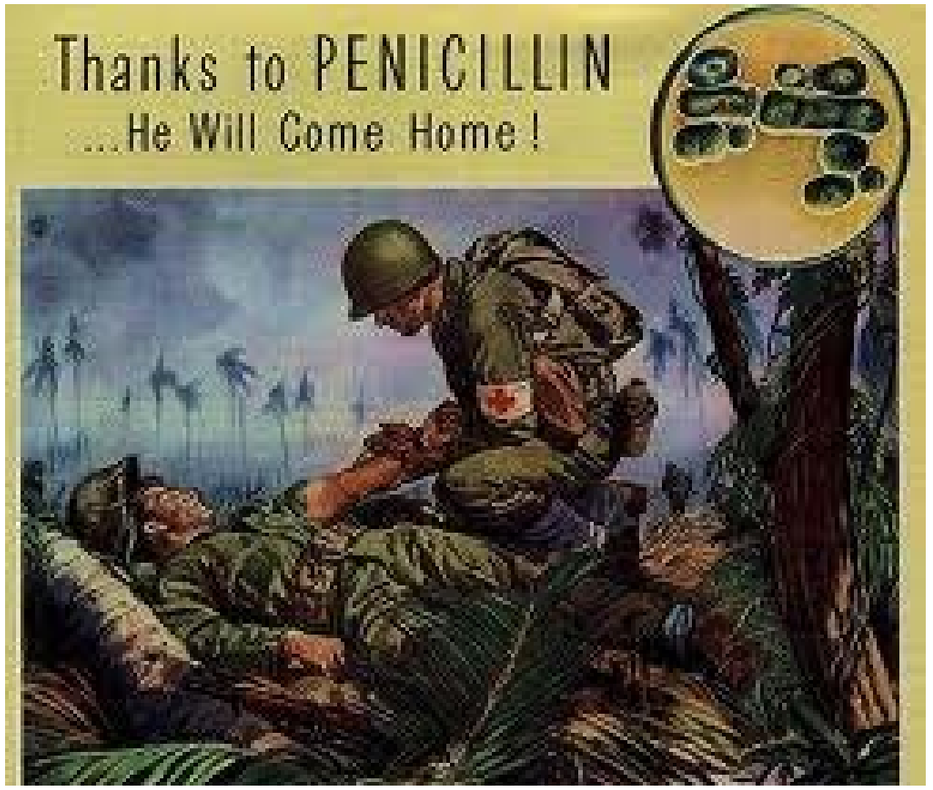
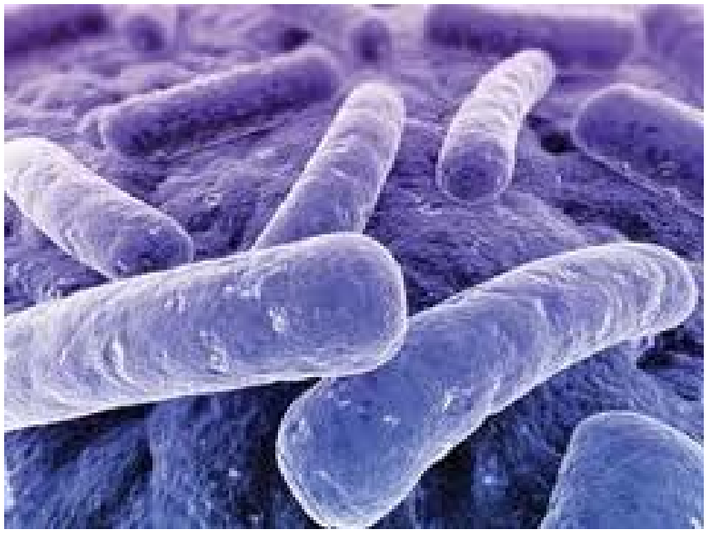
Antibiotics

- Antimicrobial substances formed by microorganisms that kill (e.g. bactericidal effect) or inhibit (e.g. bacteriostatic effect) other microorganisms.



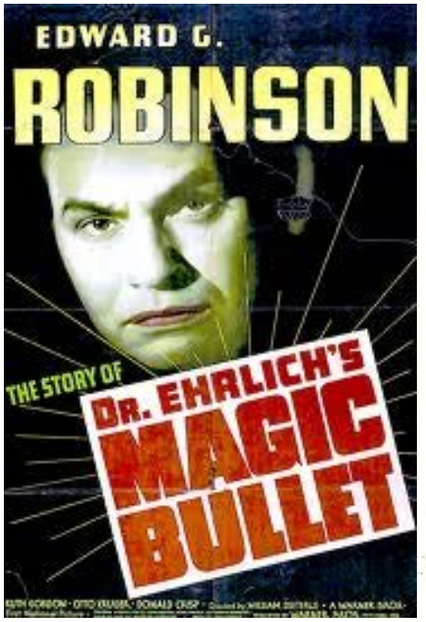


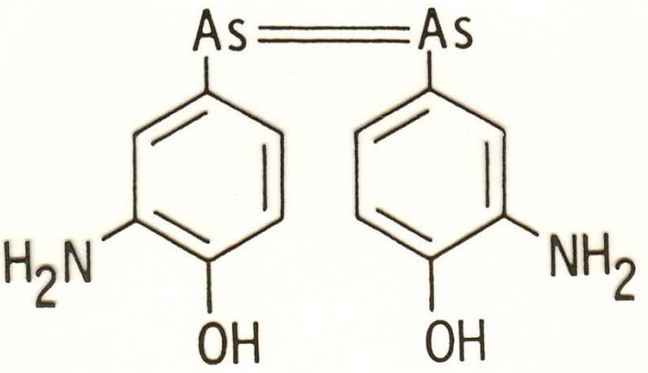
1. Koch's postulates

(The golden age of microbiology, 1857-1914)

2. Chemotherapy-selective toxicity

Treatment of human infections with antibiotics was a medical revolution





Salvarsan

Arsenical compounds

Paul Ehrlich (1854-1915)

Chemotherapy

"Selective toxicity"

I.G. Farbenindustrie

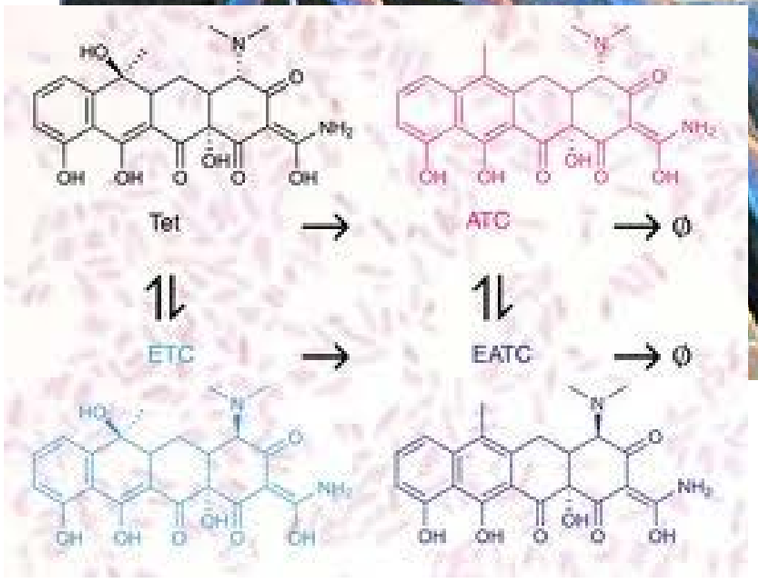
sulfa (30-talet)

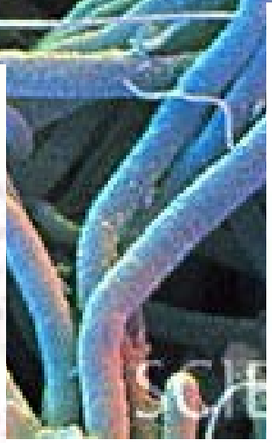
3. Penicillin “accidentally” discovered by Alexander Fleming (1928)

Sir Alexander Fleming (1881-1955) is famous as the discoverer of the antibiotic substance lysozyme and for isolating the antibiotic substance penicillin from the fungus *Penicillium notatum*.

For his achievements, Fleming was knighted in 1944 and shared the Nobel prize for Physiology or Medicine in 1945.

4. Soil microorganisms

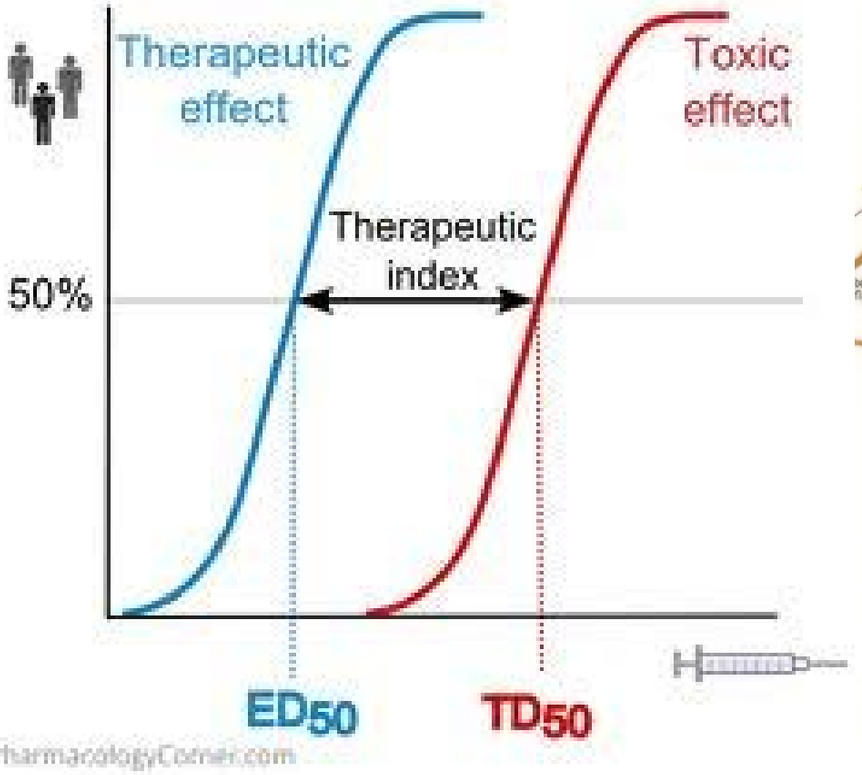


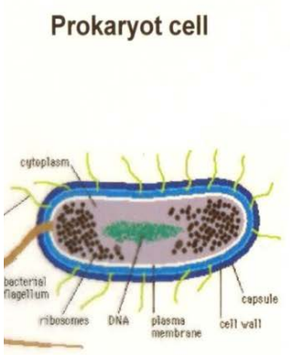


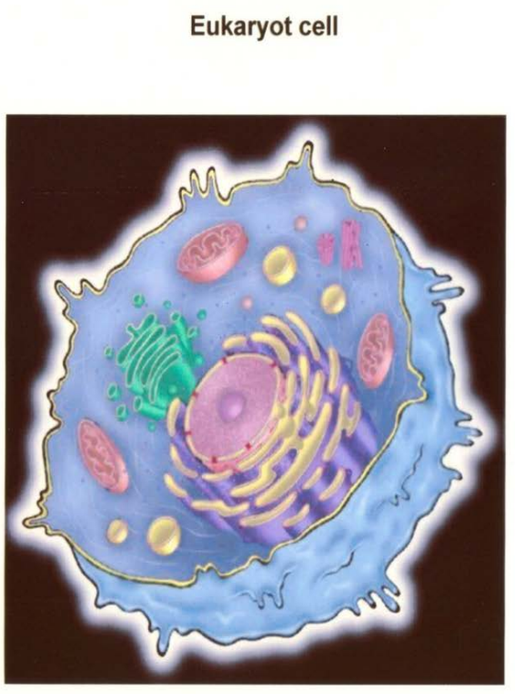
chemical warfare

- **therapeutic dose (effect)**
  - drug level required for clinical treatment
- **toxic dose (effect)**
  - drug level at which drug becomes too toxic for patient (i.e., produces side effects)
- **therapeutic index**
  - ratio of toxic dose to therapeutic dose

TD50 is the dose of drug that causes a toxic response in 50% of the population and ED50 is the dose of drug that is therapeutically effective in 50% of the population.

