Antimycobacterial Drugs

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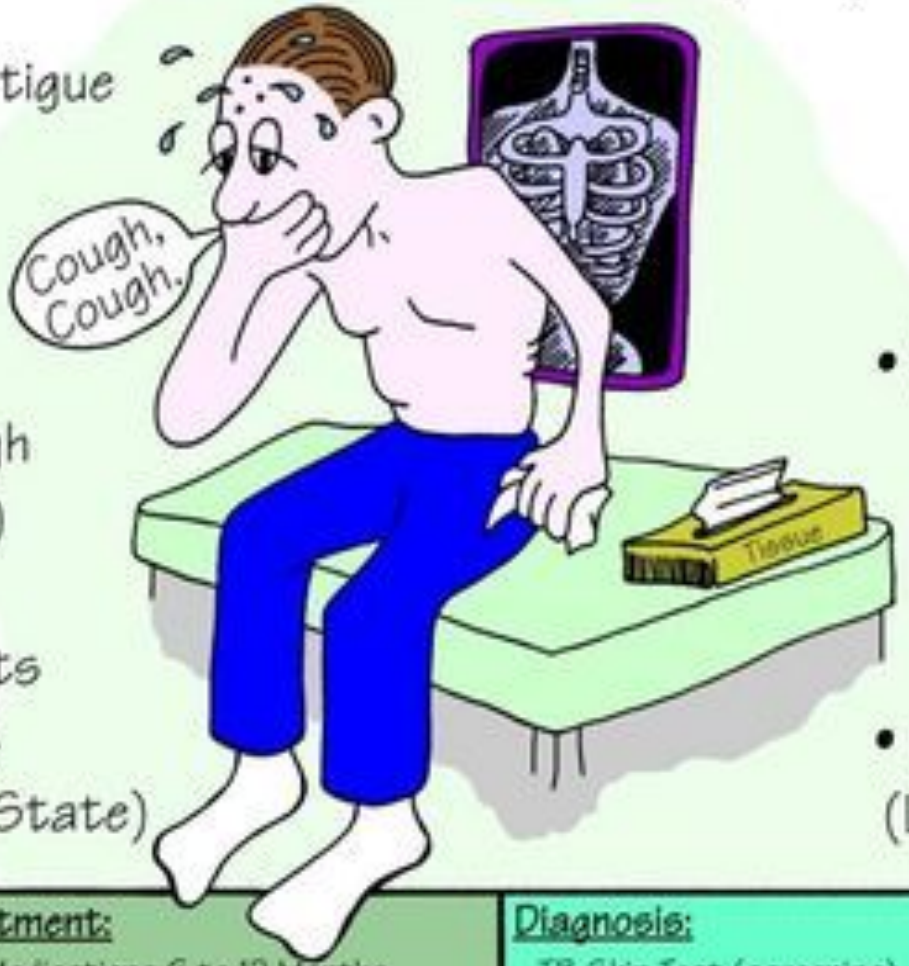
TUBERCULOSIS (TB)

- Progressive Fatigue
- Malaise
- Anorexia
- Wt. Loss



- Chronic Cough (Productive)
- Night Sweats
- Hemoptysis (Advanced State)

- Pleuritic Chest Pain
- Low Grade Temp (Late Afternoon)

Treatment:
TB Medications 6 to 12 Months
Decreased Activity
Resp Isolation Until Negative Sputum
Frequently Out-PT Basis

Diagnosis:
TB Skin Test (screening)
Chest X-Ray
Sputum Studies
(3 specimens collected on different days)

- *Mycobacterium Tuberculosis (TB)*
- *Mycobacterium Leprae (Leprosy)*

• Anti-TB drugs

- **1st line drugs:**
- **Isoniazid (INH)**
- **Rifampicin**
- **Ethambutol**
- **Pyrazinamide**
- **2nd line drugs:**
- **Streptomycin (± 1st)**
- **Capreomycin**
- **Cycloserine**
- **Clarithromycin(macrolide)**
- **Ciprofloxacin, levofloxacin**
- **Others**

- **2nd line drugs are used in infections resistant to 1st line agents**, or there are **toxic reactions to 1st line drugs.**
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- Due to **high incidence of resistance**, **combination is recommended** in treatment.
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- **Treatment include :**
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1. **Initial phase: INH + rifampicin + ethambutol + pyrazinamide for 2 months**
2. **Continuation phase : INH + rifampicin 4 months**

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- **Long term treatment** may be needed and it is indicated in **TB meningitis**, **bone + joint involvement**, **MDR-TB** "multi-drug resistant TB"

•*Isoniazid (INH)*

- its use in limited to mycobacteria (M.)
- it is **bacteriostatic for resting M**. but **bactericidal for dividing M.**
- **inhibits the synthesis of mycolic acids** (important constituents of the cell wall of M.)
- **Resistance** to the drug developed and caused by **reduced penetration** in to the M., but cross-resistance to other anti-TB drugs dose not occur.

