# BHARATHIDASAN UNIVERSITY

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## Unit-V

## Toxicology- Part 3

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# ABNORMAL ACTION OF DRUGS SUCH AS

# TOLERANCE , ADDICTION

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# TOLERANCE

DEFINITION: Tolerance occurs when a person’s response to a drug decreases after repeated use. As a results, higher doses of the drug are needed to achieve the same effect.

EXAMPLE: Opioids, benzodiazepines, and alcohol.

# TYPES OF TOLERANCE

## Pharmacokinetic tolerance

This happens when body (usually the liver) increases its efficiency in metabolizing and eliminating the drug. As a result, less of the drug reaches the site of action.

EXAMPLE: Barbiturates and carbamazepine induce their own metabolism, while renal excretion of amphetamine is accelerated after regular intake.

**Barbiturates** : after repeated use, the liver increases enzyme production, metabolizing the drug faster and reducing its effects. This happens with drug like **phenobarbital**, where the body metabolizes the drug faster, so more is needed to maintain the same level of sedation.

# PHARMACODYNAMICS TOLERANCE

Drug action is lessened; cells of the target organ become less responsive.

EXAMPLE: Morphine, barbiturates, nitrates. This may be due to desensitization\down regulation of receptors, or weakening of response effectuation.

**Opioids** : with repeated use, opioid receptors become less sensitive to pain relief effects, so the same dose no longer works as well.

# MECHANISM OF TOLERANCE;

**Receptor desensitization:**

- Continuous drug exposure reduces receptor sensitivity
- Fewer drug molecules can activate the receptors.

**Receptor downregulation:**

- The body reduces the number of receptors on cell surfaces.
- Occurs in response to prolonged activation by the drug.

**Increased drug metabolism:**

- The liver produces more enzymes to break down the drug faster.
- Reduces the drug concentration in the blood, leading to reduced effectiveness.

# CONSEQUENCES OF TOLERANCE:

**Increased dosage:**

- Users may increase the dosage to achieve the same effect, leading to higher risks of side effect, toxicity, or overdose.

**Risk of addiction:**

- Increased drug use to overcome tolerance can lead to addiction, where the user becomes both physically and psychologically reliant on the drug.

