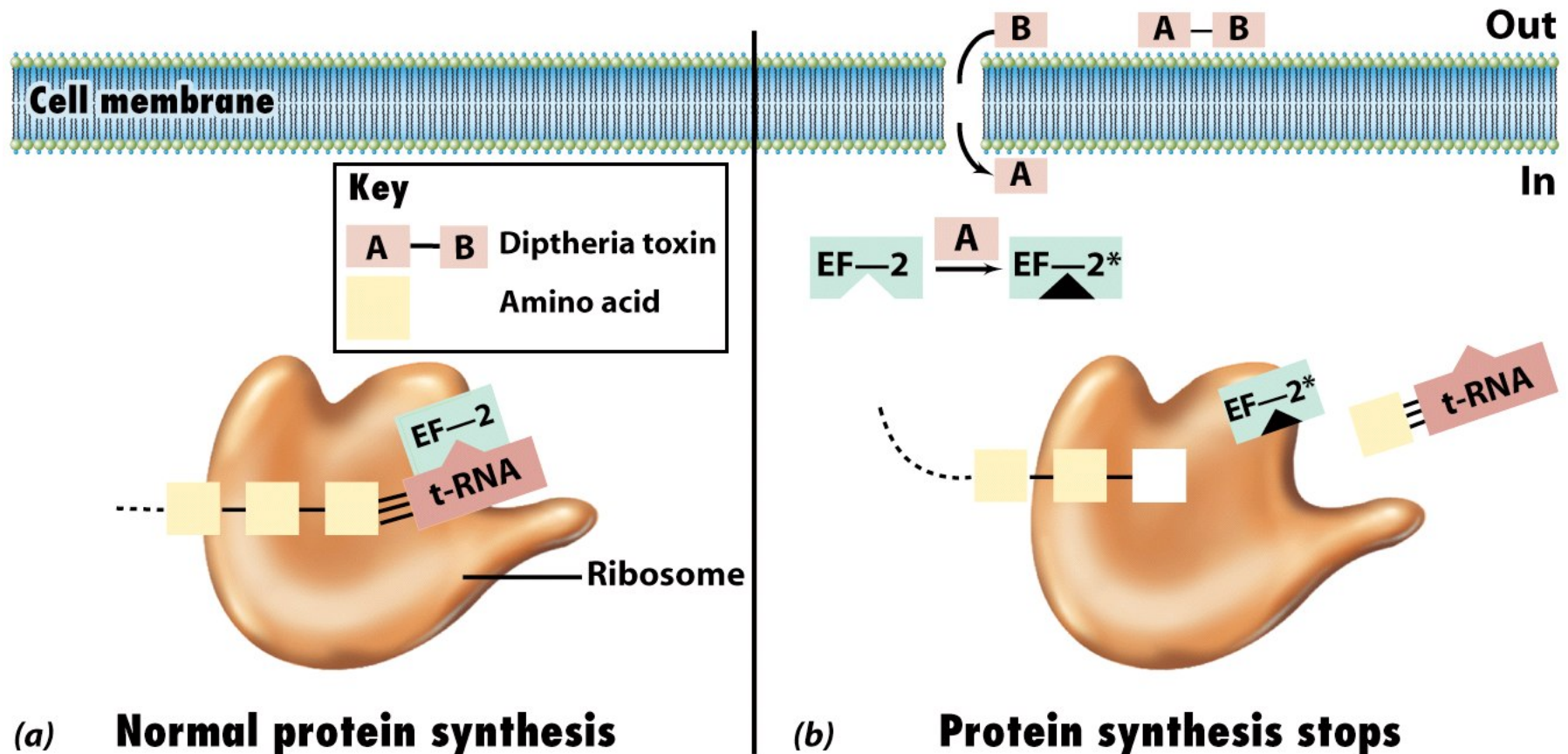
Extracellular toxic proteins released by pathogens.

1. **Cytolytic toxins** cause cell lysis.
2. **Superantigen toxins** stimulate the immune system.
3. **A-B toxins** where one part binds to surface receptor and the second enters and impacts cellular function.

