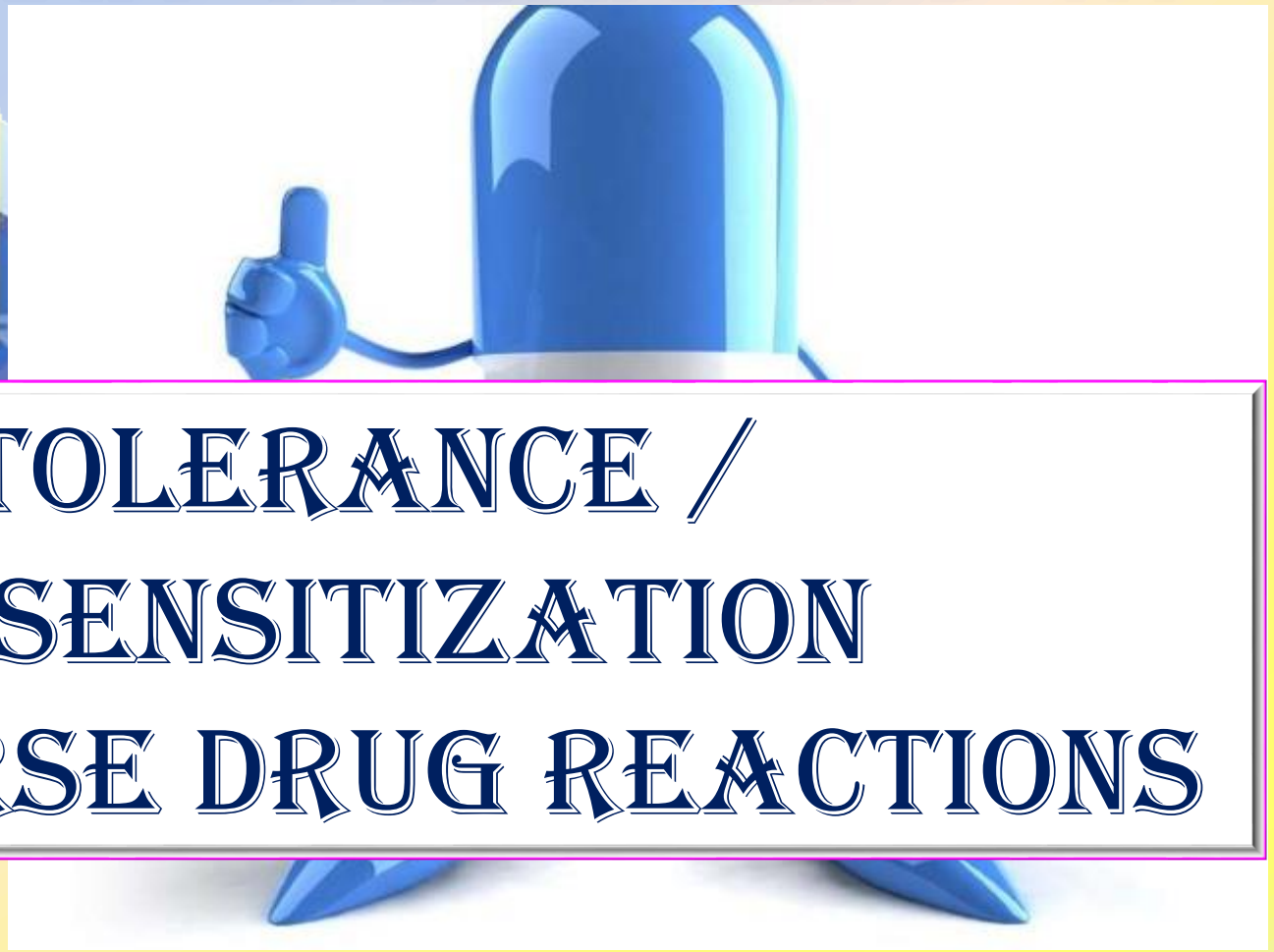
PHARMACDYNAMICS IV



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)