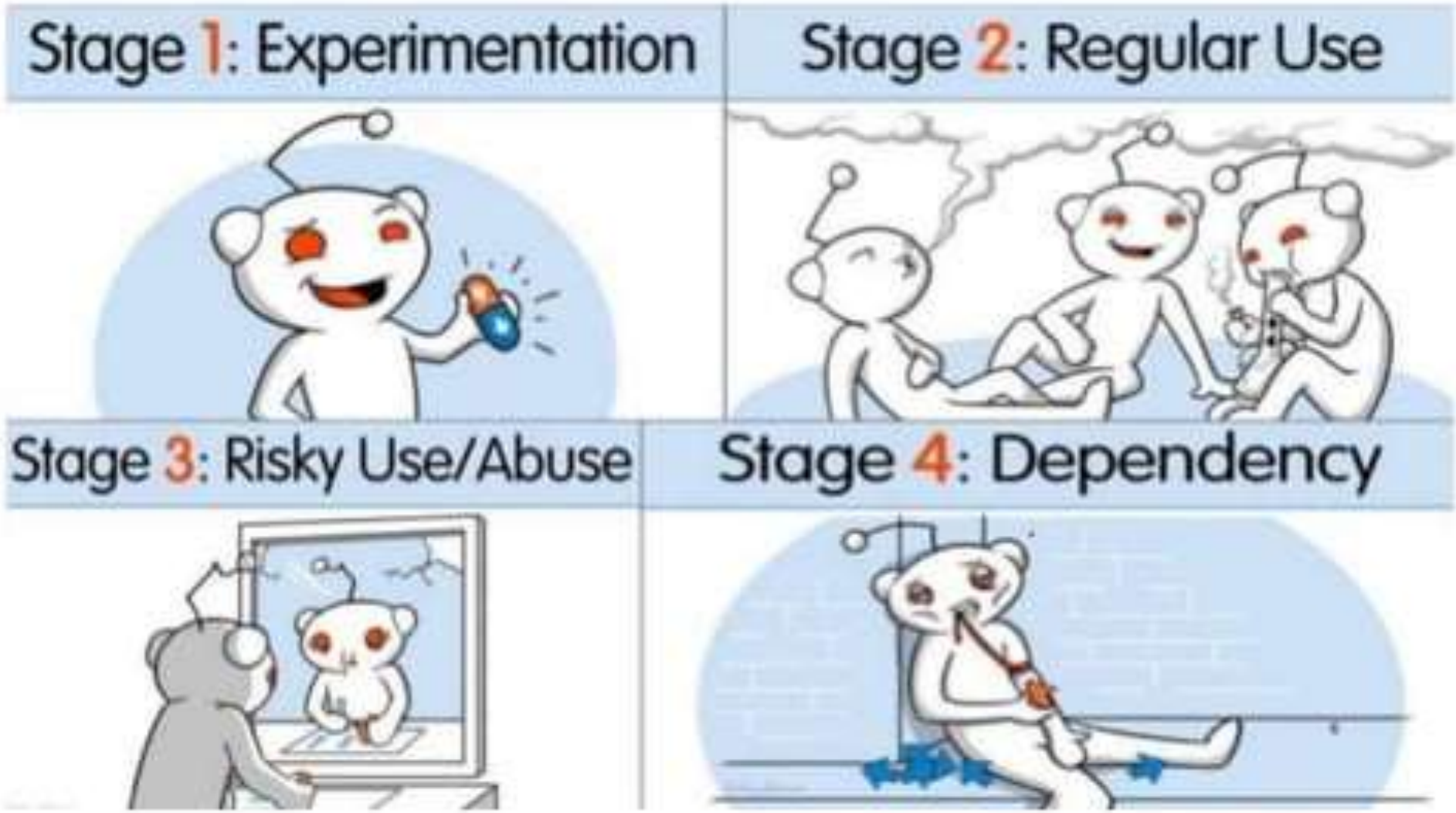
**Over dose :**

- Tolerance to the desired effects (e.g., pain relief or euphoria) may not extend to other effects, such as respiratory depression in opioid use, increase the risk of overdose.

# ADDICTION

Addiction is a chronic disorder characterized by compulsive drug seeking behavior, loss of control over drug use, and continued use despite harmful consequences. Addiction involves both physical dependences (the body’s need for the drug) and psychological dependence (the emotional and mental drive to use the drug).

# STAGES OF ADDICTION



# STAGES OF ADDICTION:

**1. Experimentation:**

Initial use of the drug, often for recreational or social reasons.

**2. Regular use:**

Drug use becomes more frequent, and the person may start developing a tolerance

**3. Dependence:**

The person develops a need for the drug to function, leading to physical or psychological dependence

**4. Addiction:**

Full-blown addiction involves compulsive drug use, inability to stop despite negative consequences, and long-term changes in brain function

# TOP TEN DRUGS

- MARIJUANA
- HEROIN
- COCAINE
- ALCOHOL
- TOBACCO
- LSD (Lysergic acid diethylamide)
- SPEEDBALL
- MDMA
- KETAMINE
- CRYSTAL- METH

# SIDE EFFECTS

- LOSS OF APPETITE
- HEADACHES
- ANXIETY
- ELEVATED BLOOD PRESSURE
- CHEST PAIN
- IRREGULAR HEARTBEAT
- COLD/BLUISH FINGERS
- DIFFICULTY IN URINATING
- CHANGES IN BODY TEMPERATURE

# Consequences of addiction:

**Health effects:**

Addiction can lead to numerous health problems, including overdose, liver disease, heart problems, and mental health disorders like depression or anxiety.

