Antibiotics

DEFINITION

- are defined as chemical substances or compounds produced by various species of microorganisms such as bacteria and fungi, which in low concentrations destroy, kill or inhibit the growth of other species of microorganisms."
- **Greek words anti = against ; bios = life**

Characteristic of antibiotics

- It should be **eliminated completely** from the body.
- It should **not side** effects.
- It should be **highly effective** in low concentrations.
- It should be **nonallergenic** to the host.
- It should be **able to reach** the part of the human body where the infection is occurring.
- It should be **inexpensive** and easy to produce.
- It should be **chemically-stable**

ANTIBIOTICS

- **Natural substances produced by various species of microorganisms**

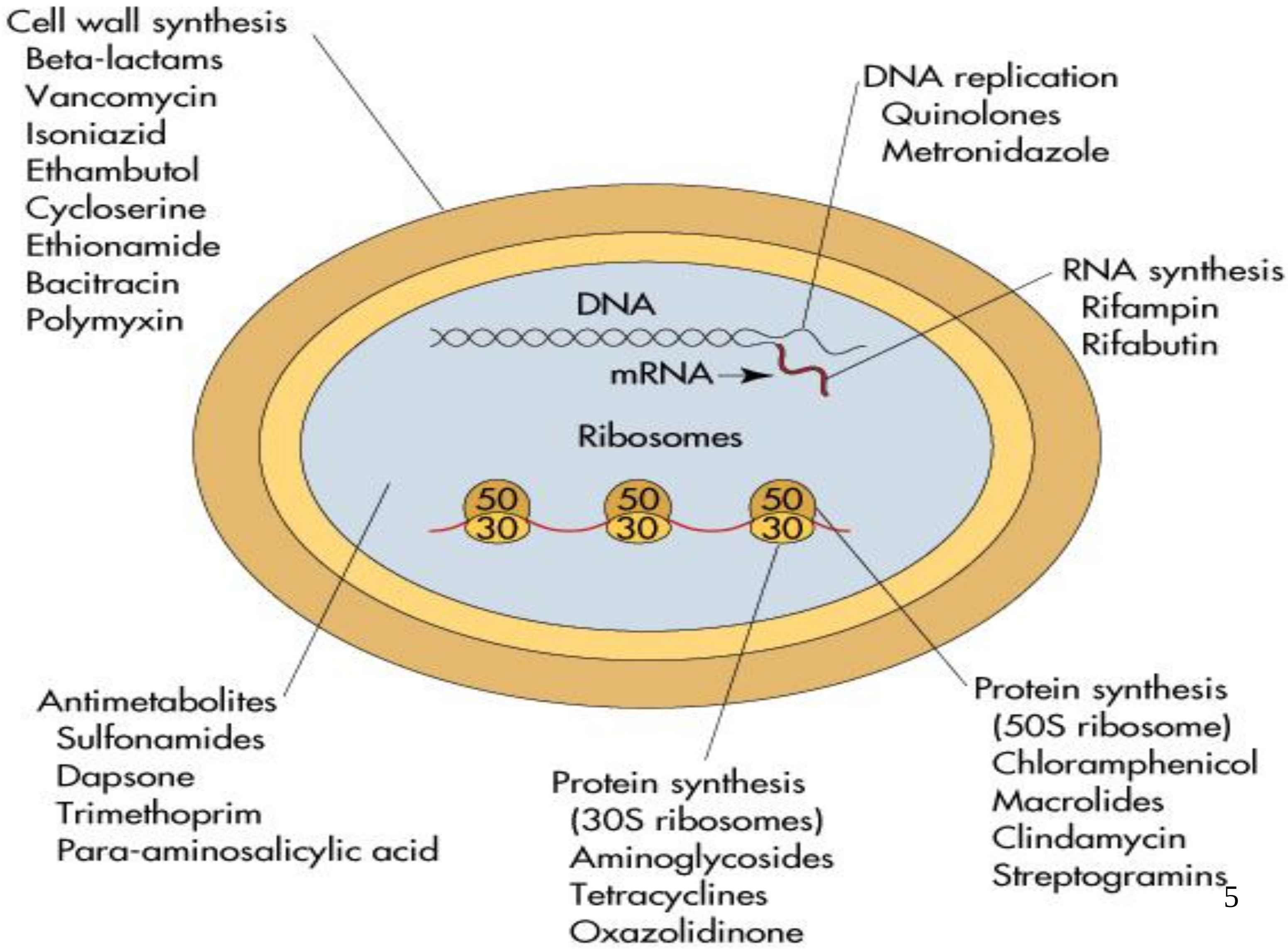
  bacteria

  fungi

  actinomycetes

- **suppress growth / kill other microorganisms**

What** are main targets of **Antibiotics?



Mechanism of Action

- **Agents that inhibit synthesis of bacterial cell walls**

Penicillins & cephalosporins, Vancomycin

- **Agents that act directly on the cell membranes of the microorganisms**

  Polymixin, Polyene antifungal agents, Alter cell membrane.

- Agents that affect the function of 30S or 50S ribosomal subunits to cause a reversible inhibition of protein synthesis
- Bacteriostatic drug

Chloramphenicol, Tetracyclines, Erythromycin, Clindamycin, Pristinamycins

-Agents that bind to 30S ribosomal subunit & alter protein synthesis, which eventually leads to cell death Aminoglycosides

- Agents that affect bacterial nucleic acid metabolism.

  Rifamycins which inhibit RNA polymerase

  Quinolones which inhibit topoisomerases

- **Anti-metabolites**

  including trimethoprim & sulphonamides

- **Antiviral agents**

  Nucleic acid analogues,

  Non-nucleoside reverse transcriptase inhibitors,

  Inhibitors of viral enzymes

TYPE OF ACTION

1- Bacteriostatic Agents

Sulphonamides, Tetracyclines, Chloramphenicol Erythromycin. Ethambutol

2 - Bactericidal Agents

Penicillins/Cephalosporins/Carbapenems

Aminoglycosides/Rifampin

- **Isoniazid**
- **Pyrazinamide**

Cephalosporins/Vancomycin/Nalidixic acid

Ciprofloxacin/Metronidazole/Cotrimoxazole

SPECTRUM Of ACTIVITY

Narrow spectrum

Penicillin G

Streptomycin

Broad spectrum

Tetracyclines

Chloramphenicol

Source of antibiotics

- **Fungi**
  - Penicillin, Griseofulvin, Cephalosporin
- **Bacteria**
  - Polymyxin B, Colistin, Bacitracin, Aztreonam.
- **Actinomycetes**.
  - Aminoglycosides, Macrolides, Tetracyclines, Polyenes, Chloramphenicol

Resistance

of

Antibiotics

Bacterial resistance to ANTIMICROBIAL AGENTS

- **3 general categories**

  I - **Drug does not reach its target**

  II - Drug is not active

  III - Target is altered

I - Drug does not reach its target

Porins

- Absence/mutation
- Reduce drug entry
- Reduced effective drug concentration at the target site.

Efflux pumps

- Transport drugs out of the cell
- Resistance to tetracyclines & β-lactam antib

II - Inactivation of Drug

- Second general mechanism of drug resistance

  β-lactam antibiotics - β-lactamase

  Aminoglycosides-Aminoglycoside modifying enzymes

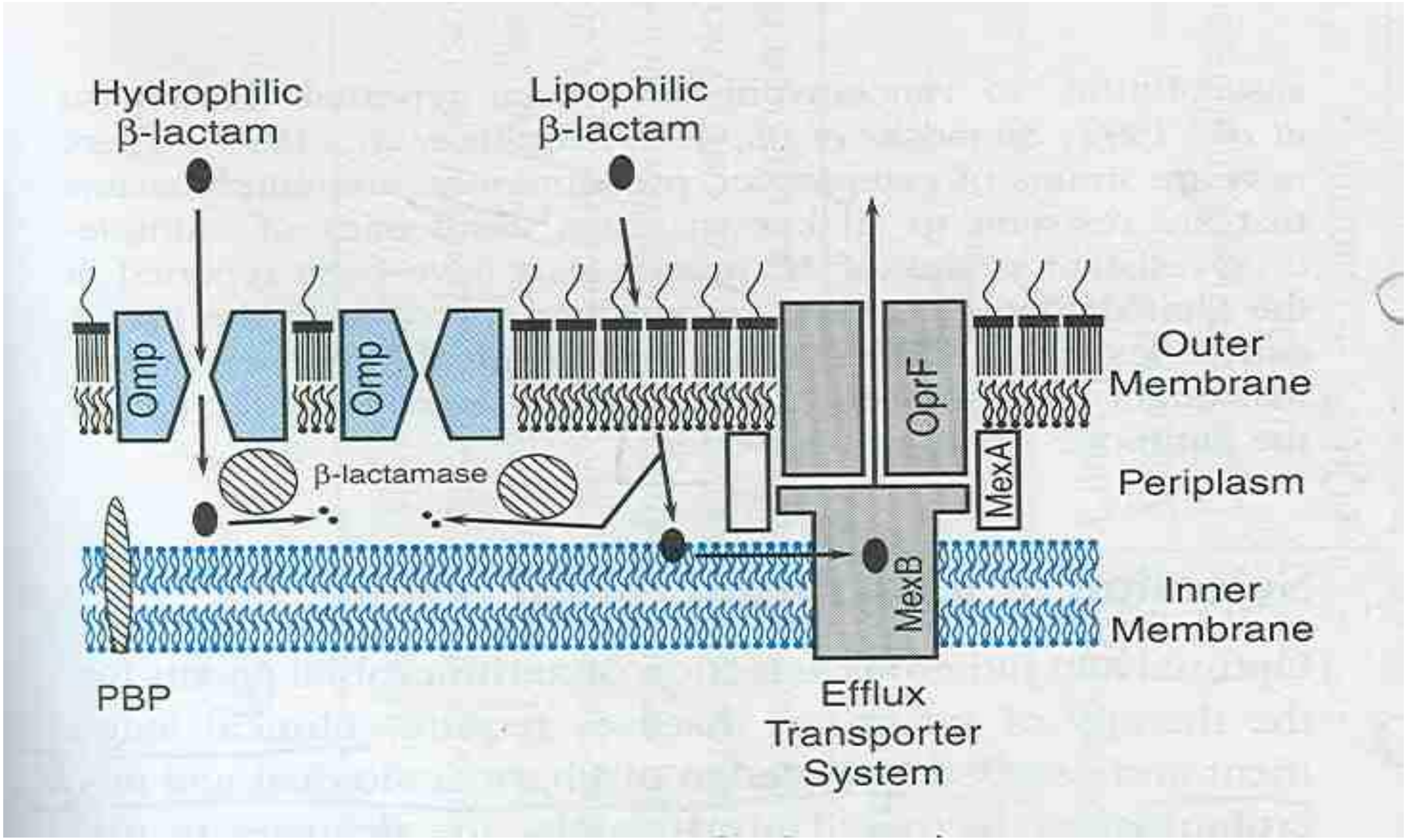
- **Variant:** failure of bacterial cell to convert an inactive drug to its active metabolite. Resistance to INH in mycobacterium TB

III - Alteration of the Target

- **Mutation** of natural target
- **Target modification**

The new target does not bind the drug for native target. Resulting in resistance to antibiotic.

Components mediating resistance to β – lactam antibiotics in pseudomonas aeruginosa


Hydrophilic
β-lactam
Lipophilic
β-lactam
Omp
Omp
OprF
Outer
Membrane
β-lactamase
MexA
Periplasm
MexB
Inner
Membrane
PBP
Efflux
Transporter
System

- β –lactam antibiotics hydrophilic
- Must cross outer membrane barrier of the cell via **outer membrane protein (Omp)** channel or **porins**
- **Mutation/missing/deleted**
- Drug entry slow or prevented.

- **β - lactamase** concentrated between the inner & outer membrane in the periplasmic space
- constitutes an enzymatic barrier
- Drug destroyed
- Effective concentration not achieved
- **Target: PBP penicillin binding protein**
- **Low affinity for drug**
- **Altered**

- **Efflux transporter**
- **Mex A, Mex B & Opr F**
- Pumps the antibiotic across the outer membrane
- Reduced intracellular concentration of active drug

Mutations

- May occur in
- Target protein
- Drug transport protein
- Protein important for drug activation
- **Random events**
- **Survival advantage upon re-exposure to the drug**

- Resistance is acquired by **horizontal transfer** of resistance determinants from a donor cell, often of another bacterial species by
- **Transduction**
- **Transformation**
- **Conjugation**
- **Insatiable need for new ntibiotics**

- Emergence of antibiotic resistance in bacterial pathogens both nosocomially & in the community setting is a very serious development that threatens the end of antibiotic era.
- Responsible approach to the use of antibiotics
- That are now available & new agents that might be developed in future
- Is essential
- If the end of antibiotic era is to be averted.

CROSS RESISTANCE

CROSS RESISTANCE

- Acquisition of resistance to one AMA conferring resistance to another antimicrobial agent to which the organism has not been exposed is called **cross resistance**
- Seen b/w chemically or mechanistically related drugs.

- Resistance to one sulphonamide means resistance to all others
- Resistance to one tetracyclines means insenstivity to all others
  - **Complete cross resistance**
- Resistance to one aminoglycoside may not extend to others, Gentamycin resistant strains may respond to amikacin.
  - **partial cross resistance**
- Sometimes unrelated drugs show partial cross resistance, e.g. Tetracyclines & Chloramphenicol

PREVENTION

DRUG

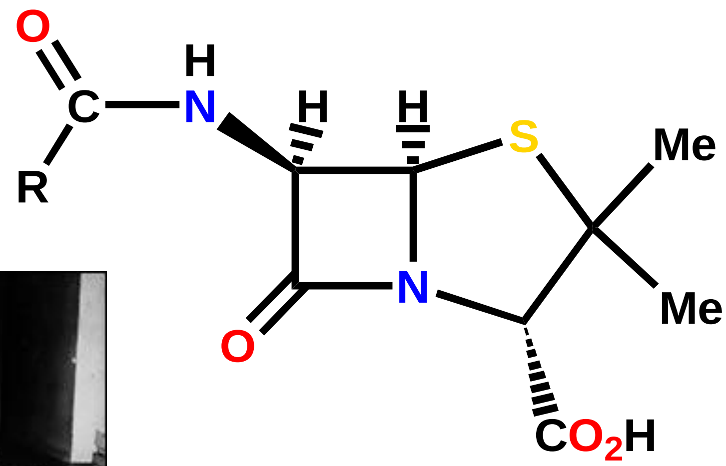
RESISTANCE

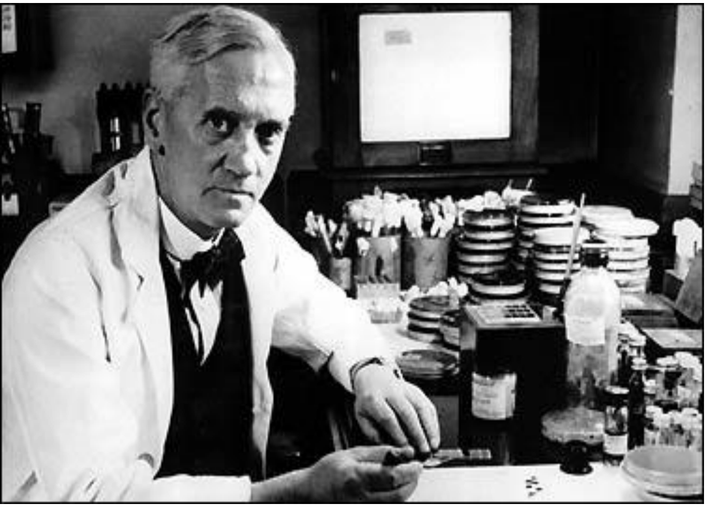
Prevention Drug Resistance

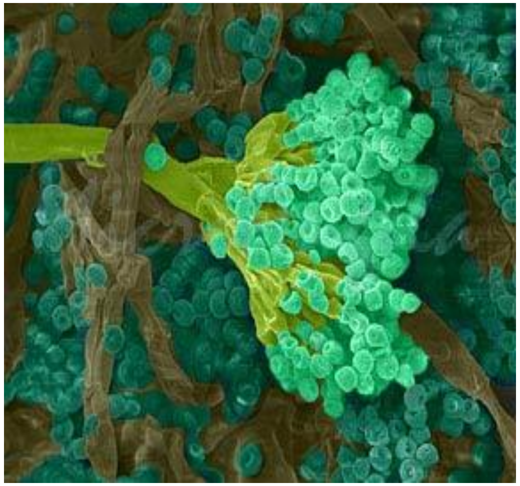
- Use of AMAs should not be:

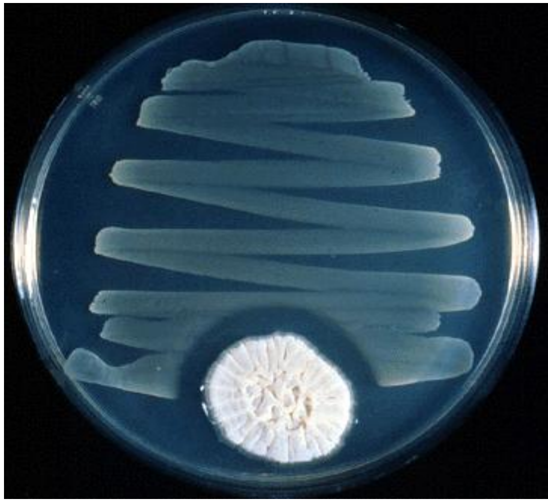
  indiscriminate. inadequate . unduly prolonged
- Use **rapidly acting & narrow spectrum** (Selective) AMA whenever possible.
- **Combination AMA**
  - whenever prolonged therapy is undertaken. Tuberculosis, SABE
- Infection by organism notorious for developing resistance Staph, E. Coli, M. Tuberculosis must be **treated intensively**.

Penicillin's



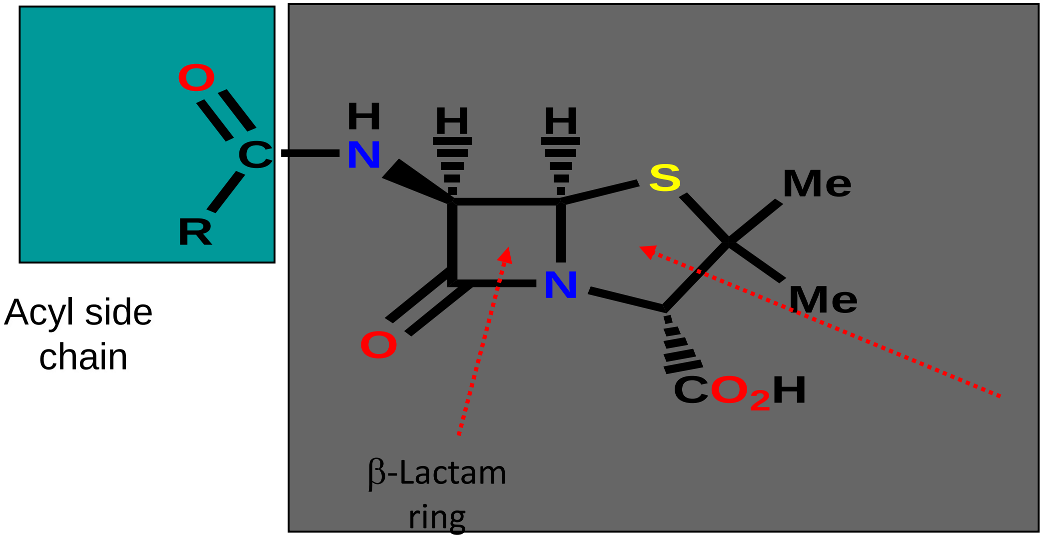






Penicillin was discovered in 1928 by Alexander Fleming, who noticed that one of his experimental cultures of staphylococcus was contaminated with mold, which caused the bacteria to lyse. Since mold belonged to the family *Penicillium, he named the antibacterial* substance penicillin.

About a decade later, a group of researchers at Oxford University isolated a crude substance made up of a few low-molecular substances, which were penicillin's (F, G, K, O, V, X).

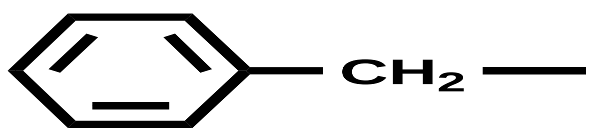


Acyl side chain

6-Aminopenicillanic acid (6-APA)

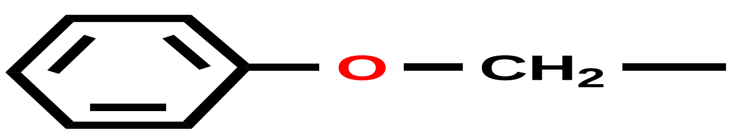
Thiazolidine ring

R =

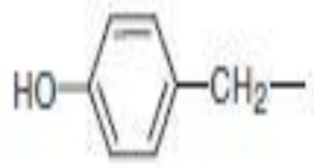


Benzyl penicillin (Pen G)

R =



Phenoxymethyl penicillin (Pen V)



Penicillin X
p-Oxybenzylpenicillin

$CH_3CH_2CH{=}CH{-}CH_2{-}$

Penicillin F
2-Pentenylpenicillin

$CH_3(CH_2)_5CH_2{-}$

Penicillin K
p-Heptylpenicillin

$CH_2{=}CH{-}CH_2{-}S{-}CH_2{-}$

PenicillinO
Allylmercaptomethylpenicillin

Classes of Penicillin's

1- Natural Penicillin's (Fermentation derived penicillin's)

Penicillin G ,Penicillin V

2-Semi synthetic Penicillinase Resistant Penicillin's (parenteral) Methicillin, Nafcillin, Isoxazolyl Penicillins (Cloxacillin / Dicloxacillin / Oxacillin / Flucloxacillin)

3- Amino penicillin's (Semisynthetic penicillinase sensitive broad spectrum penicillin's) Ampicillin , Amoxicillin

4- Carboxy penicillin's (Synthetic penicillin's sensitive to broad spectrum, Parenteral penicillin's) Carbencillin, Carbencillin phenyl, Carbencillin indanyl. Ticarcillin

5- Ureidopenicillins

Piperacillin , Mezlocillin, Azlocillin

Mechanism of action
Bacterial cell wall synthesis

•Penicillin inhibits final crosslinking stage of cell wall synthesis

•It reacts with the transpeptidase enzyme to form an irreversible covalent bond

•Inhibition of transpeptidase leads to a weakened cell wall

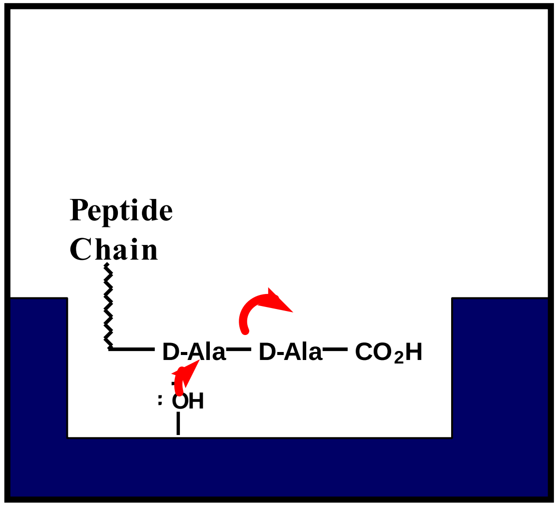
•Cells swell due to water entering the cell, then burst (lysis)

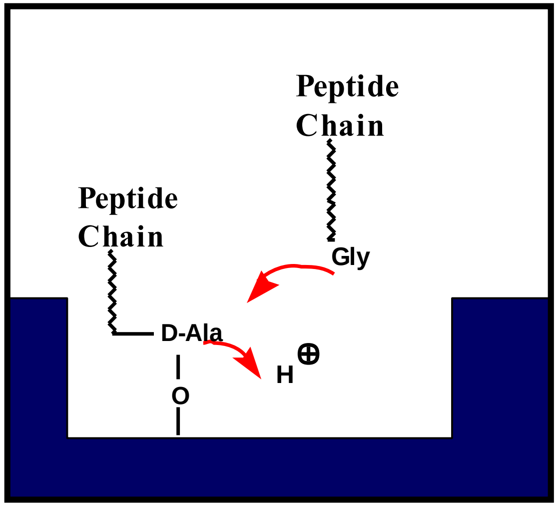
•Penicillin possibly acts as an analogue of the L-Ala-g-D-Glu portion of the pentapeptide chain. However, the carboxylate group that is essential to penicillin activity is not present in this portion

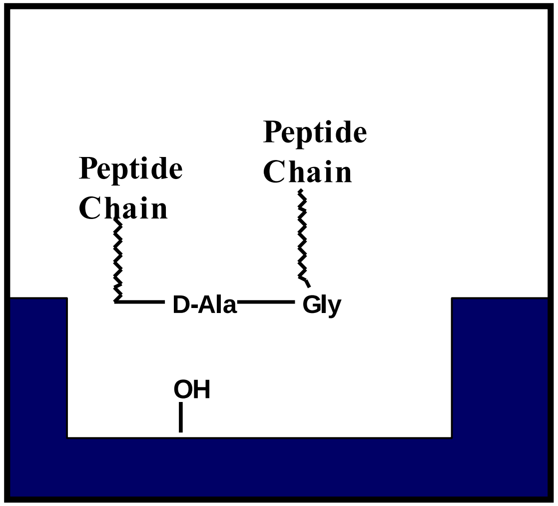
Alternative theory

Penicillin mimics D-Ala-D-Ala.

Normal Mechanism

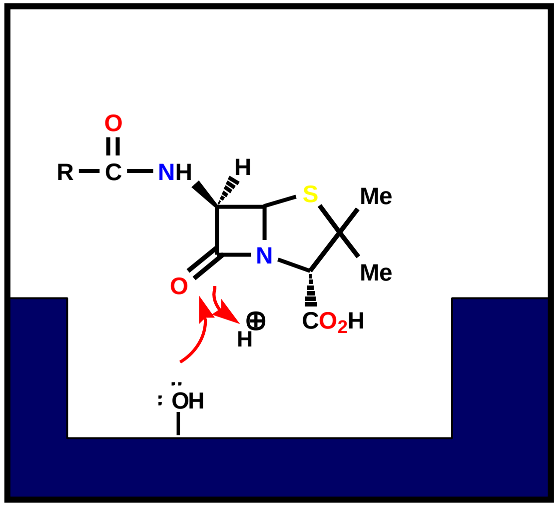


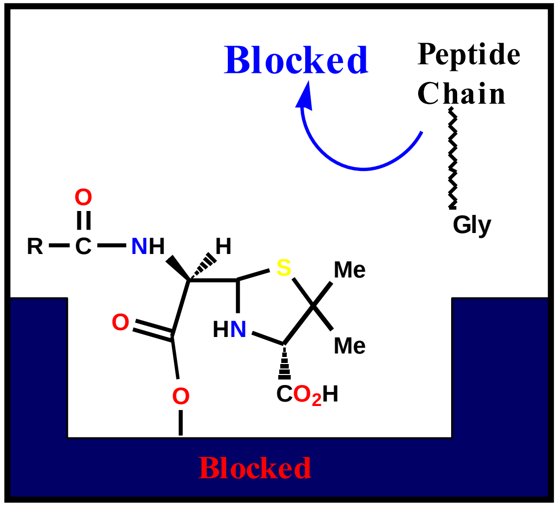


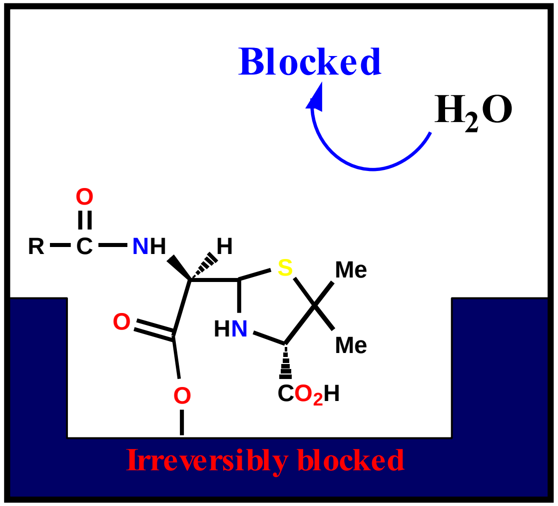


Alternative theory
Penicillin mimics D-Ala-D-Ala.