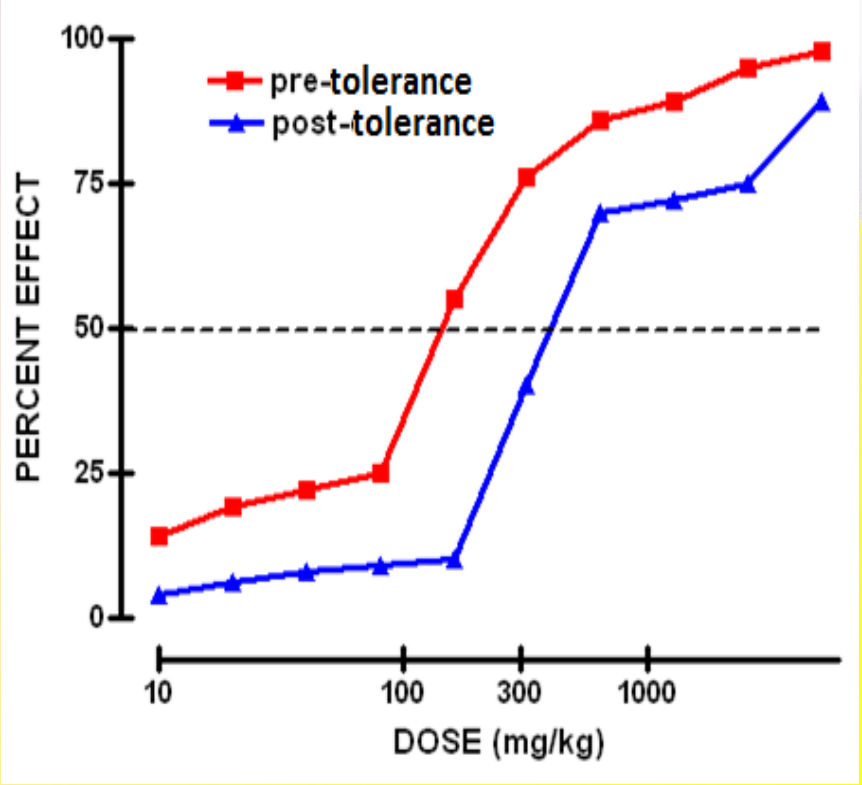
ILOS

- 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

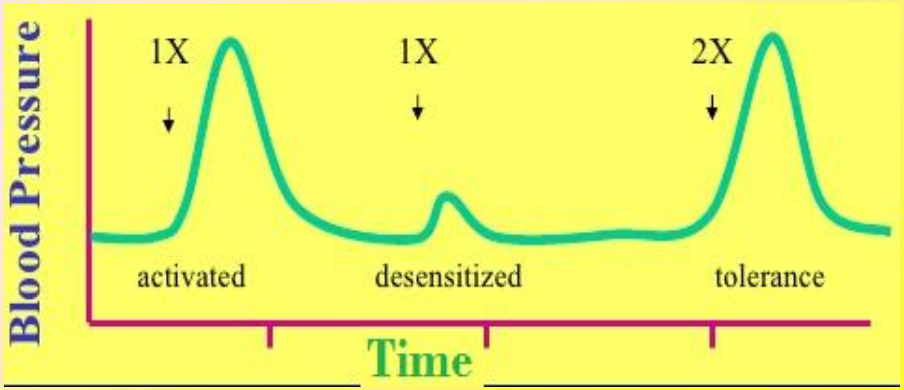
Rapid, in the course of few minutes

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

POST RECEPTOR EVENTS

Nullification of drug response by a physiological adaptative homeostatic response

Antihypertensive effects of ACE Is become nullified by activation of renin angiotensin system by NSAIDs

