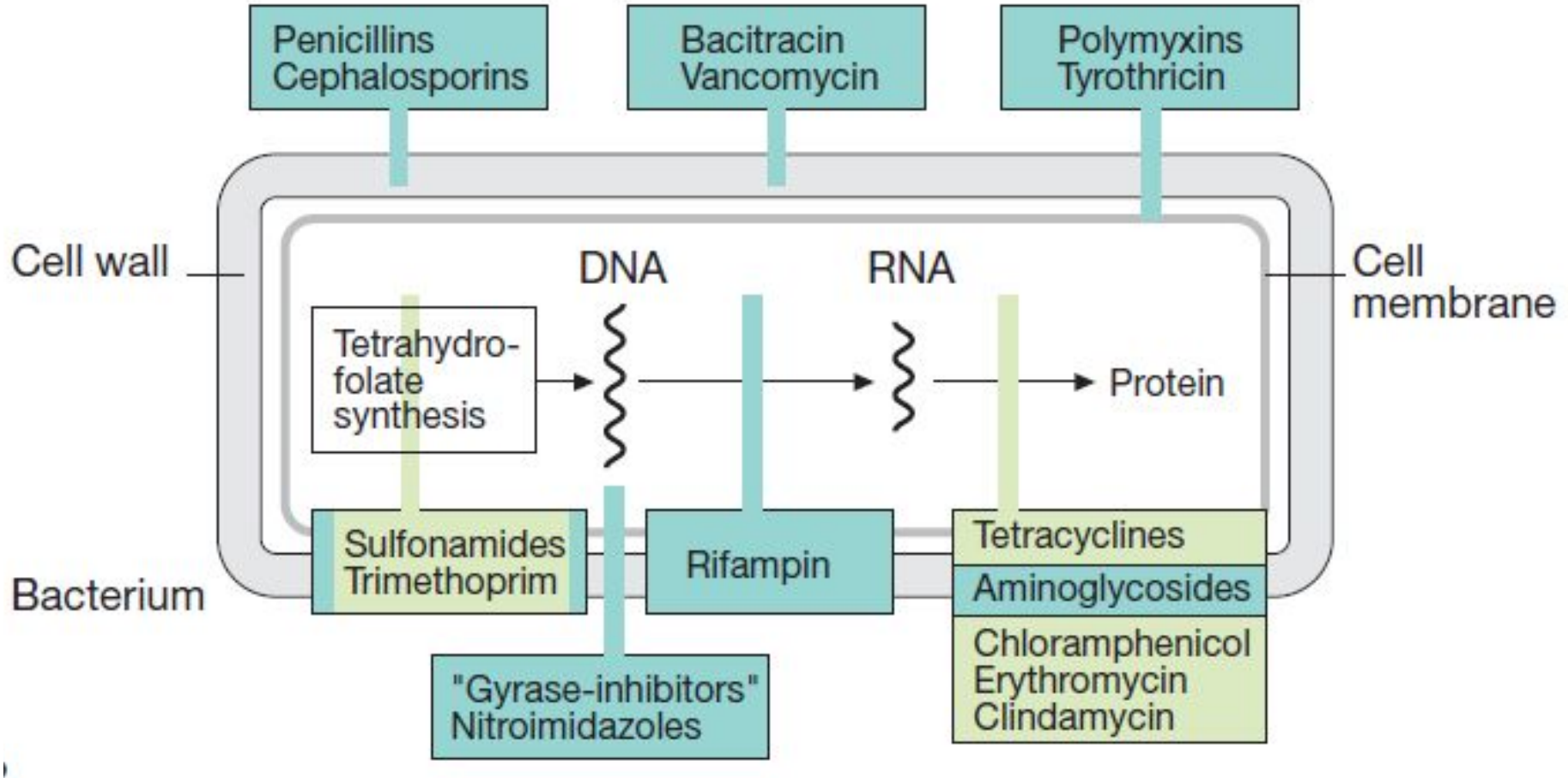
Tetracyclines, Chloramphenicol, Aminoglycosides

Anti-tuberculosis drugs


Penicillins
Cephalosporins
Bacitracin
Vancomycin
Polymyxins
Tyrothricin
Cell wall
DNA
RNA
Cell membrane
Tetrahydro-folate synthesis
Protein
Sulfonamides
Trimethoprim
Rifampin
Tetracyclines
Aminoglycosides
Chloramphenicol
Erythromycin
Clindamycin
Bacterium
"Gyrase-inhibitors"
Nitroimidazoles

- **Tetracyclins** – antibiotics, whose structure consists of 4 condensated 6-membered rings.
- Tetracyclines enter susceptible organisms via passive diffusion and also by an energy-dependent transport.
- The drugs bind reversibly to the 30S subunit of the bacterial ribosome. This action prevents binding of tRNA to the mRNA–ribosome complex, thereby inhibiting bacterial protein synthesis.
- Type of action – bacteriostatic.

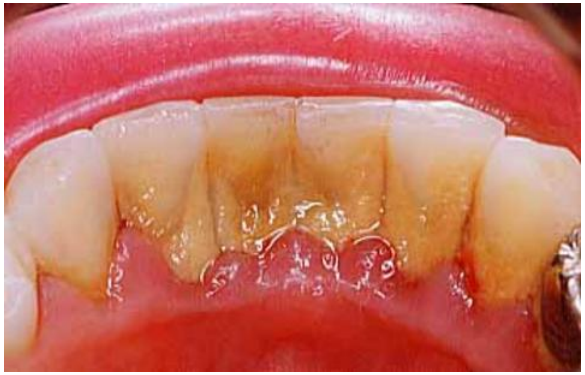
- **Drugs:** Tetracycline, Doxycycline, Oxytetracycline, Minocycline, Demeclocycline
- **Spectrum:** Cocci, Clostridia, Listeria, Corynebacteria, bacterium acnes, B. anthracis, V. cholerae, Yersinia, Campylobacter, Helicobacter pylori, Brucella, Pasteurella multocida, Spirochetes (T. pallidum and Borrelia), F. tularensis, all rickettsiae (typhus, etc.), chlamydiae, Mycoplasma and Actinomyces. Protozoa (Entamoeba histolytica and Plasmodia) are inhibited at high concentrations.

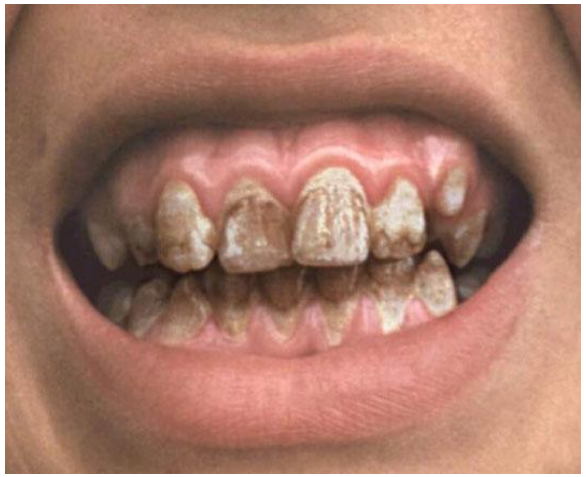
- Many strains are resistant now.
- Tetracyclines do not act on viruses, fungi, Pseudomonas aeruginosa, Proteus, mycobacteria.
- Tetracyclines are absorbed after oral ingestion. They are concentrated well in the bile, liver, kidney, gingival fluid, and skin but do not pass BBB.
- **Tetracycline** is primarily eliminated unchanged in the urine, **doxycycline** is primarily eliminated via the bile into the feces.