**Social consequences:**

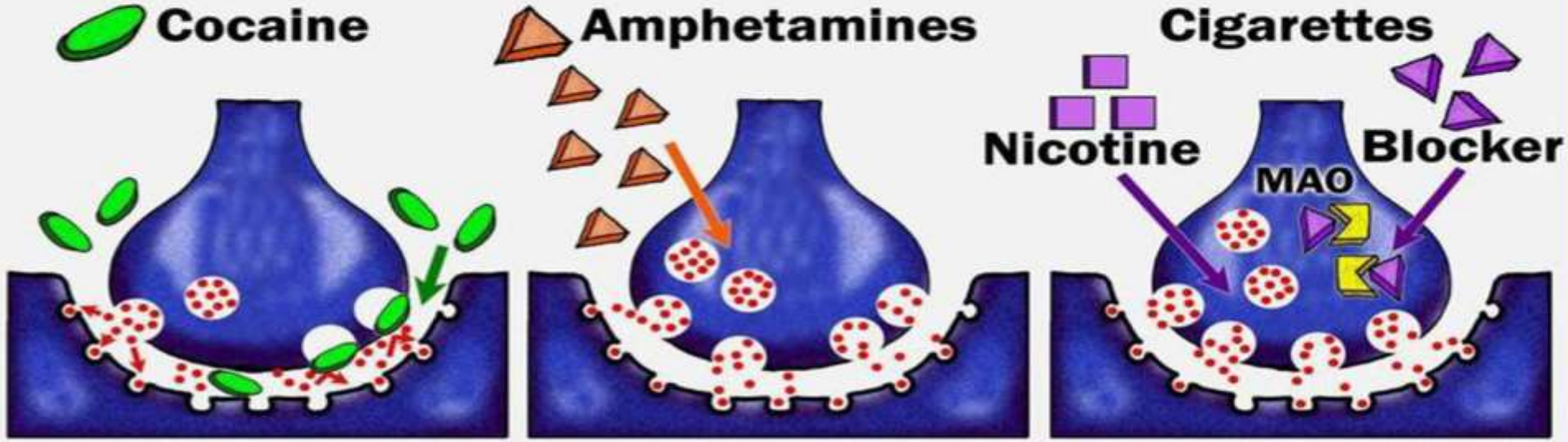
Addiction often leads to relationship problems, job loss, legal issues, and financial difficulties.

**High risk of relapse:**

Even after periods of sobriety, people with addiction are at a high risk of relapsing due to long-lasting changes in brain function and intense cravings.

# How Drug Affect Dopamine Levels

Based on *Time*, May 5, 1997




Illustrations by: Simeon Liebman

Cocaine blocks the normal absorption of dopamine. As a result, dopamine accumulates in the synapse, where is stimulates the receiver cell.

Amphetamines stimulate excess release of dopamine, overwhelming the processes of reuptake and enzyme breakdown.

Nicotine stimulates the release of dopamine, while another substance in cigarette smoke blocks the action of MAO.

# EFFECTS OF DRUG ADDICTION

## ACUTE EFFECTS

1. Cocaine – leads to feeling of paranoia & anxiety.
2. Alcohol – leads to memory lapses , distorts vision.
3. Ritalin – severe headache, anxiety, delusions
4. Marijuana – affect the part of brain that control emotion, memory and judgement and weaken problem solving ability
5. Ecstasy – difficulty in differentiating reality and fantasy

## CHRONIC EFFECTS

1. Overall health – neglecting their own health
2. Disease – Lung disease, heart problem, brain damage and possible death from overdose
3. Denial – Rationalize any behaviour which is illegal, immoral / unethical

# CONCLUSION:

**Tolerance** is primarily a physiological adaptation where the body becomes less responsive to a drug, while **addiction** is a more complex condition involving both physical and psychological dependence, driven by changes in the brain’s reward system. Both phenomena are abnormal actions of drugs that can lead to significant health risks, compulsive drug use, and long-term consequences.

# ANTAGONISM AND HYPERSENSITIVITY

# CONTENTS:

**Def**: Antagonism

Types of antagonism

**Def:** Hypersensitivity

Types of hypersensitivity

# Def: Antagonism

The effect of one drug blocked or inhibited due to another drug is said to be **“Antagonism”**.

$$\text{Effect A+B} < \text{Effect A+ Effect B}$$

# TYPES OF ANTAGONISM:

1. **Physical antagonism**
2. **Chemical antagonism**
3. **Physiological/ Functional antagonism**
4. **Pharmacological antagonism**

