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:

Bacterial Cells **~10^{14} cells/body**

Eukarya Cells **~10^{13} cells/body**

Normal Flora helps maintain our health

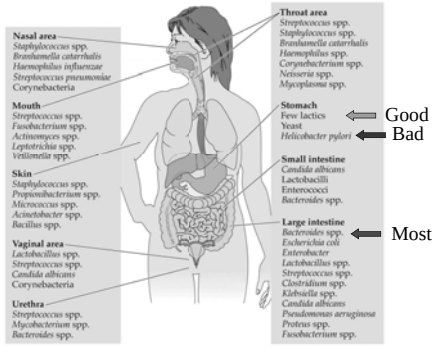
- **Provides vitamins & nutrients**
- **Detoxify many compounds**
- **Prevent colonization of pathogens**

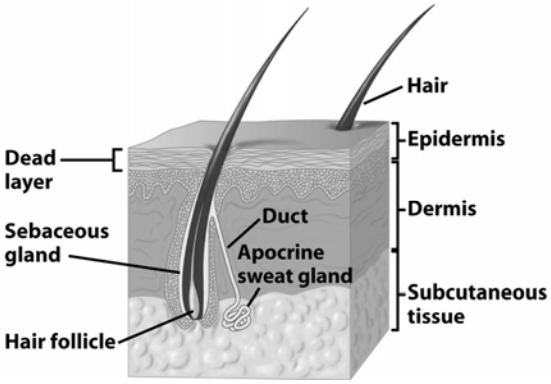
Table 21.1 Representative genera of microorganisms in the normal flora of humans

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

[a] 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:

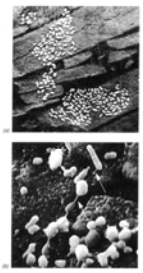
Resident Microbes:

- **Most are Gram (+)**
  - ***Staphylococcus***
  - ***Micrococcus***
- **Few G (-) & fungi**

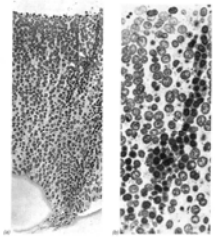
Environmental Conditions: Hostle

- **High Salt**
- **Low pH**
- **Dry**

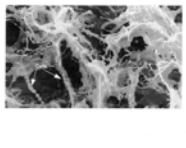
Dental Plaque Bacteria



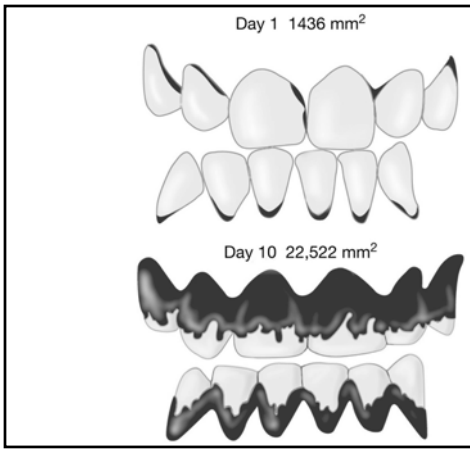
Tooth Colonies



Plaque Cross Section



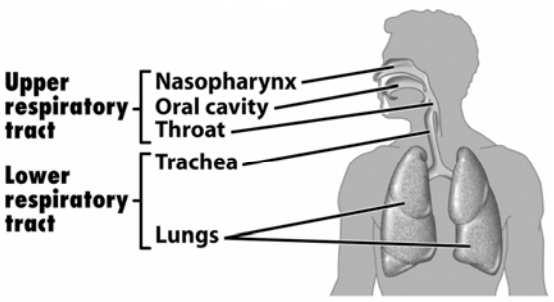
Streptococcus mutans



Mouth:

Resident Microbes:
- **Gram (+): *Streptococcus & Lactobacilli***
- **Gram (-): obligate anaerobes**
- **Spirochetes: *Borrelia***

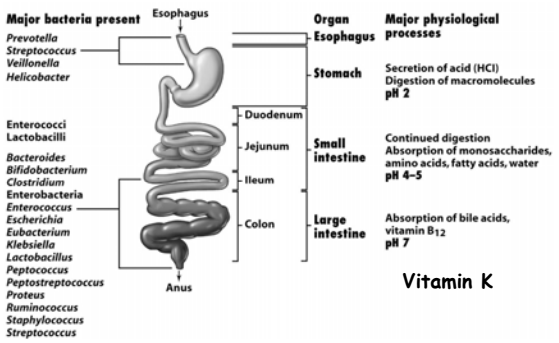
Environmental Conditions: More Favorable
- **Moist, though contains lysozyme**
- **Lots of polysaccharides**
- **Lots of amylase & protease**