- **Uses:** Empirical therapy or initial treatment of mixed infections;
- venereal diseases (chlamydial nonspecific urethritis/endocervicitis); syphilis; gonorrhoea;
- atypical pneumonia;
- cholera; amoebiasis; GIT infections;
- brucellosis; plague; relapsing fever, leptospirosis; rickettsial infections (typhus); tetanus, anthrax, actinomycosis and listeria infections;
- Conjunctivitis, acne vulgaris.

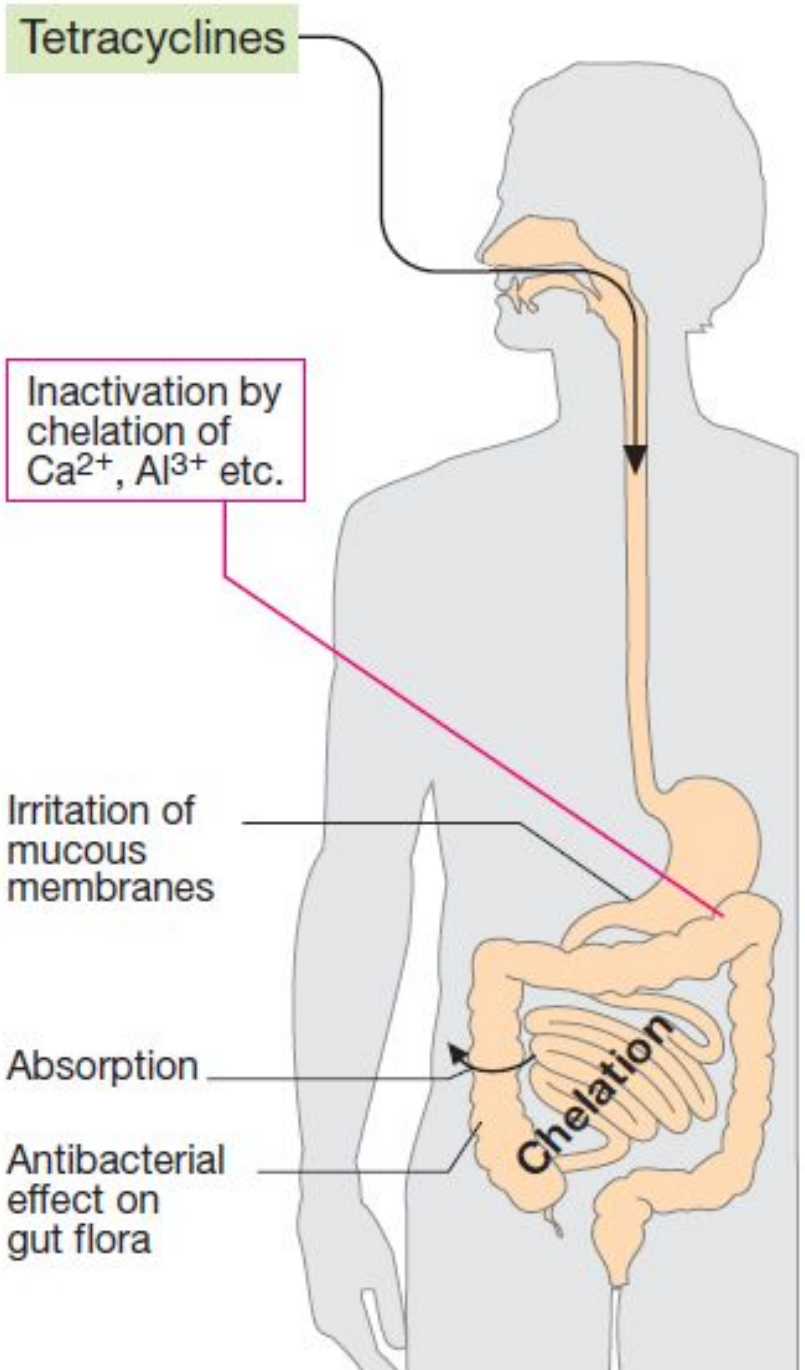
Adverse effects:

- epigastric pain, nausea, vomiting and diarrhoea,
- teratogenic effect, discoloration and hypoplasia of teeth in children,
- hepatotoxicity,
- phototoxicity,
- dysbiosis,
- superinfection,