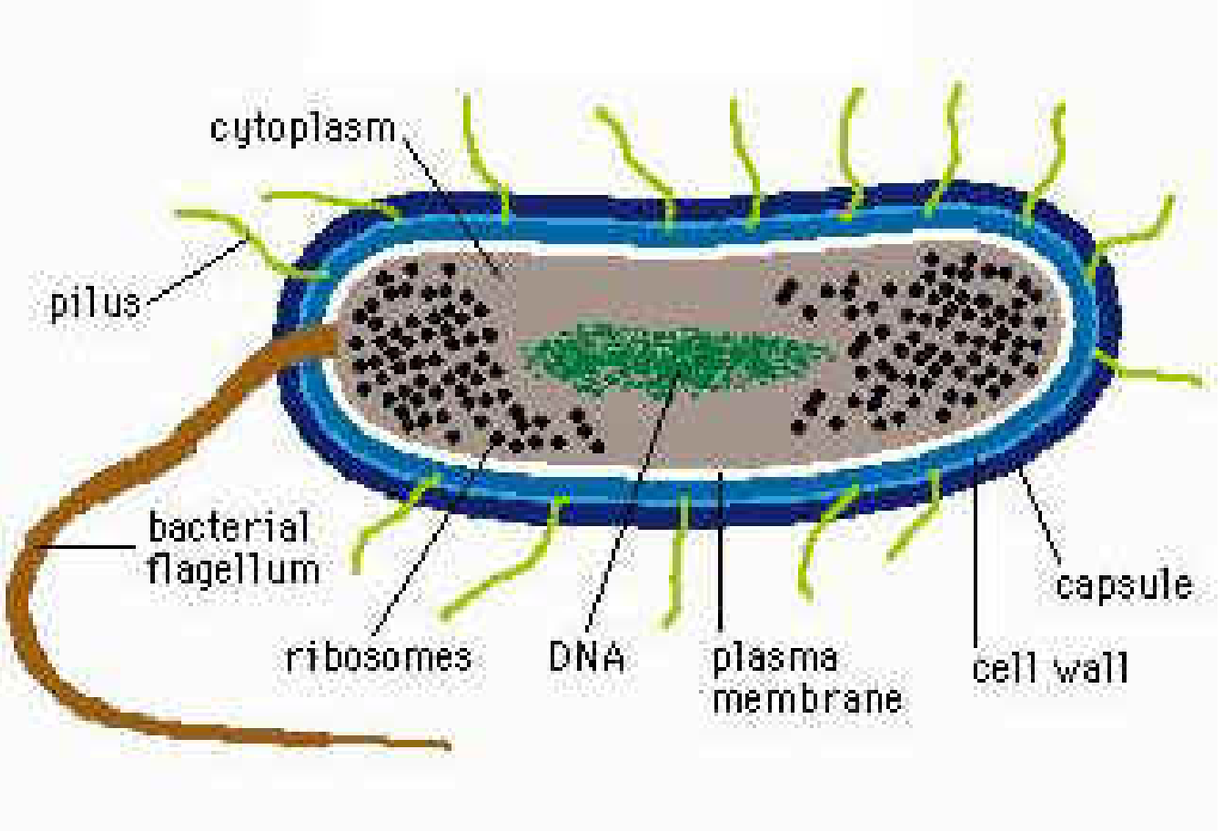




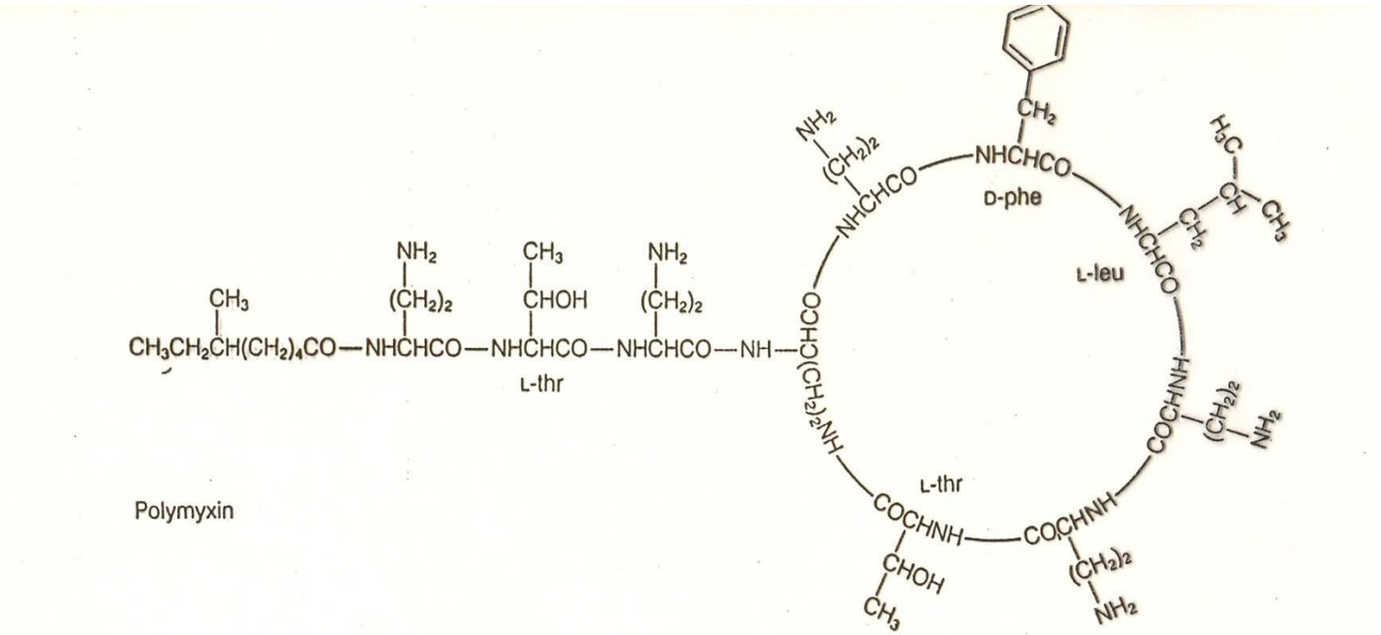


Antibiotics can be divided into four groups based on their biochemical mechanisms

1. those that affect the plasma membrane.
2. those that inhibit nucleic acid synthesis (nucleotides, DNA, RNA)
3. those that inhibit protein synthesis (the ribosome)
4. those that inhibit the synthesis of cell walls (peptidoglycan synthesis)



Cell membrane inhibitor antibiotics



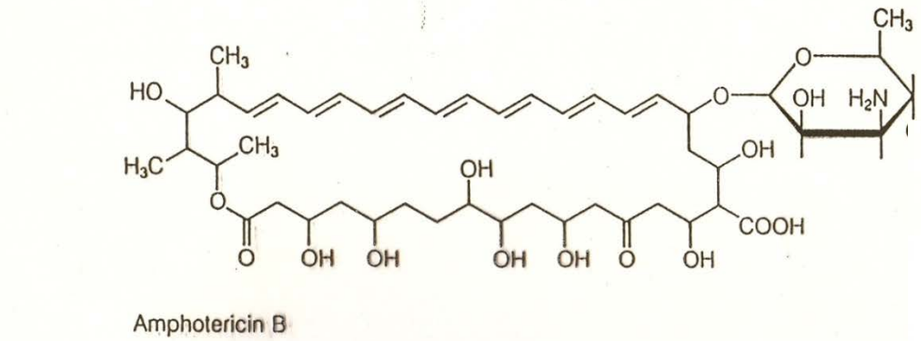
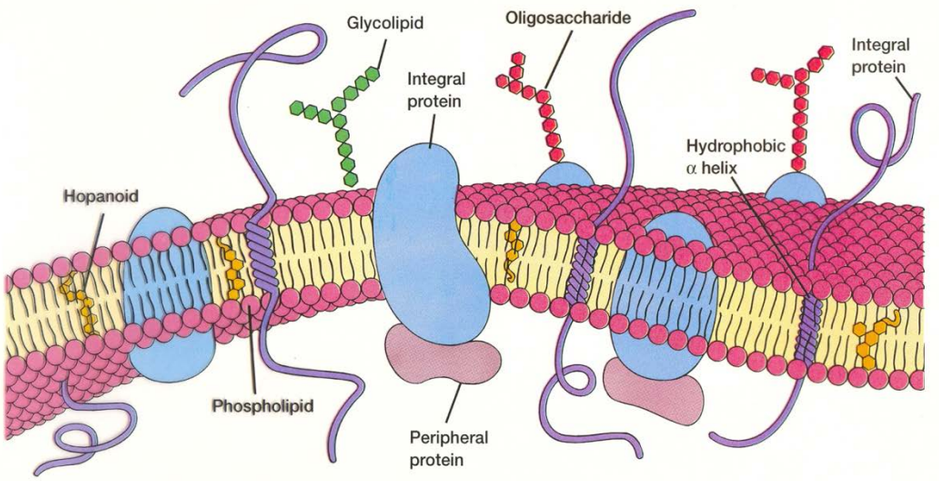
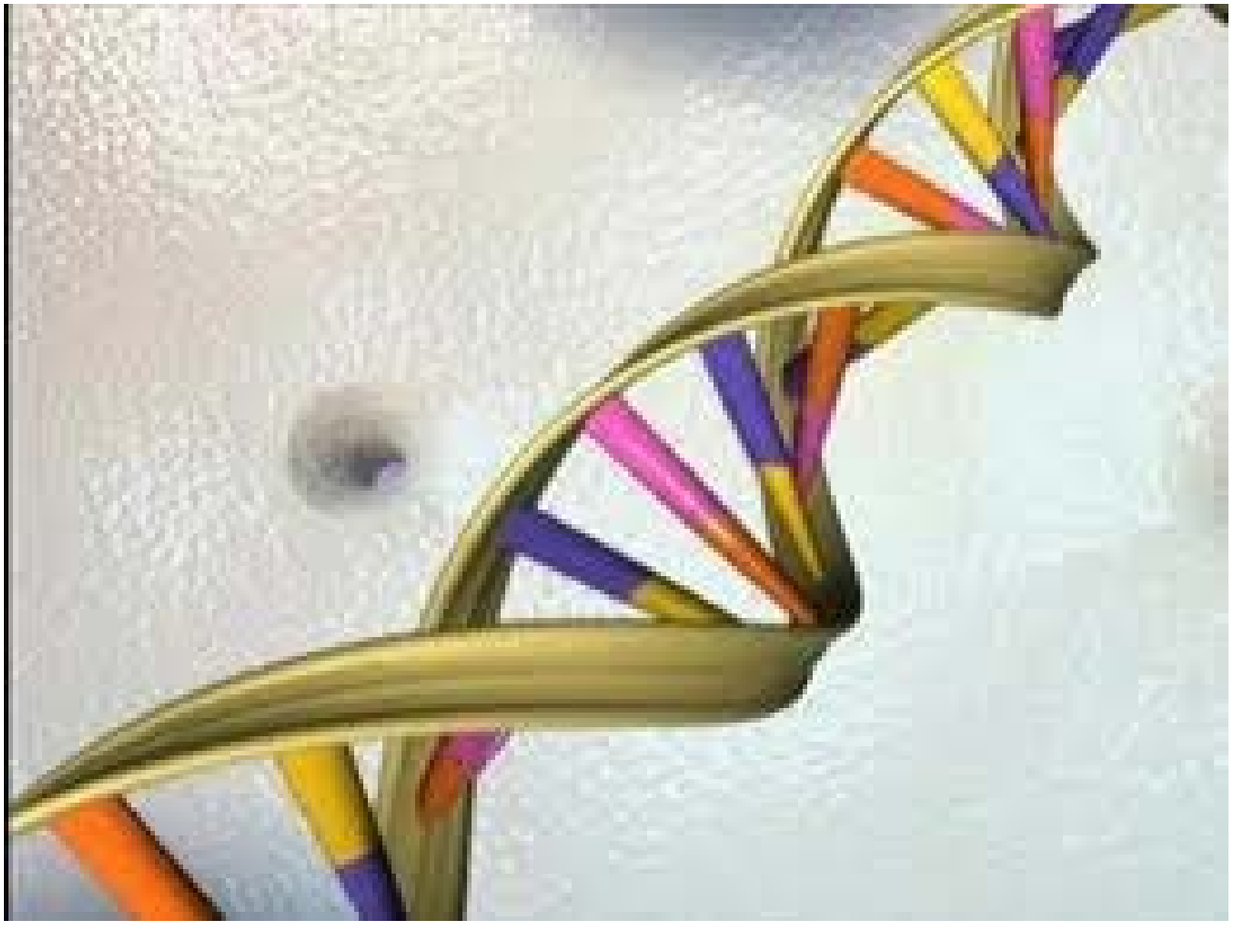