# A-B exotoxins and their cellular entry

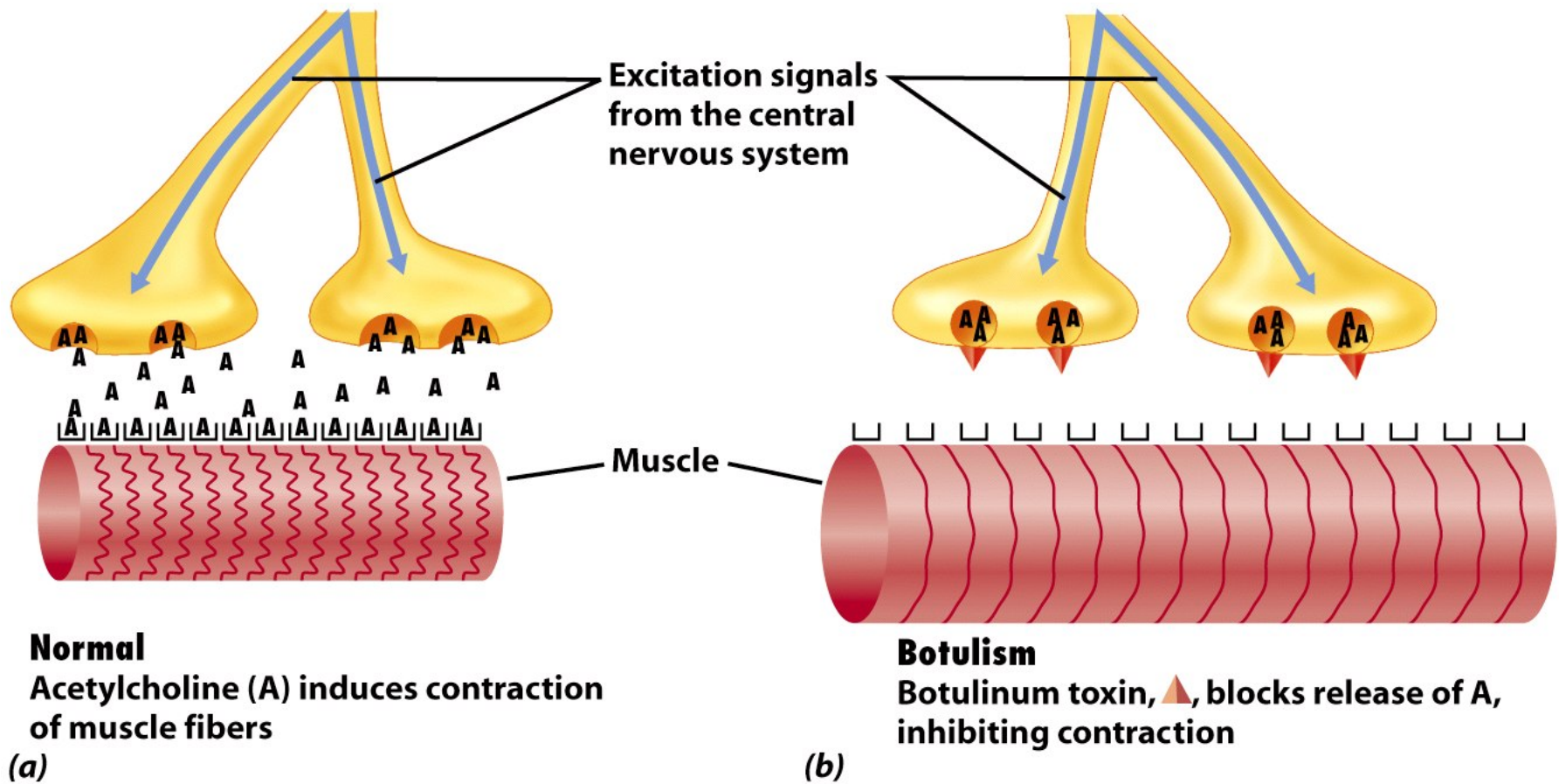


# Action of diphtheria toxin from *Corynebacterium diphtheriae*



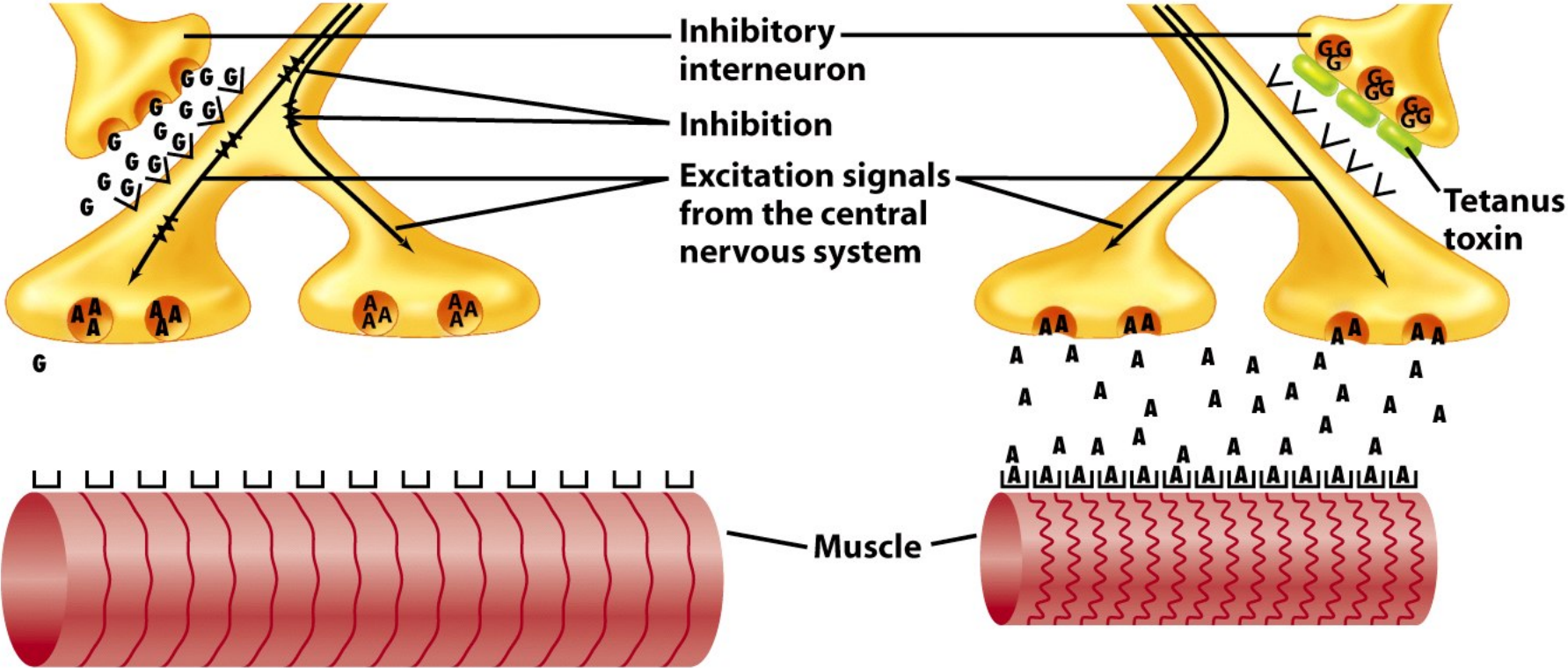
- ADP-ribosylates EF-2
- only takes one to kill cell

# Action of botulinum toxin from *Clostridium botulinum*





# Action of tetnus toxin from *Clostridium tetani*



**Normal**  
 Glycine (G) release from inhibitory interneurons stops acetylcholine (A) release and allows relaxation of muscle  
 (a)

**Tetanus**  
 Tetanus toxin binds to inhibitory interneurons, preventing release of glycine (G) and relaxation of muscle  
 (b)