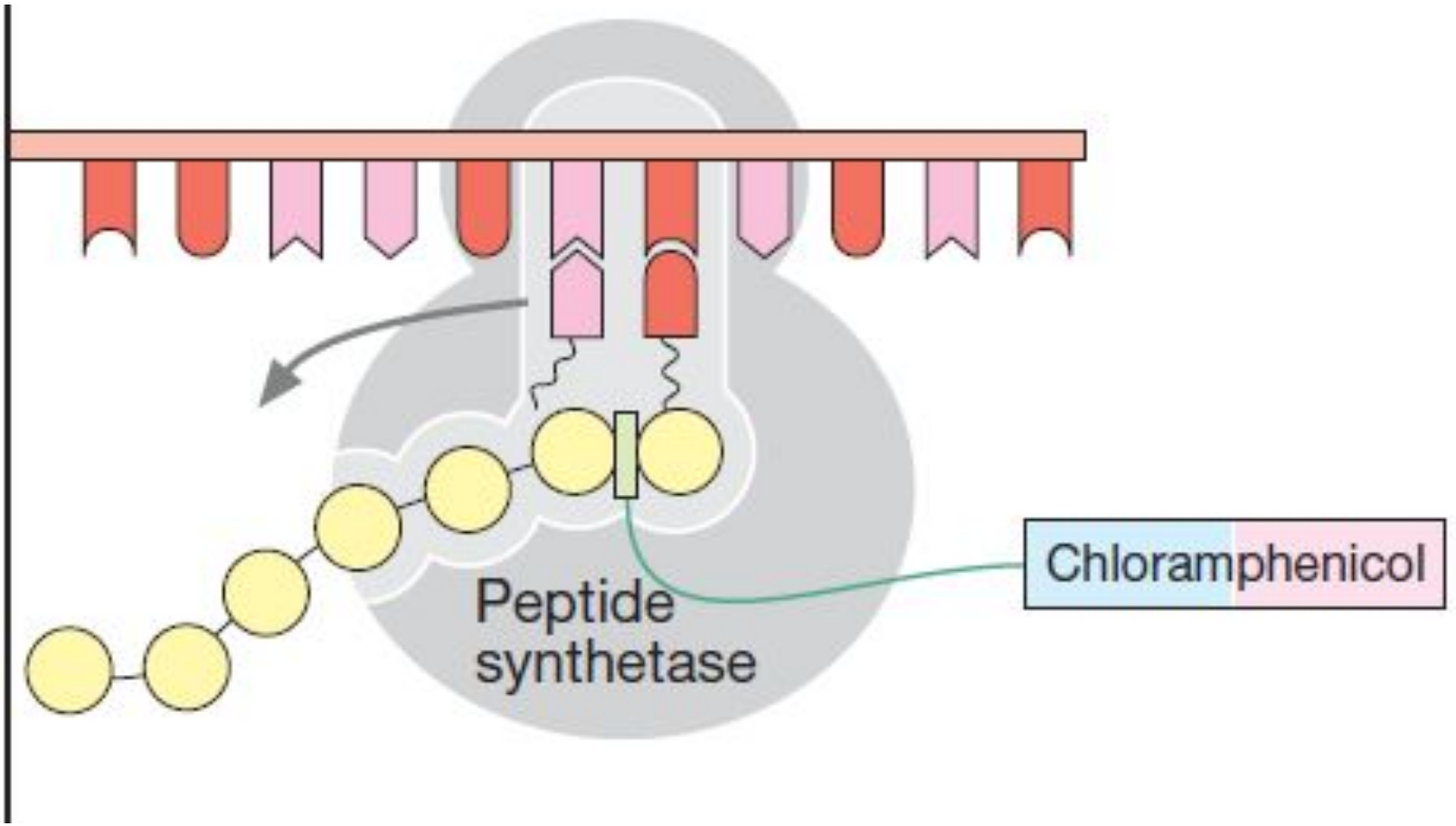


- hypersensitivity (skin rashes, urticaria, glossitis, pruritus ani and vulvae)



- **Contraindications:** Tetracyclines should not be used in pregnant or breast-feeding women or in children less than 8 years of age.

Chloramphenicol binds reversibly to the bacterial 50S ribosomal subunit and inhibits protein synthesis at the peptidyl transferase reaction.

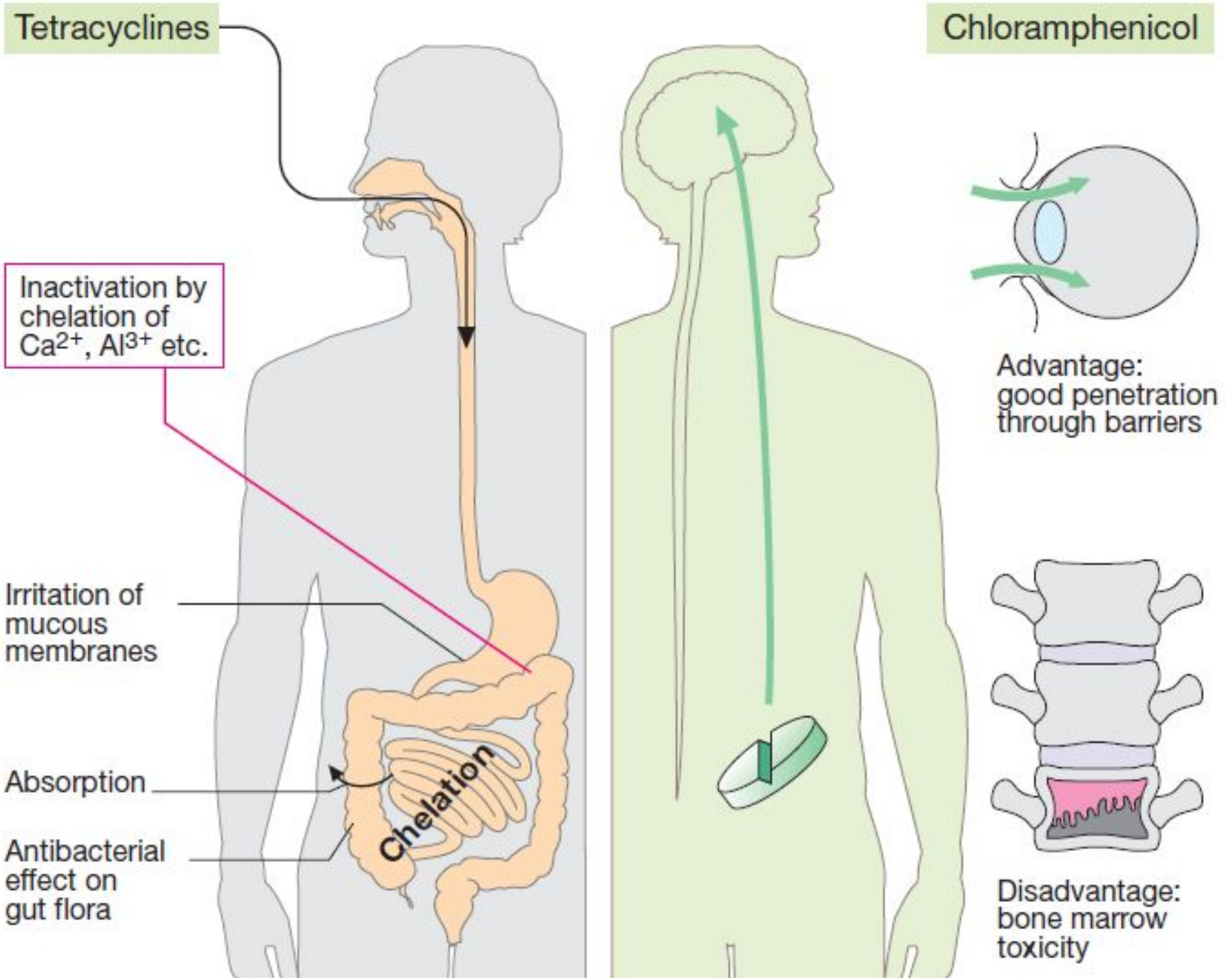


- It is active against many types of microorganisms (H. influenzae and N. meningitidis, salmonella including S. typhi, B. pertussis, klebsiella, anaerobes including Bact. Fragilis, rickettsiae, spirochetes, and anaerobes).
- The drug is primarily bacteriostatic, but depending on the dose and organism, it may be bactericidal.
- It is ineffective against Mycobacteria, Pseudomonas, many Proteus, viruses and fungi.

- It is widely distributed throughout the body.
- It reaches therapeutic concentrations in the CSF.
- It primarily undergoes hepatic metabolism to an inactive glucuronide, which is secreted by the renal tubule and eliminated in the urine.

Uses:

- Pyogenic meningitis;
- Anaerobic infections caused by Bact. fragilis and others (wound infections, intraabdominal infections, pelvic abscess, and brain abscess;
- Intraocular infections;
- Skin infections.


Tetracyclines
Chloramphenicol
Inactivation by chelation of Ca^{2+}, Al^{3+} etc.
Irritation of mucous membranes
Absorption
Antibacterial effect on gut flora
Chelation
Advantage: good penetration through barriers
Disadvantage: bone marrow toxicity

Adverse effects:

- Bone marrow depression:

❑ Non-dose related idiosyncratic reaction – aplastic anaemia;

❑ Dose and duration of therapy related myelosuppression.

