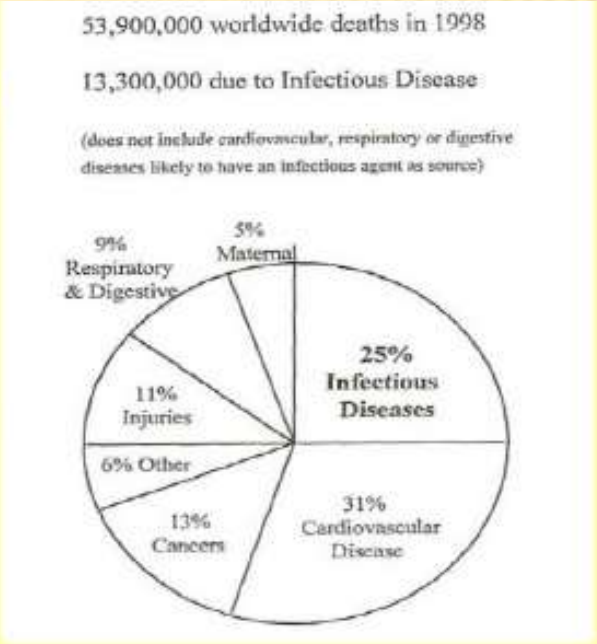
Antibiotics

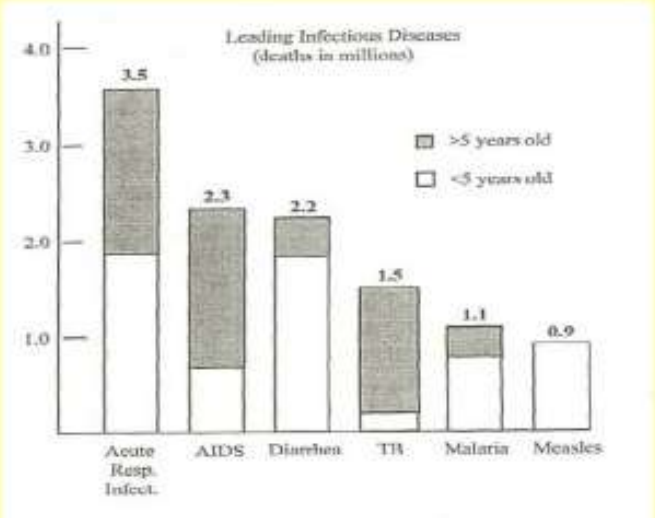
PENICILLINS

HISTORY OF ANTIBIOTICS

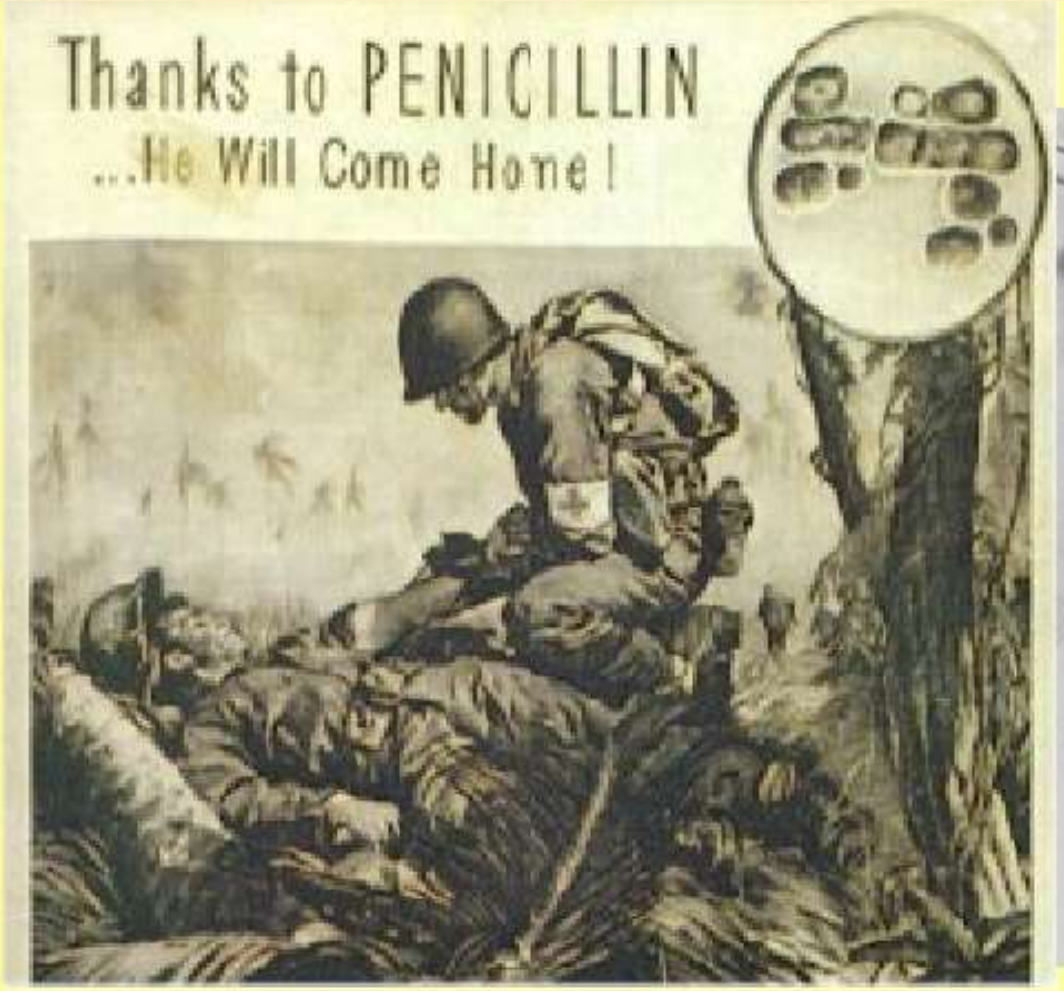
The End of Infectious Disease

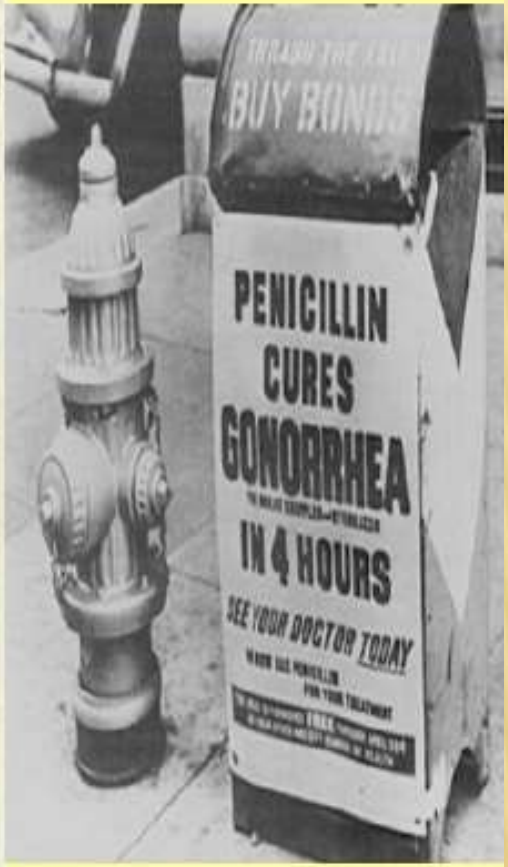
- From 1981 to 1995 deaths from infectious disease increased by 4.8% annually.
- In 1998 WHO estimated that over 13 million deaths worldwide were caused by infectious disease, almost a quarter of the total deaths in that period. That percentage was up to 26% in 2001.
- In 1995 the annual in-hospital costs associated with resistance of 6 bacterial species to a single antibiotic were estimated to be $1.3 billion.
- 37 new human pathogens have been identified in the last 30 years.
- 12% of known human pathogens have been recognized as emerging or reemerging health threats





HISTORY OF ANTIBIOTICS





HISTORY OF ANTIBIOTICS

Brief History of Antibiotics

- 1928- Penicillin discovered by Fleming
- 1932- Sulfonamide antimicrobial activity discovered {Erlich}•
- 1943- Drug companies begin mass production of penicillin
- 1948- Cephalosporins precursor sent to Oxford for synthesis
- 1952- Erythromycin derived from Streptomyces erythreus
- 1956- Vancomycin introduced for penicillin resistant staphylococcus
- 1962- Quinolone antibiotics first discovered
- 1970s- Linezolide discovered but not pursued
- 1980s- Fluorinated Quinolones introduced, making then clinically useful
- 2000- Linezolide introduced into clinical practice