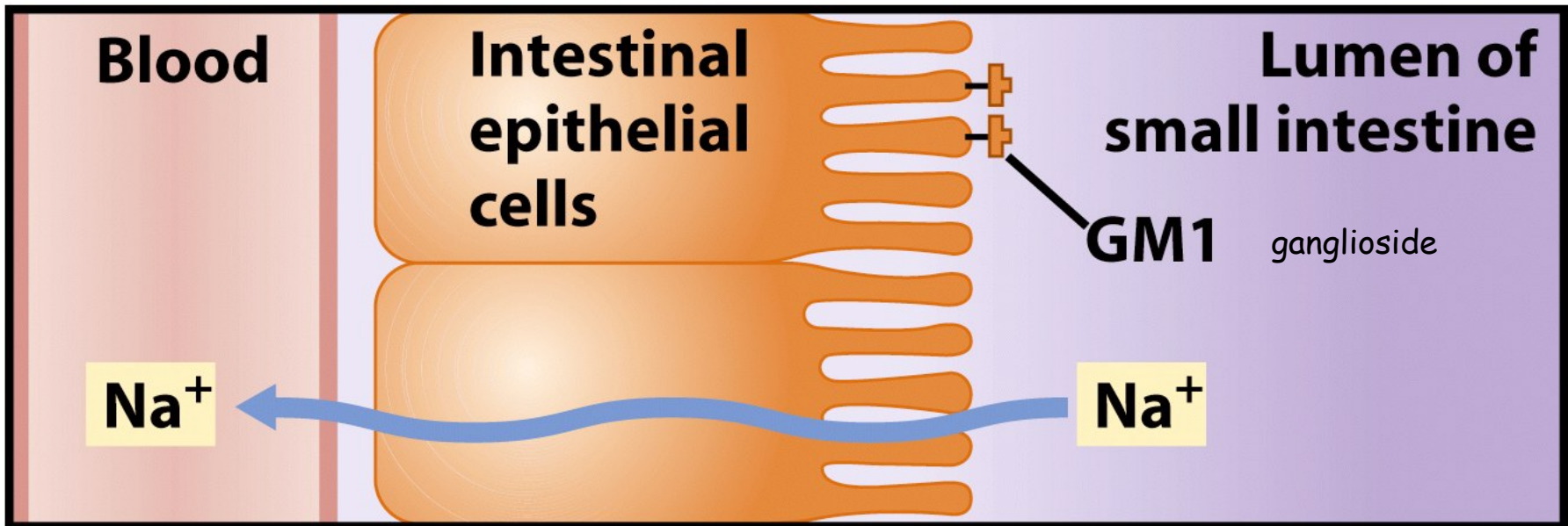
## Enterotoxins:

Exotoxins that specifically affect the small intestine.

1. Generally cause massive secretion of fluid.
2. Leads to vomiting and/or diarrhea.