Figure 5–20 **Polymyxin and Amphotericin B**



2 Plasma Membrane Structure
Figure 3.7

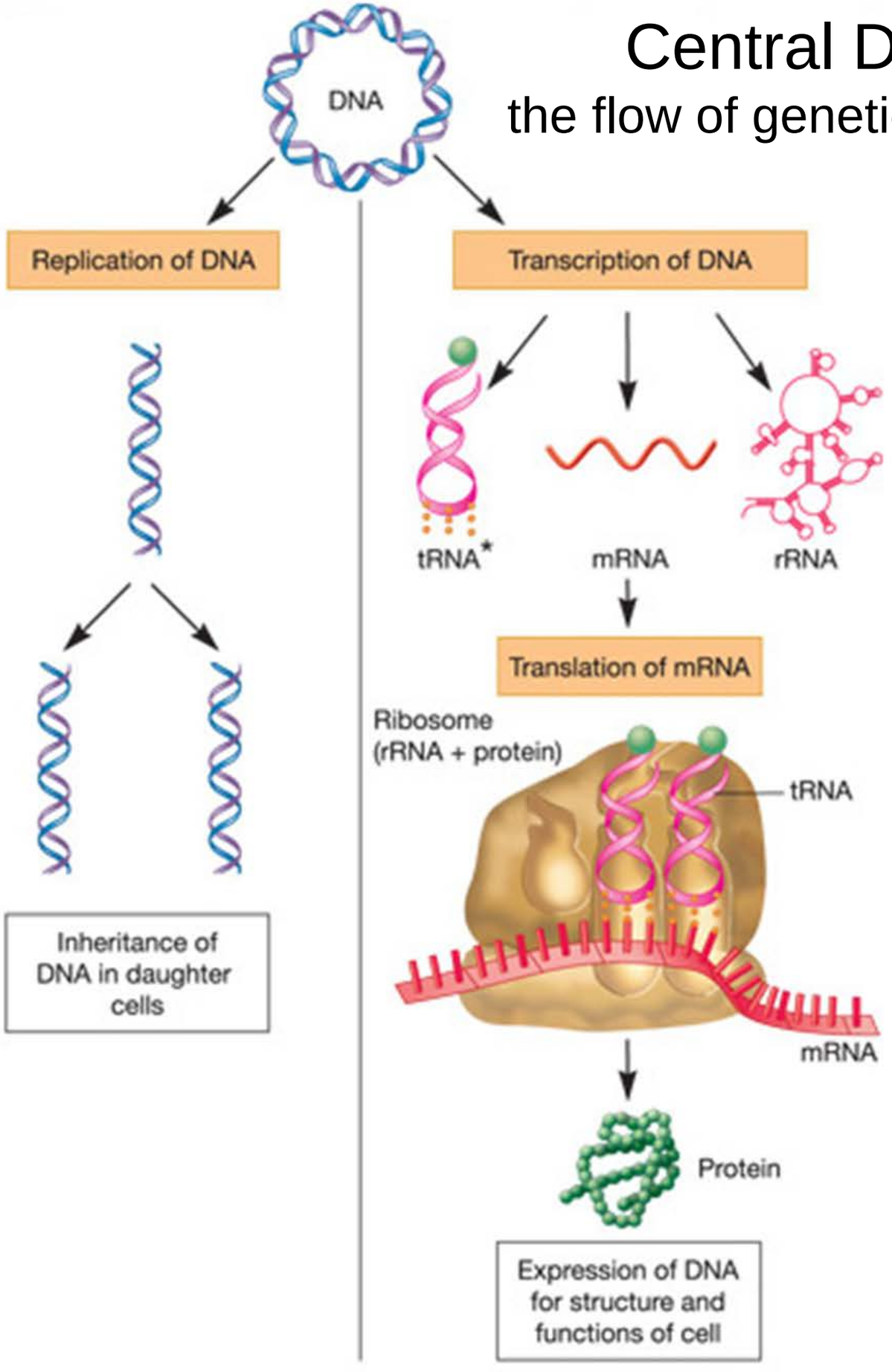
Nucleic acid inhibitor antibiotics



1. DNA inhibitors (such as the quinolones, acting upon DNA gyrase as a topoisomerase inhibitors)
2. RNA inhibitors (such as rifampin, acting upon RNA-dependent RNA polymerase)
3. Antifolates (such as sulfonamides and trimethoprim, acting upon folic acid biosynthesis enzymes)

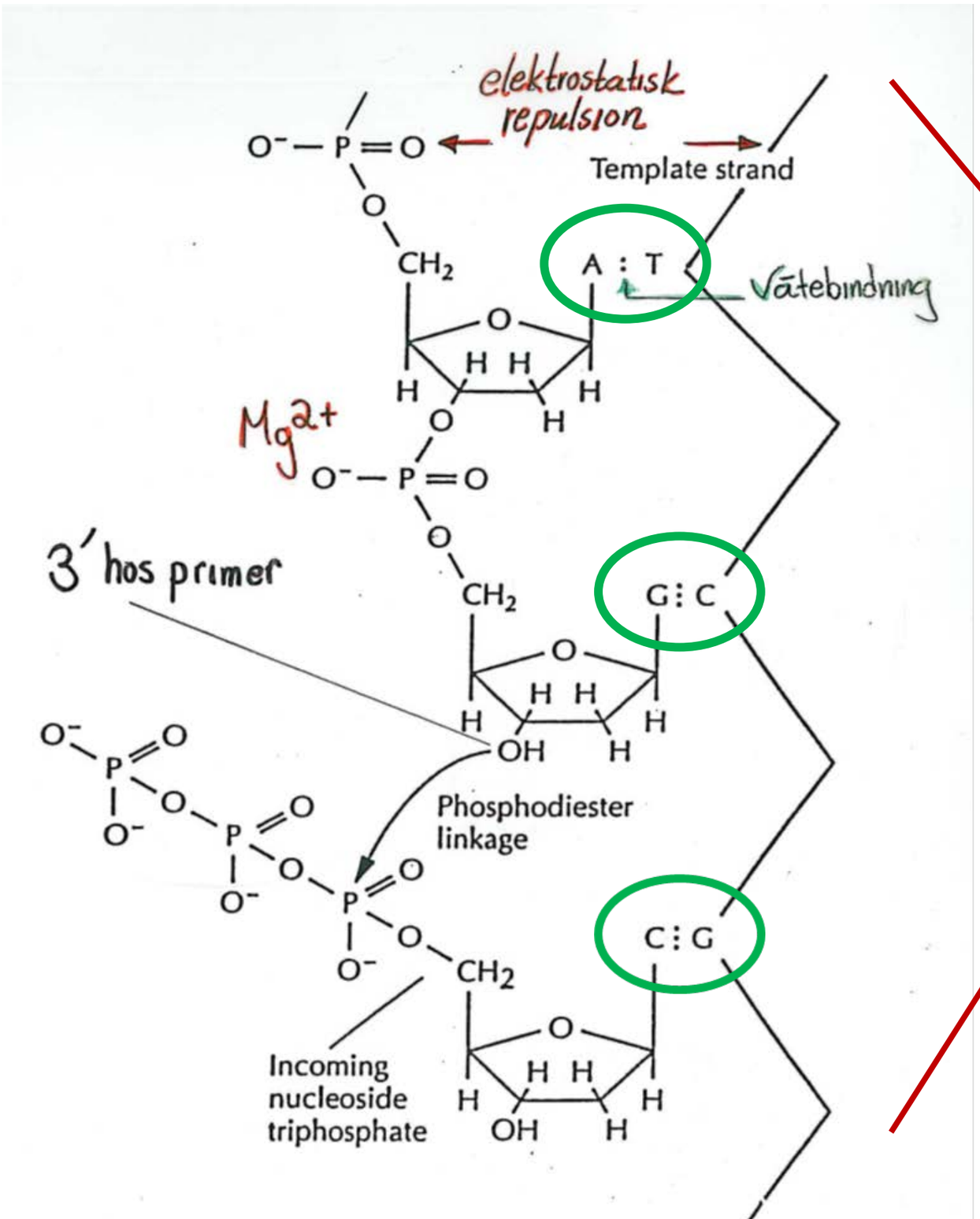
Central Dogma

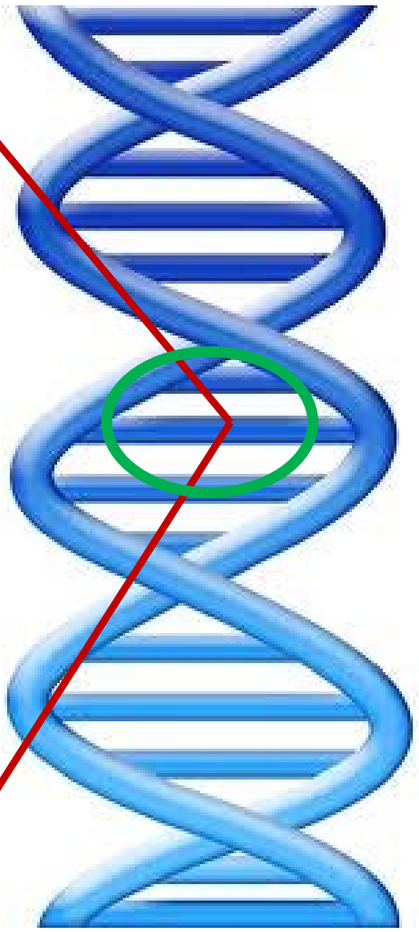
the flow of genetic information



Nucleic Acid Structure

- The nucleic acids, DNA and RNA are polymers of nucleotides
  - linked together by phosphodiester bonds





DNA Forms

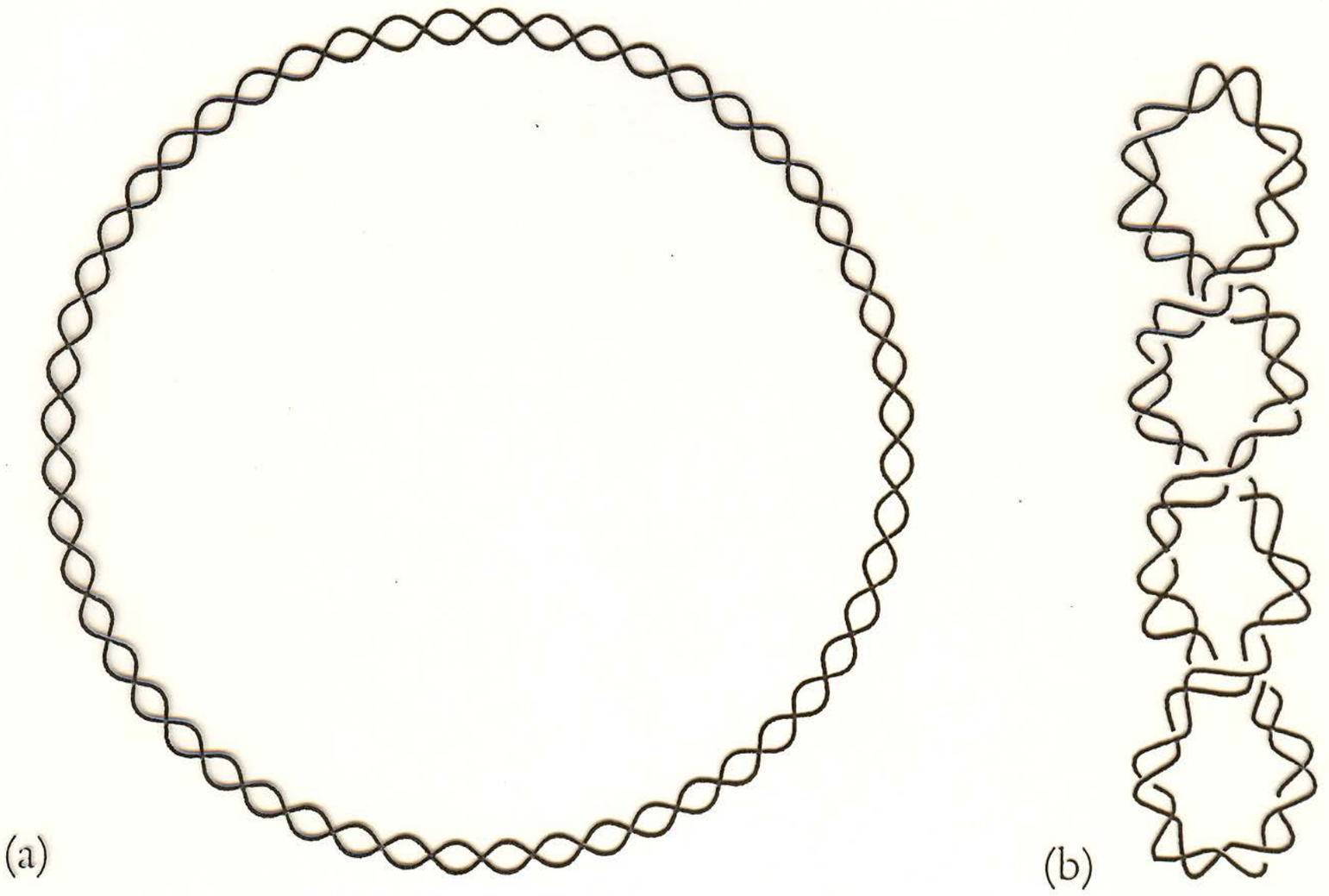


Figure 11.8 DNA Forms. (**a**) The DNA double helix of almost all bacteria is in the shape of a closed circle. (**b**) The circular DNA strands, already coiled in a double helix, are twisted a second time to produce supercoils.