LOSS OF THERAPEUTIC EFFICACY

Refractoriness

REASONS FOR DEVELOPMENT OF TOLERANCE

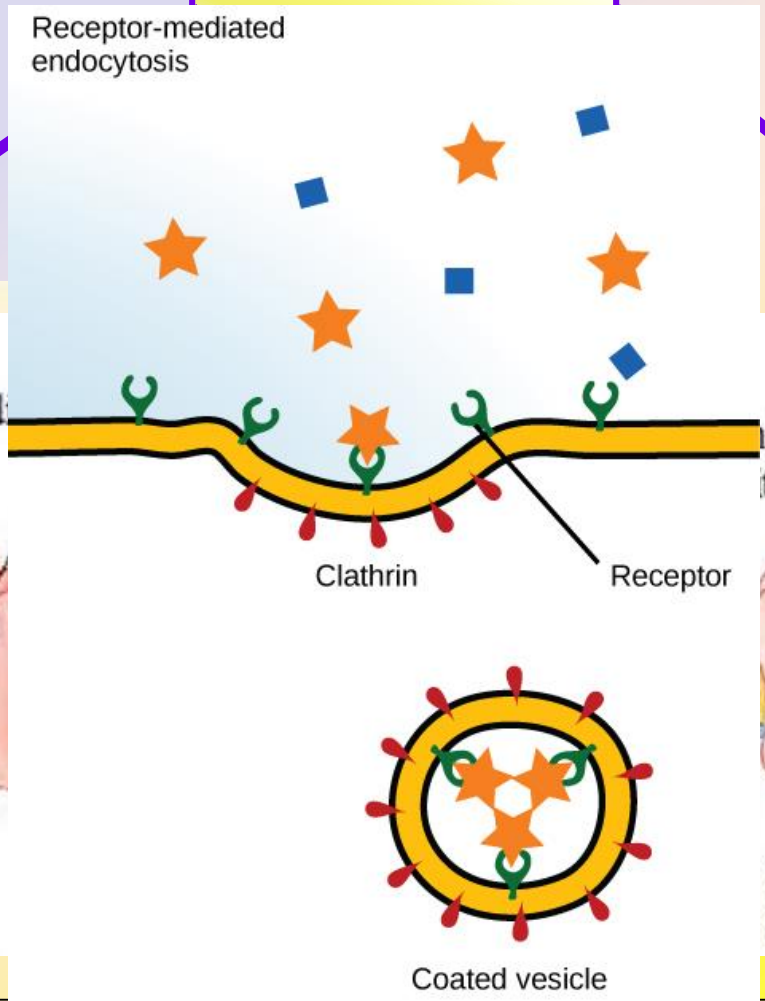
PRE RECEPTOR EVENTS

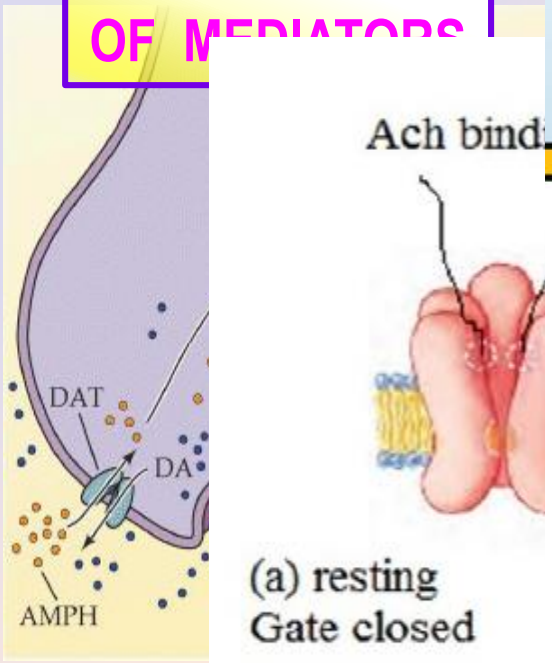
EVENTS AT RECEPTORS

POST RECEPTOR EVENTS

EXHUSTION OF MEDIATORS

DOWN REGULATION





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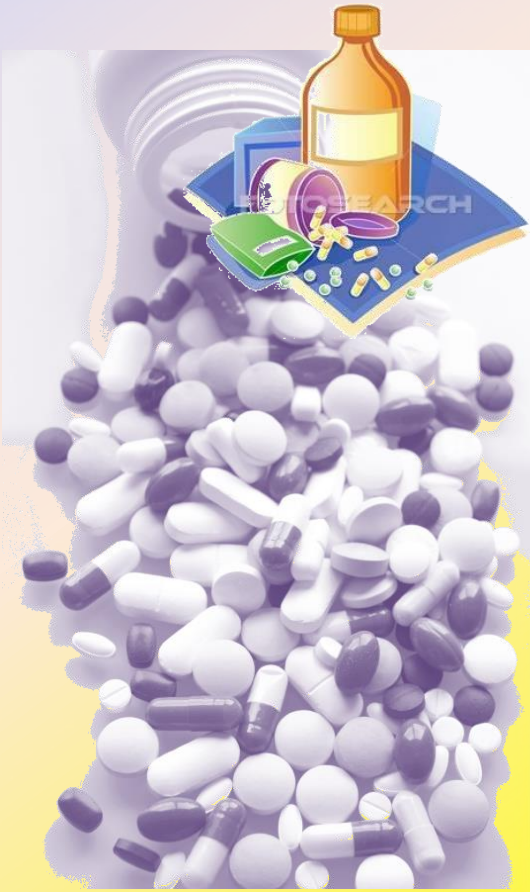
ADVERSE DRUG REACTIONS [ADRS]

- **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?

