TOLERANCE / DESENSITIZATION & ADVERSE DRUG REACTIONS

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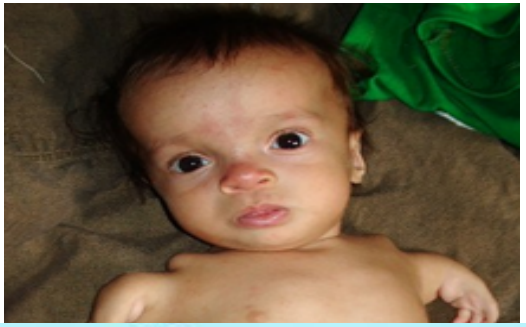
Phocomelia

Thalidomide crisis

IATROGENIC DISEASE

Thalidomide was marketed in 1958 in West Germany as a hypnotic & as for morning sickness during pregnancy

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



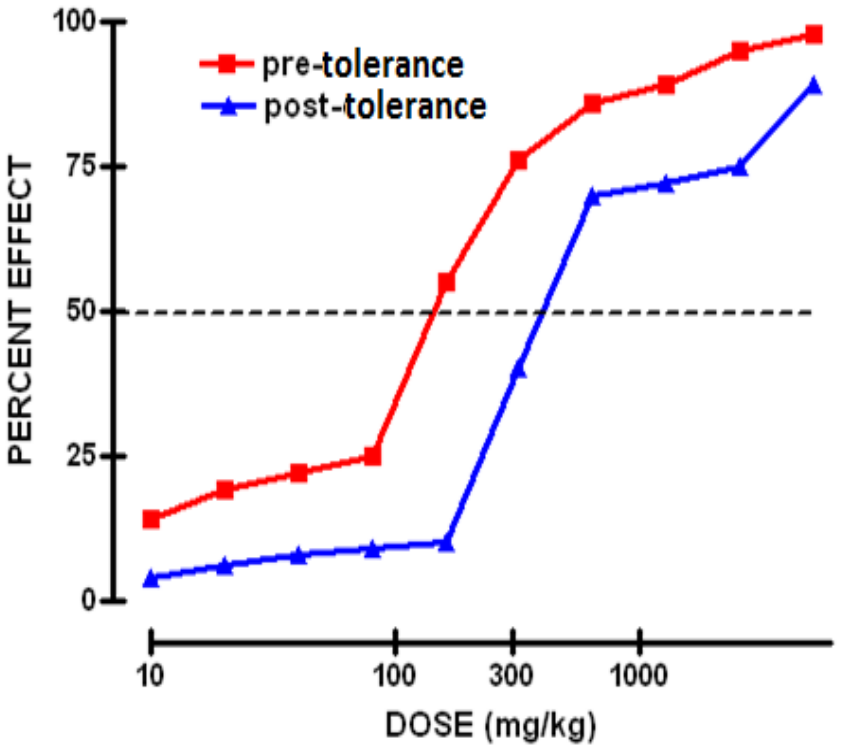
ILOS

- 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.



