PRINCIPLES OF DRUG THERAPY

# DRUGS IN TUBERCULOSIS & LEPROSY

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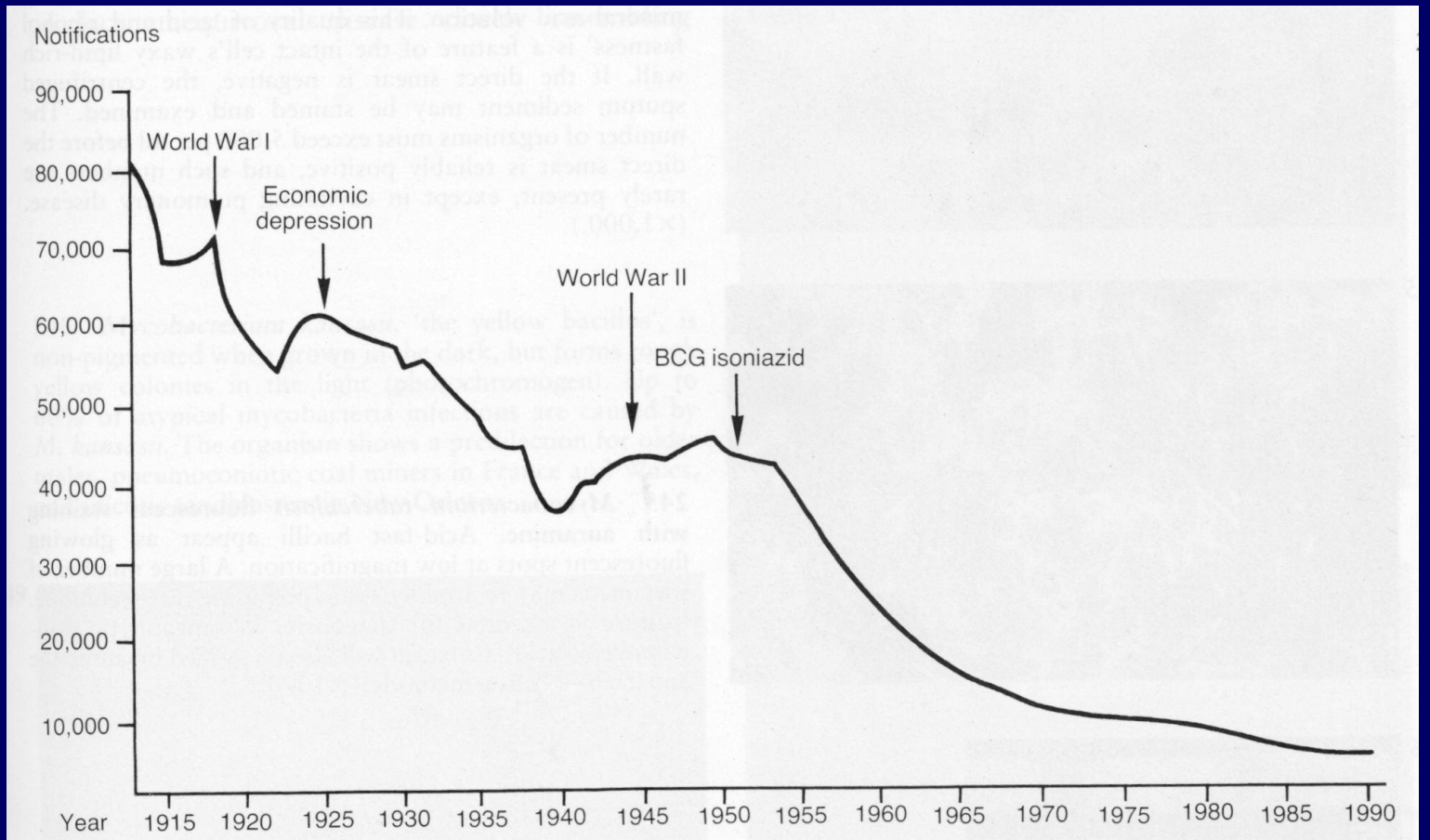
# WHY TAUGHT TOGETHER?

