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)

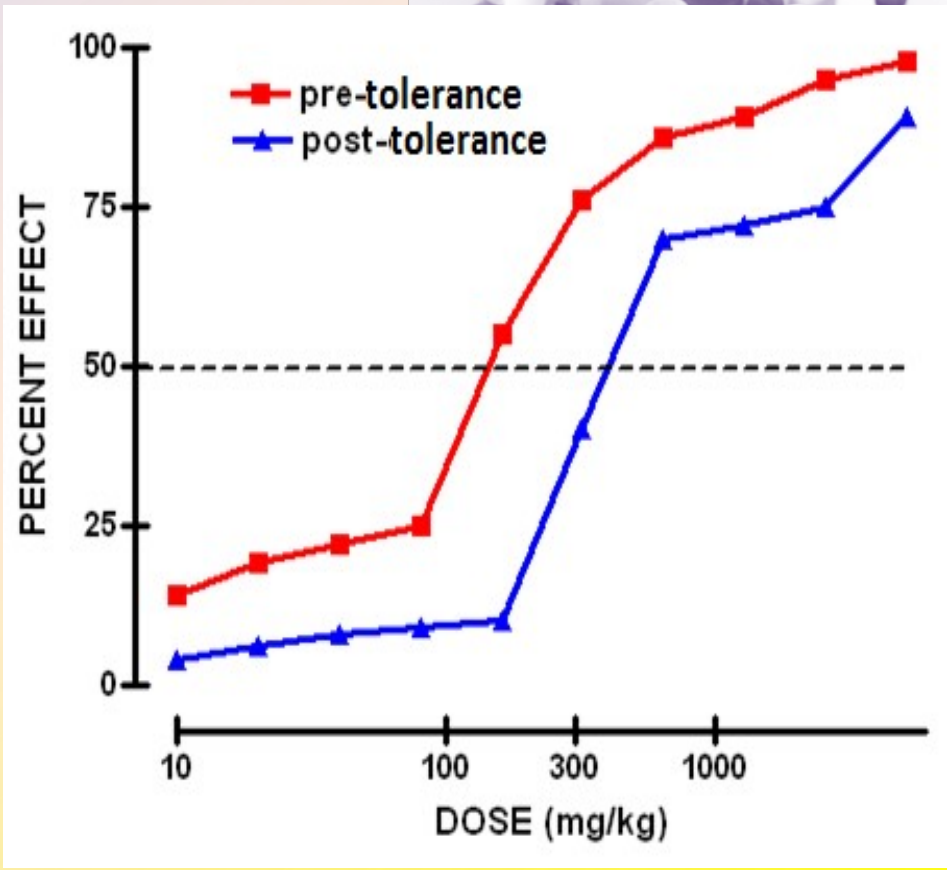
ILOS

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

- Recognize patterns of adverse drug reactions (ADR)

