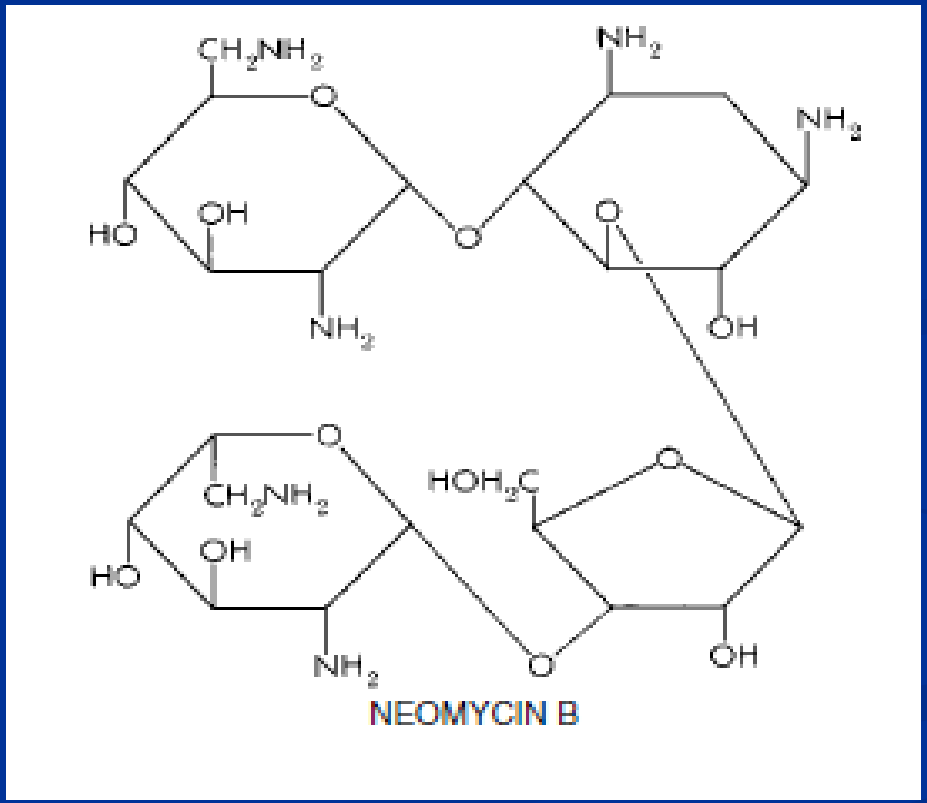
The Aminoglycosides

- Active against gram negative bacteria.
- Hydrophilic compounds, do not cross membranes, do not distribute well.
- All given by injection, or locally applied.
- Not metabolized.
- Excreted by the kidneys.
- Ototoxic and nephrotoxic.

The aminoglycosides consist of two or more amino sugars joined in glycosidic linkage to a hexose nucleus, which usually is in a central position



NEOMYCIN B

glycosidic linkage is a type of covalent bond that joins a carbohydrate (sugar) molecule to another group

a **hexose** is a monosaccharide with six carbon atoms

- The polycationic aminoglycoside chemical structure results in a binding both to the anionic outer bacterial membrane and to anionic phospholipids in the cell membranes of mammalian renal proximal tubular cells.
- The former contributes to the bactericidal effects of these compounds, while the latter binding accounts for their toxicity. Because of their hydrophilicity, the transport of aminoglycosides across the hydrophobic lipid bilayer of eukaryotic cell membranes is impeded

MECHANISM OF ANTIBACTERIAL ACTION

- The antibacterial actions of the aminoglycosides involve two possibly synergistic effects.

- First, the positively charged aminoglycoside binds to negatively charged sites on the outer bacterial membrane, thereby disrupting membrane integrity.

- It is likely that the aminoglycoside-induced bacterial outer membrane degradation accounts for the rapid concentration dependent bactericidal effect of these compounds.

MECHANISM OF ANTIBACTERIAL ACTION

- Second, aminoglycosides bind to various sites on bacterial 30S ribosomal subunits, disrupting the initiation of protein synthesis and inducing errors in the translation of messenger RNA to peptides.
- They also bind to sites on bacterial 50S ribosomal subunits, although the significance of this binding is uncertain.
- In addition, they have a post antibiotic effect; that is, they continue to suppress bacterial regrowth even after removal of the antibiotic from the bacterial microenvironment.
- It is likely that ribosome disruption accounts for this postantibiotic activity.

- The postantibiotic effect is characterized by prolonged suppression of bacterial regrowth after the initially high aminoglycoside concentration has fallen to a subinhibitory level.
- Perhaps resumption of bacterial ribosomal function requires the time-consuming synthesis of new ribosomes after their disruption by aminoglycosides.
- The postantibiotic effect explains why aminoglycosides can be given in single daily doses despite their short half-life

- Penetration of aminoglycosides through the outer bacterial membrane occurs both by outer membrane disruption and by diffusion through outer membrane porins.

- Penetration through the inner bacterial membrane occurs in two phases.

- The first requires that the cytosol have a negative electron potential and therefore be inhibited by the presence of a low pH.

- The second phase depends on aerobic bacterial metabolism and therefore will be inhibited by low oxygen tension

- The latter two observations are of considerable clinical relevance, since
- both a low pH and a low oxygen tension

frequently occur in bacterial abscesses.

- Administration of B-lactam antibiotics will reverse the negative effects of both low pH and low oxygen tension on the ability of

aminoglycosides to penetrate into bacteria;

- this ability accounts in part for the synergism that occurs between

aminoglycoside and B-lactam antibiotic drugs.

The Aminoglycosides

- Used to treat infections caused by aerobic gram-negative bacteria and rapidly bactericidal.
- They inhibit protein synthesis by binding to the 30S ribosomal subunit

and alter protein synthesis.

