



# PHARMACODYNAMICS IV

**TOLERANCE /  
DESENSITIZATION  
& ADVERSE DRUG REACTIONS**

**Phocomelia**

**Thalidomide crisis**

Thalidomide was marketed in

**LATROGENIC DISEASE**

hypnotic & as for morning sickness during pregnancy

In 1961 a report of out break of **phocomelia** in the neoborn babies(40000-100000 cases)



# ILOS

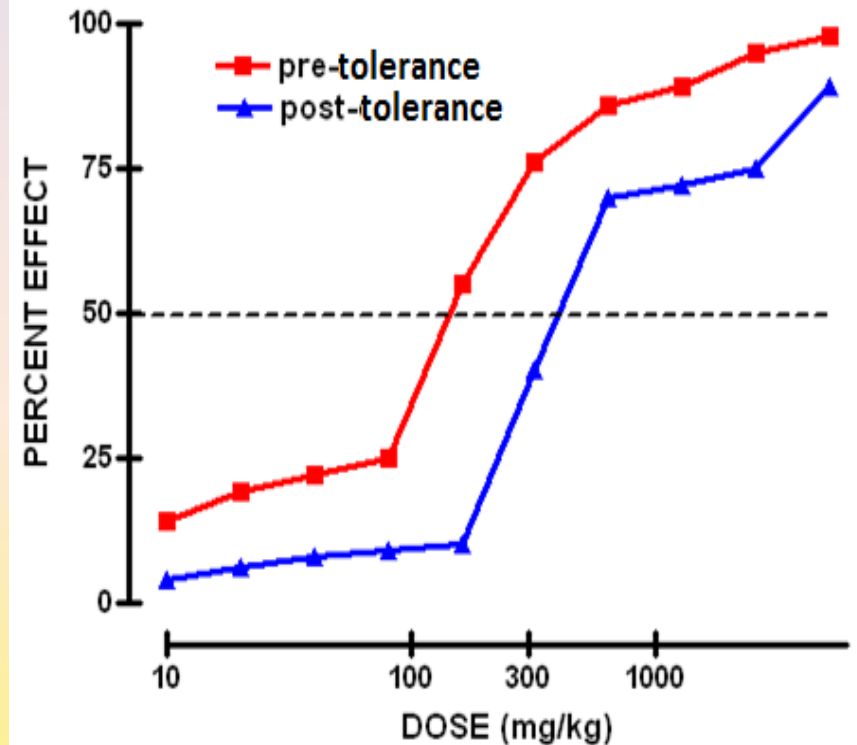
➤ Distinguish difference between tolerance and desensitization (tachyphylaxis) and reasons for their development

➤ Recognize patterns of adverse drug reactions (ADRs)



# TOLERANCE AND DESENSITIZATION

Phenomenon of variation in drug response, whereby there is a gradual diminution of the response to the drug when given continuously or repeatedly





