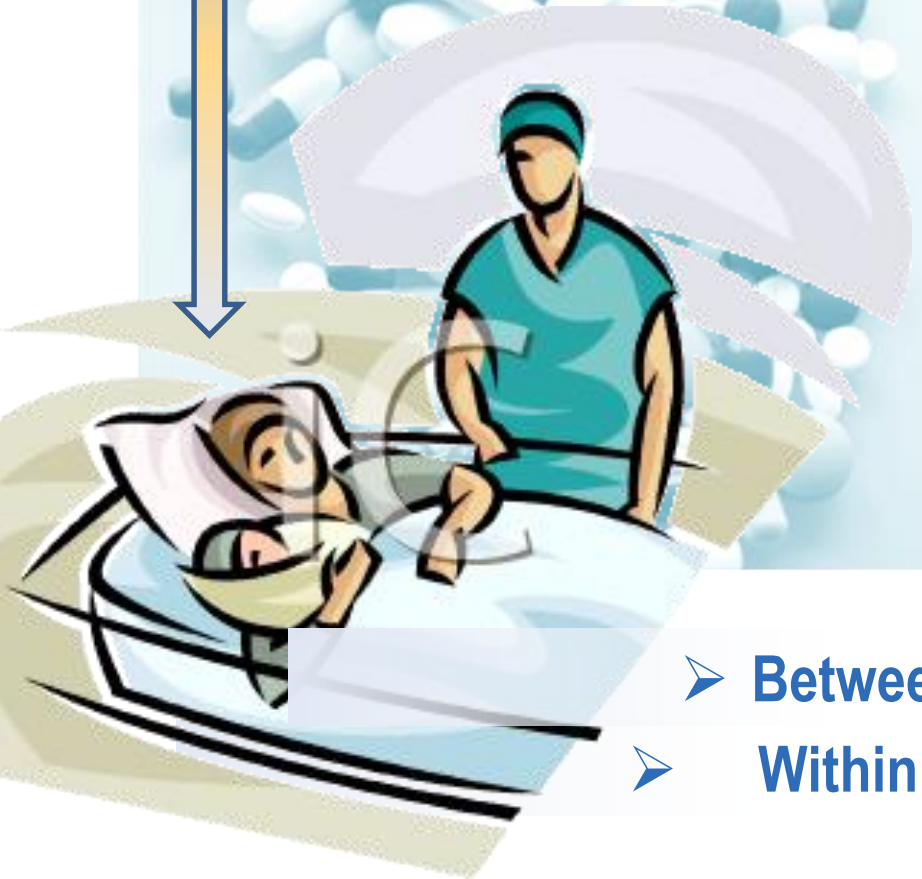
Tolerance and Adverse drug reactions

Prof. Yieldez Bassiouni

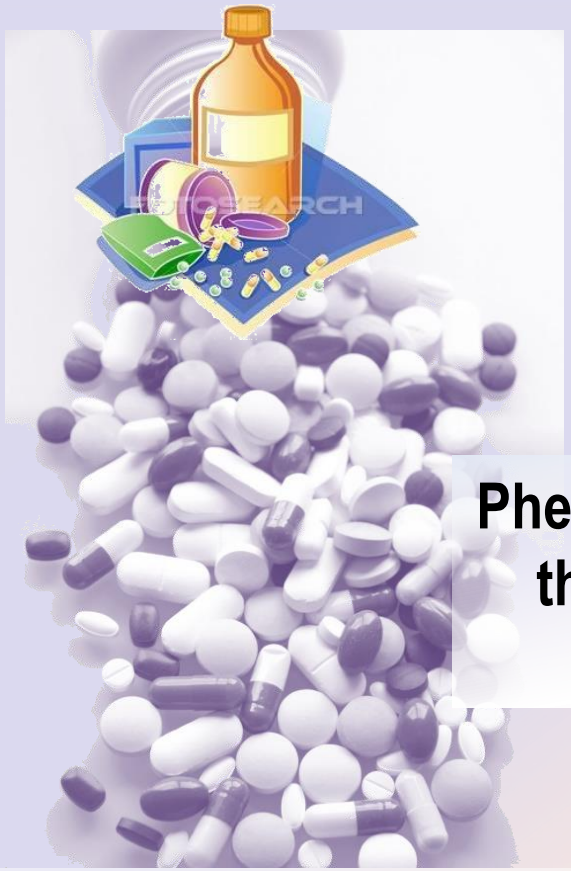
Variation in drug responsiveness

Decrease in drug effects

Development of side effects

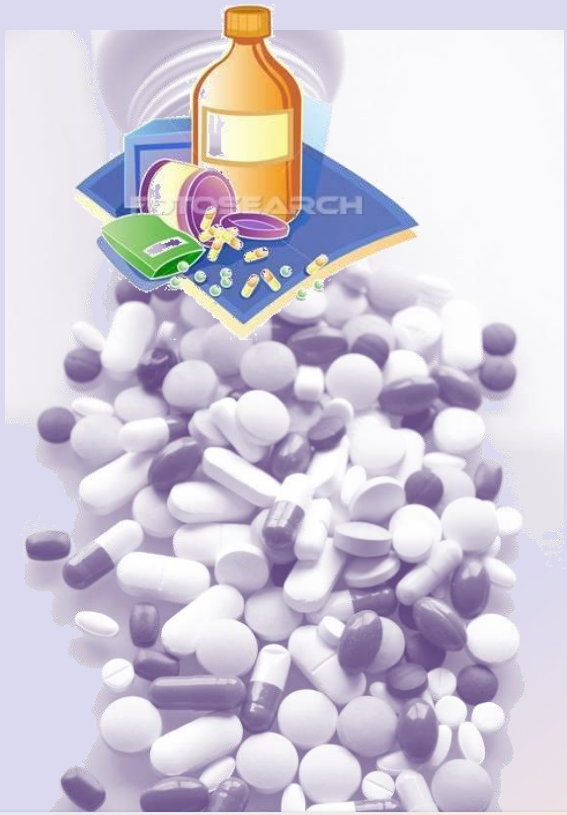


- Between different individuals
- Within the same individual



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

Tolerance and Desensitization

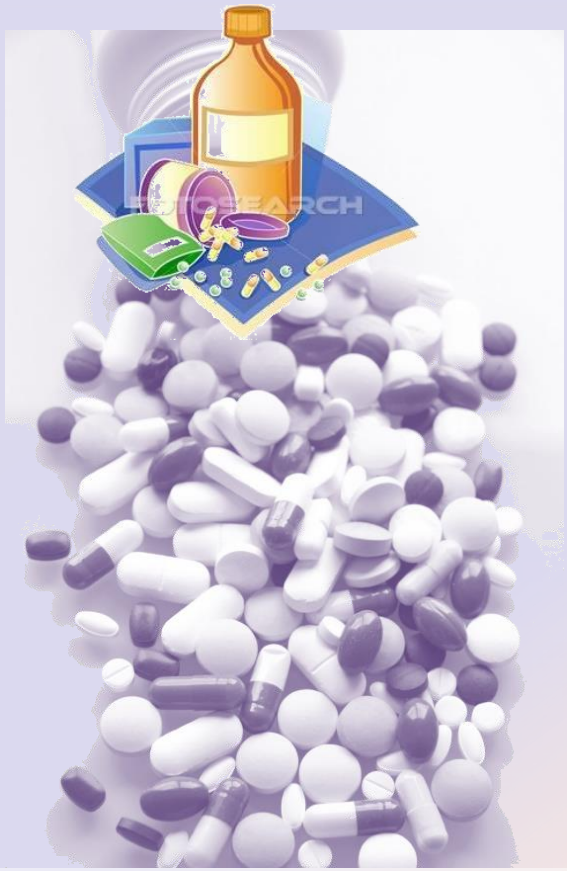


Adverse drug reactions [ADR]

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

By the end of this lecture you will be able to :

- **Distinguish difference between tolerance and desensitization (tachyphylaxis) and reasons for their development**
- **Recognize patterns of adverse drug reactions (ADRs)**



Tolerance and Desensitization

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

Tolerance

- Tolerance may be defined by either of the following:

a. a need for markedly **increased amounts** of the substance to achieve intoxication or desired effect

b. markedly **diminished effect** with continued use of the same amount of the substance

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

e.g. Barbiturates (enzyme inducers)↑ metabolism of Contraceptive pills = ↓ it availability