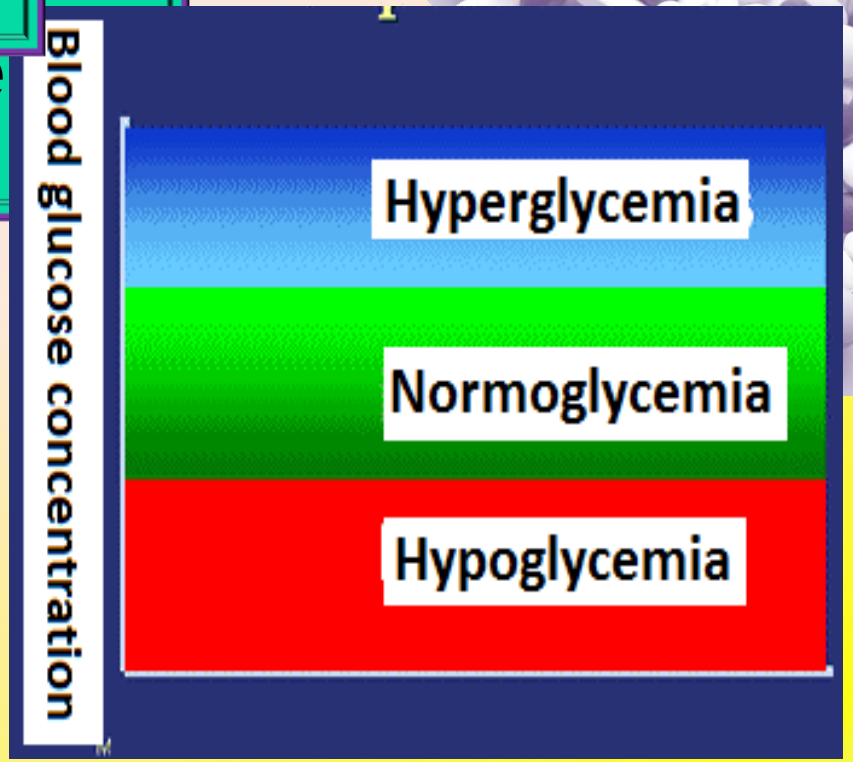
the

primary effect?

drug

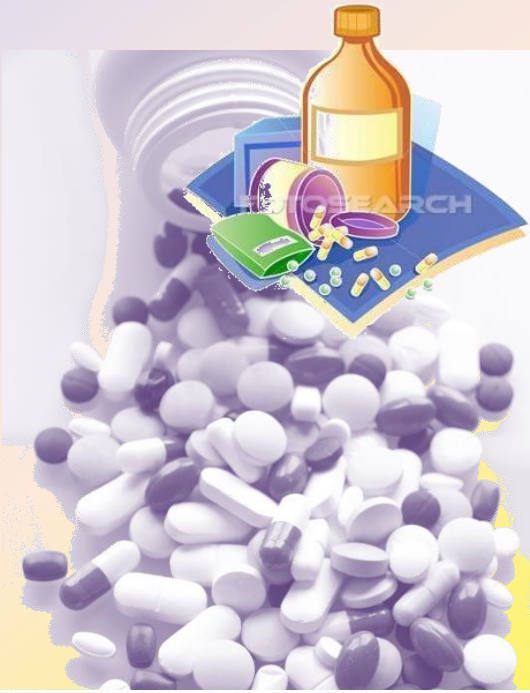
e.g. Hypoglycemia from hypoglycemic drugs

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 ?