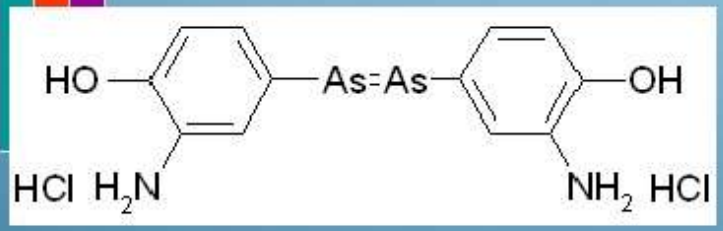
HISTORY OF ANTIBIOTICS

The History of Medicine

2000 B.C.—Here, eat this root.
1000 A.D.—That root is heathen. Here, say this prayer.
1850 A.D.—That prayer is superstition. Here, drink this potion.
1920 A.D.—That potion is snake oil. Here, swallow this pill.
1945 A.D.—That pill is ineffective. Here, take this penicillin.
1955 A.D.—Oops…bugs mutated. Here, take this tetracycline.
1960–1999—39 more "oops."Here, take this more powerful antibiotic.
2000 A.D.—The bugs have won! Here, eat this root.
—Anonymous (WHO, 2000)

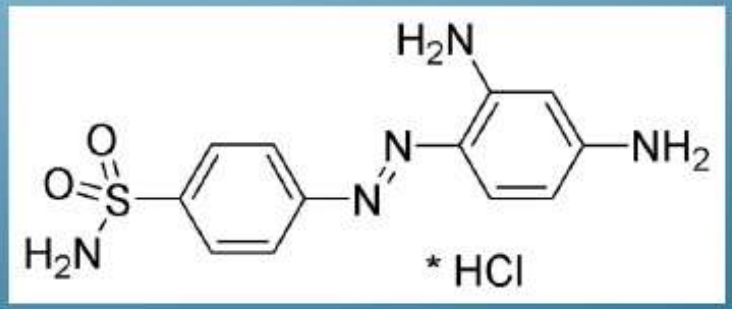
HISTORY OF ANTIBIOTICS

Ehrlich's Magic Bullets



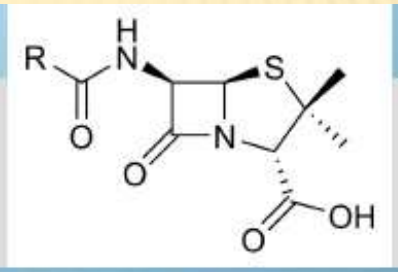
HISTORY OF ANTIBIOTICS

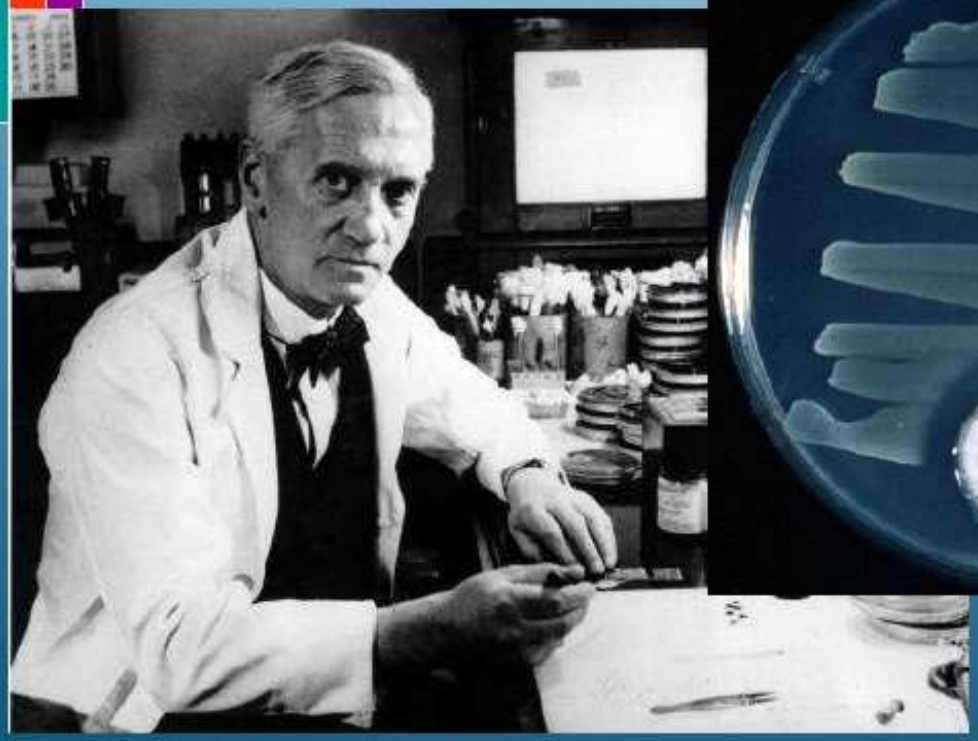
Gerhard Domagk - Prontosil

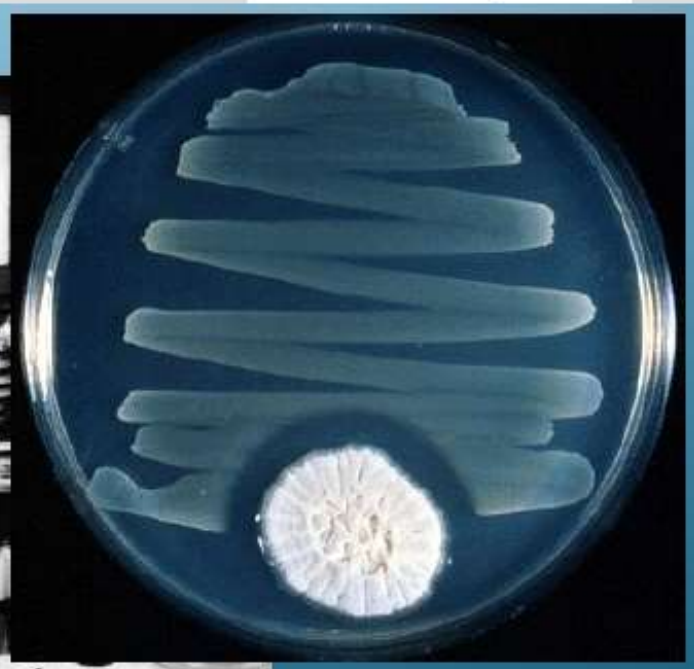


HISTORY OF ANTIBIOTICS

Fleming and Penicillin

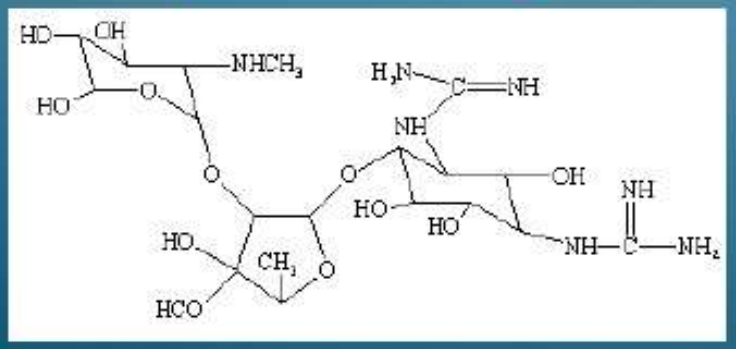






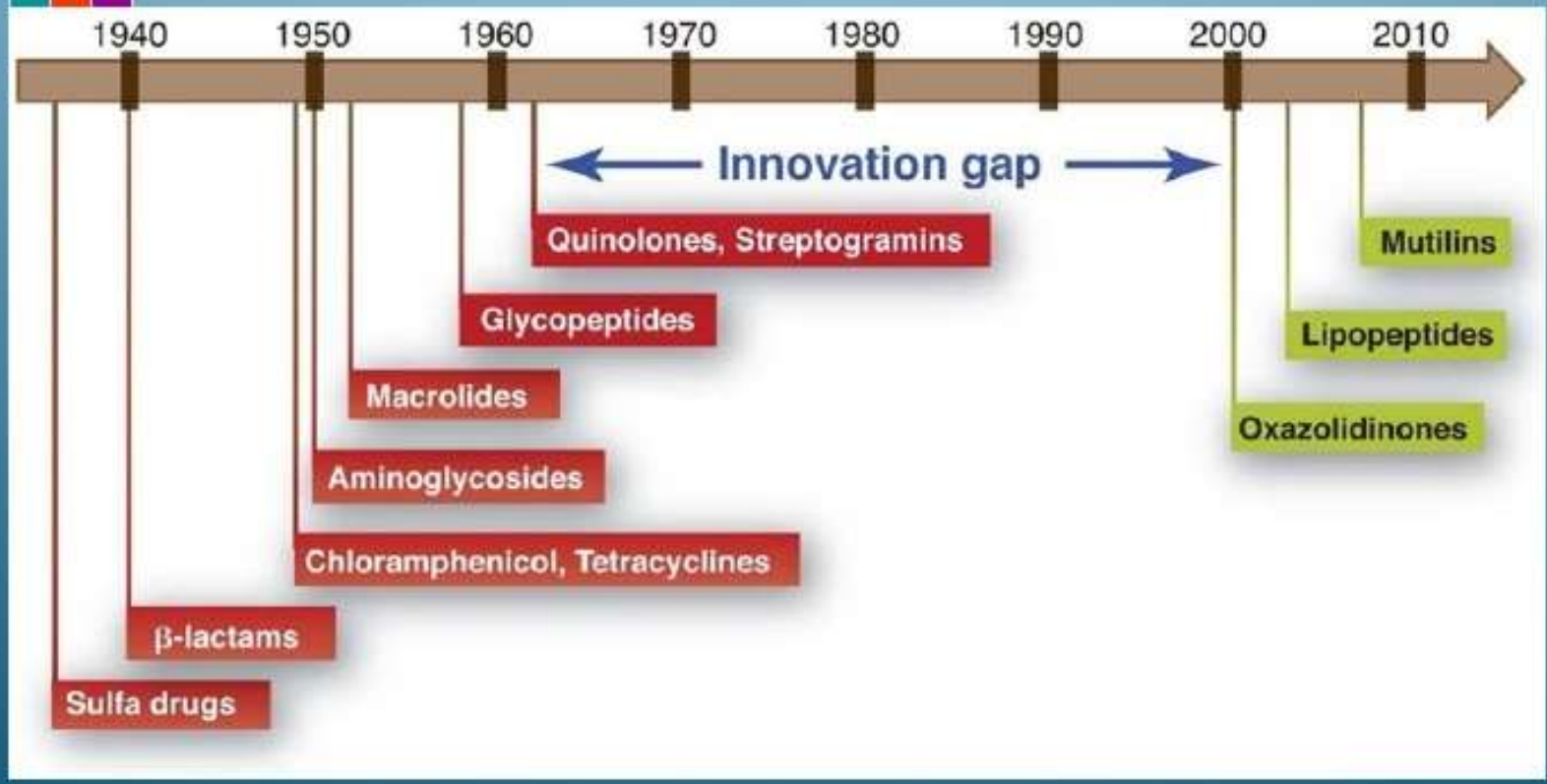
HISTORY OF ANTIBIOTICS

Selman Waksman



HISTORY OF ANTIBIOTICS

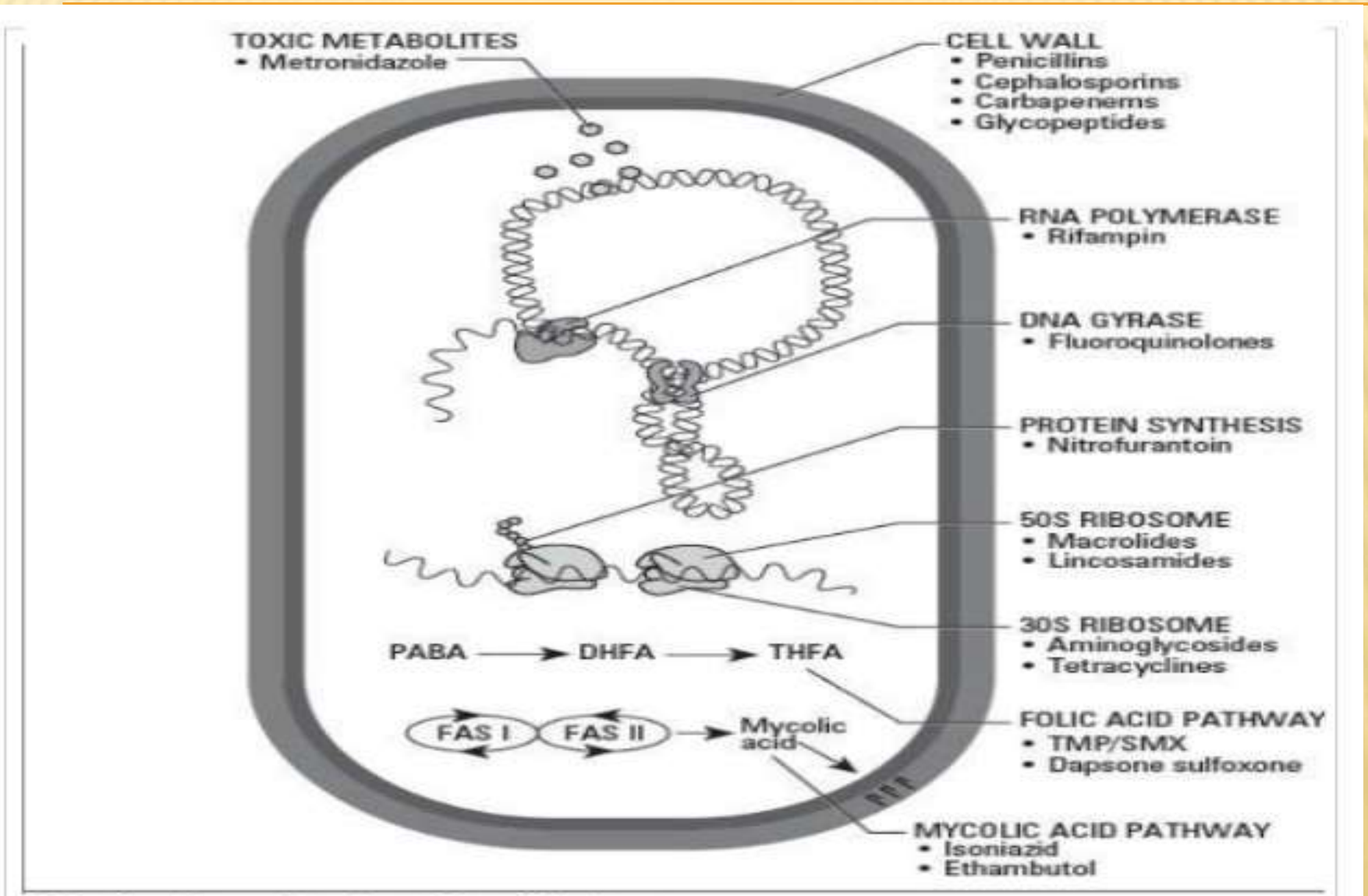
Between 1962 and 2000, no major classes of antibiotics were introduced