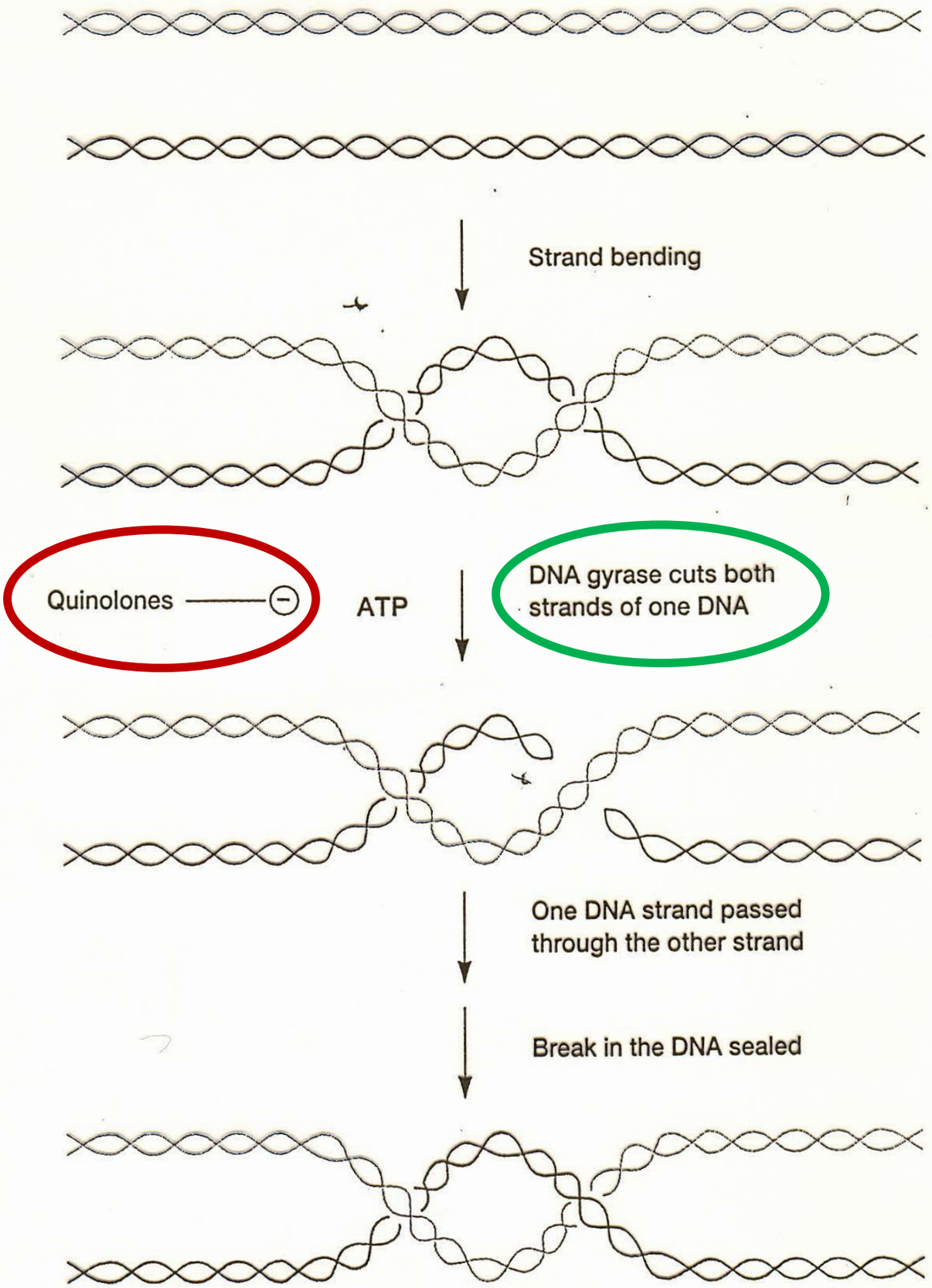


Figure 35.6 DNA Gyrase Action and Quinolone Inhibition.

J01M Antibakteriella kinolonderivat

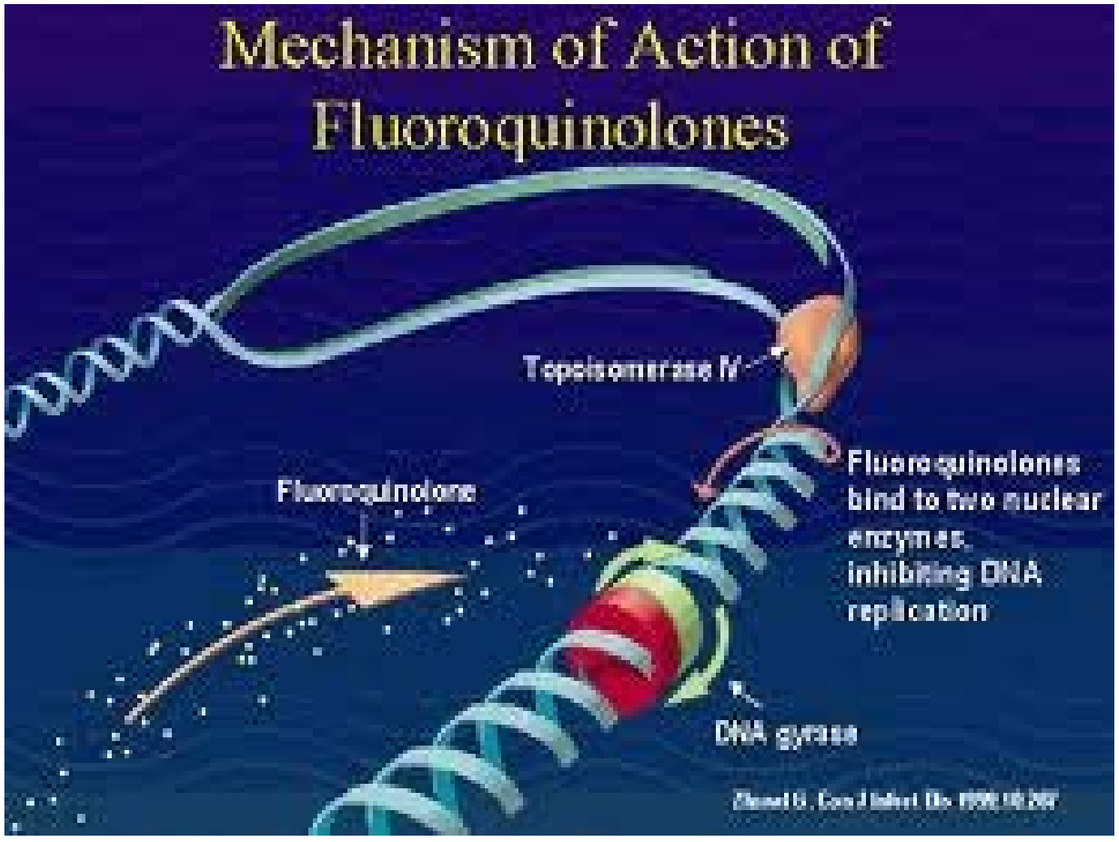
J01M A Fluorokinoloner

Ofloxacin
J01M A01 Tarivid, Hoechst, tabletter 200 mg och 400 mg, infusionsvätska 2 mg/ml

Ciprofloxacin
J01M A02 Ciproxin, Bayer, tabletter 100 mg, 250 mg, 500 mg och 750 mg, infusionsvätska 2 mg/ml

Enoxacin
J01M A04 Comprecin, Parke-Davis, tabletter 200 mg

Norfloxacin
J01M A06 Lexinor, Astra, tabletter 200 mg och 400 mg



Protein inhibitor antibiotics

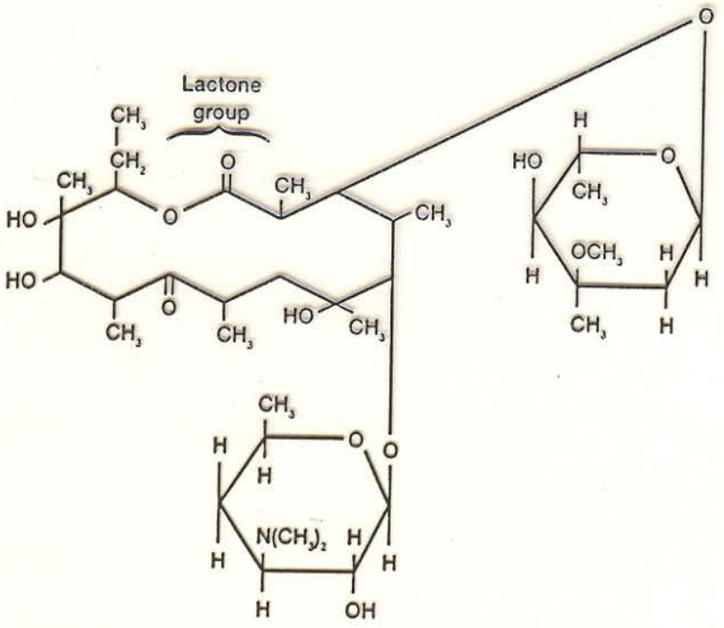


Figure 33.11 **Erythromycin, a Macrolide Antibiotic.** The 14-member lactone ring is connected to two sugars.

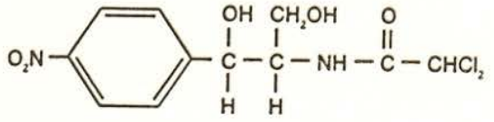


Figure 33.12 **Chloramphenicol.**

Tetracycline (chlortetracycline, doxycycline)

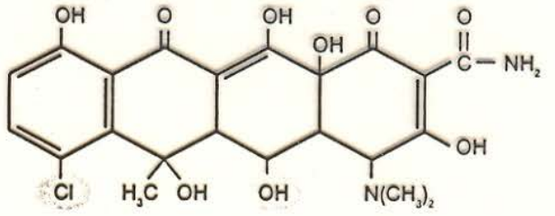
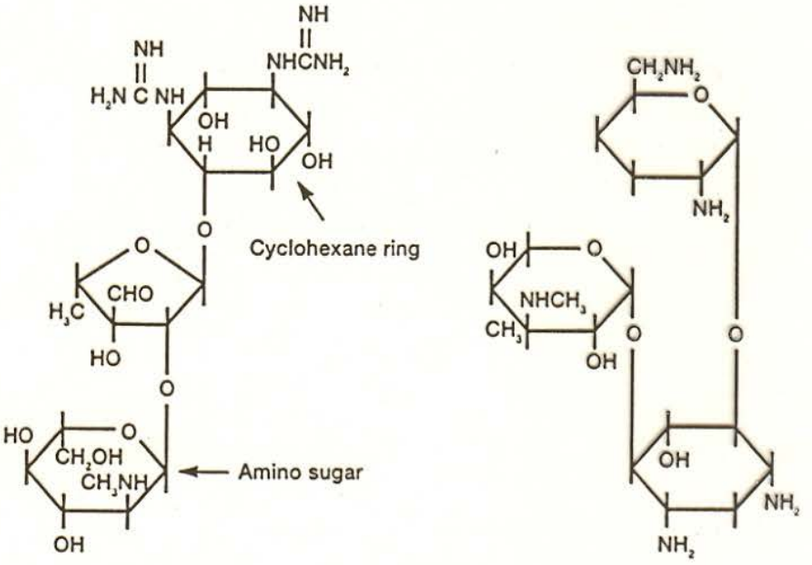


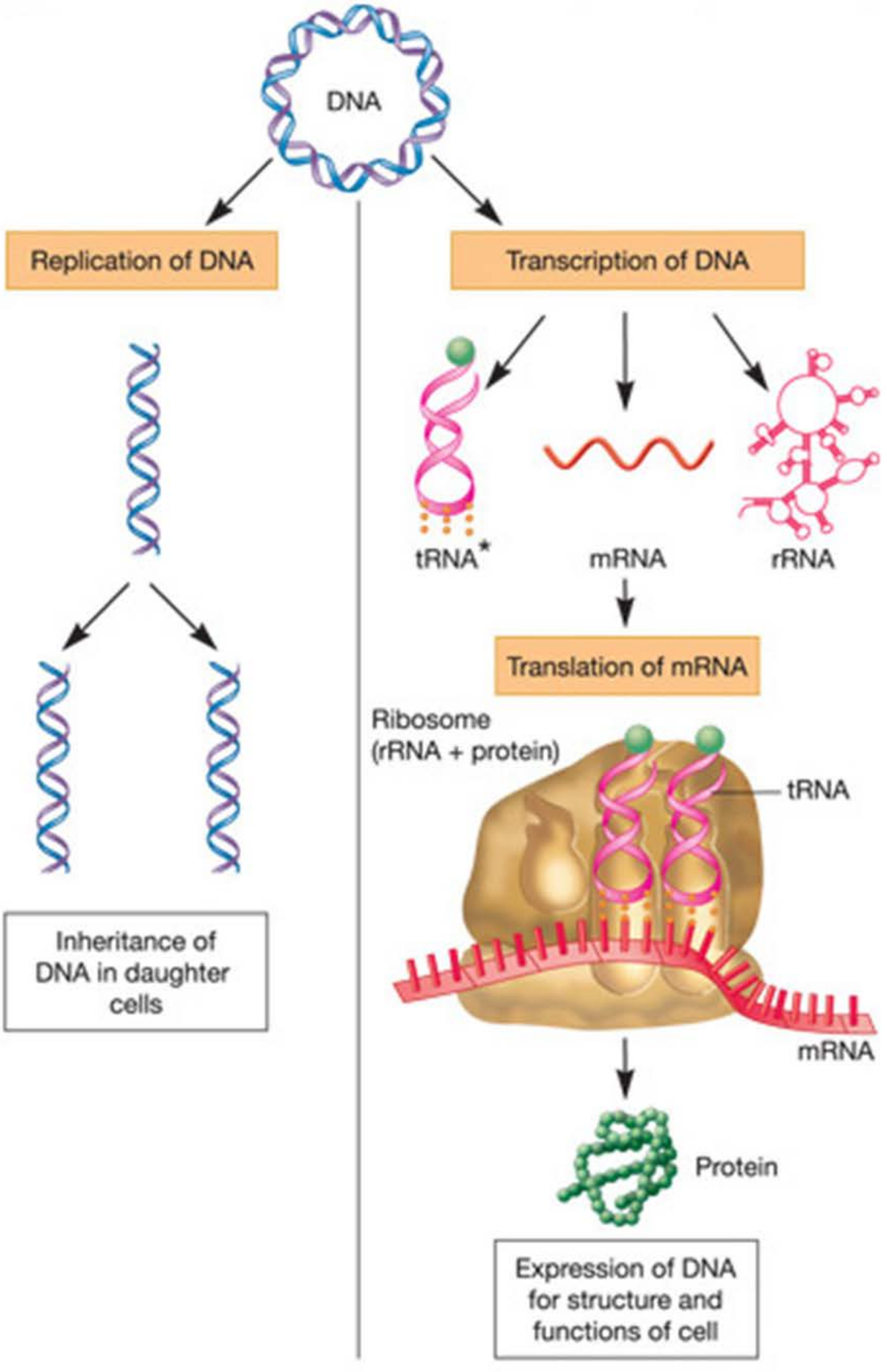
Figure 33.9 **Tetracyclines.** Three members of the tetracycline family. Tetracycline lacks both of the groups that are shaded. Chlortetracycline (aureomycin) differs from tetracycline in having a chlorine atom (blue); doxycycline consists of tetracycline with an extra hydroxyl (purple).