Mechanism inhibited
by
penicillin







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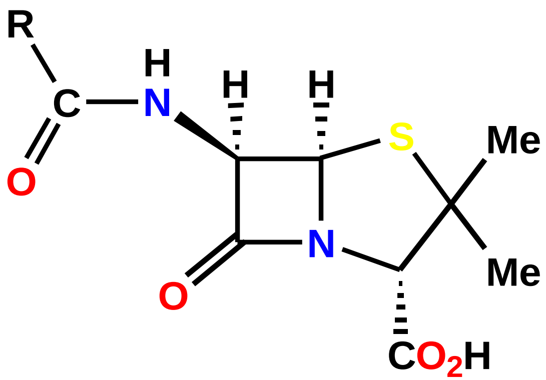
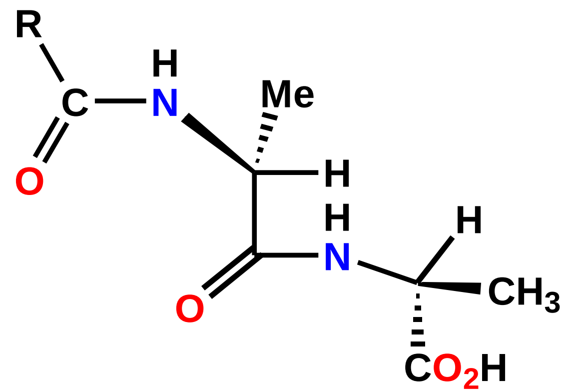
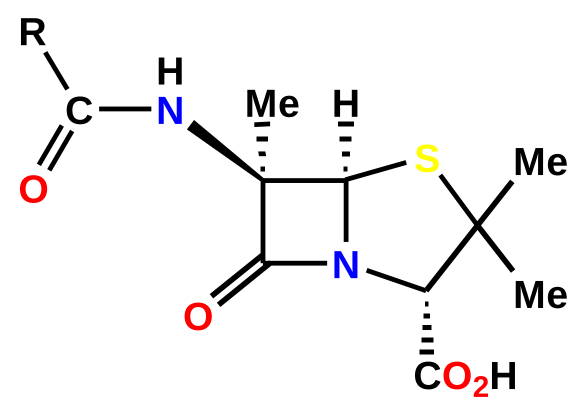


Penicillin

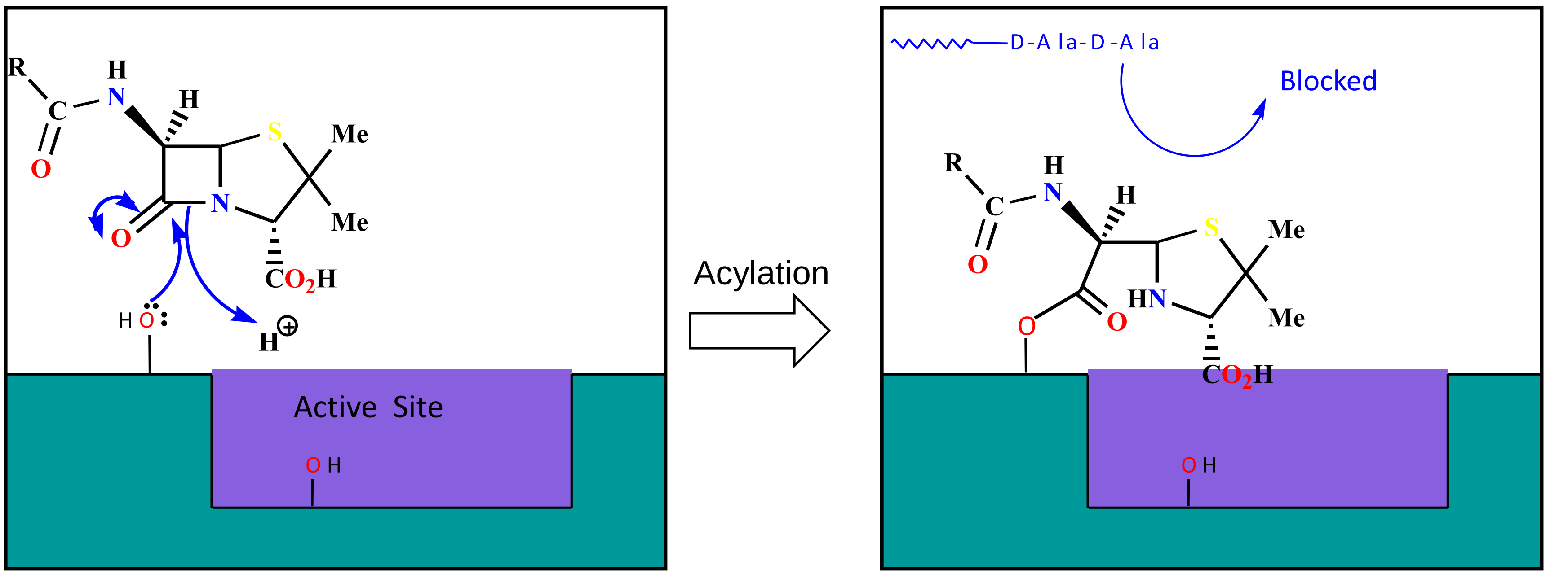


Acyl-D-Ala-D-Ala

But 6-methylpenicillin is inactive despite being a closer analogue



Penicillin may act as an ‘umbrella’ inhibitor



Penicillin's advantages and disadvantages

penicillin's advantages

1- Bactericidal against sensitive strains.

2- Relatively nontoxic.

3- Have excellent tissue penetration.

4- Efficacious in the treatment of infections.

5- Relatively inexpensive in comparison with other antibiotics.

6- Newer penicillin's are resistant to stomach acid, such as penicillin v, or have a broader spectrum, such as Ampicillin and Amoxicillin.

Penicillin's disadvantages:-

1- Acid liability - most of these drugs are destroyed by gastric acid.

2- Short duration of action - because of this short half-life, the penicillin's must be at short intervals, usually every 4 hours.

3- Lack of activity against most gram-negative organisms.

4- Drug hypersensitivity - about 10 % of population has allergy.

5- Many patients experience GI upset.

6- Painful if given intramuscularly.

COMMON SIDE EFFECTS OF PENICILLINS

Nausea

Bronchospasm

Giddiness

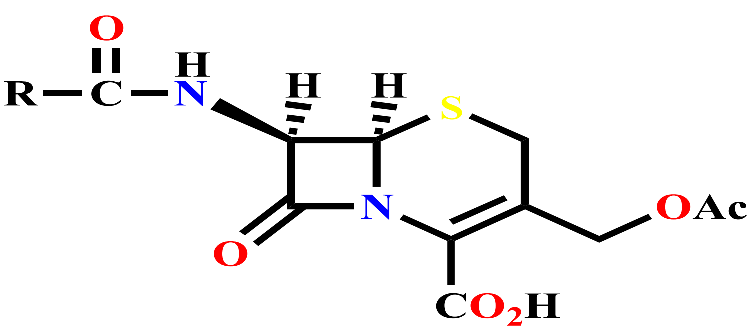
Headache

Angioedema

Skin rashes

Vomiting

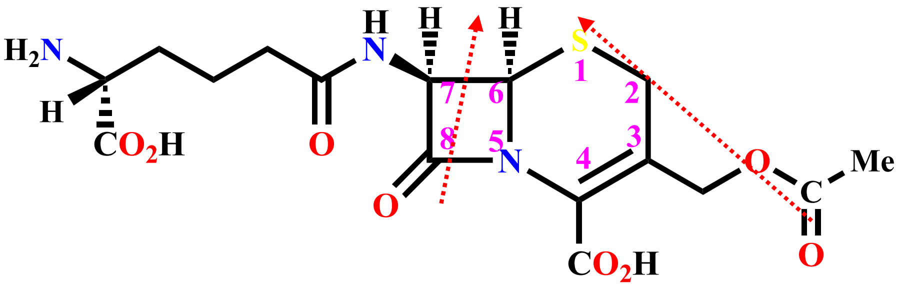
CEPHALOSPORINS



- Cephalosporin antibiotics
  - derived from “cephalosporin C”
  - obtained from fungus Cephalosporium acremonium
- Cephalosporin nucleus Consists of dihydrothiazine ring fused to a β–lactam ring
  - 7-aminocephalosporanic acid
- 7-aminocephalosporanic acid has been modified by addition of different side chains to create a whole family of cephalosporin antibiotics.
- these have been conventionally divided into 5 generations

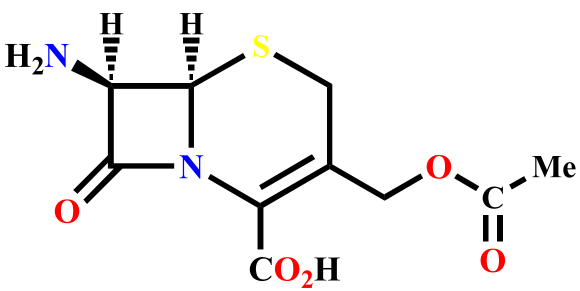
Structure of Cephalosporin C

7-Aminoadipic side chain



β-Lactam ring

Dihydrothiazine ring



7-Aminocephalosporinic acid (7-ACA)

Properties of Cephalosporin C

Disadvantages

- Polar due to the side chain - difficult to isolate and purify
- Low potency - limited to the treatment of urinary tract infections where it is concentrated in the urine
- Not absorbed orally

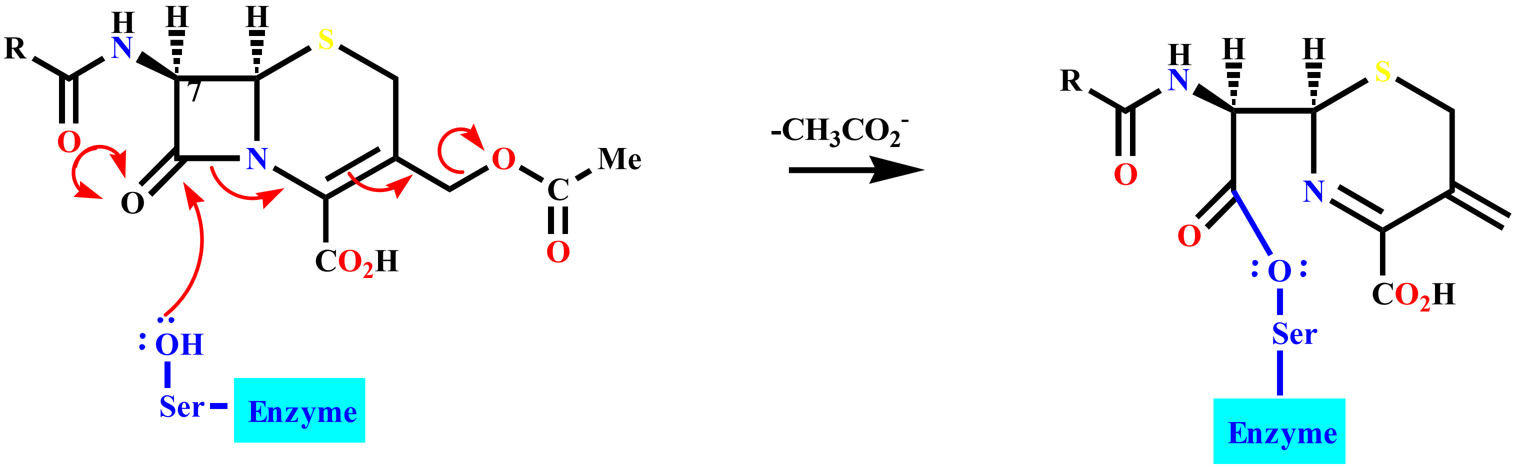
Advantages

- Non toxic
- Lower risk of allergic reactions compared to penicillins
- More stable to acid conditions
- More stable to β-lactamases
- Ratio of activity vs Gram -ve and Gram +ve bacteria is better

Conclusion

- Useful as a lead compound

Mechanism of Action



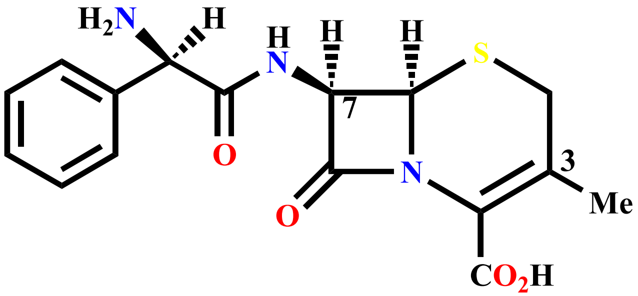
- The acetoxy group acts as a good leaving group and aids the mechanism

Mechanism of action

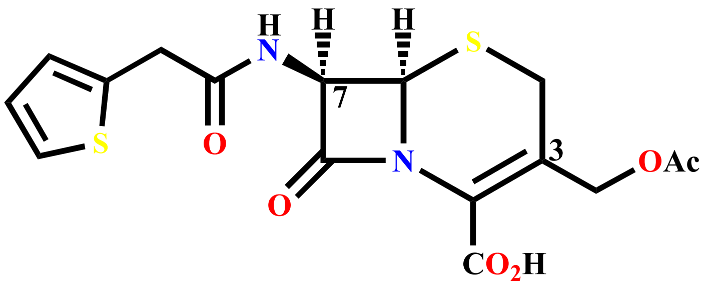
- **All cephalosporin's are bactericidal.**
- **MOA same as penicillin- Inhibit cell wall synthesis in a manner similar to penicillins**
- **Bind to different proteins than those which bind penicillin. PBP-1 & PBP-3**
- **Inhibition of transpeptidation**
- **Imperfect cell wall**
- **Osmotic drive**
- **Activation of autolysin enzymes**
- **Lysis of bacteria**
- **BACTERICIDAL**

First-generation agents

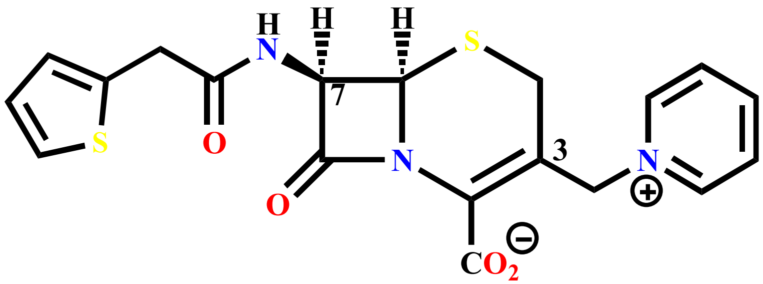
- Cephalexin (O)



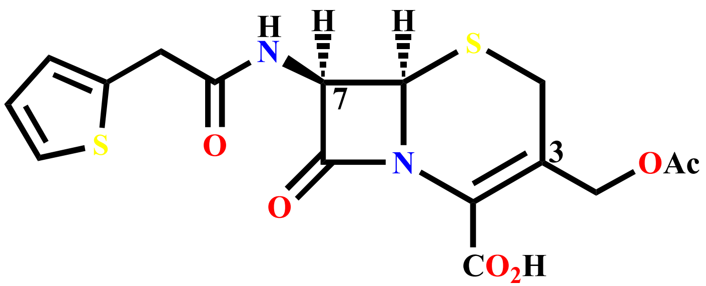
- Cephalothin



- Cephaloridine



- Cefalothin



First Generation Cephalosporins

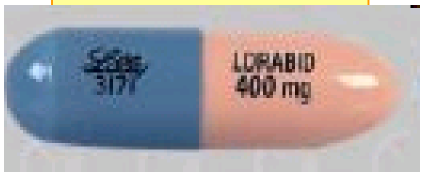
- **Generally lower activity than comparable penicillins**
- **Better range of activity than comparable penicillins**
- **Best activity is against Gram-positive cocci**
- **Useful against some Gram negative infections**
- **Useful against *S. aureus* and streptococcal infections when penicillins have to be avoided**
- **Poorly absorbed across the gut wall (except for 3-methyl substituted cephalosporins)**
- **Most are administered by injection**
- **Resistance has appeared amongst Gram negative bacteria (presence of more effective β-lactamases)**

- **Exhibit good activity against gram-positive**
- **bacteria but modest activity against gram negative organisms.**
  - Most gram-positive cocci
  - Strepto,
  - Pneumo,
  - Methicillin sens. Staph. are susceptible to first-generation cephalosporins
- **Modest activity** against E. coli, K. pneumoniae & Proteus mirabilis

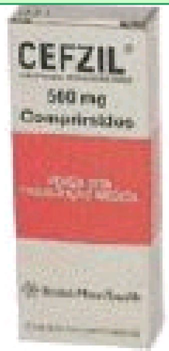
Most oral cavity **anaerobes** are sensitive. However, the ***Bacteroides fragilis*** group is resistant.

First generation Cephalosporin's

Loracarbef



Cefprosil



Cefaclor

Cefazolin

Cephradine

Cephalexin

Cefoxitin Na

Cefadroxil

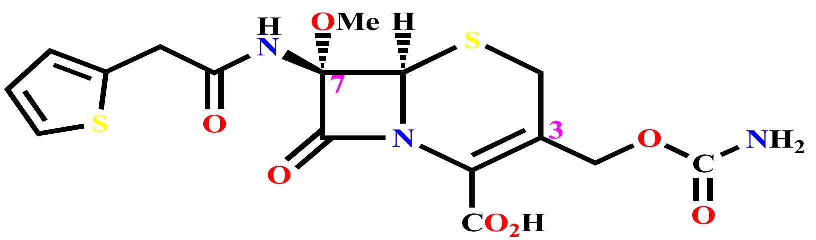
Cefoperazone

Cefuroxime Na

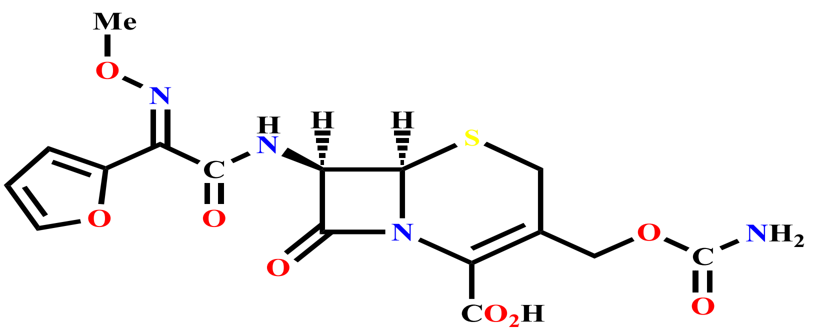
Cefixime

Second-generation agents

- Cefaclor
- Ceforanide
- Cefuroxime acetil
- Cefuroxime
- Cefoprozil
- Cefamandole
- Cefoxitin
- Cefotetan



Cefoxitin

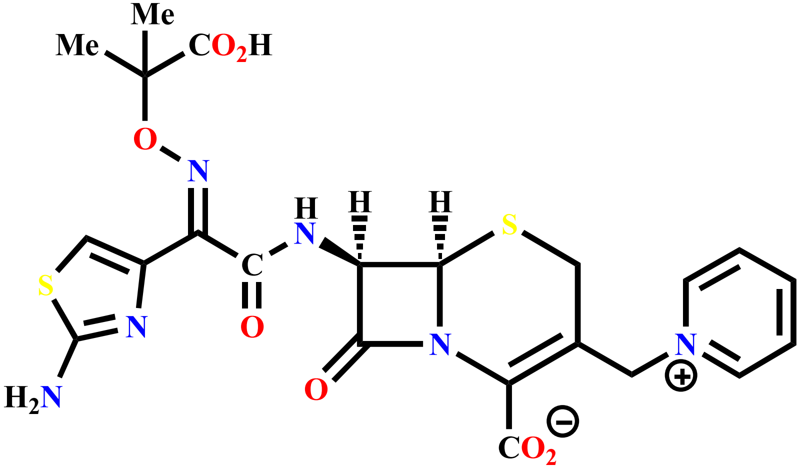


Cefuroxime

- Exhibit some what increased activity against gram negative organisms,
  - but much less active than third generation agents.
- Less active against gram positive cocci & bacilli compared to first gen. drugs.
- **Use declined**
- Clinically replaced by 3rd & 4th generation drugs .

Third-generation agents

- Cefotaxime
- Ceftriaxone
- Cefdinir
- Cefibuten
- Cefpodoxime
- Ceftizoxime
- Ceftazidime
- Cefoperazone



Ceftazidime

- Highly augmented activity against gram-negative organisms
- Less active than first generation agents against gram positive cocci & anaerobes.
- All are highly resistant to β-lactamases from gram negative bacteria.
- Some inhibit psuedomonas as well; **ceftazidime**, **cefoperazone**
- Some members of this group have enhanced ability to cross the blood-brain barrier eg. *Ceftriaxone* and are effective in treating meningitis caused by pneumococci, meningococci, H. influenzae and susceptible gram negative rods.

Third generation Cephalosporin's

Cefcapene
Cefdaloxime
Cefdinir (Omnicef, Cefdiel)
Cefditoren
Cefetamet

Cefixime (Suprax)
Cefmenoxime
Cefodizime
Cefotaxime (Claforan)
Cefpimizole

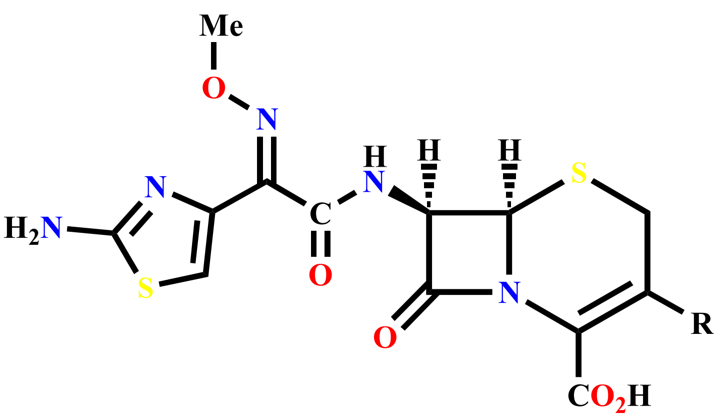
Cefpodoxime (Vantin,)
Cefteram
Ceftibuten (Cedax)
Ceftiofur

Ceftiolene
Ceftizoxime (Cefizox)
Ceftriaxone (Rocephin)

Fourth-generation agents

- **Cefpirome P/E (im/iv)**
- **Cefepime P/E (iv)**
- **Cefozopran P/E**

Oximinocephalosporins



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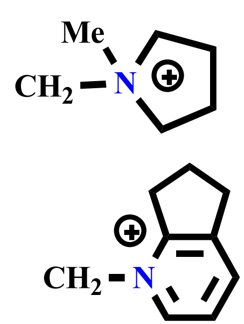


Cefipime

Cefpirome

- Highly active against G –ve organisms
- Similar to third gen drugs for g +ve bacteria
- The fourth generation drugs comparable to third generation but more resistant to hydrolysis by **β-lactamases.**
  - Effective against bacterial infections resistant to earlier drugs

Fifth-generation agents

- **Ceftobiprole**
- **Ceftaroline**
- Active against,

  g +ve cocci especially **MRSA**
- **penicillin resistant S. pneumoniae**
- and **enterococci**

Resistance

- Impermeability to the antibiotic.
  - to reach its site of action
- Alteration in PBPs -antibiotics bind with low affinity
- Elaboration of β**-lactamases;** that can hydrolyze the β-lactam ring and inactivate the cephalosporin (**most prevalent mech**)

Adverse reactions

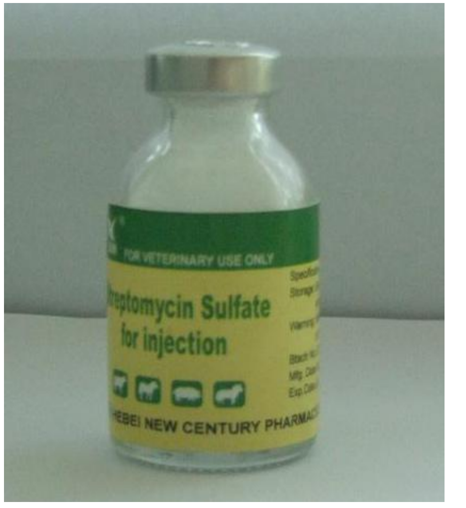
- **Pain** after im injection
- **Thrombophlebitis** of injected vein.
- **Diarrhoea** more common with
  - oral Ceferadine
  - P/E Cefoperazone (**Banned**)
- **Hypersensitivity reactions**
  - Identical to penicillins, incidence is lower.
  - shared β-lactam structure
  - Allergic to penicillins- allergic to cephalosporins. CROSS-REACTIVITY.
- Rashes, frequent, anaphylaxis, angioedema, asthma, urticaria have also occurred.

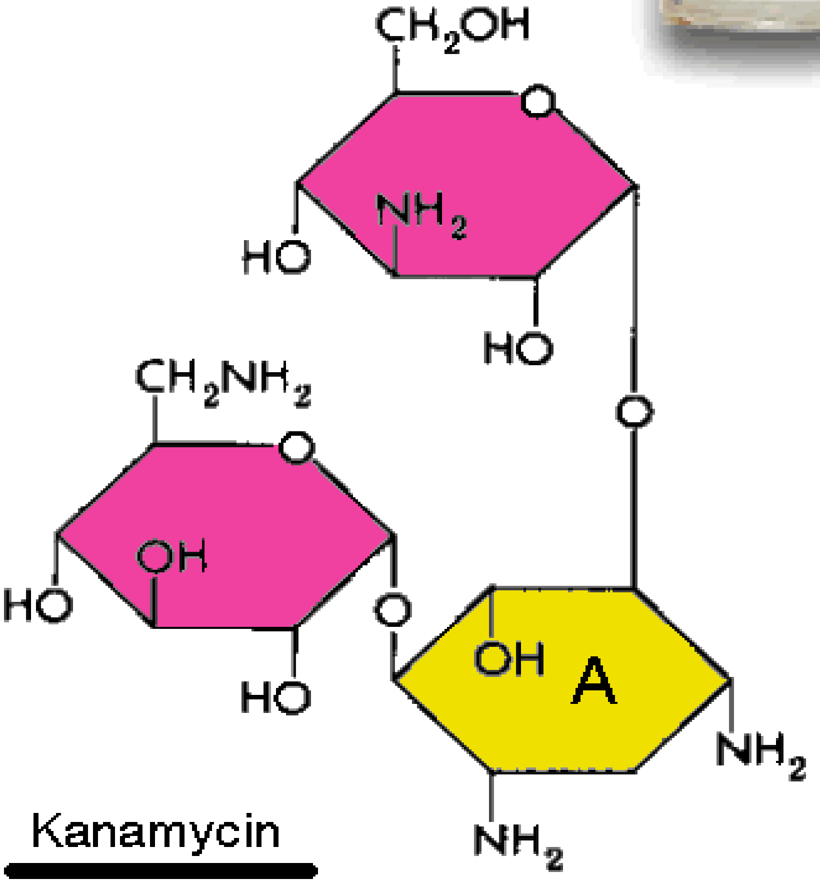
- Cephalosporins potentially **nephrotoxic drugs**
  - Cephaloridine (**withdrawn**) RTN
  - Cephalothin (**withdrawn**) Acute tubular necrosis
- Serious **bleeding**
  - Cefoperazone(**Banned**),
  - Moxalactam(**Banned**).
  - Due to hypoprothrombinemia.
- Intolerance to alcohol

  Disulfiram like reaction
  - Cefamandole (**Banned**)
  - Cefotetan (**Banned)**
  - Moxalactam (**Banned**)
  - Cefoperazone (**Banned**)

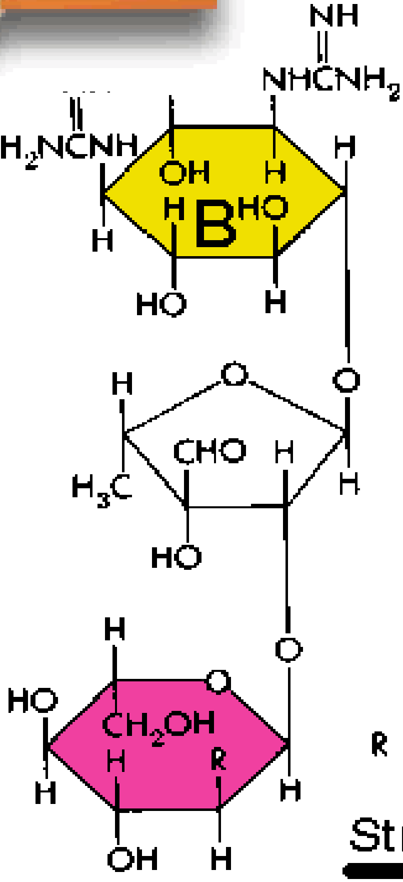
Aminoglycoside Antibiotics

■ Structure:





Kanamycin



(streptidine)

R = CH_3NH

Streptomycin

Common properties of aminoglycosides

- **First member Streptomycin discovered by Waksman in 1944**
- **Natural and semi-synthetic antibiotics**
- **Produced from Actinomycetes**
  - **Those obtained from Streptomyces – Have suffix mycin (eg. Streptomycin)**
  - **Those obtained from Micromonospora – Have suffix micin (eg. Gentamicin,)**

Structure characterized by

- **Two aminosugars joined to**
- **One aminocyclitol moiety by**
- **Glycosidic (-O-) bond**

In most of members aminoacyclitol moiety is 2-Deoxystreptamine .

In streptomycin the aminocyclitol is Streptidine.

Aminosugar -O- 2-Deoxystreptamine -O- Aminosugar

General character of Aminoglycosides group

- **Formulations are Sulfate or hydrochloric salts**
- **Formulations are water soluble and stable**
- **Highly polar basic drugs.**
- **Ionize during dissolution**
- **Distribution inside the cells is minimal**
- **Penetration through BBB is minimal**
- **Least metabolized by hepatic enzymes**
- **Excretion is mainly renal (unchanged form, through glomerular filtration)**

General character of Aminoglycosides

- Bactericidal in nature
- More active in alkaline pH
- MOA is by interfering with protein synthesis
- Attach with 30S ribosomal subunit (ATT)
- Concentration dependent (PAE)
- Mainly gram negative (plus tuberculosis by streptomycin, Kanamycin, Amikacin)
- Cross resistance is partial
- Therapeutic index is narrow

Have NONE side effects :-

Nephrotoxic, Ototoxic, Neuromuscular blockage

Members

- ***Amikacin***
- ***Streptomycin***
- **Sisomicin**
- **Spectinomycin**
- ***Kanamycin***
- **Ispepamycin**
- **Netilmicin**
- ***Gentamicin***
- ***Tobramycin***
- **Ribostamycin**
- **Arbekacin**
- **Bekanamycin**
- **Dibekacin**
- **Hygromycin**
- **Verdamicin**
- **Astromicin**
- **Paromomycin**

ASKING Truth IS Great TASK

Mechanism of action

- **Bactericidal (Gram Negative, No action on Anaerobes)**
- **Initial entry of Aminoglycosides through bacterial cell wall to periplasmic space**
  - **Through porin channels by passive diffusion (1)**
- **Later on further Entry across cytoplasmic membrane is carrier mediated (linked to electron transport chain, energy and oxygen dependent)**
  - **Active transport (2)**
- **Advantage of adding Beta lactams**
  - **Beta Lactam antibiotics weaken the bacterial cell wall**
  - **Facilitate passive diffusion of Aminoglycoside.(Synergism)**

- **Penetration is dependent on**
  - **Maintenance of polarized membrane**
  - **Oxygen dependent active process**
    - **Not active in absence of oxygen**
    - **Not effective against anaerobes**
    - **Not effective in presence of big abscess**
  - **pH alteration. Alkalization favors penetration into cell**

- **Prevent polysome formation (accumulation of nonfunctional monosomes)**
- **Inside the bacterial cell Aminoglycoside bind with 30S ribosome subunit (or at the interface of 30S and 50S)**
- **Inhibit formation of initiation complex**
- **Inhibit protein synthesis**
- **Misreading of mRNA Codon**
- **Entry of wrong amino acid in the chain**
- **Formation of wrong peptide chain**

(Check the growth of bacteria, Bacteriostatic)

How Cidal action is achieved

- Defective proteins incorporated in cell membrane.
- Due to secondary changes in the integrity of bacterial cell membrane. (Increase permeability for ions, amino acids, proteins- Leading to leaking of these out side)
- Bonus of incorporation of defective protein in cell membrane
- More entry of antibiotic occurs in to the cell. Further increasing affectivity
- Alterations in ribosomal proteins.
- Decreased permeability to the antibiotic.
- Induction of bacterial enzymes that inactivate these drugs.