- **Streptomycin: 1947.**
  - **Used only in TB.**

The Aminoglycosides

- Gentamicin.
- Tobramycin.
- Amikacin.
- Netilmicin
- Neomycin:

The Aminoglycosides

- **Gentamicin:**
  - Widely used in hospitals.
  - Good for Staphylococcus and Gram-negative organisms.
  - Short $T_{1/2.}$
  - Toxic, blood level monitoring is required.
  - Incompatible with other drugs, so given separately.

The Aminoglycosides

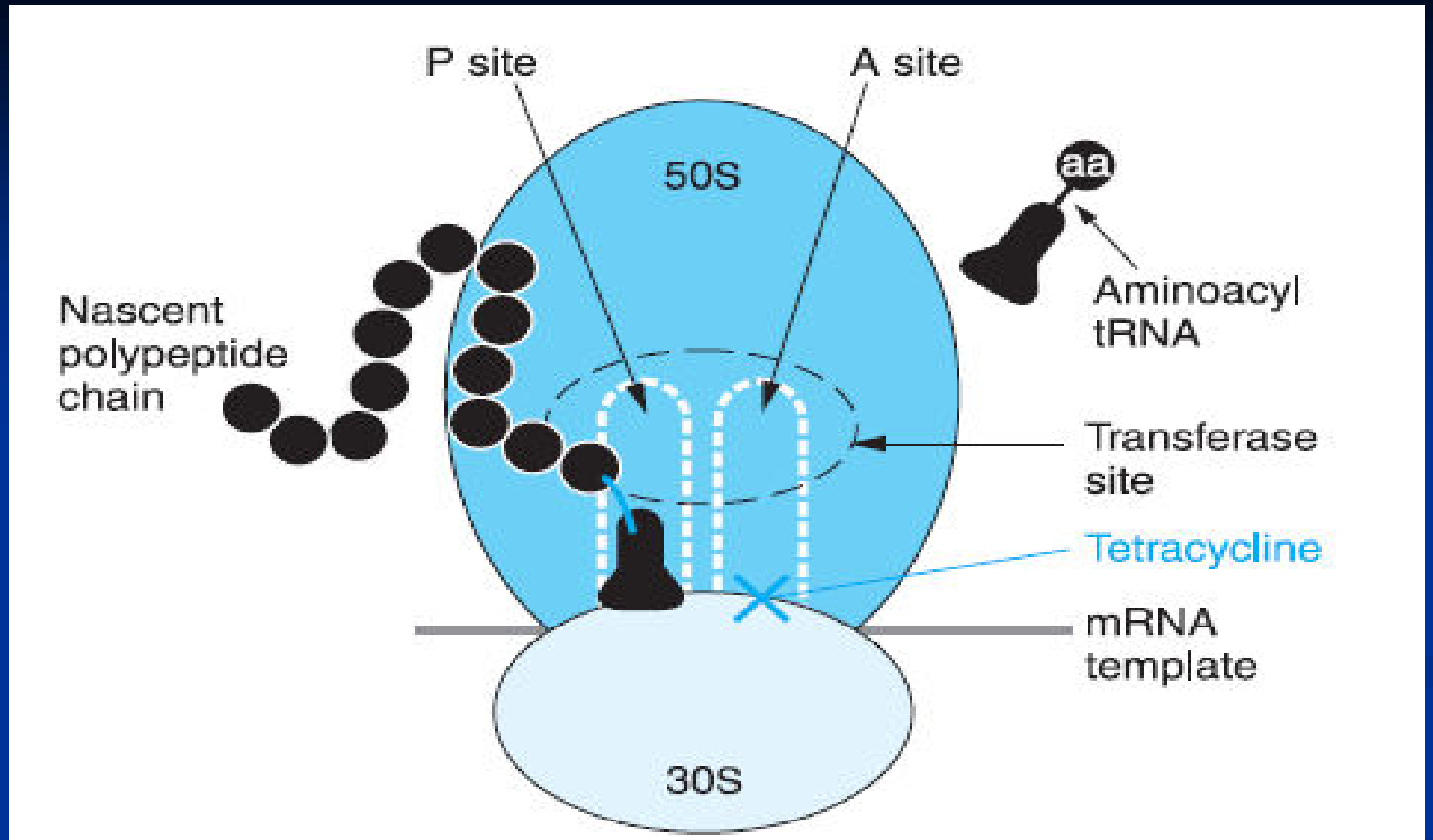
- **Neomycin:**
  - Very toxic, not given systemically.
  - Given to sterilize the bowel before surgery.
  - Also locally as drops or ointment in ear, nose, eye, or skin infections.

Tetracyclines

- Wide spectrum of activity (Gram positive and negative bacteria), but resistance develops very rapidly.
- Bacteriostatic, only stop bacterial growth, do not kill bacteria. So, we depend on the presence of a good patient's immune system.

Tetracyclines

- Disrupt function of 30S or 50S ribosomal subunits to reversibly inhibit protein synthesis.
- Orally absorbed, but absorption affected by food, and dairy products.
- Widely distributed in the body.



Tetracyclines inhibit bacterial protein synthesis by binding to the 30S subunit and blocking tRNA binding to the A site.

A transfer RNA is an adaptor molecule composed of RNA, typically 76 to 90 nucleotides in length that serves as the physical link between the mRNA and the amino acid sequence of proteins

Tetracyclines

- Rarely used nowadays, EXCEPT:
  - **Doxycycline:** given once daily for acne.
- Adverse Effects:
  - Nausea, vomiting, diarrhea.
  - Changes in normal flora leading to diarrhea and candida infection.
  - Bone deposits in children, appears on teeth