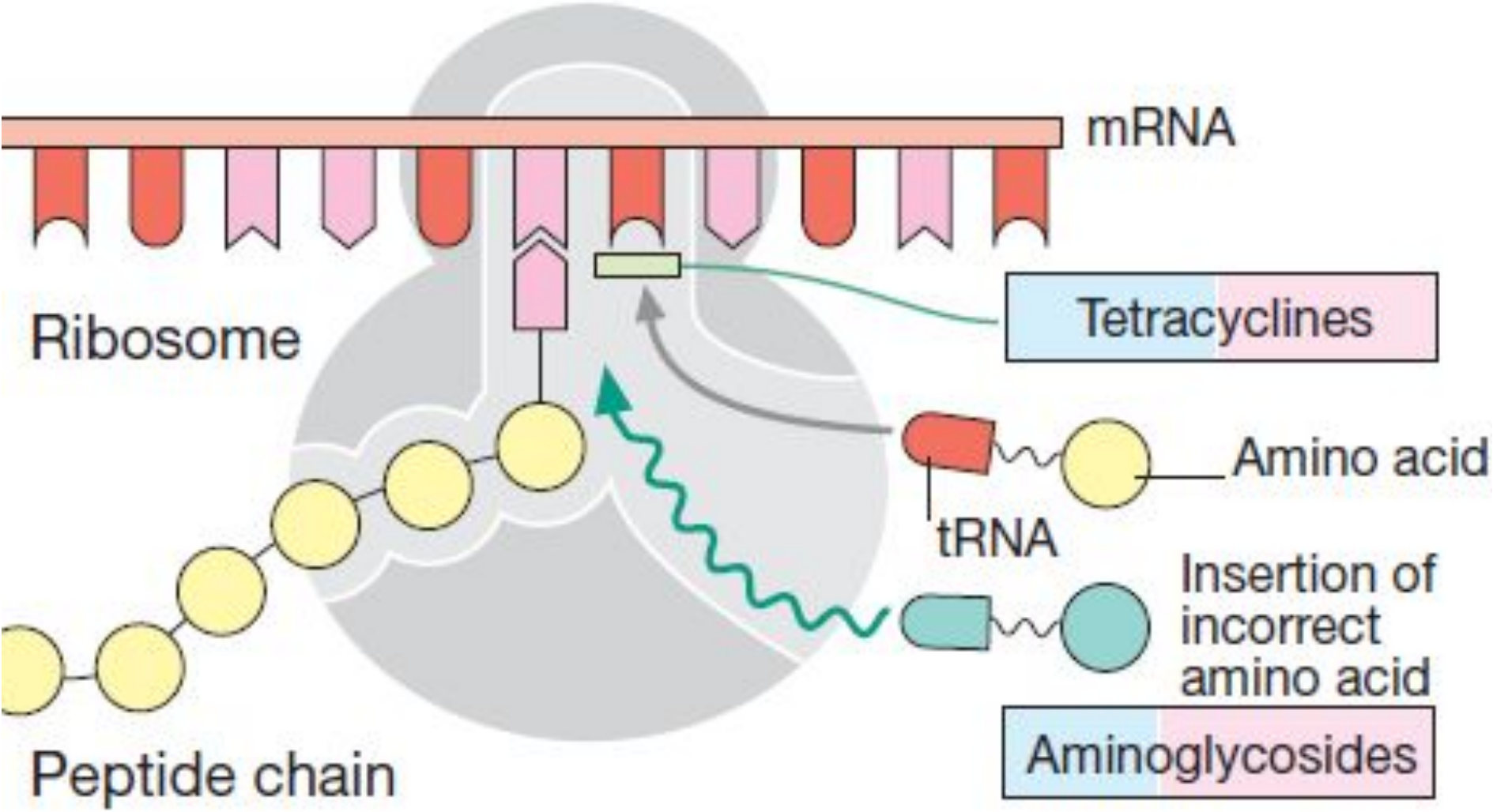
- Gray baby syndrome (hypotonia, hypothermia, abdomen distended, irregular respiration, gray cyanosis of skin, cardiovascular collapse);
- Hypersensitivity reactions (rashes, fever, angioedema);
- Irritative effects (nausea, vomiting, diarrhoea);
- Superinfections

Aminoglycosides

- These are a group of natural and semisynthetic antibiotics having two or more aminosugars.

- 1 gen.: Streptomycin, Kanamycin, Neomycin (Topical aminoglycoside)
- *2 gen.:* Gentamycin
- 3 gen: Amikacin, Sisomycin, Tobramycin
- 4 gen.:Netilmycin

- They diffuse through porin channels in the membrane of susceptible organisms. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane.
- Inside the cell, they bind the 30S ribosomal subunit, where they interfere with ribosomal apparatus and cause the 30S subunit of the completed ribosome to misread the genetic code.
- They also increase the permeability of the cytoplasmic membrane.
- Type of action – bactericidal.


mRNA
Ribosome
Tetracyclines
Amino acid
tRNA
Insertion of incorrect amino acid
Aminoglycosides
Peptide chain

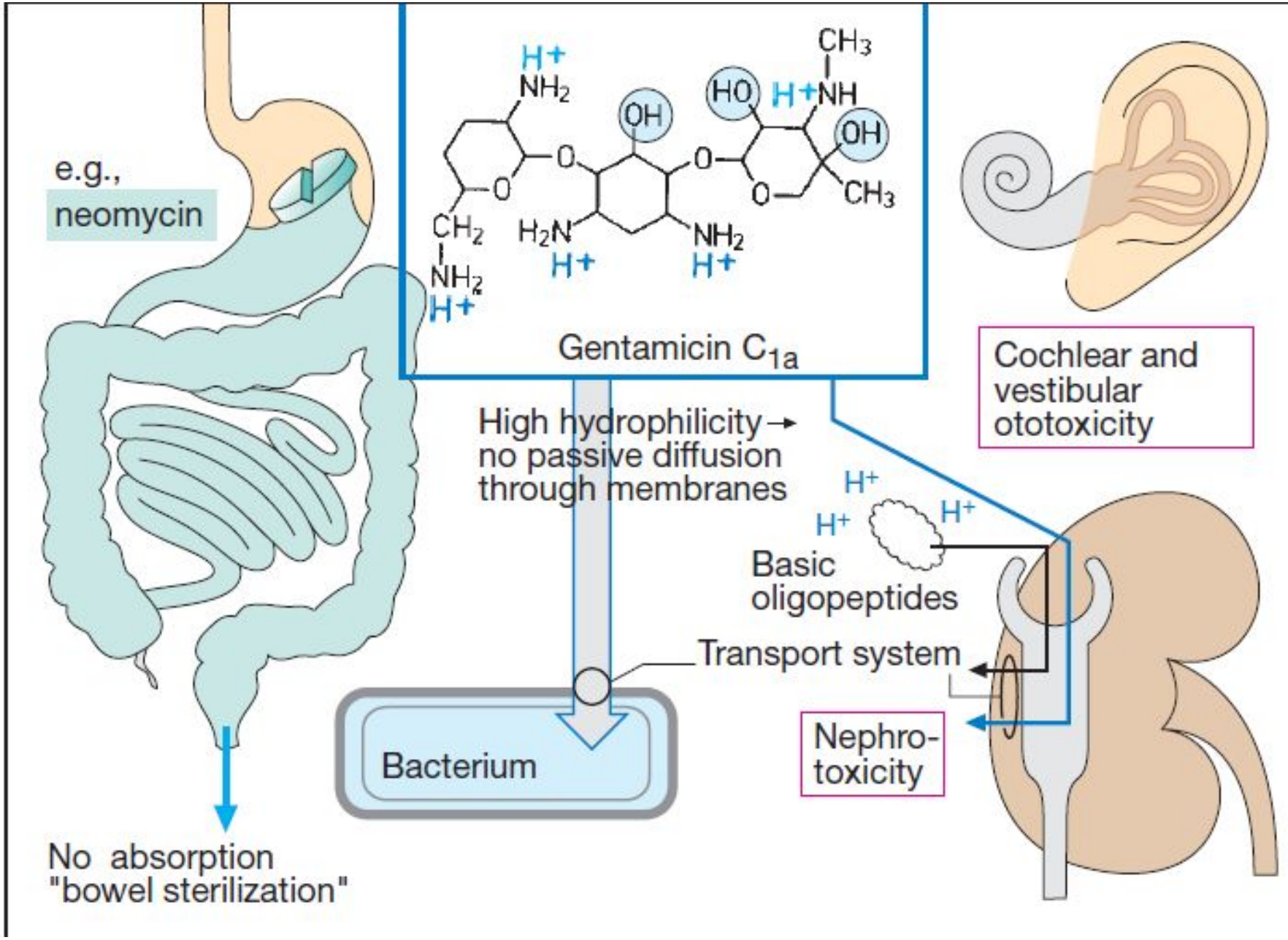
Spectrum:

- Gram-negative: Escherichia, Klebsiella, Salmonella, Shigella, Proteus, serration, Yersinia, Moraxella, Enterobacter;
- Cocci.
- The causative agents of tularemia, plague, brucellosis.
- Mycobacterium tuberculosis (streptomycin, kanamycin, amikacin).
- 2 and 3 generations act on Pseudomonas aeruginosa.
- Do not act on anaerobes, chlamydia, rickettsia, spirochetes, viruses, fungi, protozoa

- They are not absorbed in the g.i.t.
- They are distributed only extracellularly. Relatively higher concentrations are present in endolymph and renal cortex, which are responsible for ototoxicity and nephrotoxicity. Penetration in respiratory secretions is poor. Concentrations in CSF and aqueous humour are nontherapeutic even in the presence of inflammation.
- Aminoglycosides are not metabolized in the body, and are excreted unchanged in urine

Uses:

- Tuberculosis; Tularemia;
- Subacute bacterial endocarditis;
- Plague;
- Urinary tract infection, peritonitis;
- Septicaemias;
- *Pseudomonas, Proteus or Klebsiella infections:* burns, urinary tract infection, pneumonia;
- lung abscesses, middle ear infection


e.g.,
neomycin
Gentamicin C1a
Cochlear and vestibular ototoxicity
High hydrophilicity →
no passive diffusion through membranes
Basic oligopeptides
Transport system
Bacterium
Nephro-toxicity
No absorption
"bowel sterilization"

Adverse effects:

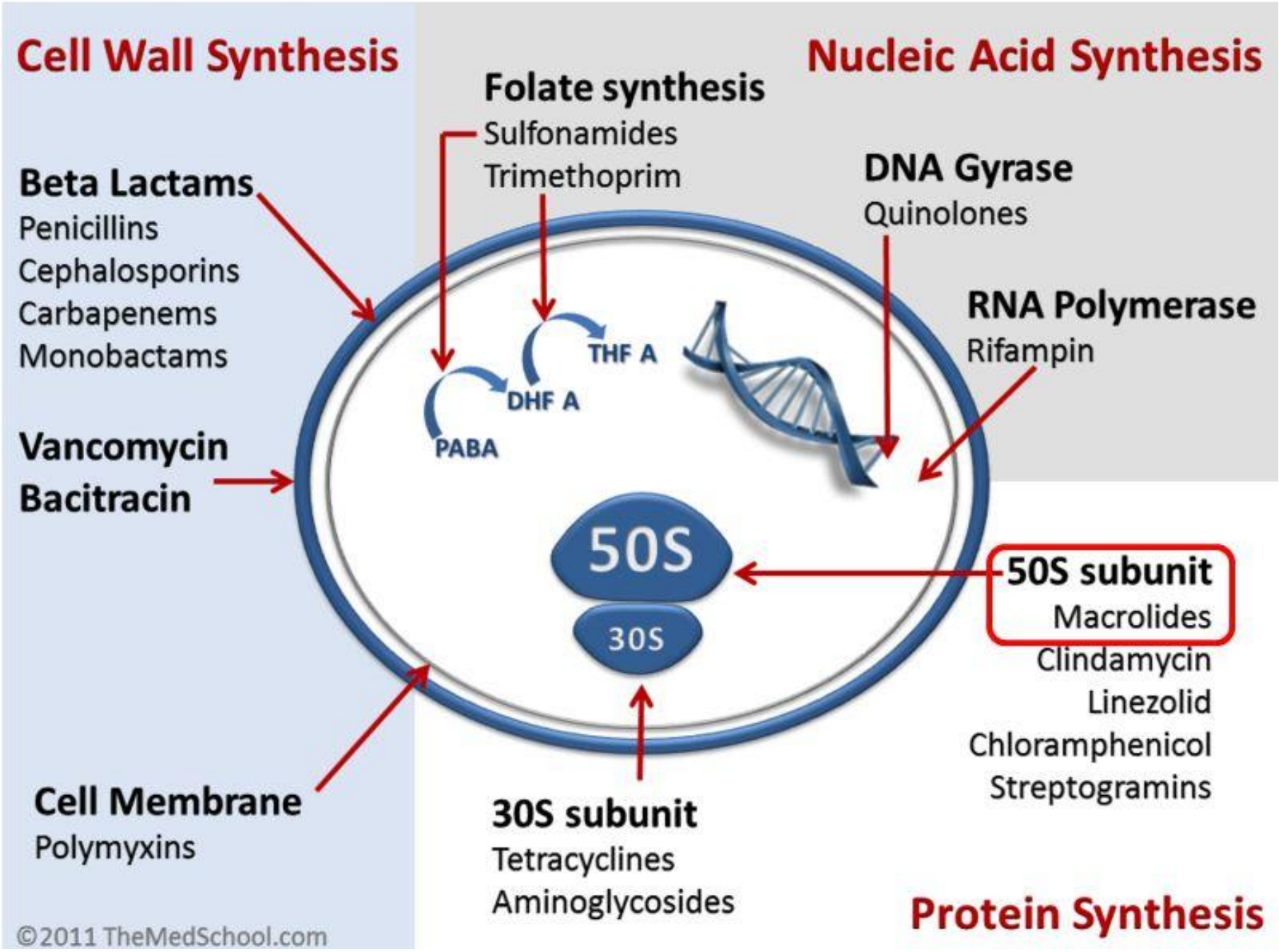
- Ototoxicity (vestibular and auditory);
- Nephrotoxicity;
- Neuromuscular paralysis;
- Allergic reactions

Lincosamides: clindamycin

- ✔ **Mechanism**: inhibits protein synthesis.
- ✔ **Type of action**: bacteriostatic.
- ✔ **Spectrum**: Staphylococcus, Streptococcus, pneumococcus, chlamydia, anaerobes.
- ✔ It passes in bones, poorly through the BBB.
- ✔ It is used per os, IV, IM, locally (gel, vaginal cream).
- ✔ **Indications:** diseases of ENT organs, bones, teeth, joints, abdominal organs, sepsis, peritonitis.
- ✔ **Side effects:** pseudomembranous colitis, dysbacteriosis, allergy, hepatotoxicity, leukopenia

Vancomycin disrupts the synthesis of cell wall, acts bactericidaly.

