Lecture VI

Basic principles of chemotherapy. Chemotherapeutic drugs. Antibiotics.

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Basics of chemical therapy

- Treatment of infectious diseases with chemotherapeutic drugs is called chemotherapy.
- The effect of these drugs is not against the individual symptoms of the disease, but only against the etiological factor that causes it, so they are called etiotropic drugs.

Paul Erlich is the founder of chemotherapy

- **Receptor theory of P.Erlich. In 1885, P.Erlich determined that the effect of chemicals on disease-causing microbes is due to the specific receptors in the latter.**
- **One of the main principles of chemical therapy was P.Erlich's idea of a "magic bullet". It consisted of the principle of "destroying the living in the living," that is, not harming the host organism while destroying the agent.**
- **Chemical therapeutic index is a measure of the ratio of the minimum therapeutic dose that a drug can kill to the maximum dose that the body can resist.**

Chemical therapeutic drugs

- Thousands of chemical compounds with antimicrobial activity are now known, only some of which are used as chemical therapeutic agents.
- The groups of microorganisms that can be affected by chemical therapeutic drugs determine their spectrum of activity.
- Depending on the effect of the microbe, antibacterial, antifungal, antimicrobial, antiviral, etc. antimicrobial drugs are distinguished.

Spectrum of action

- ***According to the spectrum of action, narrow and broad spectrum drugs are distinguished.***
- ***Drugs with a narrow spectrum of activity are active only in relation to a small number of bacteria, either Gram-positive or Gram-negative bacteria.***
- ***Broad-spectrum drugs are active against a large number of species of both Gram-positive and Gram-negative bacteria.***

Type of action

Chemicals according to the type of effect:

microbicide (bactericide, fungicide, etc.) and

microbostatic (bacteriostatic, fungostatic, etc.) may be effective.

Drugs from the first group affect the destruction of microorganisms, while the latter slow down the growth and proliferation of microbes.

Method of production

Depending on the method of production, antimicrobial chemical therapeutic drugs are divided into two main groups:

synthetic chemical preparations - obtained mainly by chemical synthesis;

Antibiotics - are mainly of natural origin, sometimes obtained by synthesis and semi-synthesis.

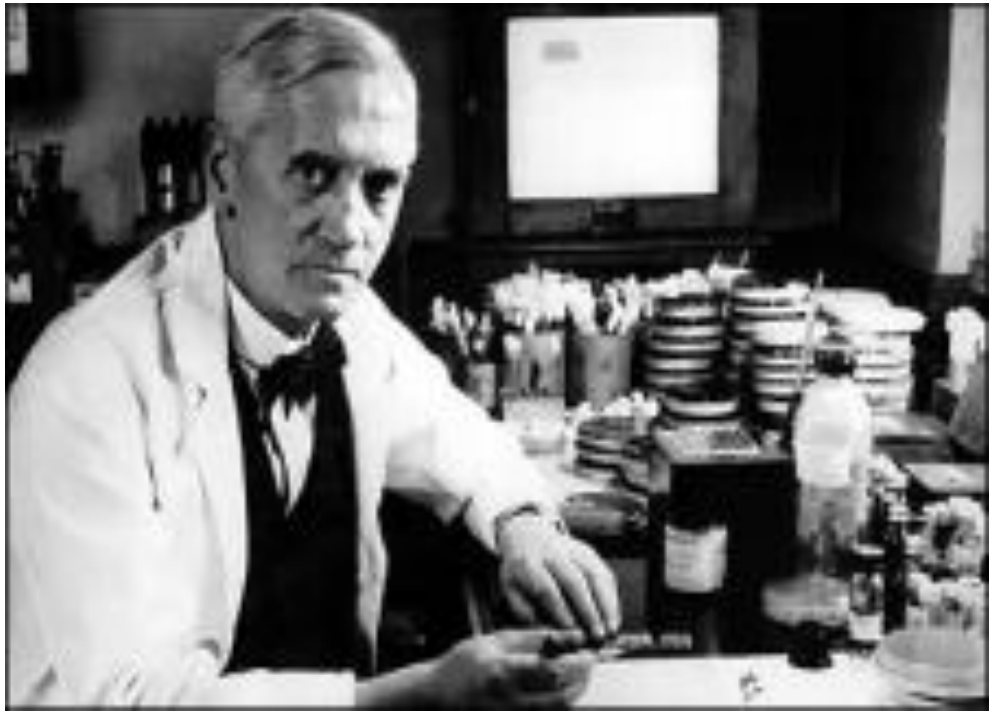
The main groups of synthetic chemical-therapeutic drugs

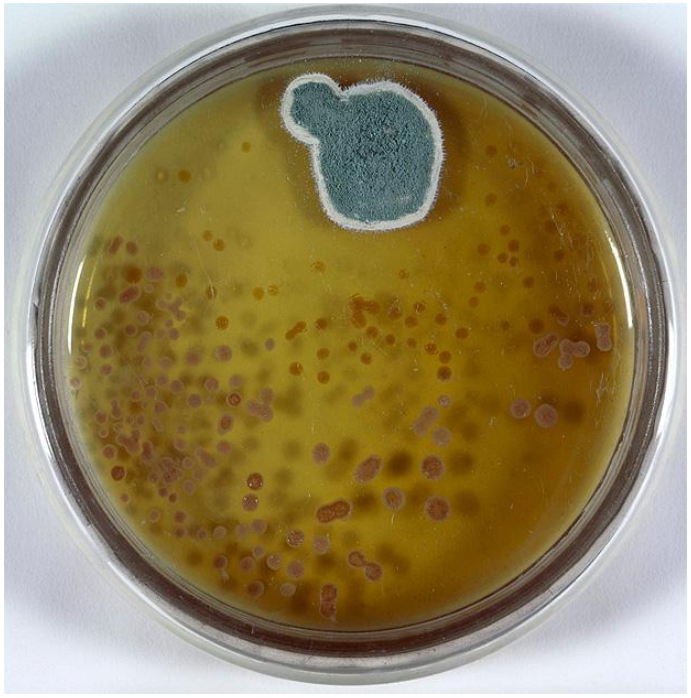
- Sulfanilamides (streptocide, sulfadimesine, sulfadimethoxine, etc.)
- Antimetabolites - nicotinic acid hydrazides (isoniazid, ftivazid, tubazid, etc.)
- Preparations from the quinolone group - nalidixic acid (nevigramon), ofloxacin, ciprofloxacin, norfloxacin, etc.
- Nitroimidazole derivatives (metronidazole, ornidazole, etc.)
- Derivatives of 8-oxyquinoline (5-nitroxoline, quinazole, intesopan, etc.)
- Nitrofuran derivatives (furacilin, furazolidone, furagin, etc.)
- Imidazole derivatives (ketoconazole, miconazole, clotrimazole, etc.)
- Triazole derivatives (fluconazole)

Antibiotics

- The most common form of antagonism is the secretion of substances by microorganisms called antibiotics (Greek, antibodies, bios-life).
- These substances stop the development of other microorganisms in very small concentrations.
- The term "antibiotic" was first coined in 1942 by S.Waxman. According to him, antibiotics are substances secreted by various microorganisms and stop the growth of certain bacteria or cause their destruction.