Death Of Bacteria

Tetracycline's

Antibiotics

a) Naturally occurring:

1-tetracycline 2-chlortetracycline

3-oxytetracycline 4-demeclocycline

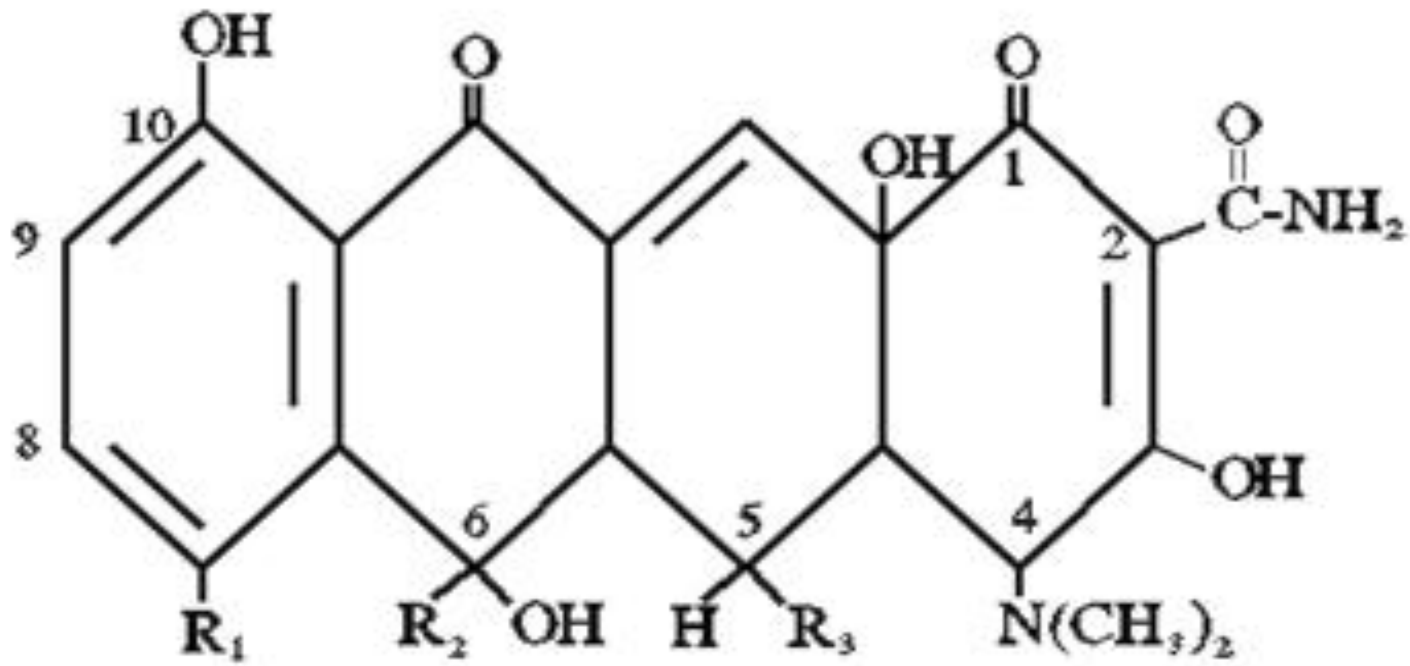
b) Semisynthetic occurring:

1-doxycycline 2-minocycline

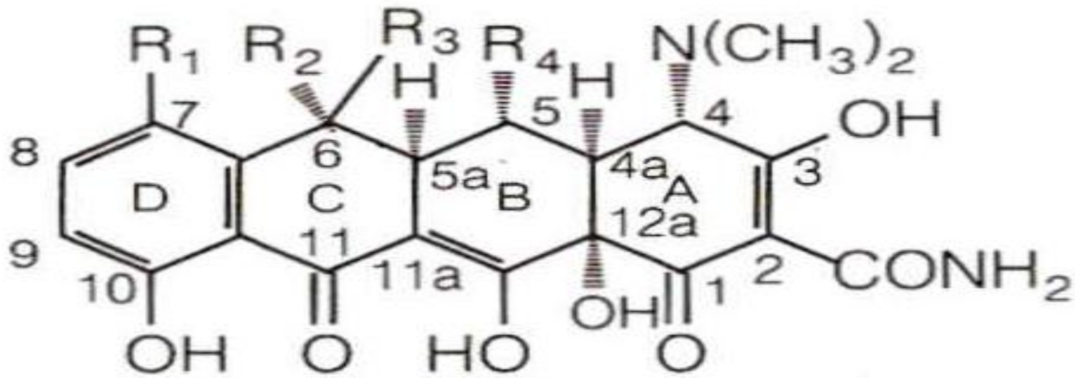
3-meclocycline 4-lymecycline

5-methacycline 6-rolitetracycline

- **Structure:**



Tetracycline Nucleus



	R5	R4	R3	R2	R1.
Chlortetracycline	H	H	OH	CH3	Cl
Oxytetracycline	H	OH	OH	CH3	H
Tetracycline	H	H	OH	CH3	H
Demethylchlortetracycline	H	H	OR	H	Cl
Rolitetracycline	+	H	OH	CH3	H
Metacycline	H	OH	-	CH2	H
Doxycycline	H	OH	H	CH3	H
Minocycline	H	H	H	N(CH3)2	

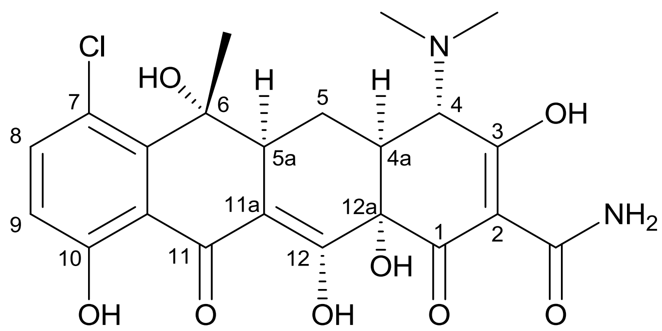
-a broad-spectrum antibiotics.

-It is commonly used to treat acne, infection, and other infections caused by bacteria.

-The first of these compounds was chlortetracycline followed by oxytetracycline and tetracycline.

Tetracyclines

- Are bacteriostatic antibiotics having broad spectrum of activity.
- Isolated from Streptomyces bacteria.
- First one isolated was chlortetracycline (1948).



Chlortetracycline

- They inhibit protein biosynthesis by binding to 30s ribosomal subunit and prevent aminoacyl tRNA from binding to the A-site.

Mechanism of action

- Tetracyclines could inhibit protein synthesis in human, but they normally can not penetrate the mammalian cell membrane.
- The transport of tetracycline into the cell (especially the gram –ve bacteria) needs:
  1. a passive diffusion through porines, this process is pH dependent and required proton-driven carrier protein. This protein is only present in bacteria not in human cell.
  2. Active transport: requires Mg^{++} and ATP.
- This is why tetracyclines are quite selective on the bacterial cell.

Mechanism of resistance :

There are three types of tetracycline resistance:

1) Tetracycline efflux.

2) Ribosomal protection.

3) Tetracycline modification.

Clinical uses of tetracycline's

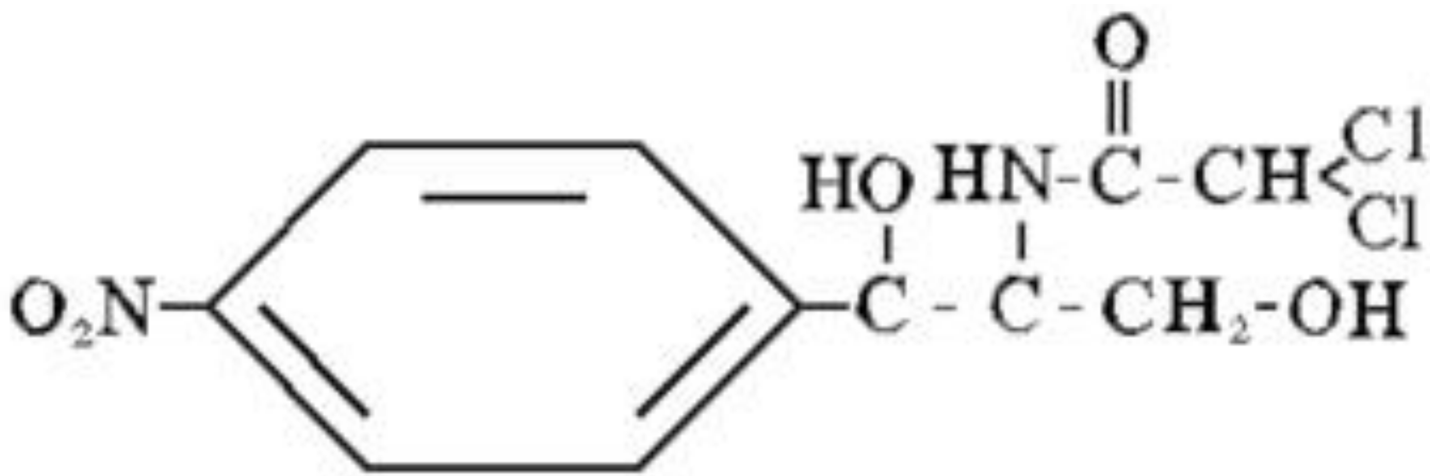
- They have the broadest spectrum of activity, on both gram +ve, gram –ve and atypical bacteria.
- Resistance has been developed rapidly against tetracyclines, as a result of that penicillins have replaced them in many infections, especially the respiratory infections.
- Tetracyclines are still used in rickettsia, Chlamydia, mycoplasma and acne infections.
- Some of them have antiparasitic properties such as the use of Doxycycline in the treatment and prophylaxis of malaria.
- They have bacteriostatic action, not recommended in life threatening infections such as septicemia, endocarditis and meningitis

Clinical uses of tetracycline's

- Tetracyclines should be avoided in children and pregnant women: they bind to the growing teeth and bones…. Lead to tooth discolorations and toxicity in fetus.
- Tetracyclines can be divided according to the duration of action into:
  1. Short acting: chlortetracycline ($t_{1/2}$ = 7hr).
  2. Intermediate acting: tetracycline and demeclocycline ($t_{1/2}$ 10-15hr).
  3. Long acting: Doxycycline and minocycline ($t_{1/2}$ = > 16hrs)

Chloramphenicol

- **Structure:**



- **Mechanism of action**
- Inhibits protein synthesis (50 s subunit)
- **blocks Peptidyl transferase enzyme**
- **prevents formation peptide bound**
- **Prevents protein synthesis**
- **Antibacterial activity**

H. Influenzae	S. typhi
N. Meningitidis	E. coli
S. Pneumoniae	V.cholera
Ricketsiae	Anaerobes- clostridium & B. fragilis

Pharmacokinetics

Rapidly & completely absorbed from GIT 30 % protein bound

Metabolized by liver–glucuronidation Well distributed, including CNS and CSF Excreted in urine

Clinical uses

Limited because of potential toxicities

(a plastic anaemia &circulatory collapse in neonates)

1. Typhoid fever- s. typhi (quinolones are preffered)
2. Meningitis – H.influenzae,N.meningitidis,S.pneumoniae (Ceftriaxone is preffered)
3. Anaerobic infections- B. fragilis (Metronidazole is the drug of choice)
4. Rickettsial infections – Doxycycline is preffered
5. Bacterial conjunctivitis (topical)

Side effects

1.Hypersensitivity- low incidence

May ppt hemolysis in G6PD deficient pts

2. A plastic anaemia (fatal)

3.Grey baby syndrome

4.Suprainfections

5. Interaction with other drugs :

Inhibits liver microsomal enzymes

Phenytoin

Tolbutamide

Chlorpropamide

Anticoagulants

Quinolones

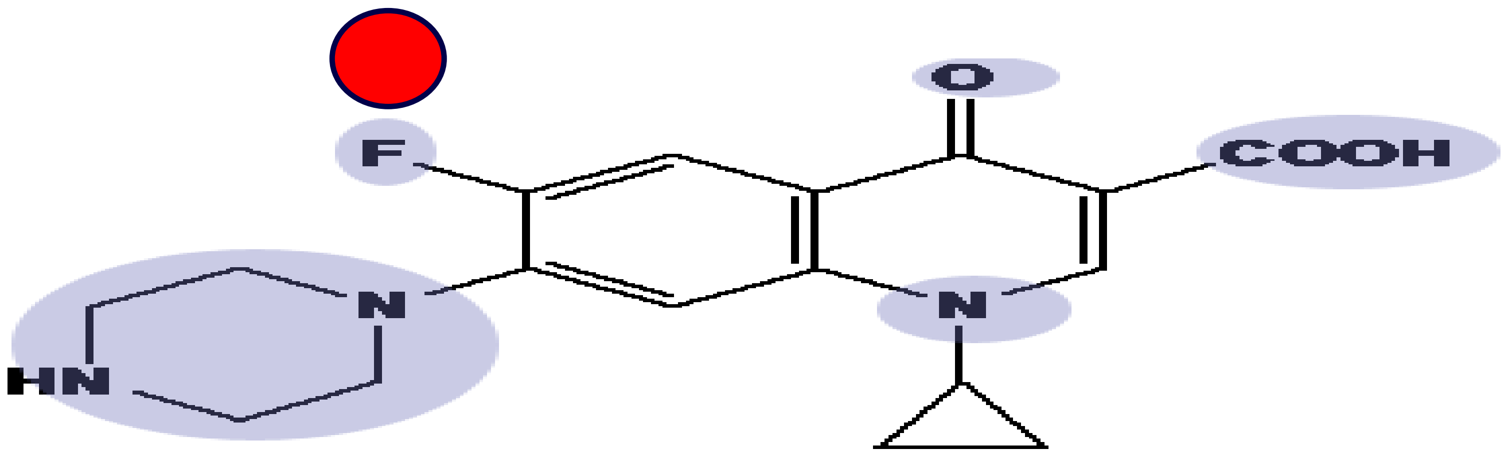
- ✓ Synthetic antimicrobials
- ✓ Bactericidal
- ✓ Primarily gram negative bacteria

- **Quinolones - Antibacterial Spectrum**
- **• 1st generation (quinolones - nalidixic acid):**
- **limited to Gram negative enteric bacteria**
- **(UTIs)**
- **• 2nd generation (fluoroquinolones -**
- **norfloxacin, ciprofloxacin): improved Gram**
- **negative coverage with activity against *S.***
- ***aureus* (systemic infections) *,* pseudomonas**
- **and also against *B. anthracis***
- **– Addition of fluorine and piperazine derivative**

- **Quinolones - Antibacterial Spectrum**
- **• 3rd generation (fluoroquinolones - levofloxacin):**
- **Improved activity against Gram positives *e.g.***
- **staphylococci and pneumococci, also has activity**
- **against mycoplasma and legionella (systemic**
- **infections)**
- **– Longer half life**
- **– Increased structural complexity, greater antimicrobial**
- **spectrum but also increase in some toxicity**
- **• Gatifloxacin and moxifloxacin are two newer**
- **agents with extended half-lives and enhanced**
- **Gram positive activity**

Quinolones and Fluoroquinolones

- **Have Quinolone structure**



- **Nalidixic acid is first member**
- **Fluorination of Quinolones - Fluoroquinolones**
- **Gram negative mainly (Plus gram positive New FQs)**

Member_Quinolones

First Generation

Nalidixic acid

- **Ciprofloxacin**
- **Norfloxacin**
- **Pefloxacin**
- **Ofloxacin**

Fluoroquinolones

New Generations

Second
- **Lomefloxacin**
- **Levofloxacin**
- **Prulifoxacin**

Third
- **Sparfloxacin**
- **Gatifloxacin**
- **Gemifloxacin**

Fourth
- **Moxifloxacin**
- **Trovafloxacin**
- **Alatrofloxacin**
- **Finafloxacin**

MAN Can SPOT Good Life

- **M**oxifloxacin
- **A**latrofloxacin
- **N**orfloxacin
- **C**iprofloxacin
- **S**parfloxacin
- **P**efloxacin
- **P**rulifoxacin
- **O**floxacin
- **T**rovafloxacin
- **G**atifloxacin
- **G**emifloxacin
- **L**omefloxacin
- **L**evofloxacin

M
A
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Can
S
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O
T
Good
Life

▪ Mechanism of action

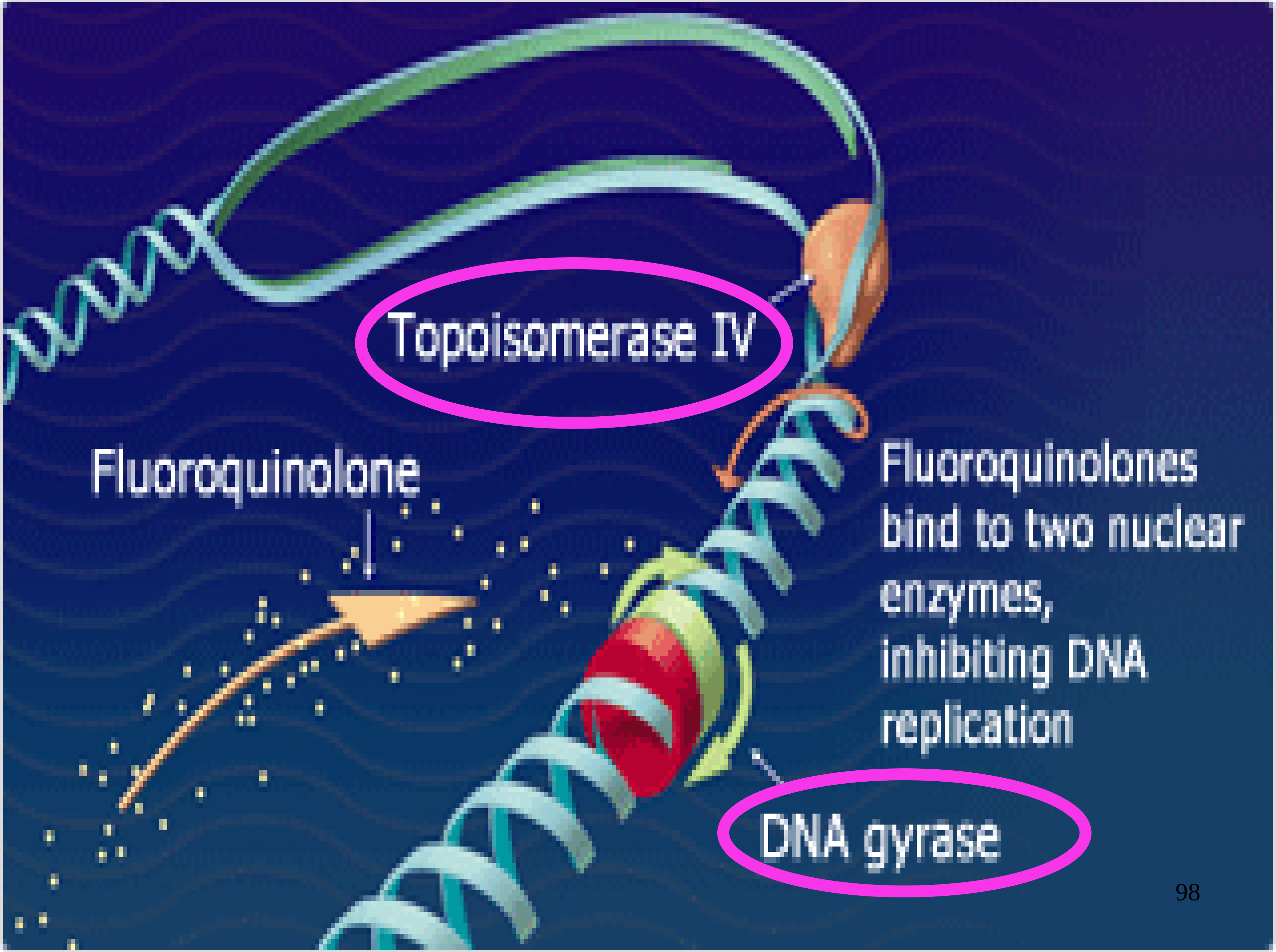
- **In gram negative –**
  - **Inhibition of DNA gyrase enzyme (Inhibit negative super coiling)**

- **In gram positive –**
  - **Inhibition of Topoiosmerase IV – Inhibition of nicking and separation of daughter DNA strands after DNA replication (Inhibition of Decatenation)**

- **The malformed DNA is digested by Exonucleases**

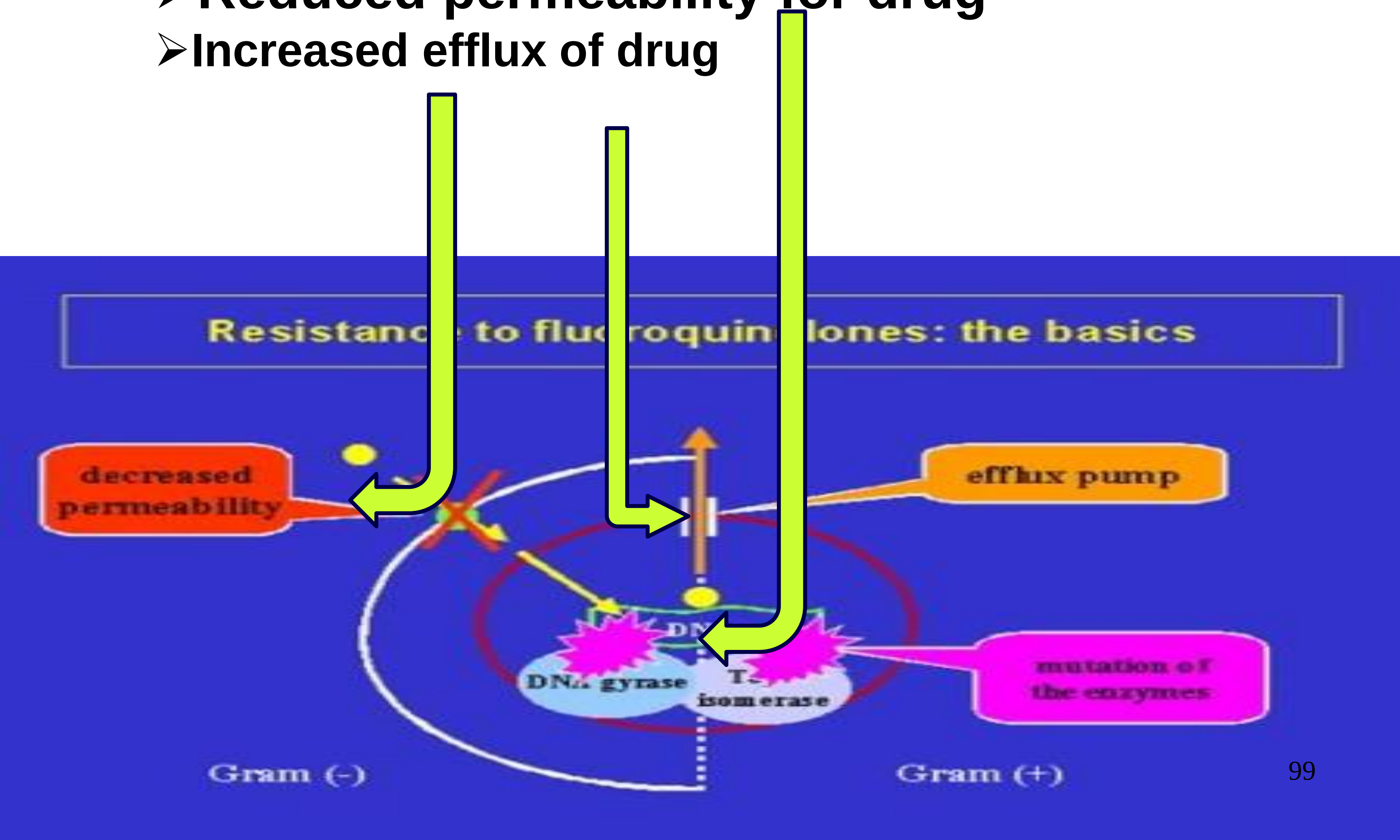
Why not human cells affected ?

Mammalian cells have Topoiosmerase II


Topoisomerase IV
Fluoroquinolone
Fluoroquinolones bind to two nuclear enzymes, inhibiting DNA replication
DNA gyrase

Resistance-Due to mutation in chromosomes

- Altered DNA gyrase and Topoisomerase IV
- Reduced permeability for drug
- Increased efflux of drug



Mechanism of resistance

- **Chromosomal mutation**

  bacteria produce DNA Gyrase/ Topoisomerase IV with **reduced affinity** for FQs

- ↑ **Efflux** of these drugs across bacterial membranes

- *No **quinolone modifying/inactivating enzymes** have been identified in bacteria*

- Resistance is **slow** to develop

Macrolides

Macrolides

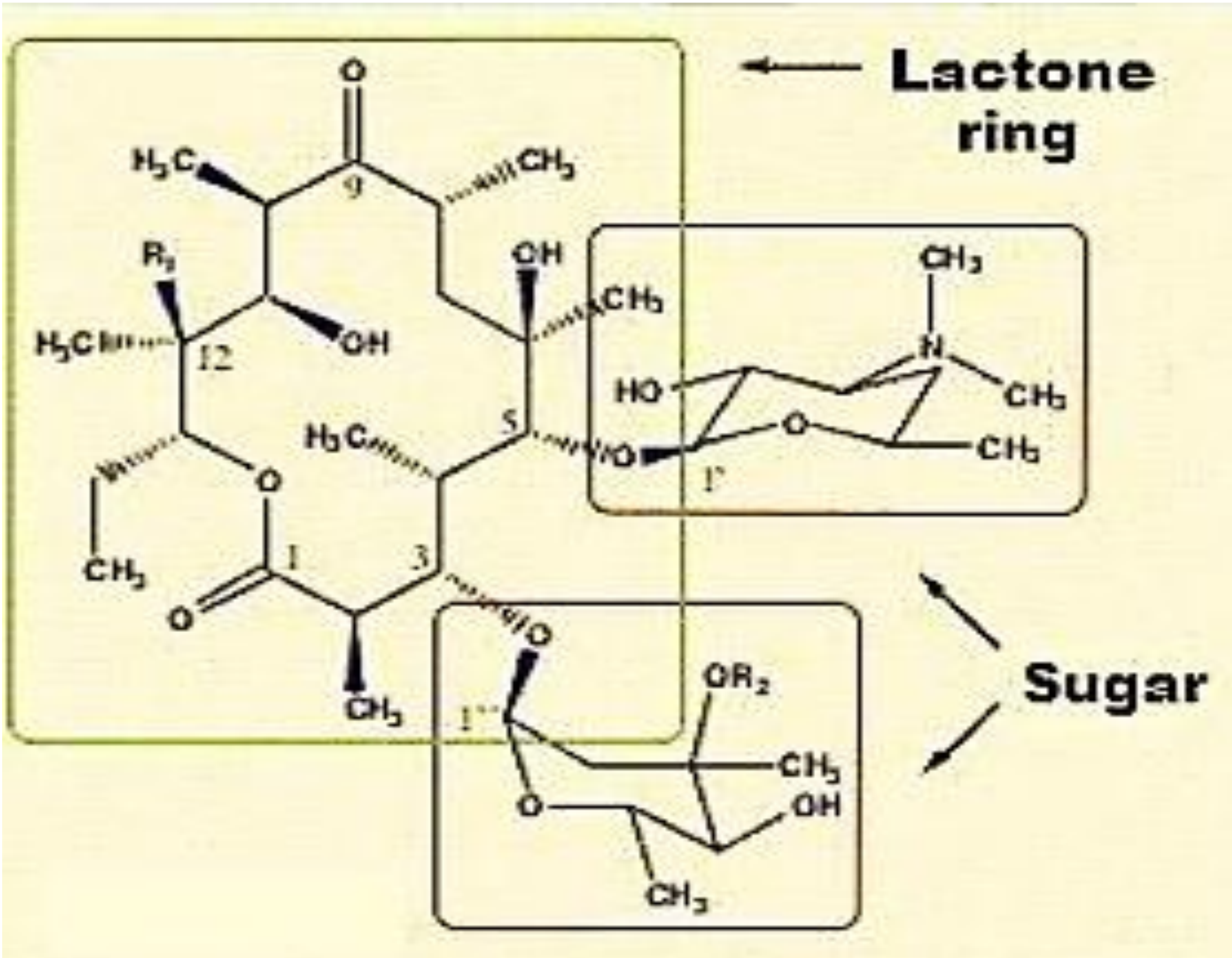
The macrolide antibiotics have three common chemical characteristics:

(a) a large lactone ring (which prompted the name macrolide),

(b) a ketone group

(c) a glycosidically linked amino sugar.

Usually, the lactone ring has 12, 14, or 16 atoms in it, and it is often unsaturated, with an olefinic group conjugated with the ketone function.


Lactone ring
Sugar

Mechanism of Action and Resistance

Some details of the mechanism of antibacterial action of erythromycin are known. It binds selectively to a specific site on the 50S ribosomal subunit to prevent the translocation step of bacterial protein synthesis. It does not bind to mammalian ribosomes. Broadly based, nonspecific resistance to the antibacterial action of erythromycin among many species of Gram-negative bacilli appears to be largely related to the inability of the antibiotic to penetrate the cell walls of these organisms

Spectrum of Activity

The spectrum of antibacterial activity of the more potent macrolides, such as erythromycin, resembles that of penicillin.