Fischbach MA and Walsh CT *Science* 2009

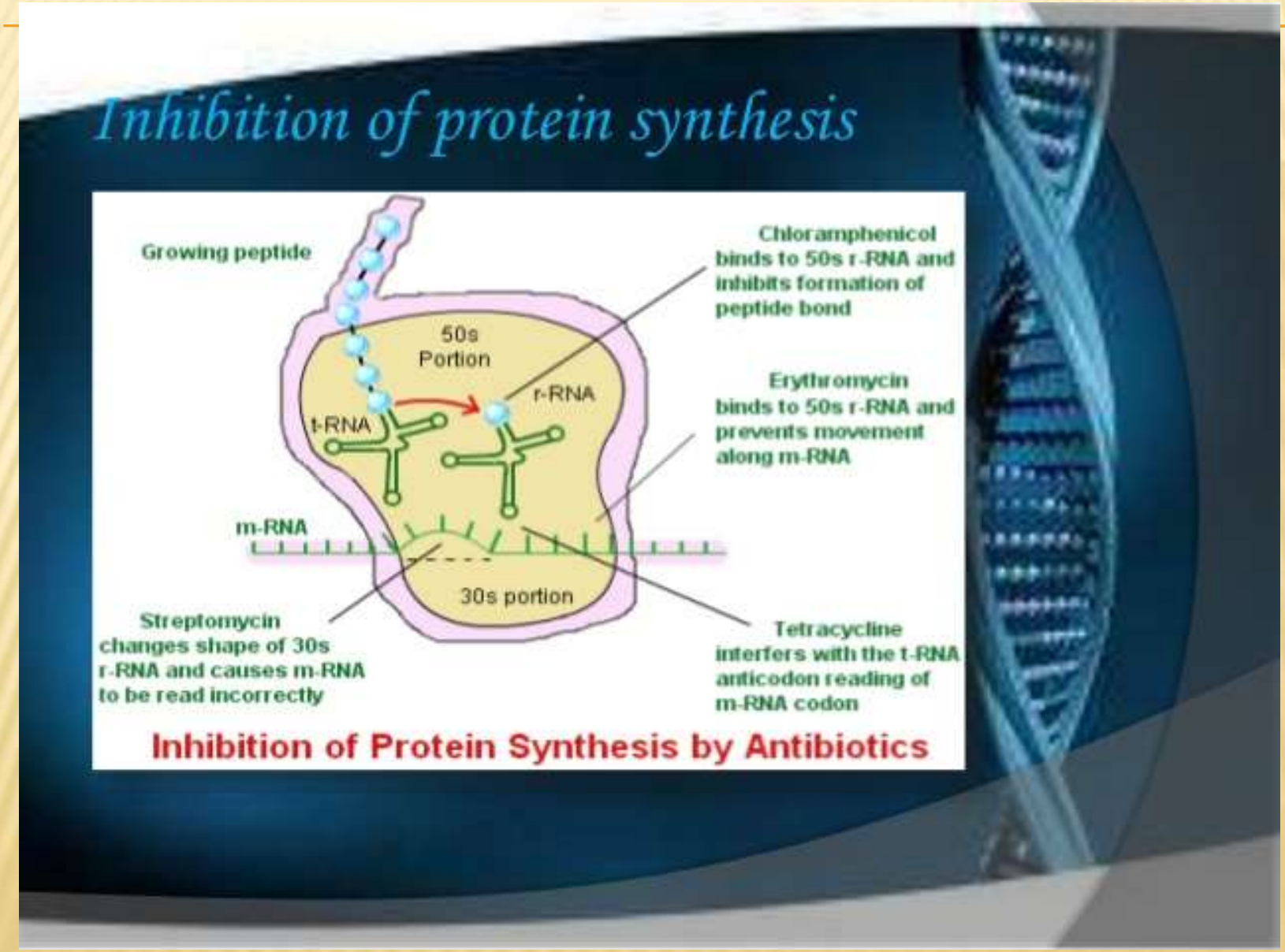
PENCILLINS

MECHANISM OF ACTION

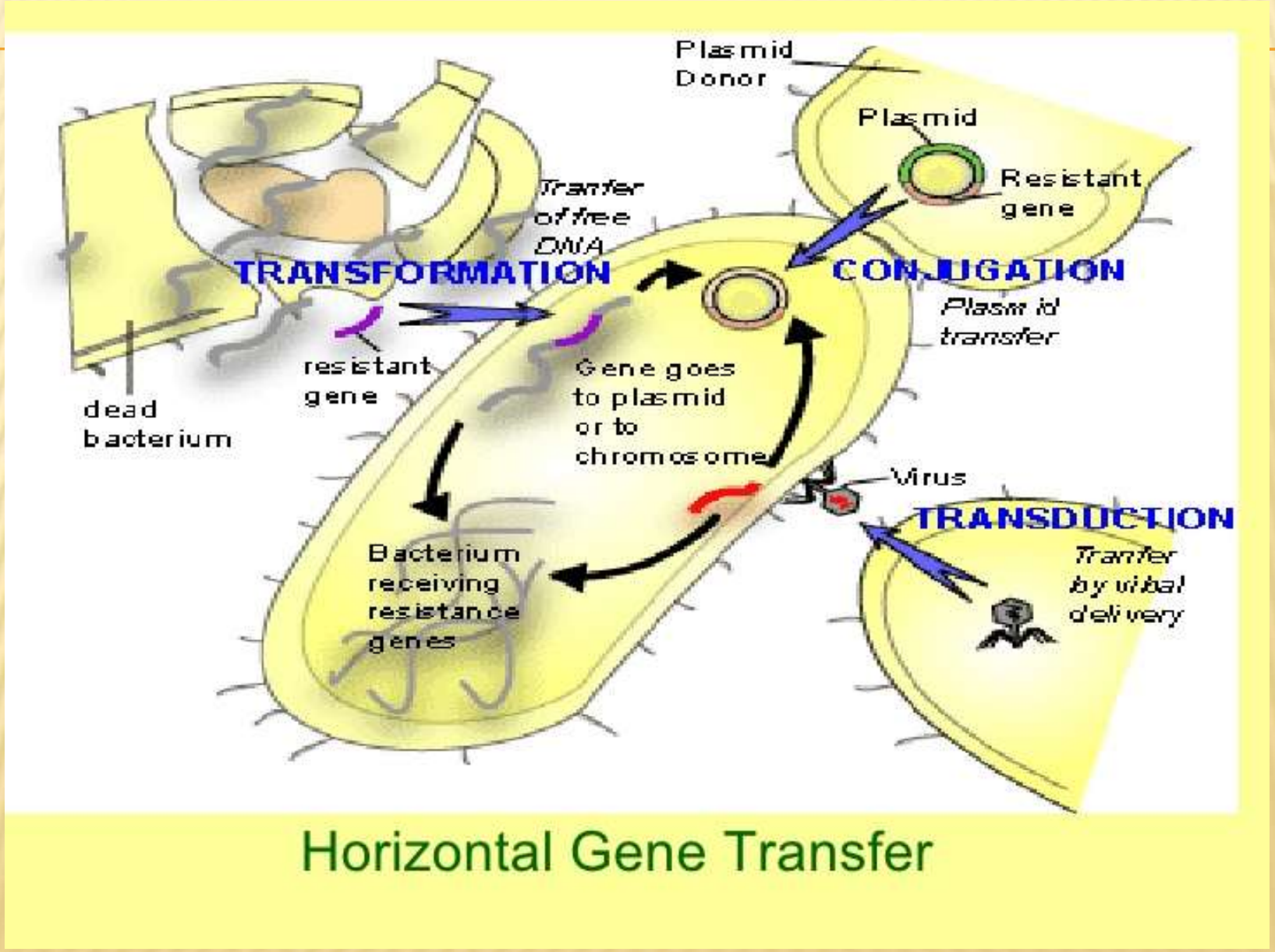


. Mechanism of action of antibiotics

MECHANISM OF ACTION

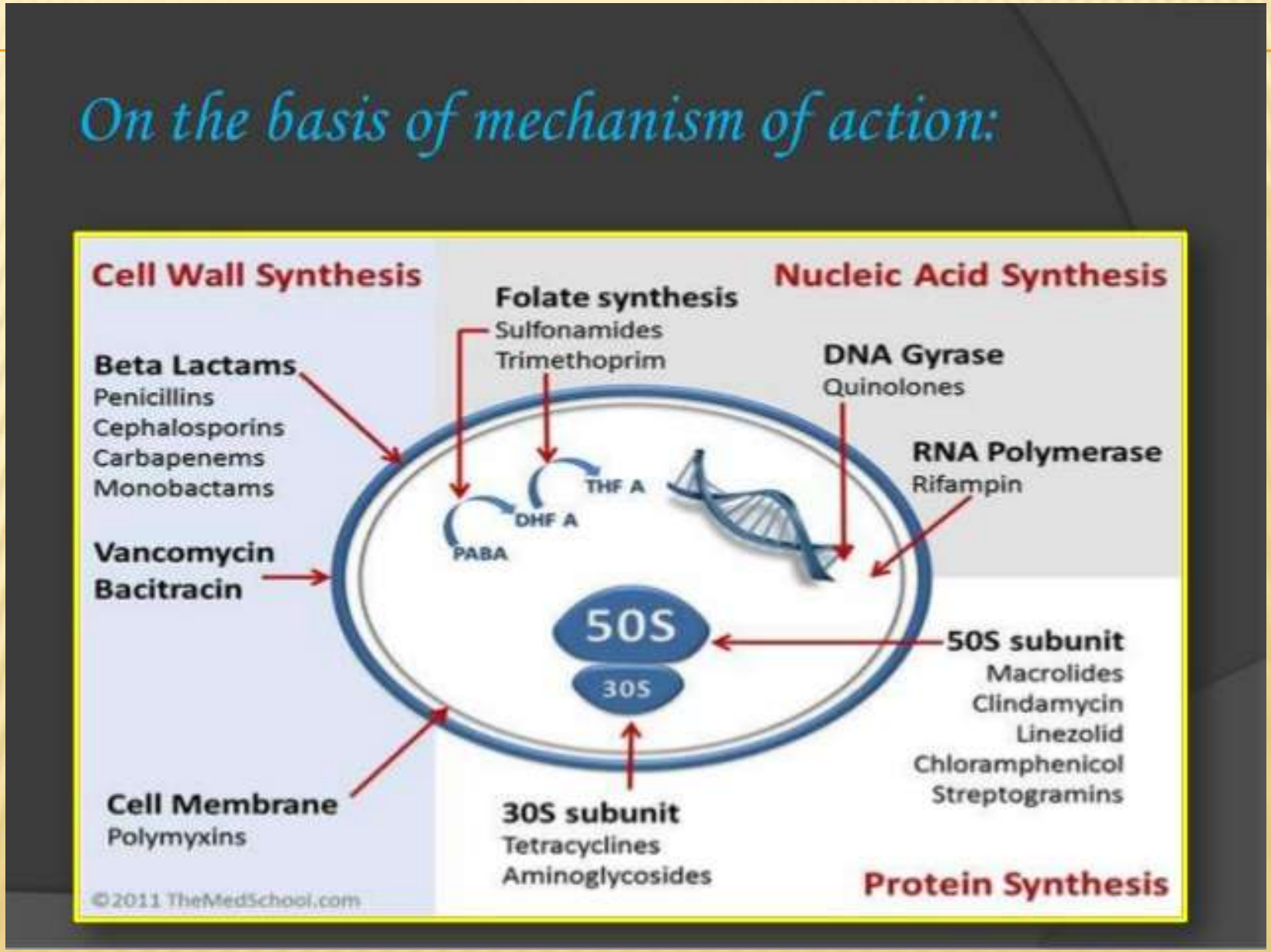


MECHANISM OF ACTION



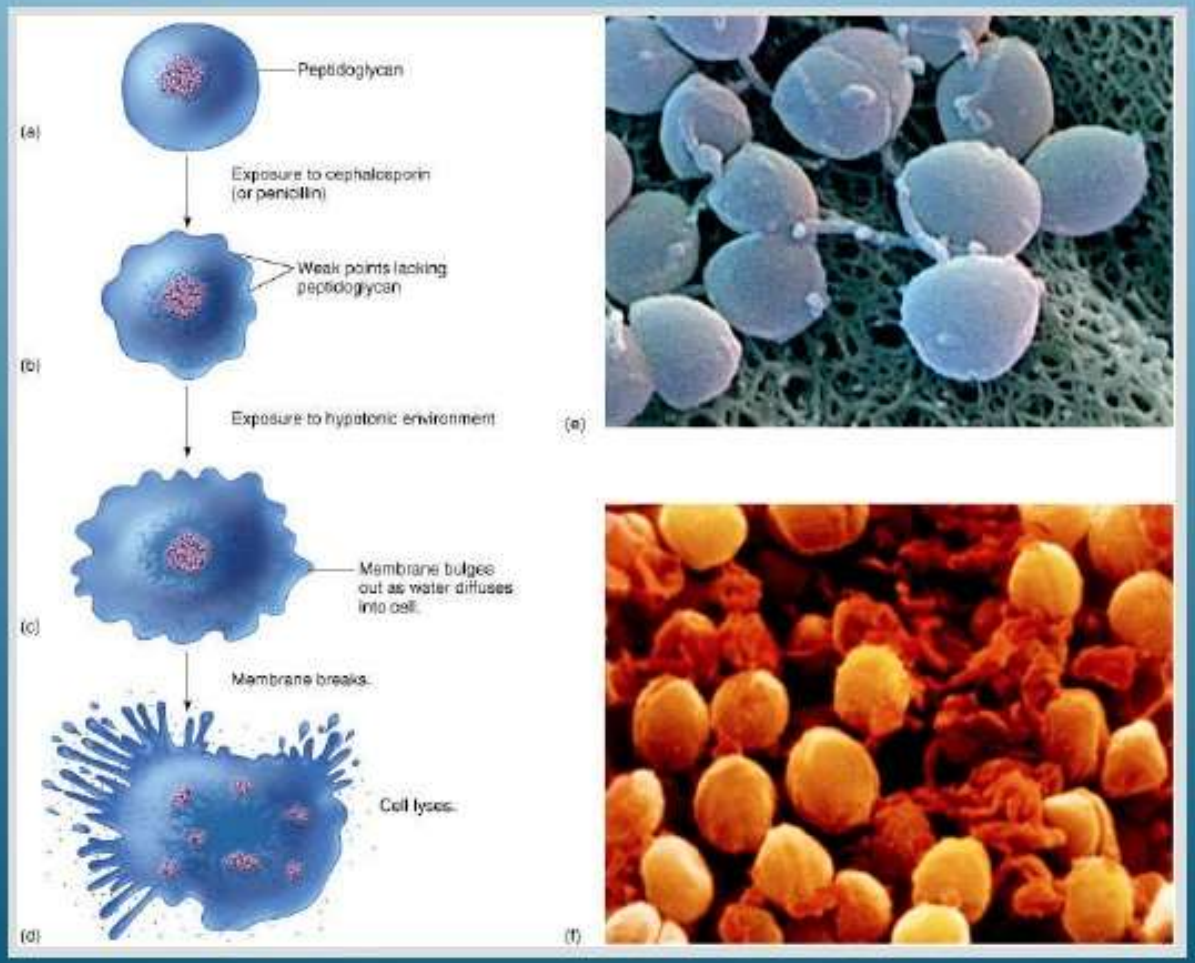
Horizontal Gene Transfer

MECHANISM OF ACTION



MECHANISM OF ACTION

Antibiotics weaken the cell wall, and cause the cell to lyse



Classification of Penicillins

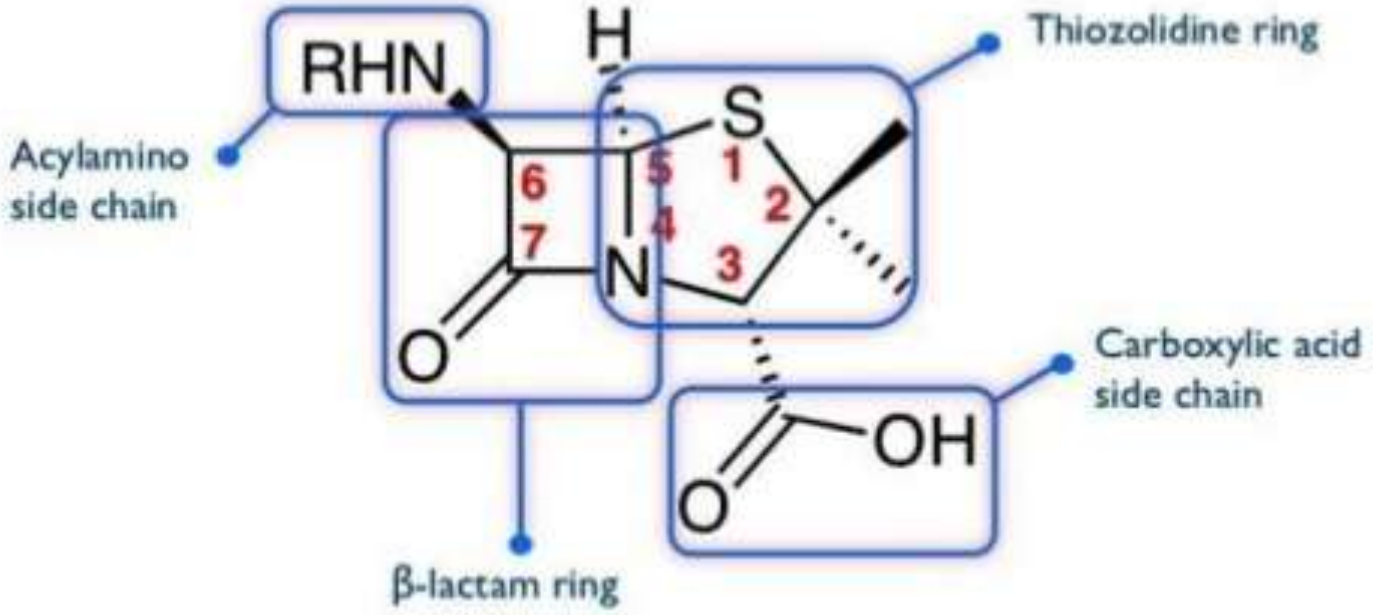
- **Fermentation derived penicillins**
  - -Penicillin G
  - -Penicillin V
- **Semisynthetic penicillanase resistant penicillins**