3. Often associated with food poisoning.

## Action of cholera enterotoxin

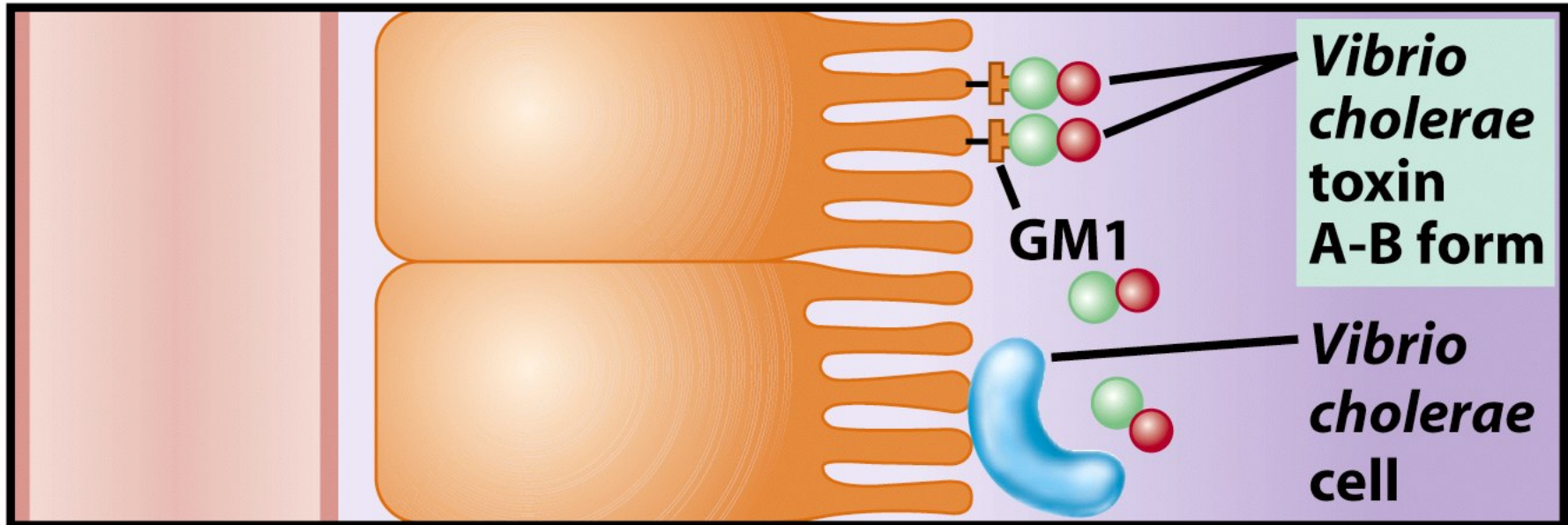
### 1. Normal ion movement, $\text{Na}^+$ from lumen to blood, no net $\text{Cl}^-$ movement