•*Pharmacokinetics*

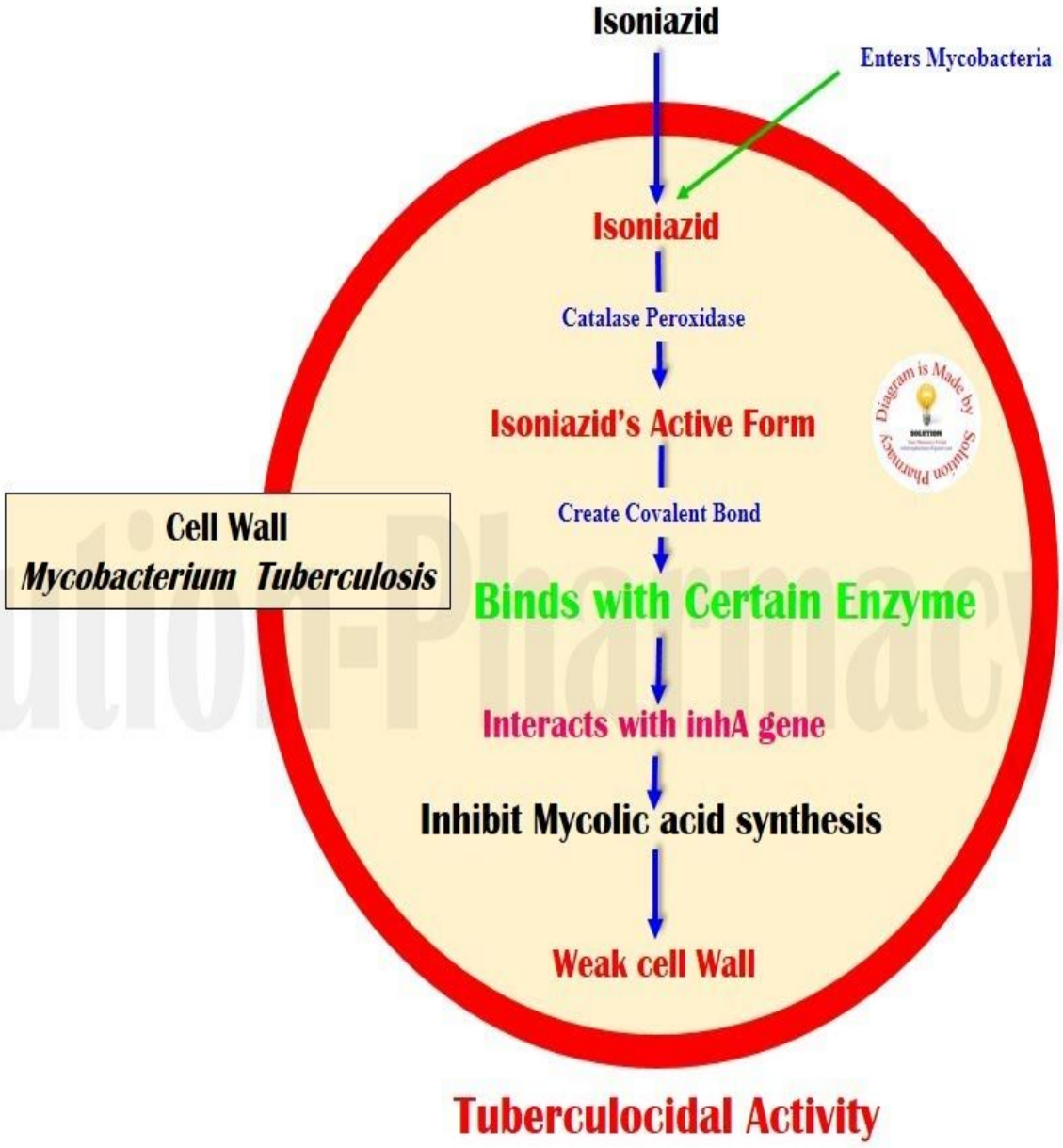
- **Readily absorbed** from GIT
- **Widely distributed** in the tissues and body fluids & CSF
- Can **penetrates the caseous tuberculous lesions**
- **Pass freely into cells**, thus effective against **intracellular** M.