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

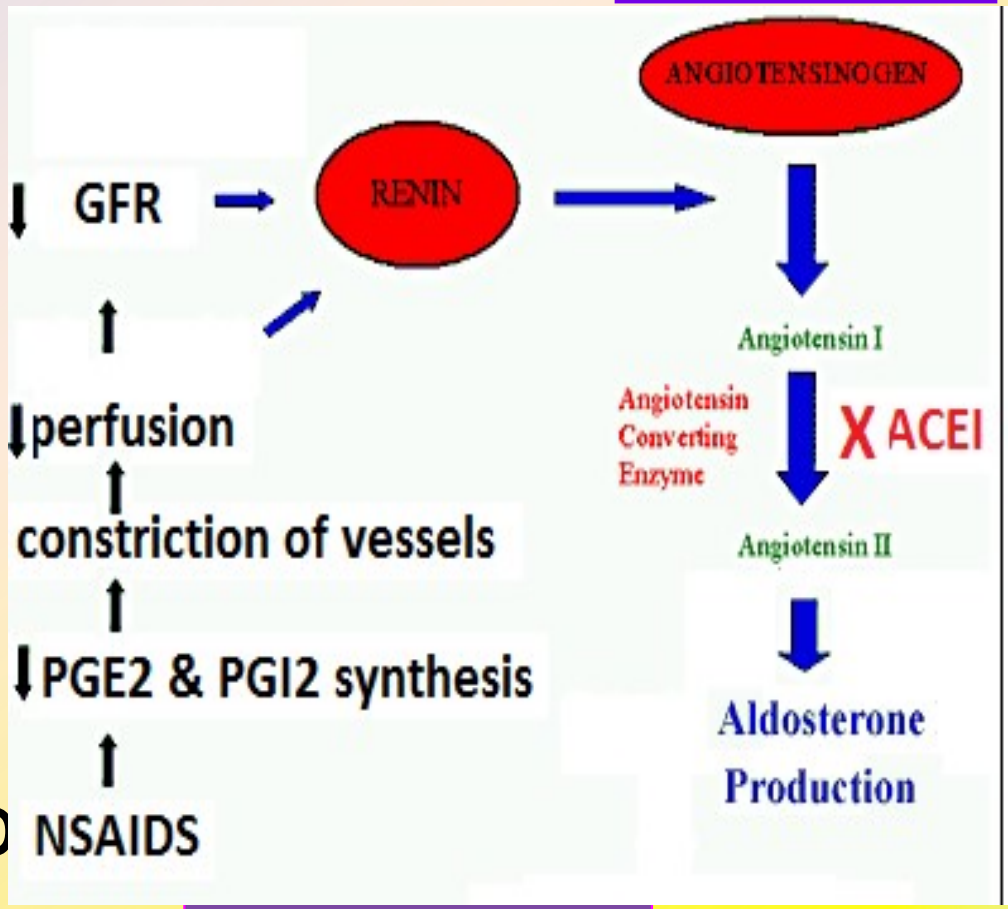
altered distribution to tissues

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

EVENTS AT RECEPTORS

LO

POST RECEPTOR EVENTS

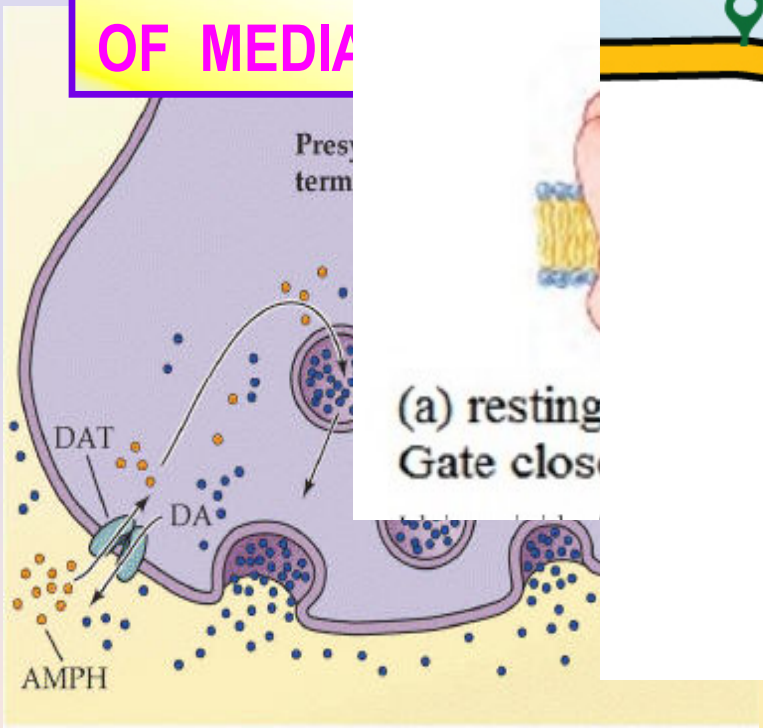


Refractoriness

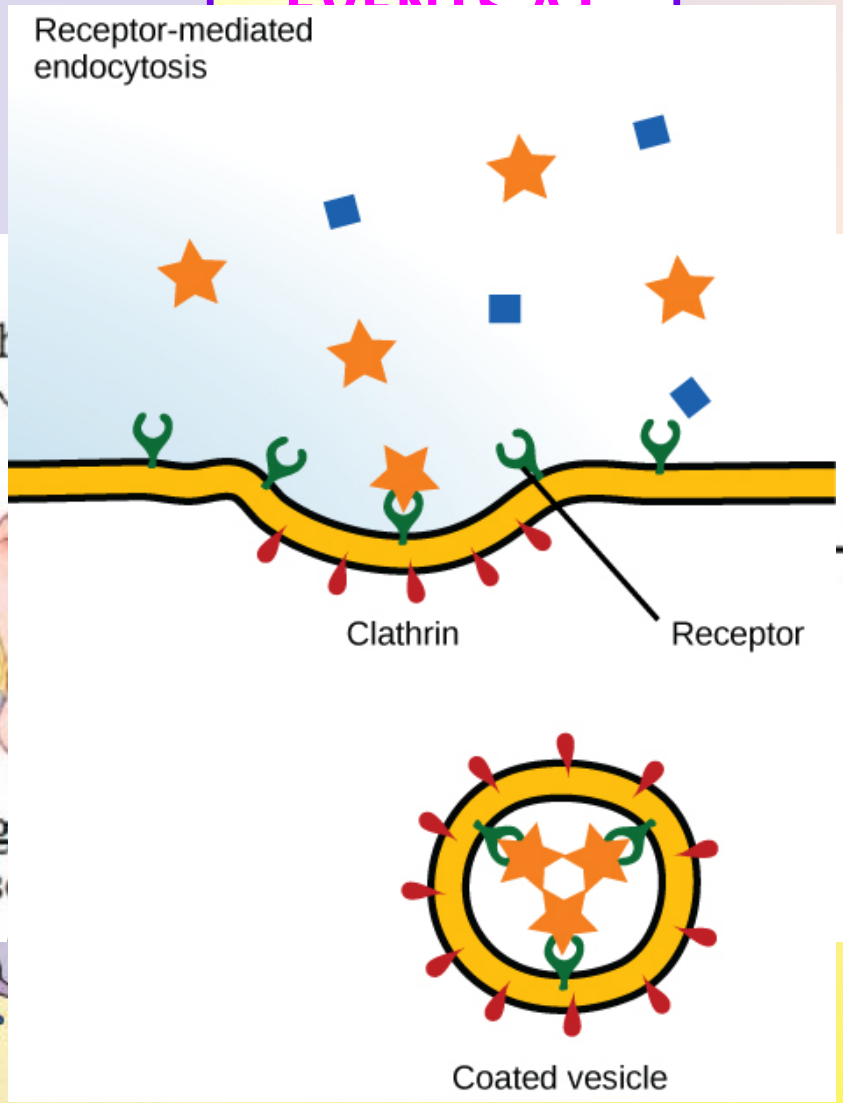