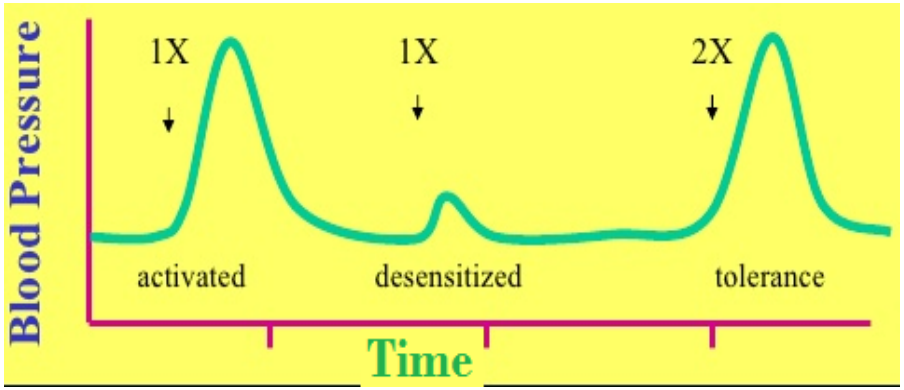
DIMINUTION OF A RESPONSE

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

↓ 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

EVENTS AT RECEPTORS

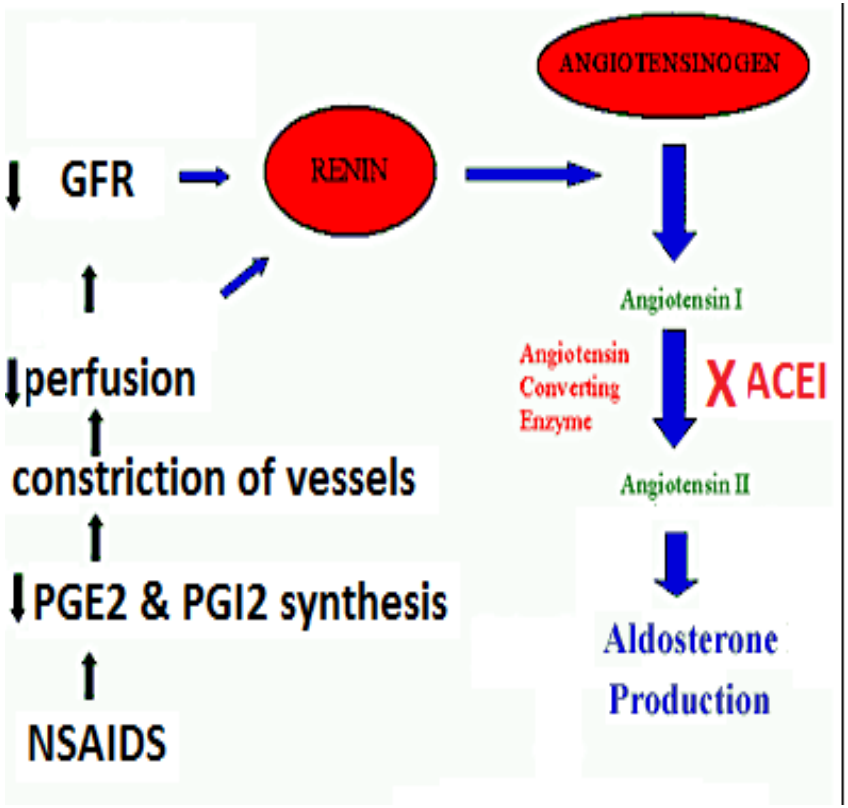
Nullification of drug response by a physiological adaptative homeostatic response

Antihypertensive effects of ACEIs become nullified by activation of renin angiotensin system by NSAIDs

POST RECEPTOR EVENTS

LOSS OF THERAPEUTIC EFFICACY

Refractoriness


ANGIOTENSINOGEN
GFR
RENIN
Angiotensin I
perfusion
Angiotensin Converting Enzyme
X ACEI
constriction of vessels
Angiotensin II
PGE2 & PGI2 synthesis
Aldosterone Production
NSAIDS

REASONS FOR DEVELOPMENT OF TOLERANCE

PRE RECEPTOR EVENTS

EVENTS AT RECEPTORS

POST RECEPTOR EVENTS

EXHUSTION OF MEDIATORS

Depletion of mediator stores by amphetamine

BINDING ALTERATION

1-Phosphorylation of receptors i.e. Tight binding of ß-adrenoceptors agonists → ↓ activation of AC

2-Desenzitiation of Ach-receptors

[Functional defect]

