

# **TOLERANCE / DESENSITIZATION & ADVERSE DRUG REACTIONS**

## **Objectives:**

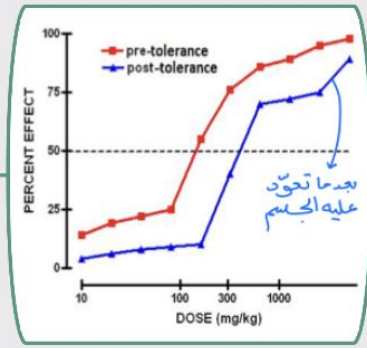
- Distinguish difference between tolerance and desensitization (tachyphylaxis) and reasons for their development.
- Recognize patterns of adverse drug reactions (ADR).

■ **Titles**   ■ **Very important**   ■ **Terms**   ■ **Extra informations**

**\*Success Doesn't Come To You, You Go To It!\***

## Tolerance & Desensitization

Phenomenon of variation in drug response, whereby there is a gradual diminution of the response to the drug when given continuously or repeatedly.



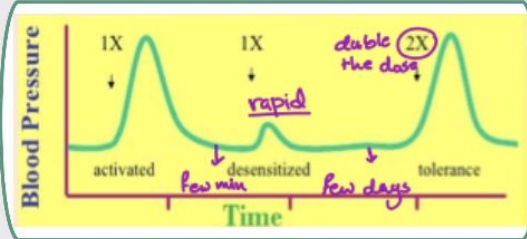
## Diminution of A Response

Tachyphylaxis / Desensitization

Rapid, in the course of few minutes

Gradual in the course of few days to weeks

Tolerance



These should be distinguished from **Resistance**, Which is the loss of effectiveness of antimicrobial agent.

## Reasons for Development of Tolerance

### Pre-receptor events

Decrease drug availability at the relevant receptors due to pharmacokinetic variables.

Drug becomes:  
-More metabolized or excreted  
-Less absorbed  
-altered distribution to tissues.

E.g. **Barbiturates**  
Increase metabolism of **Contraceptive pills** which decrease its availability

### Post-receptor events

Nullification (remove/cancel) of drug response by a physiological adaptive homeostatic response.

E.g. Antihypertensive effects of **ACE** Is become nullified by activation of renin angiotensin system by **NSAIDs**

They both lose the therapeutic efficacy (**Refractoriness**).

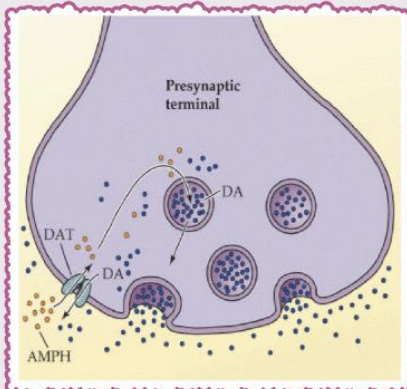
### Events at receptors

Exhaustion of mediators

Binding alteration

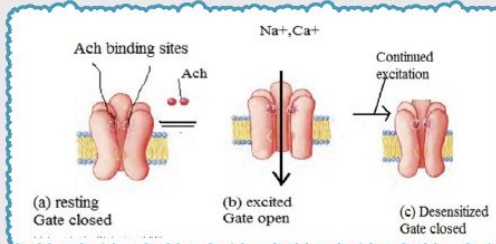
Down regulation

### Depletion of mediator stores by amphetamine



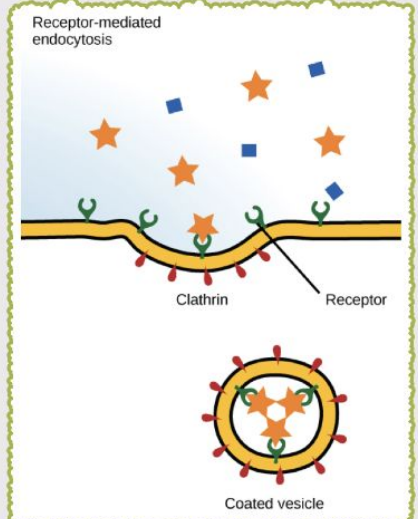
1- Phosphorylation of receptors i.e. Tight binding of **B-adrenoceptors agonists** lead to activation of AC.

2- Desensitization of ACH-receptors (functional defect)



Decrease number of receptors.

