PSMU

Department of microbiology, virology and immunology

- **Chemotherapeutic drugs.**
- **Antibiotics.**

Connection

- **For two-way communication between the lecturer and students during the lecture, please contact o.hancho@pdmu.edu.ua**

Chemotherapy

- **Chemotherapy** of infectious diseases is a treatment of bacterial, viral, fungal & protozoal infections with the help of chemotherapeutical remedies, that affects the causative organism unfavorably but do not harm the patient
- **Chemoprophylaxis** is a use of a chemotherapeutical agent as a means of preventing development of specific disease

The History of Chemotherapy

Antimicrobial Drugs

- **Paul Ehrlich** coined the term Chemotherapy
- **1928**: Fleming discovered penicillin, produced by *Penicillium*
- **1940**: Howard Florey and Ernst Chain performed first clinical trials of penicillin
- More than half of the antibiotics are produced by *Streptomyces*

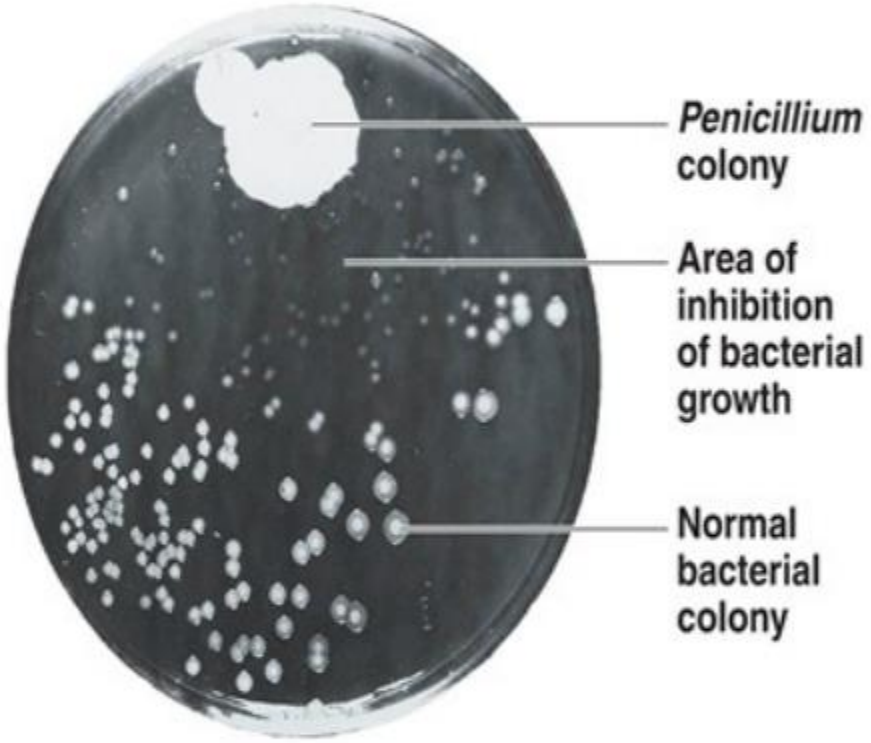


Figure 1.5

Chemotherapy

- Peruvian Indians discovered the therapeutical action of **cinchona bark**, and in the XVII-th century cinchona bark was brought to Europe. The inhabitants of Brazil successfully employed the root of **ipecacuanha** for treatment of amebiasis. **Mercury** has been employed in the treatment of syphilis

Chemotherapy

- A different kind of approach to the control of the infectious disease was developed by the German chemists **Paul Ehrlich**, who initiated an empirical search for synthetic chemicals that possess selected **toxicity** for pathogenic microorganisms. He coined the word **chemotherapy** to describe this approach to the control of infections disease.

Chemotherapy

- As a characteristic of the quality of a medical preparation, P. Erlich introduced the **chemotherapeutical index** which is the ratio of the maximal tolerated dose to minimal curative dose: **Maximal tolerated** dose (DT - dosis tolerata)
- **Minimal curative** dose (DC - dosis curativa)
- The chemotherapeutical index should not be less than **3**

Competitive Inhibitors

- **Sulfonamides (sulfa drugs)**
  - Inhibit folic acid synthesis
  - Broad spectrum
  - Bacteriostatic