Discovery of antibiotics





In 1929, when the English microbiologist Alexander Fleming was conducting an experiment, he discovered a culture of the fungus (Penicillium notatum) in the culture of the fungus (Penicillium notatum), which had grown accidentally on the surface of the nutrient medium in Petri dishes.

Obtaining of antibiotics

- During the cultivation of microorganisms, they are excreted in the nutrient medium and obtained by chemical separation from the nutrient medium.
- In some cases, antibiotics are obtained by semi-synthesis and synthesis. Thus, there are three main methods of obtaining antibiotics:
- Biosynthesis method
- Semi-synthesis method
- Method of chemical synthesis

Classification of antibiotics

According to the origin:

Antibiotics of microbial origin are divided into the following groups:

- **Antibiotics of bacterial origin (polymyxin, gramicidin, etc.);**
- **Antibiotics of actinomycete origin (streptomycin, tetracycline, chloramphenicol, etc.);**
- **Antibiotics of fungal origin (penicillins, cephalosporins, etc.);**

Antibiotics of plant origin (phytoncides)

Antibiotics of animal origin (lysozyme, interferon, etc.)

Classification of antibiotics

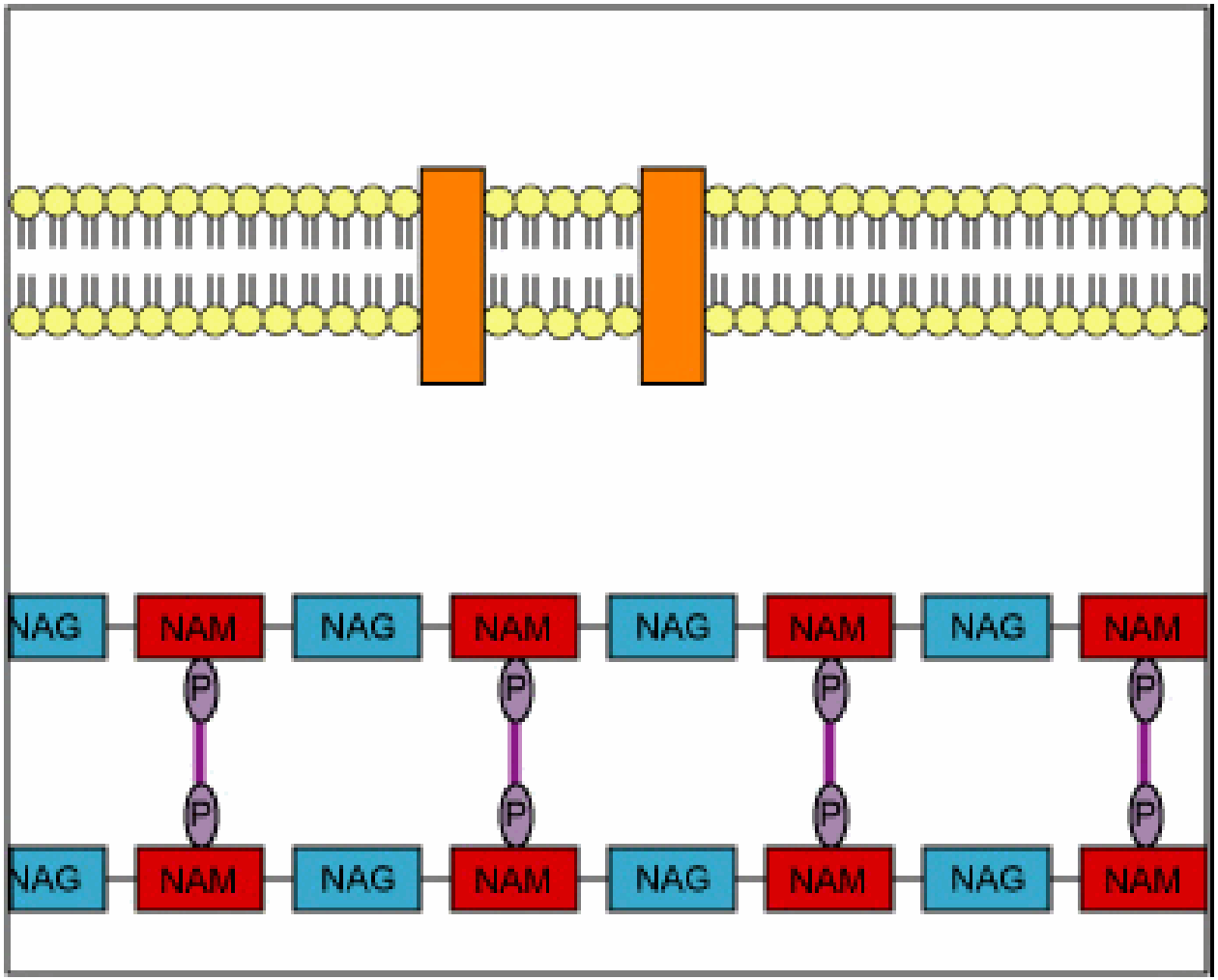
According to the chemical composition:

- **beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams)**
- **macrolides (erythromycin, spiramycin, clarithromycin, etc.)**
- **azalides (azithromycin)**
- **tetracyclines (tetracycline, doxycycline)**
- **aminoglycosides (streptomycin, kanamycin, gentamicin)**
- **levomisetin (chloramphenicol)**
- **glycopeptides (vancomycin, etc.)**
- **glycopeptides (vancomycin, etc.)**
- **rifamycins (rifampicin)**
- **cyclic polypeptides (polymyxins, basitrasins)**
- **polyenes (nystatin, levorin, amphotericin B, etc.)**