1) Similar epidemiology
2) Similar infecting agent
3) Overlapping anti-microbial drugs
4) Prolonged treatment

# TB NOTIFICATION RATES




243 Tuberculosis notifications – England and Wales 1912 to 1990.

# ANTI-TUBERCULOSIS DRUGS

# CLASSIFICATION

Drugs to treat
M. Tuberculosis

ISONIAZID H
RIFAMPICIN R
PYRAZINAMIDE Z
ETHAMBUTOL E
STREPTOMYCIN S

Drugs to treat atypical mycobacterial species

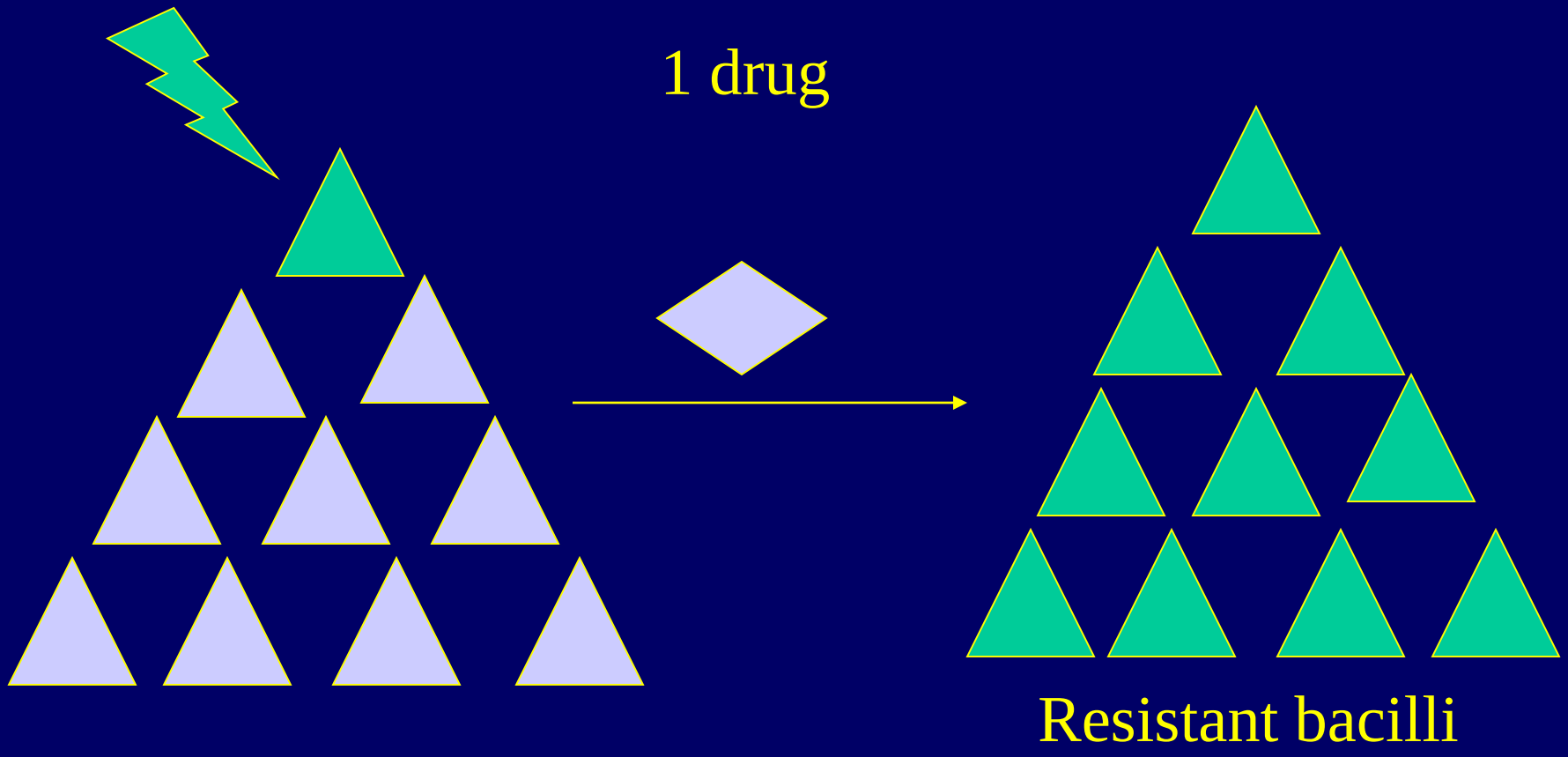
rifabutin
clarithromycin
ciprofloxacin
amikacin
doxycycline