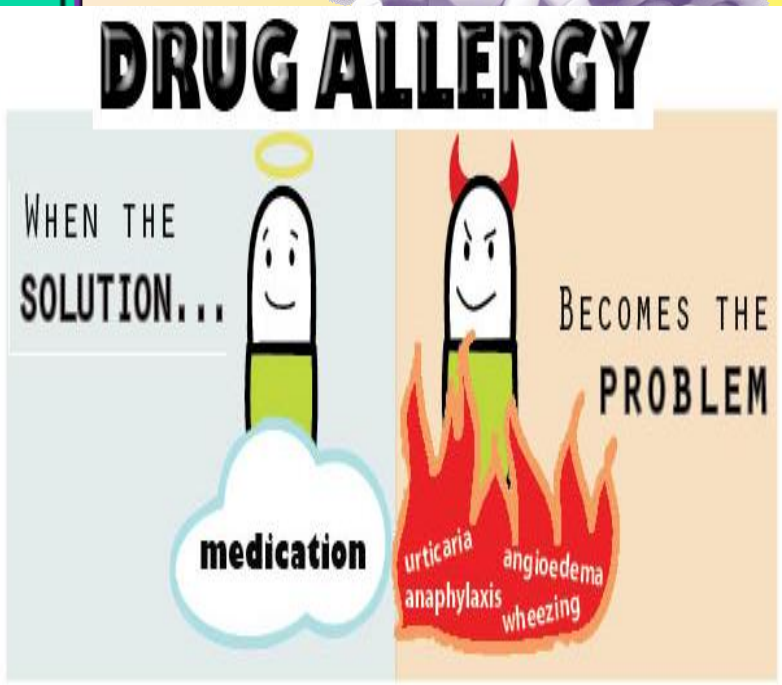
How is it treated?

qualitativel different

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

Penicillin → Anaphylactic shock

Quinine → Thrombocytopenia



Comparison between type A & B -ADRs

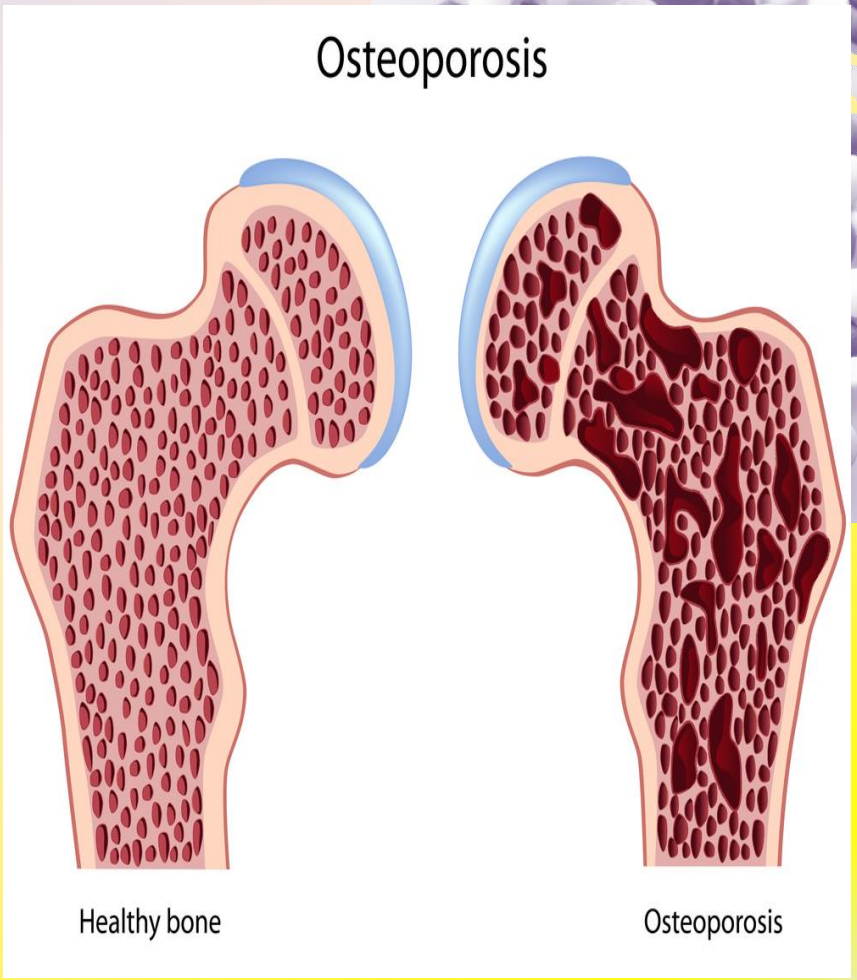
	Type A Augmentation	Type B Idiosyncratic
Pharmacological predictability	Yes	No
Nature	Quantitative [extension of pharmacology effect]	Qualitative [immune or genetic base]
Dose- dependent	Yes (dose response relationship present)	No (dose response relationship absent)
Onset of symptoms	Usually Rapid	Usually delayed
Mortality	Low	High
Treatment	Dose adjustment or Substitute by > selective + Antagonize unwanted effect of 1st drug	Stop drug + Symptomatic treatment
Example	Bradycardia → β- ADR Blockers Hemorrhage → Warfarin	Apnea → succinylcholine Thrombocytopenia → Quinine

