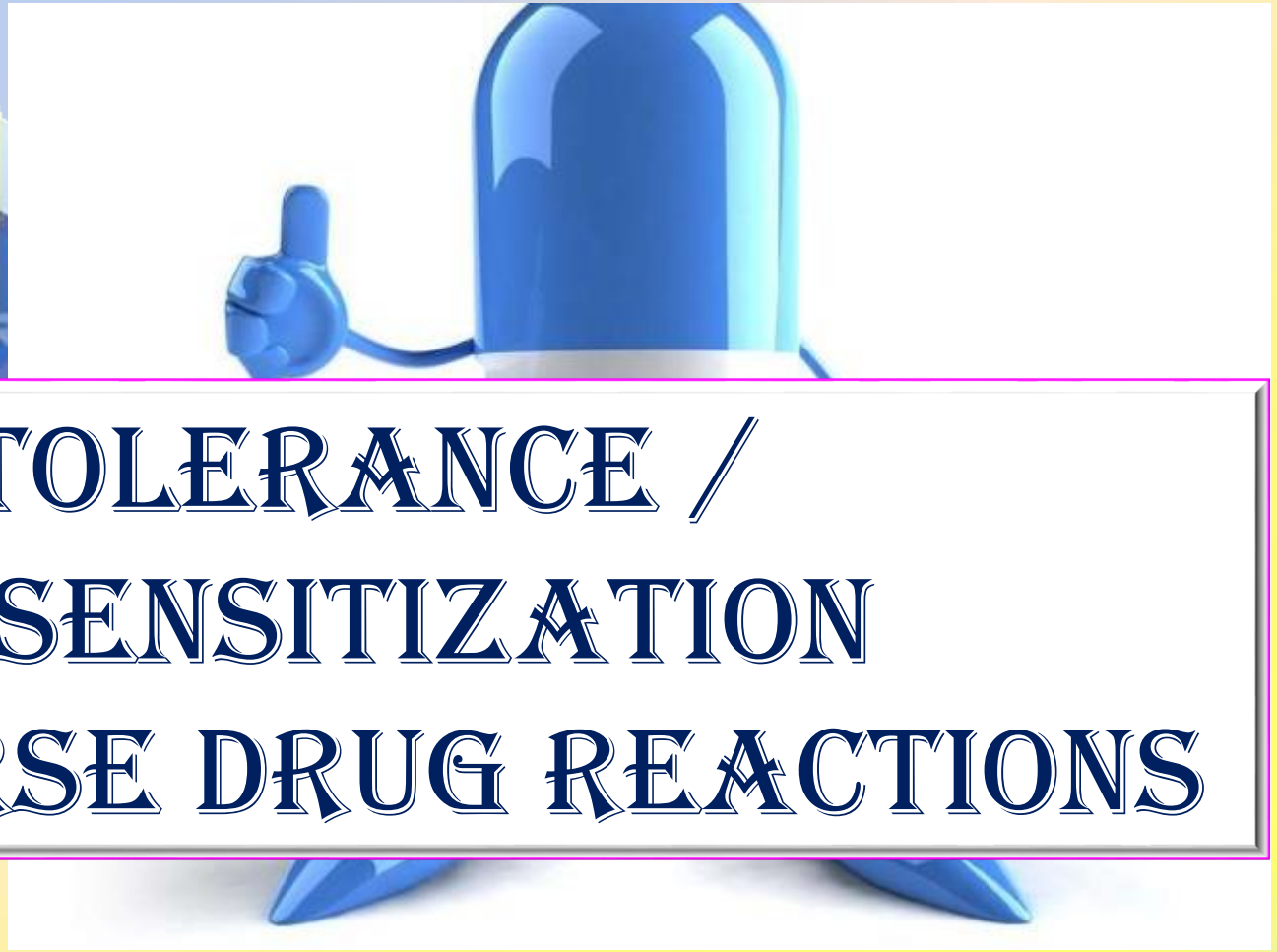
PHARMACDYNAMICS IV



TOLERANCE / DESENSITIZATION & ADVERSE DRUG REACTIONS

Phocomelia

Thalidomide crisis

Thalidomide was marketed in

IATROGENIC DISEASE

hypnotic & as for morning sickness during pregnancy

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