# PRINCIPLES OF CHEMOTHERAPY 1/2

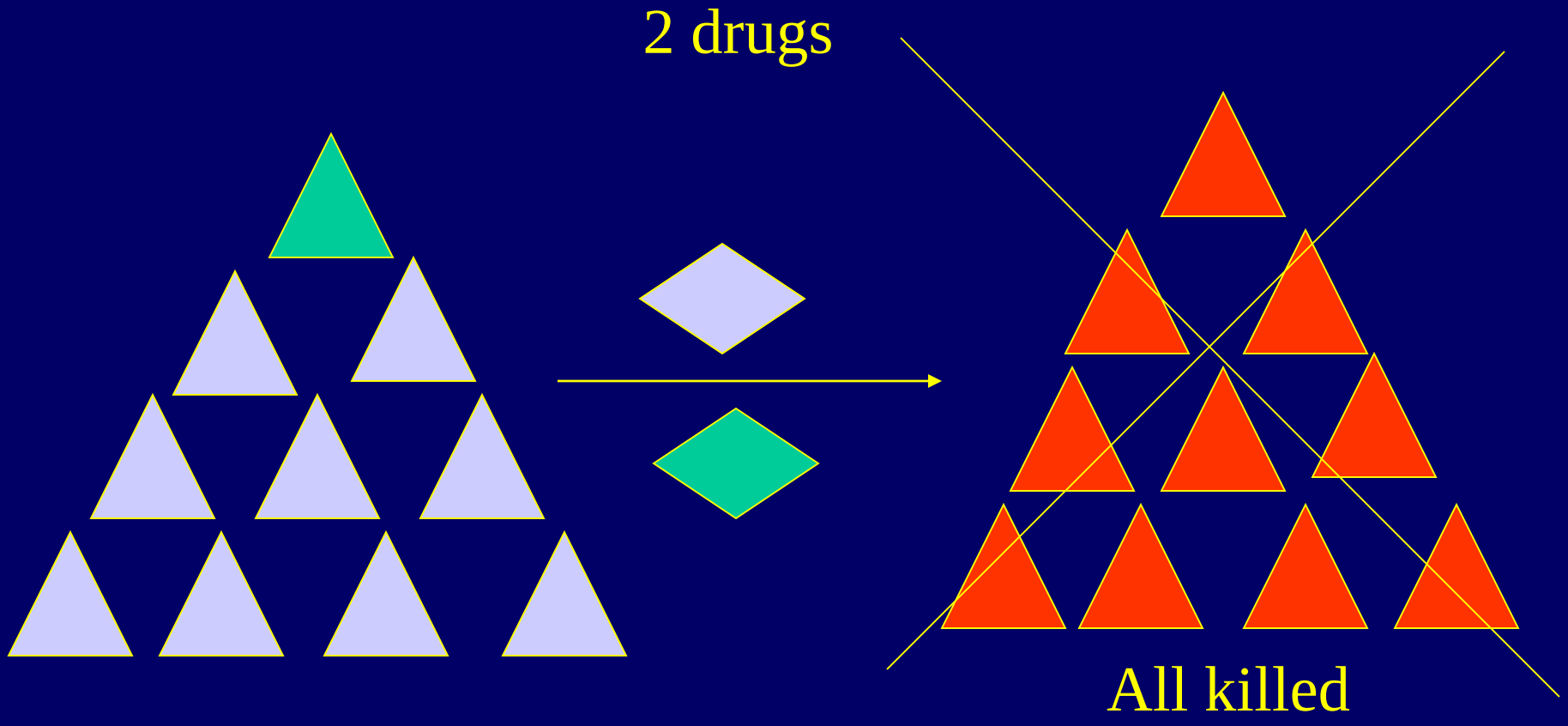
- A *large number of actively multiplying cells* must be killed: isoniazid. $10^8$ bacilli/cavity

- *prevent emergence of drug resistance* by multiple therapy to suppress drug-resistant mutants that exist in large bacterial populations: isoniazid & rifampicin

# REASON FOR COMBINATION THERAPY 1/2



# REASON FOR COMBINATION THERAPY 1/2



# PRINCIPLES OF CHEMOTHERAPY 2/2

- Treat *semi-dormant bacilli* that metabolise intermittently: rifampicin & pyrazinamide