# Action of cholera enterotoxin

## 2. Colonization and toxin production

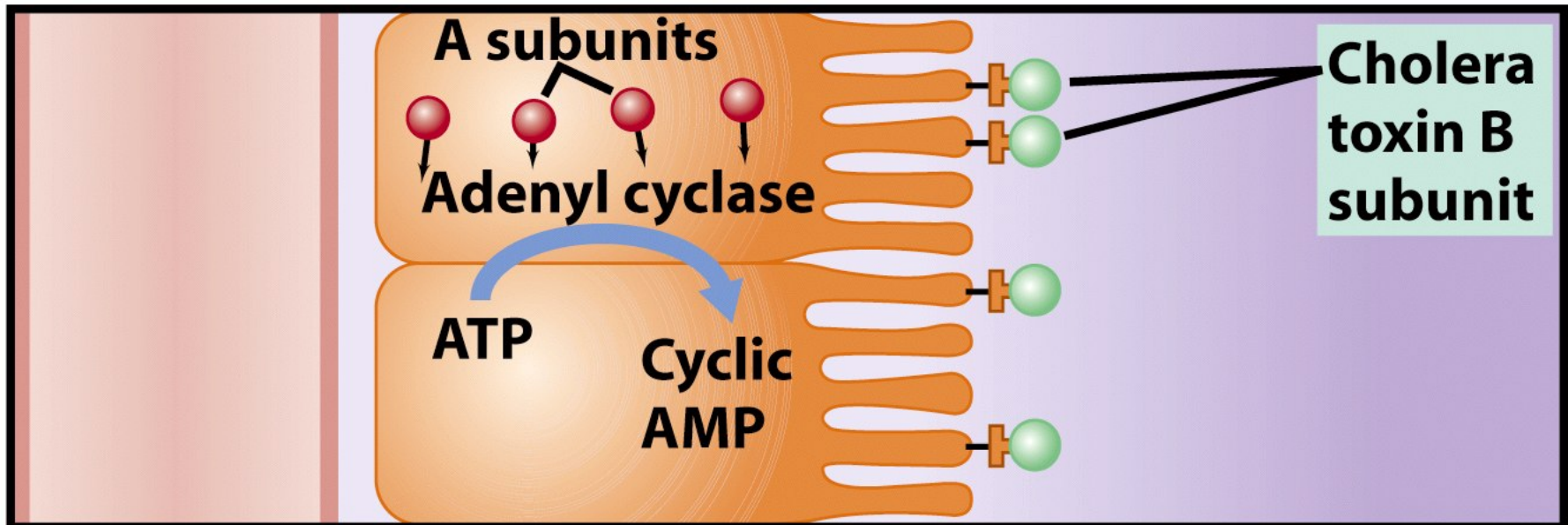
1:5 ratio



Purified "B" blocks process

## Action of cholera enterotoxin

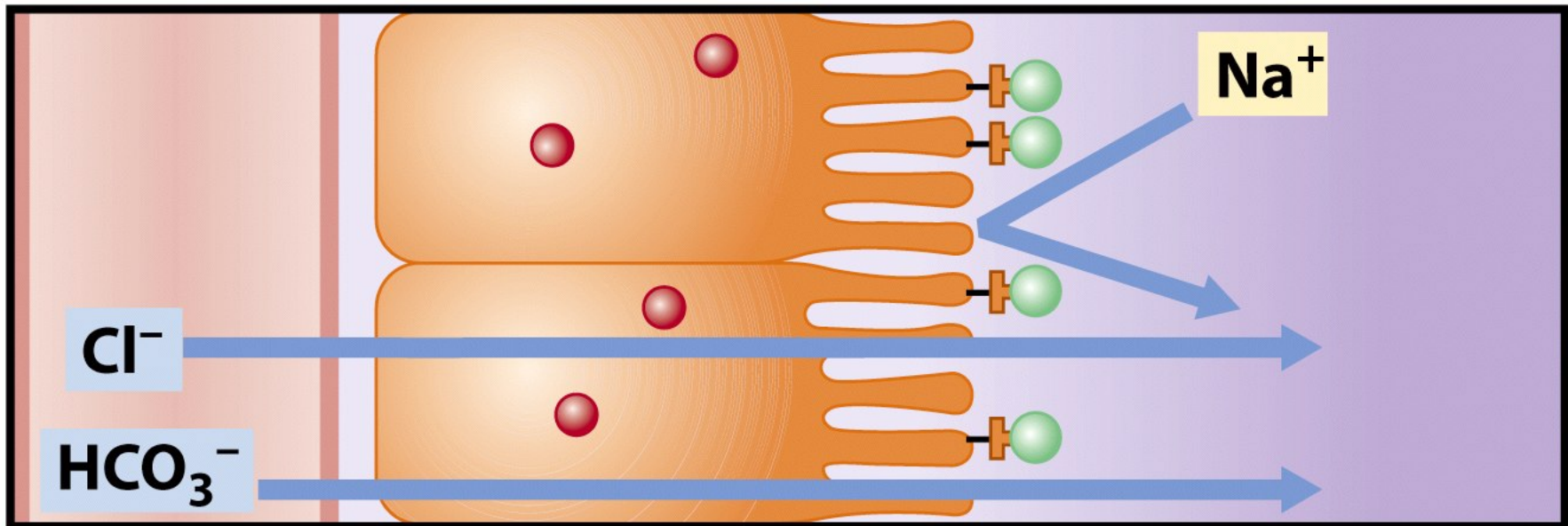
### 3. Activation of epithelial adenyl cyclase by cholera toxin



Activates this reaction!  
(Causing sodium influx blockage)