TYPE C

CONTINUED

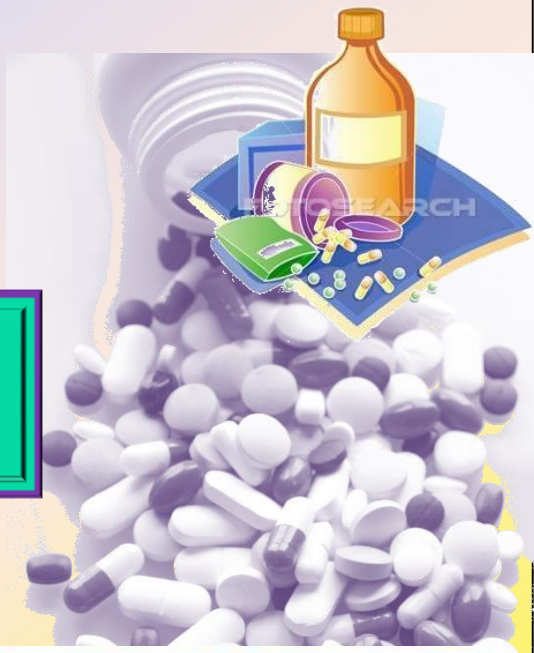
Occurs during chronic drug administration

Osteoporosis → chronic corticosteroid intake



TYPE D

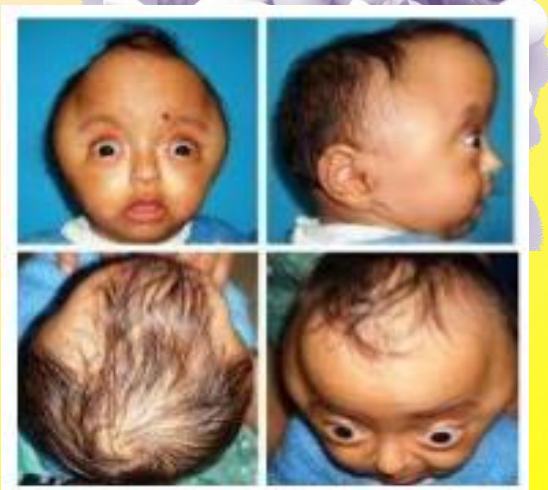
DELAYED



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

Refers to carcinogenic and teratogenic effects

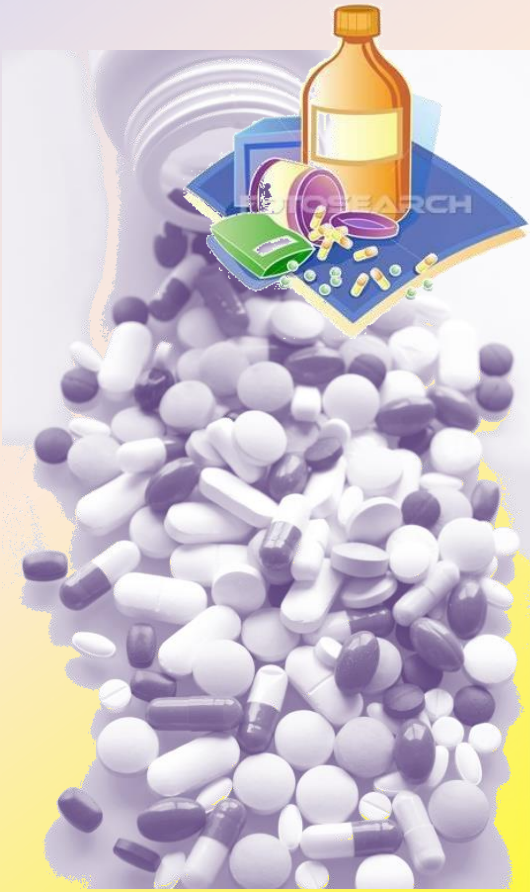
Teratogenicity→Retinoids
Carcinogenicity→ Tobacoo smoking