# DIMINUTION OF A RESPONSE

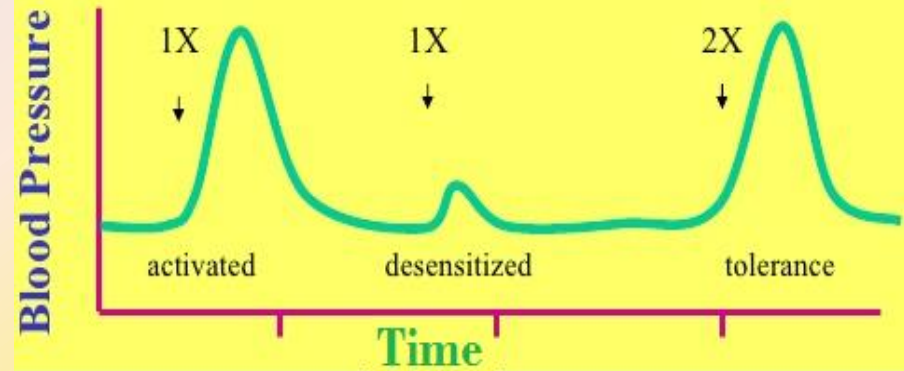
Rapid, in the course of few minutes

**TACHYPHYLAXIS /  
DESENSITIZATION**

Gradual in the course of few days to weeks

**TOLERANCE**

These SHOULD BE  
DISTINGUISHED FROM



Loss of effectiveness of  
antimicrobial agent

**Resistance**

# REASONS FOR DEVELOPMENT OF TOLERANCE



## PRE RECEPTOR EVENTS

↓ Drug availability at the relevant receptors due to pharmacokinetic variables

Drug becomes:

> metabolized or excreted

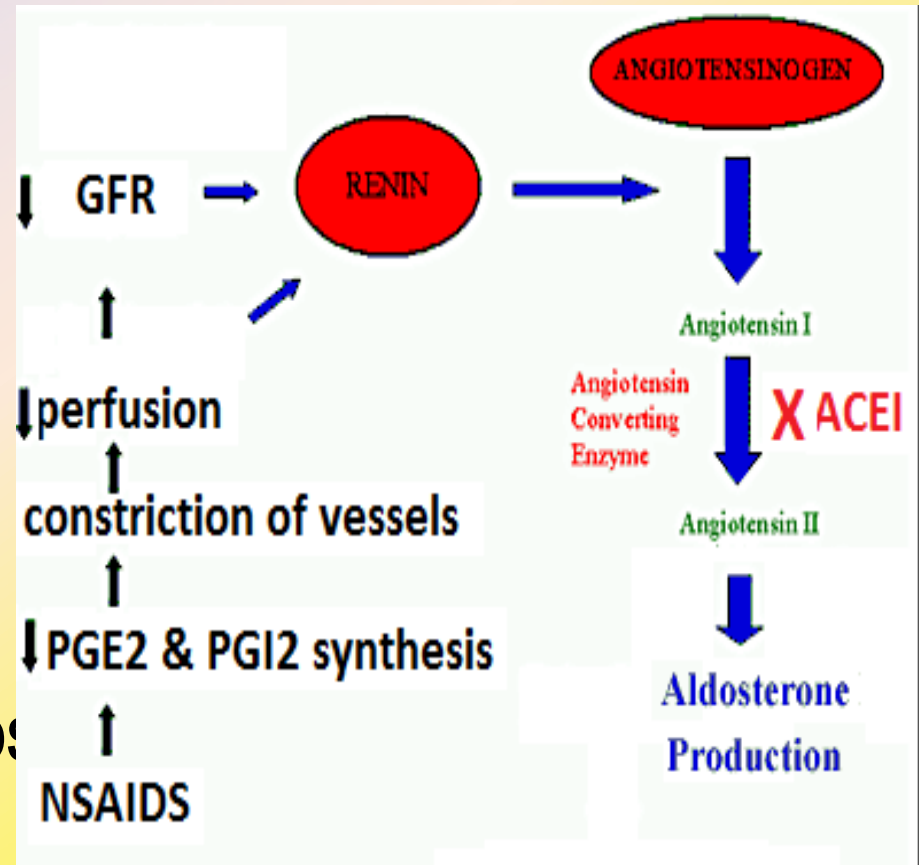
< absorbed

altered distribution to tissues

eg. Barbiturates ↑ metabolism of  
Contraceptive pills = ↓ it  
availability

## EVENTS AT RECEPTORS

## POST RECEPTOR EVENTS



LOS

# REASONS FOR DEVELOPMENT OF TOLERANCE



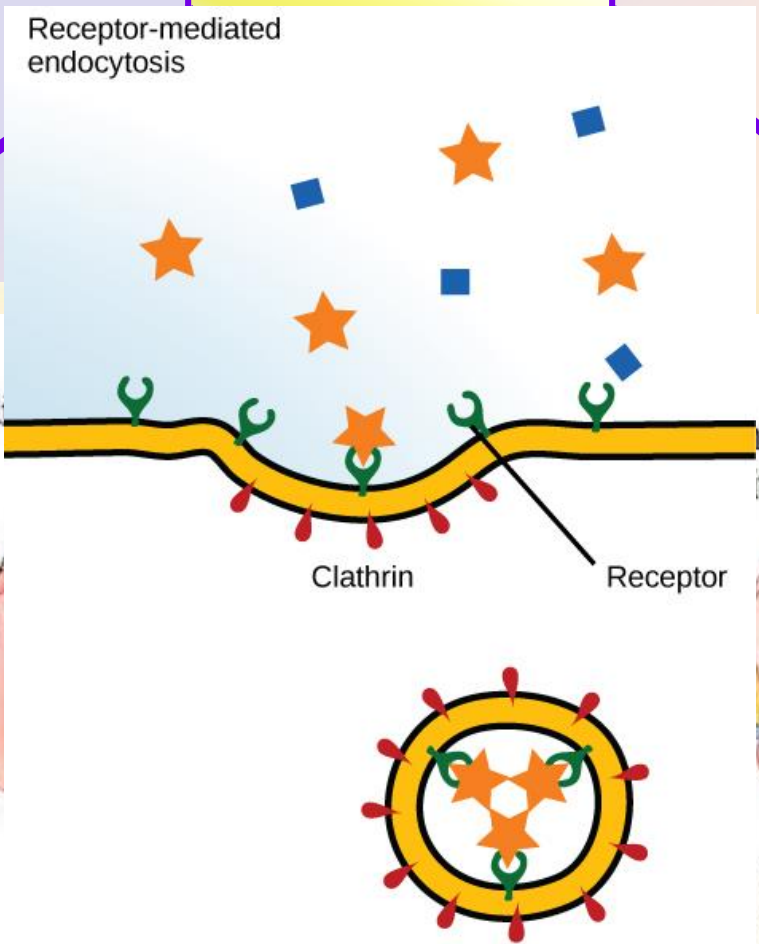
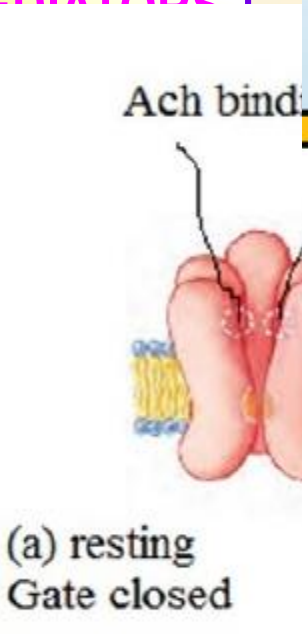
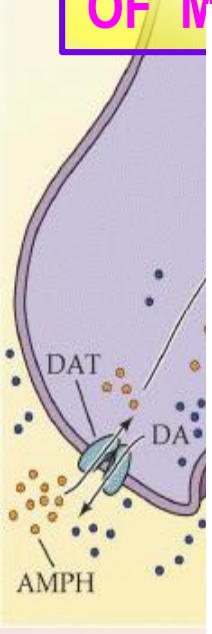
**PRE RECEPTOR EVENTS**