Streptomycin

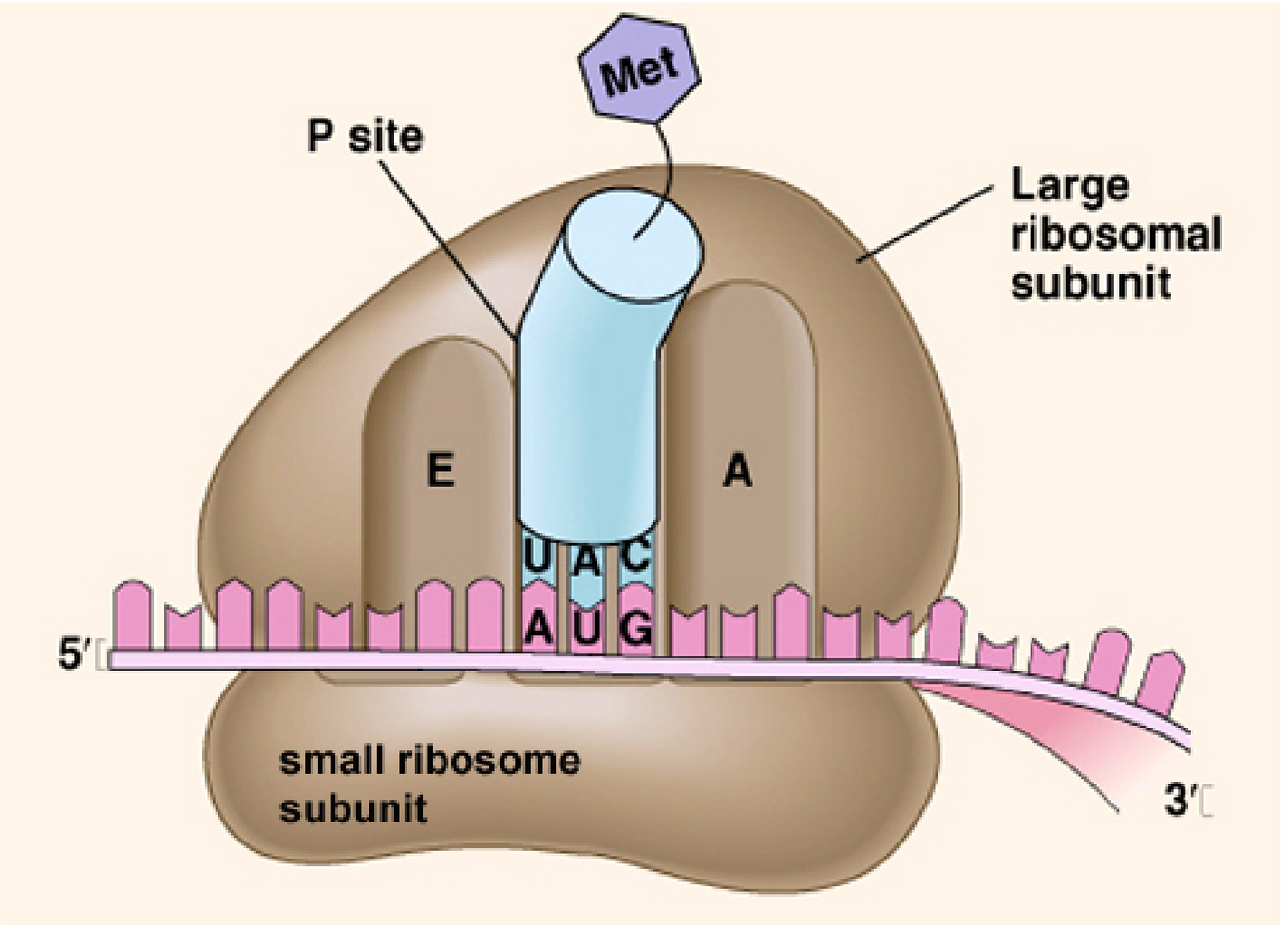
Gentamicin C_{1a}

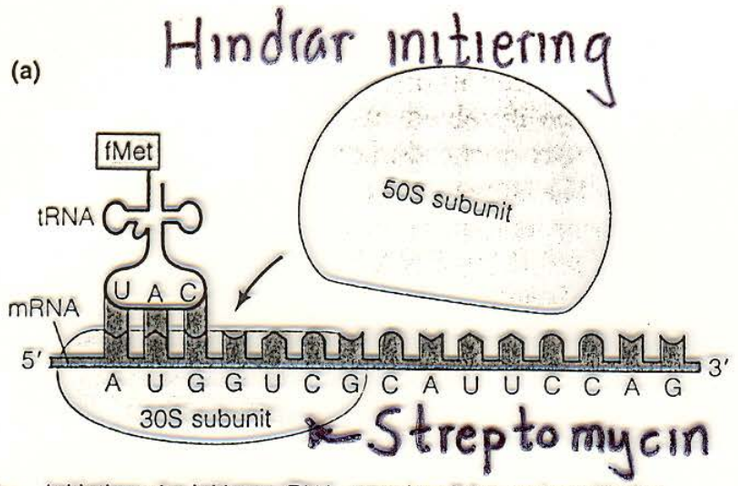
Figure 33.10 **Representative Aminoglycoside Antibiotics.**


DNA
Replication of DNA
Transcription of DNA
tRNA*
mRNA
rRNA
Translation of mRNA
Ribosome
(rRNA + protein)
tRNA
mRNA
Protein
Inheritance of DNA in daughter cells
Expression of DNA for structure and functions of cell

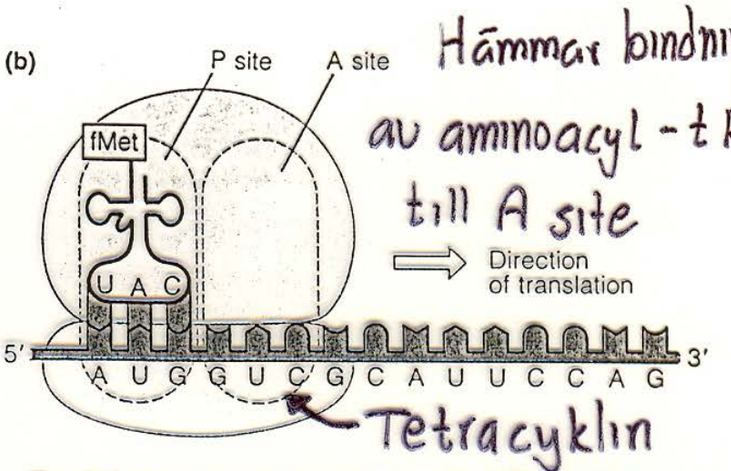
The Ribosome

- Procaryotes, 70S ribosomes = 30S + 50S subunits
- Eucaryotes, 80S ribosomes = 40S + 60S subunits
- mitochondrial and chloroplast ribosomes resemble procaryotic ribosomes
- peptidyl (donor; P) site, binds initiator tRNA or tRNA attached to growing polypeptide (peptidyl-tRNA)
- aminoacyl (acceptor; A) site, binds incoming aminoacyl-tRNA
- exit (E) site, briefly binds empty tRNA before it leaves ribosome

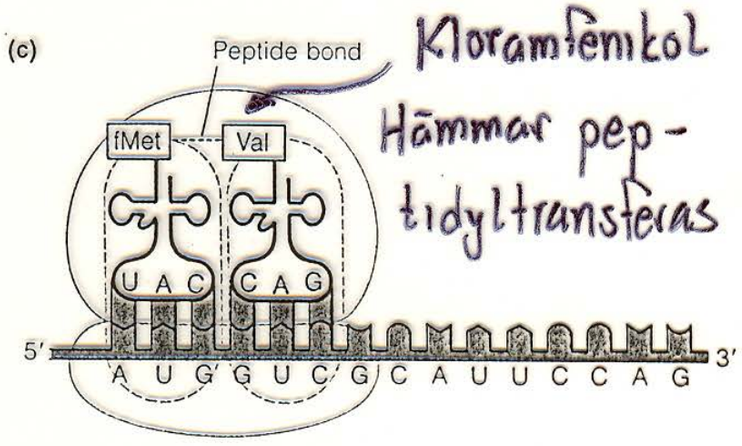




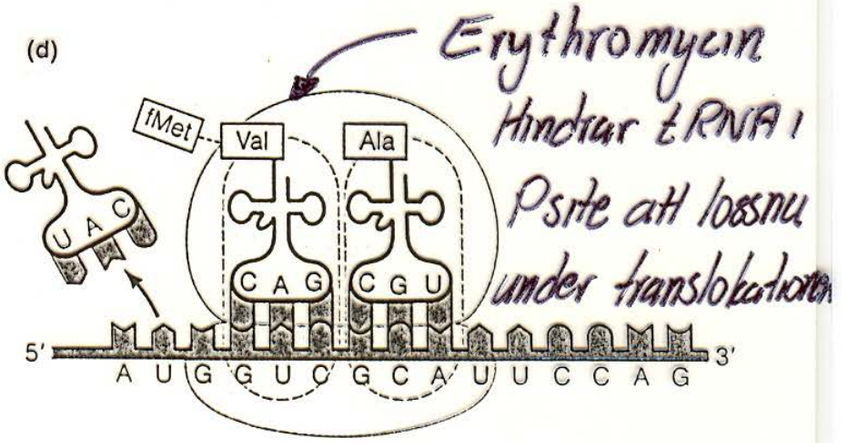
Initiation: An initiator tRNA, carrying fMet, pairs with the initiation codon AUG in the presence of the 30S ribosome subunit.



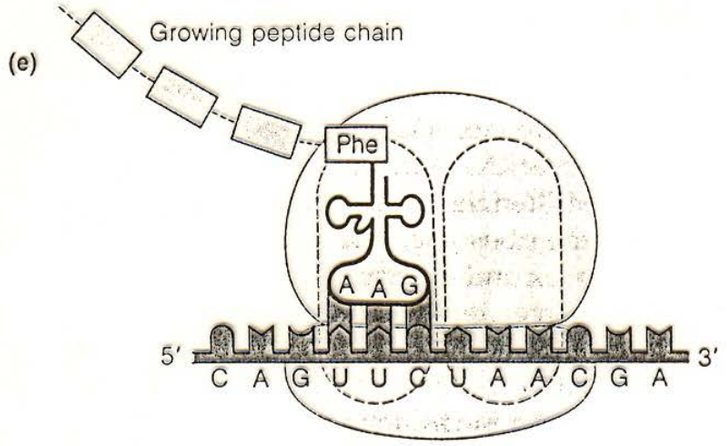
The 50S ribosome subunit joins with the 30S subunit to form the intact 70S ribosome. This completes the initiation complex.