• **metabolism by acetylation**

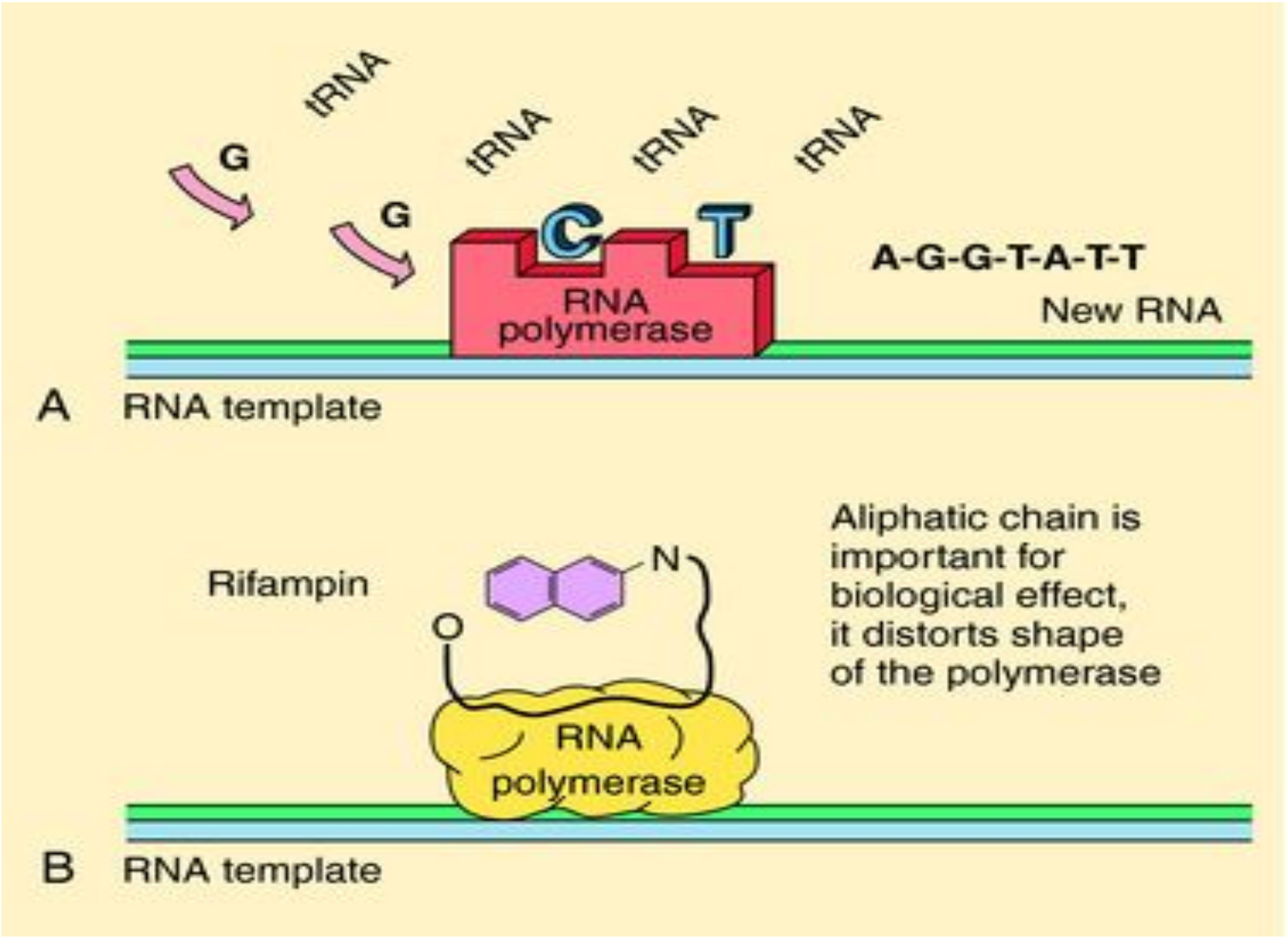
- In **slow acetylators** $t_{1/2}$=3hr (better therapeutic response but neurotoxicity may occur)
- In **fast acetylators** $t_{1/2}$=1hr. (hepatotoxicity may occur)