**EVENTS AT RECEPTORS**

**POST RECEPTOR EVENTS**

**EXHAUSTION OF MEDIATORS**

**DOWN REGULATION**

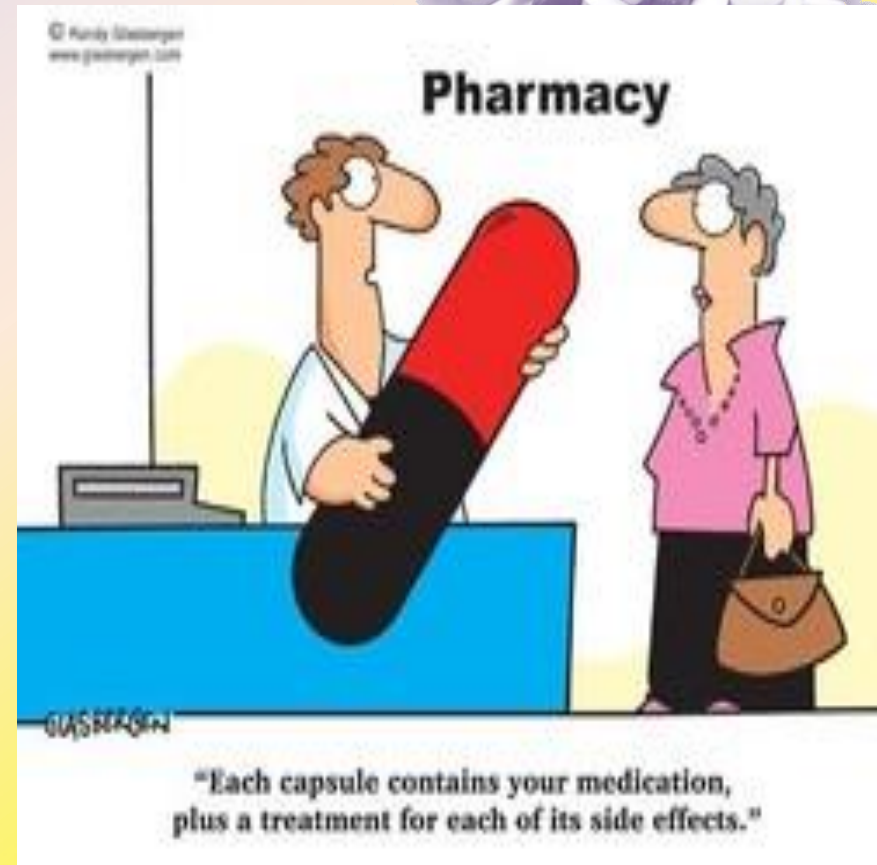


Number of receptors.  
Acetylcholine  
stimulation to  $\beta$  receptors  $\rightarrow$   $\uparrow$  recycling  
endocytosis  
[genetic defect]

# ADVERSE DRUG REACTIONS [ADRS]



**Harmful or seriously unpleasant effects occurring at doses intended for therapeutic effects.**





# TYPES OF ADRS

A

Augmented

B

Bizarre

C

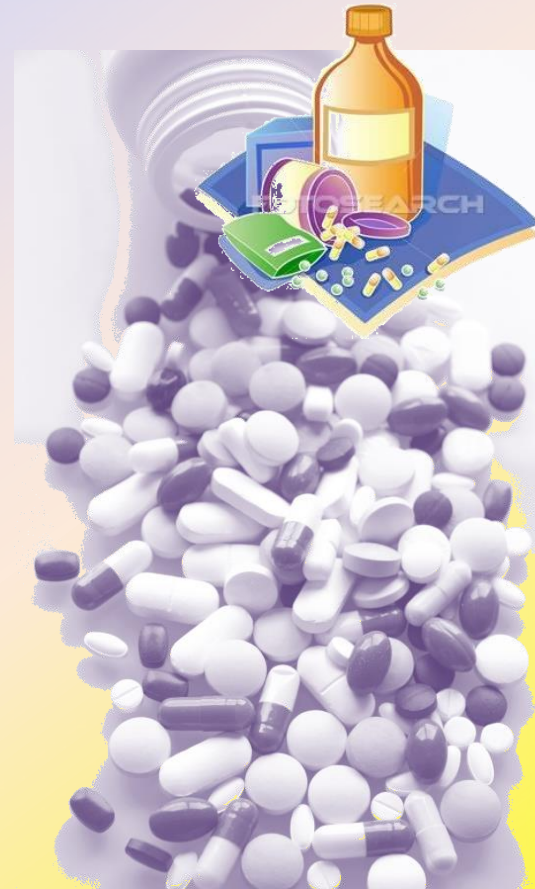
Chronic

D

Delayed

E

End of Use



**TYPE A**

**AUGMENTED**



**80% of ADRs**

Is it dose dependent?

low?