Events at receptors

Post receptor events

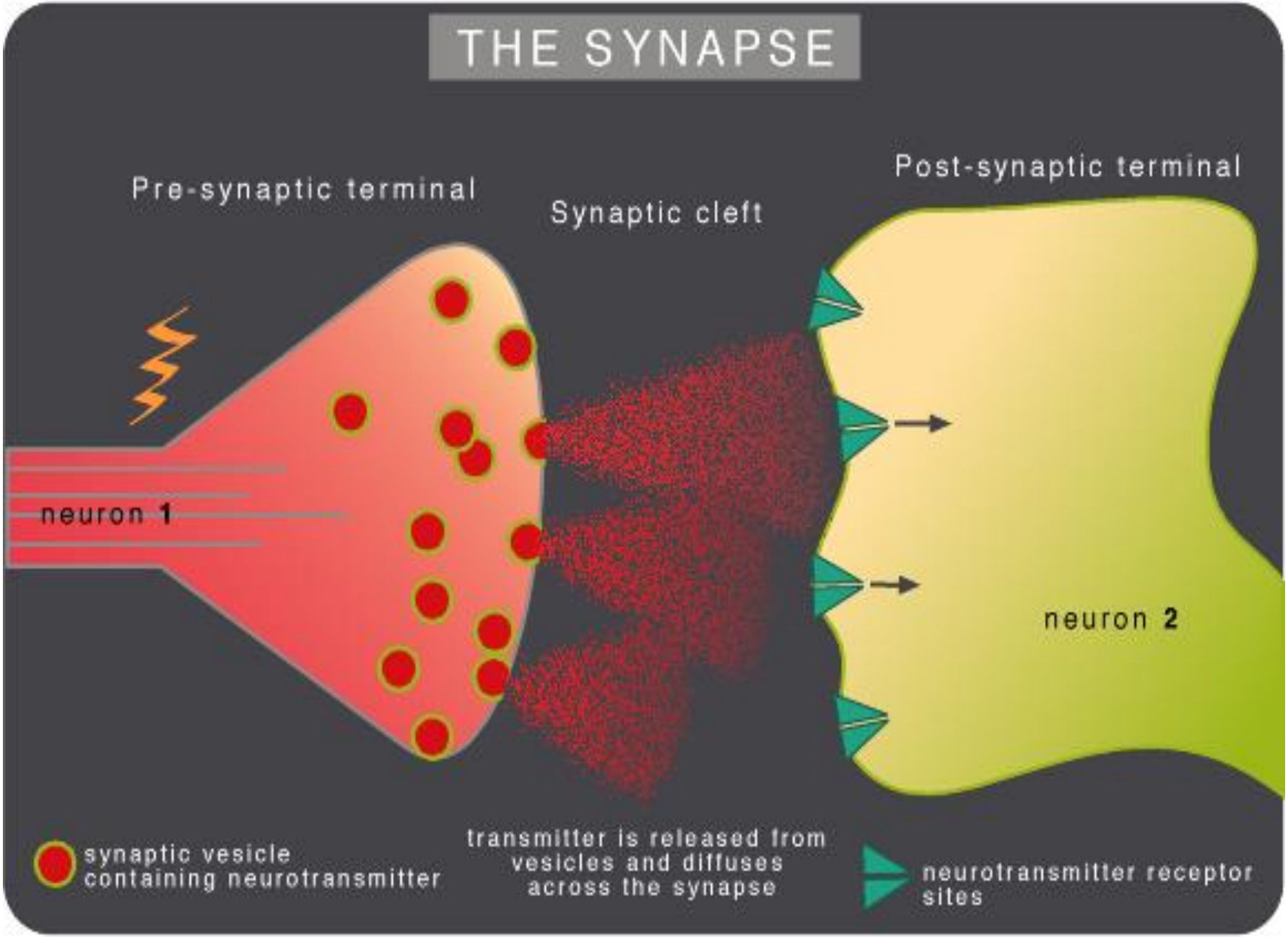
Nullification of drug response by a physiological adaptive homeostatic response

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

↓

Loss of therapeutic efficacy

Refractoriness


THE SYNAPSE
Pre-synaptic terminal
Synaptic cleft
Post-synaptic terminal
neuron 1
neuron 2
synaptic vesicle containing neurotransmitter
transmitter is released from vesicles and diffuses across the synapse
neurotransmitter receptor sites