- **Spectrum:** gram-positive bacteria, including methicillin-resistant staphylococci.
- **Indications:** severe staphylococcal and streptococcal infections (septicemia, pneumonia, abscesses of brain or lungs, meningitis, peritonitis, osteomyelitis, endocarditis).
- It is used IV or orally for pseudo membranous colitis (not absorbed from the gastrointestinal tract).
- **Side effects:** phlebitis, hearing disorders, allergy, nephrotoxicity, rash, neutropenia.


Cell Wall Synthesis
Nucleic Acid Synthesis
Folate synthesis
Sulfonamides
Trimethoprim
Beta Lactams
Penicillins
Cephalosporins
Carbapenems
Monobactams
DNA Gyrase
Quinolones
RNA Polymerase
Rifampin
THF A
DHF A
PABA
Vancomycin
Bacitracin
50S
30S
50S subunit
Macrolides
Clindamycin
Linezolid
Chloramphenicol
Streptogramins
Cell Membrane
Polymyxins
30S subunit
Tetracyclines
Aminoglycosides
Protein Synthesis
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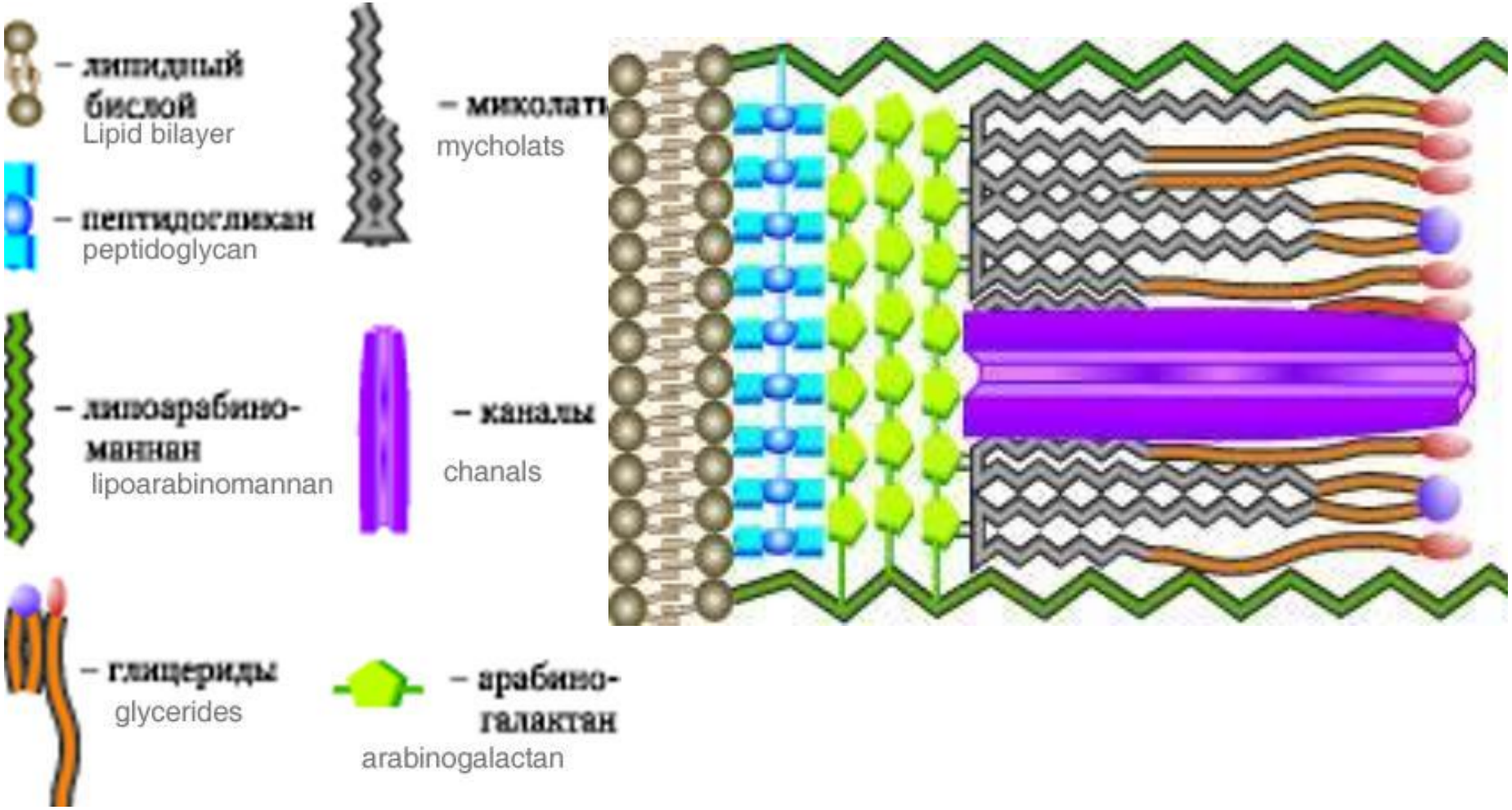
- **The polymyxins** disrupt cell membrane integrity, leading to leakage of cellular components and cell death.
- **Spectrum:** P. aeruginosa, E. coli, K. pneumoniae, Acinetobacter species, Enterobacter species, Proteus and Serratia.
- **Polymyxin B** is available in otic, ophthalmic and topical preparations.

- **Colistin (polymyxin E)** is only available as a prodrug, colistimethate sodium, which is administered IV or inhaled via a nebulizer.
- **Adverse effects**: nephrotoxicity and neurotoxicity (for example, slurred speech, muscle weakness) when used systemically.
- **Uses:** salvage therapy for patients with multidrug-resistant infections.