How is it treated?

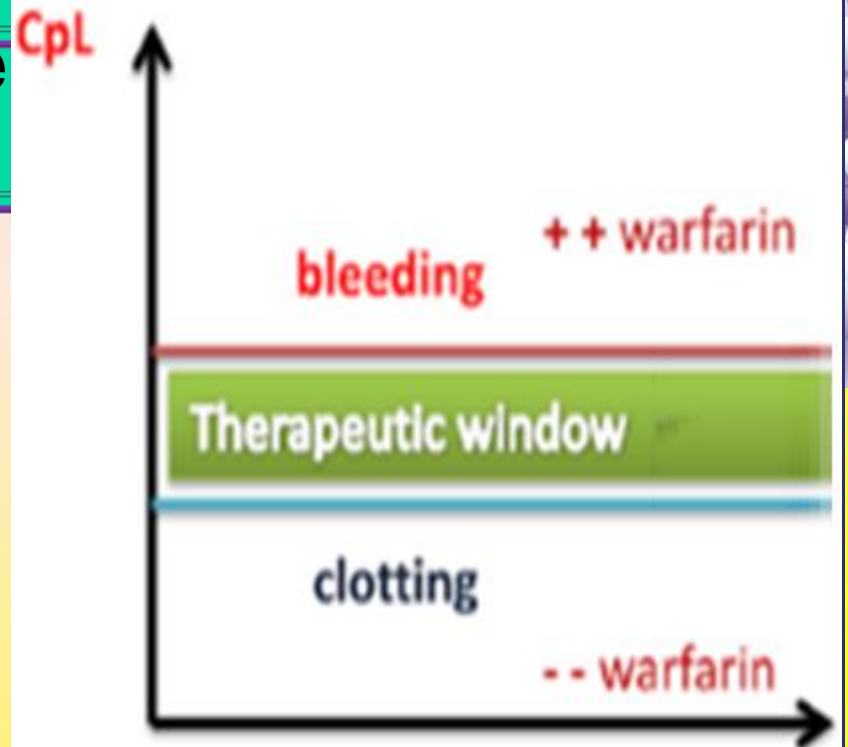
the

primary effect?

drug

e.g. Hypoglycemia from hypoglycemic drugs

**Bleeding from warfarin**



# TYPE B

# BIZARRE

Occurs different to known drug pharmacological effect [Idiosyncrotic]

Is it predictable?

Idiosyncrotic reactions are drug reactions that are unpredictable and occur in a small population

How mortal is it?

How is it treated?

qualitatively different

Usually due to  
[1] immunological response  
or [2] patient's genetic defect

Penicillin → Anaphylactic shock

Quinine → Thrombocytopenia

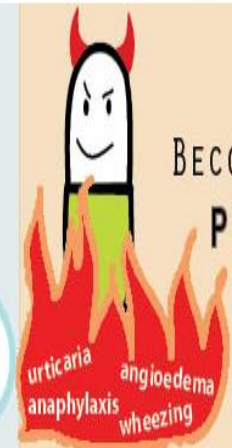


## DRUG ALLERGY

WHEN THE SOLUTION...