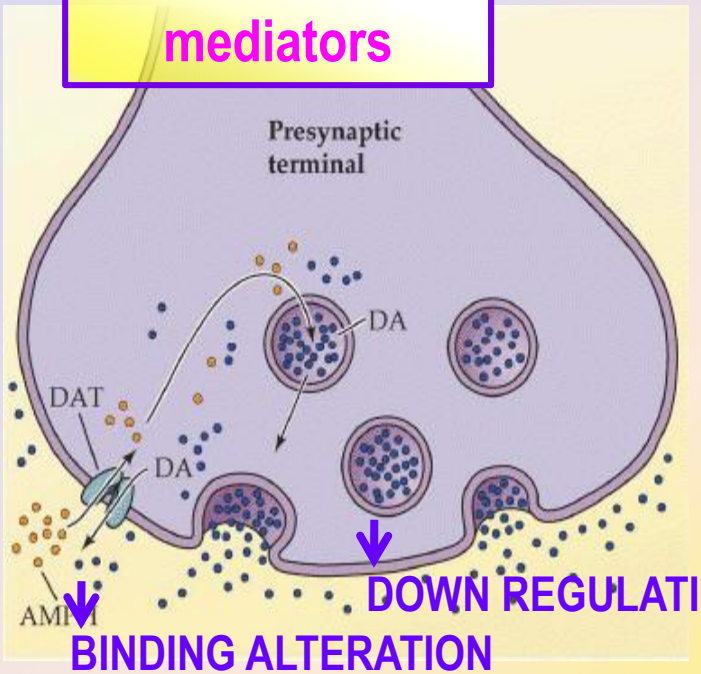
REASONS FOR DEVELOPMENT OF TOLERANCE

Pre- receptor events

Events at receptors

Post-receptors events

Exhaustion of mediators



DOWN REGULATION

BINDING ALTERATION

Binding alteration

Phosphorylation of R by ß-adrenoceptors → ↓ activation of AC to related ionic channel

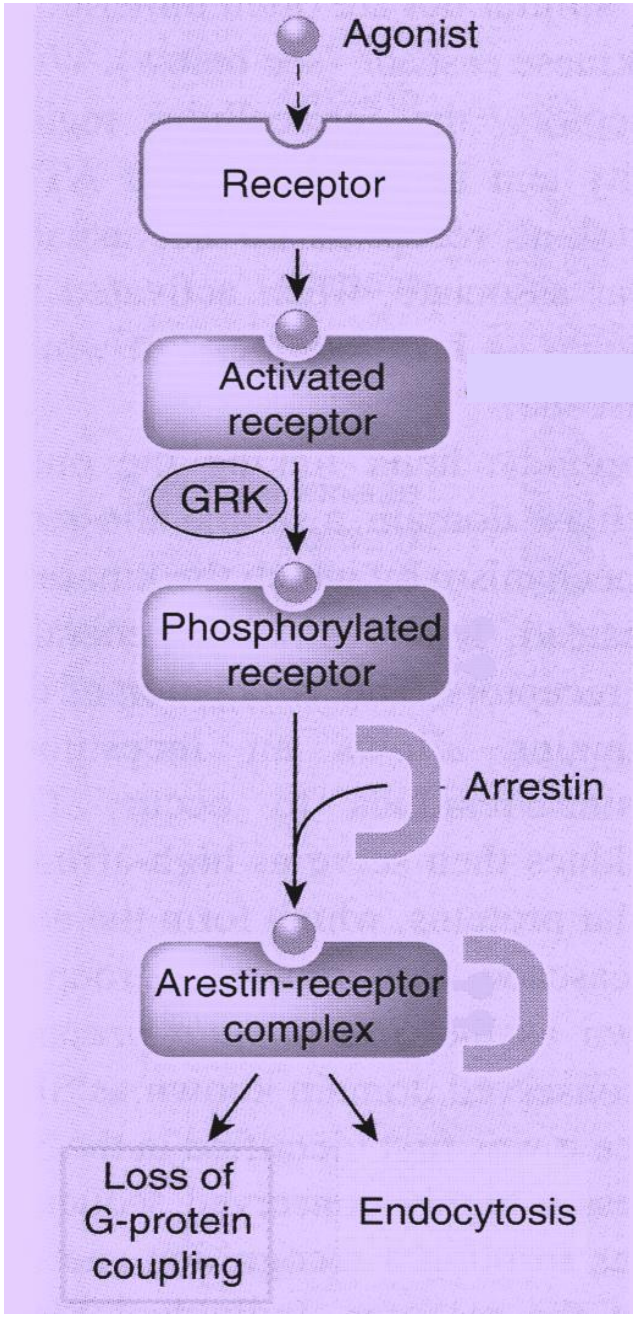
[functional defect]