- Multiple antibiotics requires combined formulations to ensure that *poor compliance* does not result in monotherapy and subsequent drug resistance

# ISONIAZID 1

First developed anti-TB drug (1945)

Mechanism of Action

- highly specific for MTB
- bacteriocidal: prevents synthesis of mycolic acids essential for cell wall structure
- also has a bacteriostatic actions

# ISONIAZID 2

Kinetics

- well absorbed
- metabolised by acetylation, 2 populations: slow acetylators (T1/2  4hrs) & fast acetylators (T1/2 1hr). eg *pharmacogenetics*
- penetrates CSF well, important in TB meningitis

# ISONIAZID 3

Uses

- anti TB therapy, most used drug worldwide
- should be used in all patients

TB cavities contains $10^8$ bacilli each, primary resistance to isoniazid is present in one in $10^6$. Therefore use in combination with other agents to prevent selecting resistant strains.

# ISONIAZID 4

Adverse effects

- generally well tolerated
- hepatitis, rarely can be fatal. risk increases with age, higher in slow acetylators.
- peripheral neuropathy (structural analogue of pyridoxine), esp in poor nutritional states and slow acetylators. Therefore given with pyridoxine cover

# RIFAMPICIN 1

Mechanism of action

- inhibits DNA replication by inhibiting RNA polymerase by forming a stable drug-enzyme complex
- bacteriocidal for both intra- and extra-cellular forms
- particularly effective for semi-dormant forms

# RIFAMPICIN 2

- Resistance develops as a rapid one-step process

Kinetics

- well absorbed T1/2 4 hrs
- good CSF penetration when meninges are inflamed, so poor entry after 1-2 months treatment
- enterohepatic circulation

# RIFAMPICIN 3

Uses

wide spectrum of anti-microbial activity: not specific

- TB and leprosy
- many gram + & - organisms including Staph. aureus and N. menigitidis (used in meningococcal prophylaxis)
- H. influenzae & Legionella species

# RIFAMPICIN 4

Adverse effects

- hepatitis, less common than isoniazid
- ‘rifampicin flu’ malaise, headache & fever
- red discoloration of body fluids (useful)
- potent inducer of hepatic microsomal enzymes. Speeds up metabolism of warfarin, steroids, oral hypoglycaemics & phenytoin. *Must increase dose*

# PYRAZINAMIDE 1

Mechanism of action

- unknown
- dependent on intrabacterial pyrazinamidases for activation of drug
- particularly effective at killing intracellular persisters
- requires an acidic pH such as found within a Langerhans cell

# PYRAZINAMIDE 2

Kinetics

- well absorbed, T1/2 9 hours
- metabolised in the liver

Uses

- bacteriostatic
- included in first-choice combinations for short course treatment of TB

# PYRAZINAMIDE 3

Adverse effects

- hepatitis, commonest drug induced cause in treating TB, monitor transaminases
- hyperuricaemia: inhibits tubular secretion of urate
- arthritis

# ETHAMBUTOL 1

Mechanism of action

- unknown
- interferes with mycolic acid metabolism in cell wall
- bacteriostatic

# ETHAMBUTOL 2

Kinetics

- well absorbed, T1/2 4hrs
- only penetrates inflamed meninges
- renal excretion, reduce dose in renal failure

Uses

- Used in combination with other anti-TB drugs to reduce risk of resistance

# ETHAMBUTOL 3

Adverse effects

recommended oral dose (15mg/kg) is safe

- optic neuritis

- reduced visual acuity and red-green colour blindness. check before starting.
- reversible if stopped promptly
- avoid if pt understanding is poor

# STREPTOMYCIN 1

First isolated aminoglycoside

First drug to show anti-TB activity

Mechanism of action

- interrupts DNA synthesis by incorporating false amino acids into the peptide chains
- bacteriocidal

# STREPTOMYCIN 2

Kinetics

- highly ionised (water soluble). Very poorly absorbed by the GI tract mucosa
- parenteral administration
- poor CSF penetration even with inflammed meninges

# STREPTOMYCIN 3

Uses

wide anti-microbial spectrum

- least used of first-choice agents for TB
  - resistance, parenteral use, adverse effects
- gram - species, staph, plague, brucella