  - -Methicillin
  - -Nafacillin
  - -Isoxazolyl Penicillins
- **Aminopenicillins**
  - -Ampicillin
  - -Amoxicillin
- **Carboxypenicillins**
  - -Ticarcillin
- **Ureidopenicillins**
  - -Piperacillin
  - -Mezlocillin
  - -Azlocillin

CHEMISTRY OF PENICILLINS

STRUCTURE

Penicillins as well as cephalosporins are called **beta-lactam antibiotics** and are characterized by **three** fundamental structural requirements:

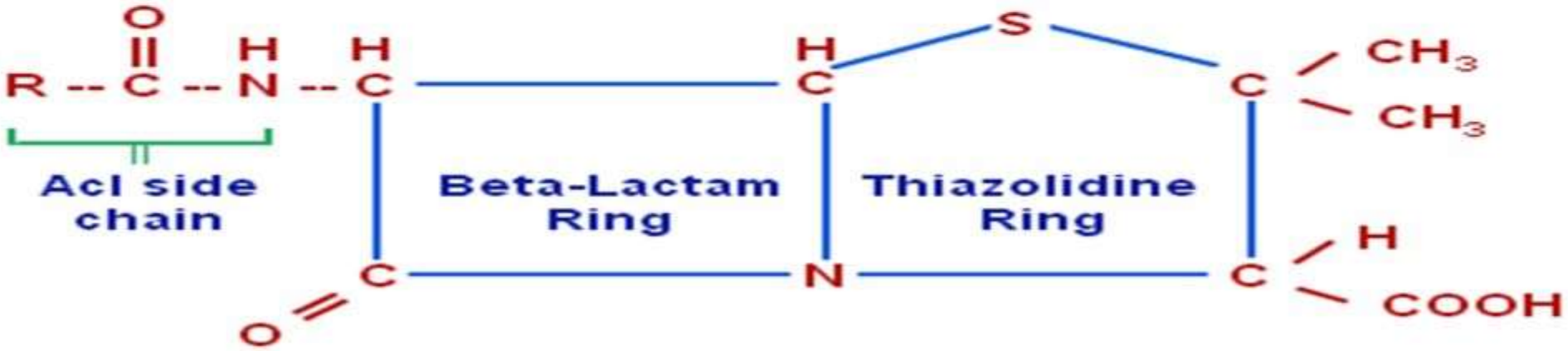
- **The fused beta-lactam & Thiazolidine ring structure.**
- **A free carboxyl acid group.**
- **One or more substituted amino acid side chains.**



