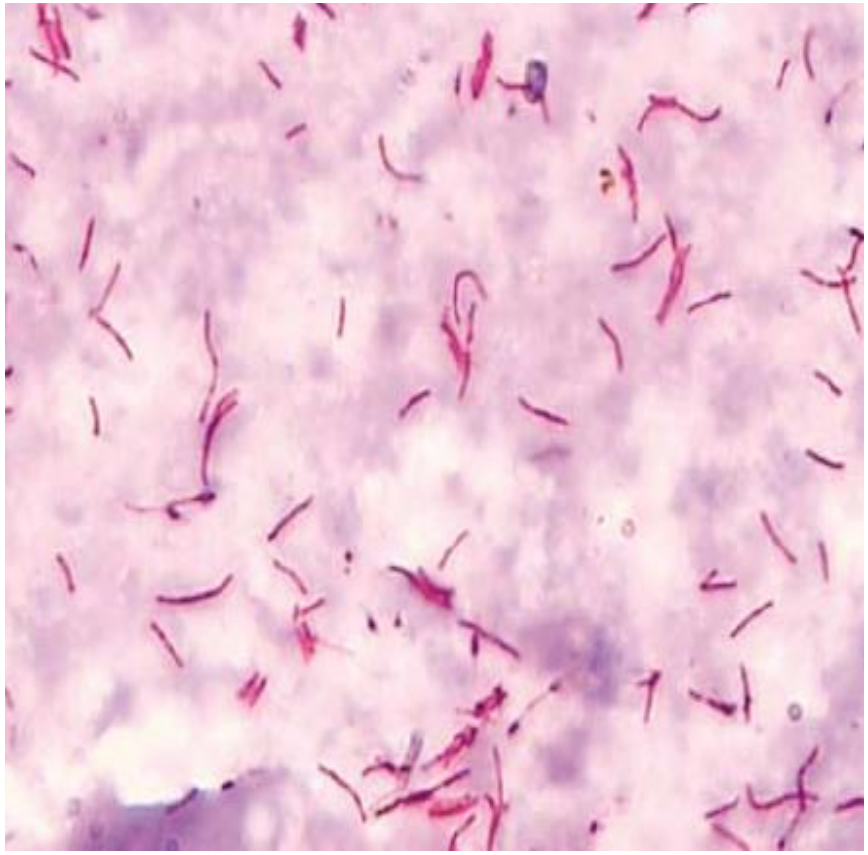
Anti-tuberculous drugs

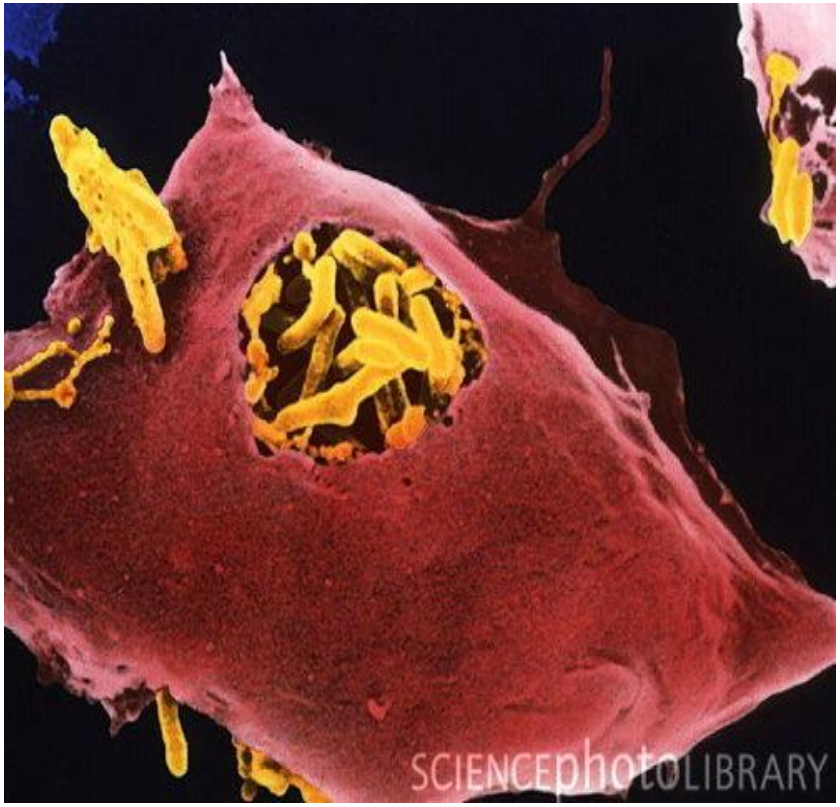
DR GEHANE

Mycobacteria

- Slow-growing bacillus



- Dormant forms in macrophages



- Kill 2 million people each year
- Increase incidence due to HIV associated Mycobateria