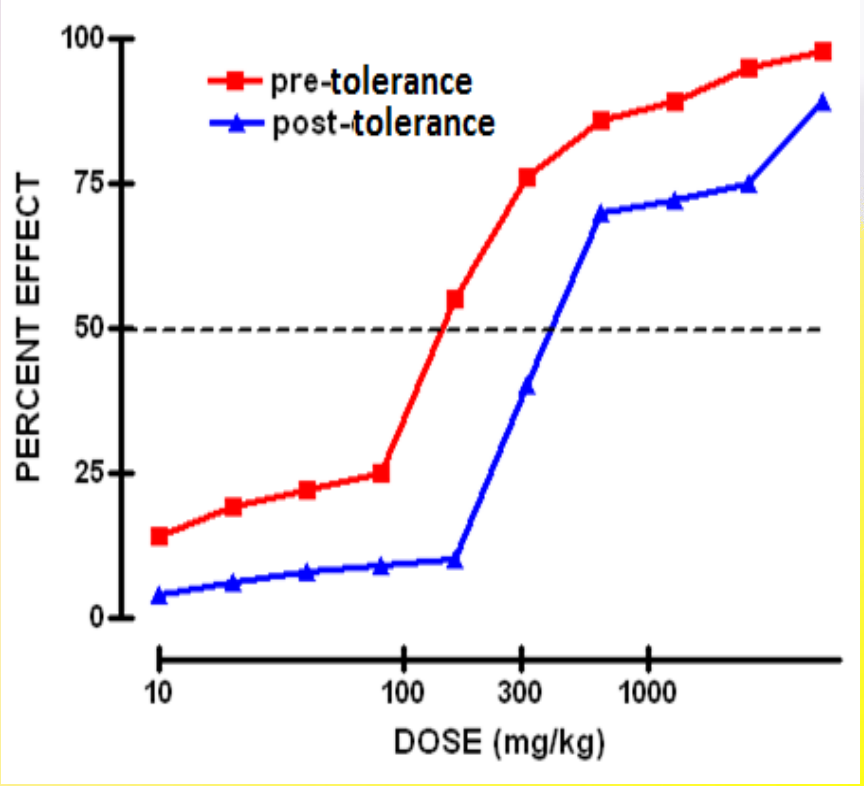
ILOS

- 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



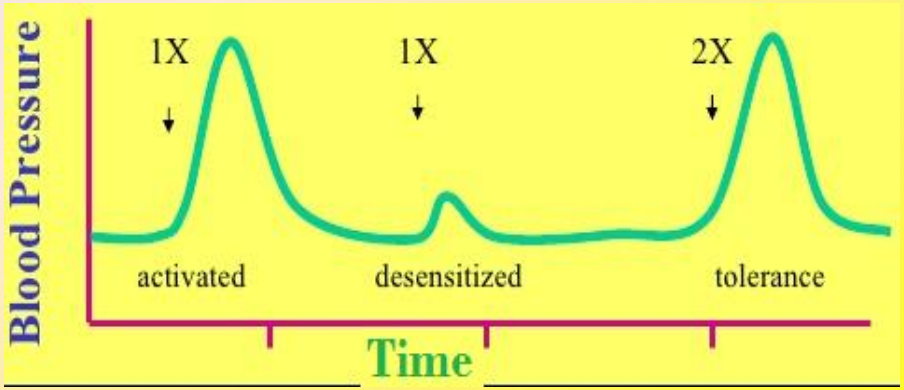
DIMINUTION OF A RESPONSE

Rapid, in the course of few minutes

Gradual in the course of few days to weeks

TACHYPHYLAXIS / DESENSITIZATION

TOLERANCE



These SHOULD BE DISTINGUISHED FROM