REASONS FOR DEVELOPMENT OF TOLERANCE

PRE RECEPTOR EVENTS

EXHUST OF MEDIA



EVENTS AT



ON

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→↑ R
by
endocytosis
[structural defect]

ADVERSE DRUG REACTIONS [ADRS]

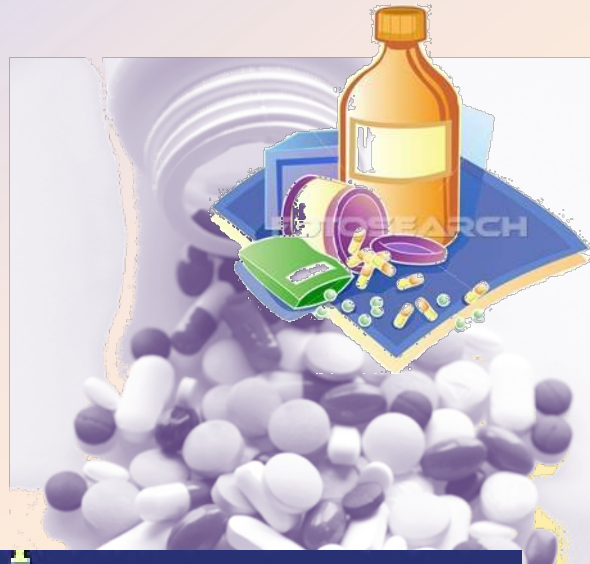
- **Harmful or seriously** unpleasant effects occurring at doses intended for **therapeutic effects.**