Chemistry

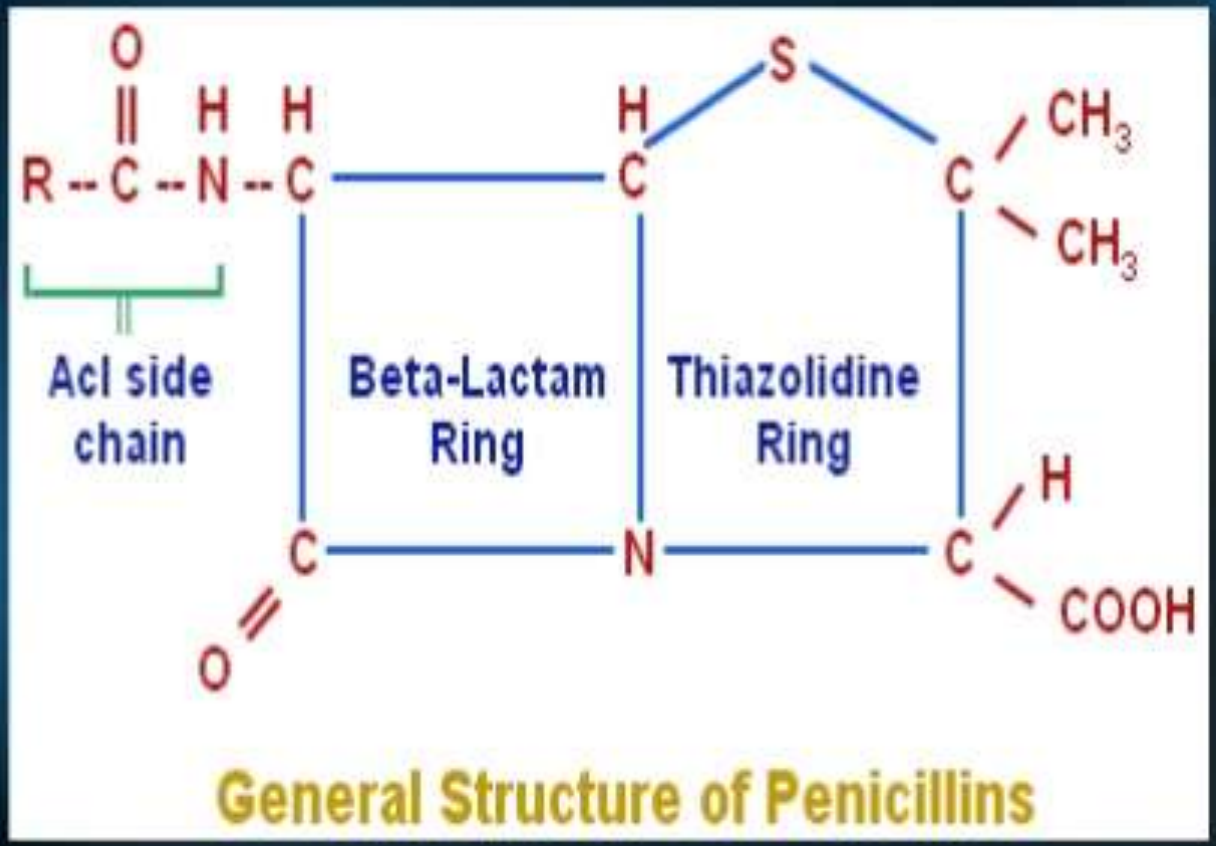
- Penicillin nucleus consists of
  - Thiazolidine ring (Ring A)-
    - Sulphur containing with COOH (Carboxyl group),
  - Beta lactam ring (Ring B) – **(Broken by Betalactamase)**
    - Side chain is attached at position – 6- (NHCOR)

- Side chains attached through amide linkage. **(Broken by Amidase)**



Synthetic antibiotics:

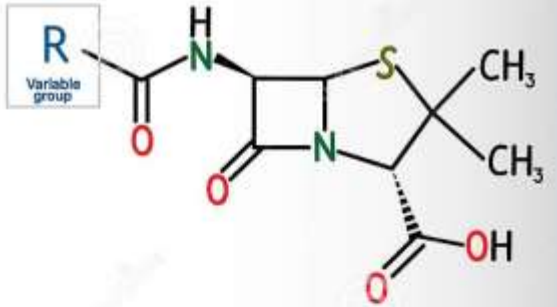
general structure of penicillin



General Structure of Penicillins

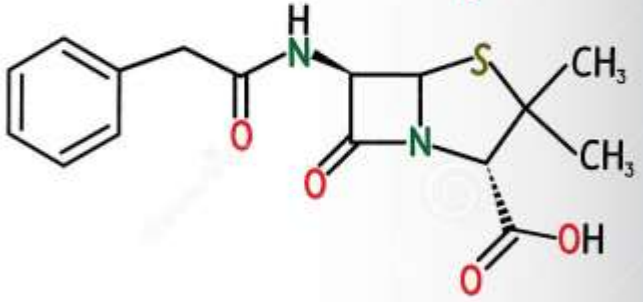
Natural penicillins

Penicillin

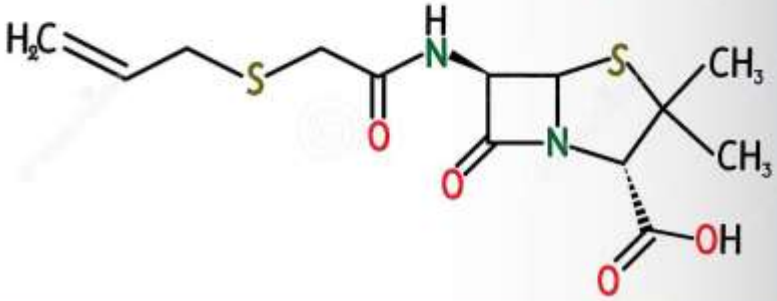


Penicillin V

Penicillin G



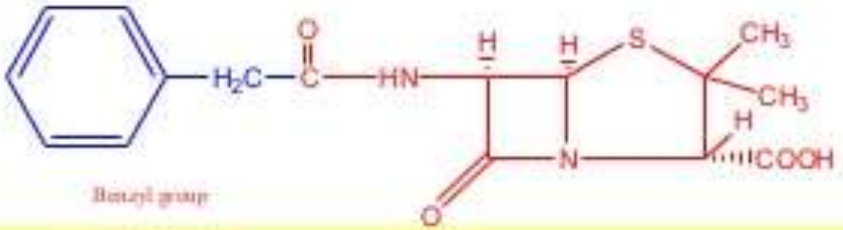
Penicillin O



Penicillin G (Benzylpenicillin)

- **Penicillin G is also referred to as gold standard penicillin.**
- **Penicillin G is not acid resistant it is acid sensitive.**
- **3 reasons for the acid sensitivity of penicillin G.**
- **1. Ring strain. (4 membered betalactam ring + 5 membered thiazolidine ring) As a result penicillins suffers large angle and torsional strains. Acid catalyzed ring opening relieves these strains by breaking open the more highly β –lactam ring.**
- **2. Highly reactive corbonyl group. The resonance stabilization is impossible for the β –lactam ring because of the increase in angle strain that would result in having a double bond within β –lactam ring. So the angle of the β –lactam ring constrained to 90' . So the lone pair is localized on the N atom, and the carbonyl group is more electrophilic than one would expect for a tertiary amide.**
- **Influence of the acyl side chain: Acyl group open up the lactam ring . So Penicillin G has a self-destruct mechanism built in its structure.**

Benzylpenicillin is broken down by stomach acid and destroyed by staphylococcus penicillinase. So it can be given by IV.



Therapeutic uses:

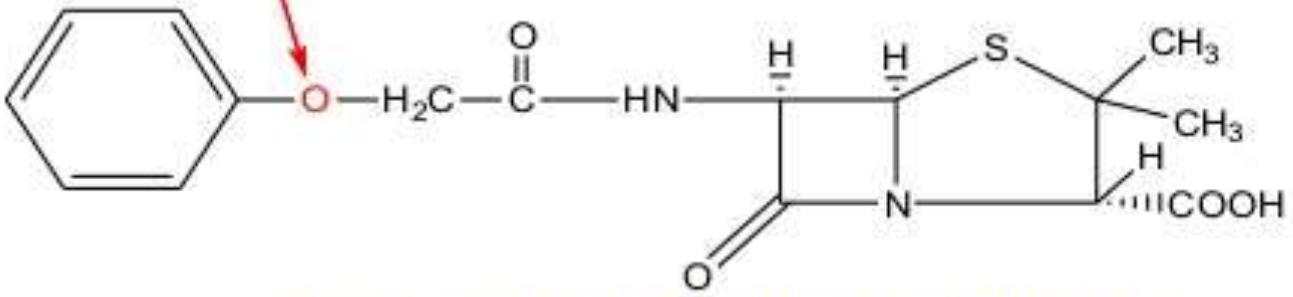
Drugs of the penicillin group are effective for infections caused by Gram-positive bacteria (streptococcus, pneumococcus, and others), spirochaetae, and other pathogenic microorganisms.