Loss of effectiveness of antimicrobial agent

Resistance

REASONS FOR DEVELOPMENT OF TOLERANCE

PRE RECEPTOR EVENTS

EVENTS AT RECEPTORS

POST RECEPTOR EVENTS

↓ Drug availability at the relevant receptors due to pharmaco-kinetic variables

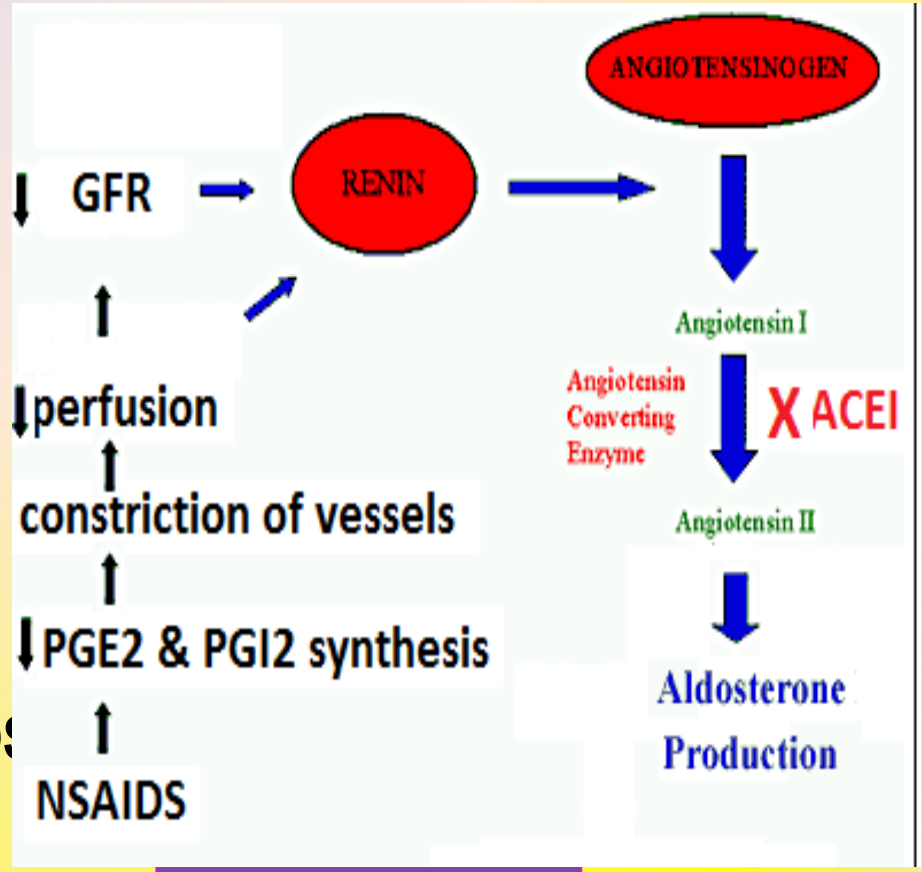
Drug becomes:

> metabolized or excreted

< absorbed

altered distribution to tissues

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



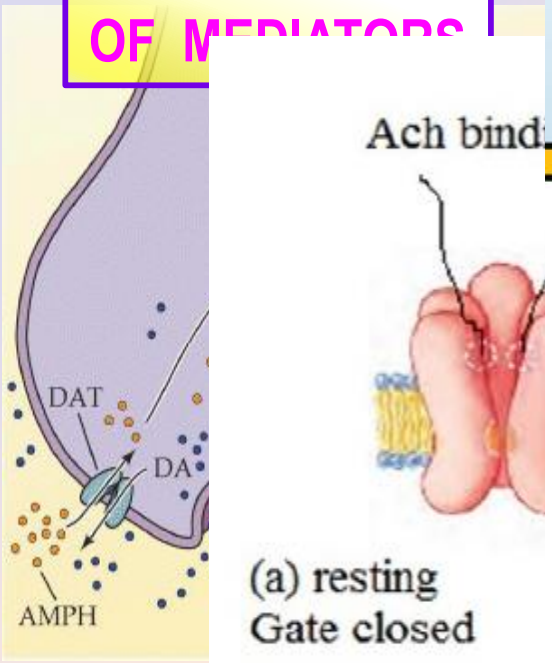
REASONS FOR DEVELOPMENT OF TOLERANCE

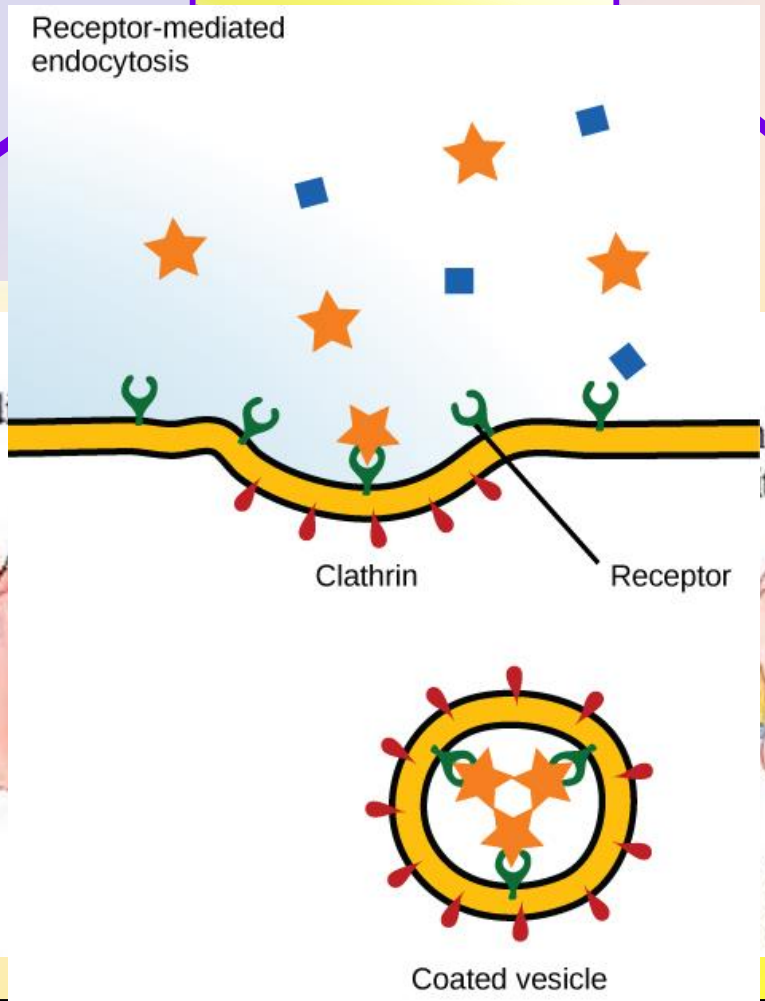
PRE RECEPTOR EVENTS

EVENTS AT RECEPTORS

POST RECEPTOR EVENTS

EXHUSTION OF MEDIATORS





DOWN REGULATION

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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?

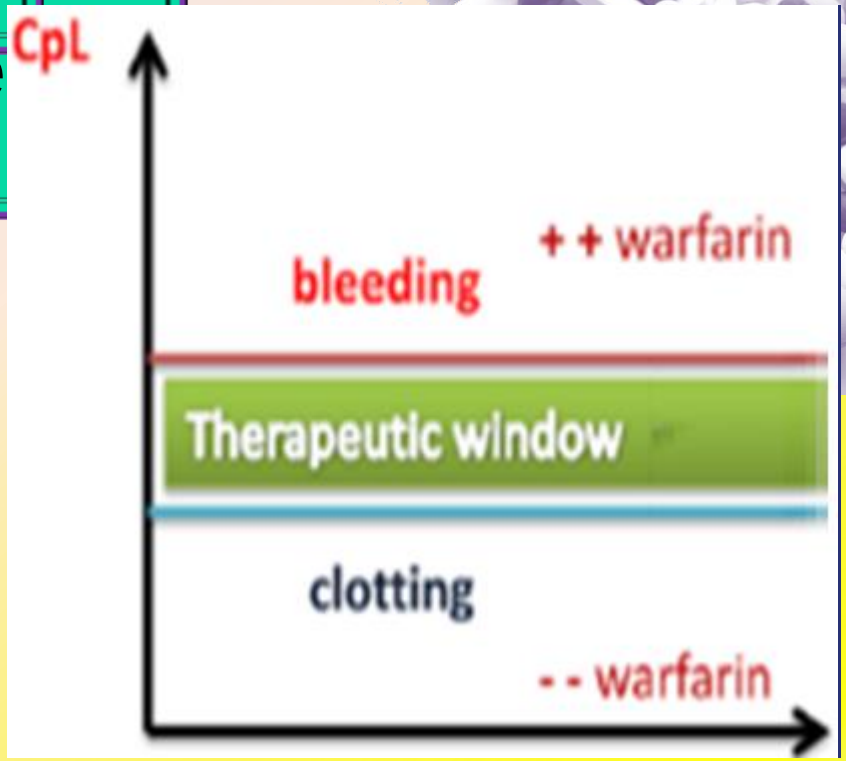
the

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?