The macrolides are generally effective against most species of Gram-positive bacteria, both cocci and bacilli, and exhibit useful effectiveness against Gram-negative cocci, especially Neisseria spp. Many of the macrolides are also effective against Treponema pallidum.

Chemotherapy

What are chemotherapy ?

- D**rug**s are chemical substance that have known biological effects on humans or other animals.

- According to pharmacology, a drug is "a chemical substance (Active Ingredient) used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being.

- Pharmaceutical drugs may be used for a limited duration, or on a regular basis for chronic disorders.

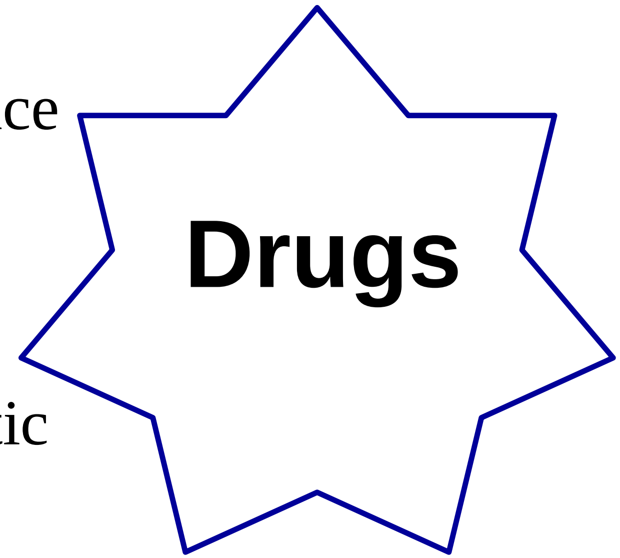
Classification of Drugs

- **Classification on the basis of their origin.**

Natural Origin (Herbal Drugs, marine origin)

Drug derived from radioactive substance

Semi synthetic Drugs (Steroidal Drugs)



Drug derived from biotechnology/genetic engineering

Synthetic Drugs (Pure Synthetic)

Drugs from microbial Origin (Antibiotics)

Drug from Animal origin (Hormones, Enzymes)

Classification on the basis of their mode of action.

Drugs

- Statins (Lovastatin,pravastatin)
- Tranquilizers (Meprobamate, chlorpromazine, diazepam
- Stimulants (Methylphenadate)
- Oral Contraceptives
- Hormone replacements (Premarin)
- Antipyretic (reducing fever)
- Analgesic (reducing pain)
- Antimalarial (treating malaria)
- Antibiotics (Inhibits germ growth)
- Antiseptics (Inhibits germ growth near burns, cuts and wound)

- **Any drugs have mainly two components**.

I. API (Active Pharmaceutical Ingredients)

II. Excipients

I. API (Active Pharmaceutial Ingredients)

This is the part of the drug substance which is responsible for the biological activity of the drugs against any disease or infection.

Drug Substance = API + Excipients

II. Excipients :

Substance used during formulation excluding API known as excipients. e.g. Starch, color, flavors, etc.

Medicinal Chemistry

Drug chemistry is best to be defined as an interdisciplinary research area incorporating different branches of chemistry and biology in the research for better and new drugs (Drug Discovery).

In other words, medicinal chemistry is the science, which deals with the discovery and design of new and better therapeutic chemicals and development of these chemicals into new medicines and drugs.

Generally properties of Drugs Chemists can:

- **Make new compounds**
- **Determine their effect on biological processes.**
- **Alter the structure of the compound for optimum effect and minimum side effects.**
- **Study uptake, distribution, metabolism and excretion of drugs.**

Drug Classification

Pure organic compounds are the chief source of agents for the cure, mitigation or the prevention of disease.

These remedial agents could be **classified according to their origin:**

- **Natural compounds:** materials obtained from both plant and animal, e.g. vitamins, hormones, amino acids, antibiotics, alkaloids, glycosides…. etc.).

- **Synthesis compounds:** either pure synthesis or synthesis naturally occurring compounds (e.g. morphine, atropine, steroids and cocaine) to reduce their cost.

- **Semi-synthesis compounds:** Some compounds either can not be purely synthesized or can not be isolated from natural sources in low cost. Therefore, the natural intermediate of such drugs could be used for the synthesis of a desired product (e.g. semi synthetic penicillins).

Drug Classification

Since there is no certain relation between chemical structure and pharmacological activity therefore, it would be unwise to arrange all drugs on the basis of their structures or origin. Thus, it is better to arrange the drugs according to **their medicinal use.**

Drugs can be classified according to their medicinal uses into two main classes:

I-Pharmacodynamic agents: Drugs that act on the various physiological functions of the body (e.g. general anaesthetic, hypnotic and sedatives, analgesic etc.).

II-Chemotherapeutic agents: Those drugs which are used to fight pathogenic (e.g. sulphonamides, antibiotics, antimalarial agents, antiviral, anticancer etc.).

Drug Classification

Drugs can treat different types of diseases:

1-Infectious diseases: Born (transmitted) from person to person by outside agents, bacteria (pneumonia, salmonella), viruses (common cold, AIDS), fungi (thrush, athletes foot), parasites (malaria)

2-Non-infectious diseases: disorders of the human body caused by genetic malfunction, environmental factors, stress, old age etc. (e.g. diabetes, heart disease, cancer. Haemophilia, asthma, mental illness, stomach ulcers, arthritis).

3-Non-diseases: alleviation of pain (analgesic), prevention of pregnancy (contraception) , anesthesia.

<u>Solubility Prediction</u>

- The relative solubility of an OMA is a function of the presence of both lipophilic and hydrophilic features within its structure, which serve to determine the extent of interaction of the OMA with lipid and/or aqueous phases.
- The relative solubility of an OMA can be determined <u>in the laboratory</u>, i.e. **the partition coefficient** [**P**; the ratio of the solubility of the compound in an organic solvent to the solubility of the same compound in an aqueous environment (i.e., P=[Drug]lipid/ [Drug]aqueous). P is often expressed as a log value.

Solubility Prediction

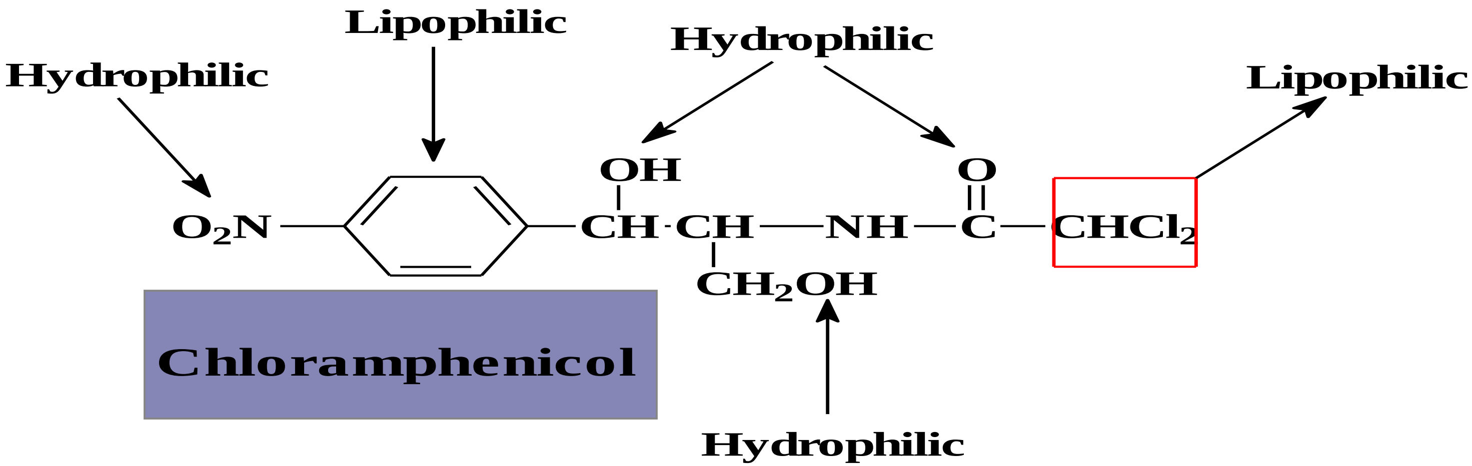
A mathematical procedures also have been developed to estimate the relative solubility of an organic molecule based upon differential contributions of various structural features to overall solubility.

For example, the relative solubility of an OMA is the sum of the contributions of each group and substituent to overall solubility.

Example:

Examination of the structure of **chloramphenicol** (indicates the presence of both lipophilic (nonpolar) and hydrophilic (polar) groups and substituents.

Solubility Prediction



The presence of oxygen and nitrogen containing functional groups usually enhances water solubility. While lipid solubility is enhanced by nonionizable hydrocarbon chains and ring systems.

Solubility Prediction

Laboratory Estimation of Relative Solubility

The relative solubility of an organic compound is measured by determining the extent of its distribution into an aqueous solvent (usually pH 7.4 buffer) and a lipid solvent (usually n-octanol). These experiments generate a value, P, the partition coefficient for that particular compound.

$$\textbf{Partition coefficient} = \frac{\textbf{Conc. of compunds in } C_8H_{16}OH}{\textbf{Conc. of compunds in } H_2O}$$

Drug-receptor Interaction

Receptor is the site in the biological system where the drug exerts its characteristic effects or where the drug acts.

Receptors have an important regulatory function in the target organ or tissue.

Most drugs act by combining with receptor in the biological system (***specific drugs***).

1-cholinergic drugs interacts with acetylcholine receptors.

2-synthetic corticosteroids bind to the same receptor as cortisone and hydrocortisone

3-non steroidal anti inflammatory drugs inhibit cyclooxygenase enzyme that will inhibit the formation of prostaglandins which will lead to inflammation symptoms.

Non-specific drugs do not act upon receptors.

The receptor substance is considered mostly to be a cellular constituent. Recent studies, however, indicate that the receptors are proteins or enzymes.

The ability of a drug to get bound to a receptor is termed as the affinity of the drug for the receptor.

Drug-receptor Interaction

The ability of a drug to get bound to a receptor is termed as the affinity of the drug for the receptor.

The receptors are also dynamic in nature and have a special chemical affinity and structural requirements for the drug. Thus, affinity represents kinetic constants that relate to the drug and the receptor.

The drug elicits a pharmacological response after its interaction with the receptor.

A given drug may act on more than one receptor differing both in function and in binding characteristics (***non-selective drugs***).

There are also many factors effect changes in receptor concentration and/or affinity.

A drug, which initiates a pharmacological action after combining with the receptor, is termed **agonist**.

Drugs which binds to the receptors but are not capable of eliciting a pharmacological response produce receptor blockage, these compounds are termed **antagonists**.

DRUG DESIGN

Drug Design

- Drug design, sometimes referred to as rational drug design or simply rational design.

- Drug design is the inventive process of finding new medications based on the knowledge of a biological target.

- The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient.

Drug Design

- Drug design involves the design of molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it.

- Drug design may be computer aided (based on computer modeling technique) or structure based drug design (based on three dimensional structure of the biomolecular target)

- The phrase "drug design" is to some extent a misnomer. A more accurate term is ligand design (i.e., design of a molecule that will bind tightly to its target generally protein)

Drug targets

- Drug target sites are biomolecular structure (most commonly a protein or nucleic acid) is a key molecule involved in a particular metabolic or signalling pathway that is associated with a specific disease condition or pathology or to the infectivity or survival of a microbial pathogen

- Small molecules (drugs) can be designed so as not to affect any other important "off-target" molecules (often referred to as antitargets)

- Drug interactions with off-target molecules may lead to undesirable side effects.

Computer Aided Drug Design

- Drug design with the help of computers is known as computer aided drug design, may be used at any of the following stages of drug discovery:

  - Hit identification using virtual screening (structure- or ligand-based design)

  - Hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)

  - Lead optimization optimization of other pharmaceutical properties while maintaining affinity

Types of Drug Design

- There are two major types of drug design.

  - **Ligands** based drug design

  - **structure** based drug design

Ligand-based drug design

- Ligand based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest.

- Pharmacophore model developed that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target and SAR generated.

Structure Based drug design

- Structure-based drug design (or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.

- Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist.

- Methods for structure-based drug design can be divided roughly into three main categories.
  - Identification of new ligands for the given target. (by docking)
  - De novo design of new drug. (by building ligand molecule)
  - Optimization of Known ligands by evaluating proposed analogs within the binding cavity.

Binding site identification

- Binding site identification usually relies on identification of concave surfaces on the protein that can accommodate drug sized molecules that also possess appropriate "hot spots" (hydrophobic surfaces, hydrogen bonding sites, etc.) that drive ligand binding.

Scoring Function

- Scoring function is related to the binding affinity of the ligands with the target (binding site of Protein), higher the score higher will be the binding affinity (higher recognition)

Optimizing target interactions

- Once the lead compound has been discovered it can be used as the starting point for drug design.
- **There are various aims in drug design:**

1. The drug should have a good selectivity for its target
2. The drug should have a good level of activity for its target
3. The drug should have minimum side effects
4. The drug should be easily synthesized
5. The drug should be chemically stable
6. The drug should have acceptable pharmacokinetics properties
7. The drug should be non-toxic

There are two important aspects in drug design and drug strategies to improve :

1. **Pharmacodynamics properties:** to optimize the interaction of the drug with its target.

1. **Pharmacokinetics properties:** to improve the drug's ability to reach its target & to have acceptable lifetime.

- Pharmacodynamics and pharmacokinetics should have equal priority in influencing which strategies are used and which analogues are synthesized.

Structure Activity Relationships (SAR)

- Once the structure of lead compound is known, the medicinal chemist moves on to study its SAR.

- The aim is to discover which parts of the molecule are important to biological activity and which are not.

- X-ray crystallography and NMR can be used to study and identify important binding interactions between drug and active site.

- SAR is synthesizing compounds, where one particular functional group of the molecule is removed or altered.

- In this way it is possible to find out which groups are essential and which are not for biological effect.

Structure Activity Relationships (SAR)

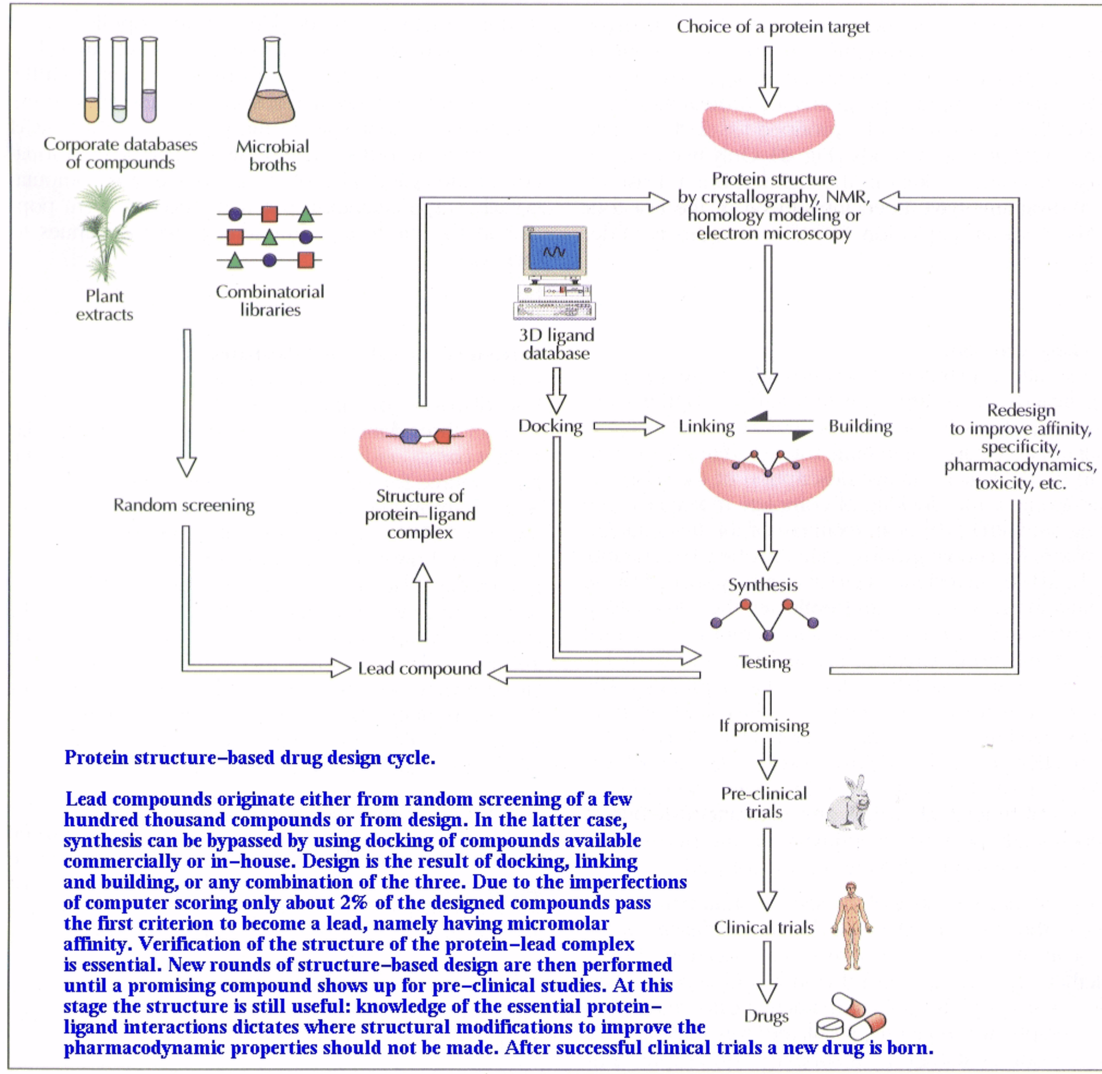
- This involves testing all analogues for biological activity and comparing them with the original compound.
- If an analogue shows a significant lower activity, then the group that has been modified must be important.
- If the activity remain similar, then the group is not essential.
- It may be possible to modify some lead compounds directly to the required analogues and other analogues may be prepared by total synthesis.

Lipinski Rule of Five (1997)

- The drug design of the molecule should be in such a way that it also follow the LipinskI rule of five.
- LipinskI rule of five state that a drug molecule must have :
  - Drug molecule not exceed more than 5 hydrogen bond donor.
  - Drug molecule not exceed more than 10 hydrogen bond acceptor.
  - Drug molecule not exceed their molecular mass more than 500
  - Drug molecule should not have log P value less than 5.

Structure-based Drug Design Cycle

- Target identification and validation
- Assay development
- Virtual screening (VS)
- High throughput screening (HTS)
- Quantitative structure – activity relationship (QSAR) and refinement of compounds
- Characterization of prospective drugs
- Testing on animals for activity and side effects
- Clinical trials
- FDA approval



Protein structure–based drug design cycle.

Lead compounds originate either from random screening of a few hundred thousand compounds or from design. In the latter case, synthesis can be bypassed by using docking of compounds available commercially or in–house. Design is the result of docking, linking and building, or any combination of the three. Due to the imperfections of computer scoring only about 2% of the designed compounds pass the first criterion to become a lead, namely having micromolar affinity. Verification of the structure of the protein–lead complex is essential. New rounds of structure–based design are then performed until a promising compound shows up for pre–clinical studies. At this stage the structure is still useful: knowledge of the essential protein–ligand interactions dictates where structural modifications to improve the pharmacodynamic properties should not be made. After successful clinical trials a new drug is born.

STABILITY OF Drugs

Stability of drugs

- Stability: is the capacity of a drug product to remain within specifications established to ensure its identity, strength quality and purity.

- Instability may cause

- Undesired change in performance, i.e. dissolution/bioavailability
- Substantial changes in physical appearance of the dosage form
- Causing product failures

Factors affecting Stability

1- Environmental factors

- Temperature - Light
- Oxygen - Moisture
- Carbon dioxide

2- Drugs or excipients in the dosage form

- Particle size of drug
- pH of the vehicle

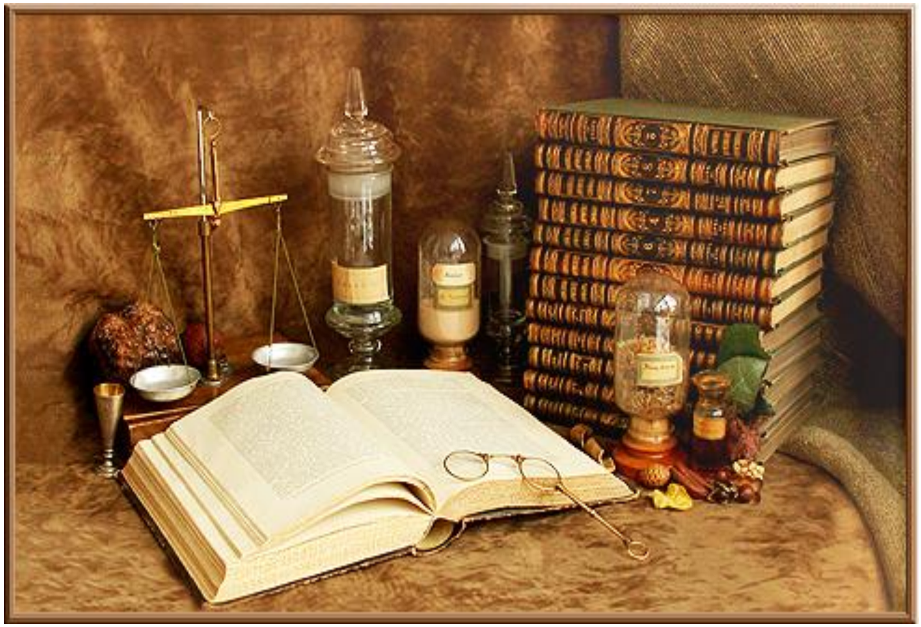
3- Microbial contamination

4- Trace metal Contamination

5- Leaching from containers

Types of stability studies:

- Physical
- Chemical
- Microbiological



Physical stability

- Physical stability implies that:

- The formulation is totally unchanged throughout its shelf life and has not suffered any changes by way of appearance, organoleptic properties, hardness, brittleness, particle size etc.

- It is significant as it affects:
  - pharmaceutical elegance
  - drug content uniformity
  - drug release rate.

Physical stability

Formulation	Likely physical instability problems	Effects
Oral solutions	1- Loss of flavour 2- Change in taste 3- Presence of off flavours due to interaction with plastic bottle 4- Loss of dye 5- Precipitation 6- discoloration	Change in smell or feel or taste

Physical stability

Formulation	Likely physical instability problems	Effects
Parenteral solutions	1. Discoloration due to photo chemical reaction or oxidation 2. Presence of precipitate due to interaction with container or stopper 3. Presence of "whiskers" 4. Clouds due to: (i) Chemical changes (ii) The original preparation of a supersaturated solution	Change in appearance and in bio-availability

Physical stability

Formulation	Likely physical instability problems	Effects
Suspensions 	1- settling 2- caking 3- crystal growth	1-Loss of drug content uniformity in different doses from the bottle 2- loss of elegance.

Physical stability

Formulation	Likely physical instability problems	Effects
Emulsions 	1- Creaming 2- coalescence	1- Loss of drug content uniformity in different doses from the bottle 2- loss of elegance

Physical stability

Formulation	Likely physical instability problems	Effects
Semisolids (Ointments and suppositories)	1. Changes in: a) Particle size b) Consistency 2. Caking or coalescence 3. Bleeding	1-Loss of drug content uniformity 2- loss of elegance 3-change in drug release rate.

Physical stability

Formulation	Likely physical instability problems	Effects
Tablets 	Change in: a) Disintegration time b) Dissolution profile c) Hardness d) Appearance (soft and ugly or become very hard)	Change in drug release

Physical stability

Formulation	Likely physical instability problems	Effects
Capsules	Change in: a) Appearance b) Dissolution c) Strength	Change in drug release

Chemical stability:

- Chemical stability implies:

The lack of any decomposition in the chemical moiety that is incorporated in the formulation as the drug, preservatives or any other excipients.

This decomposition may influence the physical and chemical stability of the drug

Mechanisms Of Degradation

Some Functional Groups Subject to Hydrolysis

1- Hydrolysis:

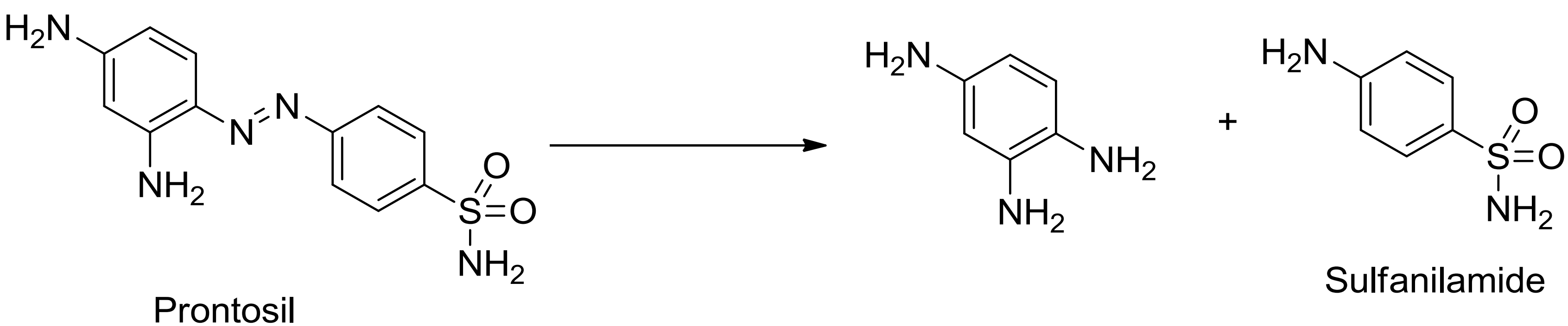
Hydrolysis means “splitting by water’’

Drug type	Examples
Esters	Aspirin, alkaloids Dexmethasne sodium phosphate Nitroglycerin
Lactones	Pilocarpine Spironolactone
Amides	Chloramphenicol
Lactams	Penicillins Cephalosporins

Sulphonamides Drugs

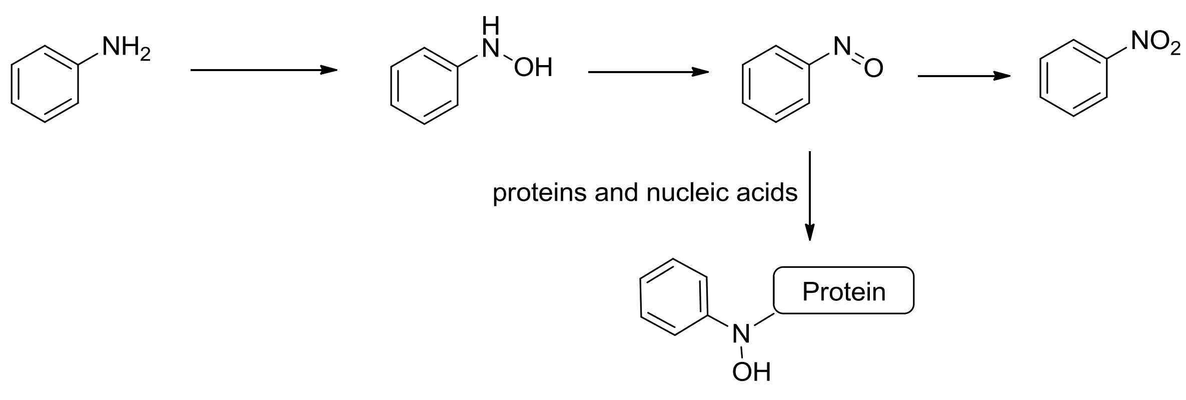
Sulfonamides antibacterial agents

- Sulfa drugs were discovered when a red dye called prontosil has shown *in-vivo* antibacterial activity while it was *in-vitro* inactive. This supports the idea that prontosil to exert its action, it has to be activated by the host metabolic pathways to give the active form.

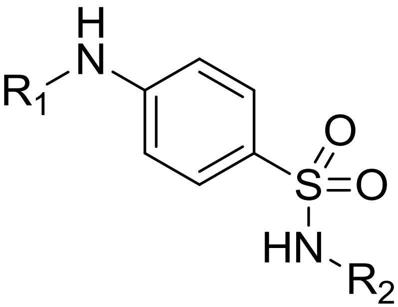


Sulfonamides antibacterial agents

- They are the first synthetic antibacterial agents.
- They have good antibacterial activity mainly on gram +ve bacteria.
- limitation of the sulfa drugs use:
  - Sulfa allergic reactions.
  - The formation of crystalluria.
  - They give toxic metabolites after the oxidation of the aromatic amine:



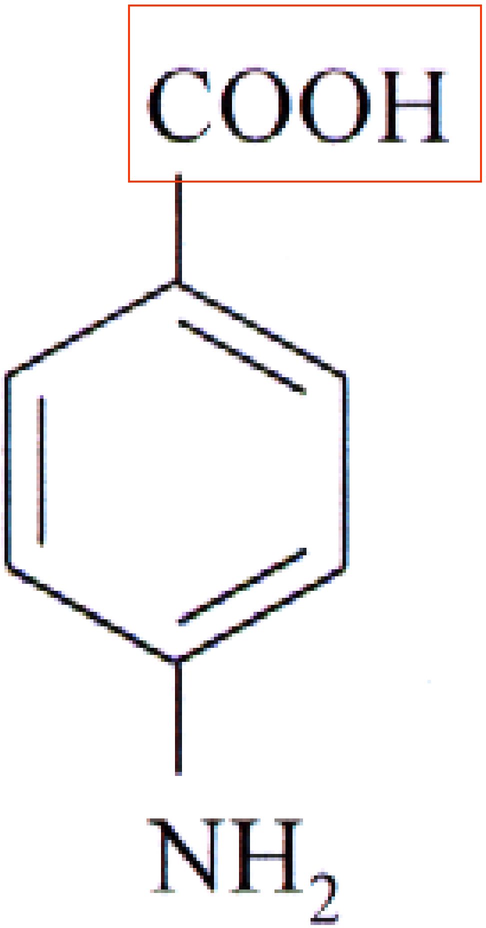
Structure Activity Relationships Sulfonamides



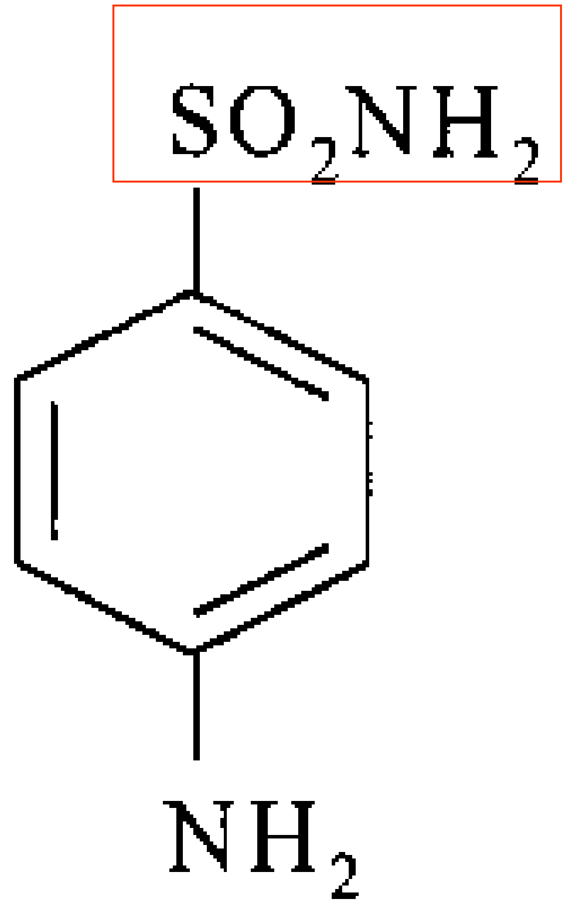
- *P*-amino group is essential for activity and should be free (unsubstituted) except in the case of prodrugs in which it will be as amide linkage that will be hydrolyzed to give the active free form.
- The aromatic ring and the sulfonamide group are important for activity.
- The sulfonamide and the amino group must be directly attached to the ring and in *P* position to each other.
- Any extra substitution will reduce activity.
- Sulfonamide nitrogen must be either primary or secondary.