Isoniazid- Mechanism of Action

Diagram is Made by- Solution-Pharmacy



- ***Unwanted effects***
  - Skin rash, fever
  - **Hepatotoxicity** (due to toxic metabolites)
  - **Neurotoxicity** (CNS + PNS) prevented by administration of **pyridoxine** (Vit. B6)
  - Hemolysis in pt. with G6PD deficiency
  - INH is enzyme inducer (p450) but it can ↓ the metabolism of antiepileptic drugs (by competition)
- **Rifampin**
- Act by binding and **inhibiting RNA polymerase** in M. but not human cells.
- It is **one of most active anti-TB agents** known
- Rifampin is **also effective** against **leprosy**, **most G+ve bacteria** and **many G-ve species**
- **Can kill intracellular M.**
- Resistance can developed by modification of the RNA polymerase


tRNA
tRNA
tRNA
tRNA
G
G
C
T
RNA polymerase
A-G-G-T-A-T-T
New RNA
A
RNA template
Rifampin
N
O
Aliphatic chain is important for biological effect, it distorts shape of the polymerase
RNA polymerase
B
RNA template

- ***Pharmacokinetics***
  - Given orally
  - **Widely distributed** in tissues and body fluids
  - Cause **Orange staining** of saliva, sputum, tears, sweat and urine.
  - **Reach the CSF** and excreted through urine and bile
  - rifampicin is **potent enzyme inducer** (P450)
- $t_{1/2}$ is 1-5 hr. and reduced during treatment (due to Enz. Induction)
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- ***Unwanted effects***
- **common:** skin eruption, fever, GI disturbance
- **less frequent but serious:** hepatotoxicity, liver damage, with jaundice (liver function should be assessed before treatment)
- rifampicin **↑ the metabolism** of warfarin, steroids, oral antidiabetic, oral contraceptives, and others → ↓ plasma concentration →treatment failure
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•*Ethambutol*

- Effective only against mycobacteria (bacteriostatic effect)
- **Inhibit the synthesis of arabinogalactan in M. cell wall.**
- Resistance can developed rapidly if the drug used alone
- Given orally, well absorbed and distributed, can reach **therapeutic concentration in the CSF** in TB-meningitis
- It is indicated **in TB-meningitis**

•*Unwanted effects:*

- **Optic neuritis** (dose – related) that cause visual disturbances like color vision and decreased visual acuity. (more in Pt. with R.F) color vision should be monitored during prolonged treatment.
- **Hyperuricemia** ? gout (decrease uric acid excretion)