## PHYSICAL ANTAGONISM:

**Based on physical property of drug,**

**e.g.. charcoal( absorb alkaloid) in alkaloidal poisoning.**

## CHEMICAL ANTAGONISM:

**The two drugs react chemically and form an inactive product.**

## Example of chemical antagonism:

**KMno4 oxidizes alkaloids- used for gastric lavage in poisoning.**

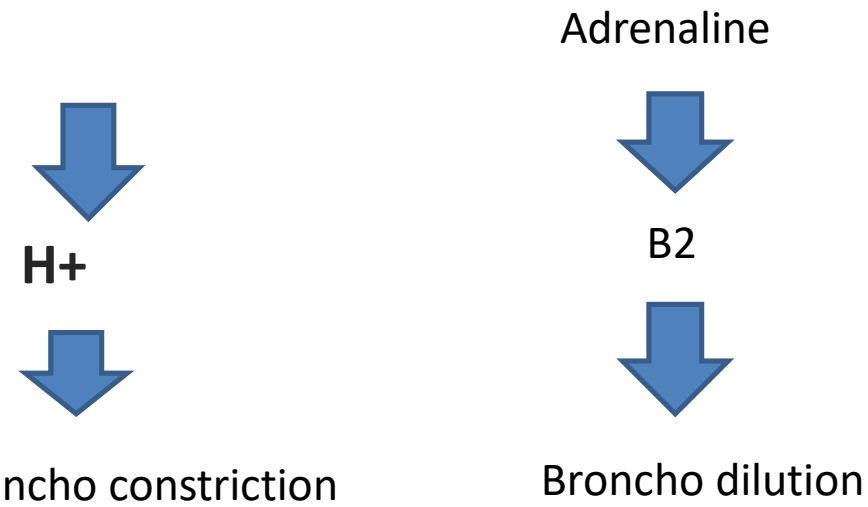
**Alkaloids( active) + KMno4 → dized alkaloids( inactive product).**

# PHYSIOLOGICAL ANTAGONISM

- It is otherwise called functional antagonism.
- Two drugs act on two different receptors or by two different action in one system or cell or organ.

Example : Histamine and adrenaline or bronchial smooth muscles…

- Histamine



# PHARMACOLOGICAL ANTAGONISM:

It classified into two:

1. Competitive
2. Non- competitive

01 COMPETITIVE ANTAGONISM

EQUILBRIUM{ REVERSIBLE}

02

NON- EQUILBRIUM{IRREVERSIBLE}

03 NON- COMPETITIVE ANTAGONISM

04

# PHARMACOLOGICAL ANTAGONISM:

- ✓ Opposite effect of two drugs binding to same receptors.
- ✓ The interaction between two substances in which one substance (antagonist) inhibits or blocks the action of another substance(agonist) at a receptor site.

- ✓ Agonist- Drugs that occupy receptor and activate them.
- ✓ Antagonist- Drugs that occupy receptor but do not activate them. Antagonist block receptor activation by agonist.

# Competitive antagonism:

- If both the agonist and antagonist compete for the same receptor in a reversible manner, they are said to be "competitive".
- The antagonist drug interacts with the receptor, and blocks it. Therefore it does not produce pharmacological action.
- Drugs interact with their receptors by weak bonds.

i.e., ionic bond or hydrogen bond.

➢ Example: NALOXONE AND OPIOID RECEPTORS

Mechanism: Naloxone is a {competitive antagonist} at opioid receptors. It competes with opioids( like morphine is agonist) for binding to same receptor.

# NON- COMPETITIVE ANTAGONISM:

In this situation, the antagonist forms a more stable bond { covalent bond} with its receptors.

- One drug bind to the receptor in a manner which makes it is impossible reverse the binding( eg.. A strong covalent bond)
- EXAMPLE: Ketamine and NMDA receptors

Ketamine acts as a non competitive antagonist at NMDA( N-methyl- D- aspartate) receptors. It binds to a different site on the receptor than  glutamate ( agonist) and inhibits its function.

| Competitive | non competitive |
| --- | --- |
| 1- antagonist binds with the same receptor as the agonist | 1- bind to another |
| 2-antagonist **resembles** chemically with agonist | 2- not |
| 3-antagonist reduces **affinity** of agonist | 3-antagonist reduces **efficacy** of agonist |
| 4-**intensity** depend on conc. Of both **agonist and antagonist** | 4-**intensity** depend only on conc. Of **antagonist** |
| 5-e.g. Ach - atropine | 5- Aspirin with cyclooxygenase |

# HYPERSENSITIVITY:

- In 1906, von picquet coined term the hypersensitivity.
- Hyper means" increase"

Sensitivity means" susceptibility or response".