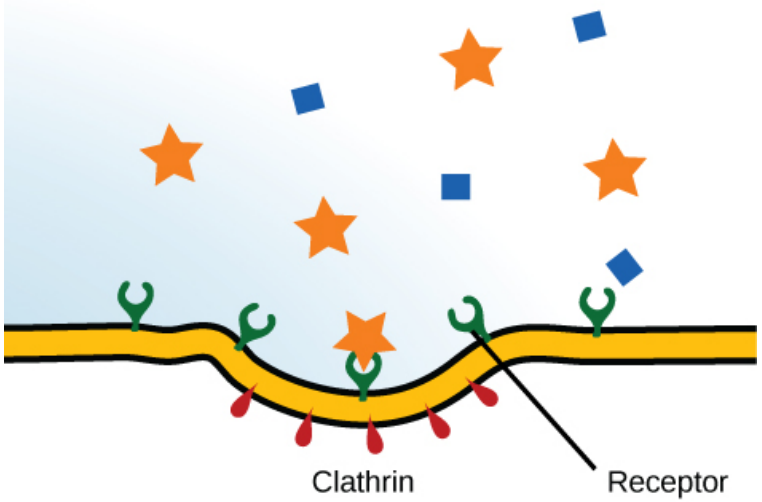
DOWN REGULATION

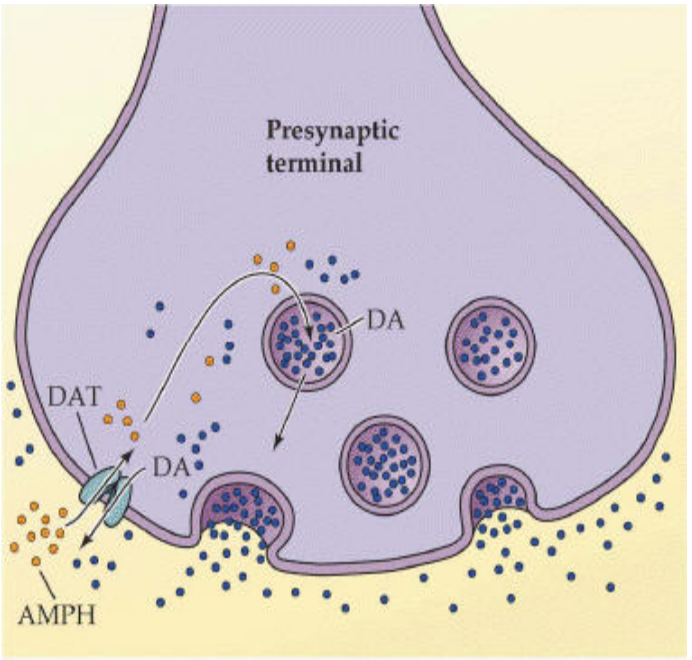
↓ Number of receptors.

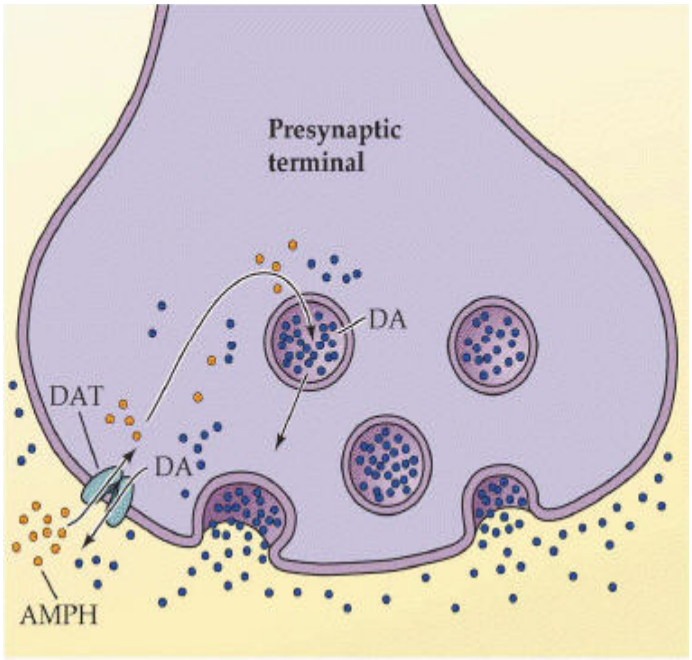
Isoprenaline activation to β receptors →↑ receptor recycling by endocytosis