**Isoprenaline** activation to B (Beta) lead to increase receptor recycling by endocytosis (structural defect)



## Adverse drugs reaction (ADR)

### Type A - Augmented

- 80% of ADRs
- Predictable
- A consequence of the primary effect of the drug

e.g. Hypoglycemia from hypoglycemic drugs

e.g. bleeding from warfarin

### Type B - Bizarre

- Occurs different to known drug pharmacological effect [idiosyncrotic ]
- 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

e.g. Penicillin → Anaphylactic shock

e.g. Quinine → Thrombocytopenia

Harmful or seriously unpleasant effects occurring at doses intended for therapeutic effects

#### Types

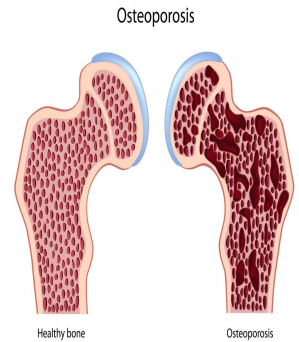
A-Augmented  
B-Bizarre  
C-chronic  
D-delayed  
E-End of use

### Comparison between type A&B -ADRs

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

### 3. Type C (Continuous)

- Occurs during chronic drug administration.
- e.g **Osteoporosis chronic corticosteroid intake.**



### 4-Type D (delayed)

- Occurs after long period of time even after drug stoppage (delayed in onset).
- Refers to carcinogenic and teratogenic effects.
- e.g Teratogenicity→Retinoids
- Carcinogenicity→Tobacco smoking



**\*\*Retinoic acid malformations is considered DELAYED ADR**

### 5-Type E (End of use)

- Occurs after sudden stoppage of chronic drug use due to existing adaptive changes.
- e.g. Patients on stoppage of
  - **Morphine develop withdrawal syndrome**
  - **Diazepam develop anxiety and insomnia**

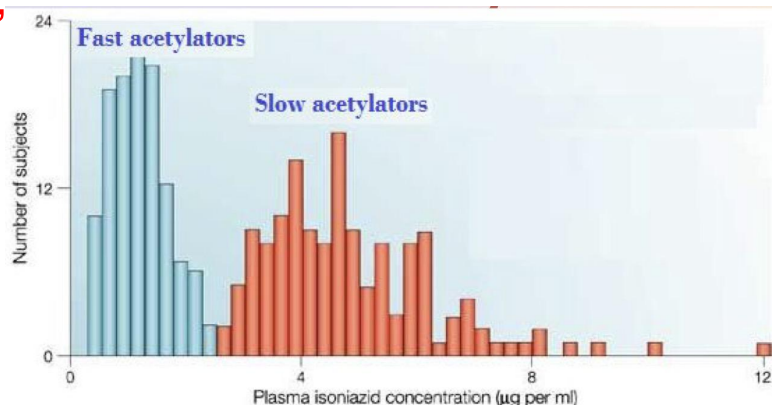
Increase body ache, insomnia, diarrhea, gooseflesh, lacrimation

### **TYPE B (2) If due to genetic defect**

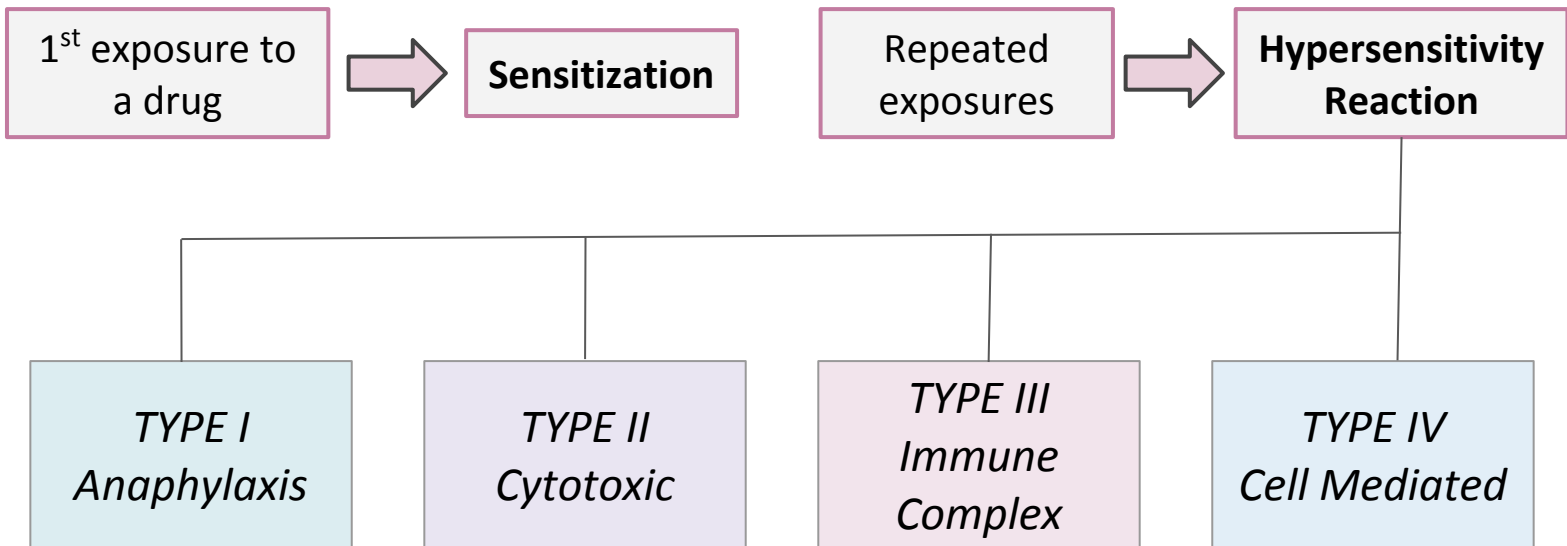
When **isoniazid** is given in identical doses /kg, two distinct groups can be identified, a group with low blood level acetylate the drug more rapidly 'fast acetylators' & 'slow acetylators'