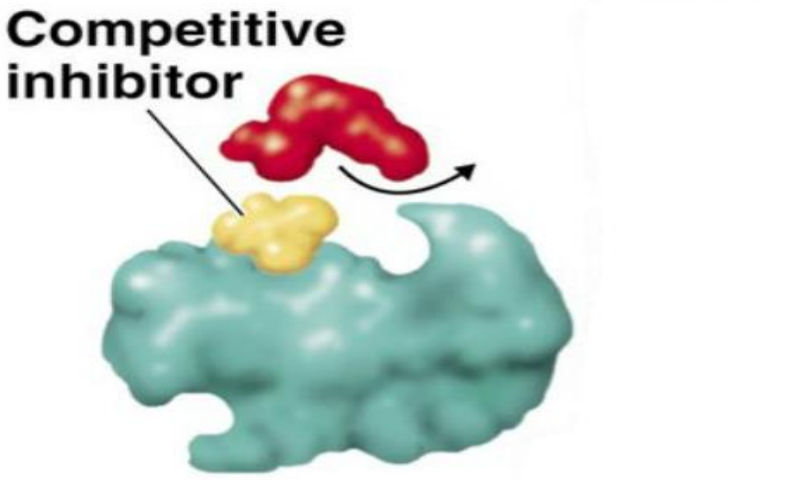


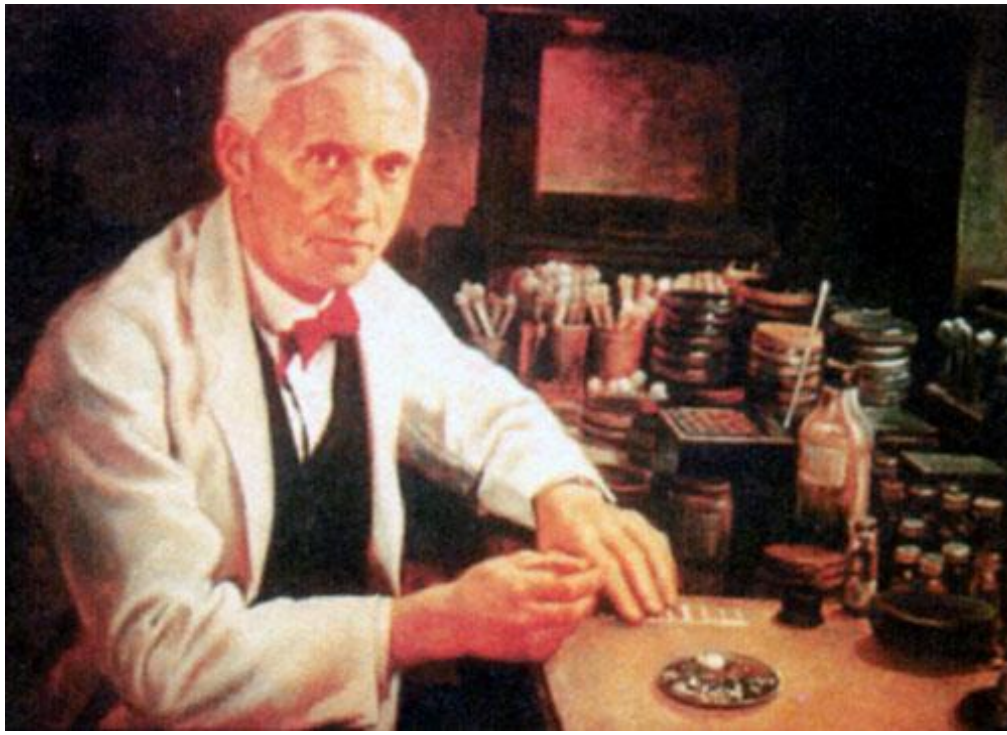
Figure 5.7b

Antibiotics

- The great modern advances in chemotherapy have come from the chance discovery that many microorganisms synthesize and excrete compounds which are selectively toxic to other microorganisms. These compounds, called ***antibiotics,*** have revolutionized modern medicine.

Antibiotics

- The first chemotherapeutically effective antibiotic was discovered by **Alexander Fleming in 1929.**
- He *called it* ***penicillin***



Antibiotics

- He observed that on a plate culture of bacteria which had become contaminated by a mold, bacterial growth in the vicinity of the mold colony was inhibited. He reasoned that the mold was excreting into the medium a chemical that prevented bacterial growth.

penicillin

He isolated the mold, which proved to be a species of *Penicillium,* and established that culture filtrates contained an antibacterial substance which

he *called penicillin.*

Antibiotics

- Clinical trials with purified material performed by British scientists H. **Flory** and E. **Chain** were grammatically successful and penicillin was being produced on an industrial scale. Success in the treatment of infections with **penicillin** prompted intensive searches for new antibiotics.

Penicillin - 1940

Representative Sources of Antibiotics

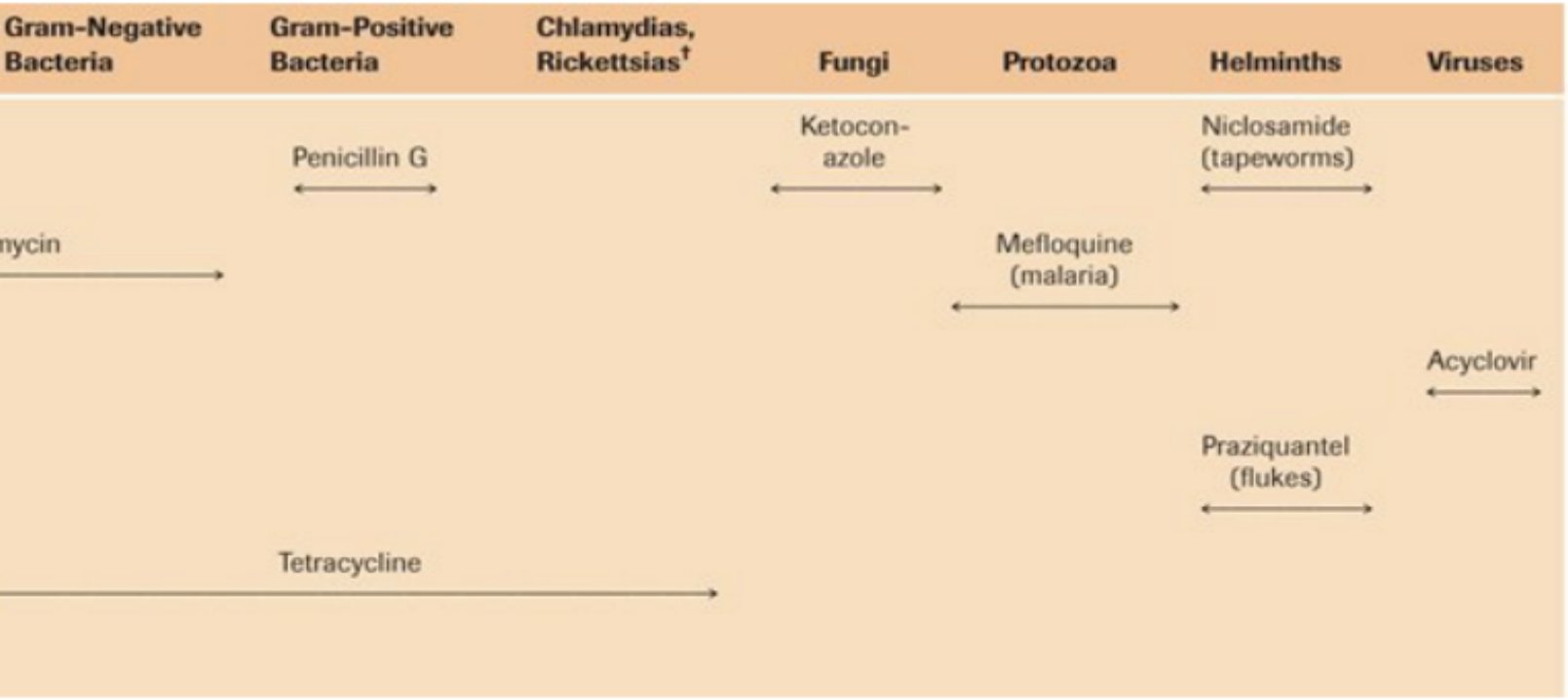
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Paenibacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomycems venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Saccharopolyspora erythraea	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpurea	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin

pectrum of Antimicrobial Activity

spectrum

w spectrum

infection



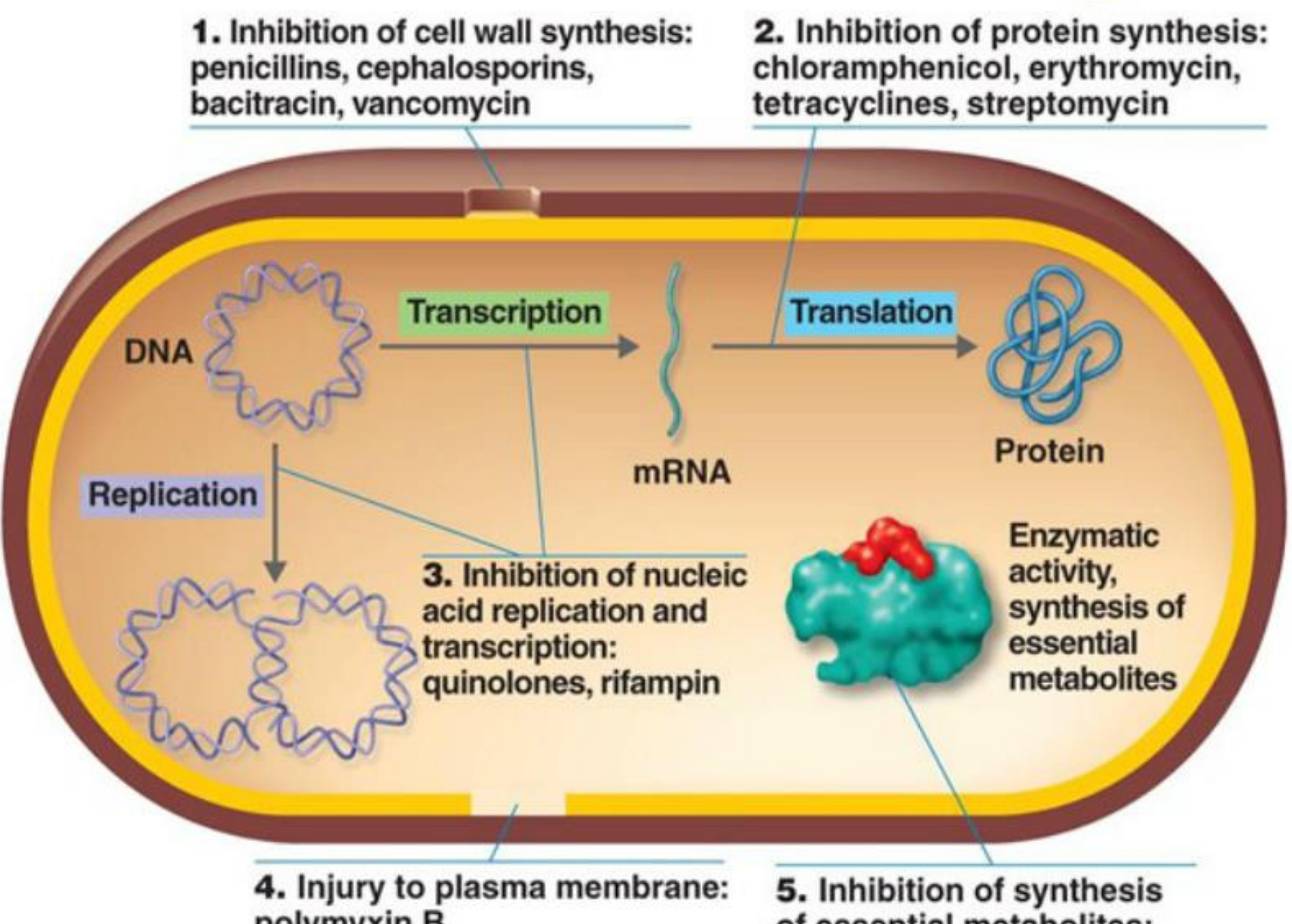
Antimicrobial Drugs

Outline

The Action of Antimicrobial Drugs

- **Bactericidal**
  - Kill microbes directly
- **Bacteriostatic**
  - Prevent microbes from growing

ne Action of Antimicrobial Drugs



ibitors of Cell Wall Synthesis

enicillin (β-Lactam compounds)

Natural penicillins

- Disadvantages of Natural Penicillin:
  - Narrow spectrum,
  - Susceptability to penicillinase

Semisynthetic penicillins

Extended-spectrum penicillins

ephalosporins

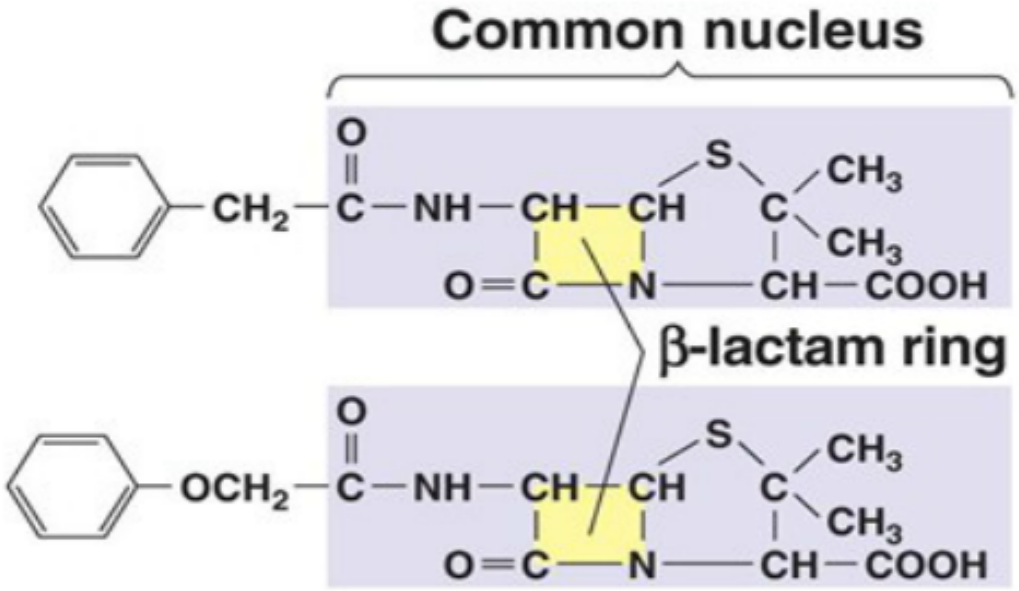
olypeptide antibiotics

tructure of Penicillins

al penicillins

G (requires injection)

V (can be taken orally)