Respiratory Tract:

Resident Microbes: Upper Only
- **Gram (+): *Streptococcus & Staphylococcus***

Environmental Conditions:
- **Mucous membranes**
- **Others compete with potential pathogens**



G.I. Tract:

Stomach: Hostle, pH ~2

- **Gram (+): *Lactobacilli & Streptococcus***
- **Gram (-): *Helicobacter pylori***

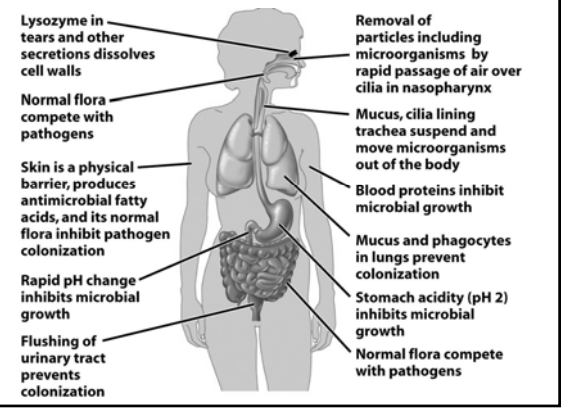
Small Intestine: Gradient in pH

- **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%**
- **Methanogens can also be detectable**

Physical, chemical, & anatomical barriers to infection



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.

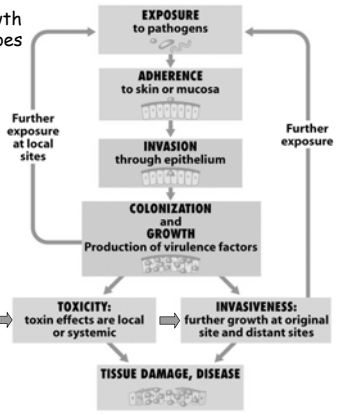
Toxigenicity: The ability of the organism to produce toxic products that cause disease and/or damage in the host.

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.



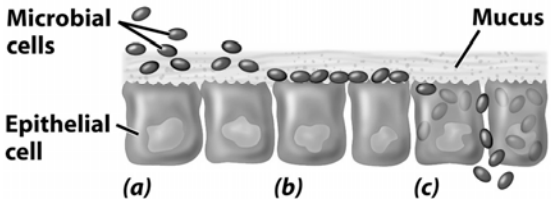
These two are key factors to the success or failure of a potential pathogen to cause disease!

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

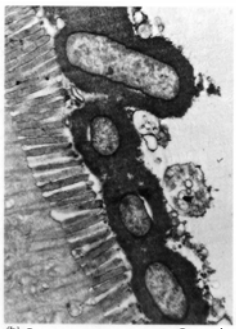
In the end it is – Numbers (of bacteria) that make you sick!