Mechanism of action

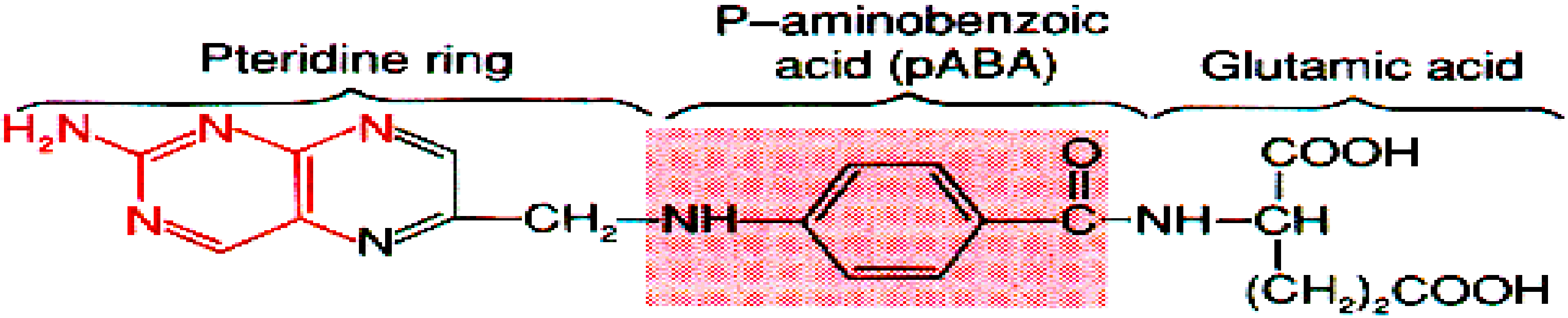
- Unlike man, most bacteria cannot utilize external folic acid, a nutrient which is essential for growth, and they have to synthesize it from para-aminobenzoic acid (PABA). Sulfonamides are structurally similar to PABA and inhibit the enzyme dihydrofolate synthetase in the biosynthetic pathway for folic acid.
- High concentrations of PABA antagonize the effectiveness of sulfonamides.



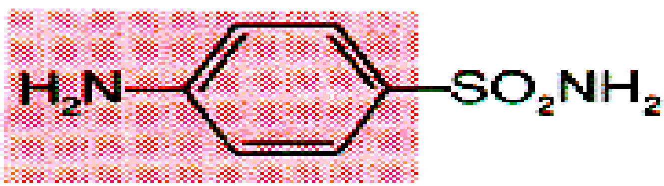
PABA



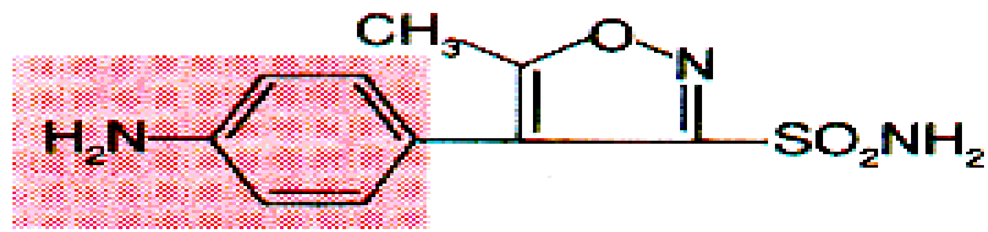
Sulfanilamide



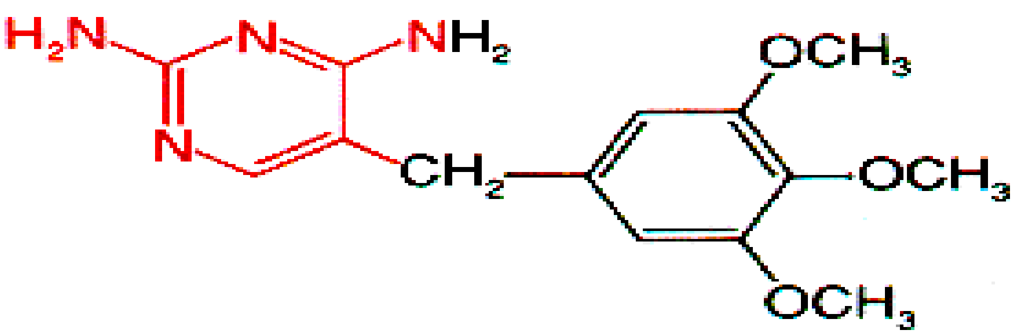
Folic acid



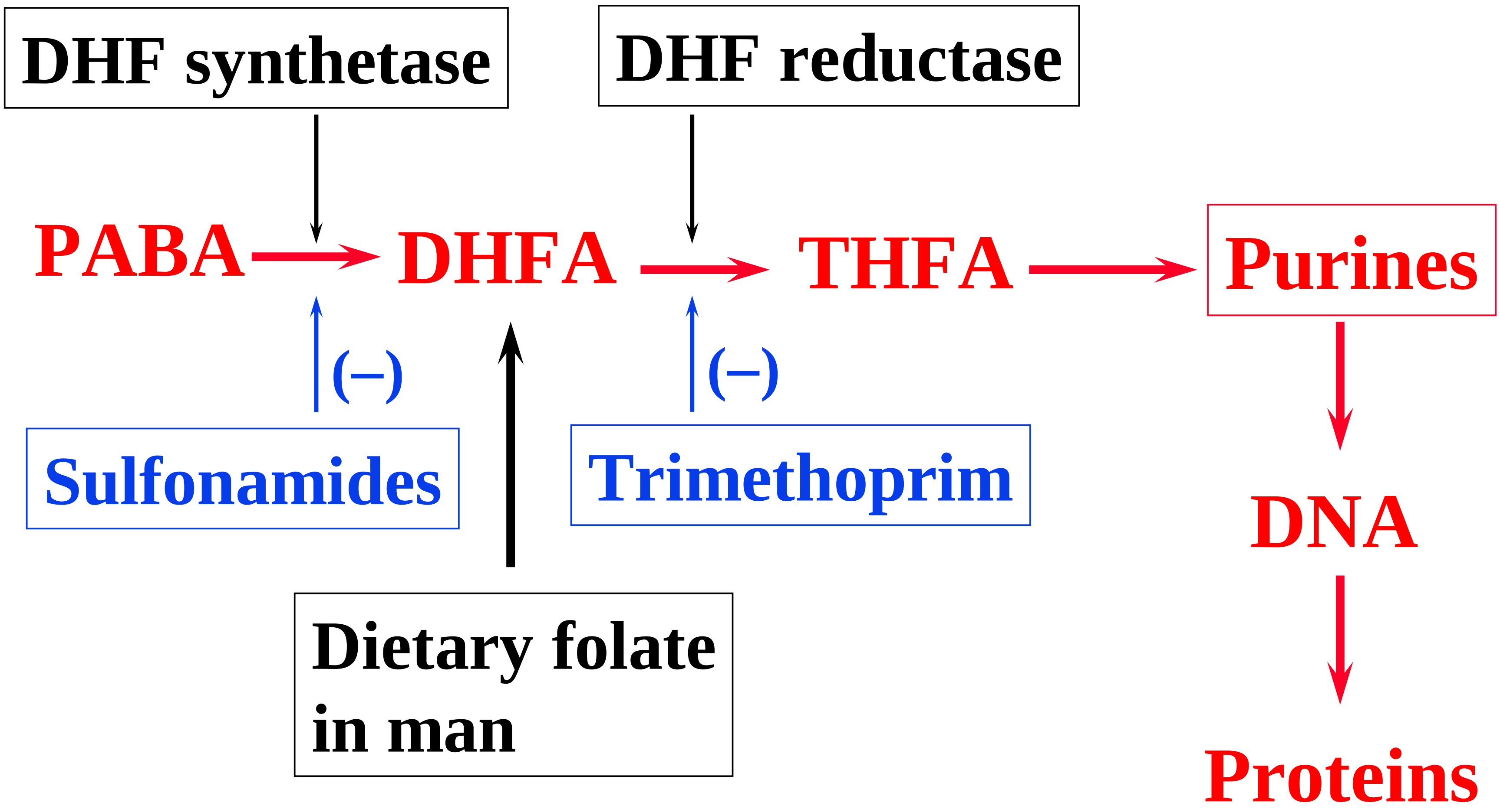
Sulphanilamide

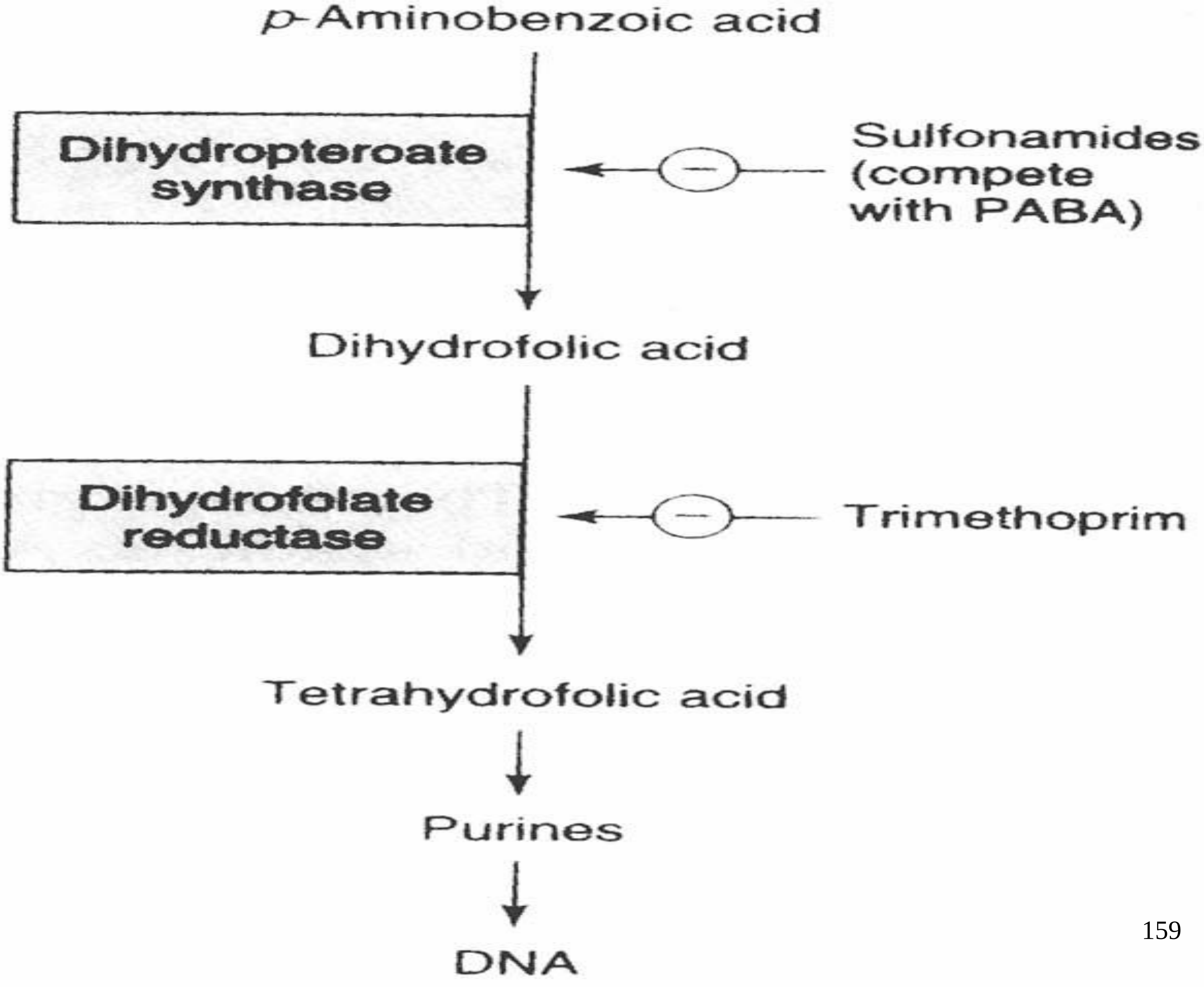


Sulphamethoxasole



Trimethoprim (dihydrofolate reductase inhibitor)


DHF synthetase
DHF reductase
PABA
DHFA
THFA
Purines
(–)
(–)
Sulfonamides
Trimethoprim
DNA
Dietary folate in man
Proteins


p-Aminobenzoic acid
Dihydropteroate synthase
Sulfonamides (compete with PABA)
Dihydrofolic acid
Dihydrofolate reductase
Trimethoprim
Tetrahydrofolic acid
Purines
DNA

Spectrum of activity

- Sulfonamides have a bacteriostatic action on a wide range of Gram-positive and Gram-negative microorganisms and also are active against toxoplasma, nocardia species, and chlamydia.
- Sulfonamides alone are usually reserved for the treatment of nocardiosis and toxoplasmosis.

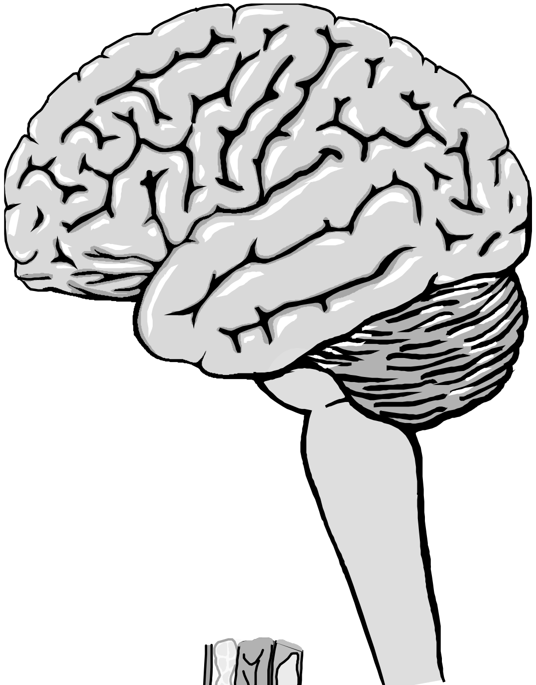
Mechanism of resistance

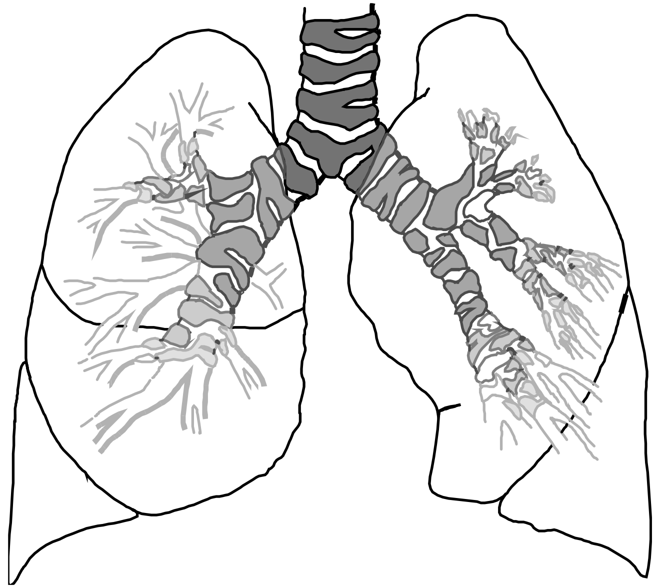
- An alterative metabolic pathway for synthesis of an essential

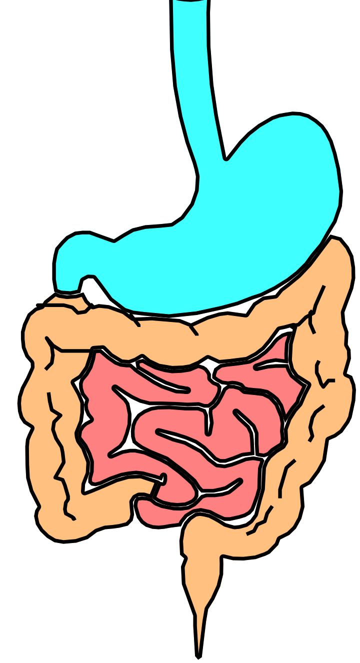
  metabolite or over-production of PABA
- Lowered affinity of dihydropteroate synthase to sulfonamides
- Decreased bacterial permeability or active efflux of sulfonamides

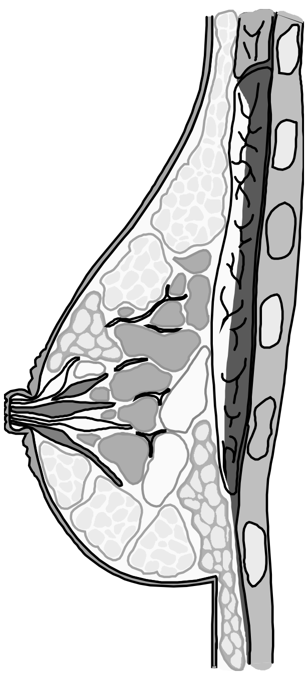
Pharmacokinetics

- **Most sulfonamides are well absorbed orally. They are widely distributed in the body and cross the BBB and placenta.**
- **Sulfonamides are metabolized in the liver, initially by acetylation which shows genetic polymorphism. The acetylated product has no antimicrobial actions but retains toxic potential.**

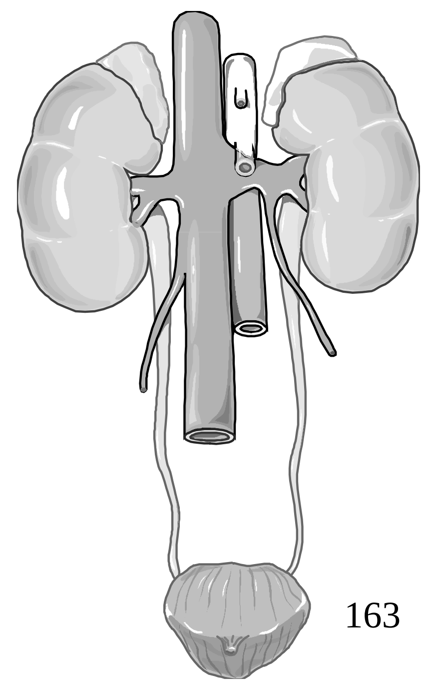








A large number of parent drugs and N-acetyl metabolites are excreted by the kidney.



Trimethoprim (TMP)

TMP inhibits bacterial dihydrofolic acid reductase. Prevents the formation of active tetrahydro form of folic acid 50,000 times less efficient in inhibition of mammalian dihydrofolic acid reductase

TMP given together with sulfonamides, produces sequential blocking of folic acid synthesis, resulting in marked enhancement (synergism) of the bacteriostatic activity

Mechanism of action

Sequential interference with folic acid synthesis results in bacterial synergism often with bactericidal activity

- Sulfonamides are structural analogues of para-amino benzoic acid (PABA), competitively inhibiting synthesis of dihydrofolic acid
- Trimethoprim is an analogue of the pteridine portion of dihydrofolic acid inhibiting synthesis of tetrahydrofolic acid

Mechanism of resistance

Resistance is reduced because of the sequential interference with steps involved in folic acid synthesis

- Sulfas: decreased permeability (plasmid mediated), increased production of PABA
- TMP: synthesis of DHFR with decreased affinity for TMP (plasmid-mediated), overproduction of DHFR
- Resistance to both TMP and SMZ has been increasing

Spectrum of activity

Excellent broad spectrum activity against a diversity of microorganisms

• Gram negatives: *E. coli, klebsiella, proteus,* salmonella, shigella, vibrio, *B. cepacia, H.influenzae, Neisseria spp.*

• Gram positives: staphylococci, streptococci, listeria, not enterococci • Miscellaneous: pneumocystis, nocardia, chlamydia

Clinical use

Urinary tract infections

• Prostatitis

• Treatment of moderately severe to severe pneumocystis pneumonia

• Upper and lower respiratory infections caused by susceptible organisms

• Diarrheal illnesses due to salmonella, shigella and enterotoxigenic *E.coli*

Adverse effects

Hypersensitive reactions : rash, fever

 GI effects: nausea, vomiting diarrhea

Toxicity from TMP-SMZ including fever, rashes, Stevens Johnson syndrome, is dramatically increased in subjects with AIDS. The reason for this is unclear.

Antidiabetic Drugs

Pancreatic islet cells and their secretory products

Cell Types	Approximate Percent of Islet Mass	Secretory Products
A cell (alpha)	20	Glucagon, proglucagon
B cell (beta)	75	Insulin, C-peptide, proinsulin, amylin
D cell (delta)	3-5	Somatostatin
F cell (PP cell)[1]	< 2	Pancreatic polypeptide (PP)

[1]Within pancreatic polypeptide-rich lobules of adult islets, located only in the posterior portion of the head of the human pancreas, glucagon cells are scarce (< 0.5%) and F cells make up as much as 80% of the cells.

Diabetes mellitus

Two major type of diabetes mellitus

- Type I, Type II

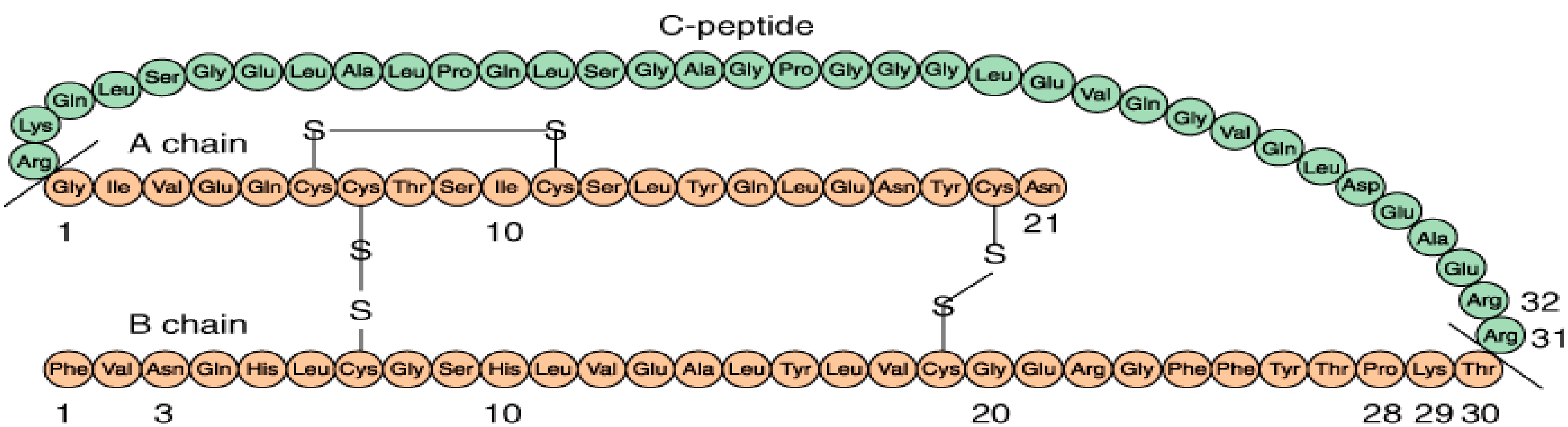
Both require careful monitoring of:

- Diet, fasting, postprandial blood glucose
- Hemoglobin $A_{1c,}$

Insulin

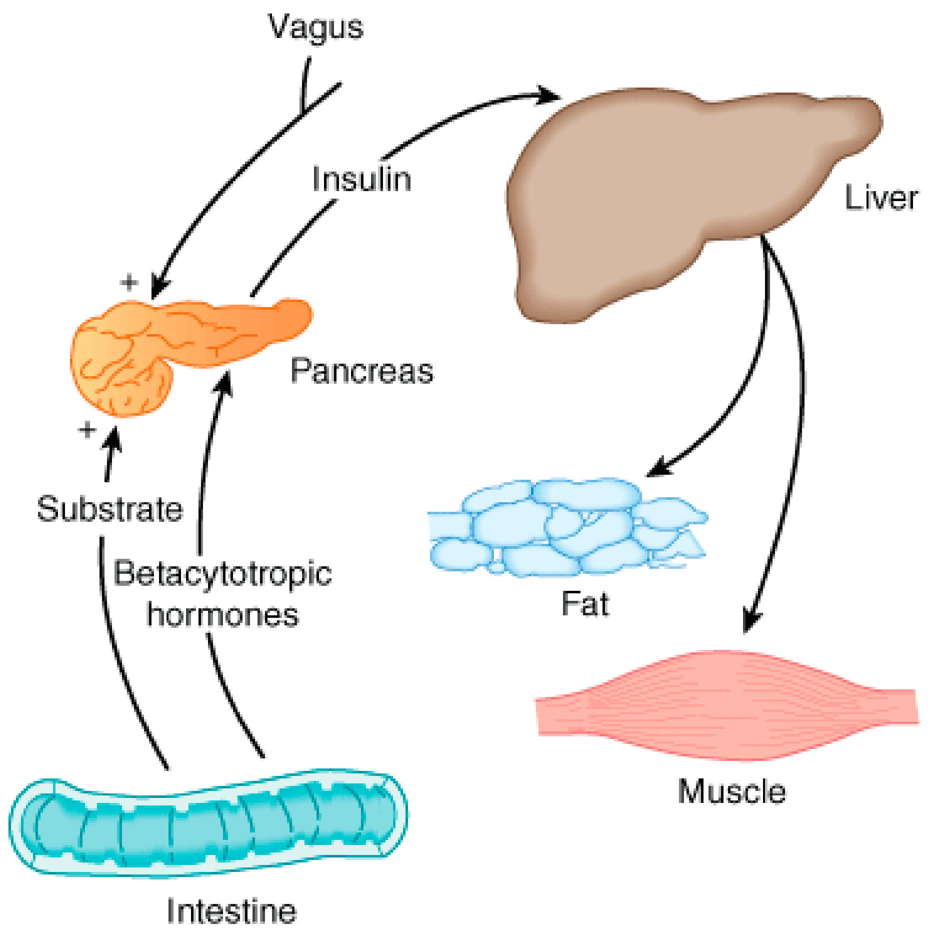
- Physiology
  - Proinsulin: 86 amino acid
  - C-peptide: 31 amino acid
- Effects on Liver, Skeletal muscle Adipose tissue

Structure of human proinsulin



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Insulin promotes synthesis



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Insulin preparation

- Rapid-acting
- Short-acting
- Intermediate-acting
- Long-acting
- Insulin delivery systems

Hazards of insulin use

- Hypoglycemia
- Insulin induced immunologic complication

Non Insulin antidiabetic drugs

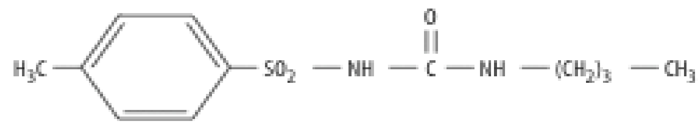
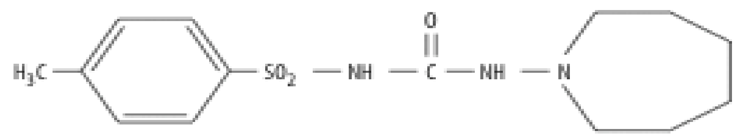
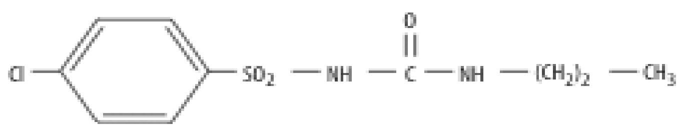
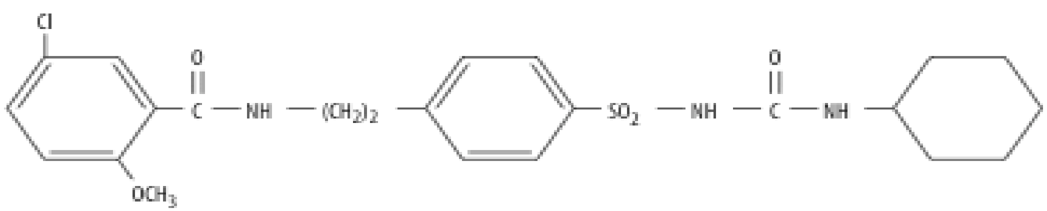
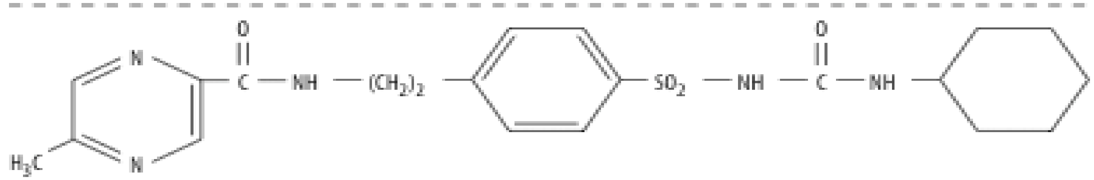
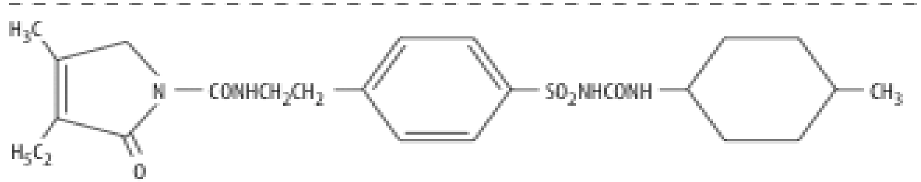
- Insulin secretagogues
- Biguanide metformin
- Thiazolidinediones
- Alpha-glucosidase inhibitors

Insulin secretagogues

- Group drugs:
  - Sulfunylureas: tolbutamide, chlorpropamide, glyburide, glipizide, glimepride
- Mechanism of action
  - Closure of potassium channel
- Toxicity
  - Hypoglycemia, allergic reactions
  - Weight gain

Insulin secretagogues: Sulfonylureas

Table 41–6. Sulfonylureas.