-Isoniazid causes peripheral neuropathy in slow acetylators

-Relapse of infection & hepatitis occur in rapid acetylators



## TYPE B (1) If due to immunological response

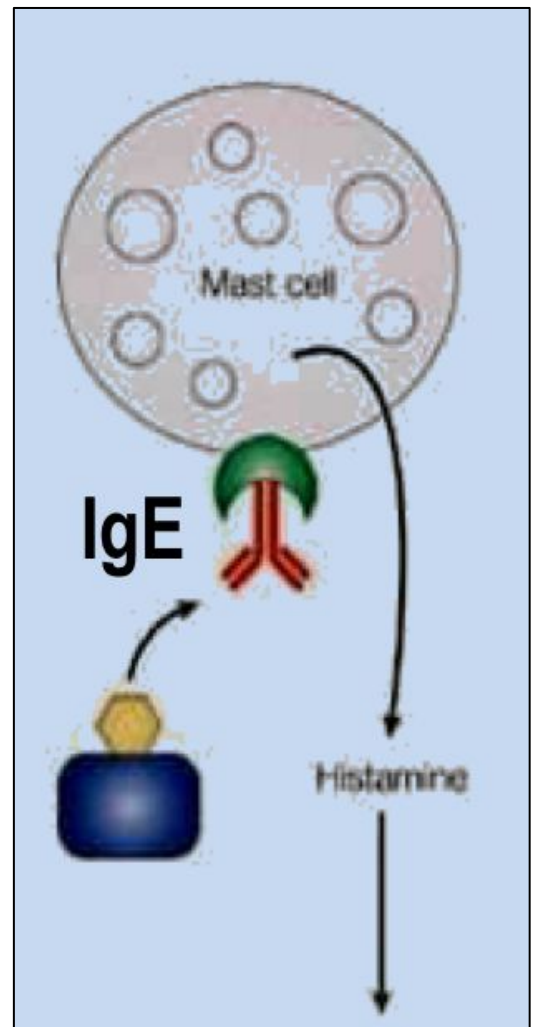


### Type I Hypersensitivity: Anaphylactic

- 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.

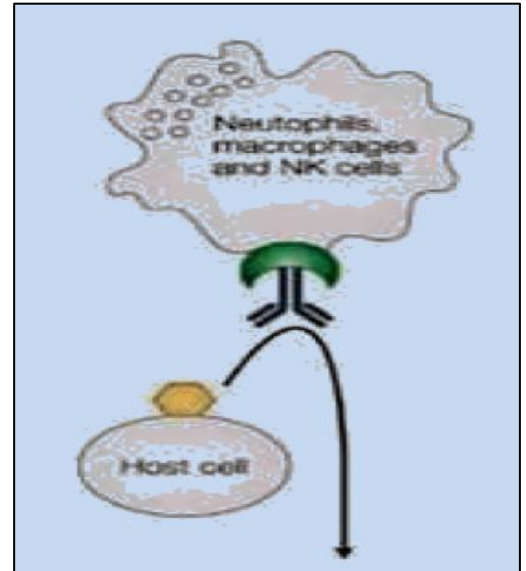




**Type II hypersensitivity : Cytotoxic**

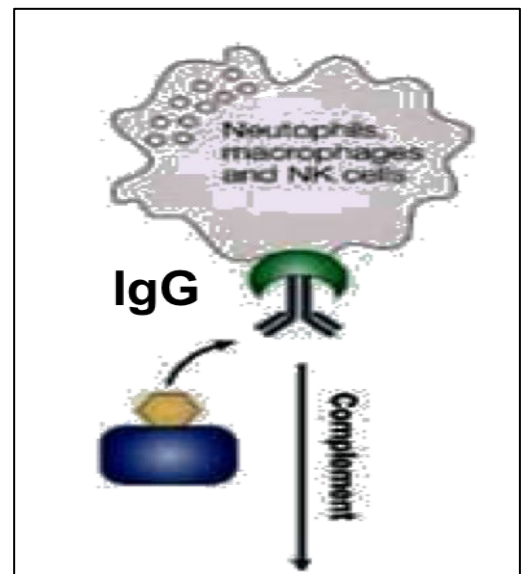
- Antibody-dependent
- The antigens may be **endogenous** or **exogenous** chemicals (haptens) which can attach to cell membranes.
- The antibodies (**IgM or IgG**) produced by the immune response bind to antigens on the patient's own cell surfaces that is perceived by the immune system as foreign, leading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