Retinoic acid malformations

TYPE E

END OF USE



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

Morphine → Withdrawal syndrome

↑ 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

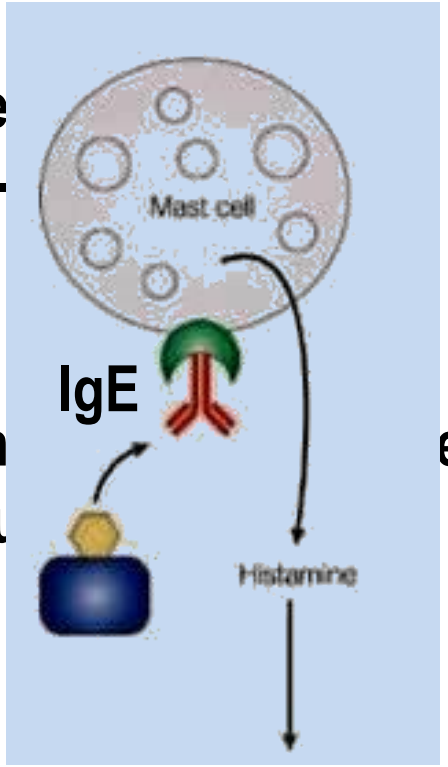
- TYPE I Anaphylaxsis
- TYPE II Cytotoxic
- TYPE III Immune complex
- TYPE IV Cell mediated

Type I hypersensitivity: Anaphylactic

- Type I hypersensitivity is an allergic reaction provoked by re-exposure to a specific antigen

- Fast response which occurs in minutes, rathe
hours or days. The reaction usually takes 15 -
the time of exposure to the antigen.

- The reaction is mediated by IgE antibodies an e
immediate release of histamine, serotonin, leu
tissue mast cells or blood basophils



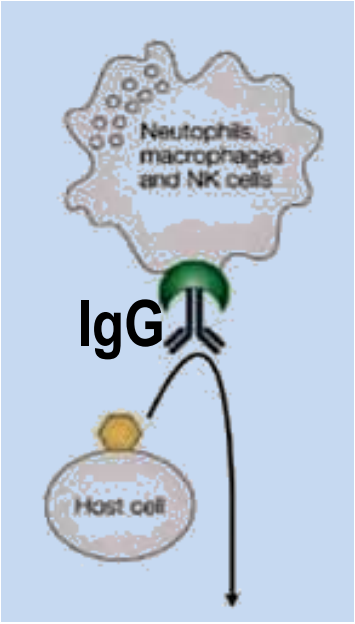
- **The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock.**

Some examples:

- **Allergic asthma**
- **Allergic conjunctivitis**
- **Allergic rhinitis "hay fever"**
- **Urticaria (hives)**
- **Anaphylaxis**

- may be caused by Penicillin, Streptomycin

Type II hypersensitivity : Cytotoxic



- Antibody-dependent
- The antigens may be endogenous or exogenous chemicals (haptens) which can attach to cell membranes
- The antibodies (IgM or IgG) produced by the immune response bind to antigens on the patient's own cell surfaces that is perceived by the immune system as foreign, leading to cellular destruction.
- The reaction takes hours to a day
- Examples: Drug-induced haemolytic anemia , thrombocytopenia by Penicillin, Quinidine

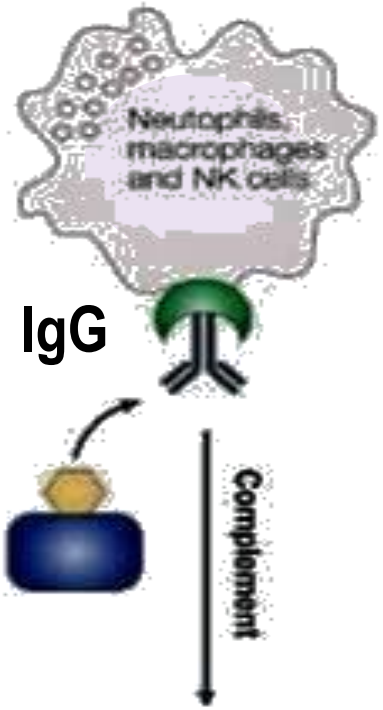
Type III hypersensitivity : Immune complex