- Hypersensitivity refers to excessive, undesirable reactions produced by the normal immune system.
- The reactions leads to damage and sometimes fatal to the death.

WHERE?

Any part of our body, commonly skin, respiratory tract and blood vessels.

# TYPES OF HYPERSENSITIVITY:

P.G.H. Cell and R.R.A. Combs revised the classification of hypersensitivity reactions based on mechanisms of pathogenesis into five types:

TYPE 1= IgE hypersensitivity

TYPE 2= Cytotoxic hypersensitivity

TYPE 3= Immune complex mediated hypersensitivity

TYPE 4= Delayed or cell mediated hypersensitivity

TYPE 5= Stimulatory hypersensitivity

ANTIBODY MEDIATED- TYPE 1,2,3

CELL MEDIATED - TYPE 4

# TYPE 1 HYPERSENSITIVITY:

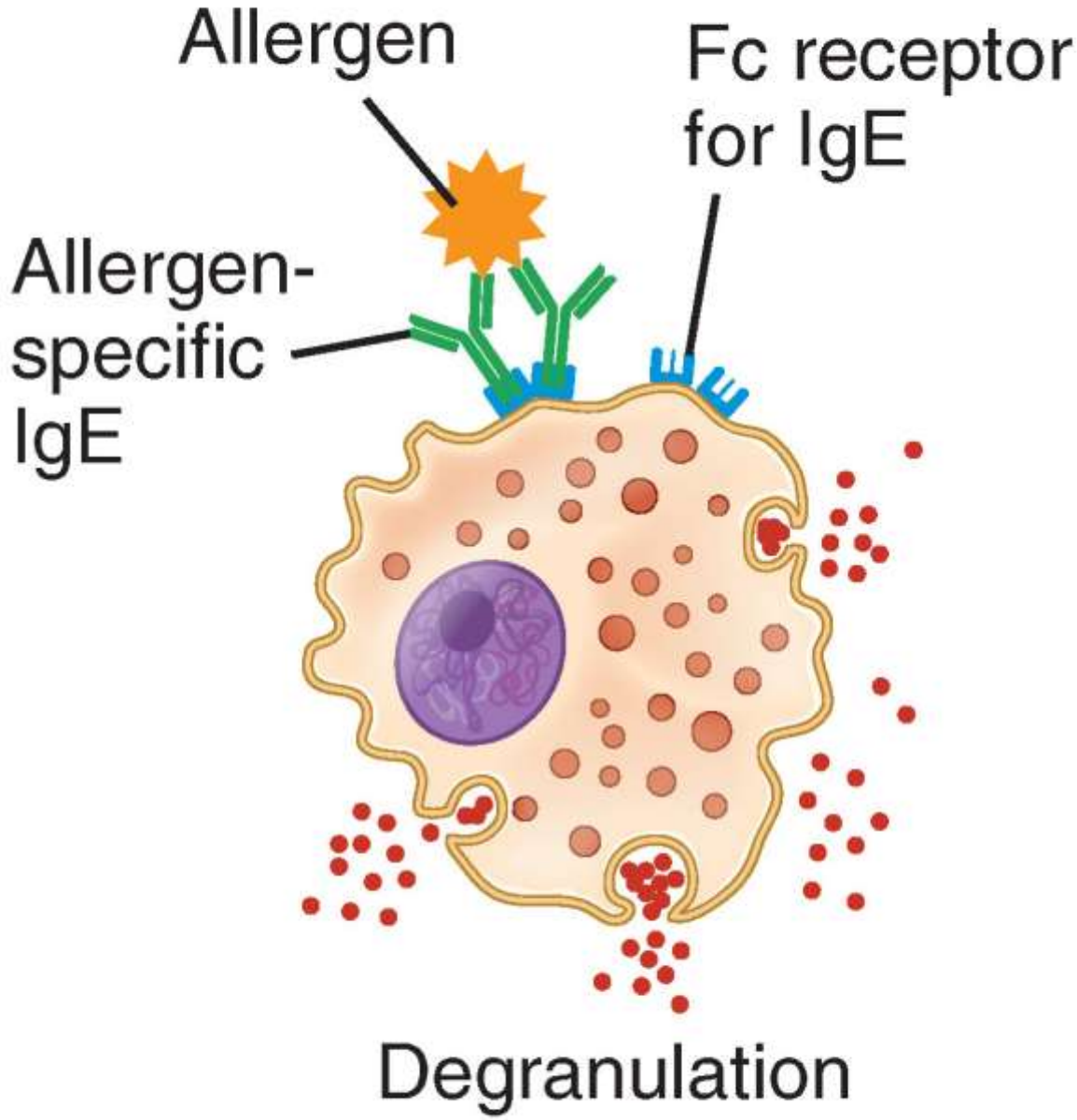
It is also called as “anaphylactic reaction”.