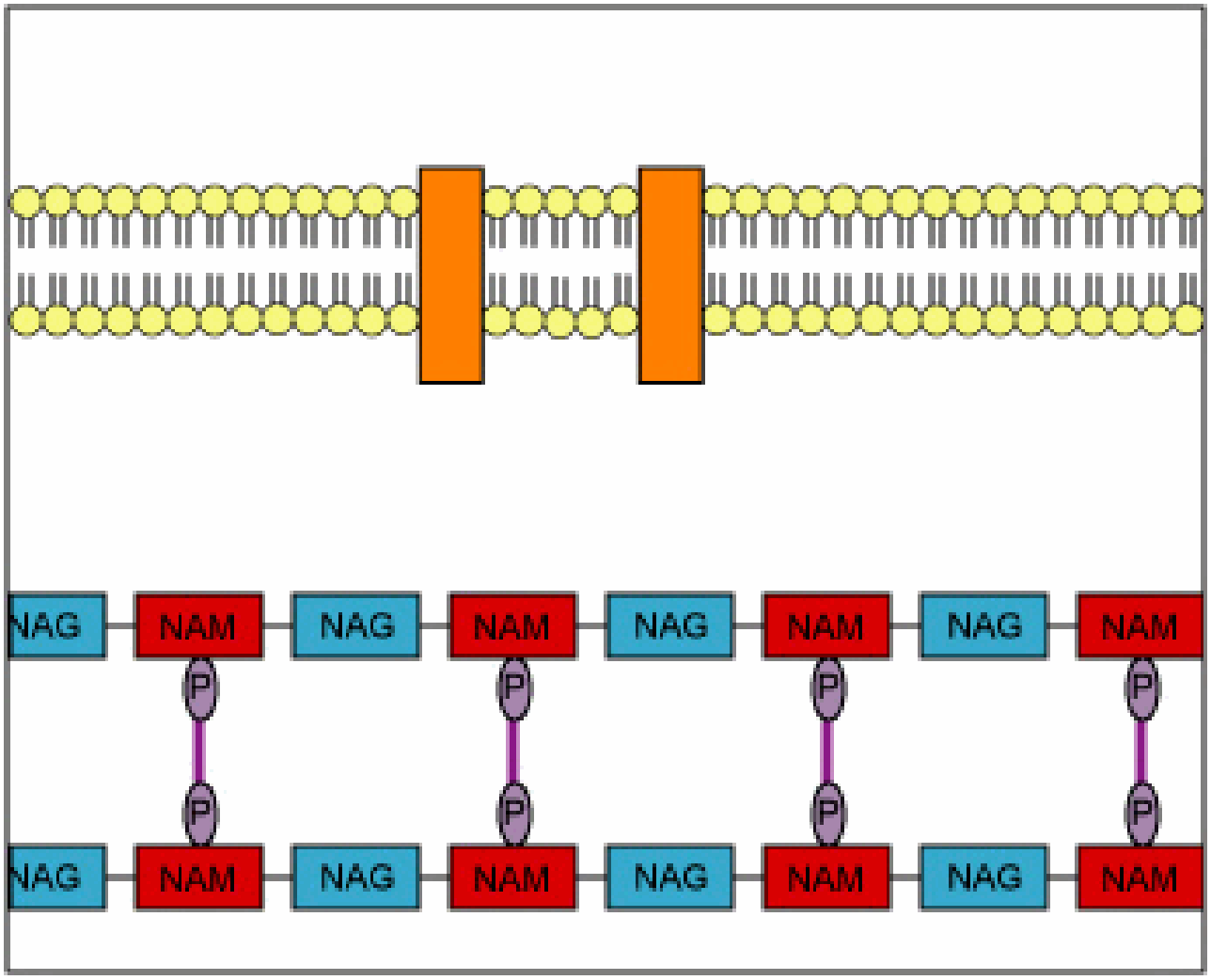
Mechanisms of antimicrobial action of antibiotics

- **Inhibitors of cell wall synthesis (antipeptidoglycan antibiotics). Beta-lactam antibiotics (penicillins and cephalosporins), glycopeptide antibiotics (vancomycin and teicoplanin)**
- **Inhibitors of protein synthesis (antiribosomal antibiotics) Aminoglycosides and tetracyclines with 30S-subcomponents of ribosomes, macrolides, chloramphenicol in the macrolides, chloramphenicol and lincoids.**
- **Inhibitors of nucleic acid synthesis - rifamycins (rifampicin) bind to RNA polymerase and block the transcription process, ie the information stops the synthesis of RNA.**
- **Antibiotics that affect the permeability of the cytoplasmic membrane (membrane-anthropic antibiotics) - polypeptides (polymyxins), polyene antibiotics (nystatin, levorin, amorphous).**

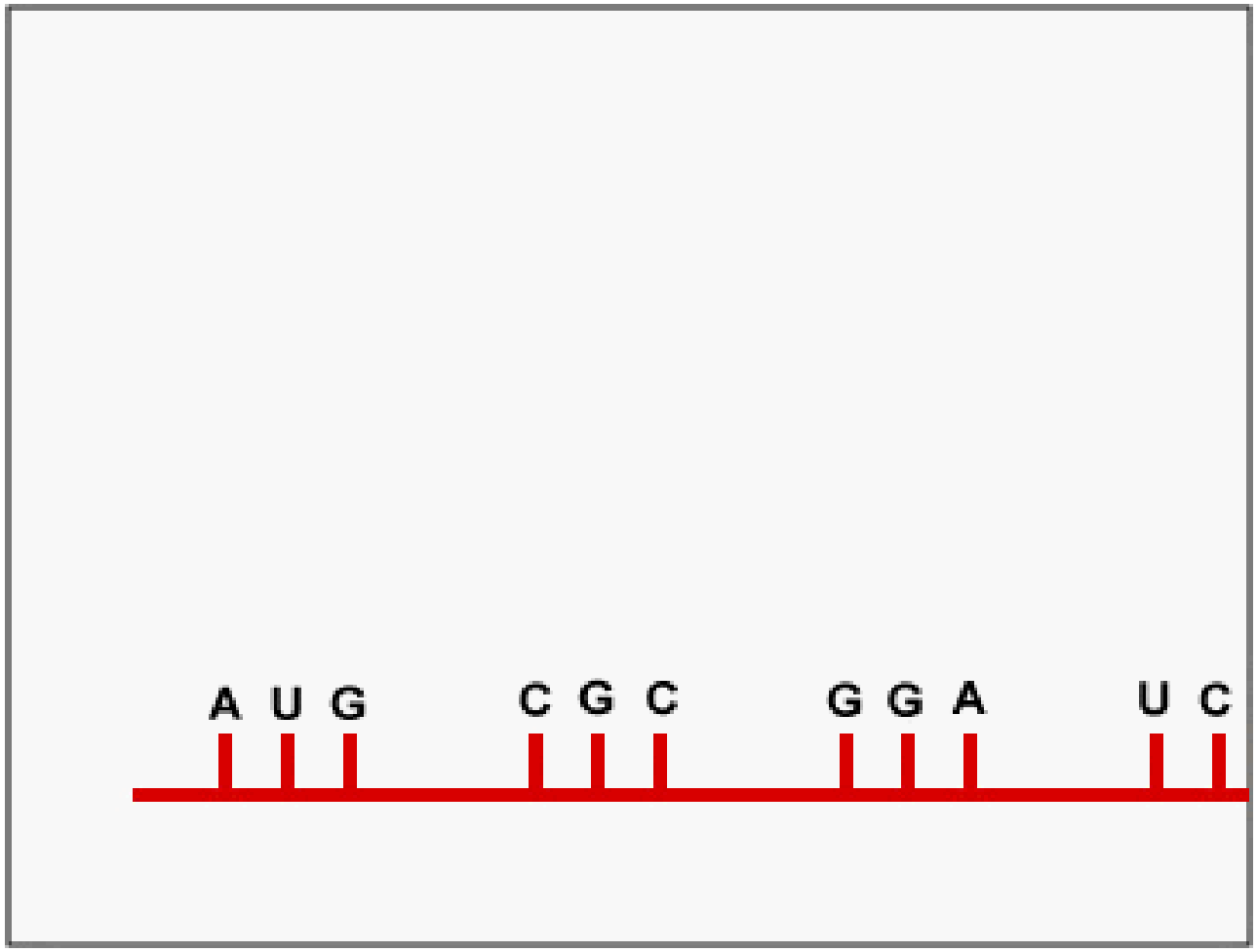
Synthesis of peptidoglycan in the cell wall



