






# Tolerance and ADRs



If you didn't  
understand any part  
from this lecture  
Click here!

-  **Important**
-  In male and female slides
-  Only in male slides
-  Only in female slides
-  Extra information

# Objectives



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

Any Future corrections will be posted  
on the editing file.  
make sure to check it **frequently**

Click **[Here](#)**

# Tolerance and Desensitization

These should be distinguished from **Resistance** (loss of effectiveness of antimicrobial agent)

Diminution of a response

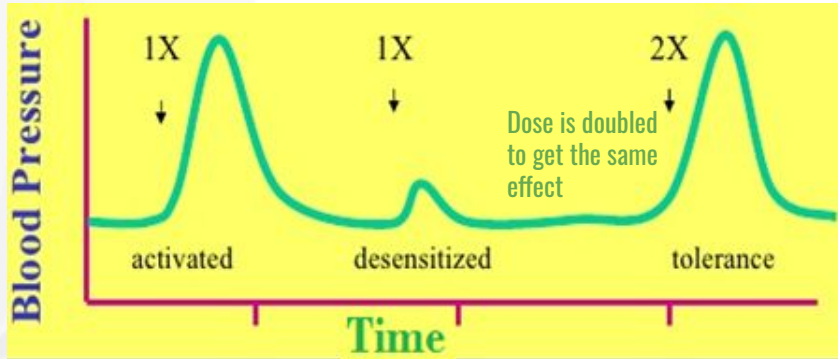
**Tachyphylaxis/Desensitization:** Rapid (takes a few minutes)

**Tolerance:** Gradual ( few days to weeks)

Pre-Receptor Event

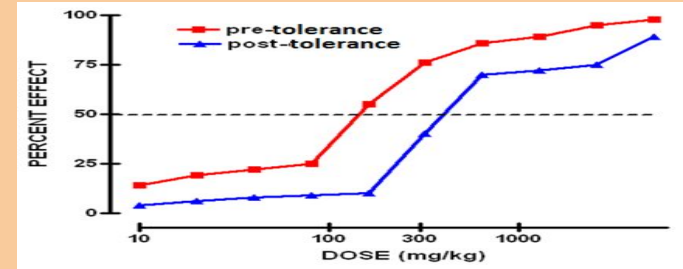
Events at Receptors

Post-Receptor Event



# Tolerance

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



## Reasons For Development of Tolerance

### Pre Receptor Events

Decrease **Drug availability** at the relevant receptors due to pharmacokinetic variables

Drug becomes:

1. > metabolized or excreted (increase)
2. < absorbed (decrease)
3. altered distribution to tissues

e.g. **Barbiturates increase metabolism of Contraceptive pills = decrease its availability**

### Post Receptor Events

**Nullification of drug response** by a physiological adaptive homeostatic response

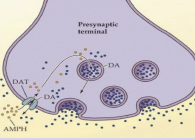
E.g. Antihypertensive effects of **ACEIs** become nullified by activation of renin angiotensin system by **NSAIDs**

Both of Pre & Post Receptor Events result in **loss of therapeutic efficacy (Refractoriness)**

# Event at receptors

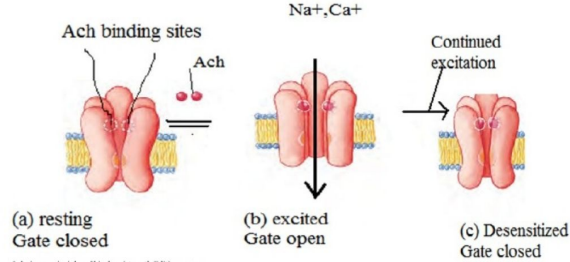
## Exhaustion of mediators

Depletion of mediator stores by **amphetamine**

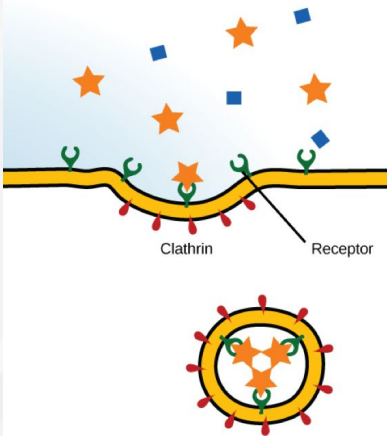


## Binding alteration

1. Phosphorylation of receptor. I.e tight binding of  **$\beta$ -adrenoceptors agonist**  $\rightarrow$  causes reduced activation of AC (Adenylyl Cyclase) to related ionic channel
2. Desensitization of Ach-receptors  
**[functional defect]**



Receptor-mediated endocytosis



**Down regulation**  
Decrease in number of receptors. Example: **isoprenaline** activation to  $\beta$  receptors  $\rightarrow$  Increase in receptor recycling by endocytosis  
**[structural defect]**

**Adverse drug reaction (ADRS)**

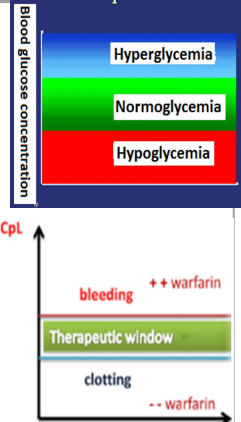
Harmful or seriously unpleasant effect occurring at doses intended for therapeutic effect (**side effects**).