BECOMES THE PROBLEM





**TYPE C**

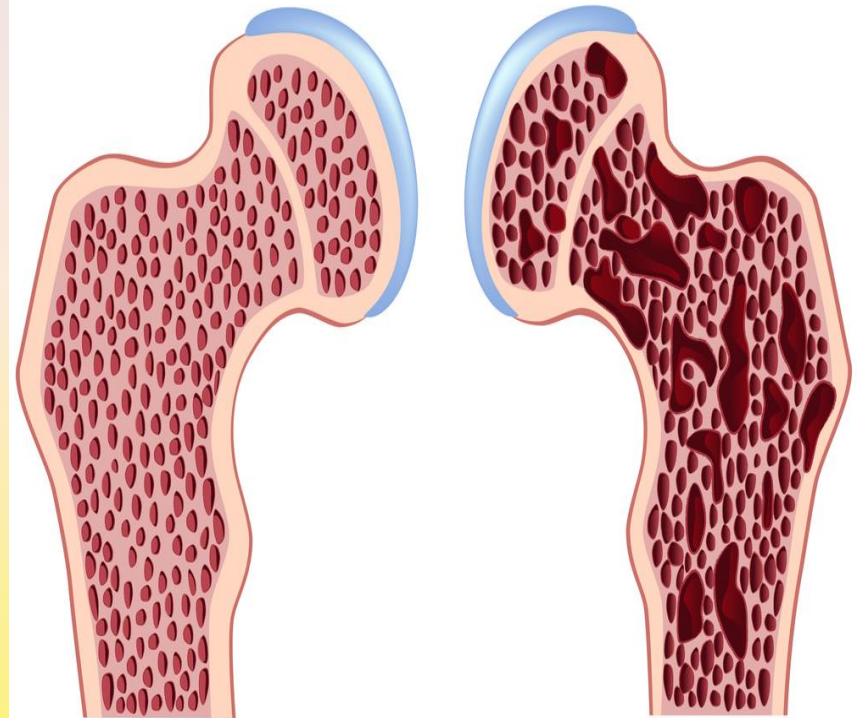
**CONTINUED**



Occurs during chronic drug administration

Osteoporosis → chronic corticosteroid intake

Osteoporosis



Healthy bone

Osteoporosis



## TYPE D

## DELAYED

Occurs after long period of time even after drug stoppage (delayed in onset)

Refers to carcinogenic and teratogenic effects

Teratogenicity → Retinoids  
Carcinogenicity → Tobacco smoking



**Retinoic acid  
malformations**

## **TYPE E**

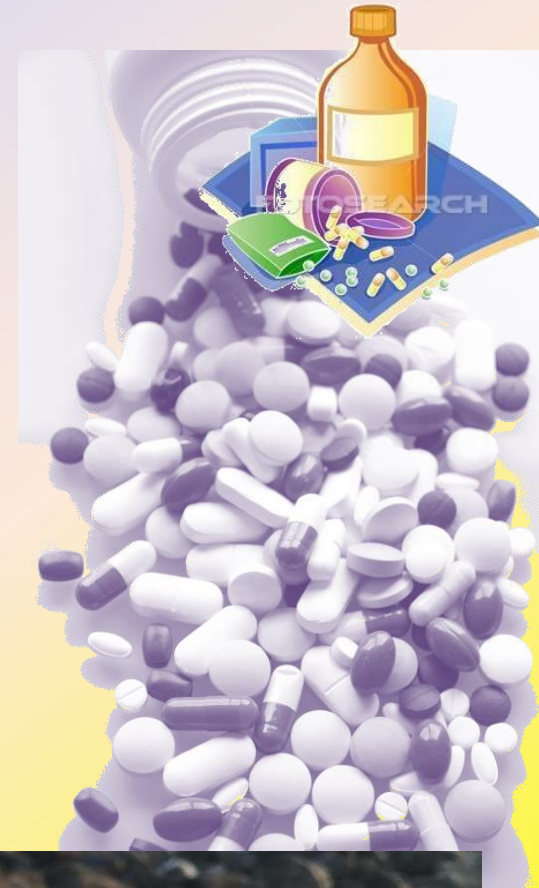
## **END OF USE**

Occurs after sudden stoppage of chronic drug use due to existing adaptive changes

Withdrawal syndrome → Morphine

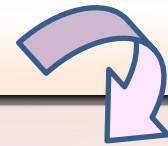
↑ Body ache, insomnia, diarrhea, goose flesh, lacrimation