# STREPTOMYCIN 4

Adverse effects

common with high doses & prolonged courses

- ototoxicity: vestibular and auditory
- nephrotoxicity, esp with reduced renal clearance and dehydration. usually reversible
- neuromuscular blockade

# TREATMENT REGIMENS

| | Initial phase | | Continuation phase | | |
|---|---|---|---|---|---|
| | drug | months | drug | months | Total months |
| Resp | HRZE | 2 | HR | 4 | 6 |
| CNS | HRZE | 2 | HR | 10 | 12 |
| others | HRZE | 2 | HR | 4 | 6 |

# COMBINATION CHEMOTHERAPY

RIFATER = rifampicin + isoniazid + pyrazinamide

RIFINAH = rifampicin + isoniazid

Reduces the number of tablets: improves compliance

Good compliance = less multi-drug resistant TB

# SUMMARY

- Individual drugs
- Need for multi-drug treatment
- Regimens
- Problems with compliance

# ANTI-LEPROSY DRUGS

# TREATMENT OF LEPROSY

Aims:

- 1) destroy the bacillus
- 2) Render the patient non-infectious

2 components:

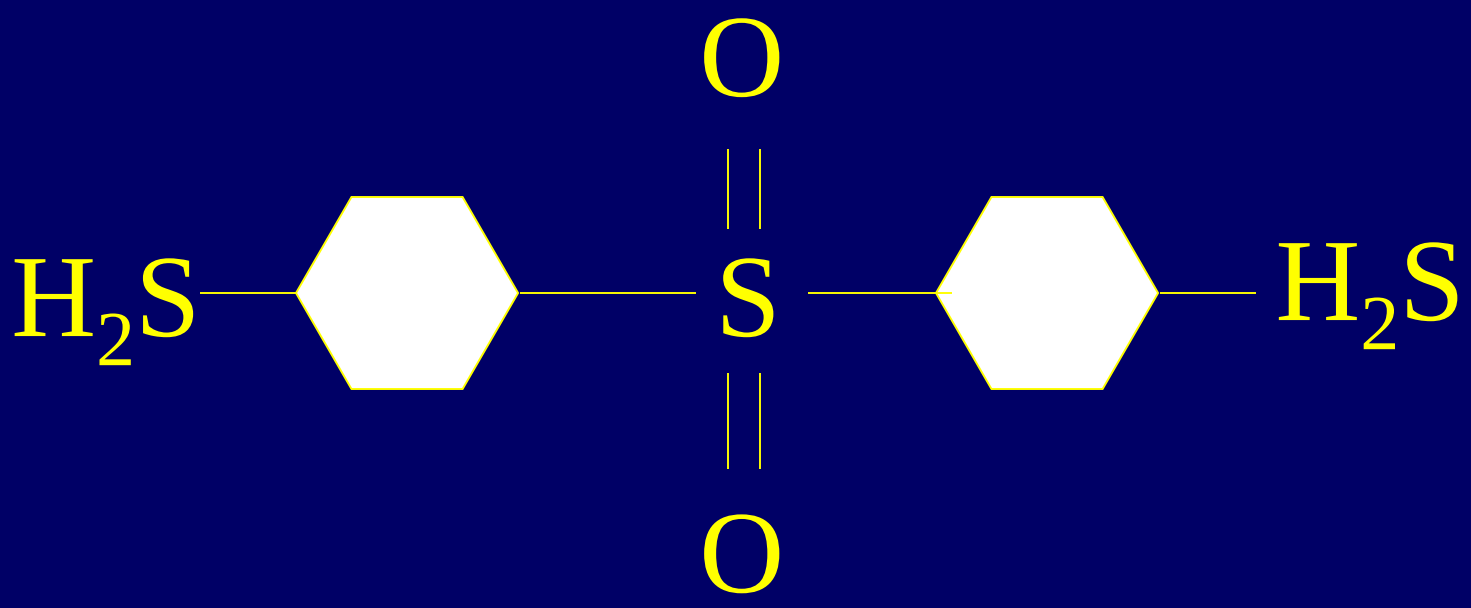
- 1) Treatment of infection
- 2) Treatment of reactions

# TREATMENT OF INFECTION

- Which drugs?