**TYPES OF ADRS**

**A Augmented**  
**B Bizarre**  
**C Chronic**  
**D Delayed**  
**E End of use**

**Type A Augmented**

- Dose dependent
- **80% of ADRS**
- Predictable (يمكن التنبأ به)
- A consequence of the primary effect of the drug
- يعني السايڊ ايفيكت للدواء عبارة عن زيادة تأثير الشئ الذي نبعي الدواء بسويه-436
- Not mortal
- Treated by stopping or changing the dose
- Quantitatively different from the primary effect
- e.g. Hypoglycemia from hypoglycemia drugs - Bleeding from warfarin
- High incidence



**Type B Bizarre**

- Occurs different to known drug pharmacological effect (**idiosyncratic**)
- Idiosyncratic reactions are drug reactions that occur rarely and unpredictably amongst the population (**Unknown mechanisms**)
- Usually due to **1- immunological response** or **2-patient's genetic defect**
- Dose independent
- qualitatively different from the primary effect
- Low incidence
- It is mortal
- Treated by stopping or using an antidote
- **Penicillin** → **Anaphylactic shock (hypersensitive)**
- **Quinine** → **Thrombocytopenia**
- (السايڊ ايفيكت هنا ما يعمل نفس عمل الدواء ، يعمل شئ مختلف)-436



# Type B

Due to genetic defect

Due to immunological response

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**"

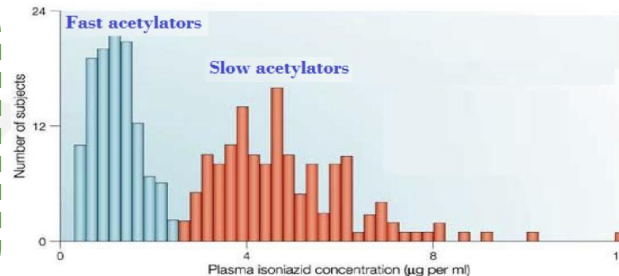
Relapse of infection & hepatitis occur in **fast acetylators** (↓ level of drug)

Isoniazid causes peripheral neuropathy in **slow acetylators** (↑ level of drug)

1st exposure to drug -> sensitization  
Repeated exposures -> **hypersensitivity reactions**

## Hypersensitivity reactions

- 1- Anaphylaxis
- 2- Cytotoxic
- 3- Immune Complex
- 4- Cell mediated





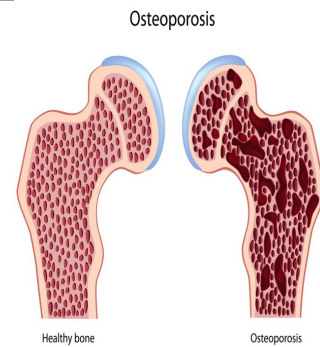
Hypersensitivity Reactions	TYPE I Anaphylaxis	<ul style="list-style-type: none"><li>● Release of mediators from mast cells or blood basophil (few minutes)</li><li>● Urticaria rhinitis, bronchial, asthma by <b>Penicillin</b></li></ul>
	TYPE II Cytotoxic	<ul style="list-style-type: none"><li>● Antibody- directed cell- mediated lysis (hours to days)</li><li>● Haemolytic anaemia ,thrombocytopenia by <b>Quinine</b></li></ul>
	TYPE III Immune complex	<ul style="list-style-type: none"><li>● Deposition of soluble antigen–antibody- complement complexes in small blood vessels (hours to days )</li><li>● Serum sickness (fever arthritis enlarged lymph nodes, urticaria) by <b>Sulphonamides, Streptomycin</b></li></ul>
	TYPE IV Cell mediated	<ul style="list-style-type: none"><li>● Interaction release cytokines that attracts inflammatory cell infiltrate(long time )</li><li>● Contact dermatitis by <b>local anaesthetics creams</b></li></ul>



## TYPES OF ADRS

### Type C Continued

- Occurs during **chronic** drug administration (**long-term use**)
- (**هشاشة العظام**) **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** → Tobacco smoking

436 note - Teratogenic drugs: A teratogen is an agent that can disturb the development of the embryo or fetus.



**Retinoic acid malformations**

### Type E End of use

- Occurs after **sudden stoppage** of chronic drug use due to existing adaptive changes
- Withdrawal syndrome → **Morphine**
- increases Body ache, insomnia (**أرق**), diarrhea, goose flesh, lacrimation (**secretion of tears**)
- Withdrawal of **diazepam** → anxiety, insomnia



**1) Which of the following considered “Delayed”**

- A) -anxiety due to diazepam    B) - Teratogenicity due Retinoids    C) - bleeding due to warfarin    D) -thrombocytopenia due to quinine

**2) Both of Pre & Post Receptor Events result in ?**

- A) Osteoporosis    B) Refractoriness    C) Adverse drug reaction    D) Tolerance

**3) Haemolytic anaemia is caused by ?**

- A) Penicillin    B) Sulphonamides    C) Quinine    D) Streptomycin

**4) Serum sickness that caused by sulfonamides is considered as?**

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

**ANSWERS**

1	B
2	B
3	C
4	C

**1) In which type of ADRs Anaphylactic shock happens due to penicillin**

**2) Nullification of drug response happen at ?**

**3) Loss of effectiveness of antimicrobial agent is called?**

**4) What does Chronic corticosteroid intake cause?**

## **ANSWERS**

A1) Type B - Bizarre

A2) Post Receptor Events

A3) Resistance

A4) osteoporosis

# GOOD LUCK!



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## Girls team members

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رانيا المطيري  
نورة الدخيل  
اسيل الشهري   
الجوهرة البنيان  
شادن العبيد   
سديم آل زايد  
روان باقادر  
ميس العجمي  
نورة السالم  
نوف السبيعي  
ندى بابلي  
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حمد الموسى  
راكان الدوهان  
فيصل العتيبي  
محمد القهيدان  
يزيد القحطاني 