Ethambutol

Mechanism of action

- Inhibit mycobacterial arabinosyl transferase enzyme

Enzyme in arabinoglycan polymerization

Arabinoglycan = Essential component of mycobacterial cell wall

Mechanism of resistance

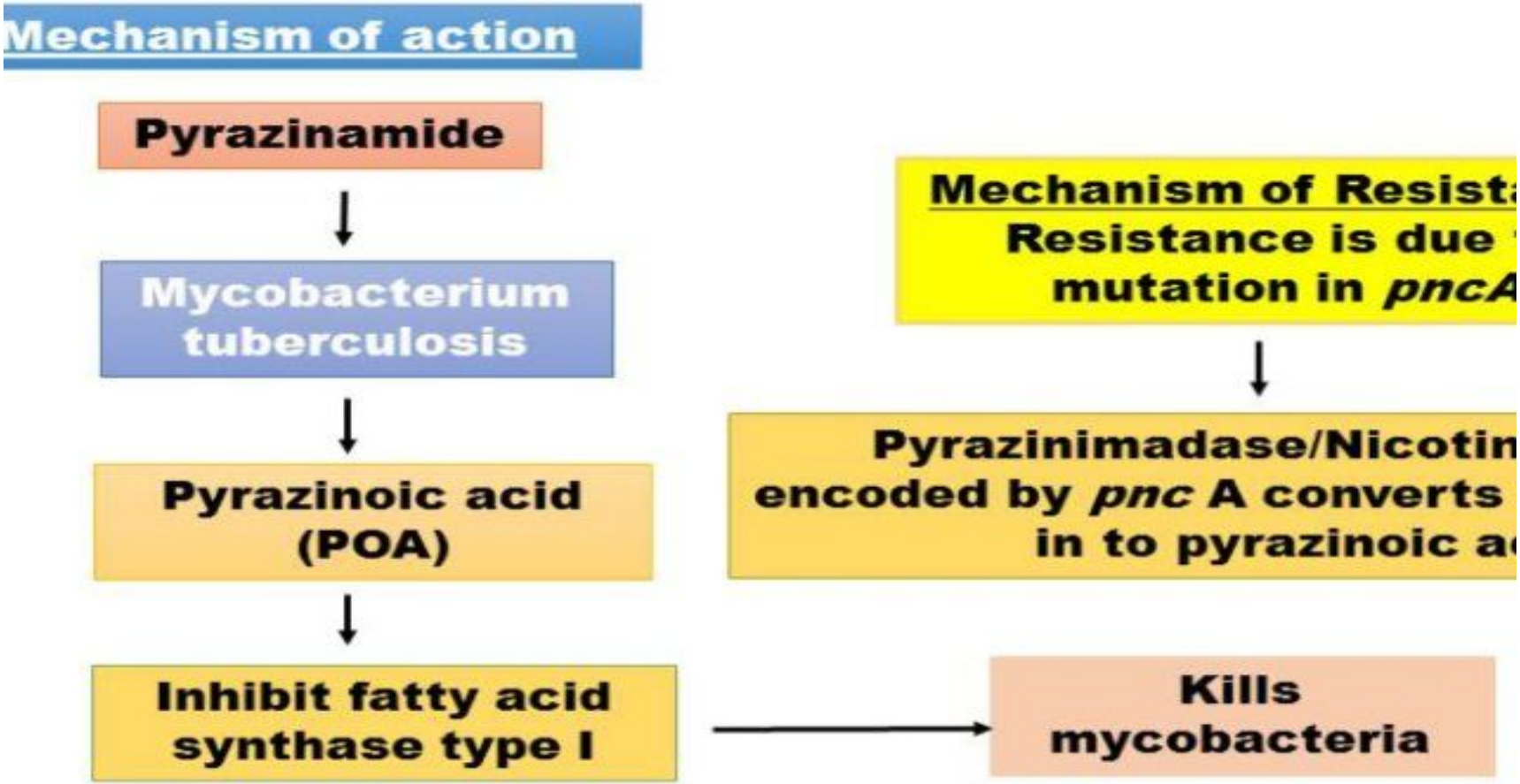
Mutation of mycobacterial arabinosyl transferase enzyme

- ***Pyrazinamide***
- Inactive at neutral PH, but tuberculostatic at **acidic PH**.
- Effective against **intracellular M. (low PH)**
- Given orally, well absorbed and widely distributed
- Good penetration to CSF, excreted by the kidneys
- Resistance □ rapid
- ***Unwanted effects:***
- **Hyperuricemia** □gout
- **GIT upsets and Liver damage** with high dose (liver function should be assessed be for treatment)

Pyrazinamide

Mechanism of Action

Pyrazinamide's exact mechanism of action is not known. Susceptible strains release pyrazinamidase, which converts PZA to pyrazinoic acid (POA). POA decreases the pH below that which retards the growth of *M. tuberculosis* and inhibiting the fatty acid synthesis .Studies indicate that PZA is most effective in the initial stages of treatment, which may be the result of diminished organism populations in macrophages early in therapy.


Mechanism of action
Pyrazinamide
Mycobacterium tuberculosis
Pyrazinoic acid (POA)
Inhibit fatty acid synthase type I
Kills mycobacteria
Mechanism of Resist
Resistance is due
mutation in pncA
Pyrazinimadase/Nicotin
encoded by pnc A converts
in to pyrazinoic a