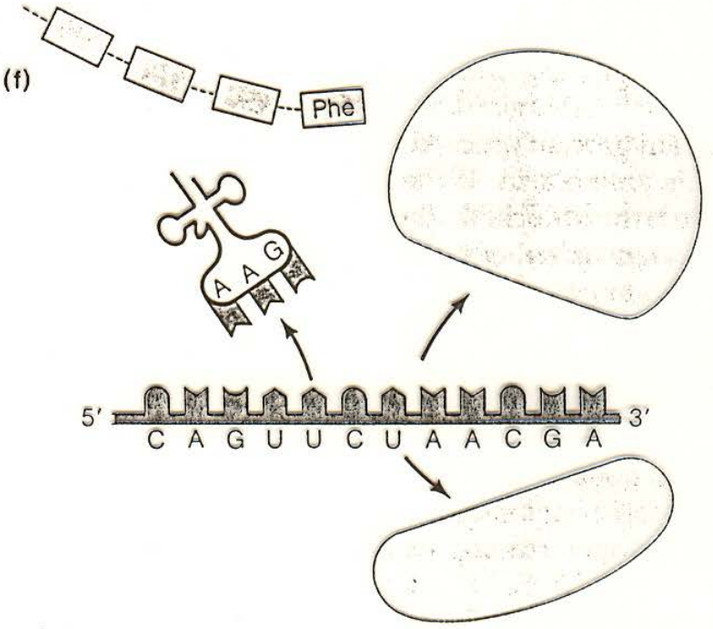
Elongation: An aminoacyl tRNA (carrying valine in this example) binds to the complementary codon (GUC in this example) at the A site of the ribosome. A peptide bond is formed between fMet and Val, and the ester bond between the tRNA in the P site and its amino acid (fMet) is cleaved.



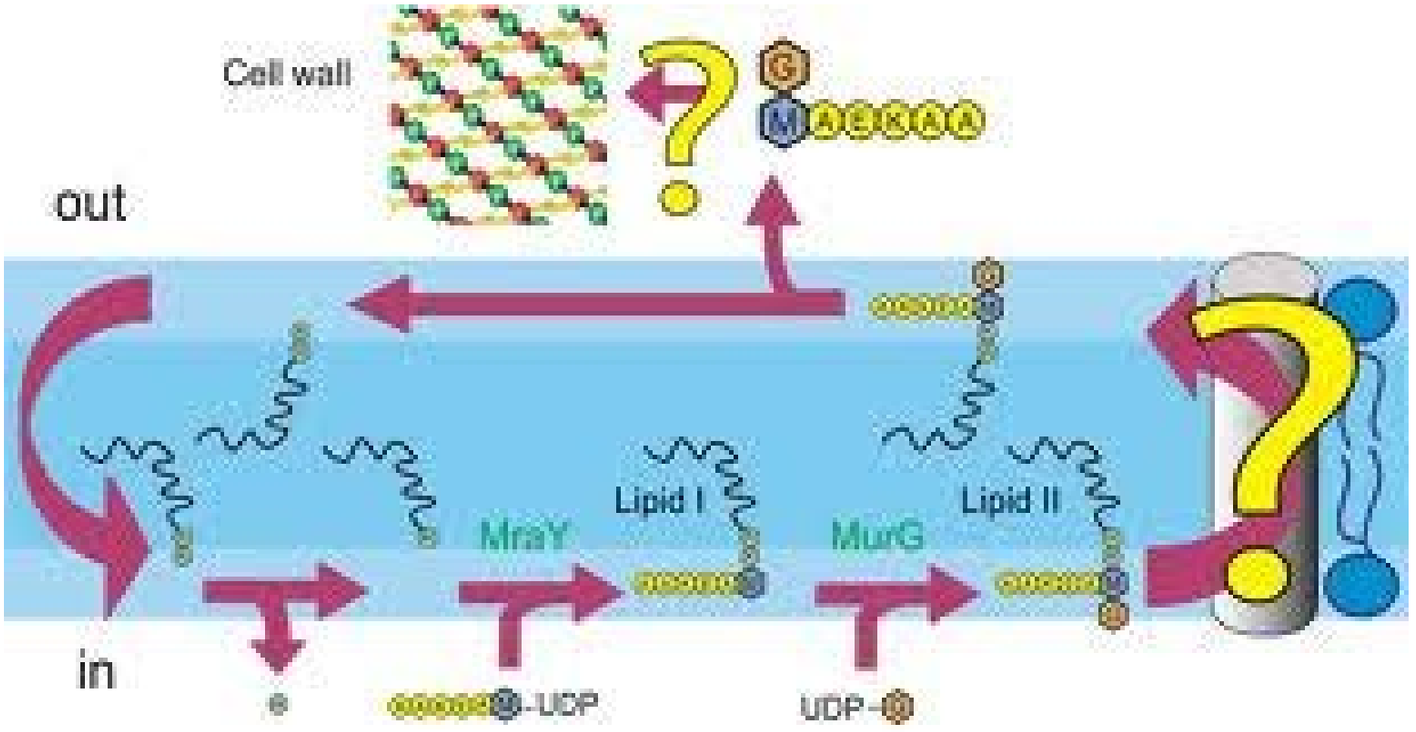
In translocation, the peptidyl tRNA on the A site is transferred to the P site on the ribosome and displaces the free tRNA in the P site. The A site is now free to receive a new aminoacyl-tRNA and the cycle of chain elongation is repeated.



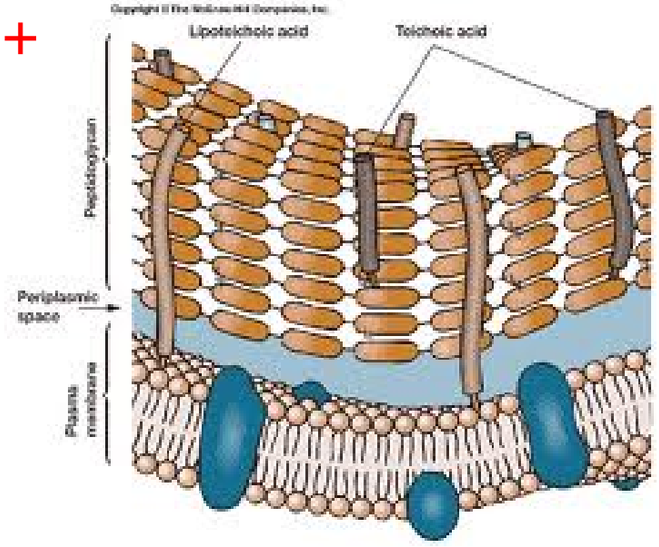
Termination: When the ribosome reaches a nonsense codon (UAA in this example) on the mRNA, protein synthesis is terminated.