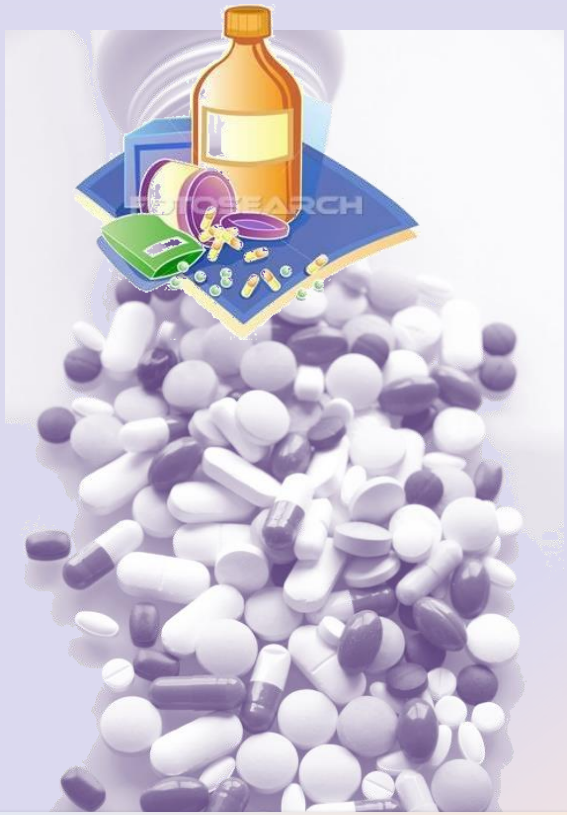
Down regulation

↓ number of receptors.

Isoprenaline activation to β receptors →↑ R recycling by endocytosis

[structural defect]


Agonist
Receptor
Activated receptor
GRK
Phosphorylated receptor
Arrestin
Arestin-receptor complex
Loss of G-protein coupling
Endocytosis



Adverse drug reactions [ADR]

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

Types of ADR

Type A

Augmented

Predictable

Occurs consequent but in excess of drug primary pharmacological effect.
Of quantitative nature

Type B

Bizarre

Unpedictable

Occurs different [heterogenous / idiosyncratic] to known drug pharmacological effect usually due to patient's genetic defect or immunological response.
Of qualitative nature

Type C

Continuous

Occurs during chronic drug administration

Type D

Delayed

Occurs after long period of time even after drug stoppage

Type E

End-of-Use

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

TYPES OF ADR

Type C — Continuous

e.g. Patients can develop

1. Osteoporosis
   secondary to chronic corticosteroid intake

2. Dependence

a. Psychological [Craving] as by cannabis

b. Psychological [Craving] + Physical withdrawal manifestations (syndrome)
   = Addiction as by morphine

Type E — End-of-Use

e.g. Patients on stoppage of
- Clonidine develop rebound hypertension
- Morphine develop withdrawal syndrome

Type D — Delayed

Long after patients can show:

- Teratogenicity after retinoids
- Carcinogenicity after tobacco smoking

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

Examples of TYPE A & B -ADR

Drug	Type A	Type B
Chlorpromazine	Sedation	Cholestatic jaundice
Naproxen	GIT haemorrhage	Agranulocytosis
Phenytoin	Ataxia	Hepatitis, lymphadenopathy
Thiazides	Hypokalaemia	Thrombocytopenia
Quinine	Tinnitus	Thrombocytopenia
Warfarin	Bleeding	Breast necrosis

Genetics Variation / defect
Immunological Predisposition

TYPE B

Immunological Predisposition

The drug or its bi-product [*protein macromolecules or haptens*] react as antigens and provoke immune response that results in damage to the tissue→ Hypersensitivity Reaction

1st exposure to a drug → **Sensitization**

Repeated exposures → HYPERSENSITIVITY REACTION

Classification of hypersensitivity reactions

Type I – Immediate (atopic, or anaphylactic)