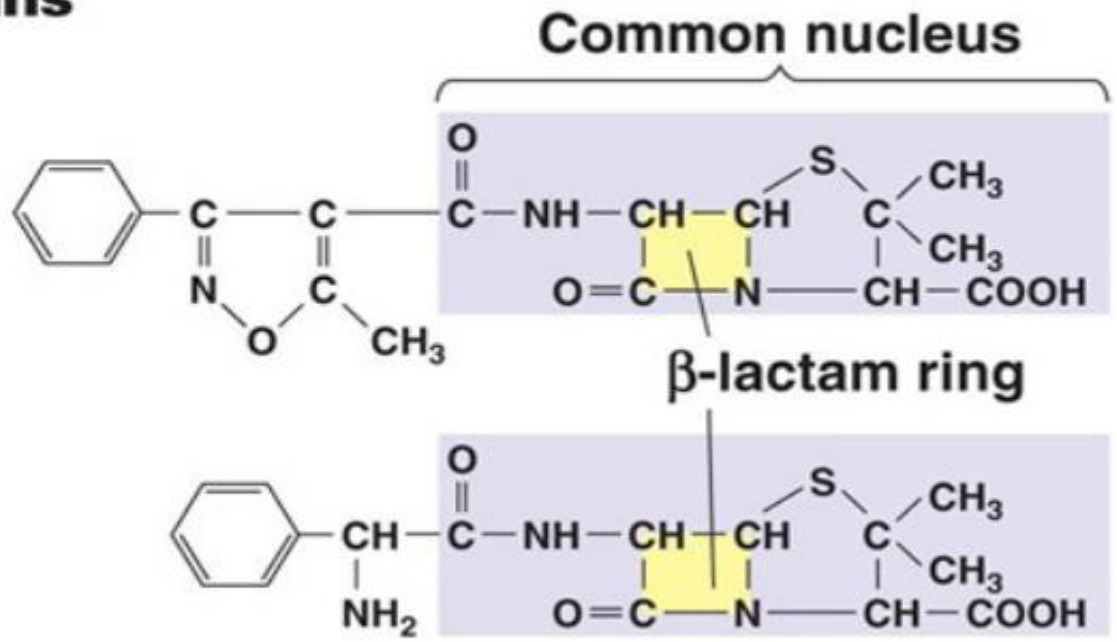


The Structure of Penicillins

b) Semisynthetic penicillins

Oxacillin:
narrow spectrum, only
gram-positives, but resistant
o penicillinase

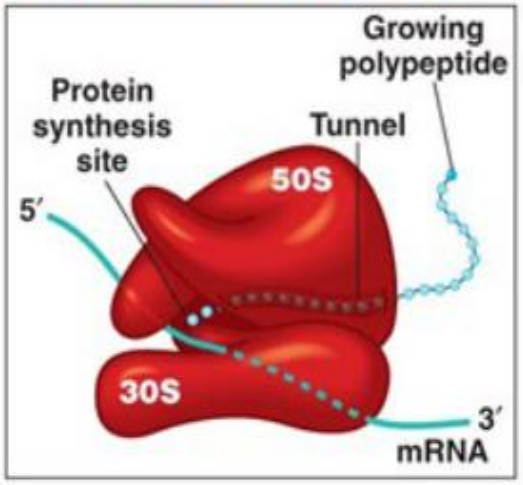
Ampicillin:
Extended spectrum,
many gram-negatives



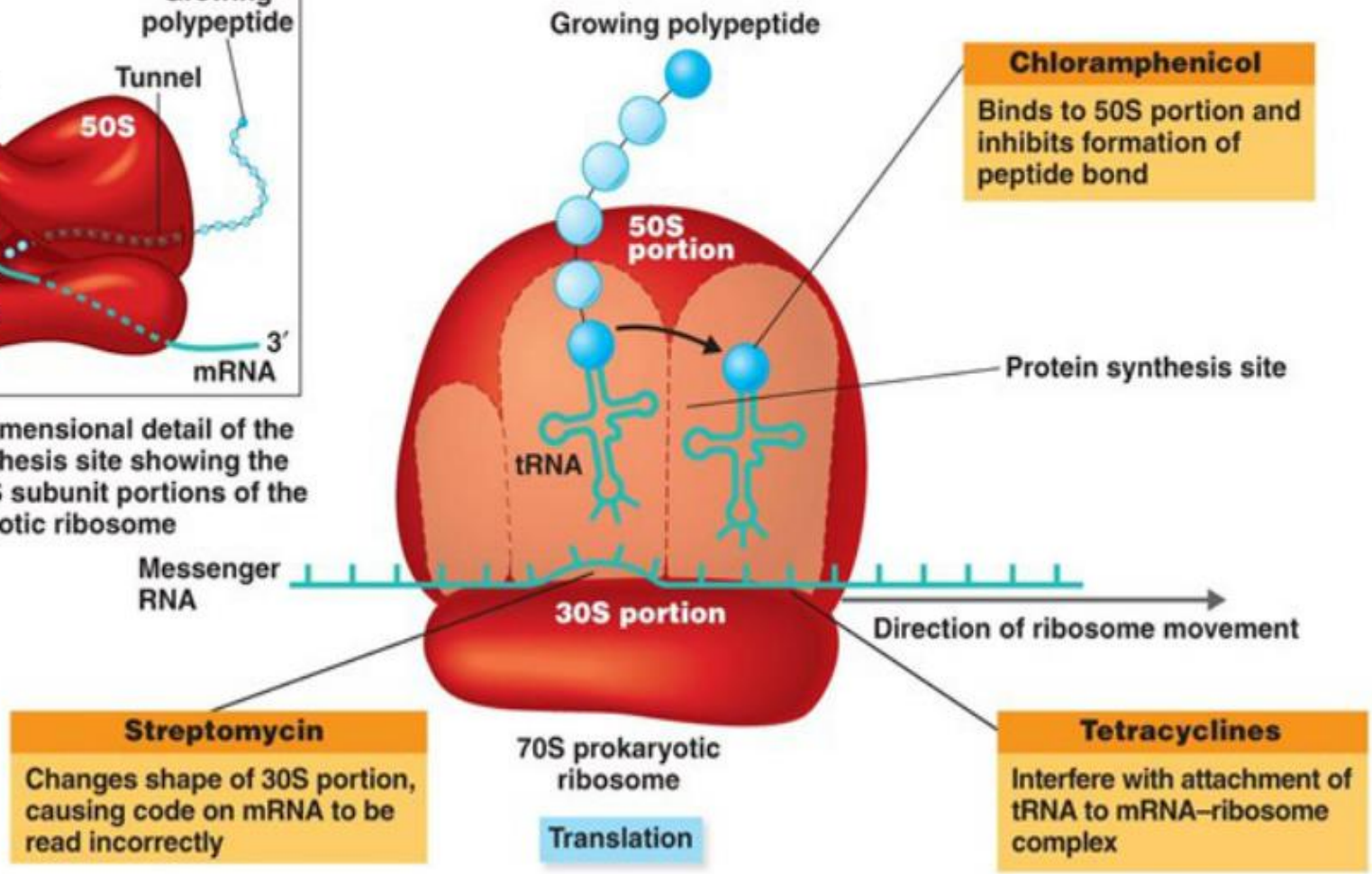
Inhibitors of Cell Wall Synthesis

- **Polypeptide antibiotics**
  - **Bacitracin**
    - Topical application
    - Against gram-positives
  - **Vancomycin**
    - Glycopeptide
    - Narrow spectrum
    - Important "last line" against antibiotic-resistant *S. aureus (MRSA)*

The Inhibition of Protein Synthesis by Antibiotics



(a) Three-dimensional detail of the protein synthesis site showing the 30S and 50S subunit portions of the 70S prokaryotic ribosome



(b) Diagram indicating the different points at which chloramphenicol, the tetracyclines, and streptomycin exert their activities

Figure 20.4

hibitors of Nucleic Acid Synthesis

Rifamycin

ex:rifampin

- Inhibits mRNA synthesis
- Antituberculosis
- Penetrate tissues and reach therapeutic levels in cerebrospinal fluids and abscesses.