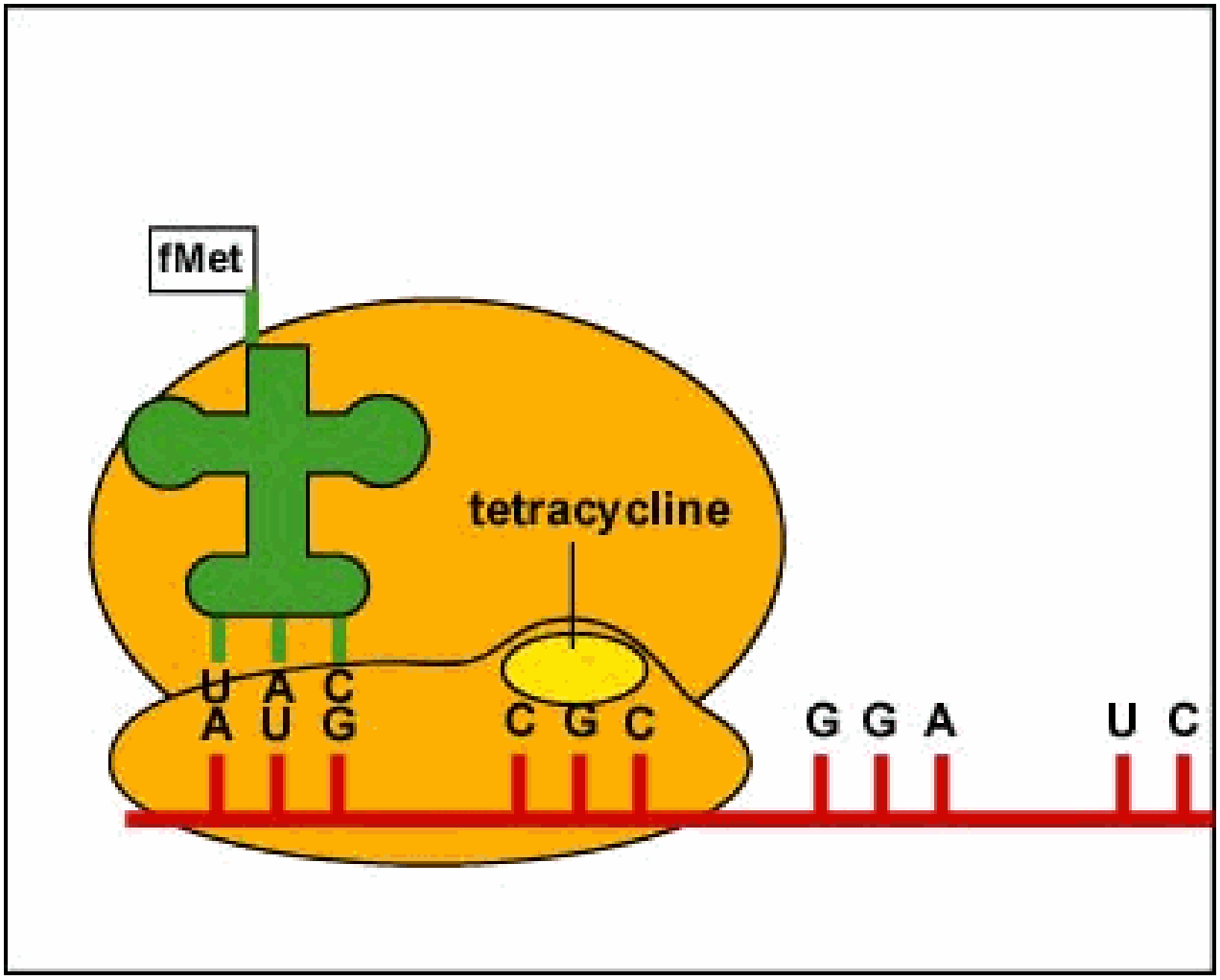
Inhibition of peptidoglycan synthesis in the cell wall with penicillin



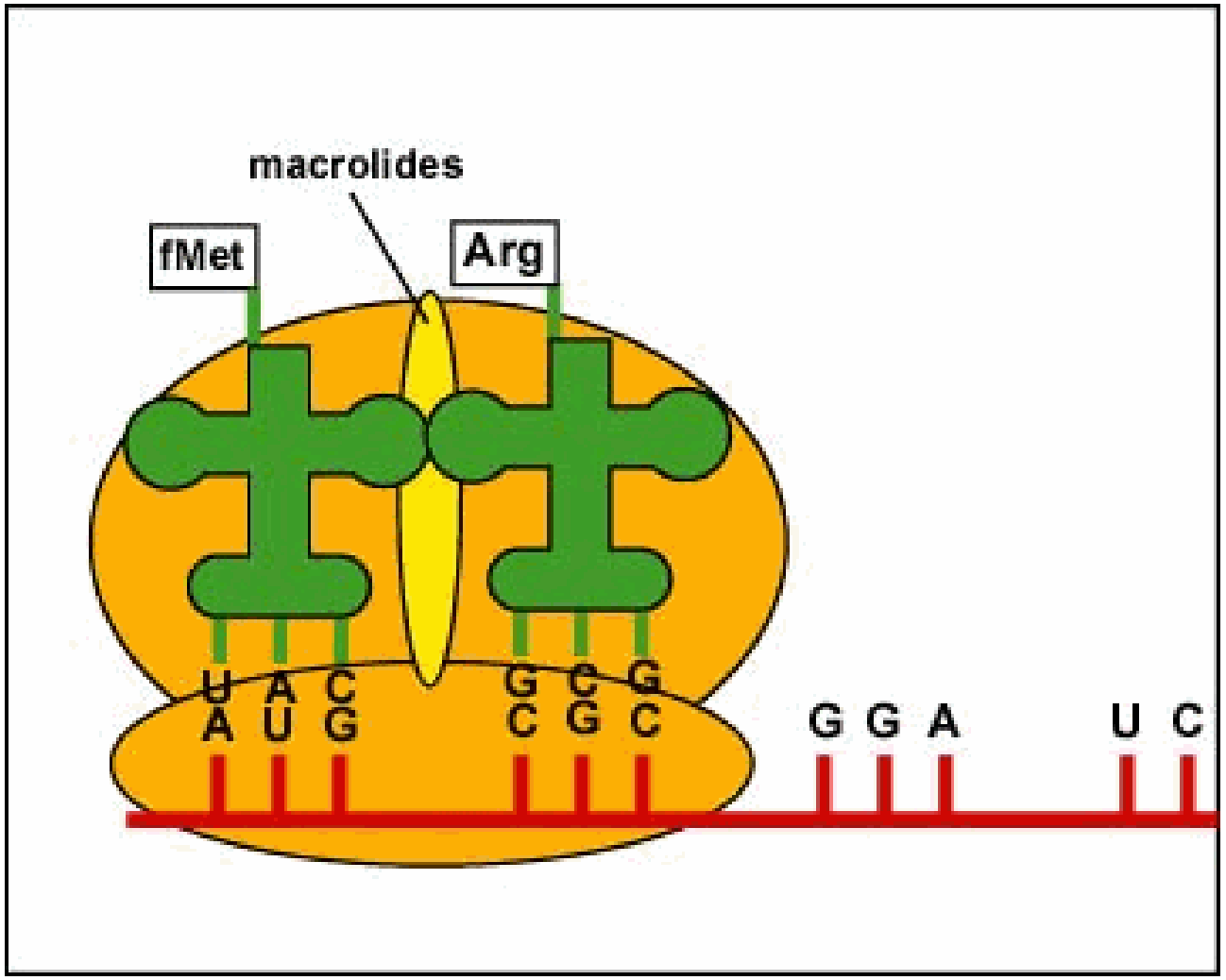
Aminoglycosides combine with 30S subcomponents of ribosomes to stop protein synthesis in bacterial cells