Second line drugs

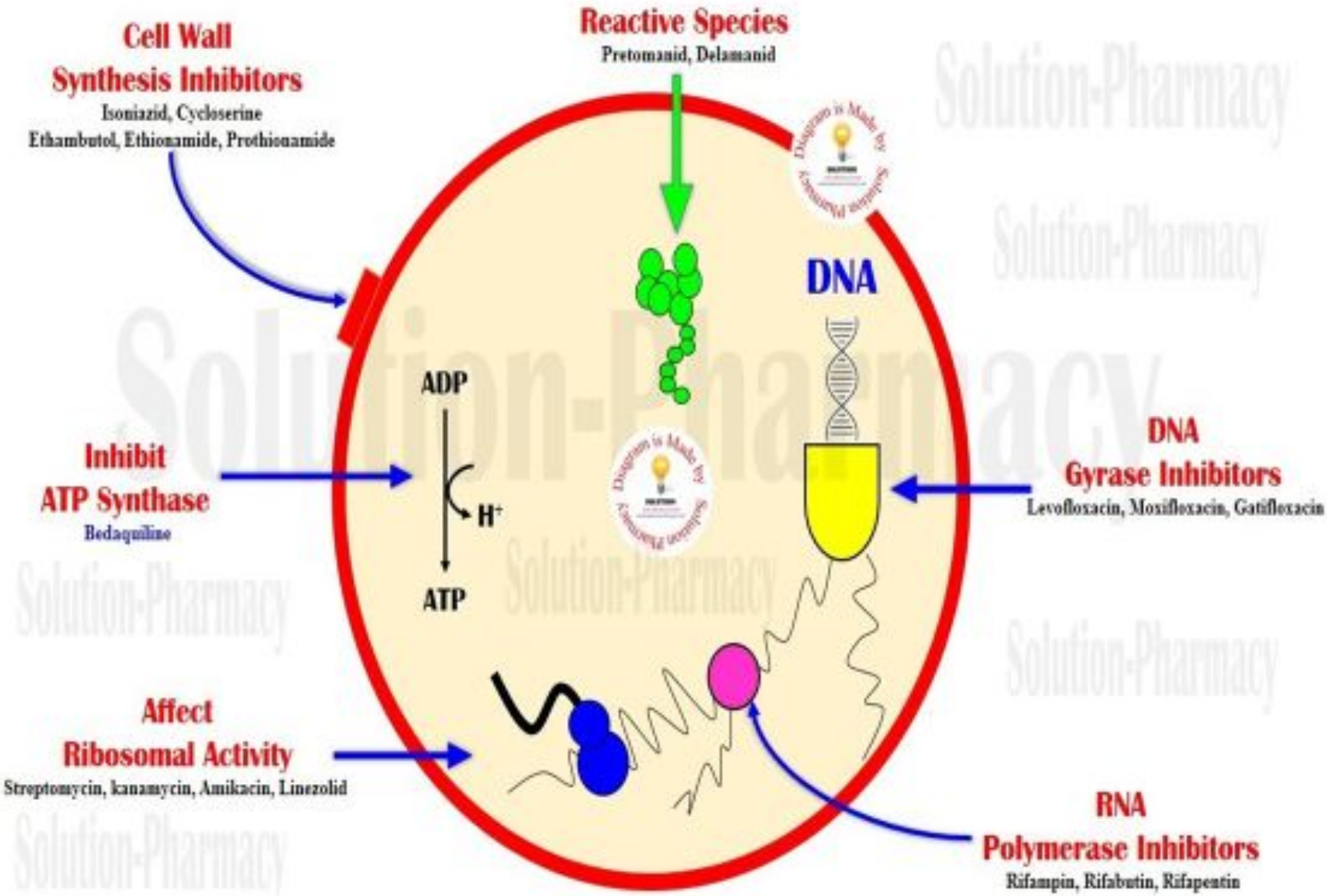


Figure- Antitubercular Drugs- Site and MOA of Action (Diagram is Made by Solution-Pharmacy)