- **Soluble immune complexes (aggregations of antigens and IgG and IgM antibodies) form in the blood, are not completely removed by macrophages and are deposited in various tissues (typically the skin, kidney and joints)**

- **The reaction takes hours to days to develop**

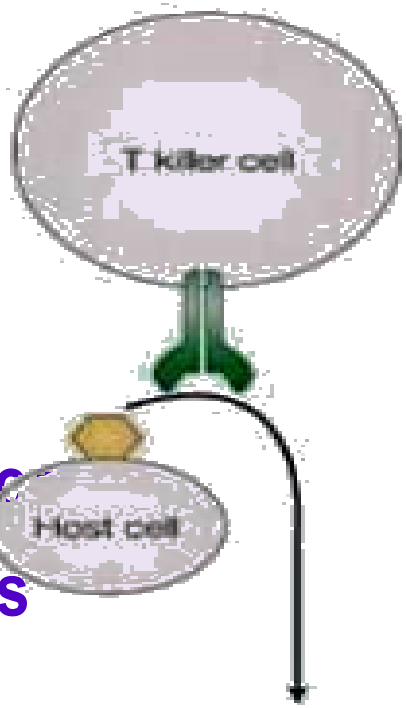
- **Example: Serum sickness *(fever, arthritis, enlarged lymph nodes, urticaria)***

- **by Sulphonamides, Penicillin, Streptomycin**



Type IV Hypersensitivity: Cell-mediated

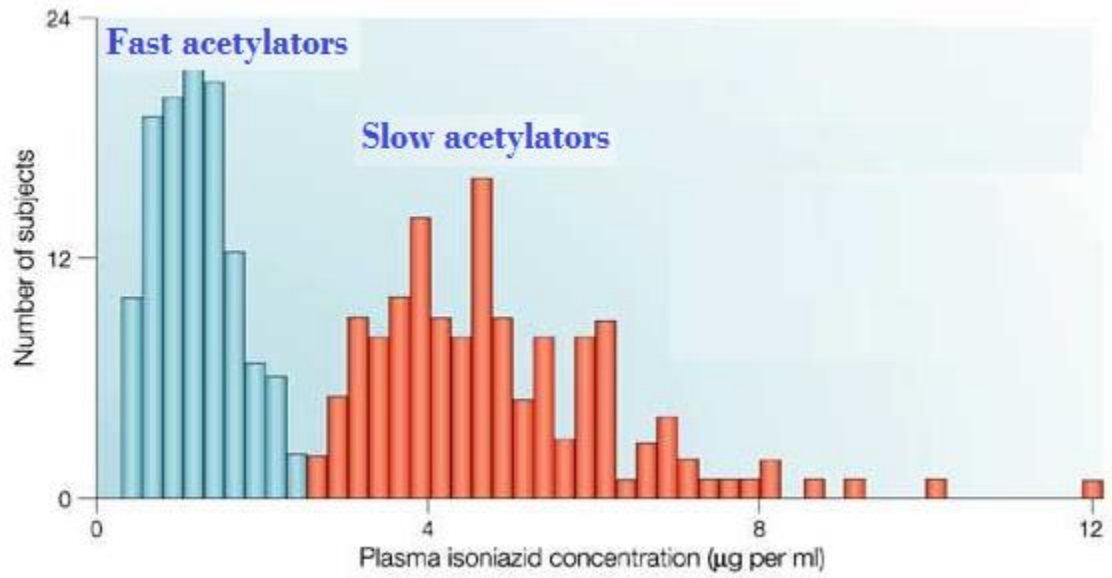
- also known as delayed type hypersensitivity as the reaction takes two to three days to develop.
- Unlike the other types, it is not antibody- mediated but rather is a type of cell-mediated response.
- Cytotoxic T cells cause direct damage whereas helper T cells secrete cytokines that attracts inflammatory cell infiltrate
- Example : Contact dermatitis by local anesthetic creams, anti -histamine creams, topical antibiotics



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**' & '**slow acetylators**'



Isoniazid causes **peripheral neuropathy** in slow acetylators

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

GOOD LUCK