Antitubercular Drugs

The structure of the cell wall of mycobacteria



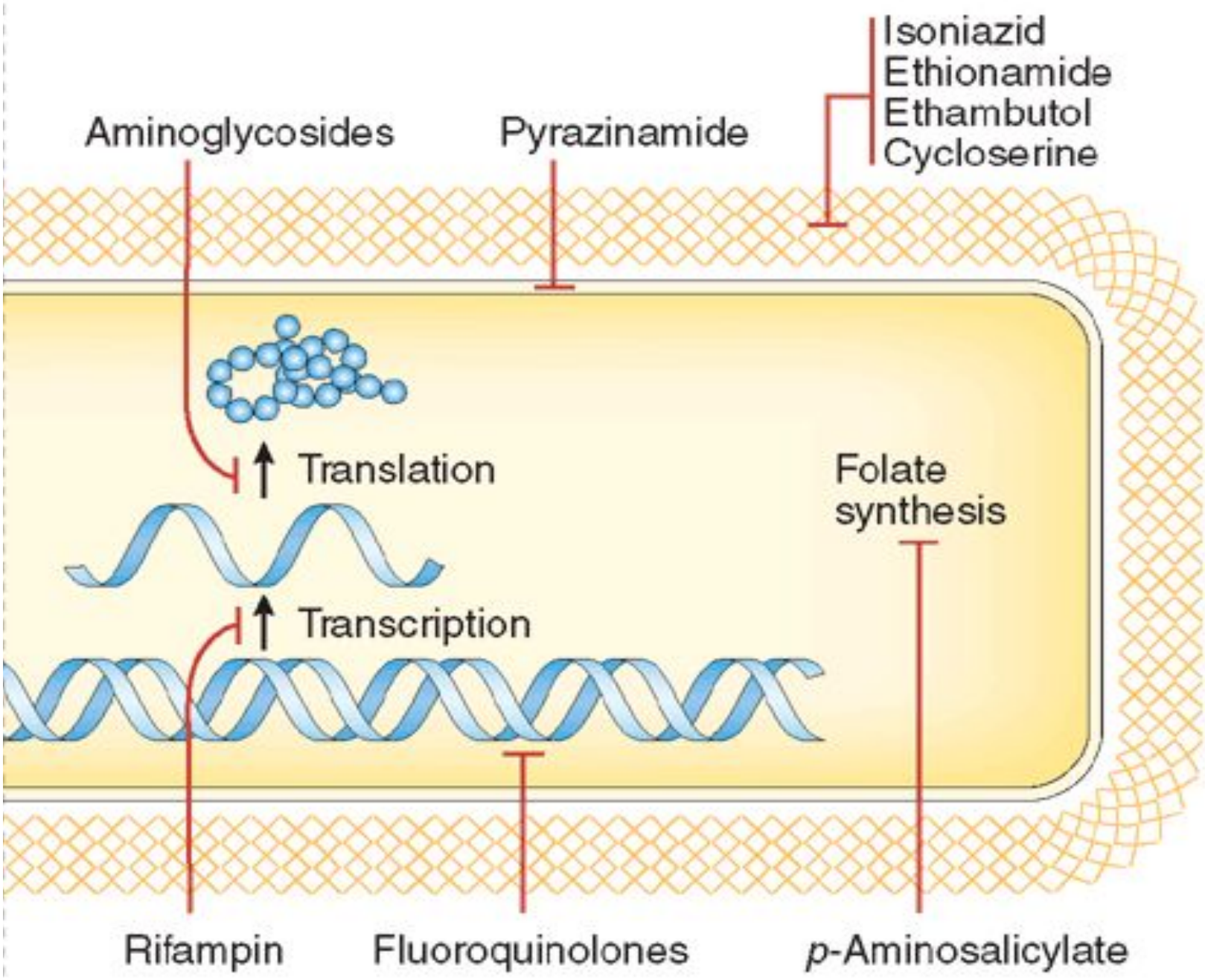
Classification

- ***First line:*** These drugs have high antitubercular efficacy as well as low toxicity; are used routinely:

Isoniazid, Ethambutol, Pyrazinamide, Rifampin, Streptomycin;

- ***Second line:*** These drugs have either low antitubercular efficacy or higher toxicity or both; and are used as reserve drugs:

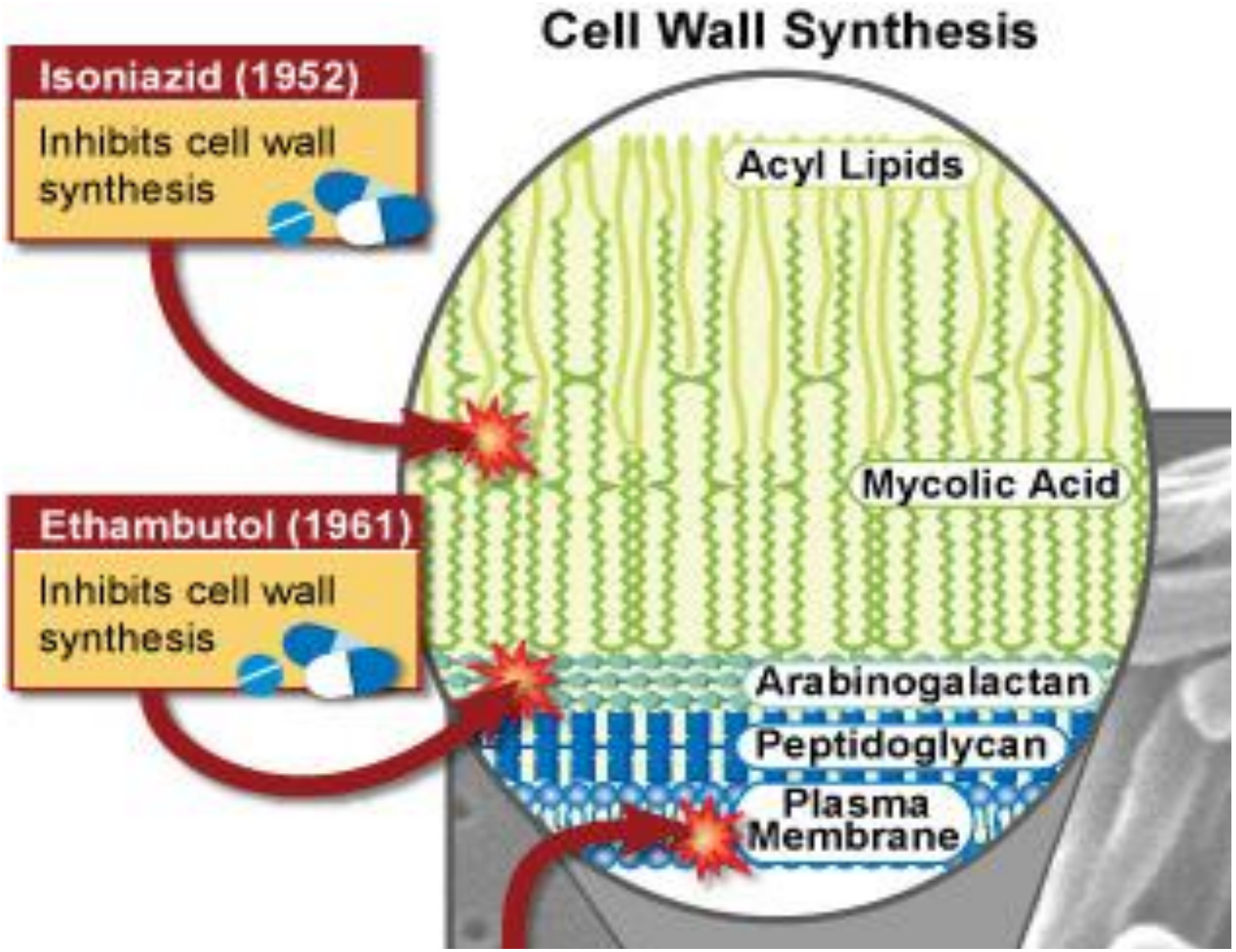
Ethionamide, Prothionamide, Cycloserine, Fluoroquinolones (Ofloxacin, Levofloxacin, Moxifloxacin, Ciprofloxacin), Kanamycin, Amikacin, Rifabutin, Para-aminosalicylic acid


Isoniazid
Ethionamide
Ethambutol
Cycloserine
Aminoglycosides
Pyrazinamide
Translation
Folate
synthesis
Transcription
Rifampin
Fluoroquinolones
p-Aminosalicylate

Principles of tuberculosis treatment:

- ❑ Early intensive care.
- ❑ The use of the most active drugs.
- ❑ Combination of 2-3 drugs.
- ❑ Long-term therapy for 6-8-12 months.