- ***Capreomycin***
- Peptide antibiotic given by i.m. injection
- Used for MDR-TB
- It is 2nd-line anti-TB drug.
- ***Unwanted effects:***
- Ototoxicity deafness & ataxia (it should not be given together with streptomycin or other ototoxic drugs)
  - Nephrotoxicity
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- ***Cycloserine***
- broad spectrum antibiotic, **inhibit cell wall synthesis**
- used as 2nd –line anti-TB drug (in resistant cases)
- given orally, widely distributed, excreted by kidneys
- ***Unwanted effects:***
- Neurotoxicity (CNS +PNS) prevented by pyridoxine
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- ***PAS (Para-Amino Salicylic acid)***
- structurally similar to **sulfonamides**, acts by **inhibition of folate synthesis.** It was 1st –line drug but it's use decreased now because other drugs are better-tolerated.
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- ***Ethionamide***
- related to Isoniazid but less tolerated
- **cause intense gastric irritation**.
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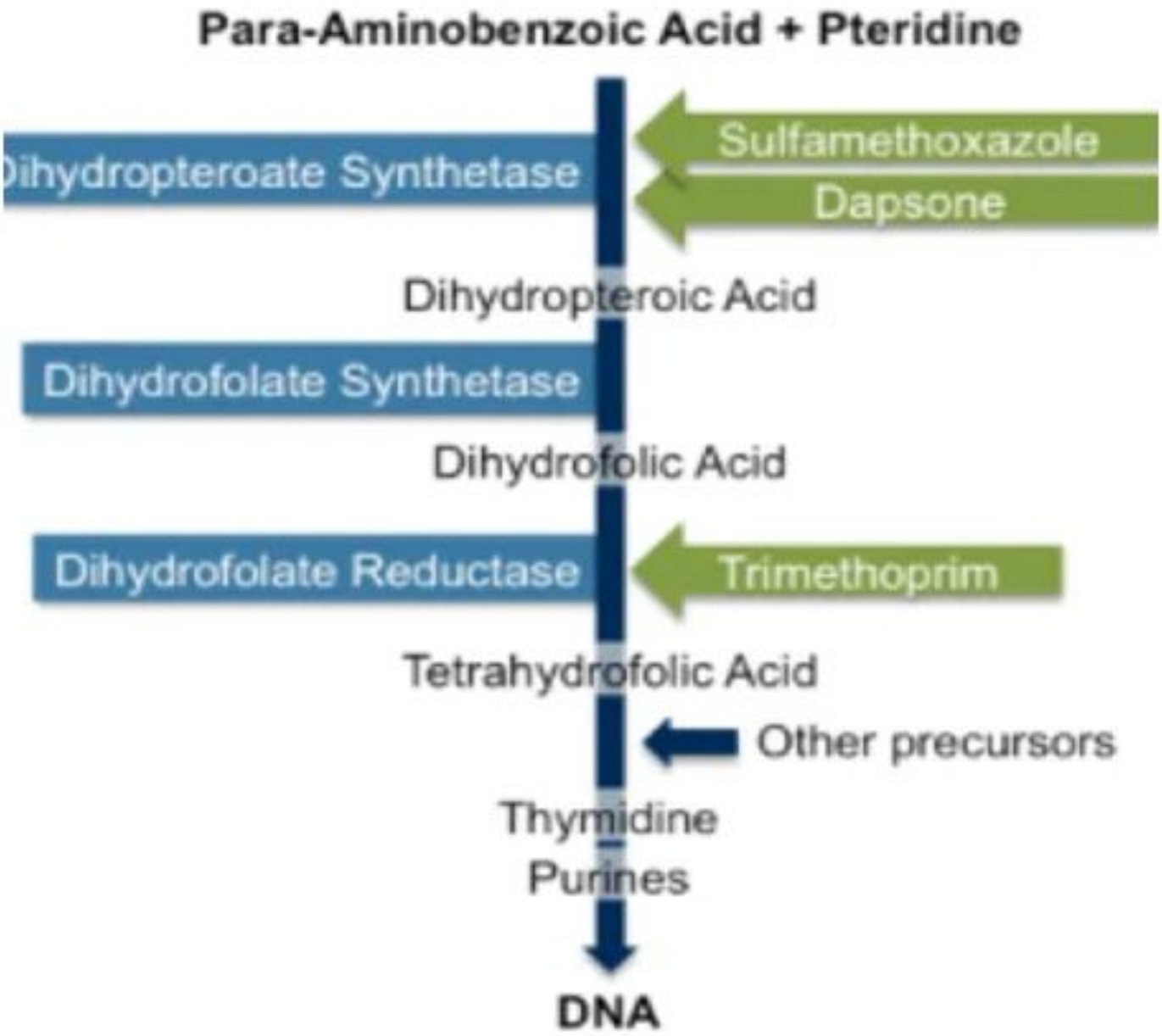
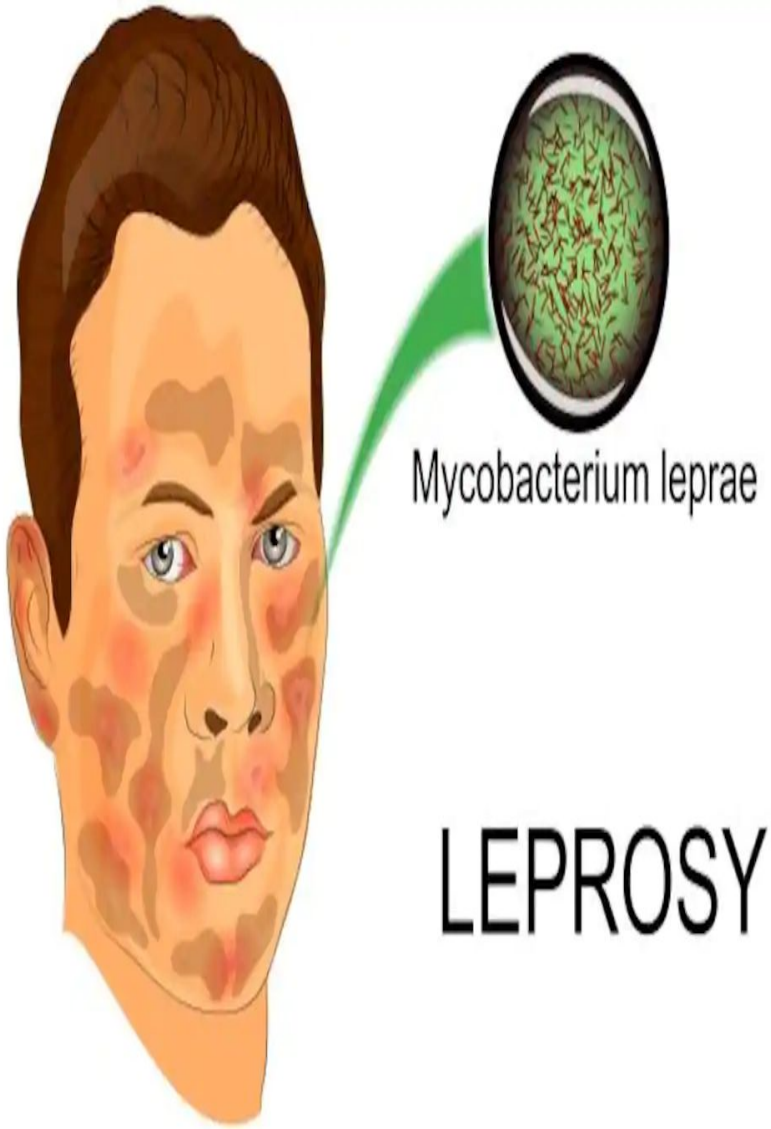
- ***Rifabutin***
- derived from rifampicin and indicated **for TB in pt. with HIV** infection because of **less induction of cytochrome P450 enzyme**, that keep therapeutic levels of antiviral drugs