Quinolones and **fluoroquinolones**

- Nalidixic acid: Urinary infections
- Ciprofloxacin
- Inhibits DNA gyrase

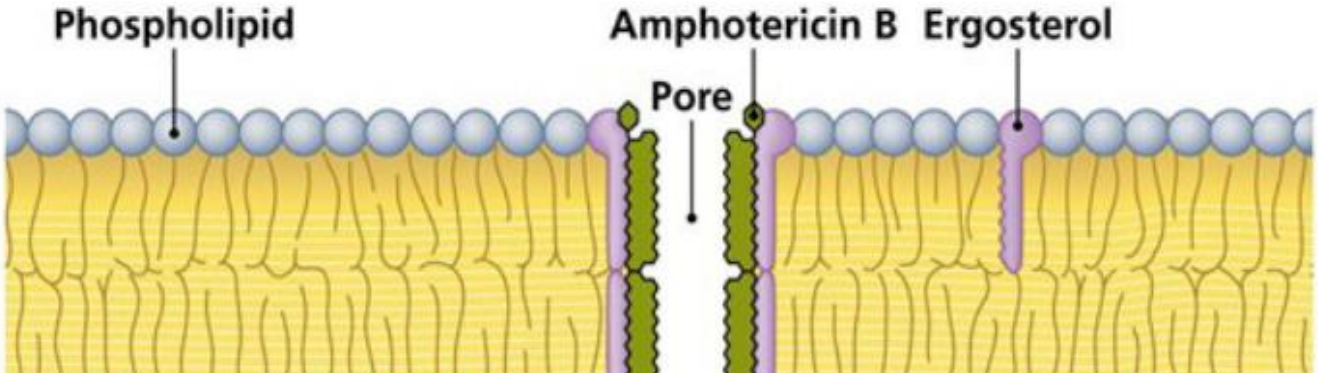
Antifungal Drugs

Difficult to find a point of selective toxicity in eukaryotes.

- Agents Affecting Fungal Sterols
  - Polyene- Amphotericin B
  - Azoles – most widely used antifungal drugs.
- Agents Affecting Fungal Cell Walls
  - Echinocandins- Cancidas
- Agents Inhibiting Nucleic Acids
  - Flucytosine –incorporates into RNA and disrupt protein synthesis.
- Other Antifungal Drugs
  - Griseofulvin-Inhibits microtubule formation

Antifungal Drugs

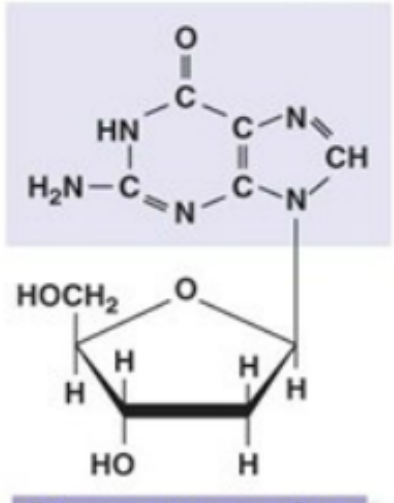
- Difficult to find a point of selective toxicity in eukaryotes.
- Inhibition of ergosterol synthesis
- **Polyenes**
  - Amphotericin B

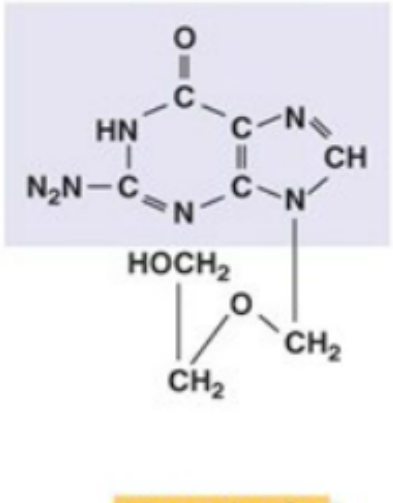


Antiviral Drugs

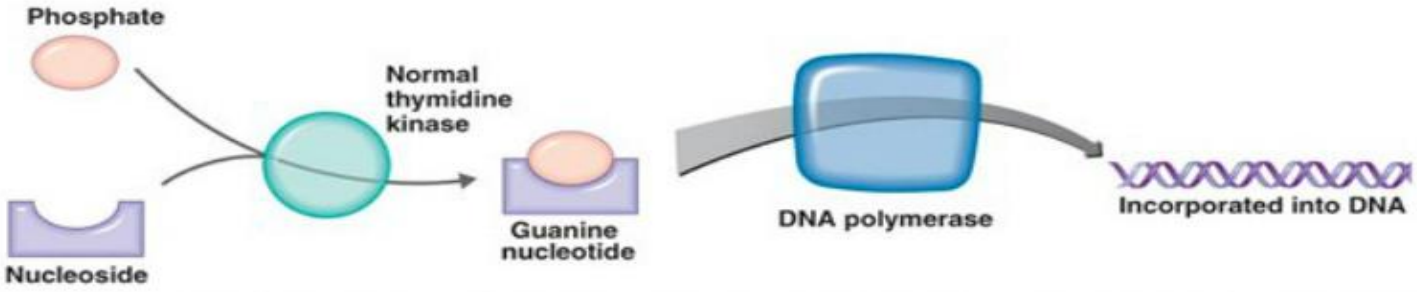
- Few antiviral drugs.
- Difficult to target Virus without damaging the host.
- Nucleoside and nucleotide analogs

Guanine

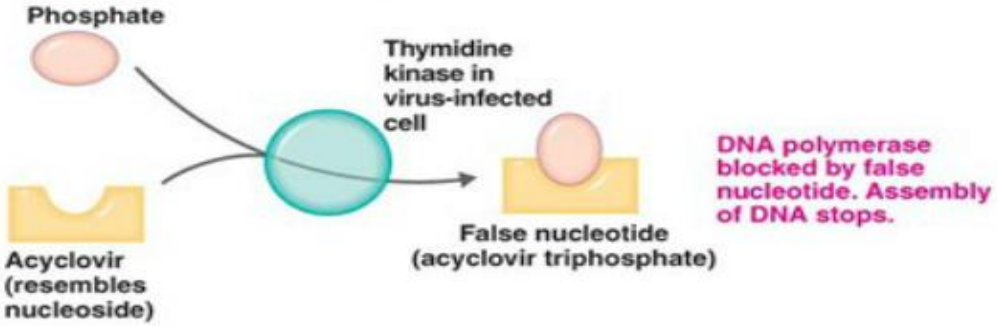




Nucleoside and Nucleotide Analogs



(b) The enzyme thymidine kinase combines phosphates with nucleosides to form nucleotides, which are then incorporated into DNA.