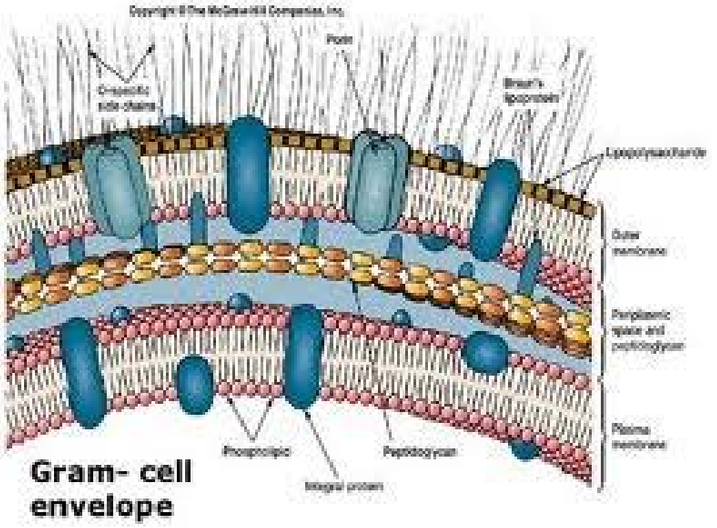
Cell wall inhibitor antibiotics



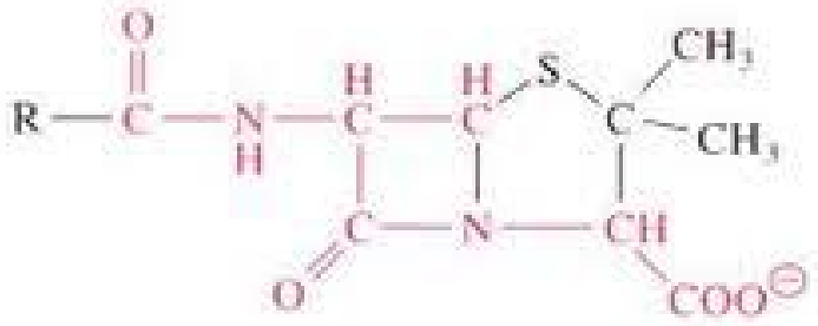
G+

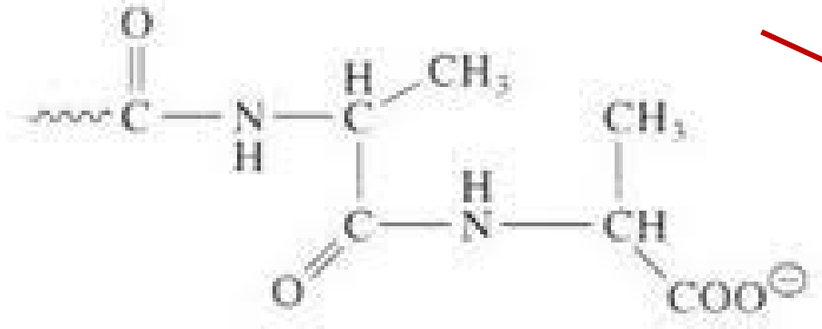


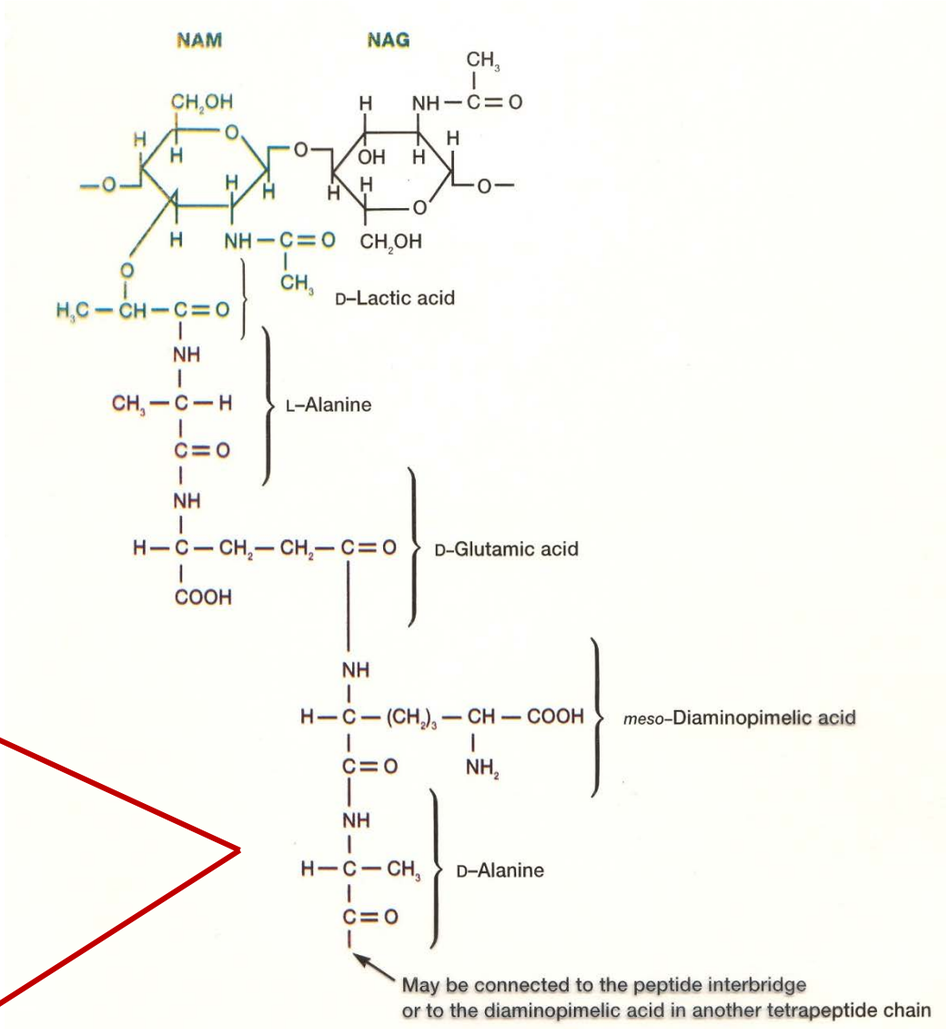
G-



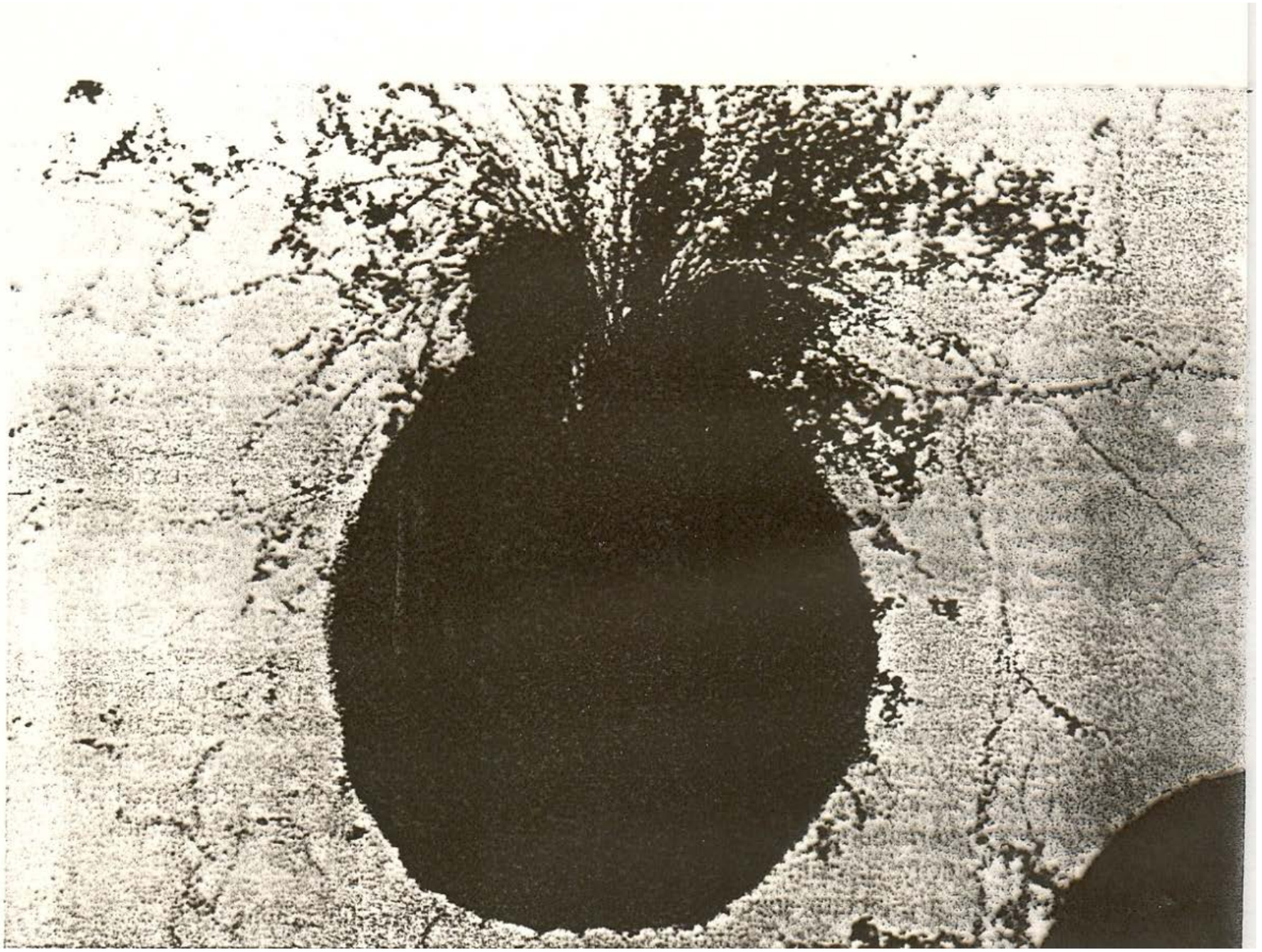
Penicillin inhibits its target protein transpeptidase also known as penicillin-binding protein (PBP) by mimicking D-alanine-alanine



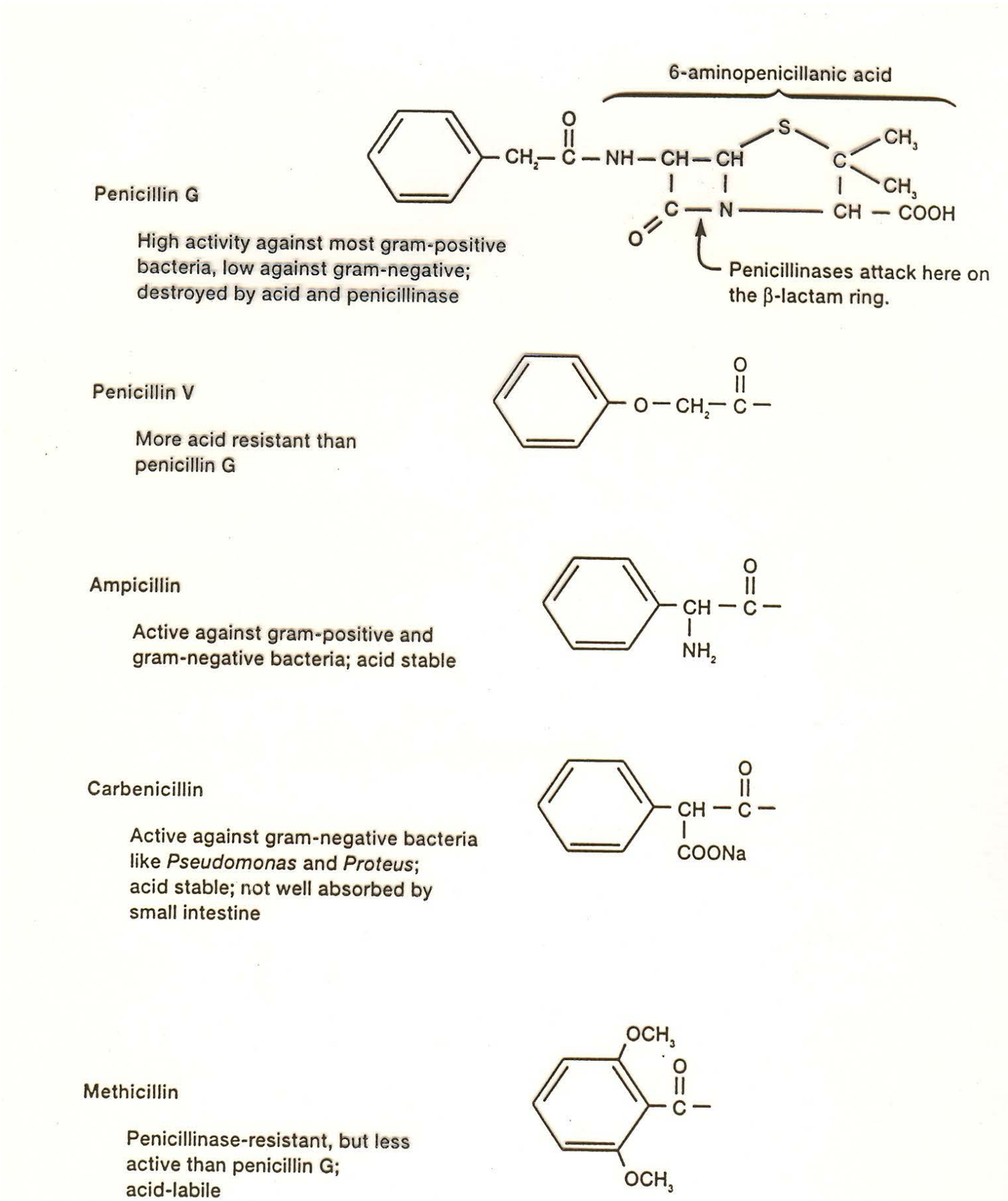




β-lactam antibiotics inhibit growing bacteria



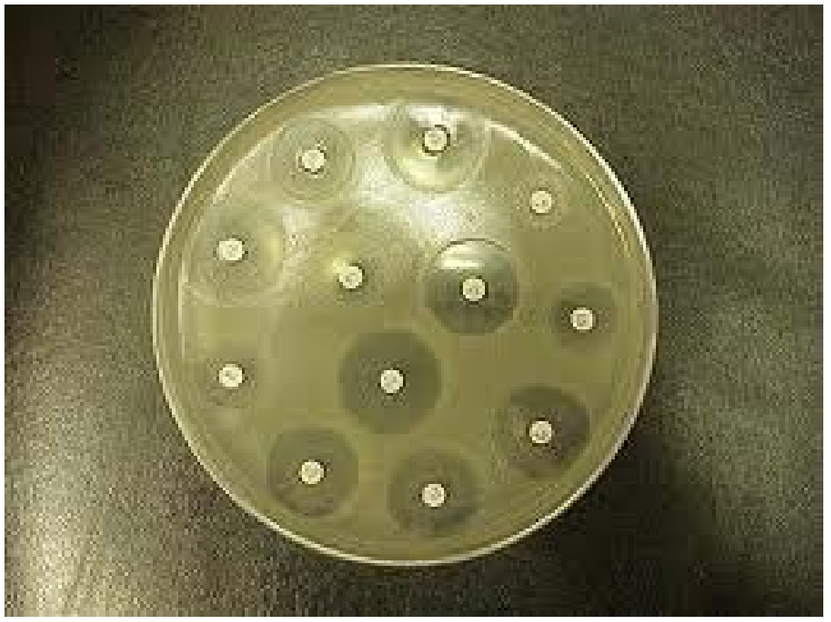
R group of penicillin result in altered chemical and physiological properties



Antibiotic Sensitivity Testing

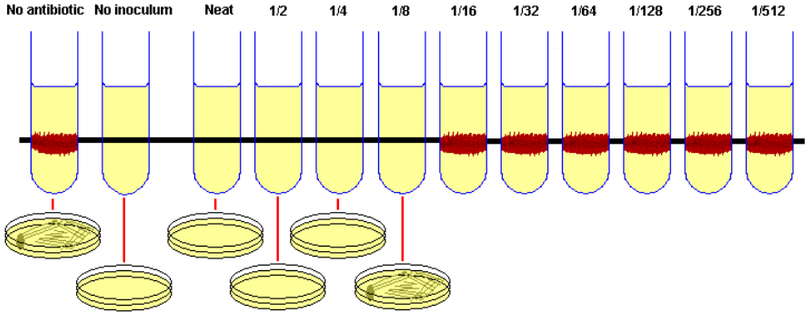
Disk Diffusion Tests

- disks impregnated with specific drugs are placed on agar plates inoculated with test microbe



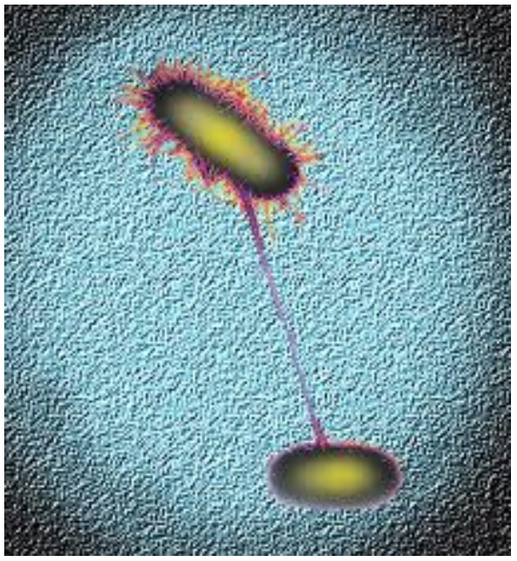
Effectiveness

- minimal inhibitory concentration (MIC)
  - lowest concentration of drug that inhibits growth of pathogen
- minimal lethal concentration (MLC)
  - lowest concentration of drug that kills pathogen



Resistance to antibiotics is divided into natural resistance and acquired resistance

- an increasing problem
- once resistance originates in a population it can be transmitted to other bacteria
- resistance mutants arise spontaneously and are then selected
- Resistance to antibiotics can be acquired by mutation or recombination (e.g. plasmids).



Tbc sprids snabbt i Baltikum

Aldrig förr har så många människor i världen insjuknat i tuberkulos.

Mest ökar sjukdomen i Ryssland och i Baltikum.

Sydsvenskans utsända Petra Martinsson och Lars Ottosson har besökt tbc-sjukhuset i litauiska Panevezys som ligger i ett område som drabbats hårt av den resistenta tuberkulosen.

Här har den gamla sporthallen, som tidigare tillhörde stadens stora arbetsplats, blivit sjukhus och många patienter tillbringar månader i de spartanska lokalerna.

Multiresistenta stammar av tbc-bakterien sprids snabbare än väntat över hela världen. Än är det dock bara ett fåtal svenskar som insjuknar i tbc.