Type II – Cytotoxic

Type III – Immune complex

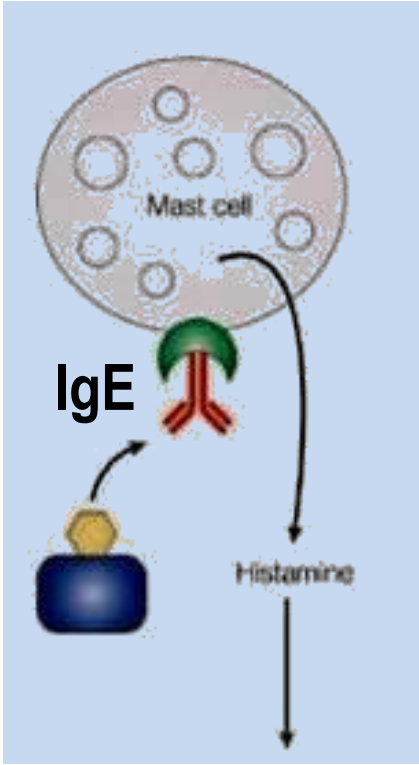
Type IV – Cell-mediated or delayed

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, rather than multiple hours or days. The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen.

- The reaction is mediated by IgE antibodies and produced by the immediate release of histamine, serotonin, leukotrienes from tissue mast cells or blood basophils



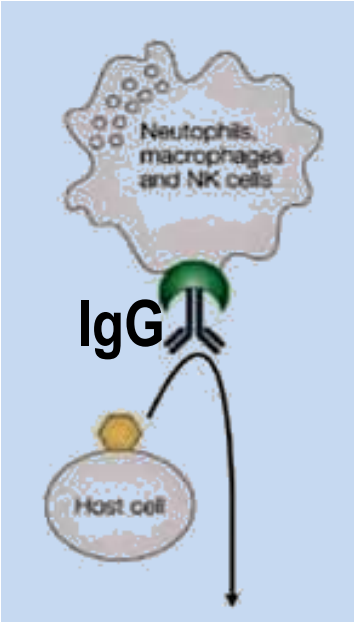
- The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock.

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

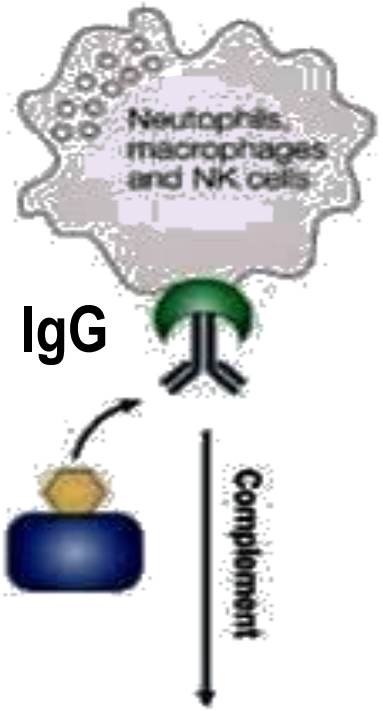
Type III hypersensitivity : Immune complex

- **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**

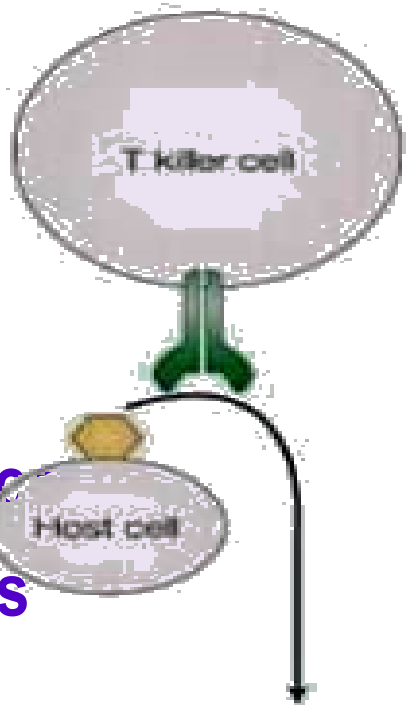
- **Example: Serum sickness *(fever, arthritis, enlarged lymph nodes, urticaria)***

- **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



GOOD LUCK