Idiosyncratic reactions are drug

How mortal is it ?

reac d

How is it treated?

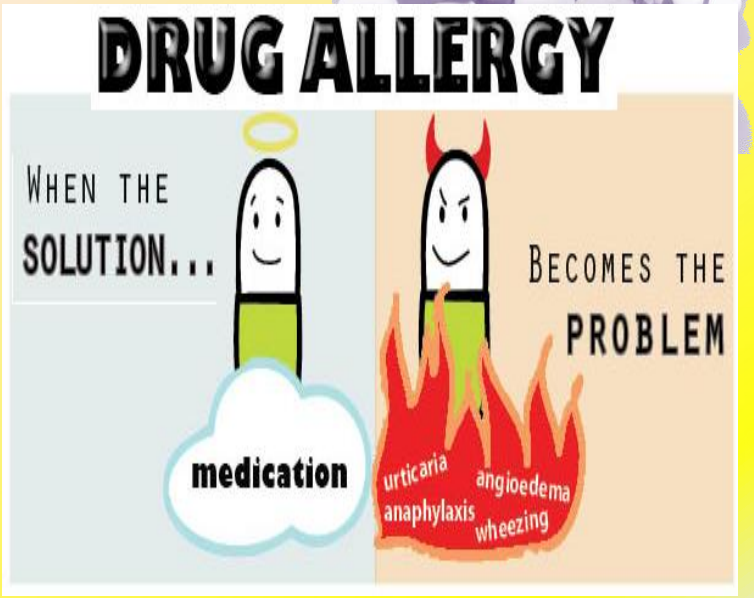
unp opulation

qualitatively different

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

Penicillin➔ Anaphylactic shock

Quinine➔Thrombocytopenia

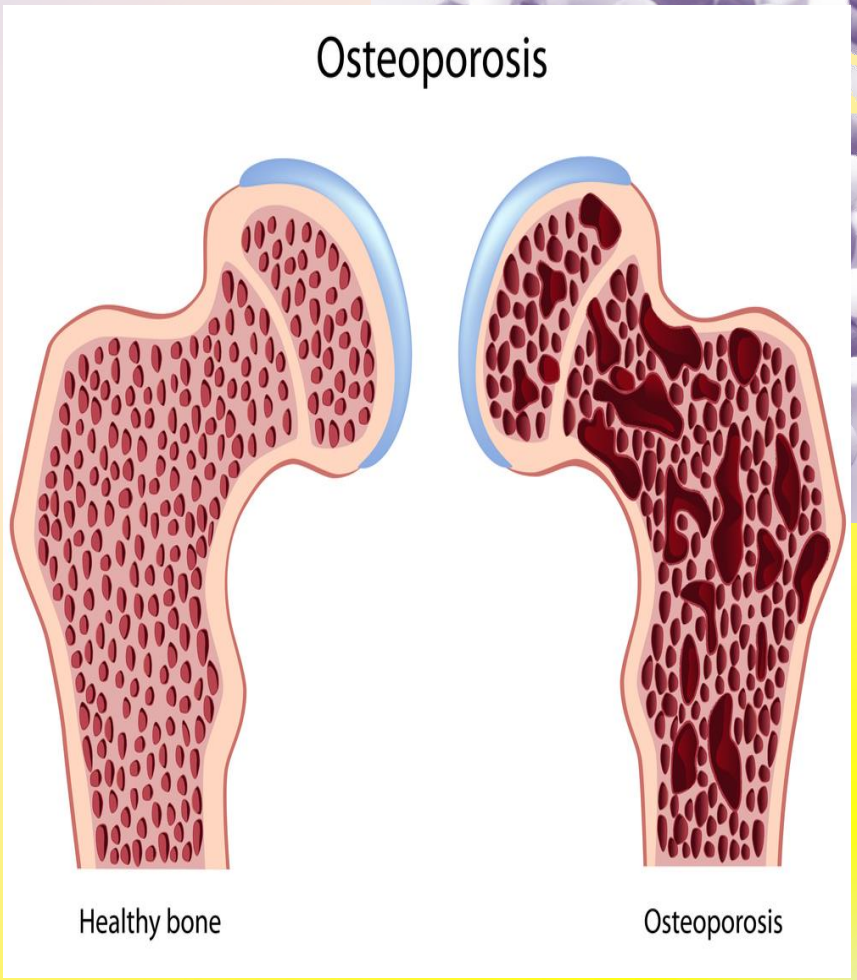


TYPE C

CONTINUED

Occurs during chronic drug administration

Osteoporosis → chronic corticosteroid intake



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→ Tobaco 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

1st exposure to a drug → Sensitization

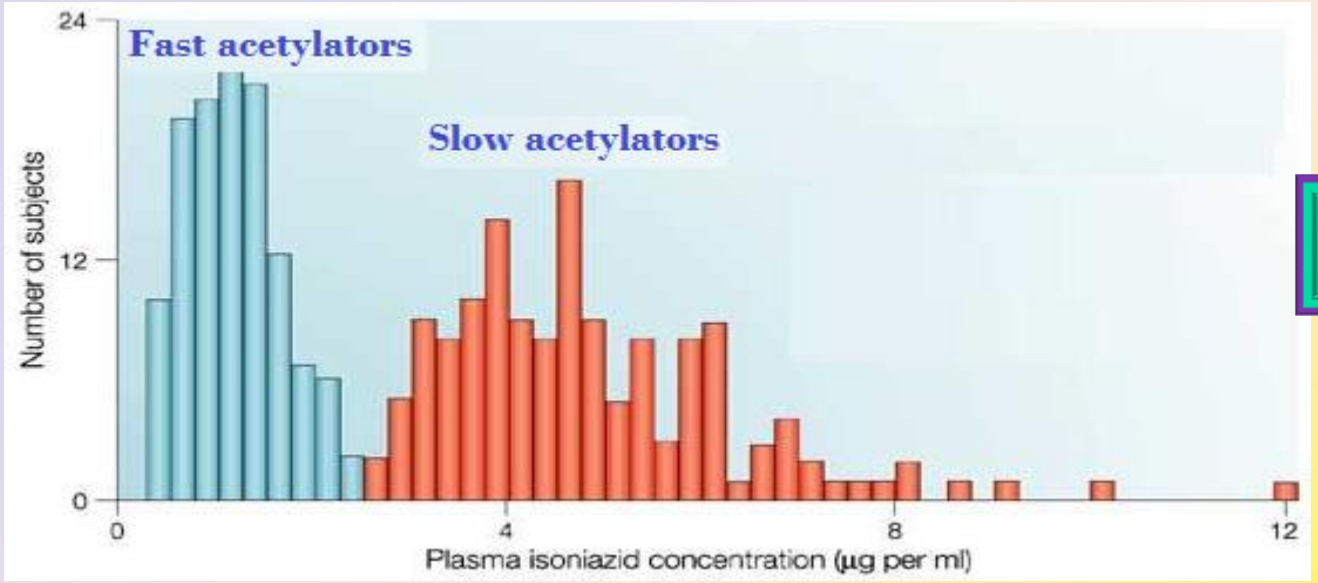
Repeated exposures → HYPERSENSITIVITY REACTION

TYPE I Anaphylaxsis	TYPE II Cytotoxic	TYPE III Immune complex	TYPE IV Cell mediated
Release of mediators from mast cells or blood basophils	Antibody-directed cell-mediated lysis	Deposition of soluble antigen–antibody-complement complexes in small blood vessels	Interaction release cytokines that attracts inflammatory cell infiltrate
Urticaria rhinitis, bronchial asthma by Penicillin,	Haemolytic anaemia thrombocytopenia by Quinine	Serum sickness *(fever, arthritis, enlarged lymph nodes, urticaria)* by Sulphonamides, Streptomycin	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