Tetracyclines combine with 30S subcomponents of ribosomes to stop protein synthesis in bacterial cells



Macrolides combine with 50S-subcomponents of ribosomes to stop protein synthesis in bacterial cells



Resistance of microorganisms to antibiotics and their mechanisms

Resistance to antibiotics is of two types, natural and acquired.

Natural sustainability is related to the structural and biological properties of microorganisms.

Acquired sustainability is associated with the adaptation of microorganisms to the external environment and occurs as a result of the action of antibiotics.

- Decreased permeability of the cell wall to the antimicrobial agent and impairment of its perception of intracellular targets
- Accelerate the removal of the antimicrobial agent from the cell.- Modification of the target of antimicrobial action
- Inactivation of antimicrobial agent

Decreased permeability of the cell wall to the antimicrobial agent and disruption of its transport to intracellular targets

- The entry of drugs into the microorganism depends on the nature of the cell wall.
- Changes in the structure of pores under the influence of various factors, for example, mutagenic factors, are accompanied by a decrease in their permeability.
- R-forms, which are devoid of polysaccharide capsules and have relatively low levels of lipopolysaccharide, are sensitive to most antibiotics.

Accelerate the removal of the antimicrobial agent from the cell

- Some bacteria are resistant by increasing the synthesis of carrier proteins that allow the release of antibiotics (eg, tetracycline) from the cell.

Modification of the target of antimicrobial action

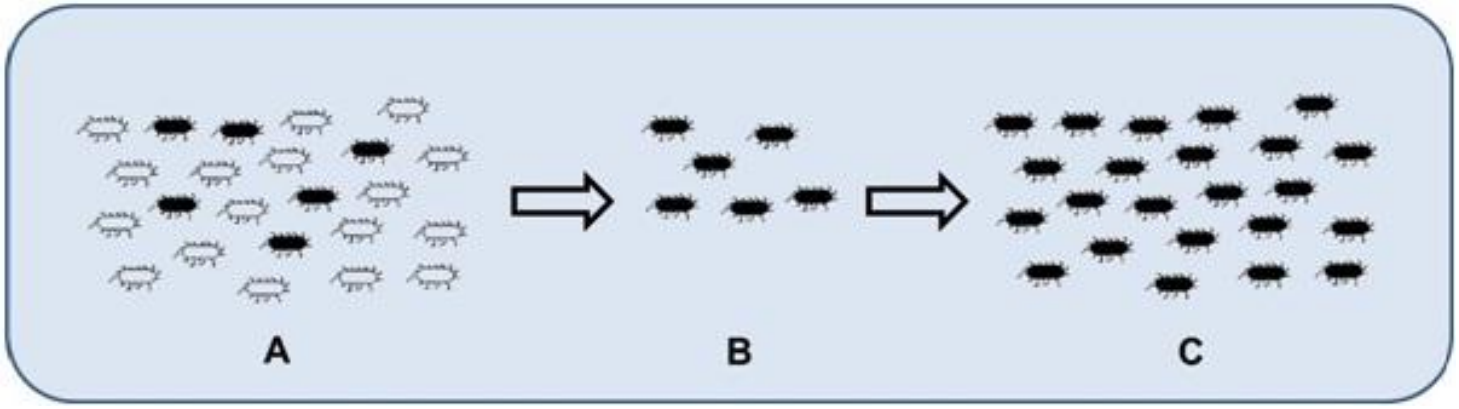
- Methylation of RNA (ribosomal RNA) in the 50S subcomponent of ribosomes is one of the main mechanisms of resistance to macrolides and linosamides.
- Metallization of the nucleotide of only two adenes prevents the combination of these antibiotics with the 50S-components. The synthesis of the enzyme that catalyzes this process - methylase - is encoded in the R-plasmid.

Inactivation of an antimicrobial agent

- It is one of the main mechanisms of drug resistance of microorganisms.
- Some bacteria have the ability to synthesize special enzymes that inactivate antibiotics.
- Beta-lactamase (penicillin), a beta-lactamase (penicillin) that breaks down the beta-lactam ring in penicillins and cephalosporins to form inactive compounds between these enzymes.
- Synthesis of beta-lactamases is encoded in R-plasmid.

Genetic basis of antibiotic resistance

- Resistance to antibiotics is mainly provided by resistance genes (r-genes). Plasmids that have resistance genes are called R-plasmids, or R-factor. Resistance genes primarily encode the synthesis of enzymes (eg, beta-lactamase, etc.) that ensure the drug resistance of microorganisms.
- Antibiotics do not induce the formation of r-genes, but only cause the selection of microbial populations that possess these genes.



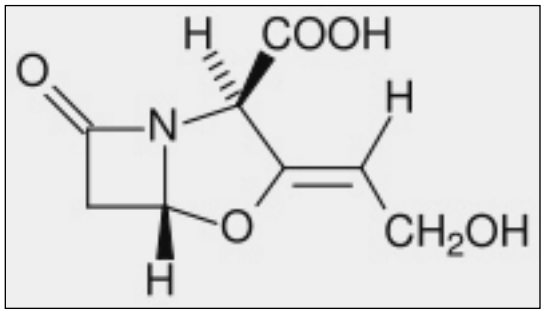
Genetic basis of antibiotic resistance

- Mutations in the microbial population also play a role in ensuring the resistance of microorganisms to antibiotics.
- For example, the persistence of some S. aureus strains to methylcellulose is due to gene mutations in them that result in penicillin binding proteins, which is unable to bind to beta-lactam antibiotics. For this reason, methicillin-resistant S. aureus (MRCA) strains are resistant to all beta-lactam antibiotics.