RIFAMPICIN
DAPSONE
CLOFAZIMINE

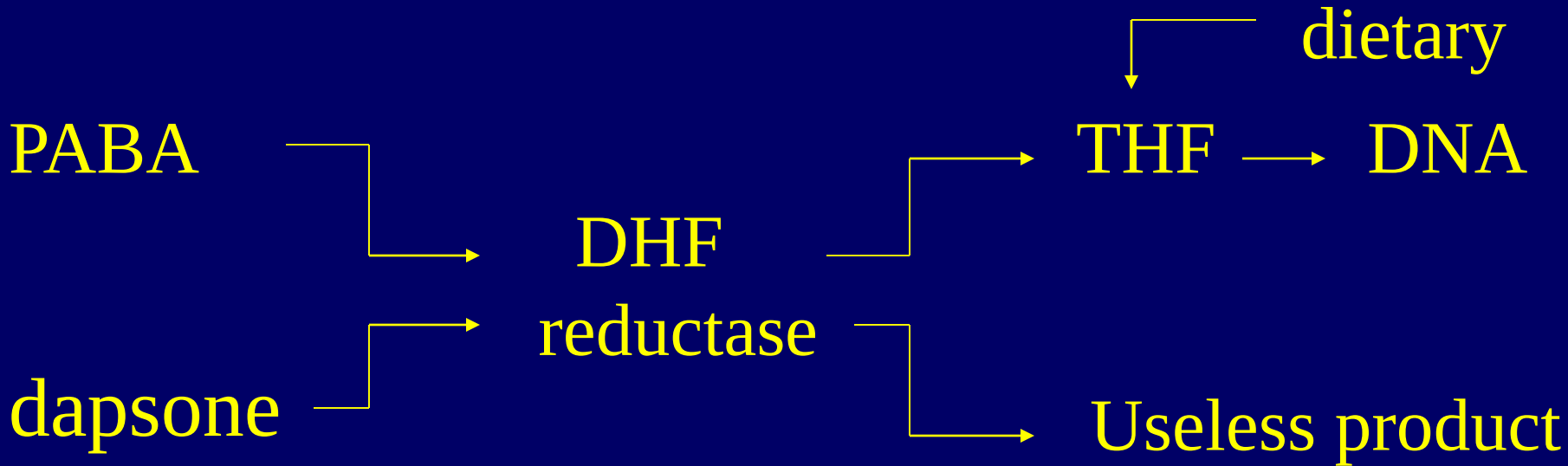
# DAPSONE 1




Related to sulphonamides

# DAPSONE 2

- Mechanism of Action
  - PABA (para-amino benzoic acid) analogue
  - Bacteriostatic



# DAPSONE 3

- Kinetics
  - Well absorbed, T1/2 24 hrs (ideal for daily dosing)
  - Partly metabolised (acetylator status dependent)
  - Enterohepatic circulation

# DAPSONE 4

- Uses
  - Leprosy
  - Dermatitis herpetiformis
  - Malaria prophylaxis (combined with pyrimethamine)

# DAPSONE 5

- Adverse effects
  - high risk of haemolysis in G6PD deficiency
  - agranulocytosis
  - allergic dermatitis
  - nausea & vomiting

# CLOFAZIMINE 1

- Mechanism of action
  - binds to DNA template and interferes with replication
  - bacteriostatic action against M. leprae
  - anti-inflammatory effect prevents erythema nodosum leprosum (ENL)
  - activity against some Mycobacterial spps

# CLOFAZIMINE 2

- Kinetics
  - well absorbed
  - long T1/2  (70hrs) leads to tissue accumulation

- Uses
  - Leprosy (including dapsone-resistant forms)
  - Anti-inflammatory action useful in ENL
  - Buruli ulcer (M. ulcerans)