Sulfonylureas	Chemical Structure	Daily Dose	Duration of Action (hours)
Tolbutamide (Orinase)		0.5–2 g in divided doses	6–12
Tolazamide (Tolinase)		0.1–1 g as single dose or in divided doses	10–14
Chlorpropamide (Diabinese)		0.1–0.5 g as single dose	Up to 60
Glyburide (gli-benclamide[1]) (Diaβeta, Micronase, Glynase PresTab)		0.00125–0.02 g	10–24
Glipizide (gly-diazinamide[1]) (Glucotrol, Glucotrol XL)		0.005–0.03g (0.02 g in Glucotrol XL)	10–24[2]
Glimepiride (Amaryl)		0.001–0.004 g	12–24

[1]Outside USA.

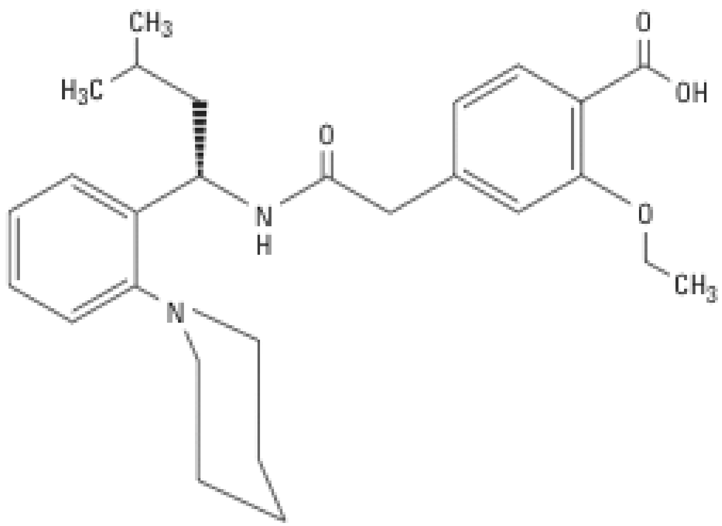
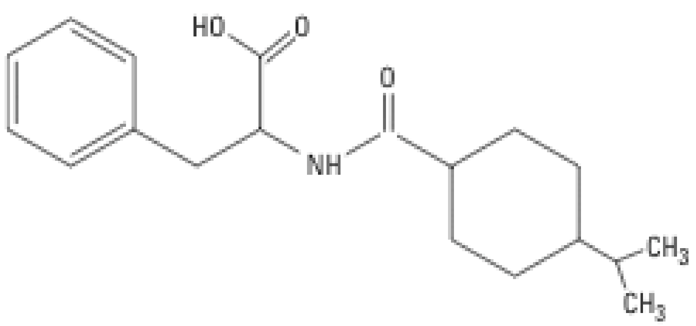
[2]Elimination half-life considerably shorter (see text).

Insulin secretagogues: Sulfonylureas

- First-Generation Sulfonylureas
  - **Tolbutamide, Chlorpropamide, Tolazamide**
- Second-Generation Sulfonylureas
  - **Glyburide, Glipizide, Glimepiride**

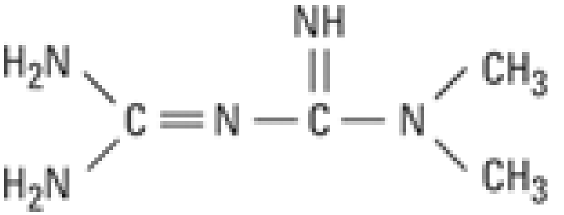
Insulin secretagogues: Meglitinides

Table 41–7. Meglitinides.

Drug	Chemical Structure	Oral Dose	$t_{1/2}$	Duration of Action (hours)
Repaglinide (Prandin)		0.25–4 mg before meals	1 hour	4–5
Nateglinide (Starlix)		60–120 mg before meals	1 hour	4

Biguanides: metformin

- Mechanism of action
  - Inhibit gluconeogenesis
  - Induction of glucose uptake in periphery
  - Slowing the absorption of glucose
  - Reduction of glucagon level
- Toxicity
  - Gastrointestinal distress
  - Lactic acid in some patiets



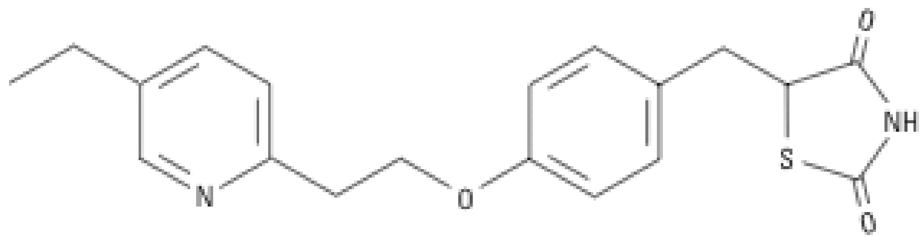
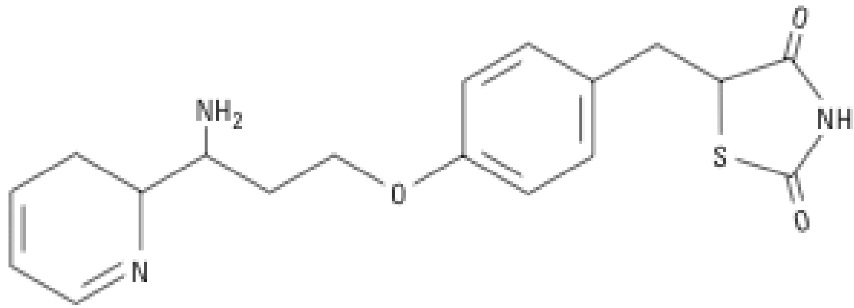
Metformin

Thiazolidinedione's

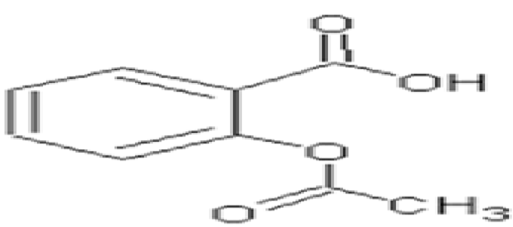
- Group drugs:
  - rosiglitazone, pioglitazone
- Mechanism of action
  - Increase target tissue sensitivity
  - Activating: peroxisome proliferator-activated receptor-gamma nuclear receptor (PPAR-γ receptor)
- Toxicity
  - Fluid retention, MI, bone fracture
  - Liver enzyme inducers

Thiazolidinedione's

Table 41–8. Thiazolidinediones.

Thiazolidinedione	Chemical Structure	Oral Dose
Pioglitazone (Actos)		15–45 mg once daily
Rosiglitazone (Avandia)		2–8 mg once daily

Aspirin



Aspirin

Acetylsalicylic Acid

$C_9H_8O_4$

- Aspirin act as an analgesic, antipyretic, Anti-inflammatory also inhibit platelet aggregation & prolongs bleeding time, because of its effect on G.I.T it is contraindicated in peptic ulcer, in this case we use paracetamol .
- Aspirin is not given to children because is may cause raye’s syndrome.

1. Antipyretic Effects

- "normal" temperature: slightly affected
- "elevated" temperature: reduced
- The higher temperature, the more potent
- Mechanisms of Antipyretic Action

Blocks pyrogen-induced prostaglandin production in thermoregulatory center (CNS)

2. Analgesic Effects

- Effective to mild to moderate pain

0.5 g of aspirin is a weak or mild analgesic that is effective in short, intermittent types of pain as encountered in neuralgia, myalgia , toothache.

- Pain may arise from:

Musculature, dental work , vascular , postpartum conditions, arthritis , bursitis

- Sites of action:

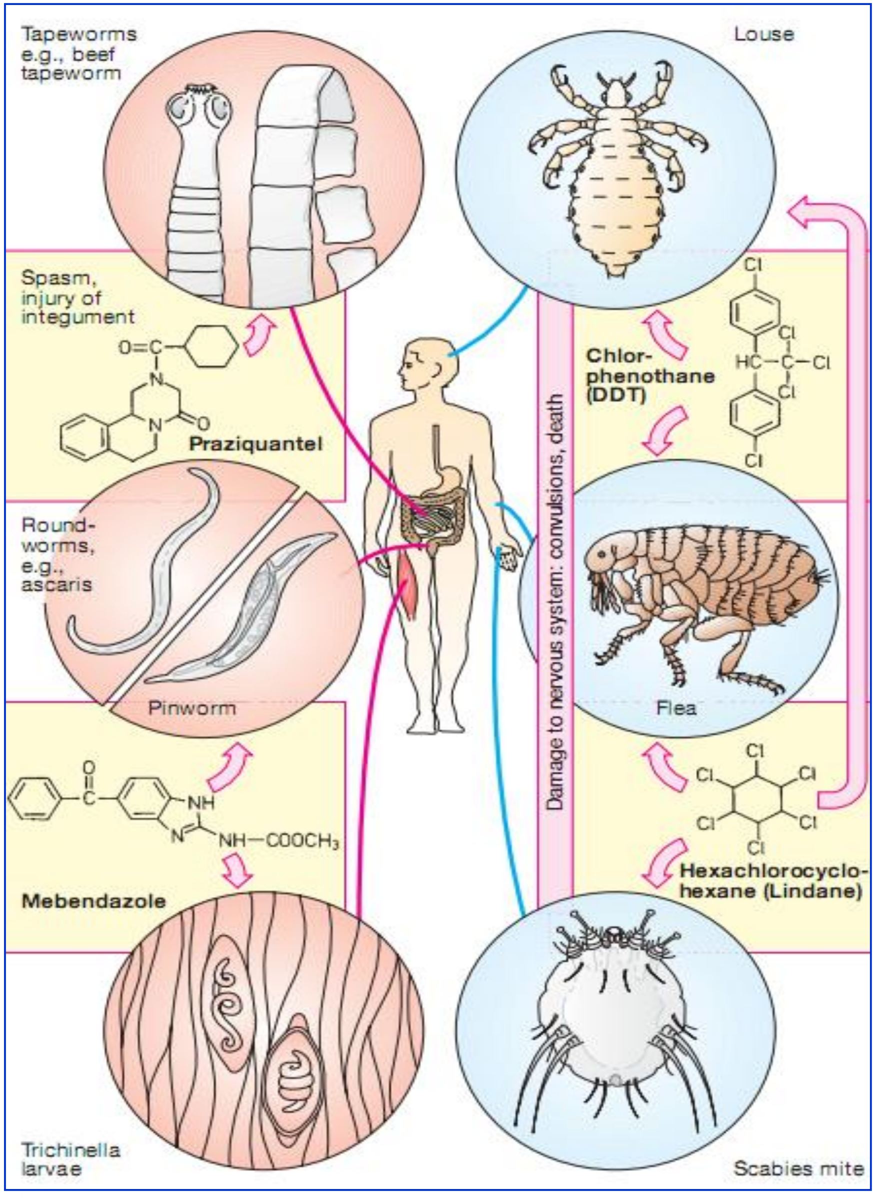
  peripherally -- sites of inflammation

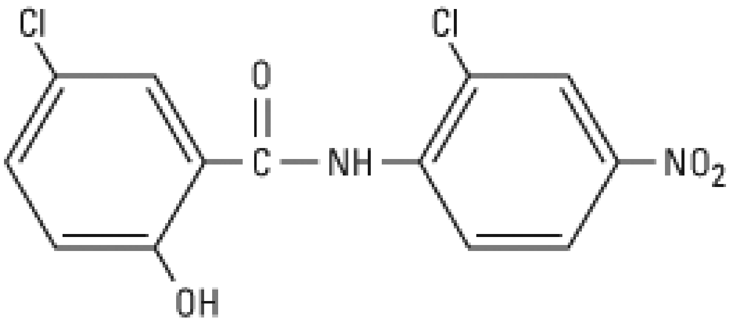
  subcortical sites

3. Anti-inflammatory Effects

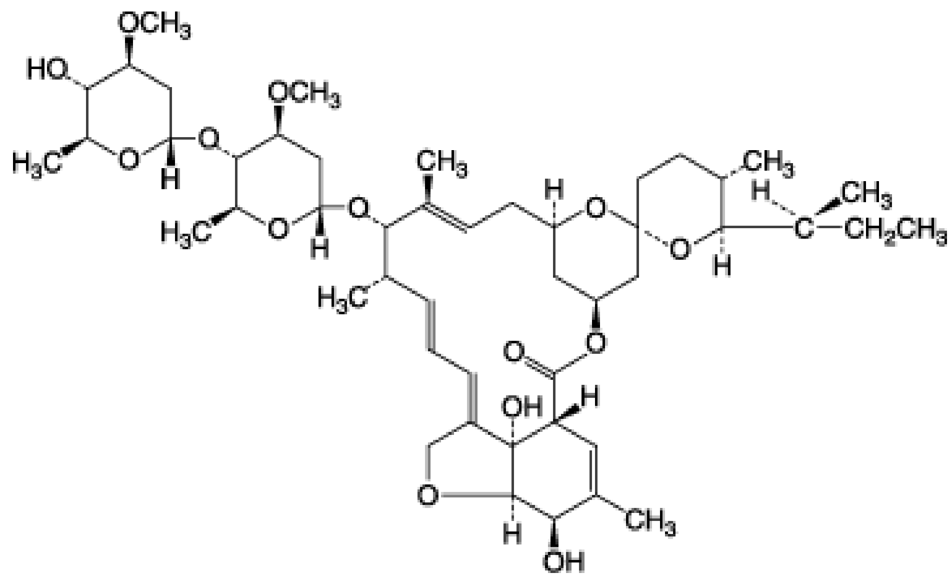
- NSAIDs only inhibit the symptoms of inflammation
- But they neither arrest the progress of the disease nor do they induce remission
- Reduced synthesis:
  - --eicosanoid mediators
- Interference:
  - --kallikrein system mediators
  - --inhibits granulocyte adherence
  - --stabilizes lysosomes
  - --inhibits leukocyte migration

Anthelmintic drugs
Insecticides

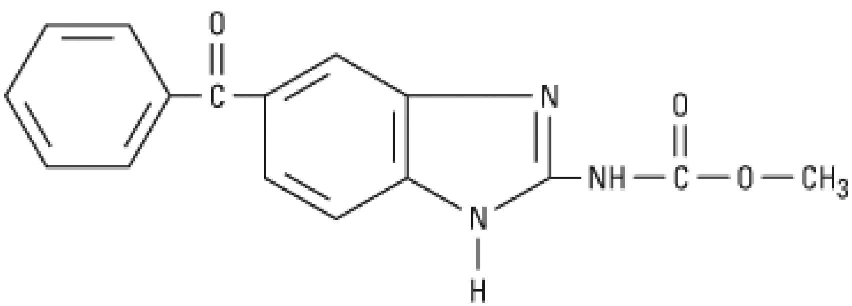




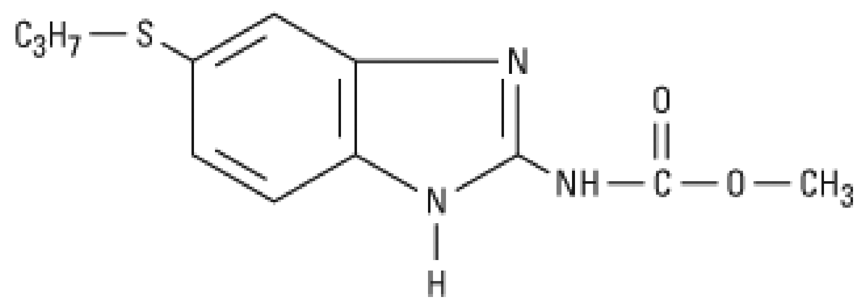
Niclosamide



IVERMECTIN



Mebendazole



Albendazole

Niclosamide *blocks glucose uptake* by intestinal tapeworms. It may cause some mild GI symptoms.

Piperazine may cause hypersensitivity reactions, *neurological symptoms* (including “worm wobble”) and may precipitate epilepsy.

Praziquantel paralyses both adult worms and larvae. It may cause nausea, headache, dizziness, and drowsiness; it cures with a single dose (or divided doses in one day).

Mebendazole

blocks glucose uptake by nematodes. Mild GI distarbunces may be caused, and it should not be used in pregnancy or in children under the age of 2.

Albendazole is similar to mebendazole.

Levamisole

paralyses the musculature of sensitive nematodes which, unable to maintain their anchorage, are expelled by normal peristalsis. It may cause abdominal pain, nausea, vomiting, headache, and dizziness.

Thiabendazole <u>inhibits cellular enzymes</u> of susceptible helminths. Gastrointestinal, neuro-logical and hypersensitivity reactions, liver damage, and crystalluria may be induced.

Pyrantel <u>*depolarises neuromuscular junctions*</u> of susceptible nematodes which are expelled in the faeces. It cures with a single dose. It may induce GI disturbance, headache, dizziness, drowsiness, and insomnia.

Diethylcarbamazine kills both microfilariae and adult worms. Fever, headache, anorexia, malaise, urticaria, vomiting, and asthmatic attacks following the first dose are due to products of destruction of the parasite, and reactions are minimised by slow increase in dosage over the first 3 days.

Ivermectin may cause immediate reactions due to the death of the *microfilaria (early stage in the life cycle of certain parasitic nematodes)* . It can be effective in a single dose, but it works best if repeated at 6–12-month intervals.

Cestodes (tapeworms)

Beef tapeworm – *Taenia saginata*

Pork tapeworm – *Taenia solium*

Cysticercosis – *Taenia solium*

Fish tapeworm – *Diphyllobothrium latum*

Hydatid disease – *Echinococcus granulosus*

Worms (helminths)	Drug of choice
Tapeworms (cestodes)	Niclosamide or Praziquantel or Albendazole
Roundworms (nematodes) • *Enterobius vermicularis* (pinworm) • *Ascaris lumbricoides* • *Trichuris trichiura* (whipworm) • *Trichinella spiralis* (trichinellosis)	Mebendazole or Pyrantel Mebendazole or Pyrantel Mebendazole or Albendazole Mebendazole and Thiabendazole
• *Strongyloides stercoralis* • *Necator americanus* (hookworm) • *Ancylostoma duodenale*	Thiabendazole Mebendazole or Pyrantel Mebendazole, Pyrantel, or Albendazole
• *Onchocerca volvulus* (Onchocercosis) • *Wuchereria bancrofti (Elephantiasis)*	Ivermectin Diethylcarbamazine
Flukes (trematodes) • *Schistzoma* (Schistozomes)	Praziquantel

Malaria

-Caused by ***Plasmodium*** **protozoa**

– 4 different species

-Cause: the bite of an **infected** adult female anopheline **mosquito**

-Also transmitted by **infected individuals via blood transfusion, congenitally, or infected needles by drug abusers**

Malaria is one of the most widespread diseases caused by protozoan parasite of the genus, *Plasmodium*. These parasites spend an asexual phase in man and sexual phase in female anopheles mosquito. *M*alaria is caused by four species of one-cell protozoan of the *Plasmodium* genus: *P. falciparum*, *P. vivax*. *P. malariae* and *P. ovale*. No antimalarial drug is effective against all four species.

Malarial Parasite (*Plasmodium*)

Two interdependent life cycles

- Sexual cycle: occurs in the mosquito

    -Asexual cycle: occurs in the human

Asexual cycle: two phases

Exoerythrocytic phase Occurs “outside” the erythrocyte

Also known as the tissue phase Erythrocytic phase Occurs

“inside” the erythrocyte Also known as the blood phase

- Knowledge of the life cycles is essential in understanding

antimalarial drug treatment

-Drugs are effective only during the asexual cycle

CLASSIFICATION Antimalarial agents

Antimalarial agents are chemically classified as •Cinchona alkaloids: eg. Quinine, Cinchonine.
•4- Amino quinolones: eg. Chloroquine, Amodiaquine, Hydroxy chloroquine.
•8 - Amino quinolines: eg. Bulaquine, Primaquine, Pamaquine.
•9- Amino acridine: eg. Mepacrine.
•Biguanides: eg. Proguanil, Cycloguanil.
•Pyrimidine analogue: eg. Pyrimethamine.
•Polycyclics: eg. Doxycycline, Halofantrine.
•Newer antimalarial agents: eg. Artemisinin, Fosmidomycin. •Sesquiterpene lactones: eg. Arteether, Arteemether, Artesunate.
•Miscellaneous: eg. Metaloamine, Sulphadoxine, Mefloquine.

Antimalarial: Mechanism of Action

1- 4-Aminoquinoline derivatives: chloroquine and hydroxychloroquine

-- Bind to parasite nucleoproteins and interfere with protein synthesis; also alter pH within the parasite

--Interfere with parasite’s ability to metabolize and use erythrocyte hemoglobin

--Effective only during the erythrocytic phase

2 – Primaquine

Only exoerythrocytic drug (works in both phases) Binds and alters parasitic DNA

3 - Sulfonamides, tetracycline's, clindamycin

Used in combination with antimalarial to increase protozoacidal effects

4- 4-Aminoquinoline derivatives: quinine and Mefloquine (Lariam)

-- Alter pH within the parasite

--Interfere with parasite's ability to metabolize and use erythrocyte hemoglobin --Effective only during the erythrocytic phase

5- Diaminopyrimidines (pyrimethamine (Daraprim) & trimethoprim)

--Inhibit protein synthesis essential for growth and survival

--Only effective during the erythrocytic phase

--These drugs may be used with sulfadoxine or dapsone or synergistic effects

ANTIVIRAL
and
ANTIRETROVIRAL
DRUGS

ANTIVIRAL AND ANTIRETROVIRAL DRUGS

Introduction

- Antiviral and antiretroviral agents are compounds active against viruses including retroviruses.
- Since viruses are obligate intracellular microorganisms, drugs that target viral processes must penetrate host cells.
- Therefore, drugs that negatively impact on a virus are also likely to negatively impact normal pathways of the host.
- Consequently, antiviral drugs have a narrow therapeutic margin as compared to antibacterial drugs.

Antivirals

Key characteristics of antiviral drugs

- **Able to enter the cells infected with virus**
- **Interfere with viral nucleic acid synthesis and/or regulation**
- **Some drugs interfere with ability of virus to bind to cells**
- **Some drugs stimulate the body's immune system**
- **Best responses to antiviral drugs are in patients with competent immune systems**
- **A healthy immune system works synergistically with the drug to eliminate or suppress viral activity**

Classification of antifungal drugs

- **Based on chemical structures**: The classes include pyrimidine nucleosides, purine nucleosides analogues and antimetabolites prodrugs.

- **Based on their modification of host biological functions**: Biologic Response Modifiers like cytokines

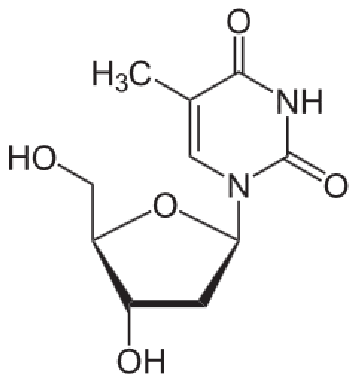
- **Based on the type of viruses they act on:** DNA based viruses or RNA based retroviruses

- **Miscellaneous antiviral drugs**

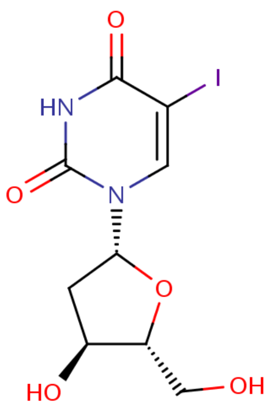
Pyrimidine nucleosides analogues

- Pyrimidine nucleoside analogues mimics pyrimidine nucleosides in their chemical structures and includes **Idoxuridine** and **Trifluridine**.

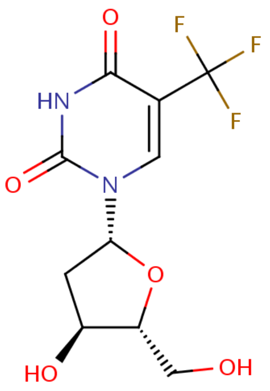
Pyrimidine nucleosides **Deoxythymidine analogues**



Deoxythymidine



Idoxuridine



Trifluridine

Mechanisms of actions of idoxuridine and trifluridine

- The pyrimidine nucleosides analogues substitute pyrimidine for thymidine, causing defective DNA molecules.

- In particular, idoxuridine inhibits viral replication by substituting itself for thymidine in viral DNA.

- This in turn inhibits the functions of thymidylate phosphorylase and viral DNA polymerases resulting in inability of the virus to reproduce and infect tissue.

Mechanisms of action of idoxuridine and trifluridine

- The mechanism of action of **trifluridine** has not been fully determined, but is thought to inhibit viral replication.

- It does this by incorporating into viral DNA during replication and forms defective proteins and cause an increased mutation rate.

- This drug also reversibly inhibits thymidylate synthetase, an enzyme that is necessary for DNA synthesis.

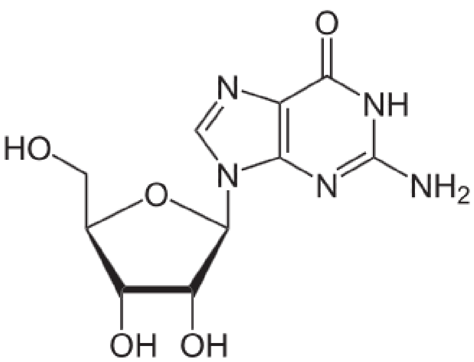
Clinical applications of idoxuridine and trifluridine

- Idoxuridine is effective against herpesvirus infection of the superficial layers of the cornea (herpesvirus keratitis) and of the skin, but is toxic when administered systemically.

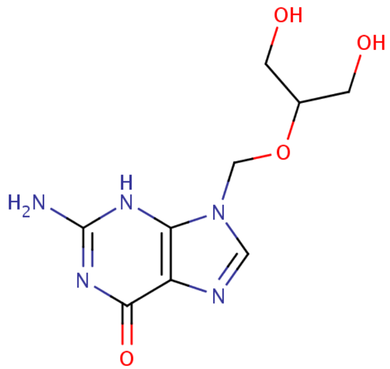
- Trifluridine is the agent of choice for the treatment of herpesvirus keratitis in humans.

Purine nucleosides analogues

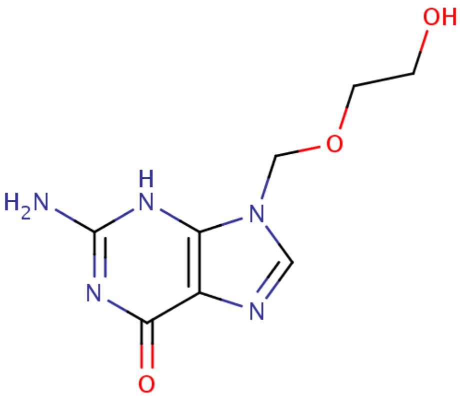
- These purine nucleoside analogues mimics guanosine nucleosides in their chemical structures and includes **vidarabine acyclovir,** and **ganciclovir**.



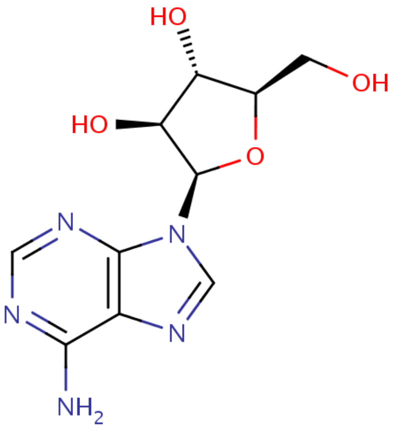
Guanosine



Ganciclovir



Acyclovir,



vidarabine

Mechanisms of actions

- **Vidarabine** is phosphorylated by cellular kinases to a triphosphate compound, which is an inhibitor and a substrate of viral DNA polymerase.

- When used as a substrate for viral DNA polymerase, the phosphrylated compound competitively inhibits dATP leading to the formation of ‘faulty’ DNA.

- This results in the prevention of DNA synthesis, as phosphodiester bridges can longer to be built, destabilizing the strand

Mechanisms of actions

- Acyclovir is phosphorylated by virus-induced thymidine kinase to the triphosphate form, which is a better substrate and inhibitor of viral DNA polymerase, compared with host.

- Binding to DNA polymerase is irreversible and once incorporated into viral DNA, the DNA chain is terminated.

- The mechanism of action of ganciclovir is similar to that of acyclovir.