Drugs of this group are ineffective with respect to viruses, mycobacteria tuberculosis, fungi, and the majority of Gram-negative microorganisms.

Benzylpenicillin is the drug of choice for infections caused by sensitive organisms. This includes streptococci infections (except enterococci), gonococci, and meningococci that do not produce beta-lactam anaerobes. Benzylpenicillin is used for croupous and focal pneumonia, skin infections, soft tissue and mucous membranes, periotonitis, cystisis, syphilis, diphtheria, and other infectious diseases.

PENICILLIN- V

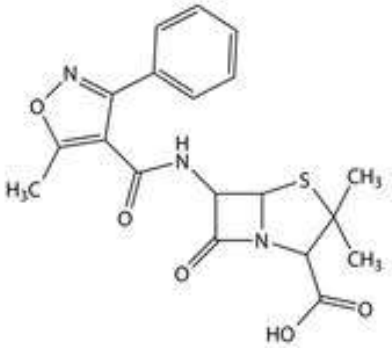
It withdraws the electrons away from the corbonyl oxygen and reduce the tendency to act as a nucleophile



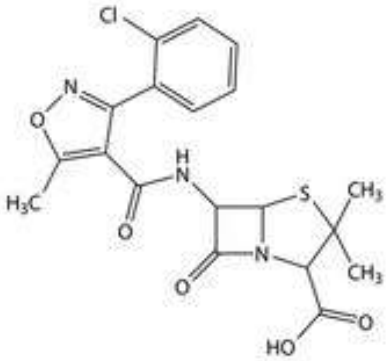
Phenoxy methyl Penicillin (Penicilln V)

- By placing electron with drawing group in the side chain **which could draw electrons away from the corbonyl oxygen and reduce its tendency to act as a nucleophile**.
- Penicillin- V has electro –ve oxygen on the acyl side chain with electron withdrawing effect. It has more acid stability than penicillin G .
- It is more stable in acid in the stomach, so it can be given orally.
- Infact acid sensitivity can be solved by having an electron withdrawing group on the Acyl side chain.

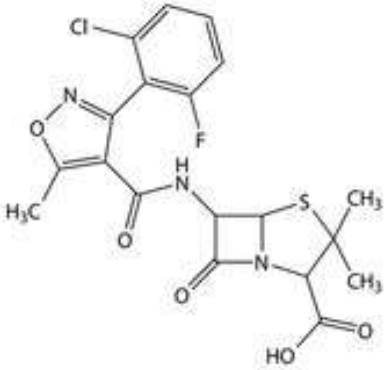
Isoxazole penicillins. Part 6



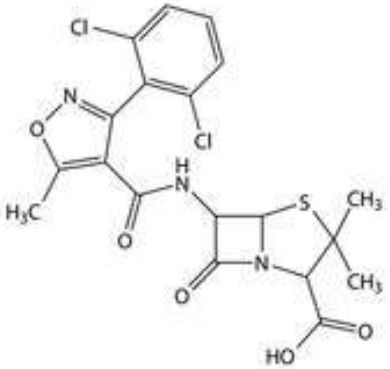
Oxacillin



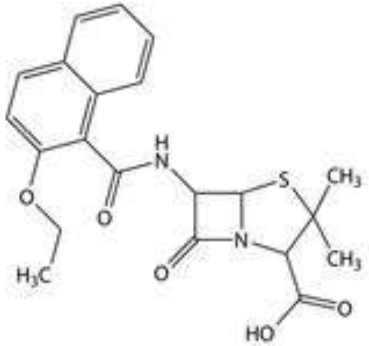
Cloxacillin



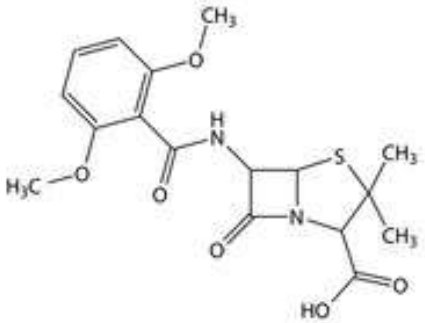
Flucloxacillin



Dicloxacillin

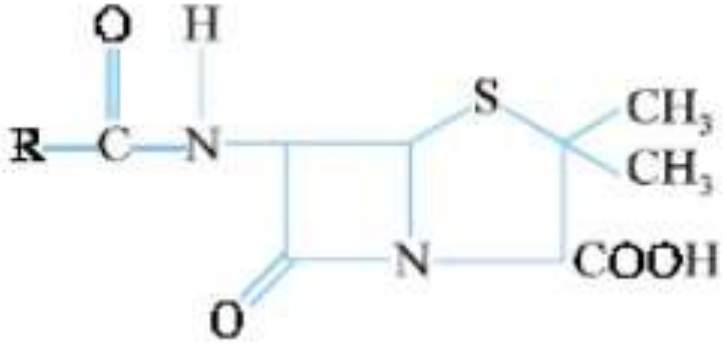


Nafcillin



Meticillin

Penicillins



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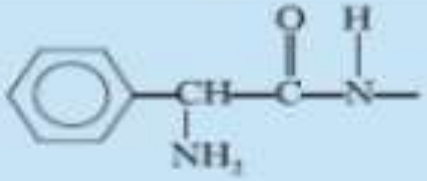
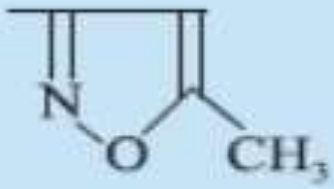
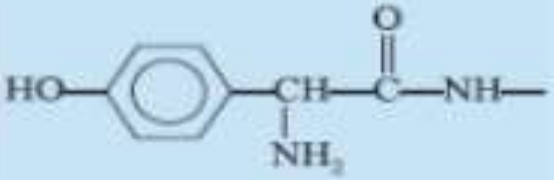
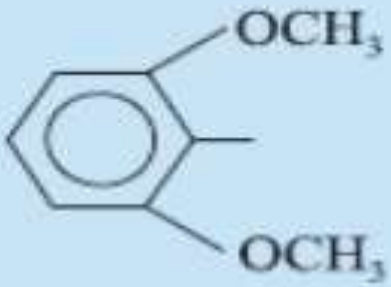
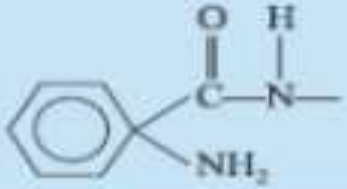
Ampicillin		Cloxaxillin Sodium	
Amoxicillin Trihydrate		Methicillin Sodium	
Ciclacillin			

Structural Activity Relationship (SAR)

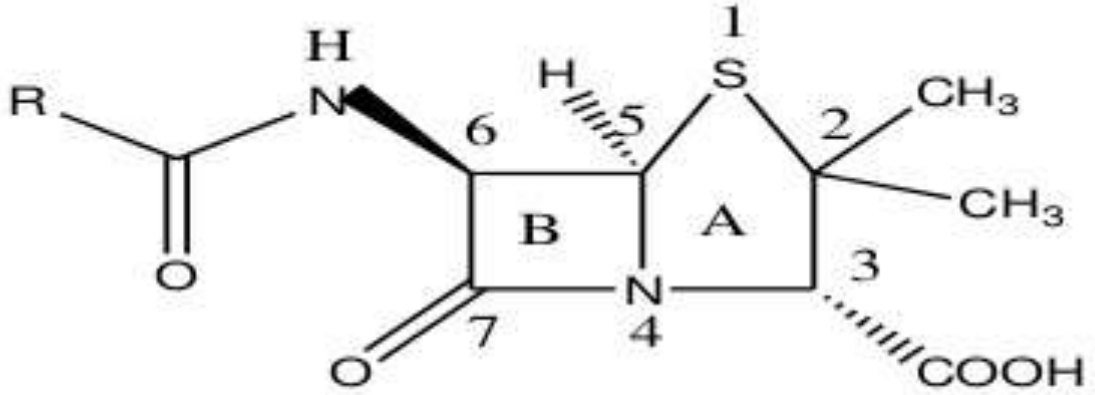
Position 1 – When the sulfur atom of the Thiazolidine ring is oxidized to a sulfone or sulfoxide, it improves acid stability, but decreases the activity of the agent.