Ways to prevent resistance to antibiotics

- Rational use of antimicrobials
- synthesis of new antibiotics
- Combination of some antibiotics with beta-lactamase enzyme inhibitors (sulbactam and clavulanic acid):

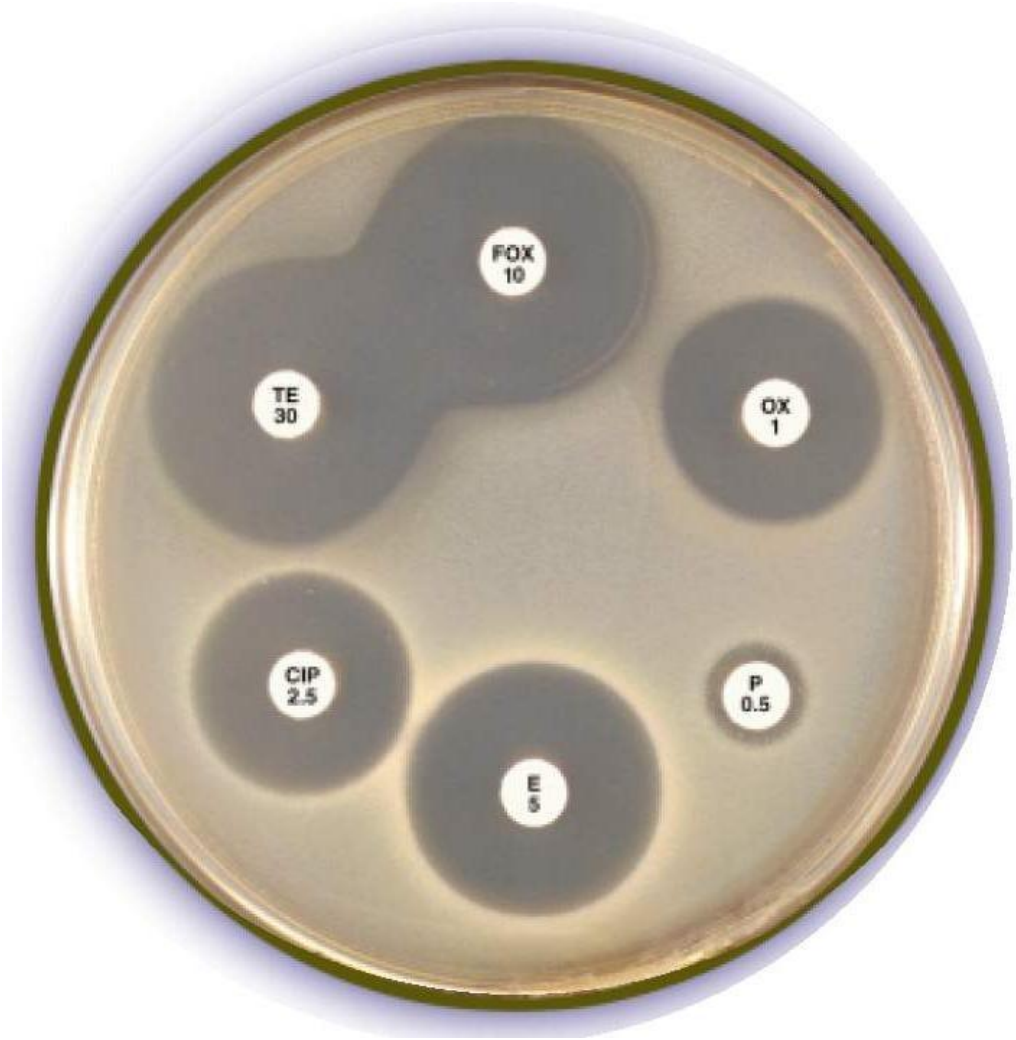
- The beta-lactam ring in these substances combines with beta-lactamases to neutralize them, thereby counteracting the effect of these enzymes on beta-lactam antibiotics.
- Preparations of ampicillin combined with sulbactam (ampicid, etc.) and amoxicillin with clavulanic acid (augmentin, amoxiclav, etc.) are widely used in medical practice.



Ways to prevent resistance to antibiotics

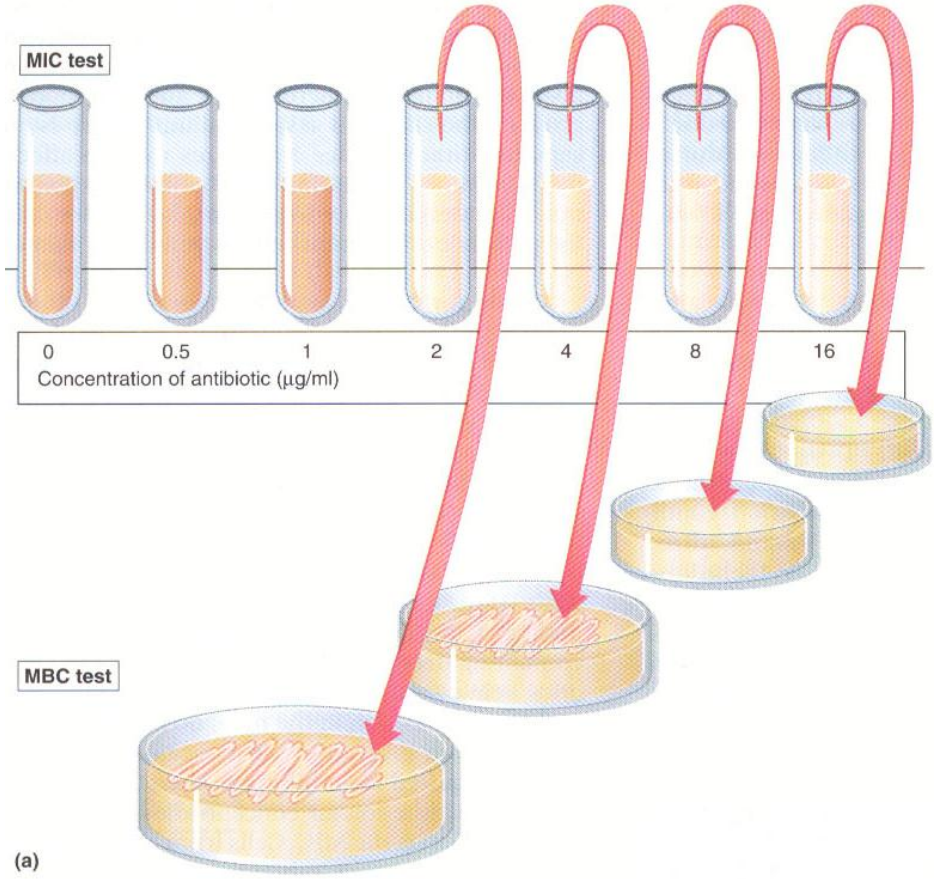
- One of the ways to prevent the resistance of microorganisms to antibiotics is to take into account the sensitivity to antibiotics during treatment.
- Qualitative and quantitative methods are used to determine the susceptibility of bacteria to antibiotics.
- Quality method. The disk-diffusion method (Kirby-Bauer method) is more widely used.
- The quantitative method allows to determine the minimum inhibition of antibiotics and bactericidal concentrations.

Disc-diffusion method



Determination of the minimum inhibitory concentration by the method of sequential dilution.

The principle of the method is based on the cessation of the growth of microorganisms in a nutrient medium to which certain concentrations of antibiotics are added.