Regarded type 1 and also 2



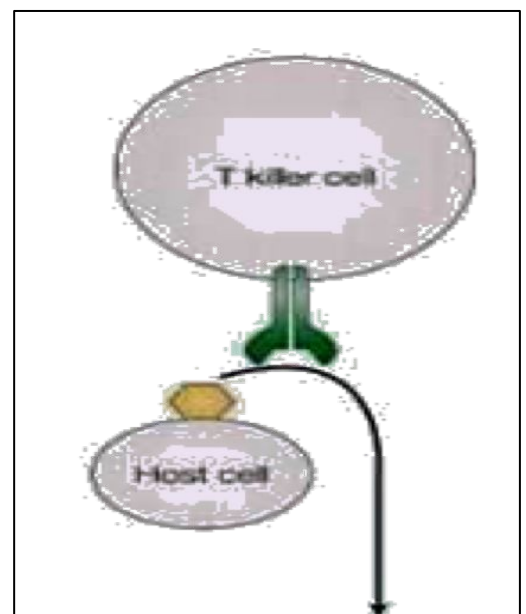
Could say **OR**  
**Type III hypersensitivity : Immune complex** **OR**

- 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 anesthetics** creams, anti-histamine creams, topical antibiotics.



## MCQs

### 1-which of the following is correct

- A-Tachyphylaxis is gradual while tolerance is rapid
- B-Tachyphylaxis is rapid while tolerance is gradual
- C-both are rapid
- D-both are gradual

### 2-Which one of the following is considered “End of Use”

- A- anxiety due to diazepam
- B-malformation due to retinoids
- C-osteoporosis due to corticosteroid
- D-hemorrhage due to warfarin

### 3-Which one of the following is considered “continued ”

- A- anxiety due to diazepam
- B-malformation due to retinoids
- C-osteoporosis due to corticosteroid
- D-hemorrhage due to warfarin

### 4-Which one of the following is considered “delayed ”

- A- anxiety due to diazepam
- B-malformation due to retinoids
- C-osteoporosis due to corticosteroid
- D-hemorrhage due to warfarin

### 5-Which one of the following does Not depend on antigen & antibody

- A-TYPE I Anaphylaxis
- B-TYPE II Cytotoxic
- C-TYPE III Immune complex
- D-TYPE IV Cell mediated

### 6-releasing of histamine from the mast cells is considered as A-

- TYPE I
- B- TYPE II
- C- TYPE III
- D-TYPE IV

### 7-anaphylactic caused by penicillin is considered as

- A- TYPE I
- B- TYPE II
- C- TYPE III
- D-TYPE IV

### 8- hemolytic anemia caused by penicillin is considered as

- A- TYPE I
- B- TYPE II
- C- TYPE III
- D-TYPE IV

Answers  
1-B 2-A 3-C 4-B 5-D 6-A 7-A 8-B

## MCQs

**9-Quinidine induced thrombocytopenia due to destruction of the Patients own cells is considered as**

- A-Anaphylaxis
- B-Cytotoxic
- C-Immune complex
- D- Cell mediated

**10-sulphonamide induced serum sickness is considered**

- A-Anaphylaxis
- B-Cytotoxic
- C-aggregation of antigen & antibodies
- D- Cell mediated

**11-Contact dermatitis by local anesthetics creams is considered as**

- A- TYPE I
- B- TYPE II
- C- TYPE III
- D-TYPE IV

**12-Isoniazid causes peripheral neuropathy in**

- A- slow acetylators
- B-rapid acetylators
- C-both A& B
- D-neither A or B

**13-Relapse of infection & hepatitis occur in**

- A- slow acetylators
- B-rapid acetylators
- C-both A& B
- D-neither A or B

9-B 10-C 11-D 12-A 13-B  
**Answers**



# Team members:

## Girls:

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Ghada Alqarni  
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Norah Aldubaib  
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Rahaf AlShammari  
Rahaf Althnayan  
Reem Alqarni  
Rinad Alghoraiby  
Shaden AlOtay  
Shahad Alzahrani