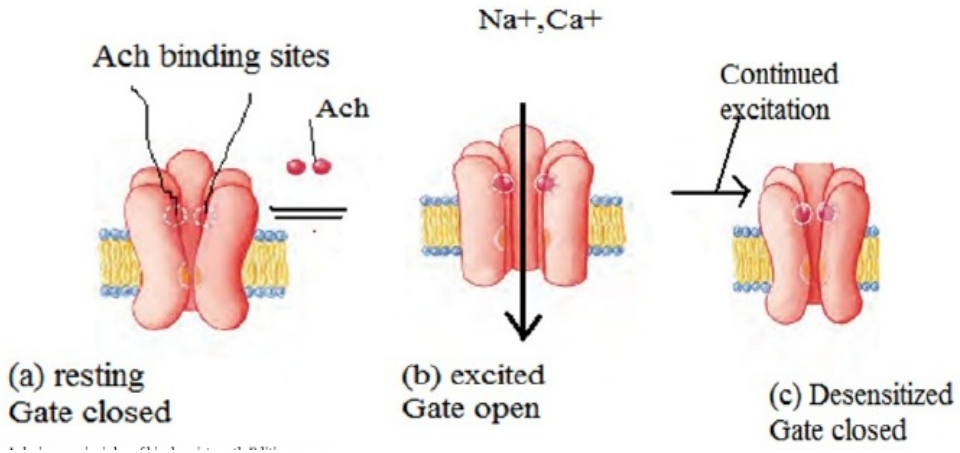
[Structural defect]