Determination of minimum inhibitory concentration by agar diffusion method (E-test)

Complications that can occur under the influence of antibiotics and ways to prevent them

- **Hypersensitivity reactions - allergic reactions- consideration of hypersensitivity reactions**
- **Dysbiosis and dysbacteriosis**
- **Combination of antibiotics with antifungal drugs during long-term use- use of eubiotics**
- **representatives of normal microflora during long-term use**

Toxic effects

- consideration of contraindications and side effects

Principles of chemical therapy of viral infections

- Due to the nature of action and clinical significance, drugs used to treat viral infections can be divided into the following groups:
- Etiotropic (antivirus) drugs;
- Pathogenetic drugs (drugs that affect the development of the disease);
- Symptomatic (drugs that eliminate the symptoms of the disease).

Etiotropic drugs

- Etiotropic drugs used in the treatment of viral diseases can be divided into several groups:
- chemical preparations
- interferons and their inductors

Antiviral chemicals

Antiviral drugs selectively slow down the individual stages of virus reproduction without causing significant damage to macroorganism cells. Based on this, synthetic antiviral drugs can be divided into the following groups:

Inhibitors of adsorption of viruses into the host cell

Inhibitors of viral degradation in host cells (amantadine and rementadine)

Inhibitors of viral DNA polymerase enzyme

- Analogues of nucleosides (purine and primidine bases) (idoxyuridine, vidarbin, etc.)
- those that selectively act within the infected cell (acyclovir, gansiclovir, famsyclovir, ribavirin, foscarnet, etc.)

Inhibitors of the reverse transcriptase enzyme - azidothymidine (zidovudine), zalcitabine, lamivudine, etc.

Inhibitors of viral proteases (saquinavir, ritonavir, etc.)

Inhibitors of the synthesis of the latest viral proteins (methicone and marboran)

Inhibitors of adsorption of viruses into the host cell

- Analogues of immunoglobulins (anti-gp120) and recombinant CD4 molecules against the surface glycoproteins (gp120) of the human immunodeficiency virus (HIV) in the cell culture of the virus.
- Both drugs bind to gp120, a surface glycoprotein of the virus, thereby preventing the virus from being adsorbed into the host cell. The possibility of using these drugs for treatment is currently being studied.

Inhibitors of viral deproteinization in the host cell

- Due to their chemical nature, amantadine and remantadine, which are human derivatives, have antiviral activity against influenza A virus.
- These drugs interact with the matrix protein (M2-protein) involved in the deproteinization of the virus. This protein ensures the transport of protons into the virion by forming an ion channel in the lipid membrane of the virus, thus deproteinization the virus.

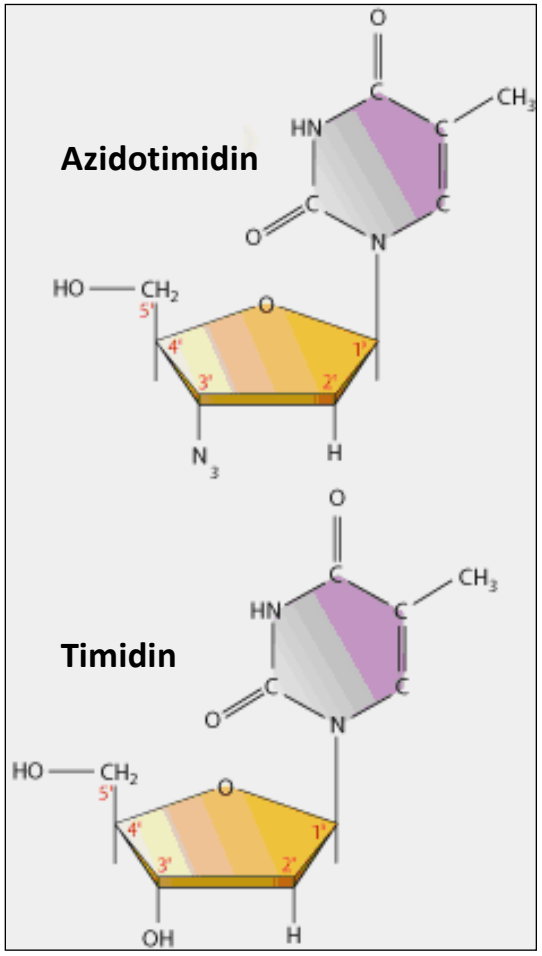
Inhibitors of viral DNA polymerase enzyme

- These drugs (idoxyuridine, vidarbin, etc.), which are mainly used in the treatment of herpesvirus infections, do not contain radicals that can form chemical bonds. Thus, they cannot bind to other nucleotides and stop their synthesis when they enter the DNA chain. These drugs have serious side effects because they inhibit the synthesis of not only viral DNA, but also cellular DNA.
- Some of them are even used as a cytostatic drug, for example, in the treatment of tumors.Some of the nucleoside analogues (acyclovir, gancyclovir, famciclovir, etc.) selectively act within the infected cell. The virus-specific enzyme thymidine kinase activates (phosphorylates) these drugs, so these drugs can not affect the synthesis of DNA in non-virus-infected cells. It is mainly used in the treatment of herpesvirus infections. Recently, nucleoside analogues (ribavirin, foscarnet, etc.) with a wide range of effects are also applied.

Inhibitors of reverse transcriptase enzymes

Drugs from this group interact with retroviruses, including MIA reverse transcriptase enzymes. It is reminiscent of thymidine due to its chemical structure.

The drug inhibits the reverse transcriptase enzyme by competitively inhibiting it, as well as binding it instead of thymidine in the nucleic acid chain. Azidothymidine (zidovudine), as well as zalsitabine, lamivudine, etc. It is used in the treatment of HIV infection