Men epidemierna i våra grannländer kan vara en fara, därför har de nordiska länderna gått samman för att hjälpa Baltikum att få bukt med spridningen. **Sidorna B1 och B3**

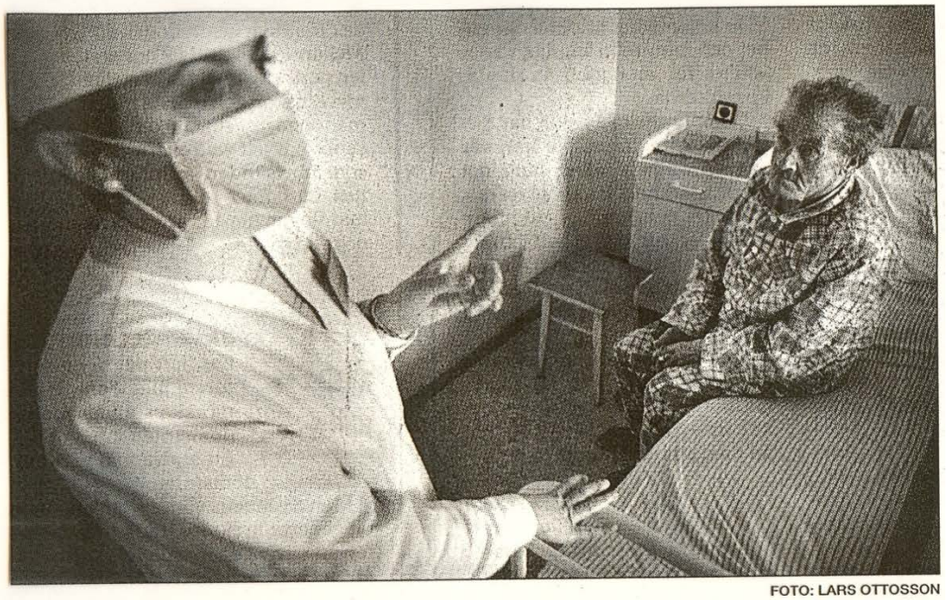


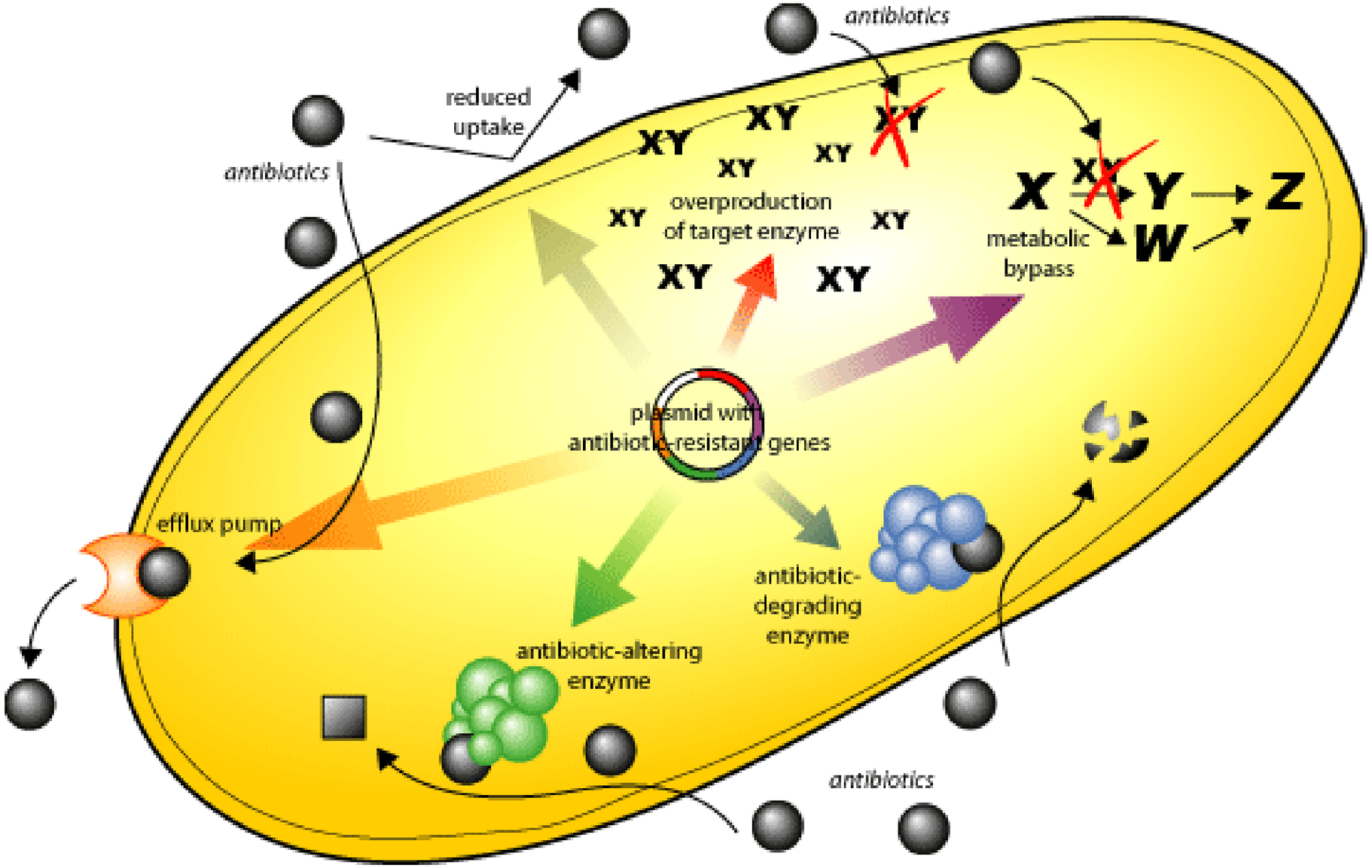
FOTO: LARS OTTOSSON

Jurate Valentinaviciene arbetar som sjuksköterska på tuberkulossjukhuset i Panevezys i Litauen. Hon och de andra på sjukhuset oroas över ökningen av tbc i området. Linas är en av hennes patienter. Han är svag och måste stanna i sängen i flera månader.

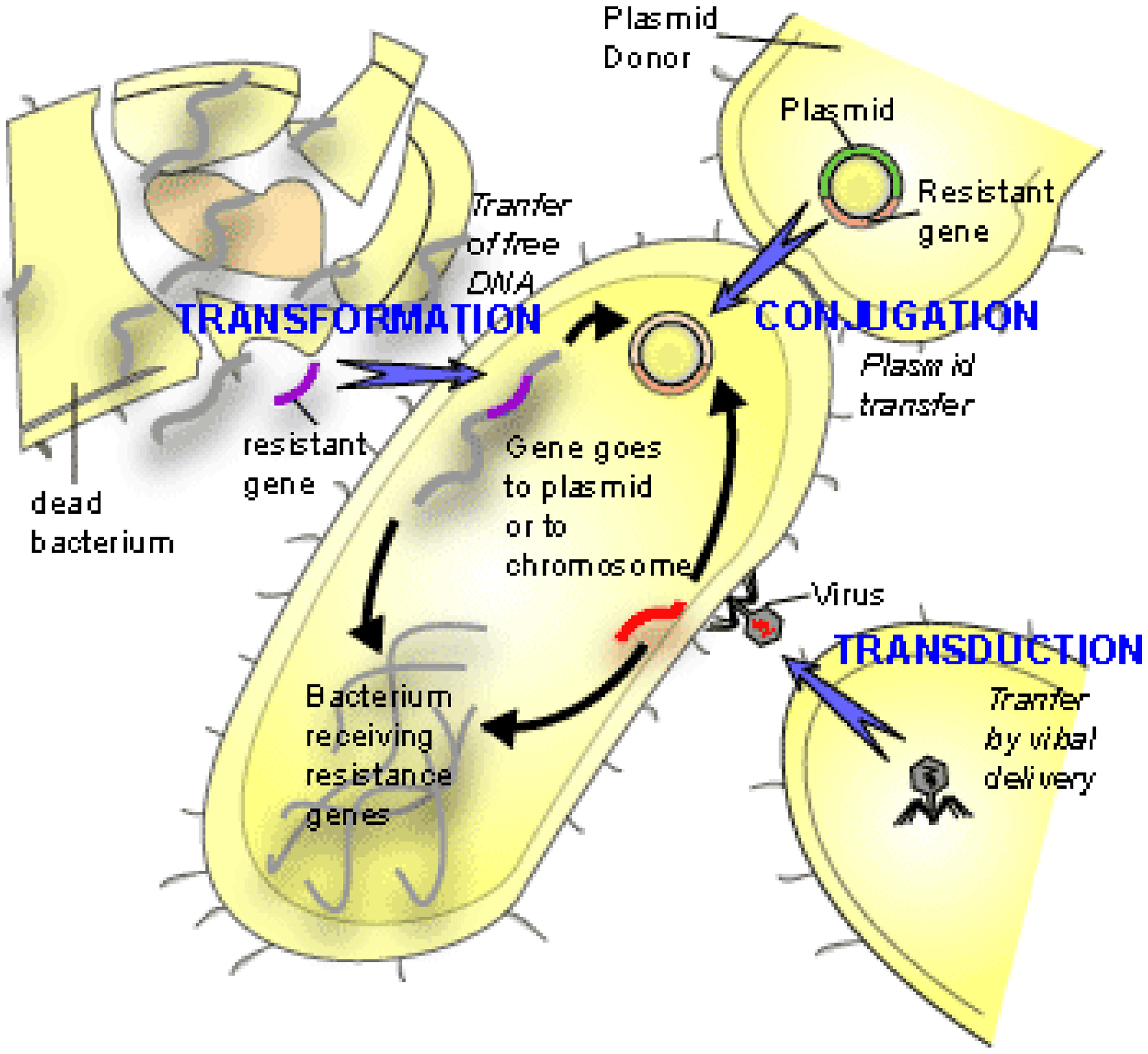
Sydsvenskan
31/1-00

Mechanisms of Drug Resistance

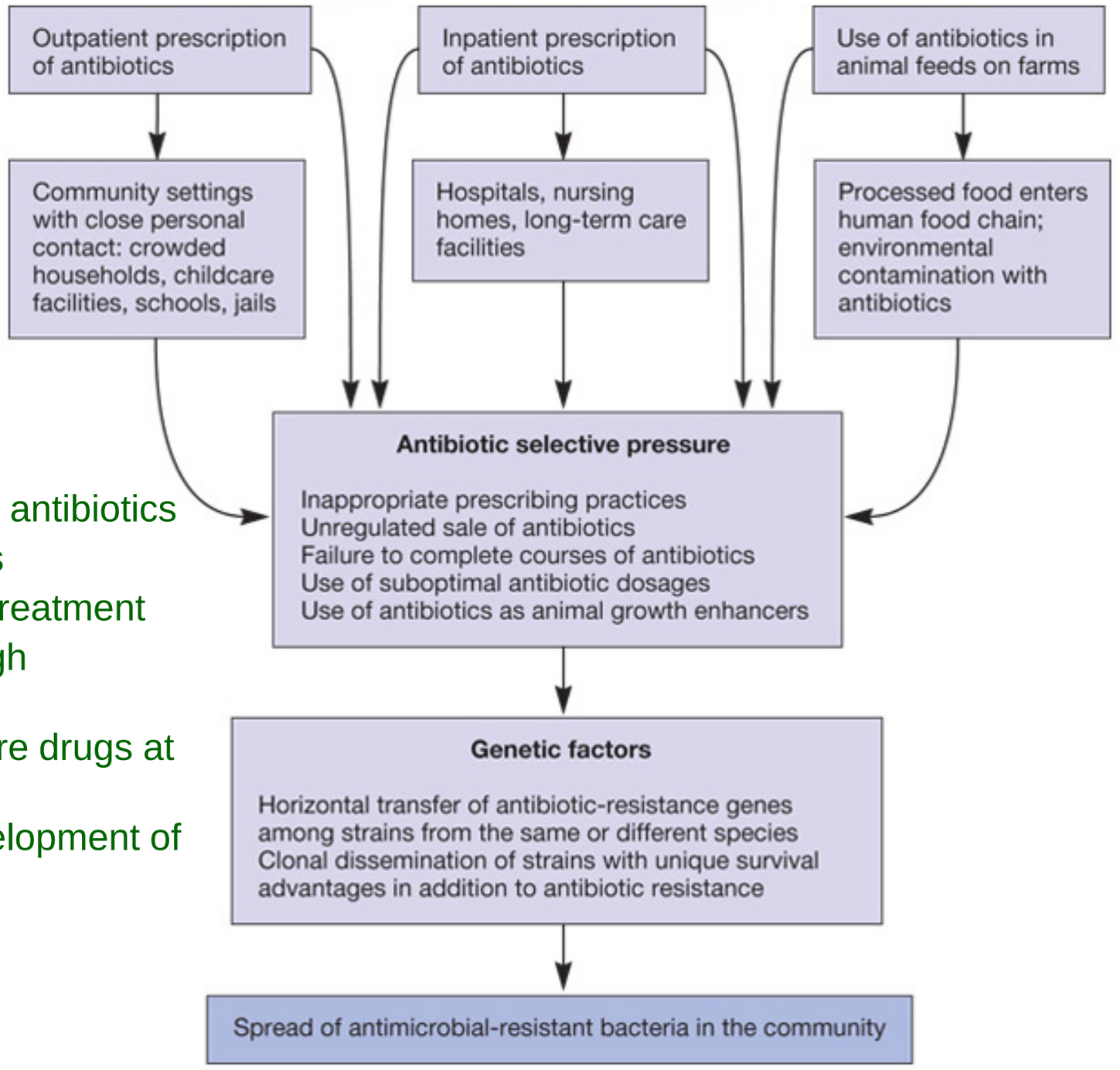
- detoxification of the antibiotic (modification or inactivation of the active substance)
- changes in the target structure
- alternative target structure (enzymes)
- increased amount of enzyme or substrate
- alternative synthesis route
- changes in the permeability



Transmission of Drug Resistance



Preventing emergence of drug resistance



1. reduced use of antibiotics
2. sensitivity tests
3. other kinds of treatment
4. give drug in high concentrations
5. give two or more drugs at same time
6. continued development of new drugs