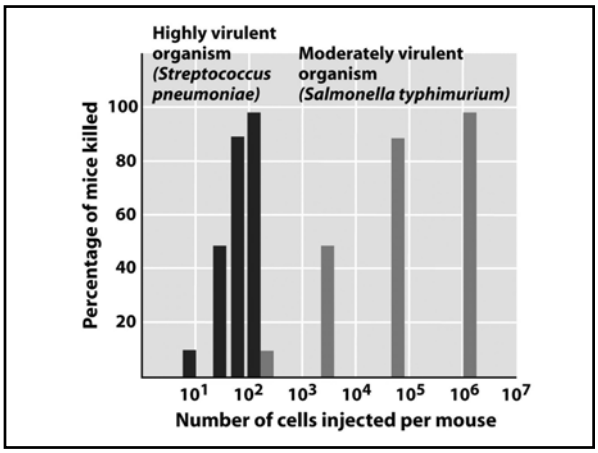
Loose association Adhesion Invasion

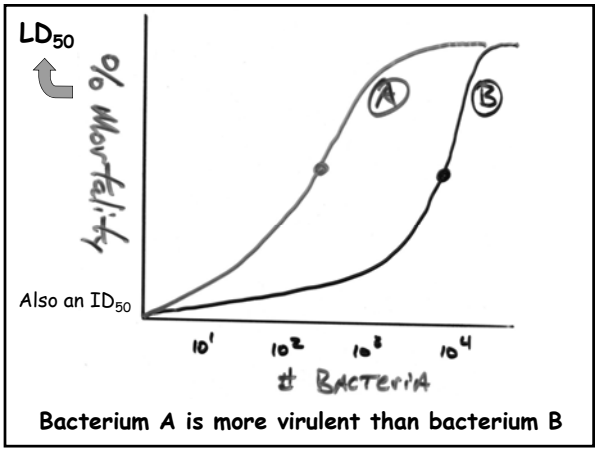
Adherence of microorganisms

(a) Entero-toxic *Vibrio cholerae*



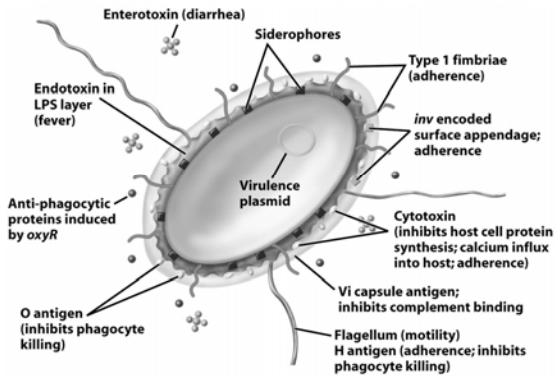
(b) Entero-invasive *E. coli*





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)	*Proteus mirabilis*—urinary tract infections
	Neisseria gonorrhoeae—attach to urinary epithelia
	Salmonella—attach to intestinal epithelia
	Streptococcus pyogenes—M protein attaches to epithelia
Capsule (glycocalyx)	*Streptococcus mutans*—dextrans attach to teeth
	Streptococcus salivarius and *S. sanguis*—attach to tongue epithelia
Teichoic acids Lipoteichoic acids	*Staphylococcus aureus*—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	*Clostridia*	Breaks down collagen in connective tissue
Coagulase	*Staphylococcus aureus*	Clot formation around point of entry protects from host defenses
⇨ Elastase	*Pseudomonas aeruginosa*	Disrupts membranes
Hyaluronidase	*Streptococcus*	Hydrolyzes hyaluronic acid–intercellular cement
	Staphylococcus	
	Clostridium	
⇨ Lecithinase	*Clostridia*	Disrupts phosphatidylcholine in membranes
Streptokinase	*Staphylococcus*	Digests fibrin clots
	Streptococcus	

⇨ Also considered cytolytic toxins!

Virulent Factors: Plasmids

Table 26.4 Virulence factors that are generally encoded in plasmids

Organism	Factor	Disease
Escherichia coli	Enterotoxin	Diarrhea
Clostridium tetani	Neurotoxin	Tetanus
Staphylococcus aureus	Coagulase enterotoxin	Boils/skin infections, food poisoning
Streptococcus mutans	Dextransucrase	Tooth decay
Agrobacterium tumefaciens	Tumor	Crown gall
Staphylococcus 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:

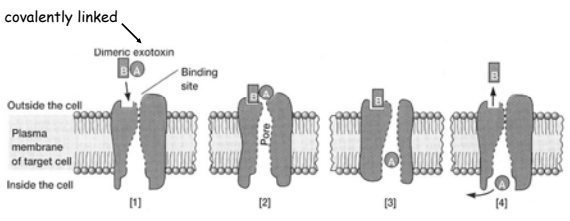
Extracellular toxic proteins released by pathogens.

1. **Cytolytic toxins** cause cell lysis.

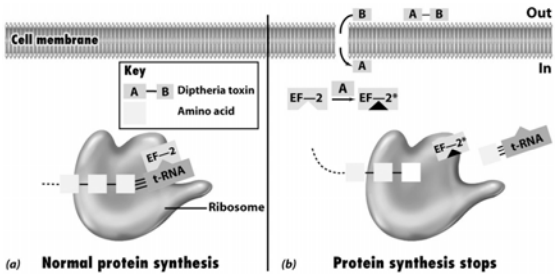
2. **Superantigen toxins** stimulate the immune system.