Clinical applications

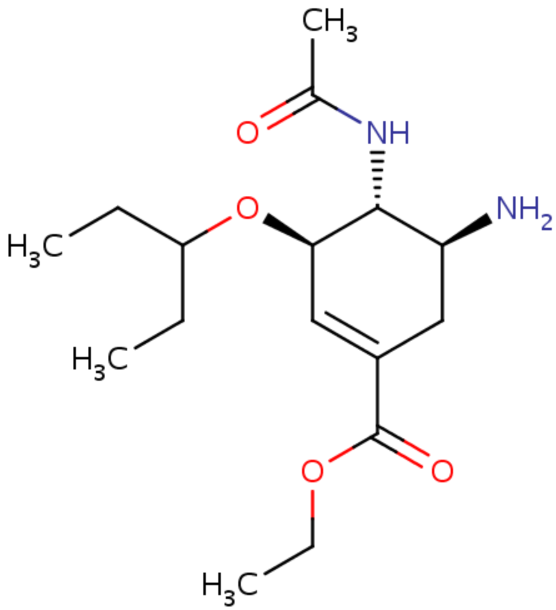
- Herpesviral enzymes are ~20-fold more susceptible vidarabine compared with host DNA.
- **Vidarabine** is effective against chickenpox - varicella, herpes zoster and herpes simplex.
- **Acyclovir** is useful against the herpesvirus family and is available as an ophthalmic ointment, a topical ointment and cream, an IV preparation, and oral formulations.
- **Ganciclovir** is effective against human cytomegalovirus.

Side effects

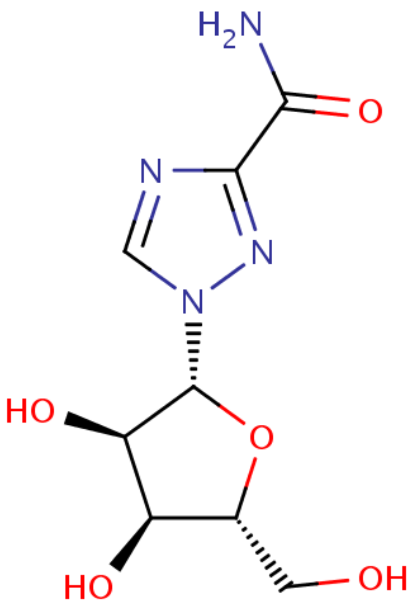
- Ganciclovir use may cuase neutropenia and thrombocytopenia, fever, rash, GIT symptoms, confusion and seizure.
- Vidarabine may cause bone marrow suppression and CNS problems when high blood levels are reached.

Antiviral prodrugs

- Ribavirin is a synthetic triazole nucleoside while is Oseltamivir an acetamido cyclohexene that is analogue of sialic acid



Oseltamivir



Ribavirin

Mechanism of action of ribavirin

- Ribavirin is readily phosphorylated intracellularly by adenosine kinase to ribavirin triphosphate.
- Ribavirin triphosphate is a potent competitive inhibitor of inosine monophosphate (IMP) dehydrogenase, viral RNA polymerase and viral mRNA guanylyltransferase.
- Guanylyltranserase inhibition stops the capping of mRNA
- This causes a marked reduction of intracellular guanosine triphosphate pools and inhibition of viral RNA and protein synthesis.
- Ribavirin is also incorporated into the viral genome causing lethal mutagenesis and a subsequent decrease in specific viral infectivity.

Clinical uses of ribarivin

- Ribavirin has a broad spectrum of activity against many RNA and DNA viruses.

- It is active against adenoviruses, herpesviruses, orthomyxoviruses, paramyxoviruses, poxviruses, picornaviruses, rhabdoviruses, rotaviruses, and retroviruses.

- Ribavirin does not have a wide margin of safety in domestic animals

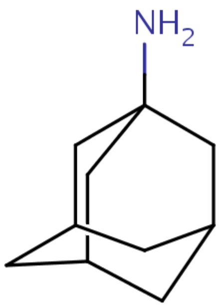
Mechanism of action of oseltamivir

- Oseltamivir is hydrolysed to oseltamivir carboxylate, the active form, which inhibits influenza virus neuraminidase and thus may alter virus particle aggregation and release.

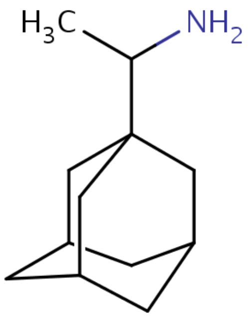
- Oseltamivir (Tamiflu) is effective against influenza infection in and has been used for the prophylaxis of influenza in humansr

Cyclic amine antiviral drugs

- Amantadine and rimantadine, are cyclic amine antiviral drugs.



Amantadine



Rimantadine

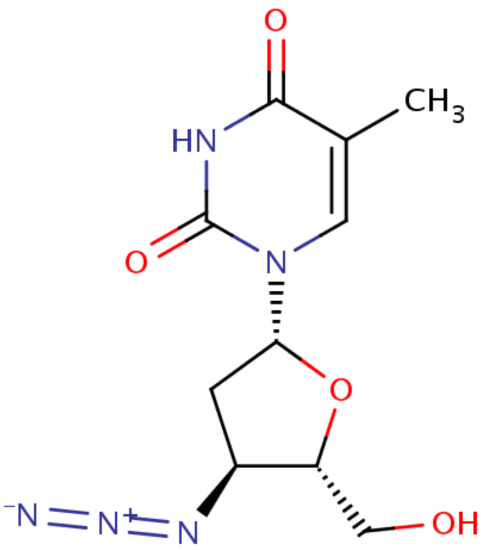
Mechanisms actions of cyclic amine antiviral drugs

- **Amantadine** drug interferes with a viral protein, M2 (an ion channel needed for the viral particle to become "uncoated" once it infects the cell.
- This leads to inhibition or delay of the uncoating process that precedes primary transcription.
- Amantadine may also interfere with the early stages of viral mRNA transcription.
- It is absorbed from the GI tract, and ~90% of a dose administered PO is excreted unchanged in the urine over several days (human data).
- The mechanism of action of rimantadine is not fully understood.
- It appears to exert its inhibitory effect early in the viral replicative cycle, possibly inhibiting the uncoating of the virus.

Antiretroviral drugs

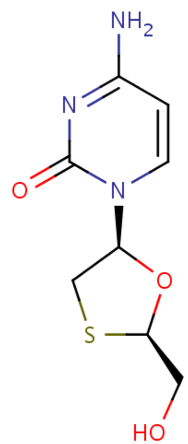
- Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV.

Thymidine analogue



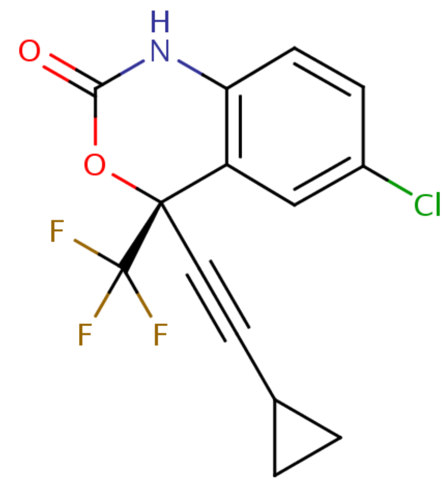
Azidothymidine, AZT

Synthetic nucleoside analogue



Lamivudine

Synthetic purine derivative



Efavirenz

Mechanisms of actions of antiretroviral drugs

- Generally, antiretroviral drugs inhibits retroviral reverse transcriptase and subsequent DNA transcription in host cells preventing viral replication.

- In particular, AZT inhibits viral reverse transcriptase, which converted the viral RNA into double-stranded DNA before it is integrated into the host cell genome and prevents viral replication.

- Efavirenz also inhibits the activity of viral reverse transcriptase but the drug must be converted intracellularly to the active triphosphorylated form.

Clinical use of antiretroviral drugs

- These drugs are mainly used in management of HIV and are of limited use in veterinary medicine

- The drugs are effective for acute infections but are relatively ineffective for chronically infected cells because they inhibit early viral replication.

- Granulocytopenia and anemia are the major adverse effects of AZT in human patients

Biologic response modifiers

- Biologic response modifiers include cytokines such as;
  - Interferons (IFN),
  - Interleukins (IL),
  - Hematopoietic growth factors
- Recombinant Interferon Alfa-2a has been produced

Mechanisms of actions of interferon 2α

- Interferons modulate the host immune response and thus may help in fighting viral infections.

- They bind to receptors on other cells and induce antiviral proteins that protect the cell from infection.

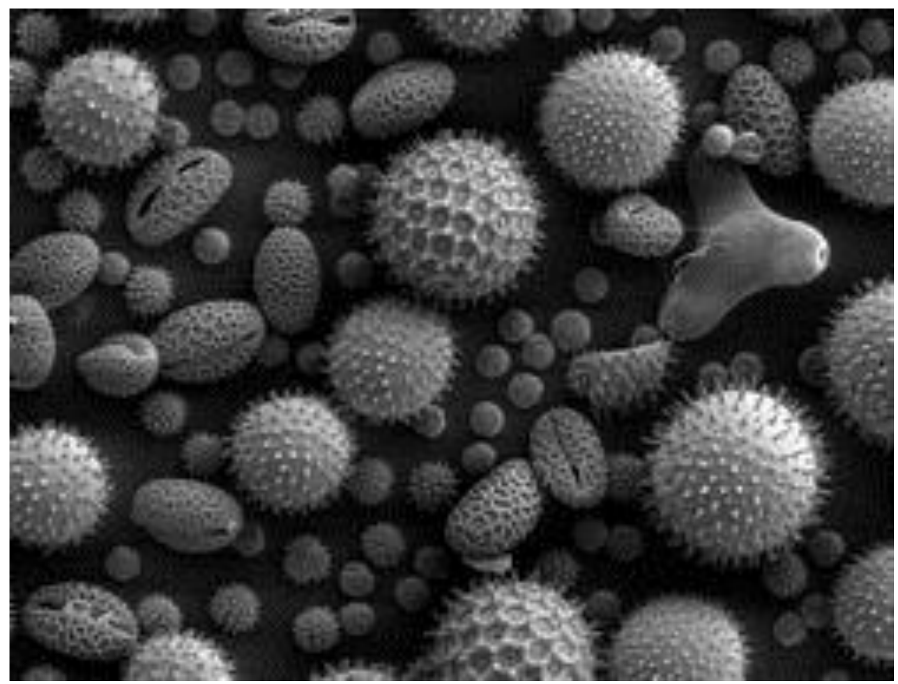
- IFNs also have antitumor, antiparasitic, and immuno-modulatory effects.

Clinical application of BRM

- Recombinant Interferon Alfa-2a may be used for treatment of chronic hepatitis C, and oral warts arising from HIV infection.

- In veterinary medicine, Interferon α-2 (3×10^6 IU/vial) may used to manage feline leukemia virus, feline infectious peritonitis and feline immunodeficiency virus.

Antihistamine Drugs



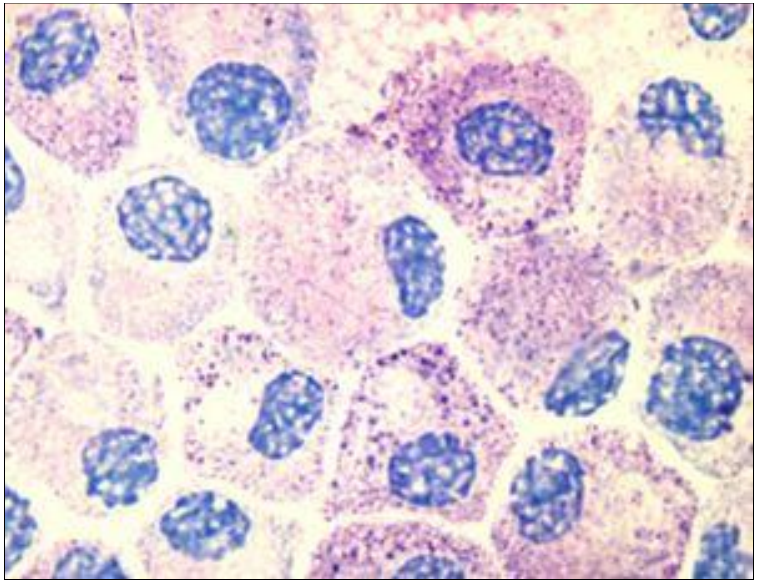
What is an antihistamine?

- A drug that reduces or eliminates the effects mediated by the chemical histamine
- Histamine is released by your body during an allergic reaction and acts on a specific histamine receptor
- True antihistamines are only the agents that produce a therapeutic effect that is mediated by negative modulation of histamine receptors (other agents may have antihistaminergic action but are not true antihistamines)
- The term antihistamine **only refers to H_1 receptor antagonists** (actually inverse agonists)
- Antihistamines compete with histamine for binding sites at the receptors. Antihistamine cannot remove the histamine if it is already bound

What are allergies?

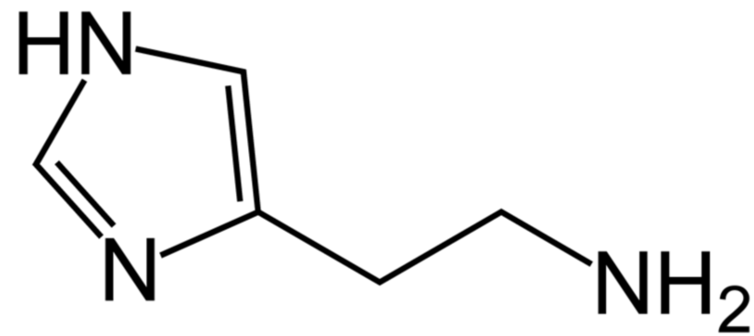
- Allergies are caused by a hypersensitivity reaction of the antibody class **<u>IgE</u>** (which are located on mast cells in the tissues and basophils in the blood)
- When an allergen is encountered, it binds to IgE, which excessively activates the mast cells or basophils, leading them to release massive amounts of histamines.
- These histamines lead to inflammatory responses ranging from runny nose to anaphylactic shock
- If both parents have allergies, you have a 70% of having them, if only one parent does, you have a 48% chance (American Academy of Asthma, Allergies and Immunology, Spring 2003).

Allergies



Mast Cells

•Histamine is distributed in Mast Cells in all peripheral tissues of the body and basophils, which circulate in the blood

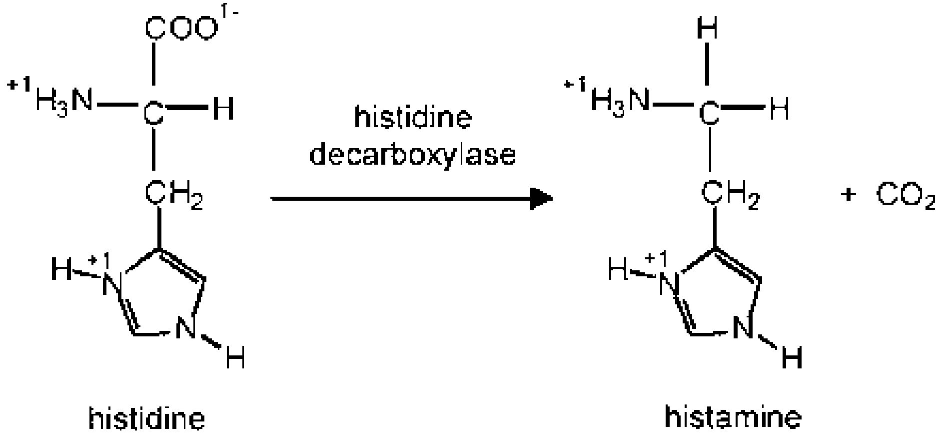


Structure of Histamine

•When it is released, histamine causes inflammation by increasing vasodilation, capillary permeability, causing smooth muscle contraction, mucus secretion, and parasympathetic nerve stimulation

Synthesis of Histamine

- Formed from the amino acid Histadine in a decarboxylation reaction with the enzyme histadine decarboxylase
- Occurs primarily in mast cells and basophils



The different Histamine receptors

	Location	Type of receptor	Effect	Treatment
H1	Throughout the body, specifically in smooth muscles, on vascular endothelial cells, in the heart and the CNS	G-protein coupled, linked to intercellular Gq, which activates phospholipase C	Mediate an increase in vascular permeability at sites of inflammation induced by histamine	Allergies, nausea, sleep disorders
H2	In more specific locations in the body mainly in gastric parietal cells, a low level can be found in vascular smooth muscle, neutrophils, CNS, heart, uterus	G-protein coupled, linked to intercellular Gs	Increases the release of gastric acid	Stomach ulcers
H3	Found mostly in the CNS, with a high level in the thalamus, caudate nucleus and cortex, also a low level detected in small intestine, testis and prostate.	G-protein coupled, possibly linked to intercellular Gi	Neural presynaptic receptor, may function to release histamine	Unknown
H4	They were recently discovered in 2000. They are widely expressed in components of the immune system such as the spleen, thymus and leukocytes.	Unknown, most likely also G-protein coupled	Unknown	In addition to benefiting allergic conditions, research in the h4 receptor may lead to the treatment of autoimmune diseases. (rheumatoid arthritis and IBS)

Clinical Uses of Antihistamines

- Allergic rhinitis (common cold)
- Allergic conjunctivitis (pink eye)
- Allergic dermatological conditions
- Urticaria (hives)
- Angioedema (swelling of the skin)
- Puritus (atopic dermatitis, insect bites)
- Anaphylactic reactions (severe allergies)
- Nausea and vomiting (first generation H_1-antihistamines)
- Sedation (first generation H_1-antihistamines)

The future of antihistamines

- The anti-inflammatory activity of second generation antihistamines, about which little is known, will continue to be researched and possibly lead to an effective alternative to corticosteriods in the treatment of allergic airways conditions.
- The action of the H4 receptor will also continue to be researched and will possibly lead to effective treatment of autoimmune dieseases.
- Creating antihistamines with higher selectivity and less adverse side effects will continue to be the goal

Anesthetics Drugs

Definition of anesthesia

It is a reversible blocking of pain feeling in whole body or in a part of it using pharmacology or other methods

Anesthesia- division

Local- regional anesthesia, patient is conscious or sedated

General- anesthesia interact with whole body, function of central nervous system is depressed:

– Intravenous

– Inhalation (volatile)

– Combined, balanced

Anesthetics divide into 2 classes

Inhalation Anesthetics	**Intravenous** Anesthetics
• Gasses or Vapors • Usually Halogenated	• Injections • Anesthetics or induction agents

Inhalation Anesthetics

Nitrous oxide

Halogenated anaes:

- Halothane
- Isoflurane
- Sevoflurane
- Enflurane

Mechanism of Action

- Interaction with protein receptors
- Volatile A – increase GABA and Glycine

  (inhibitory neurotransmitters)

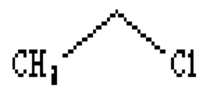
What are General Anesthetics?

- A drug that brings about a reversible loss of consciousness.
- These drugs are generally administered by an anesthesiologist in order to induce or maintain general anesthesia to facilitate surgery.

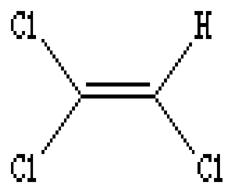
Inhaled Anesthetics

- Halothane
- Enflurane
- Isoflurane
- Desflurane

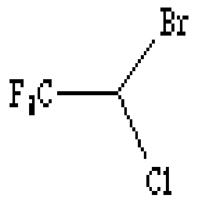
Halogenated compounds:
- Contain Fluorine and/or bromide
- Simple, small molecules



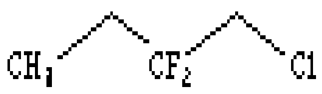
ethyl chloride



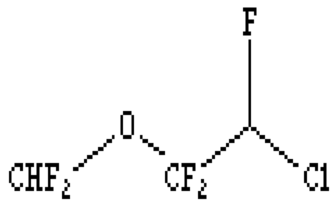
trichloroethylene



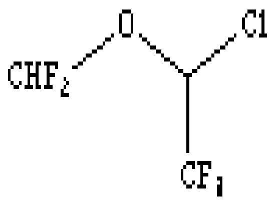
halothane, U.S.P.
(Fluothane®)



methoxyflurane, U.S.P.
(Penthrane®)



enflurane, U.S.P.
(Enthrane®)



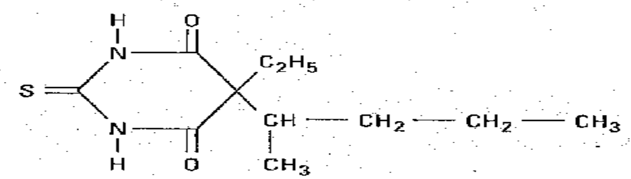
isoflurane
(Forane®)

Physical and Chemical Properties of Inhaled Anesthetics

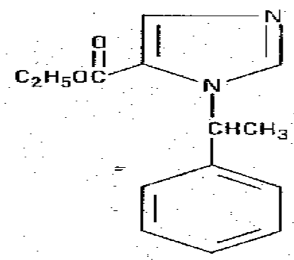
- Although halogenations of hydrocarbons and ethers increase anesthetic potency, it also increase the potential for inducing cardiac arrhythmias in the following order F<Cl<Br.1
- Ethers that have an asymmetric halogenated carbon tend to be good anesthetics (such as Enflurane).
- Halogenated methyl ethyl ethers (Enflurane and Isoflurane) are more stable, are more potent, and have better clinical profile than halogenated diethyl ethers.
- fluorination decrease flammibity and increase stability of adjacent halogenated carbons.
- Complete halogenations of alkane and ethers or full halogenations of end methyl groups decrease potency and enhances convulsant activity. Flurorthyl (CF3CH2OCH2CF3) is a potent convulsant, with a median effective dose (ED50) for convulsions in mice of 0.00122 atm.
- The presence of double bonds tends to increase chemical reactivity and toxicity.

Intravenous Anesthetics

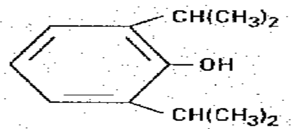
- Used in combination with Inhaled anesthetics to:
  - Supplement general anesthesia
  - Maintain general anesthesia
  - Provide sedation
  - Control blood pressure
  - Protect the brain



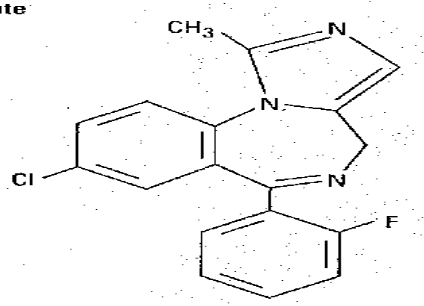
Thiopental



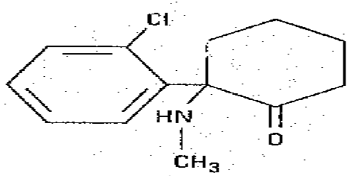
Etomidate



Propofol



Midazolam



Ketamine

Essential Components of Anesthesia

- Analgesia- perception of pain eliminated
- Hypnosis- unconsciousness
- Depression of spinal motor reflexes
- Muscle relation

* These terms together emphasize the role of immobility and of insensibility!

Hypotheses of General Anesthesia

1. Lipid Theory: based on the fact that anesthetic action is correlated with the oil/gas coefficients.
   - The higher the solubility of anesthetics is in oil, the greater is the anesthetic potency.
   - Meyer and Overton Correlations
   - Irrelevant

2. Protein (Receptor) Theory: based on the fact that anesthetic potency is correlated with the ability of anesthetics to inhibit enzymes activity of a pure, soluble protein. Also, attempts to explain the $GABA_A$ receptor is a potential target of anesthetics action.

Mechanism of Action

UNKNOWN!!

- Most Recent Studies:
  - General Anesthetics acts on the CNS by modifying the electrical activity of neurons at a molecular level by modifying functions of ION CHANNELS.
  - This may occur by anesthetic molecules binding directly to ion channels or by their disrupting the functions of molecules that maintain ion channels.

Pharmacokinetics of Inhaled Anesthetics

1. Amount that reaches the brain

   Indicated by oil:gas ratio (lipid solubility)

2. Partial Pressure of anesthetics

   5% anesthetics = 38 mmHg

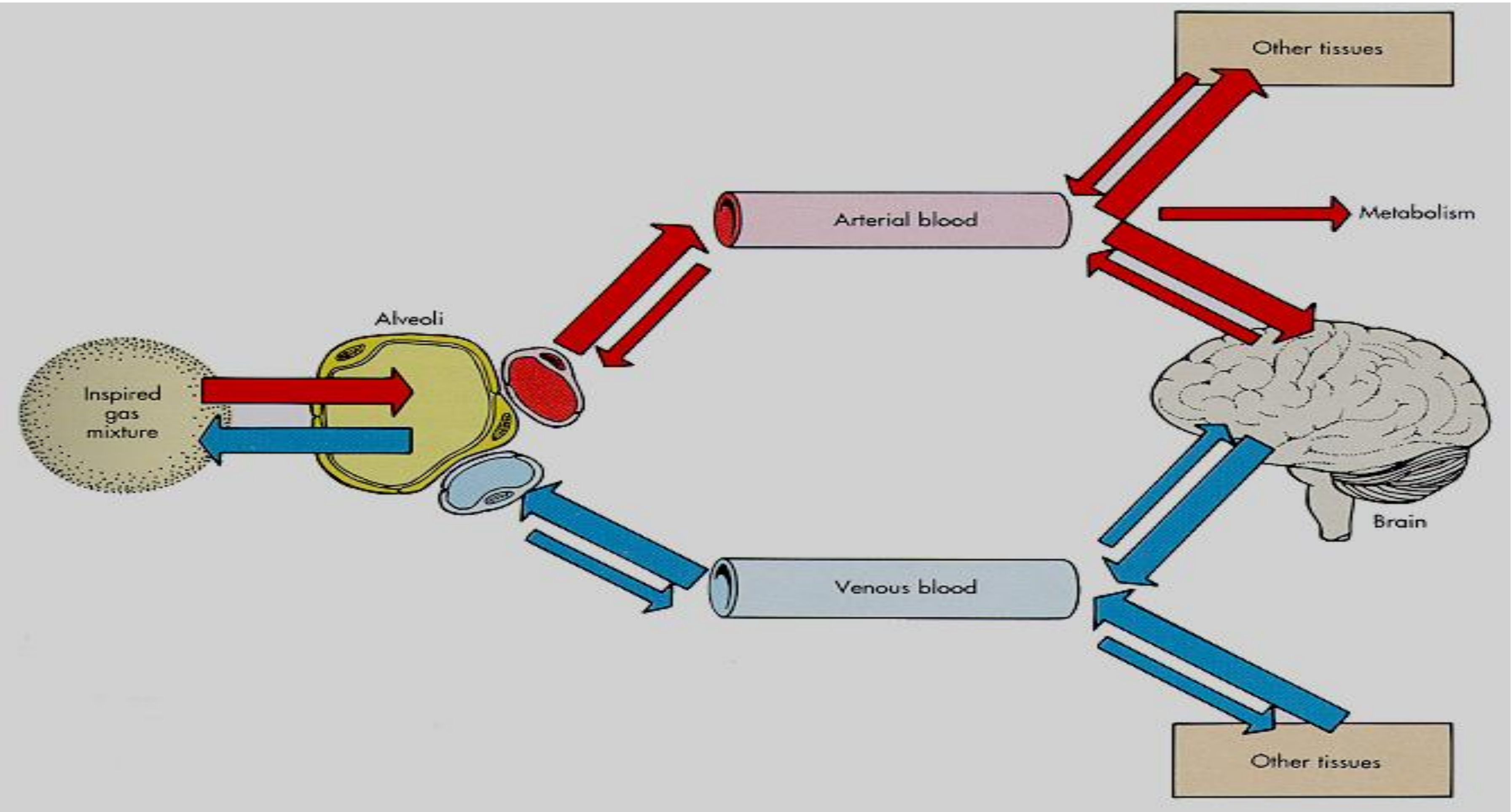
3. Solubility of gas into blood

   The lower the blood:gas ratio, the more anesthetics will arrive at the brain

4. Cardiac Output

   Increased CO= greater Induction time

Pathway for General Anesthetics



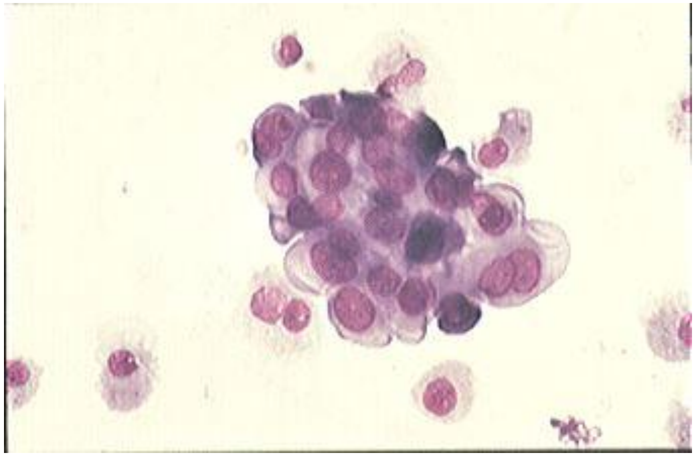
Toxicity and Side Effects

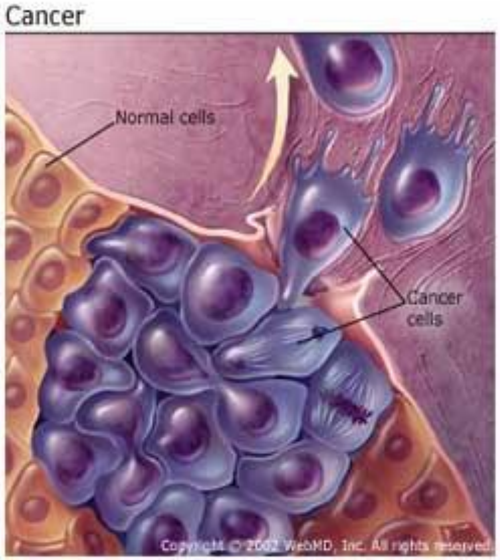
- **Depression of respiratory drive**
  - **Decreased CO_2 drive (medullary chemoreceptors), Takes MORE CO_2 to stimulate respiration**
- **Depressed cardiovascular drive**
- **Gaseous space enlargement by NO**
- **Fluoride-ion toxicity from methoxyflurane**
  - **Metabolized in liver = release of Fluoride ions**
    - **Decreased renal function allows fluoride to accumulate = nephrotoxicity**