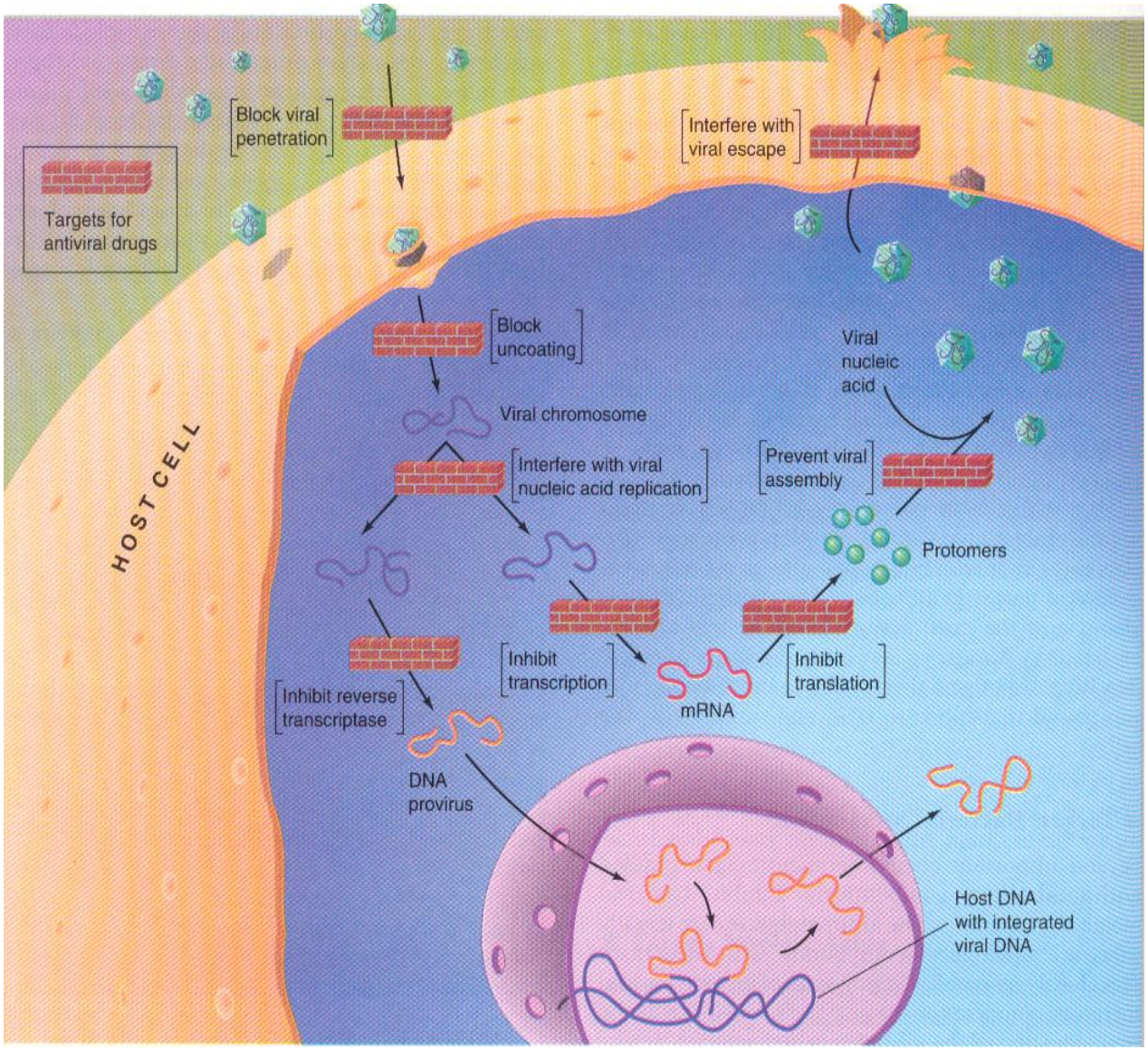
Inhibitors of viral proteases

- Non-hydrolyzed synthetic peptides (saquinavir, ritonavir, etc.) have antiviral effects by competitively inhibiting viral proteases.
- It is mainly used in the treatment of HIV infection

Inhibitors of the synthesis of the latest viral proteins

- They have active antiviral activity, mainly against viruses of the genus Poxviridae (natural flower virus).
- Due to its chemical nature, metisasone and marboran, which are derivatives of thiosemcarbazone, are highly effective in natural flower disease.
- These drugs are also effective in the treatment of recurrent genital herpes and herpes zoster.

Targets of antiviral drugs



Interferons

- In 1957, A. Isaacs and J.Lindemann studied the interference of viruses.
- Interferon is a protein-glycolipid with a molecular weight of 15-70 kD, which is synthesized in the cells of the immune system and connective tissue.
- There are three types of interferon, depending on which cells synthesize them:

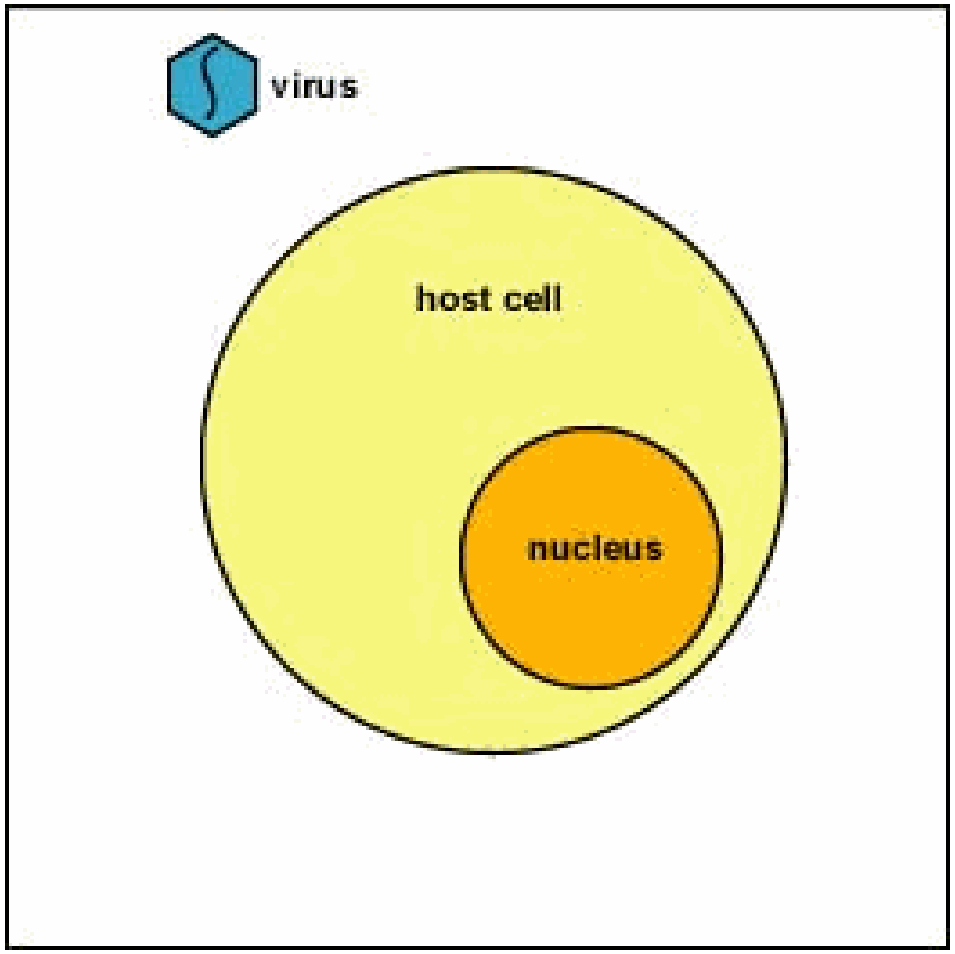
Interferons

- Alpha-interferon is synthesized in leukocytes and is called leukocyte interferon;
- Beta-interferon is synthesized in connective tissue cells (fibroblasts) and is called fibroblast interferon;
- Gamma-interferon is called immune interferon and is synthesized by activated T-lymphocytes, macrophages, natural killers, and generally by immune cells.

The mechanism of action of interferons

- Interferon does not directly affect viruses outside the cell, but binds to specific receptors and slows down the reproduction of viruses at the stage of protein synthesis.
- In addition to antiviral action, interferons have immunomodulatory activity.

The mechanism of action of interferons



Inductors of interferon **- interferonogens**

- Infection of cells with viruses dramatically increases the production of interferon.
- Interferon yields also depend on interferon inducers, such as RNA, DNA, complex polymers, and so on. is also observed during the impact.
- Such inductors of interferon are called interferonogens. At present, synthetic interferonogens (cycloferon, etc.) are widely used in medical practice.