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

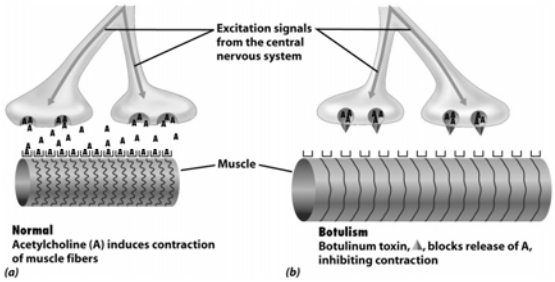


Action of diptheria toxin from *Corynebacterium diphtheriae*

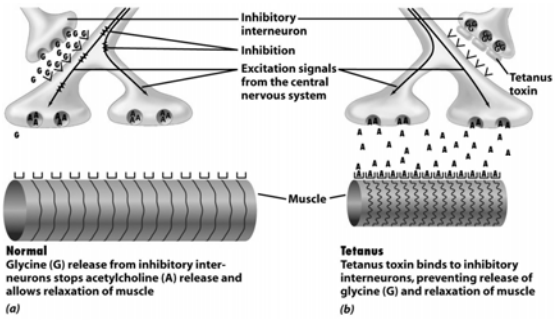


- **ADP-ribosylates EF-2**
- **only takes one to kill cell**

Action of botulinum toxin from *Clostridium botulinum*



Action of tetnus toxin from *Clostridium tetani*

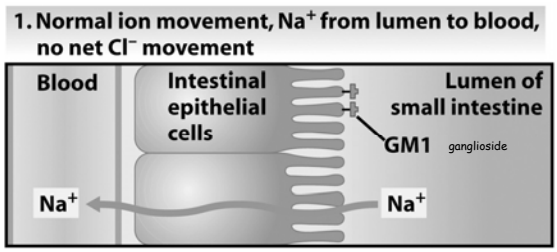


Enterotoxins:

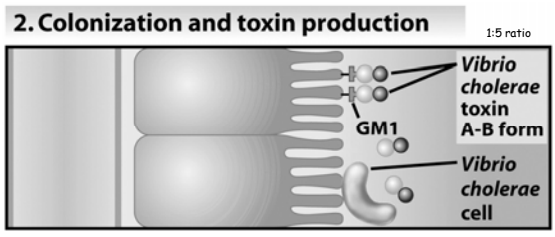
Exotoxins that specifically affect the small intestine.

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

Action of cholera enterotoxin

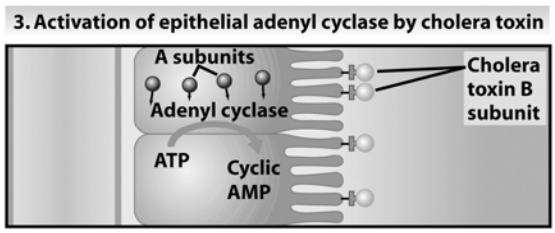


Action of cholera enterotoxin



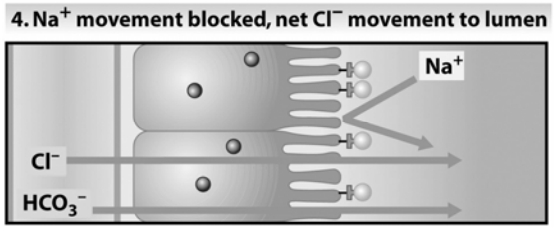
Purified "B" blocks process

Action of cholera enterotoxin



Activates this reaction!
(Causing sodium influx blockage)

Action of cholera enterotoxin



Action of cholera enterotoxin

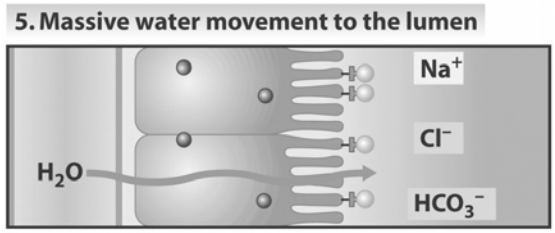


Table 26.6 Characteristics of exotoxins and endotoxins

Exotoxins	Endotoxins
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)*

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

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

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

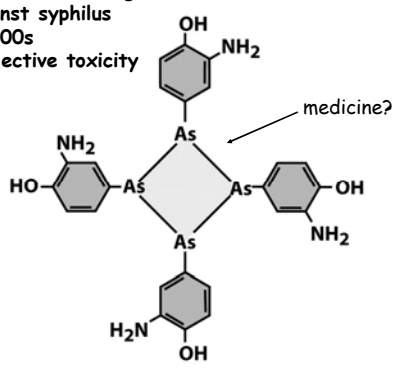
Classification of Antibiotics:

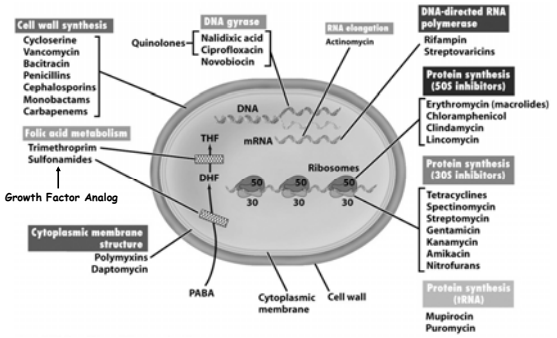
1. Inhibit growth – "stat"
   Kill bacterium – "cide"

2. Broad and Narrow spectrum

3. Production Types:
   - Natural
   - Synthetic
   - Semi-synthetic

Salvarsan: The first magic bullet
Works against syphilus
Ehrlich, 1900s
Idea of selective toxicity





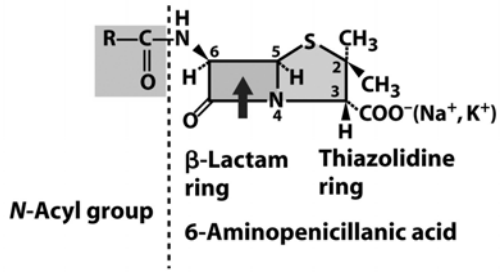
Antibiotics Affecting Replication, Transcription, & Translation

DNA replication:
Nalidixic Acid & Novobiocin – Inhibits DNA gyrase

Transcription:
Rifampin – Beta subunit of RNA polymerase
Actinomycin – DNA binding, blocks elongation

Translation:
Streptomycin – Blocks initiation on SSU of ribosome
Chloramphenicol – Blocks elongation on LSU via peptide bond
Tetracycline – Blocks elongation SSU
Cycloheximide – Eucarya ribosome specific
Diptheria Toxin – EF blocker; both Archaea and Eucarya

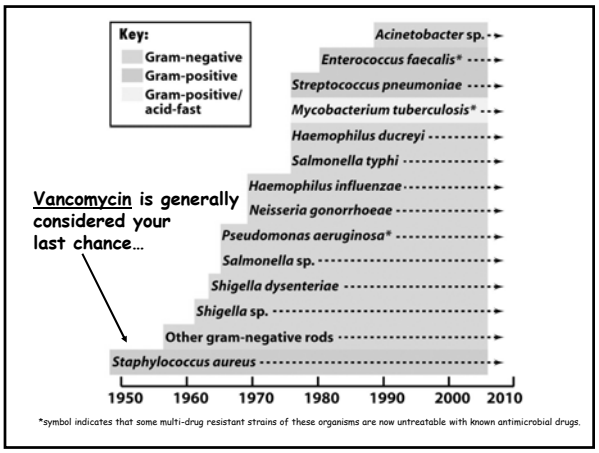
How to build a better mouse trap: Penicillin
A β-lactam antibiotic



Inhibits transpeptidation of peptidoglycan chains
Forms the old 1-2-punch with autolysins

Mechanisms of Antibiotic Resistance

1. Lacks structure antibiotic inhibits:
   Mycoplasms lack a typical cell wall.
2. Impermeable to the antibiotic:
   Gram - bacteria impermeable to penicillin G.
3. Alteration of antibiotic:
   β-lactamase degrades antibiotic e.g., springs open the mouse trap.
4. Modifies the target of the antibiotic.
5. Genetically modifies the pathway that the antibiotic affects.
6. Efflux of the antibiotic:
   Tetracycline gets pumped back out of the cell.



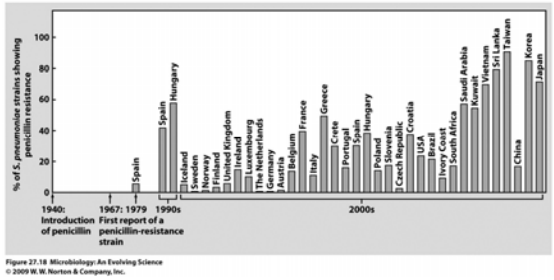


Figure 27.18 Microbiology: An Evolving Science
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