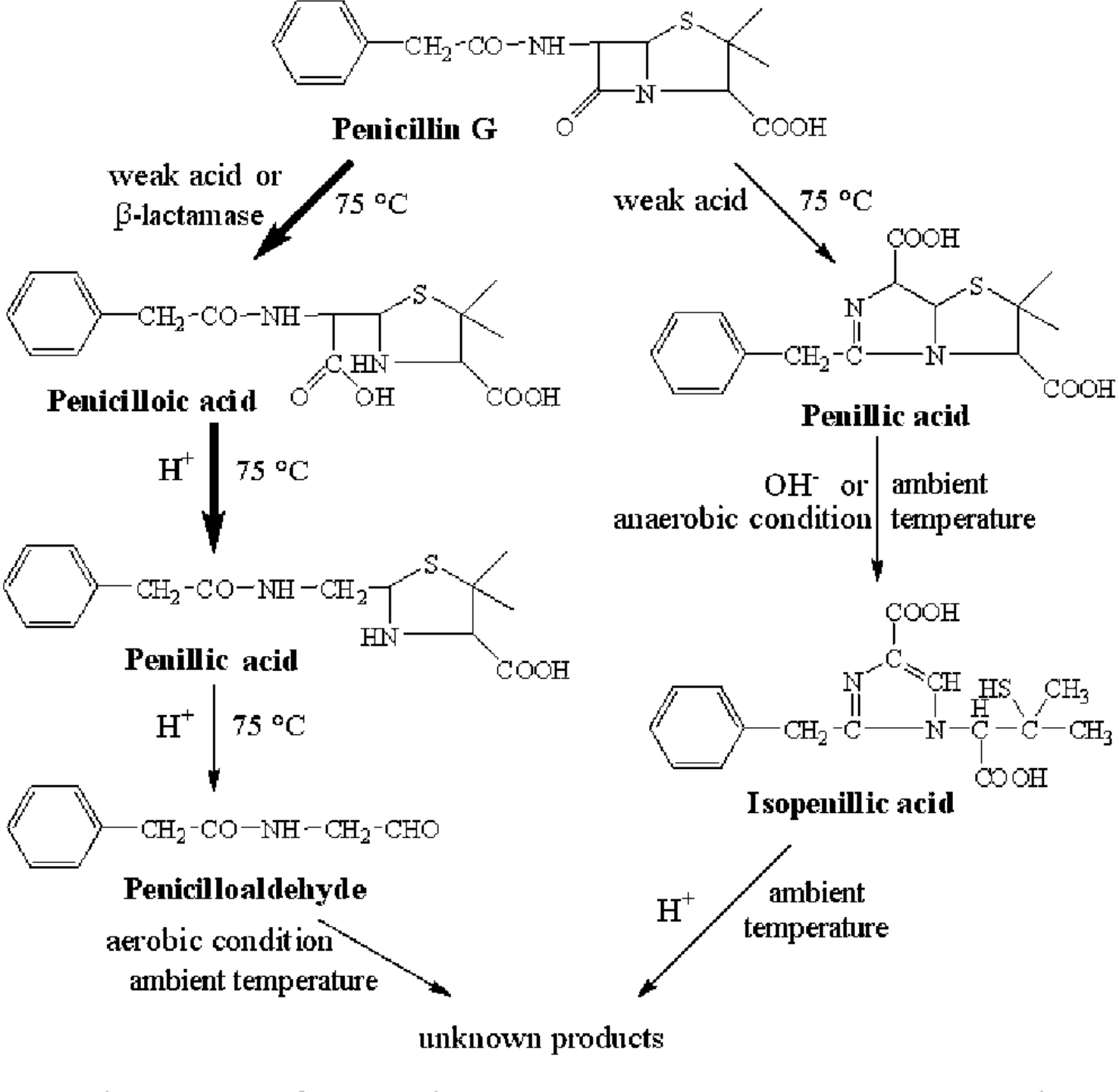
Position 2 – No substitutions allow at this position, any change will lower activity. The methyl groups are necessary

Position 3 – The carboxylic acid of the Thiazolidine is required for activity. If it is changed to an alcohol or ester, activity is decreased.

Position 4 – The nitrogen is a must.

Position 5 – No substitutions allowed.



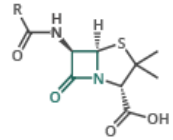

Penicillin G
weak acid or
β-lactamase
75 °C
weak acid
75 °C
Penicilloic acid
Penillic acid
H+
75 °C
OH- or
anaerobic condition
ambient
temperature
Penillic acid
Isopenillic acid
H+
75 °C
Penicilloaldehyde
H+
ambient
temperature
aerobic condition
ambient temperature
unknown products

DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

Key: COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION — COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH

ß-LACTAMS

MOST WIDELY USED ANTIBIOTICS IN THE NHS



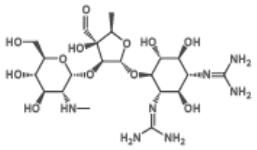
All contain a beta-lactam ring

EXAMPLES
Penicillins (shown) such as amoxicillin and flucloxacillin; *Cephalosporins* such as cefalexin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

AMINOGLYCOSIDES

FAMILY OF OVER 20 ANTIBIOTICS



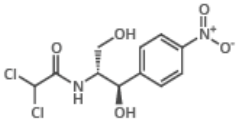
All contain aminosugar substructures

EXAMPLES
Streptomycin (shown), neomycin, kanamycin, paromomycin.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

CHLORAMPHENICOL

COMMONLY USED IN LOW INCOME COUNTRIES



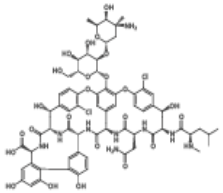
Distinct individual compound

MODE OF ACTION
Inhibits synthesis of proteins, preventing growth.

No longer a first line drug in any developed nation (except for conjunctivitis) due to increased resistance and worries about safety.

GLYCOPEPTIDES

COMMON 'DRUGS OF LAST RESORT'



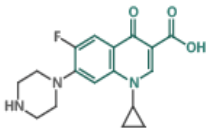
Consist of carbohydrate linked to a peptide formed of amino acids

EXAMPLES
Vancomycin (shown), teicoplanin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

QUINOLONES

RESISTANCE EVOLVES RAPIDLY



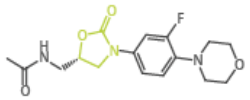
All contain fused aromatic rings with a carboxylic acid group attached

EXAMPLES
Ciprofloxacin (shown), levofloxacin, trovafloxacin.

MODE OF ACTION
Interfere with bacteria DNA replication and transcription.

OXAZOLIDINONES

POTENT ANTIBIOTICS COMMONLY USED AS 'DRUGS OF LAST RESORT'



All contain 2-oxazolidone somewhere in their structure

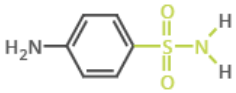
EXAMPLES
Linezolid (shown), posizolid, tedizolid, cycloserine.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

DISCOVERY — 1930 — 1940 — 1950 — 1960 — 1970 — 1980

SULFONAMIDES

FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES



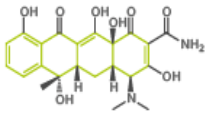
All contain the sulfonamide group

EXAMPLES
Prontosil, sulfanilamide (shown), sulfadiazine, sulfisoxazole.

MODE OF ACTION
Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

TETRACYCLINES

BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE



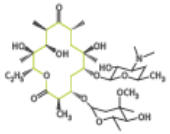
All contain 4 adjacent cyclic hydrocarbon rings

EXAMPLES
Tetracycline (shown), doxycycline, limecycline, oxytetracycline.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

MACROLIDES

SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS



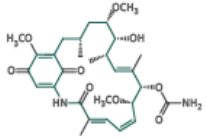
All contain a 14-, 15-, or 16-membered macrolide ring

EXAMPLES
Erythromycin (shown), clarithromycin, azithromycin.

MODE OF ACTION
Inhibit protein synthesis by bacteria, occasionally leading to cell death.

ANSAMYCINS

CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY



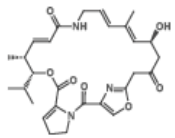
All contain an aromatic ring bridged by an aliphatic chain.

EXAMPLES
Geldanamycin (shown), rifamycin, naphthomycin.

MODE OF ACTION
Inhibit the synthesis of RNA by bacteria, leading to cell death.

STREPTOGRAMINS

TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGISTICALLY



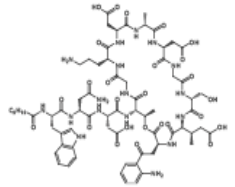
Combination of two structurally differing compounds, from groups denoted A & B

EXAMPLES
Pristinamycin IIA (shown), Pristinamycin IA.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

LIPOPEPTIDES

INSTANCES OF RESISTANCE RARE



All contain a lipid bonded to a peptide

EXAMPLES
Daptomycin (shown), surfactin.

MODE OF ACTION
Disrupt multiple cell membrane functions, leading to cell death.