- 40 years ago drugs were developed
- Now multi- drug resistance strains are emerging

Anti-tuberculous drugs

First-line

- Isoniazid
- Rifampicin
- Ethambutol
- Pyrazinamide

Second-line

- Clarithromycin
- Ciprofloxacin
- Capreomycin
- Cycloserine
- Kanamycin
- Amikasin
- streptomycin

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Isoniazid (INAH)

- Acts only on mycobacteria
- Interferes with mycolic acid synthesis (unique to mycobacterial cell wall)

Isoniazid cont:

- Passes freely to mammalian cell wall
- Effective for intracellular organism
- Bacteriostatic – to resting organism
- Bactericidal – to multiplying organism

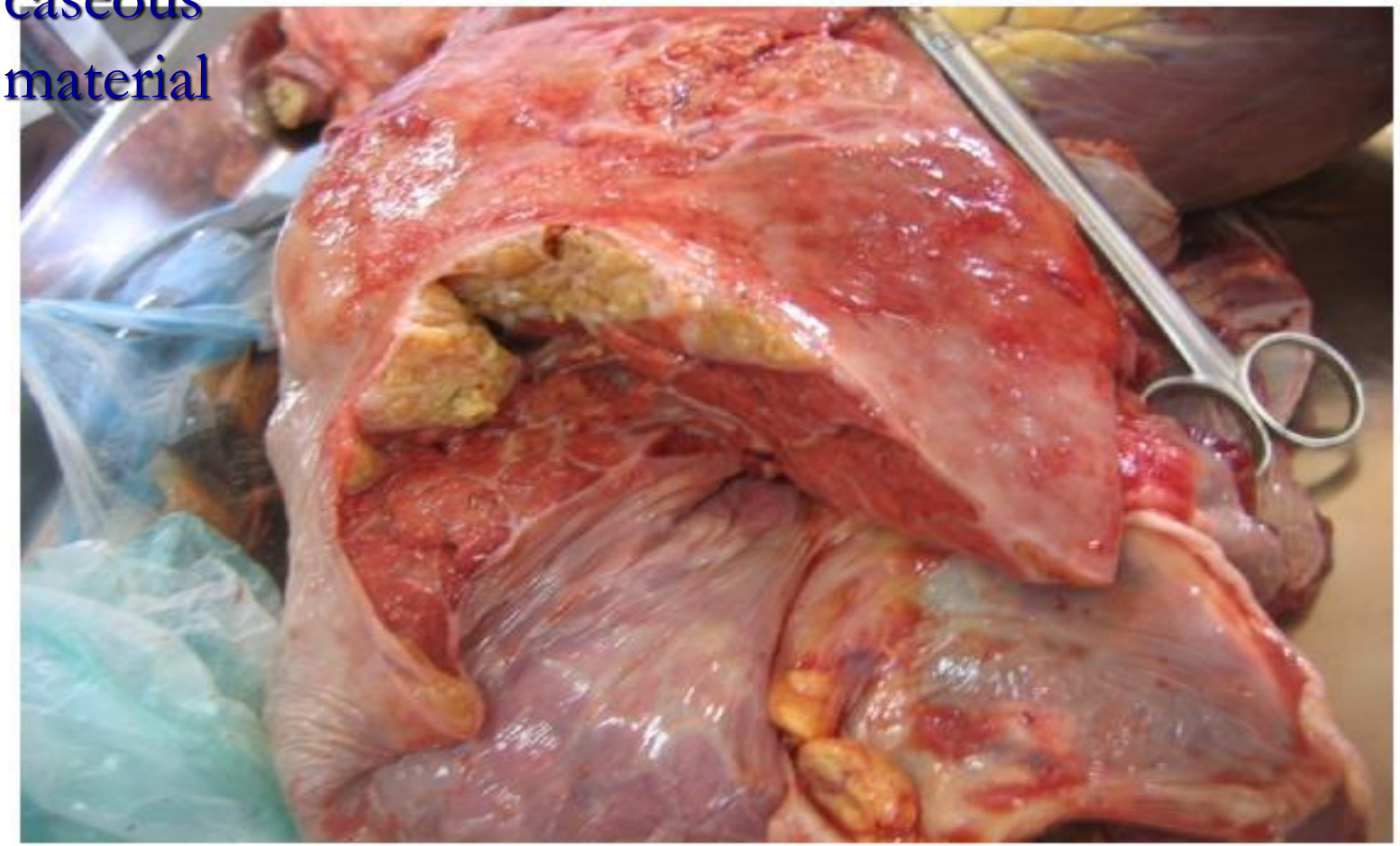
Isoniazid cont:

Pharmacokinetics

- Well absorbed from GIT
- Fatty food & aluminum-containing antacids may reduce absorption
- CSF penetration: 20% of plasma concentration with non-inflamed meninges
- Penetrate well into caseous material
- Excretion - urine

Isoniazid cont:

caseous material



Isoniazid cont:

Metabolism

- By acetylation – genetically determined

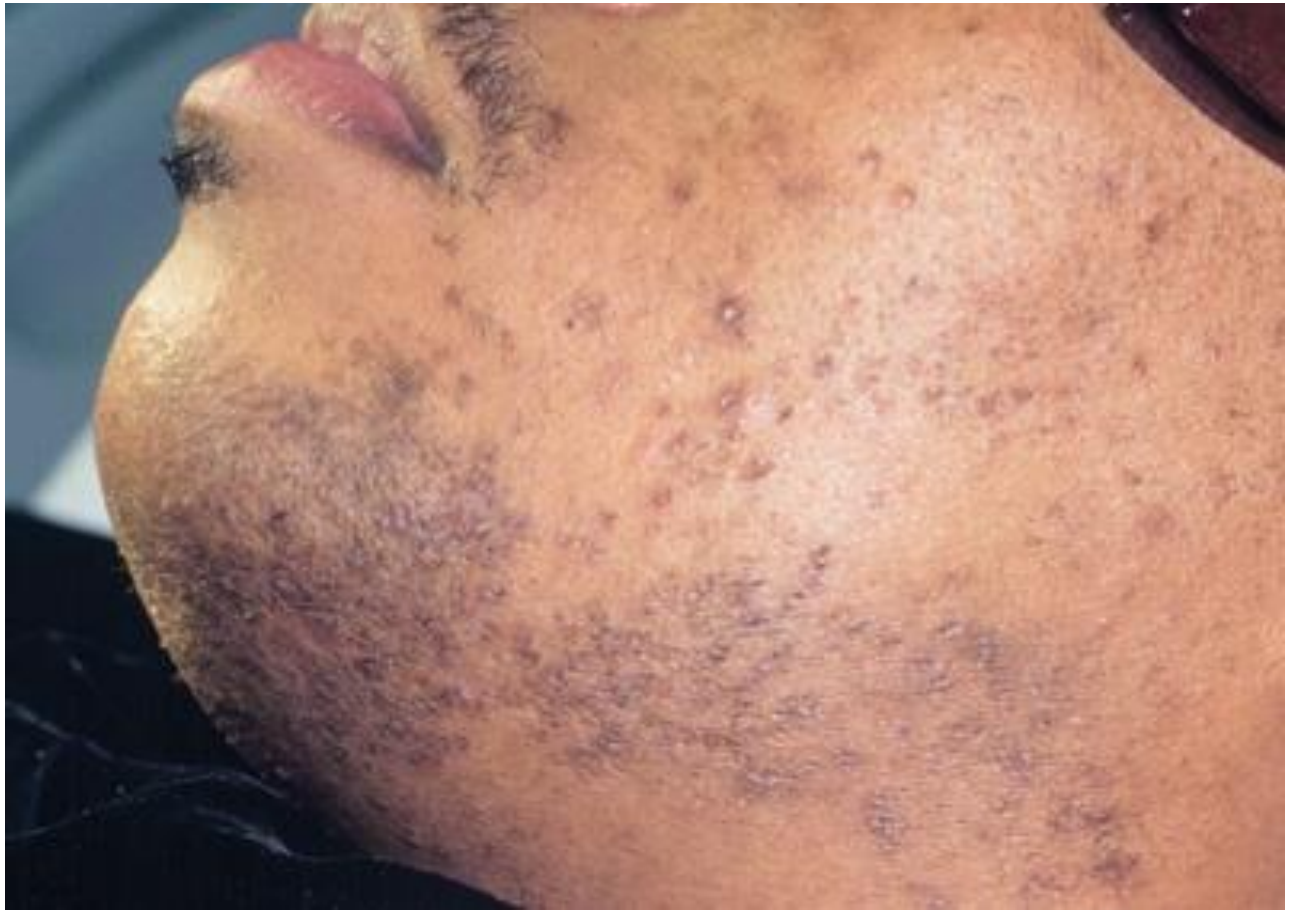
- Slow acetylation – better response
  t ½ - 3h
- Fast acetylation – t ½ - 1h