Receptor-mediated endocytosis





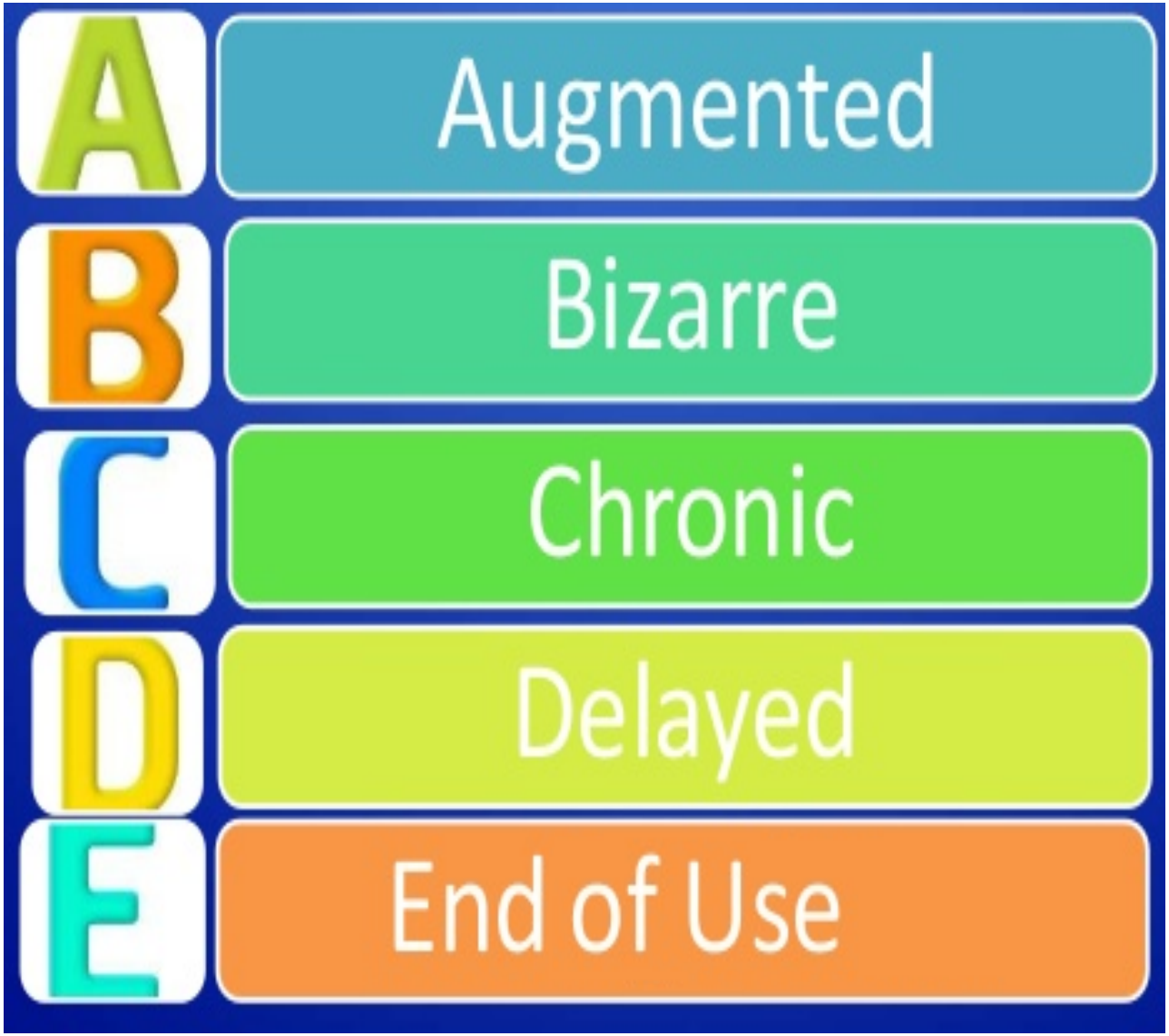




ADVERSE DRUG REACTIONS [ADRS]

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

TYPES OF ADRS



TYPE A AUGMENTED

Is it dose dependent?

80% of ADRs

Is it predictable?

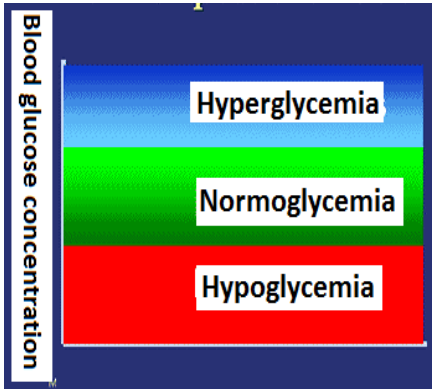
Is the incidence high or low?

A consequence of the primary effect of the drug

Is the ADR quantitatively or qualitatively different from the primary effect?

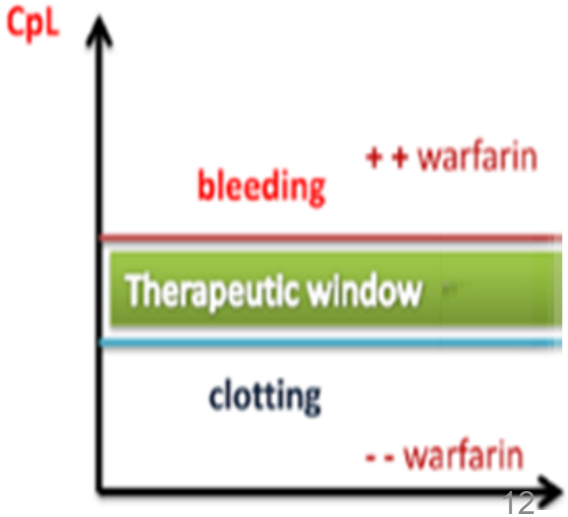
e.g. Hypoglycemia from hypoglycemic drugs

Bleeding from warfarin



How mortal is it ?

How is it treated?



TYPE B

BIZARRE

Is it predictable?

Occurs different to known drug pharmacological effect [idiosyncratic]

Idiosyncratic reactions are drug reactions that occur rarely and unpredictably amongst the population

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

Is the incidence high or low?

How mortal is it ?

How is it treated?

Is the ADR quantitatively or qualitatively different from the primary effect?

Is it dose dependent?