Para-Aminobenzoic Acid + Pteridine
Dihydropteroate Synthetase
Sulfamethoxazole
Dapsone
Dihydropteroic Acid
Dihydrofolate Synthetase
Dihydrofolic Acid
Dihydrofolate Reductase
Trimethoprim
Tetrahydrofolic Acid
Other precursors
Thymidine
Purines
DNA

leprosy



• Drugs used to treat leprosy

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• ***Dapsone***

- chemically related to **sulfonamides**
- act by **inhibition of folate synthesis** in M. Leprae
- resistance is increasing, so combination with new drugs is recommended
- given orally, **$t_{1/2}$=24-48 hr.**
- there is **enterohepatic recycling**
- in addition to leprosy, dapsone is also used in the treatment of **Dermatitis Herpetiformis** (chronic blistering skin disease)

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• **unwanted effects:**

- **hemolytic anemia**
- **methemoglobinemia** (oxidation of Hb from ferrous (Fe^{++}) to ferric (Fe^{+++}) methemoglobin (met-Hb cannot carry O2 cyanosis & tissue hypoxia)
- allergic dermatitis and neuropathy

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- ***Clofazimine***
- Works by binding to guanine bases of bacterial DNA, thereby blocking the DNA and inhibiting bacterial proliferation.

- it is a dye that given orally, and can accumulate in macrophages, action is delayed for 6-7 weeks. ($t_{1/2}$ = 8 wks)

- **unwanted effects**
  1. GI disturbance and headache
  2. red color skin & red color urine
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Rifampin is effective in treatment of leprosy •

THANK YOU!