Withdrawal of diazepam → anxiety, insomnia

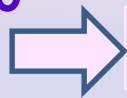


# TYPE B

[1] If due to immunological response

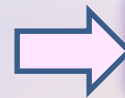


1<sup>st</sup> exposure to a drug



**Sensitization**

Repeated exposures



**HYPERSENSITIVITY REACTION**



**TYPE I**  
**Anaphylaxis**

Release of mediators from mast cells or blood basophils

Urticaria rhinitis, bronchial asthma by **Penicillin**,

**TYPE II**  
**Cytotoxic**

Antibody-directed cell-mediated lysis

Haemolytic anaemia thrombocytopenia by **Quinine**

**TYPE III**  
**Immune complex**

Deposition of soluble antigen-antibody-complement complexes in small blood vessels

Serum sickness (*fever, arthritis, enlarged lymph nodes, urticaria*) by **Sulphonamides, Streptomycin**

**TYPE IV**  
**Cell mediated**

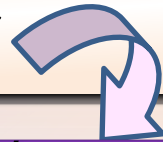
Interaction release cytokines that attracts inflammatory cell infiltrate

Contact dermatitis by **local anaesthetics** creams

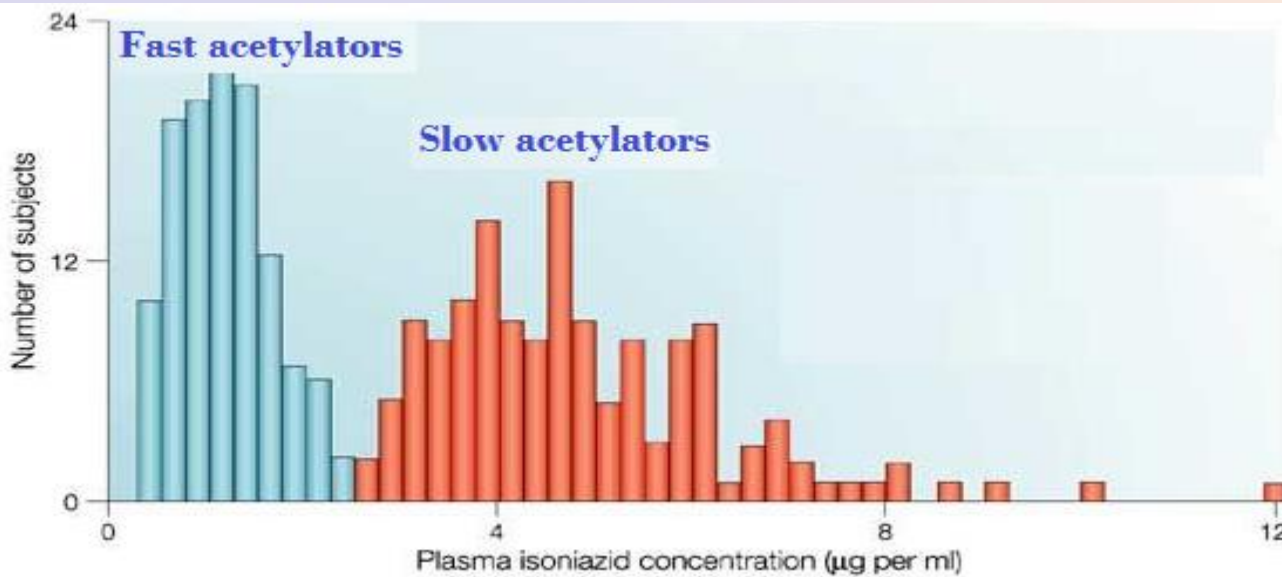


## TYPE B

## [2] IF DUE TO GENETIC DEFECT



When **isoniazid** is given in identical doses /kg, two distinct groups can be identified, a group with low blood level acetylate the drug more rapidly '**fast acetylators**' & a group with high blood level acetylate the drug slowly '**slow acetylators**'



Genetic polymorphism

**Relapse of infection & hepatitis** occur in fast acetylators

Isoniazid causes **peripheral neuropathy** in slow acetylators