Isoniazid cont:

Adverse effect

- Hepatotoxicity
  - Elderly, slow acetylators more prone
- Polyneuropathy
  - Prevented by concurrent pyridoxine
- Rashes, acne
- Heamatological – haemolytic anaemia in G6PD deficiency

Isoniazid cont:



Acne

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Rifampicin

- Inhibits bacterial DNA-dependent RNA polymerase
- bactericidal
- Gram positive and negative
- kill intracellular organism

Rifampicin cont:

- Resistance – chemical modification of DNA-dependent RNA polymerase

Rifampicin cont:

Pharmacokinetics

- Well absorbed from GIT
- CSF penetration: 10-40% of plasma concentration with non-inflamed meninges
- Elimination hepatic, renal

Rifampicin cont:

Adverse effects

- Rashes, hepatotoxicity, thrombocytopenia
- Mild elevation of liver enzymes - common

Rifampicin cont:

- Orange discoloration of urine, sweat, tears

- Potent CYP-P450 inducer- reduce the serum level of drugs
- warfarin, oestrogen

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Ethambutol

- Inhibits arabinosyl transferases involved in cell wall biosynthesis
- Bacteriostatic to *M.tuberculosis*
- Resistance develops rapidly if used alone

Ethambutol cont:

Pharmacokinetics

- Well absorbed from GIT
- bioavailability 80%
- CSF penetration poor
- Elimination renal

Ethambutol cont:

Adverse effects

- Optic retro-bulbar neuritis
  - Red-green colour blindness → reduced visual acuity
  - Dose-related
  - Reversible
  - May be unilateral

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- streptomycin

Pyrazinamide

- Interferes with mycobacterial fatty acid synthesis
- Inactivate mycobateria at acidic PH
- Effective against intracellular organism in machrophages –

Pyrazinamide cont:

- Well absorbed from GIT
- CSF penetration: equal to plasma concentration
- Hepatic metabolism
- Excreation - kidney

Pyrazinamide cont:

Adverse effect

- GI disturbances
- Hepatotoxicity
- Hyperuricaemia – gout
- Arthralgia

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Streptomycin

- Aminoglycoside - Inhibits protein synthesis
- Bactericidal
- Poorly absorbed from GIT - given IM.
- CSF penetration: poor
- Renal elimination

Streptomycin cont:

Adverse effects

– Ototoxicity, vestibular toxicity, nephrotoxicity

Uses

– very ill patients
– Multi- drug resistance
– Not responding to treatment

Capreomycin

- Peptide antibiotic
- IM
- effect 8th cranial nerve – deafness, ataxia

Cycloserine

- Broad spectrum antibiotic
- Reaches the CSF well
- Causes CNS side effects
- Use in drug resistant TB

Pulmonary TB

Initial phase –

- INAH+Pyridoxine
- Rifampicin
- Ethambutol
- Pyrazinamide

2 months

Continuation phase –

- INAH+Pyridoxine
- Rifampicin

4 months

Anti-TB therapy

- Multiple drugs are used to reduce the emergence of resistance
- Given as combination tablets
- Taken 30 min before the breakfast as absorption of rifampicin is influenced by food

Anti-TB therapy cont:

- A fixed dose combination (FDC) - formulation of two or more active ingredients combined in a single dosage
- Improve medication compliance

Anti-TB therapy cont:

- For pulmonary TB – 6 months treatment
- For renal, bone and CNS infection – longer treatment

Drug resistance

- Multidrug resistance (MDR)
  - Resistant to at least isoniazid & rifampicin
  - MDR-TB rate - 1.4% among newly diagnosed cases in Sri Lanka

- Extensive drug resistance (XDR)
  - MDR strains also resistant to any fluoroquinolone & at least one injectable second-line drugs (amikacin, capreomycin, kanamycin)

Drug resistance cont:

Primary drug resistance

- Those exposed to resistance organism

Secondary drug resistance

- After initial drug sensitivity
- Due to non compliance

Drug resistance cont:

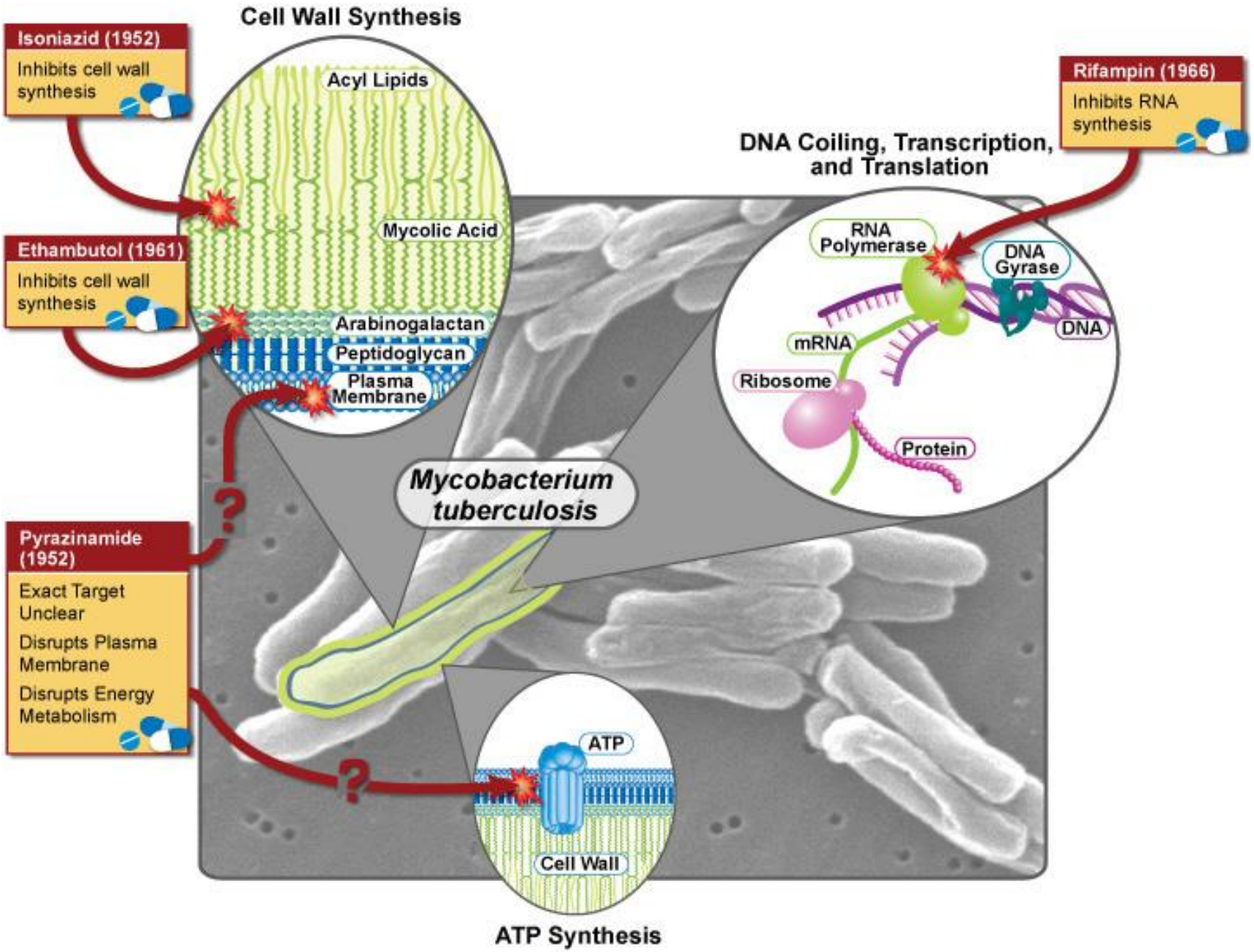
- Treatment for 2 years
- HIV positive patients 12 months after negative culture

Drug resistance cont:

- Directly observed therapy (DOT) -To improve the compliance
- Hospital stay for uncooperative people

Summary

- Use combination of drugs for a long period
- Resistance is emerging
- First line drugs and second line drugs


Cell Wall Synthesis
Isoniazid (1952)
Inhibits cell wall synthesis
Acyl Lipids
Mycolic Acid
Ethambutol (1961)
Inhibits cell wall synthesis
Arabinogalactan
Peptidoglycan
Plasma Membrane
Rifampin (1966)
Inhibits RNA synthesis
DNA Coiling, Transcription, and Translation
RNA Polymerase
DNA Gyrase
DNA
mRNA
Ribosome
Protein
Mycobacterium tuberculosis
Pyrazinamide (1952)
Exact Target Unclear
Disrupts Plasma Membrane
Disrupts Energy Metabolism
ATP
Cell Wall
ATP Synthesis

Summary cont:

- Isoniazid – bactericidal to rapidly dividing bacteria
- Rifampicin - kill intracellular bacteria
- Ethambutol – bacteriostatic against multiplying bacteria
- Pyrazinamide - kill dormant mycobacteria

Thank you