Anti-cancer drugs

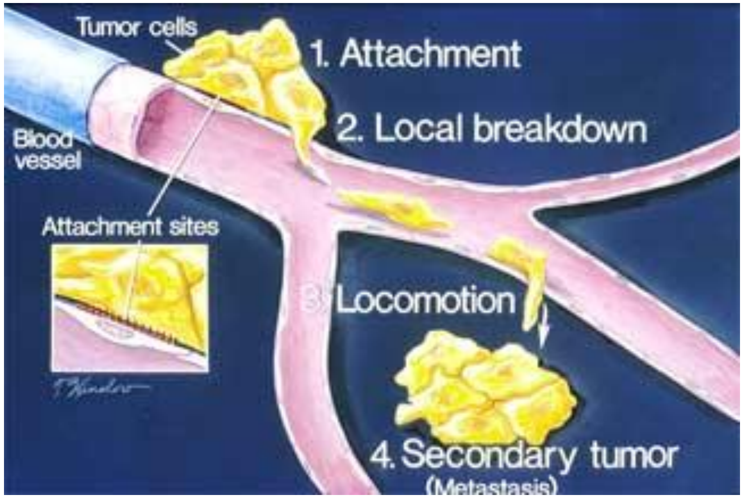
Cancer

- ✓ Abnormal, uncontrolled cell division
- ✓ Damage to genes controlling cell growth
- ✓ Cancer cells lose normal functions
- ✓ Divide rapidly
- ✓ Invade surrounding cells

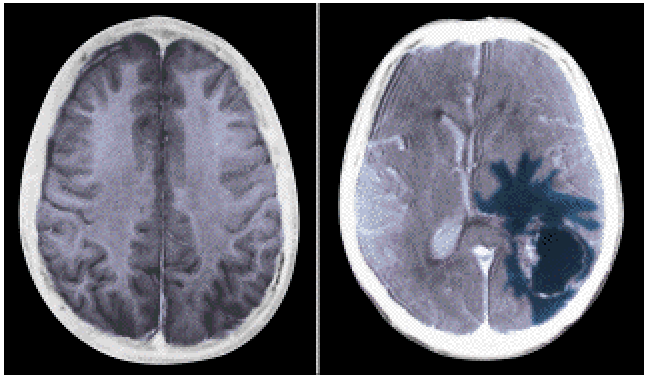




Definitions

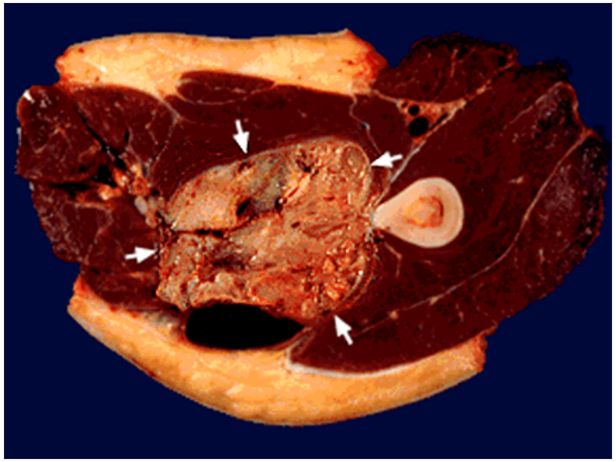


- ✓ **Metastasis: abnormal cells traveling to different sites and starting new tumors**
- ✓ **Tumor: abnormal enlargement**
- ✓ **Neoplasm: same as tumor**



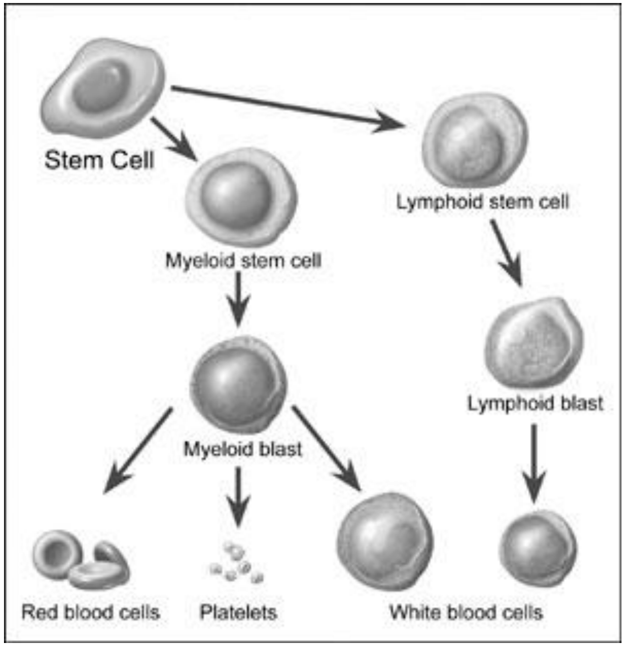
Tumors

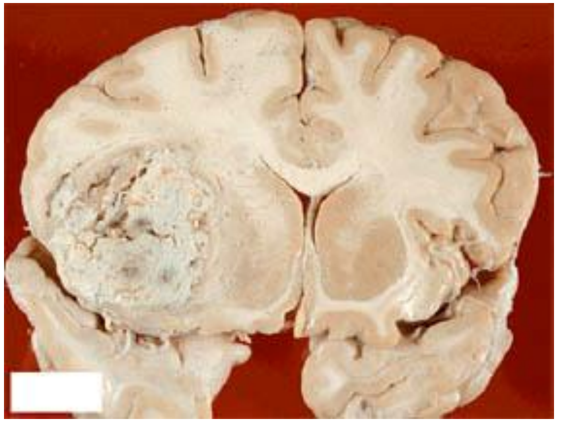
- Benign – slow growing, do not mets
  - Adenoma
- Malignant – fast growing, usually mets, can result in death
  - Sarcoma – connective tissue
  - Carcinoma – epithelial tissue (more common)



Tumors

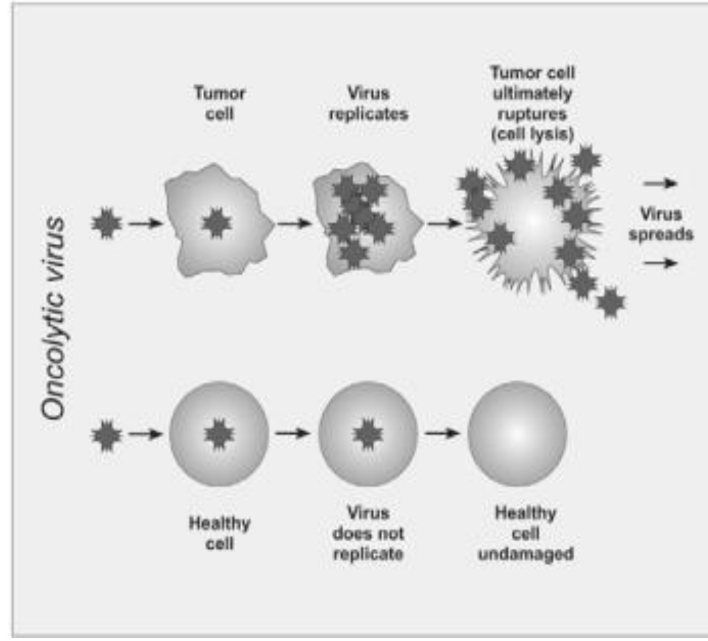
- ✓ Leukemia – cancer in blood-forming cells in bone marrow
- ✓ Lymphoma – cancer of lymph tissue
- ✓ Glioma – cancer in glial cells





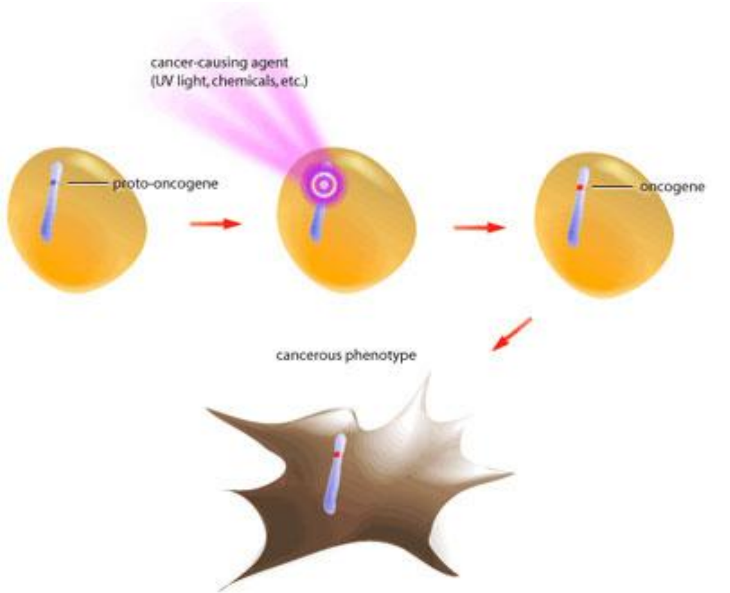
Causes of Cancer

- ✓ Carcinogens
- ✓ Exposure to large amounts of radiation or sun
- ✓ Viruses
- ✓ Genetic components



Genetic cancers

- ✓ Oncogenes: mutated genes that contribute to cancer development by disrupting a cell's ability to control its own growth and DNA repair mechanisms
- ✓ Ties with environmental component

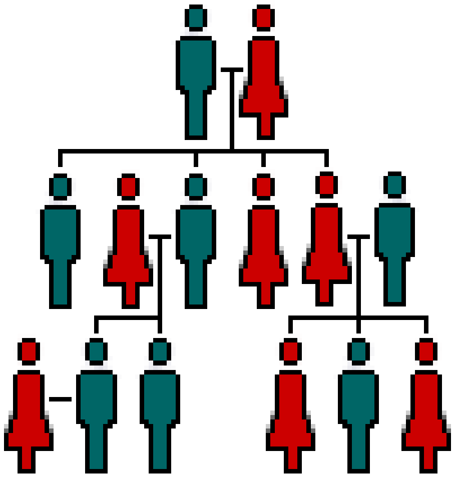


Minimizing Chance of Cancer

- ✓ Healthy lifestyle with check-ups
- ✓ No smoking, drinking
- ✓ Low fat, increase fiber
- ✓ Exercise
- ✓ Self-exams

Minimizing chances of Cancer

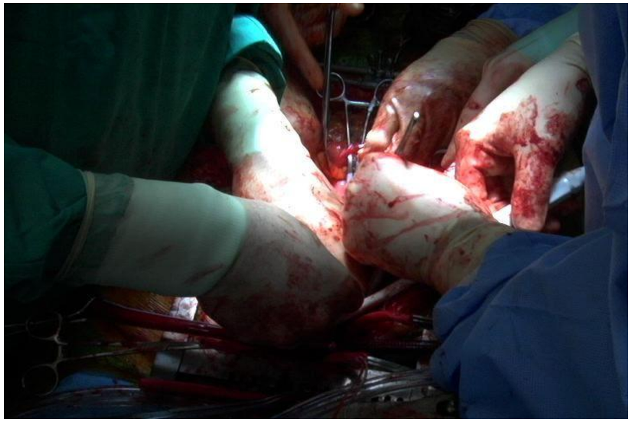
- ✓ Periodic testing if genetic ties with cancer
- ✓ Cancer curable if caught early
- ✓ Protect from direct sun if sensitive or fair skin
- ✓ Watch moles and freckles



Testicular Ca

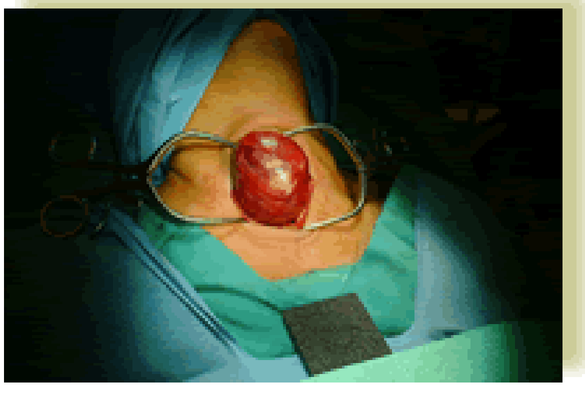
Treatment

- ✓ Goal: Removal of ALL cancer cells
- ✓ Surgery
- ✓ Radiation therapy
- ✓ Drug therapy



Surgery

- ✓ Large tumors reduced by radiation or removed by surgery
- ✓ Check "borders" for cells
- ✓ Then chemo to eradicate micro metastasis
- ✓ Combination chemotherapy has a higher cancer cell-kill than single drug

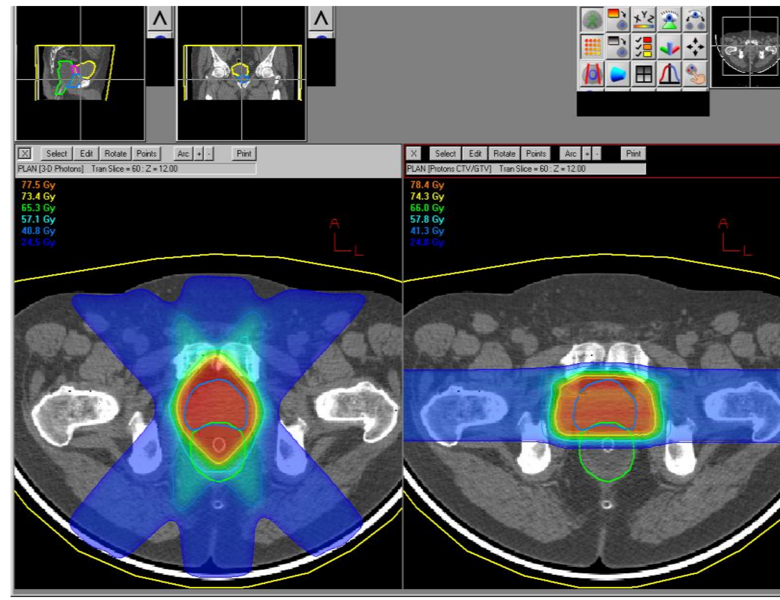


Radiation

- ✓ Effective non-surgical treatment
- ✓ High doses of radiation directed at tumor
- ✓ Confined to area of tumor
- ✓ Palliation: shrinking of inoperable tumors for comfort

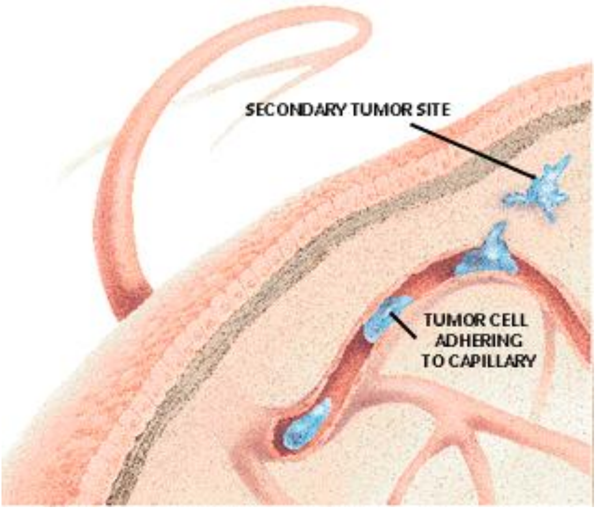
Radiation - Proton

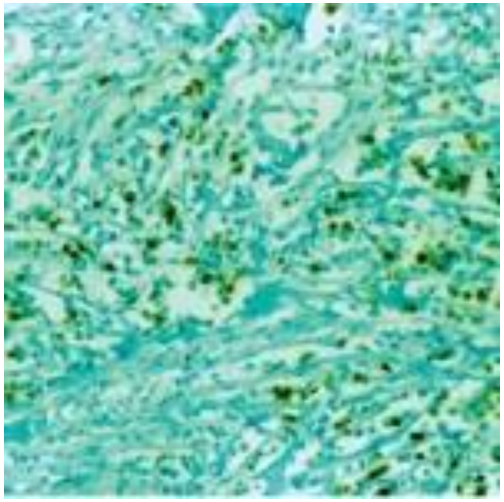
- ✓ Effective non-surgical treatment
- ✓ Proton beam aimed directly at tumor
- ✓ Radiate tumor only
- ✓ Changes ionization
- ✓ Change atoms of diseased cells



Chemotherapy

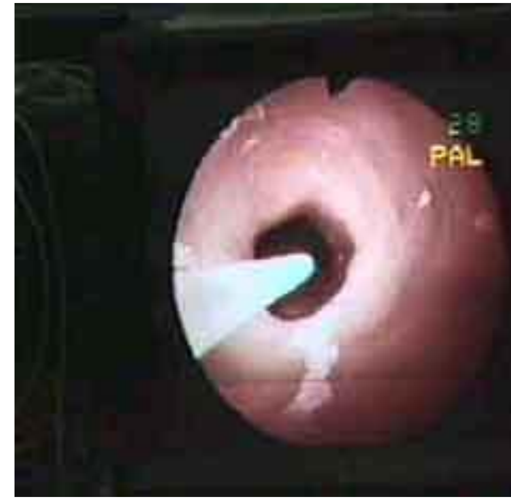
- ✓ Drugs transported via blood
- ✓ Reduce size of tumor for surgical removal or for palliation
- ✓ Prophylaxis to prevent recurrence of cancer
- ✓ Growth fraction: # tumor cells undergoing mitosis



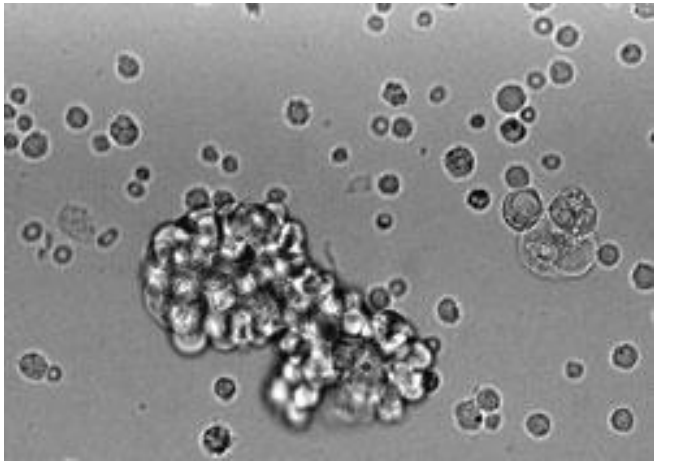


Chemotherapy administration

- ✓ Intravascular – peripheral versus central lines
- ✓ Oral
- ✓ Topical
- ✓ Intra cavity



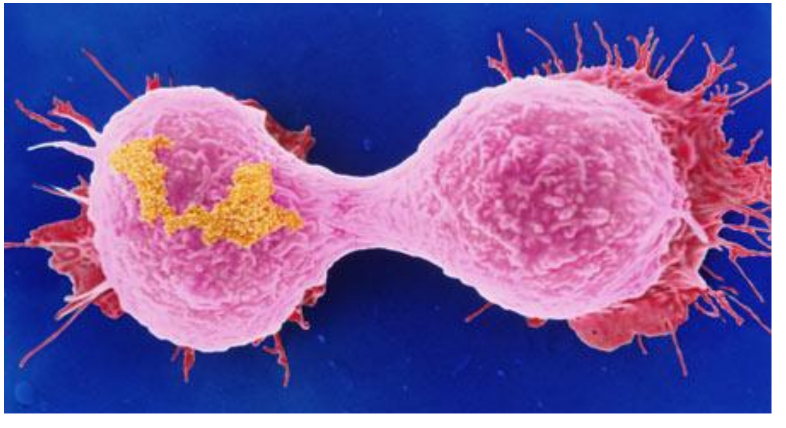
Principles of Chemotherapy



- ✓ Most effective against small tumors – good blood supply
- ✓ Small tumors have higher percent of dividing cells
- ✓ Nadir: lowest point neutrophil count has been depressed – increase chance for infection

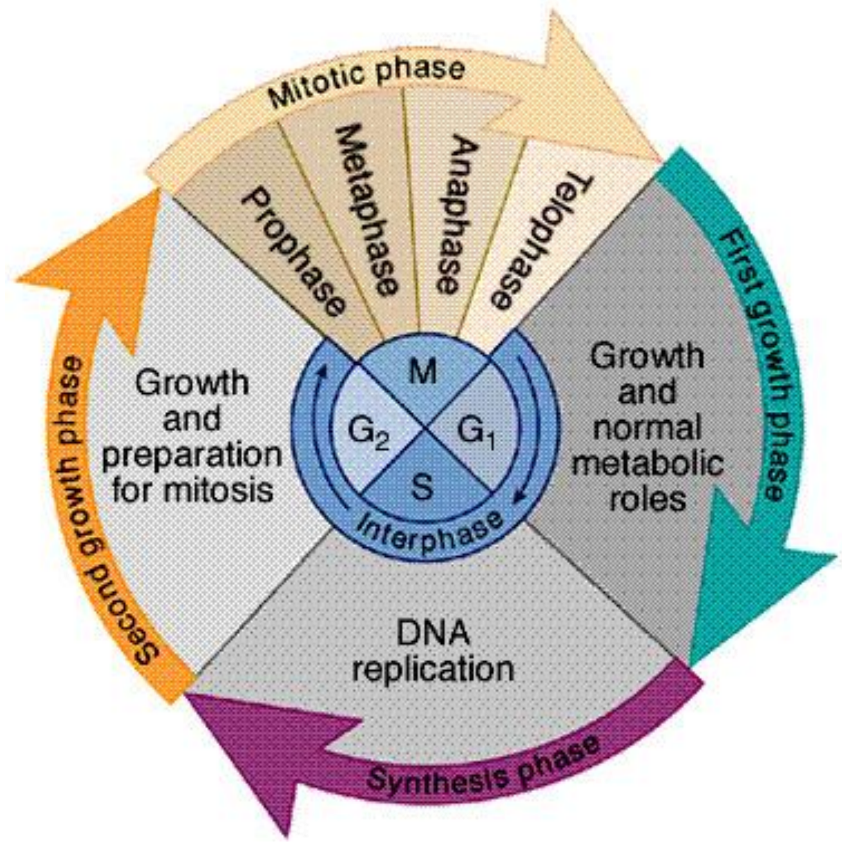
Cell cycle

- ✓ **Tumor cells similar to non-cancerous cells**
- ✓ **Neoplastic and normal cell differ in the number of cells undergoing cell division**
- ✓ **Cancer cells lack normal mechanism of suppressing cell growth**
- ✓ **Anti-cancer drugs target cells that are dividing**



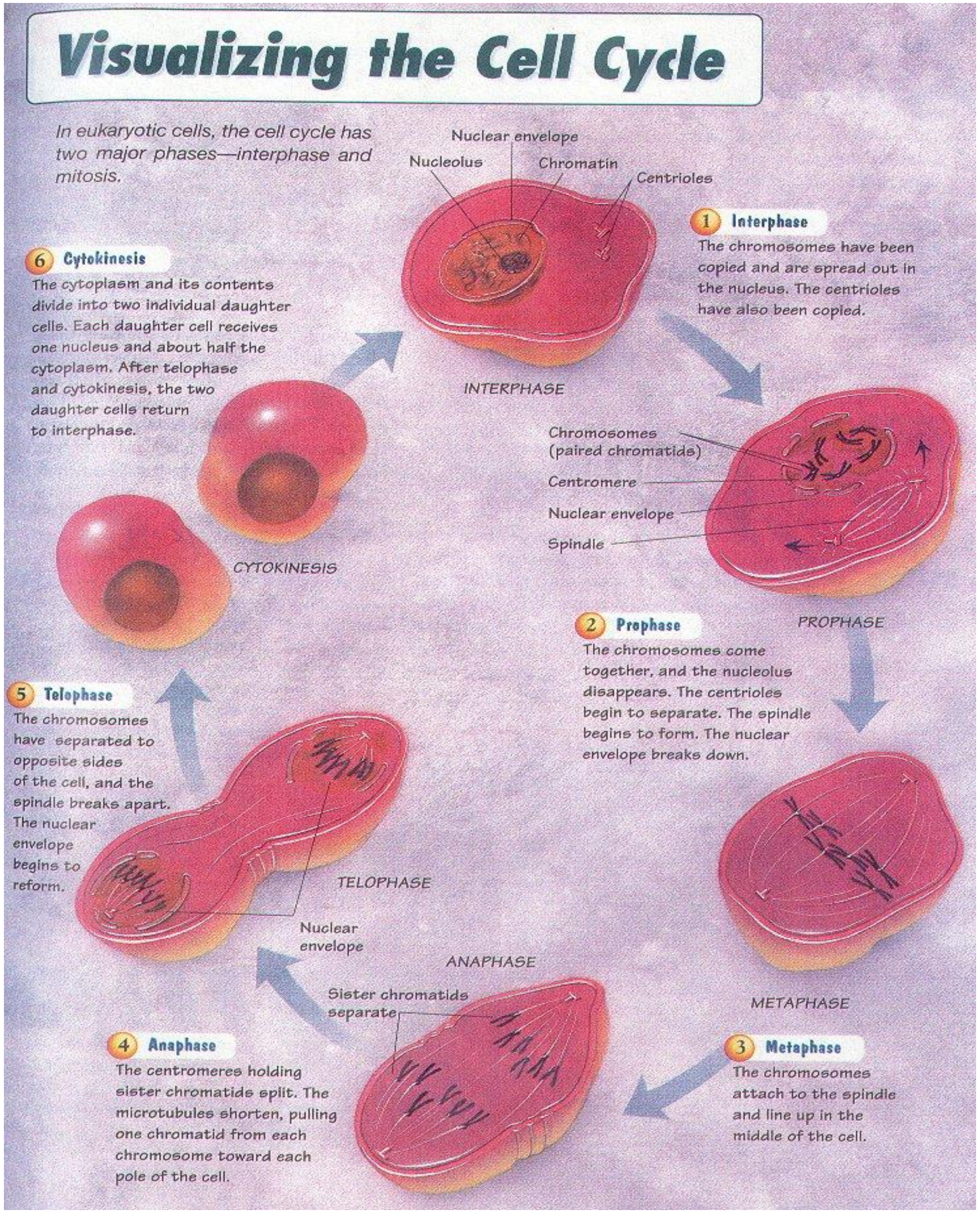
Cell cycle

- ✓ Interfere with DNA, RNA, or protein synthesis – S-phase specific
- ✓ Inhibit microtubule formation during mitosis – M-phase



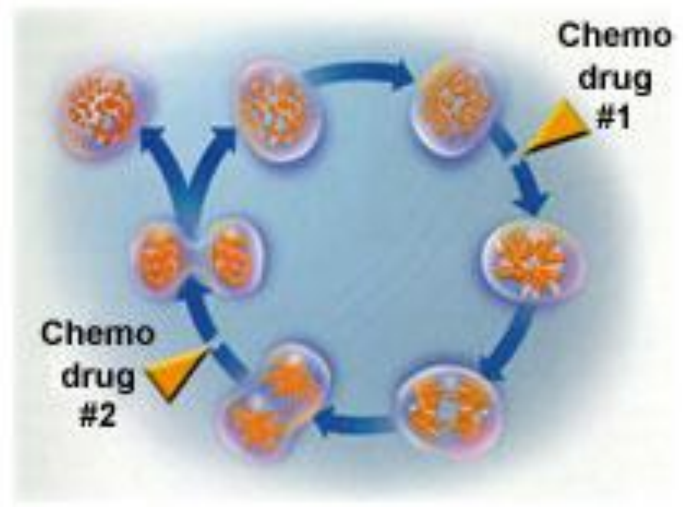
Cell cycle

- ✓ Damage DNA
- ✓ Cell-cycle non-specific
- ✓ DNA alkylating agents damage tumor cells whether dividing or not



Combination Chemotherapy

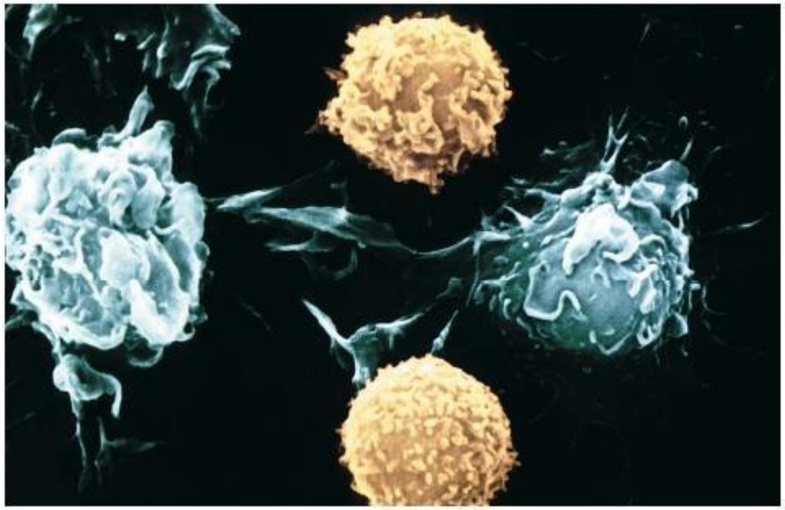
- ✓ Each drug active against the cancer
- ✓ Different site of action
- ✓ Different toxicity levels
- ✓ If similar, toxic levels occur at different times
- ✓ Nadirs different times



Different chemotherapy drugs are effective during differnt phases of the cycle of cell growth and division.

Total Cure

- ✓ Destroy all cancer cells
- ✓ One cancer cell can be enough to re-start proliferation of cells
- ✓ Not really total cure, "remission" where cancer cells not active



Anti-cancer drugs

- ✓ "Kills" cells
- ✓ Interfere with cell proliferation
- ✓ Damage cell DNA
- ✓ Prevent DNA repair in cell