Penicillin → Anaphylactic shock

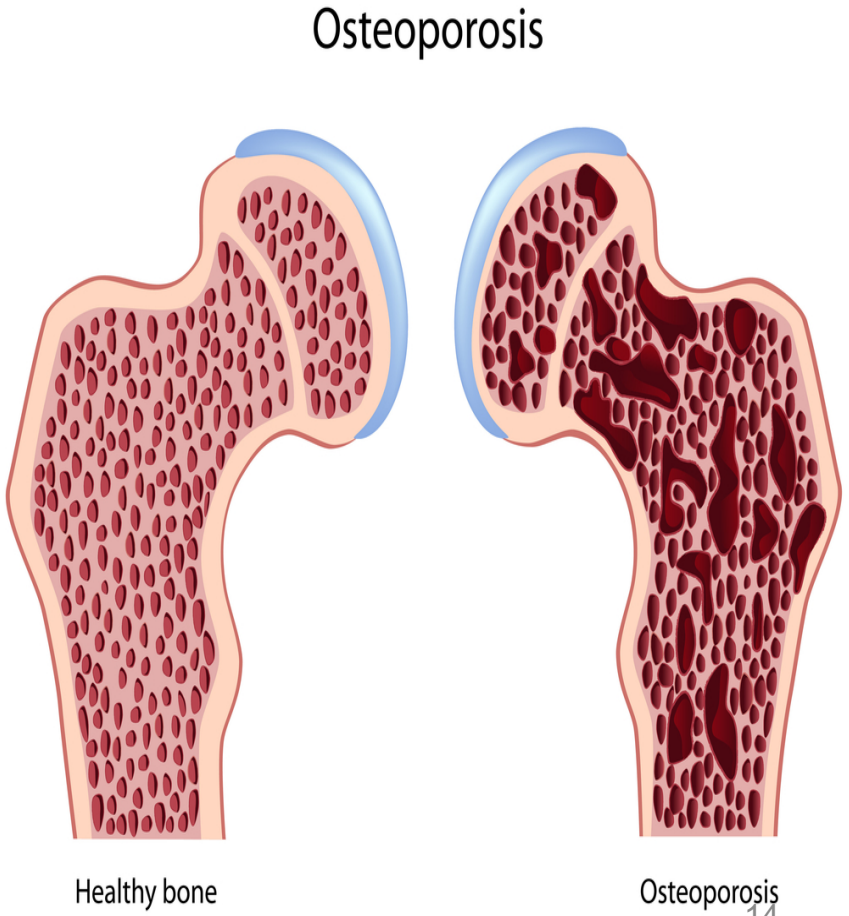
Quinine → Thrombocytopenia

TYPE C

CONTINUED

Occurs during chronic drug administration

Osteoporosis ➜ chronic corticosteroid intake



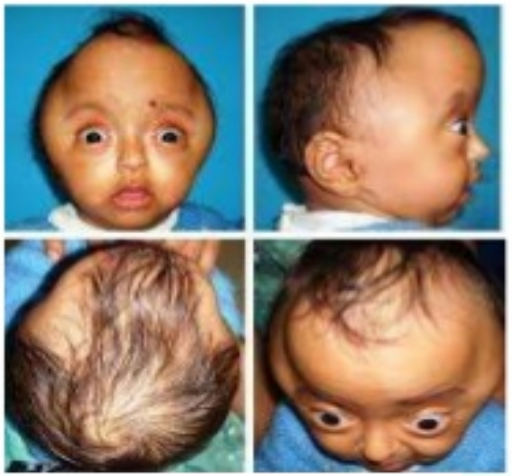
TYPE D

DELAYED

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

Refers to carcinogenic and teratogenic effects

Teratogenicity→Retinoids
Carcinogenicity→ Tobacoo 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

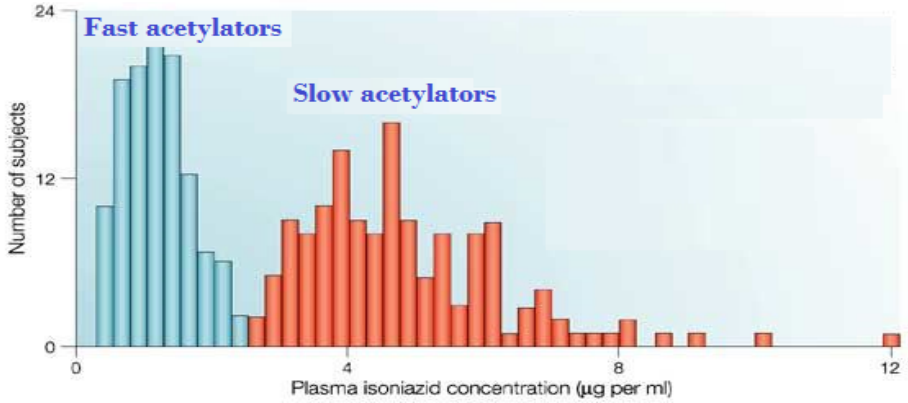
Repeated exposures → HYPERSENSITIVITY REACTION

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**'



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

Isoniazid causes **peripheral neuropathy** in slow acetylators