TYPES OF ADRS

TYPE A	AUGMENTED
TYPE B	BIZARRE
TYPE C	CONTINUED
TYPE D	DELAYED
TYPE E	END OF USE

TYPE A

AUGMENTED



80% of ADRs

Is it dose dependent?

low?

How is it treated?

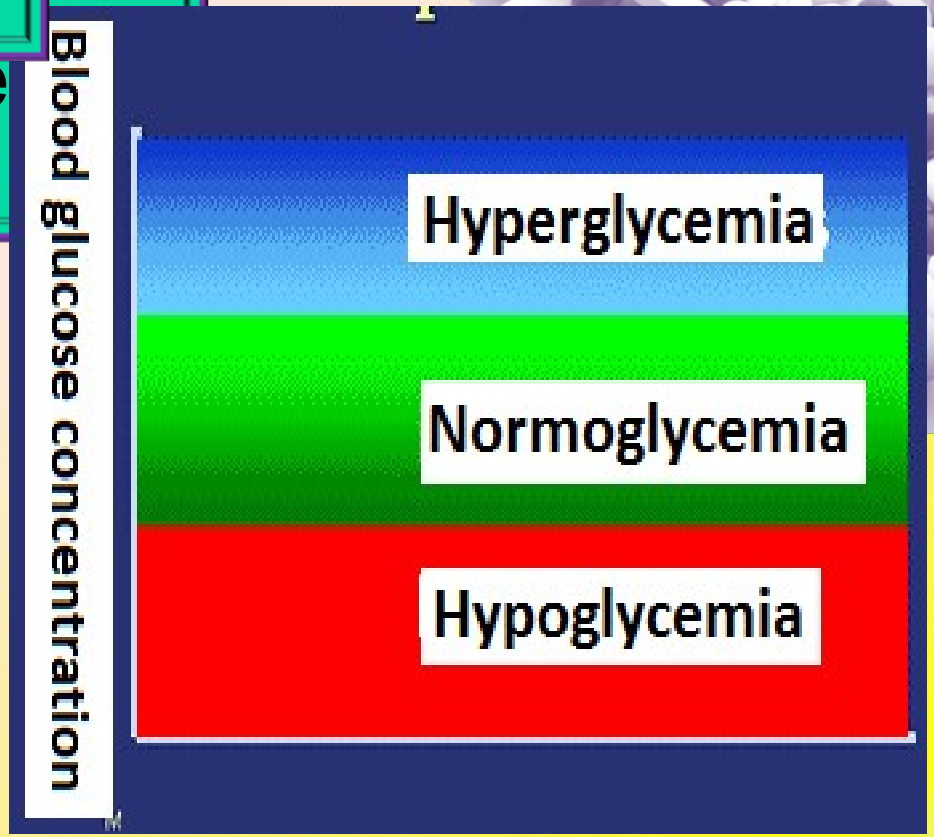
the

primary effect?

drug

e.g. bleeding from warfarin

Hypoglycemia from hypoglycemic drugs



TYPE B

BIZARRE

Occurs different to known drug pharmacological effect[idiosyncrotic]

Is it predictable?

How mortal is it ?

How is it treated?

qualitativel different from the primary effect?

Idio ug
reac d
unpr opulation

Usually due to patient's genetic defect or immunological response.