# CLOFAZIMINE 3

- Adverse effects
  - Red discoloration of skin
  - eosinophilic enteritis

# PRINCIPLES OF CHEMOTHERAPY

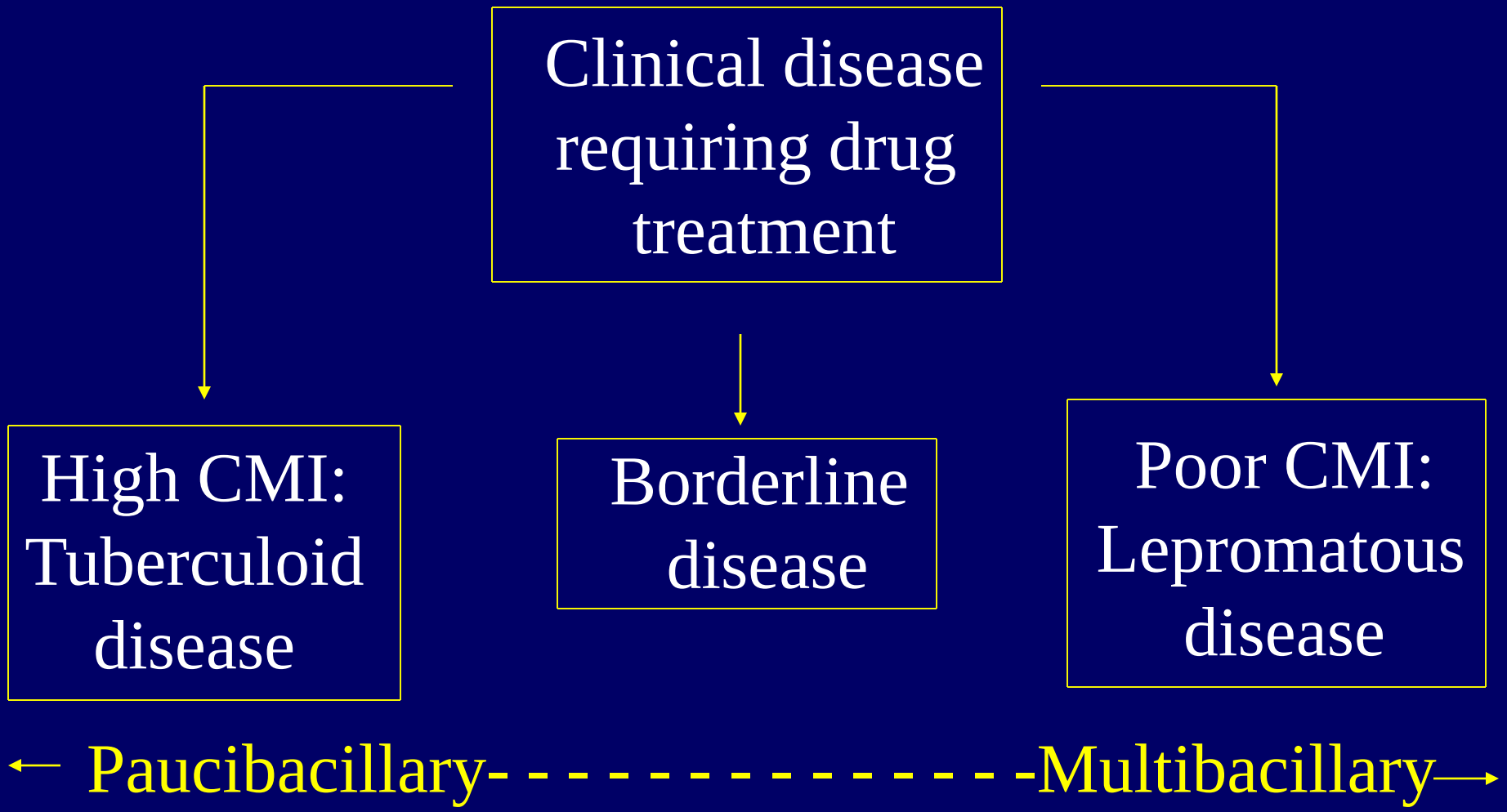
Steps to avoid development of resistance to chemotherapy:

1) Rapid reduction of bacillus population using combination drug therapy

2) Give full doses from the start

3) Do not stop effective chemotherapy during any kind of reaction.

# TREATMENT OF INFECTION



# TREATMENT REGIMENS

Multibacillary Leprosy

- Rifampicin 600mg monthly (supervised)
- Clofazimine 300mg monthly (supervised) and 50mg daily
- Dapsone 100mg daily

UNTIL SLIT SMEAR NEGATIVE

Paucibacillary leprosy

- Rifampicin 600mg monthly (supervised)
- Dapsone 100mg daily

6 MONTHS TREATMENT

# TREATMENT OF REACTIONS

- Erythema nodosum leprosum
  - Ag/Ab complex disease causes inflammation
  - rest, aspirin, clofazimine, steroids, thalidomide
- Reversal reactions
  - Up grading: URGENT, steroids, nerve decompression
  - Down grading: start standard chemotherapy