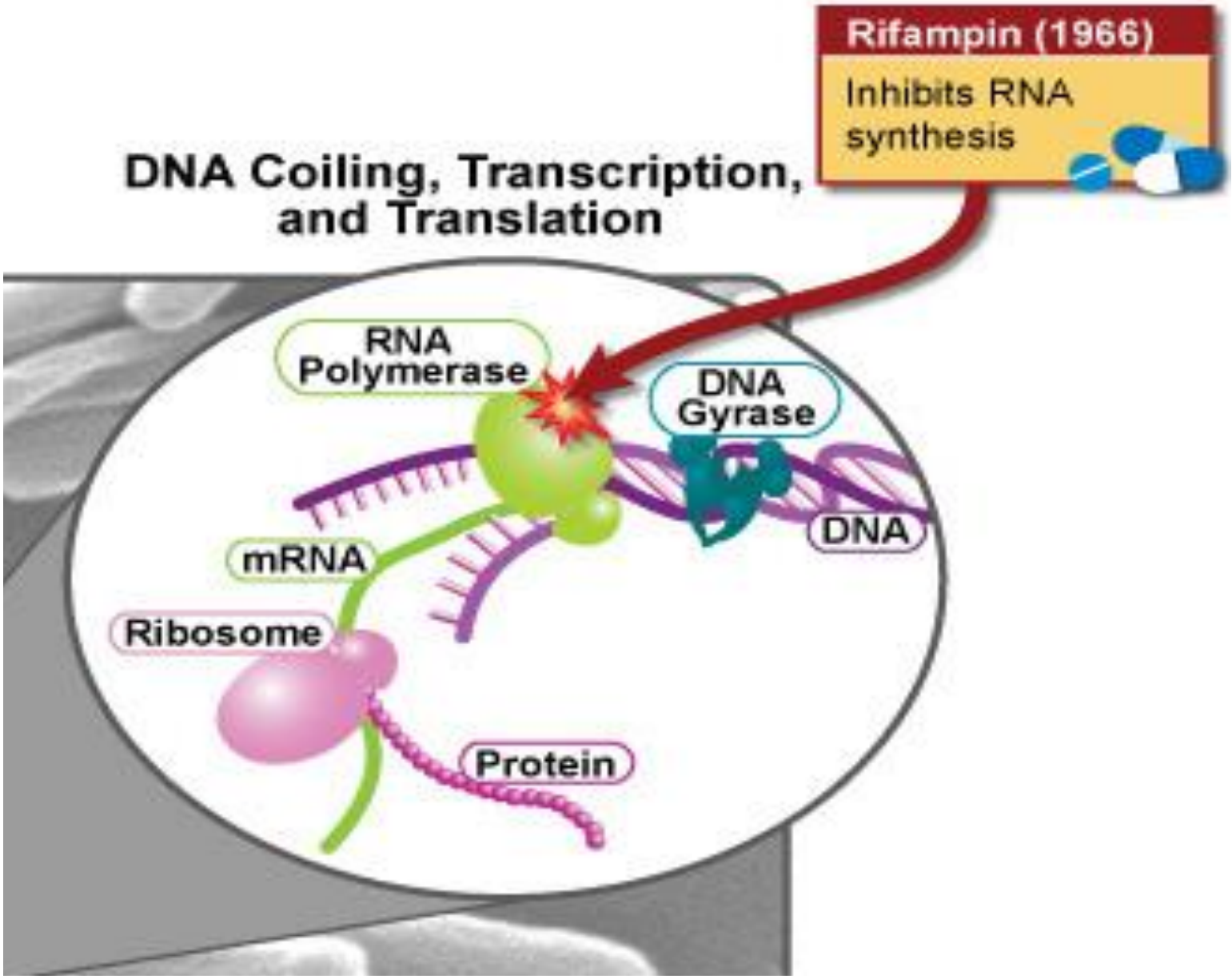
- **Isoniazid** disrupts the synthesis of mycolic acids. It increases the permeability of the cell membranes, facilitates the penetration of chemotherapeutic substances into the Mycobacterium.
- It disrupts the tissue respiration.
- It acts bactericidal.
- It is used orally, IV, into the cavities.
- It is well absorbed, penetrates into all tissues, through BBB, into caseous foci, into cells. Isoniazid is acetylated slowly when it is combined with paraaminosalicylic acid


Cell Wall Synthesis
Isoniazid (1952)
Inhibits cell wall synthesis
Ethambutol (1961)
Inhibits cell wall synthesis
Acyl Lipids
Mycolic Acid
Arabinogalactan
Peptidoglycan
Plasma Membrane

- **Side effects:** rash, skin itching, headache, dizziness, peripheral neuritis (optic neuritis), euphoria, insomnia, psychosis, convulsions, epilepsy attacks, liver dysfunction. Development of resistance.
- Apply Vit. B1 and B6 for the prevention of neuritis .

Rifampicin is a semisynthetic antibiotic.

- It is bactericidal to M. tuberculosis, M. leprae and many other gram-positive and gram-negative bacteria like Staph. aureus, N. meningitidis, H.influenzae, E. coli, Klebsiella, Pseudomonas, Proteus and Legionella.
- Rifampin interrupts RNA synthesis by binding to β subunit of mycobacterial DNA-dependent RNA polymerase.


Rifampin (1966)
Inhibits RNA synthesis
DNA Coiling, Transcription, and Translation
RNA Polymerase
DNA Gyrase
DNA
mRNA
Ribosome
Protein

- It is well absorbed orally. It is widely distributed in the body: penetrates intracellularly, enters tubercular cavities, caseous masses and placenta, passes BBB. It is metabolized in liver to an active metabolite which is excreted in bile, in urine.

Adverse effects:

- Hepatitis;
- Cutaneous syndrome (flushing, pruritus, rash, redness and watering of eyes);
- Flu syndrome (chills, fever, headache, bone pains);
- Abdominal syndrome (nausea, vomiting, abdominal cramps, diarrhoea);
- Urine and secretions may become orangered.

Ethambutol is selectively tuberculostatic and is active against mycobacteria only.

- It violates the synthesis of the cell wall of M.
- Resistance to E develops slowly.
- About 3/4 of an oral dose of E is absorbed. It is distributed widely, but penetrates meninges incompletely and is temporarily stored in RBCs.
- **Adverse effects:** loss of visual acuity/colour vision, field defects due to optic neuritis; nausea, rashes, fever, rarely peripheral neuritis, hyperuricemia.

Pyrazinamide acts on the slowly multiplying intracellular bacilli, probably inhibits mycolic acid synthesis.

- Type of action – weakly tuberculocidal.
- Tolerance of bacteria develops rapidly if it is used alone.
- It penetrates through the BBB, into the caseous foci.
- **Adverse effects:** dyspepsia, allergic reactions, arthralgia, gout exacerbation, liver dysfunction.

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