(c) Acyclovir has no effect on a cell not infected by a virus, that is, with normal thymidine kinase. In a virally infected cell, the thymidine kinase is altered and converts the acyclovir (which resembles the nucleoside deoxyguanosine) to a false nucleotide, which blocks DNA synthesis by DNA polymerase.

Figure 20.16b ,c

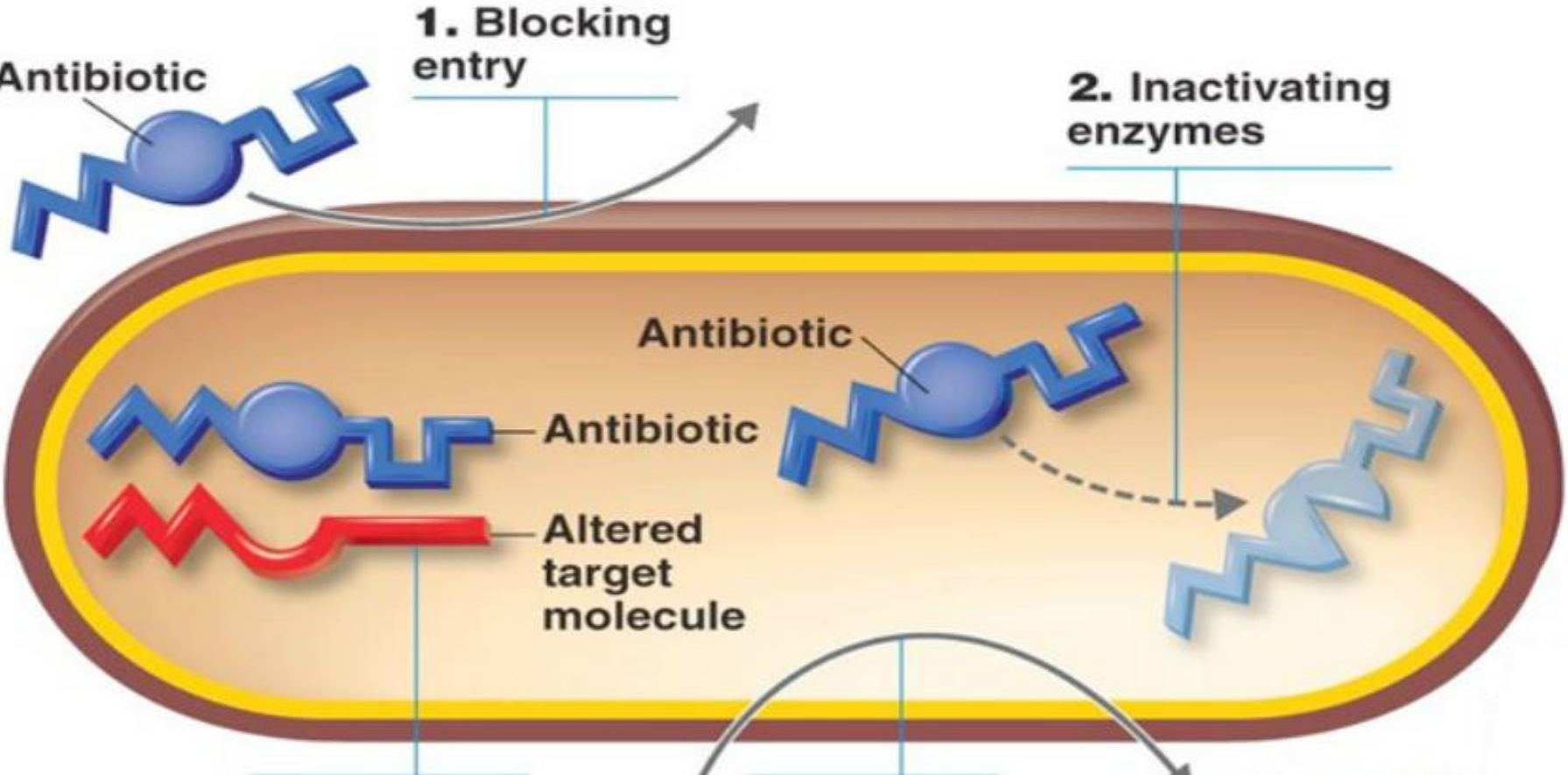
Interferons

- Prevent spread of viruses to new cells
  - Alpha interferon: Viral hepatitis
- **Imiquimod**
  - Promotes interferon production

Resistance

- The antibiotic era of medicine began abruptly some 60 years ago. How long it will last has become an open question. Although the search for new antibiotics continues, the rate of their discovery has declined sharply; most of the really effective antibiotics have probably already been discovered. Furthermore, strains of pathogens **resistant** to antibiotics have begun to develop at an alarming rate.

Resistance to Antibiotics (Mechanisms of Resistance)



Resistance

- A problem of even greater concern is the appearance of bacterial strains that are simultaneously resistant to several antibiotics, the so-called ***multiply-resistant strains.***
- ***MRSA***

Resistance

- **Resistance** can also be acquired as result of infection of the bacterial cell by a plasmid belonging to the class *of **resistance factors*** (**R factors**). These **plasmid** often confer simultaneous resistance to several antibiotics.

Antibiotic Resistance

- A variety of mutations can lead to antibiotic resistance
- Mechanisms of antibiotic resistance
  1. Enzymatic destruction of drug
  2. Prevention of penetration of drug
  3. Alteration of drug's target site
  4. Rapid ejection of the drug
- Resistance genes are often on plasmids or transposons that can be transferred between bacteria

Tests to Guide Chemotherapy

- **MIC**: Minimal inhibitory concentration
- **MBC**: Minimal bactericidal concentration
- **Antibiogram;** Periodic reports from hospitals recording the antimicrobial susceptibility of organisms encountered clinically.

  -useful in detecting emergence of antimicrobial resistance.