## Action of cholera enterotoxin

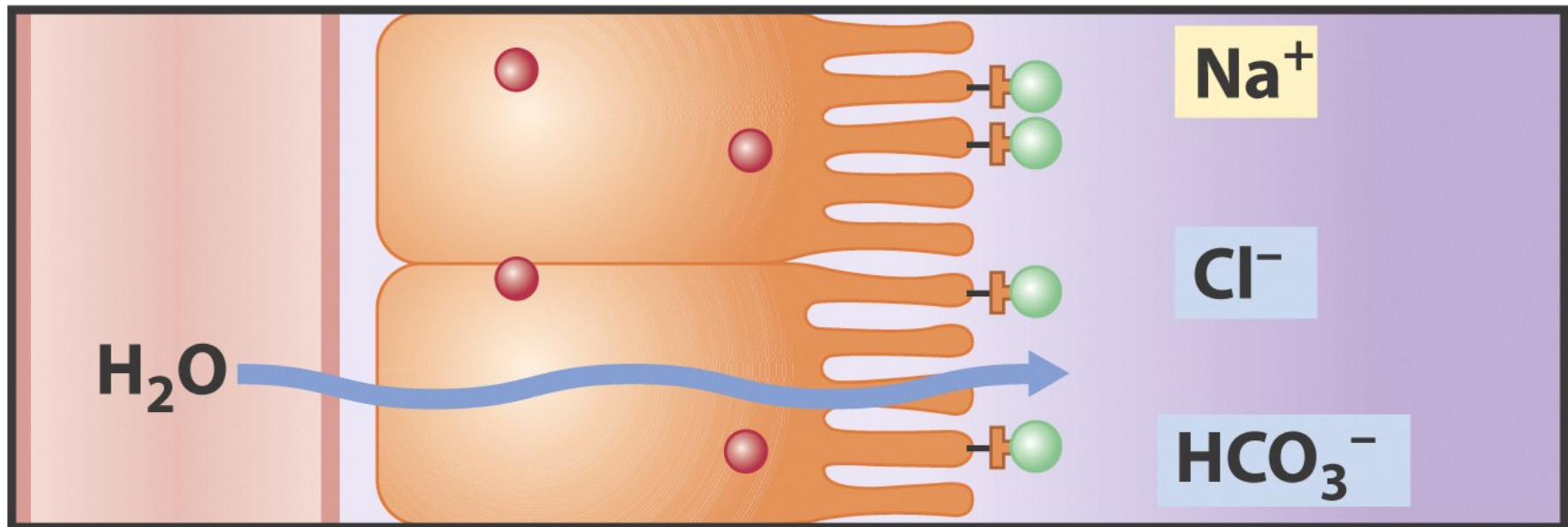
### 4. $\text{Na}^+$ movement blocked, net $\text{Cl}^-$ movement to lumen





## Action of cholera enterotoxin

### 5. Massive water movement to the lumen



**Table 26.6****Characteristics of exotoxins and endotoxins**

<b>Exotoxins</b>	<b>Endotoxins</b>
Heat labile 60°C to 80°C	Heat stable
Immunogenic	Weakly immunogenic
Cause no fever	Cause fever
Can be lethal at low concentrations	Toxic at high doses
Different genera produce different toxins	Similar regardless of source
Released by live bacterium	Released on lysis of bacterium
Inactivated by chemicals that affect proteins	Not generally harmed by chemicals that affect proteins

Rem: Lipid A region of LPS

**Table 26.7****Some exotoxins produced by bacteria (Part 1)**

<b>Exotoxin</b>	<b>Producing Organism</b>	<b>Disease</b>	<b>Effect</b>
Diphtheria toxin	<i>Corynebacterium diphtheriae</i>	Diphtheria	Inhibits protein synthesis; affects heart, nerve tissue, liver
Botulism toxin	<i>Clostridium botulinum</i>	Botulism	Neurotoxin; flaccid paralysis
Perfringens toxin	<i>Clostridium perfringens</i>	Gas gangrene	Hemolysin, collagenase, phospholipase
Erythrogenic toxin	<i>Streptococcus pyogenes</i>	Scarlet fever	Capillary destruction
Pyrogenic toxin	<i>Staphylococcus aureus</i>	Toxic shock syndrome	Fever, shock
Exfoliative toxin	<i>Staphylococcus aureus</i>	Scalded skin	Massive skin peeling
Exotoxin A	<i>Pseudomonas aeruginosa</i>	— (~ Diphtheria)	Inhibits protein synthesis

**Table 26.7****Some exotoxins produced by bacteria (Part 2)**

<b>Exotoxin</b>	<b>Producing Organism</b>	<b>Disease</b>	<b>Effect</b>
Pertussis toxin	<i>Bordetella pertussis</i>	Whooping cough	Stimulates adenyl cyclase
Anthrax toxin	<i>Bacillus anthracis</i>	Anthrax	Pustules; blood poisoning
Enterotoxin	<i>Escherichia coli</i>	Diarrhea	Water and electrolyte loss
Enterotoxin	<i>Vibrio cholerae</i>	Cholera	Water and electrolyte loss
Enterotoxin	<i>Staphylococcus aureus</i>	“Staph” food poisoning	Diarrhea, nausea
Enterotoxin	<i>Clostridium perfringens</i>	Food poisoning	Permeability of intestinal epithelia
Neurotoxin	<i>Clostridium tetani</i>	Tetanus	Rigid paralysis