Anaphylaxis- severe allergic reaction which can life threatening.

## How?

- An antigen stimulate B- CELL to produce Ig E.
- IgE binds with MAST CELLS/ BASOPHILS.
- When same/ similar antigen re-enters.
- The antigen binds with adjacent Ig E molecules causing CROSS LINKING.
- The mast cells release HISTAMINE, SEROTONIN and other inflammatory chemicals.

**Symptoms:** Asthma, vomiting, Most allergies are type 1, The reactions is immediate.


Allergen
Fc receptor for IgE
Allergen-specific IgE
Degranulation

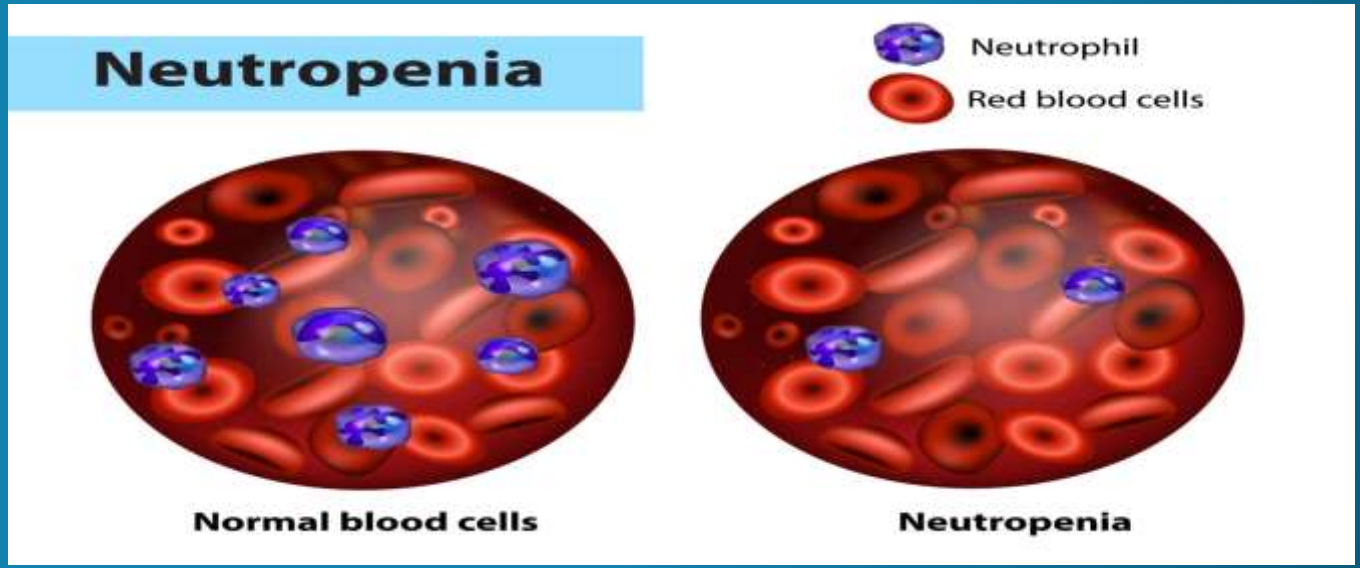
## TYPE 2 HYPERSENSITIVITY:

It is also called as cytotoxic mediated reaction.

### How?

- Ig G or Ig M antibodies bind to antigens on the surface of the cells.
- The antibodies bound cells are marked for destruction.
- They bind to Fc receptor of phagocytes. or
- Destroy the cells by complement system/ NK cells.
- Most Autoimmune diseases are type 2 hypersensitivity.