Tests to Guide Chemotherapy

The Disk-Diffusion Method

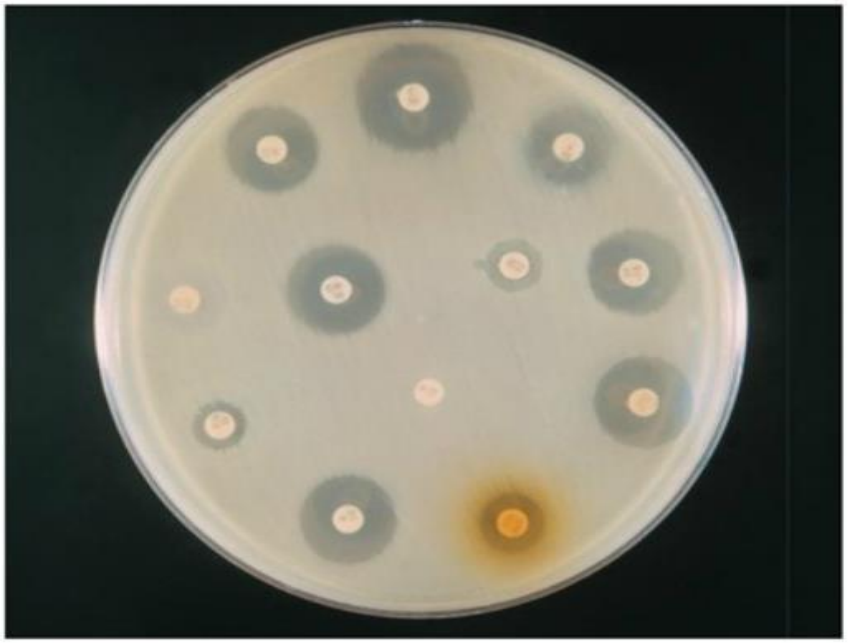
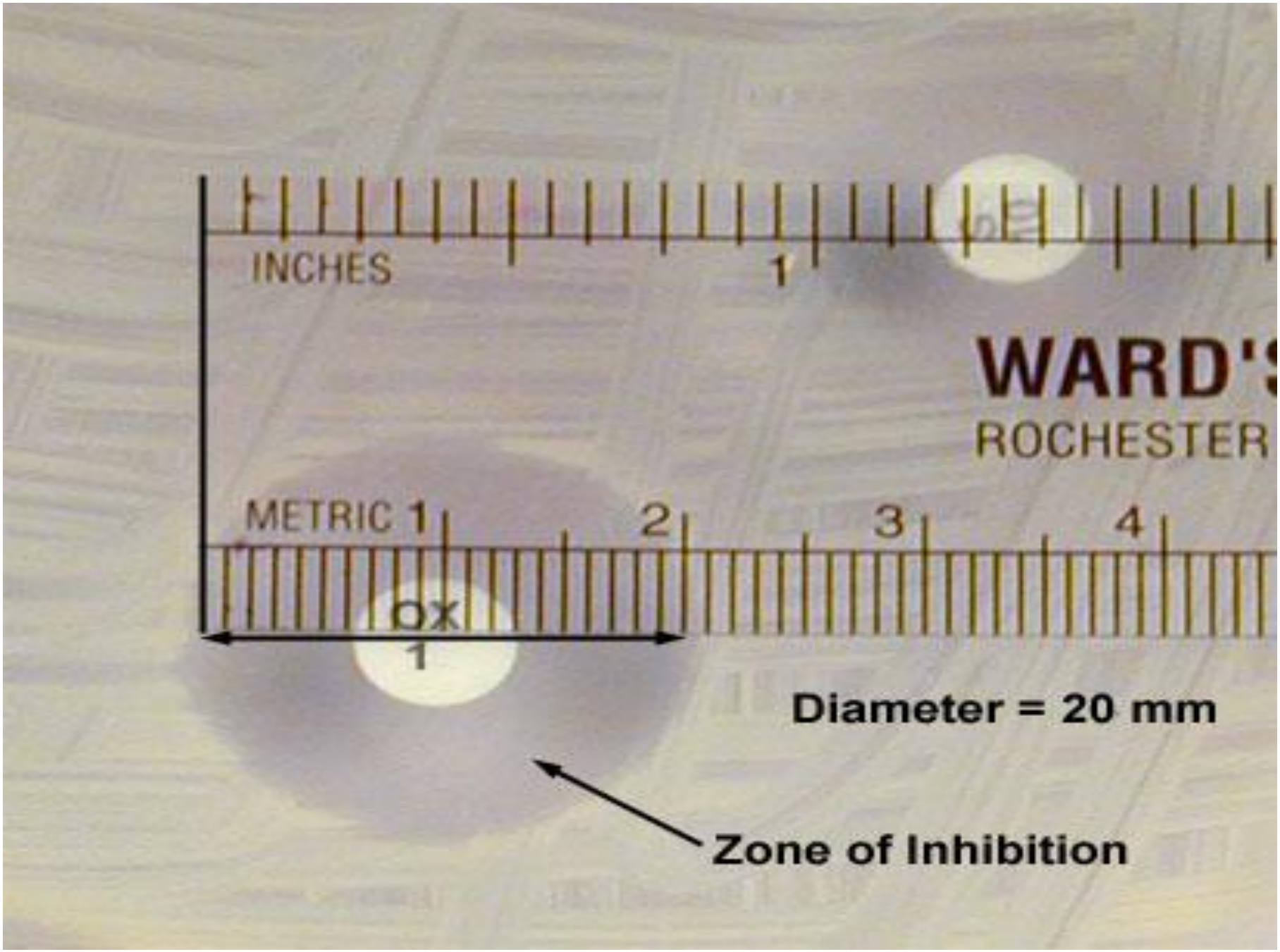


Figure 20.17


BBL
BBL


INCHES
1
WARD'S
ROCHESTER
METRIC 1
2
3
4
Diameter = 20 mm
Zone of Inhibition

The E Test

- Enables to estimate MIC(Minimum Inhibitory Concentration)