Penicillin → Anaphylactic shock

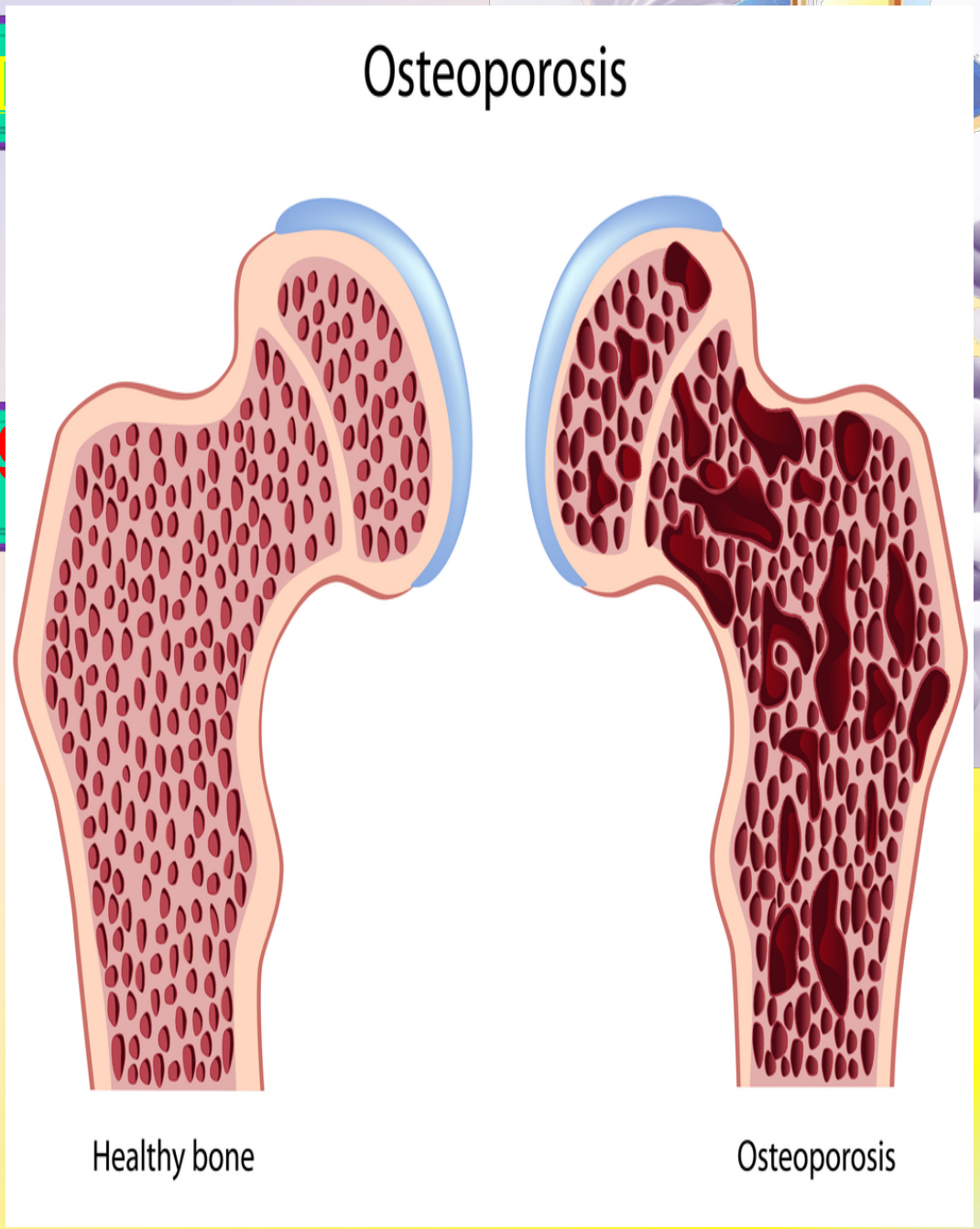
Thrombocytopenia → Quinine

TYPE C

CONTI

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

TYPE E

END OF USE

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

Withdrawal syndrome ➔ Morphine

Withdrawal of diazepam ➔ anxiety, insomnia

TYPE B

If due to immunological response

1st exposure to a drug → Sensitization

Repeated exposures → HYPERSENSITIVITY REACTION

TYPE I Anaphylaxsis

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 Quinidine

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,

TYPE IV Cell mediated

Interaction release cytokines that attracts inflammatory cell infiltrate

Contact dermatitis by local anaesthetics creams