**Diseases:** Immune neutropenia



# TYPE 3 HYPERSENSITIVITY:

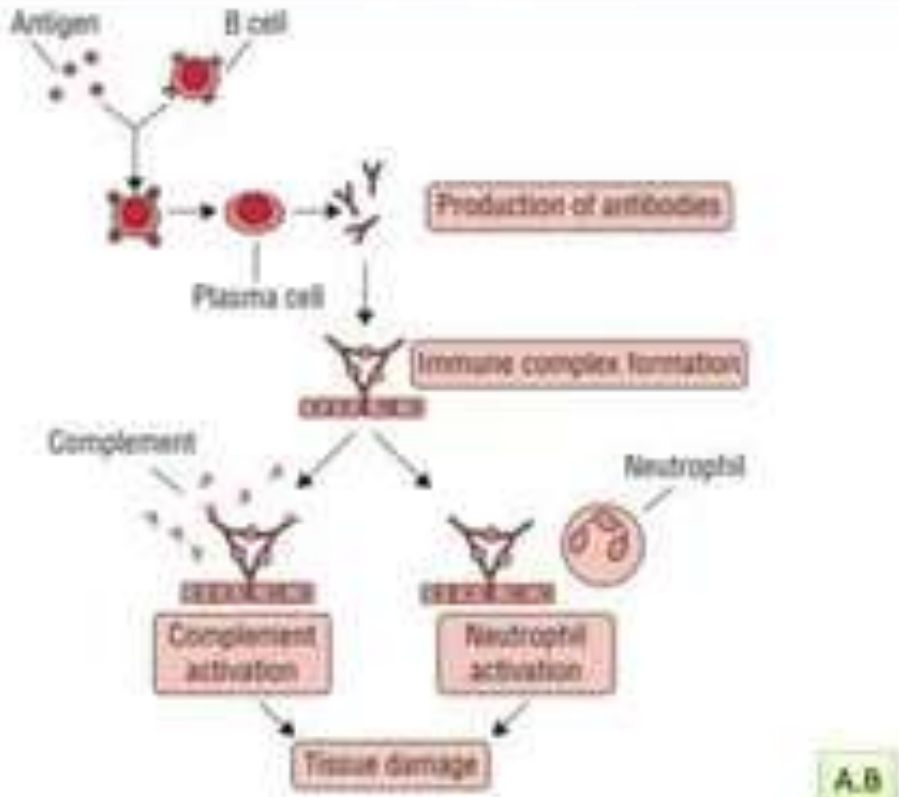
It is also called as immune complex mediated reaction.

**How?**

- Ig G/ Ig M binds to free floating antigens.
- Antibody- antigen complex is formed (globules)
- The globules are deposited on various tissues.
- The complement system is activated and inflammation occurs.
- Cause thrombosis and leading to necrosis of organs.

**Disease:** Arthus reaction: localized reaction, antigen<antibodies, Arthritis in joints, nephritis in kidney.

# Mechanism of Type III (Immune Complex) Hypersensitivity




A.B

# TYPE 4 HYPERSENSITIVITY:

It is called as delayed T cell mediated reaction.