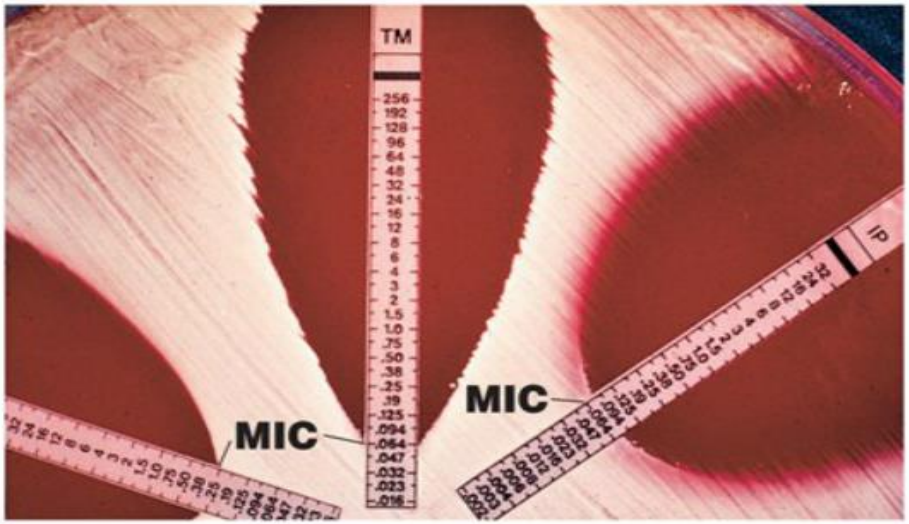
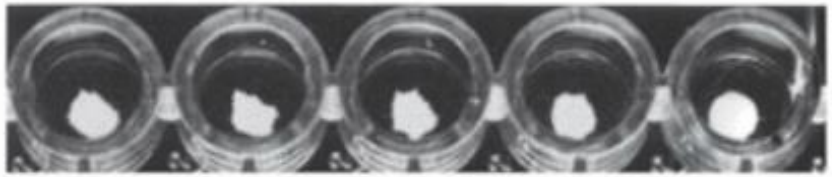


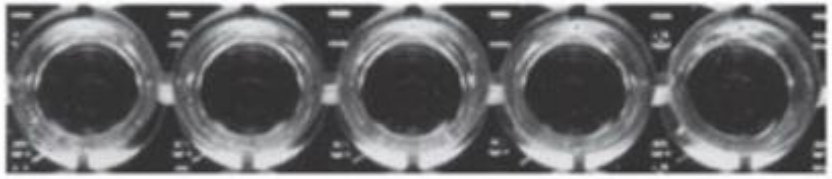
Figure 20.18

Broth Dilution Test



Doxycycline
(Growth in all wells, resistant)

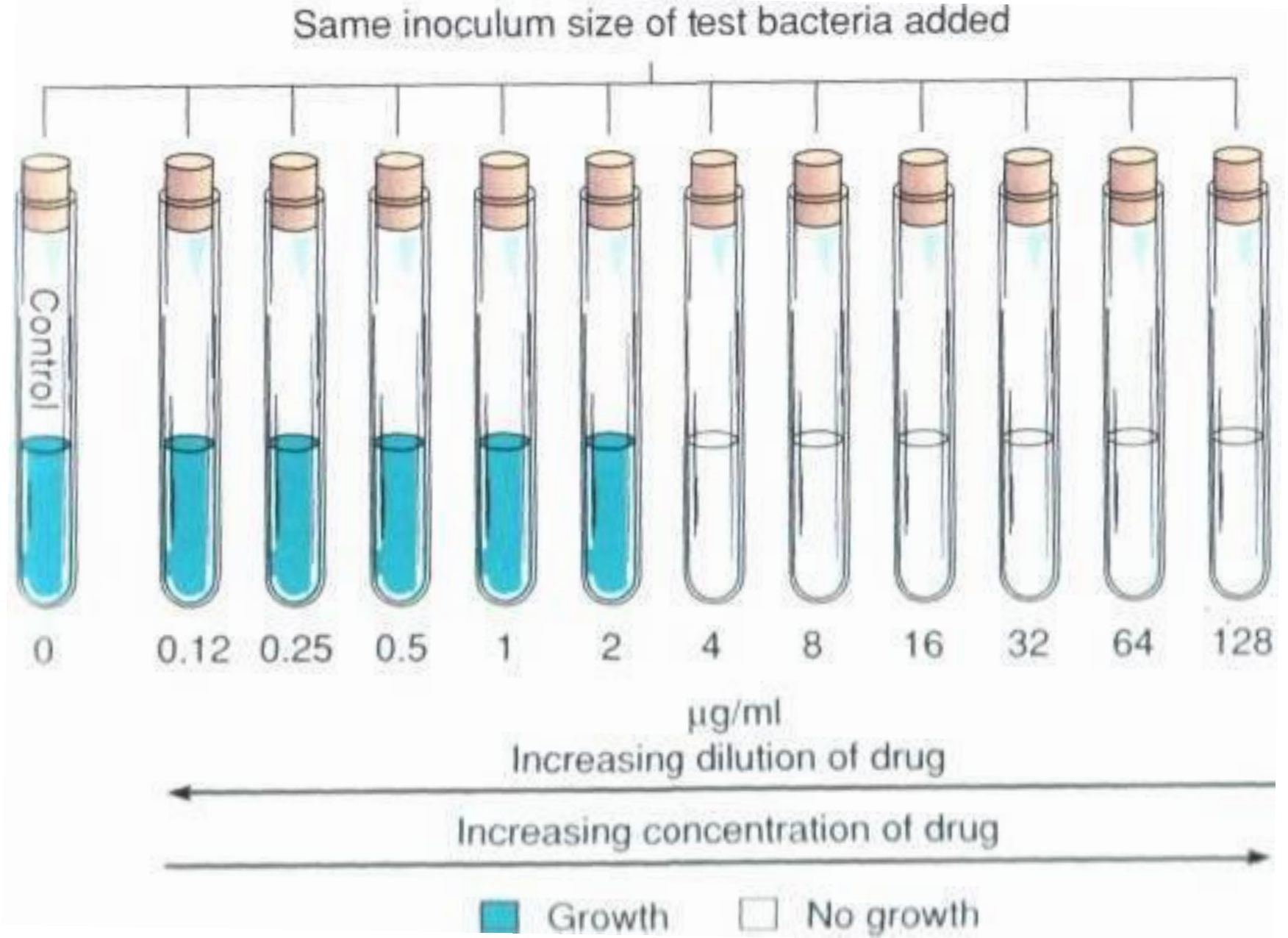
Sulfamethoxazole
(Trailing end point; usually read where there is an estimated 80% reduction in growth)



Streptomycin
(No growth in any well; sensitive at all concentrations)

Ethambutol

(Growth in fourth wells; equally sensitive to ethambutol and kanamycin)


Same inoculum size of test bacteria added
Control
0
0.12
0.25
0.5
1
2
4
8
16
32
64
128
µg/ml
Increasing dilution of drug
Increasing concentration of drug
Growth
No growth

Side effects of antibiotics

- It has been established that large dosis of streptomycin and others aminoglycosides have a neurotoxin action, tetracycline's affect the liver levomycetine has a toxic affect on the haematopoietic organs. Upon injection of penicillin and streptomycin different allergic reactions or allergic asthma may occur. In prolonged use of penicillin or levomycetine collapse is one of the severe side effects.


Thanks for attention!