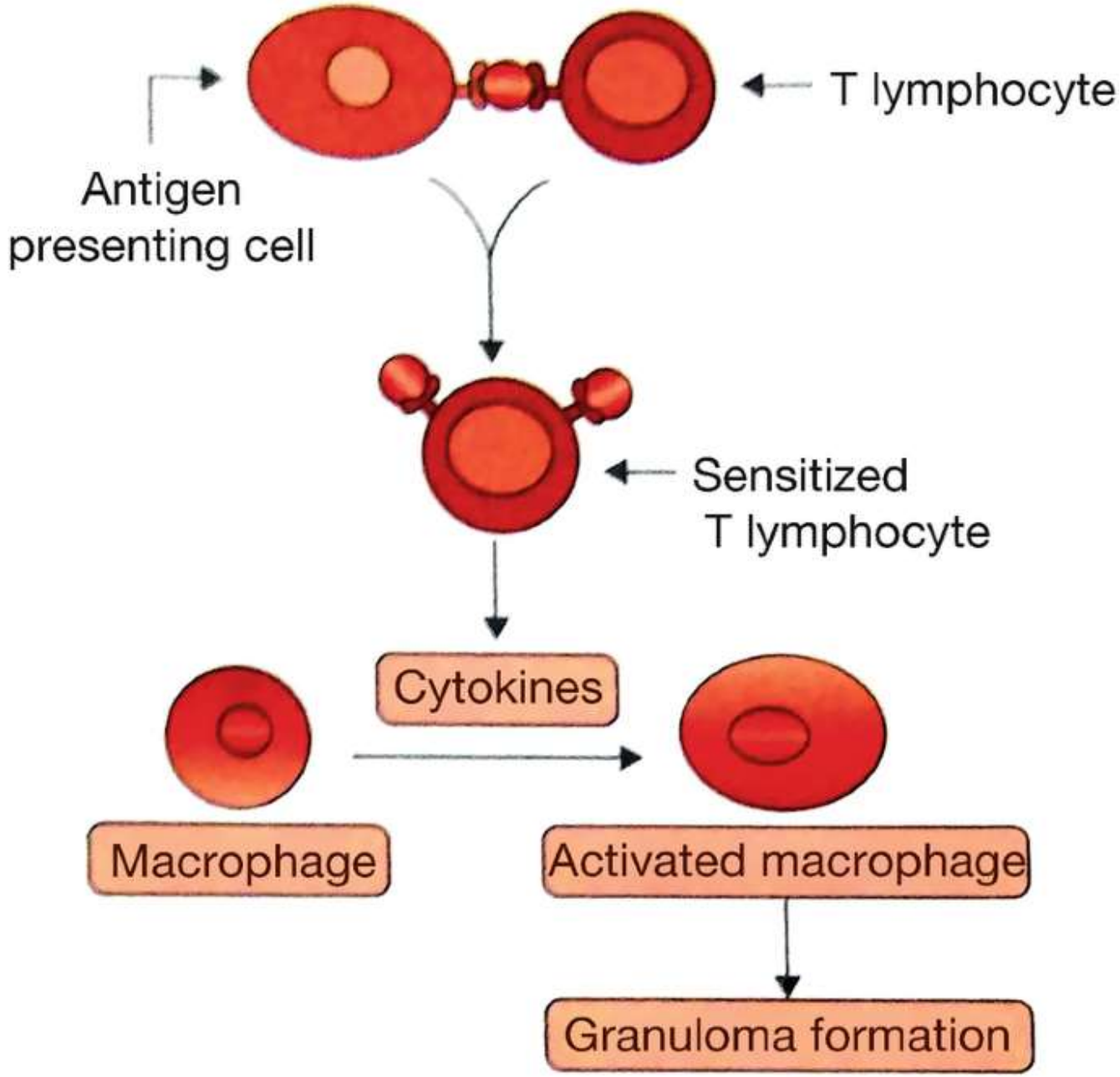
No antibodies required.

This reaction takes delayed time( 48 to 72 hours).

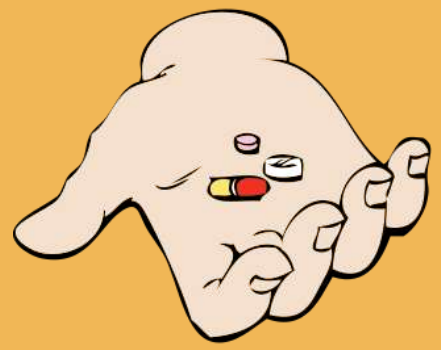
**How?**

- Initially APCs presents antigens( like haptens) to T cells.
- T cells are sensitized for the antigens.
- When the antigen re- enters, T cell activated and release cytokines.
- Particularly, interferon- gamma and tumor necrosis factor- alpha.
- These cytokines activate macrophages.
- Macrophage attack the antigen and release more inflammatory mediators.
- Causing inflammation, tissue damage and formation of granulomas.

**Disease**: Contact dermatitis- reactions of cosmetics and metals in jewels especially nickel.


T lymphocyte
Antigen
presenting cell
Sensitized
T lymphocyte
Cytokines
Macrophage
Activated macrophage
Granuloma formation

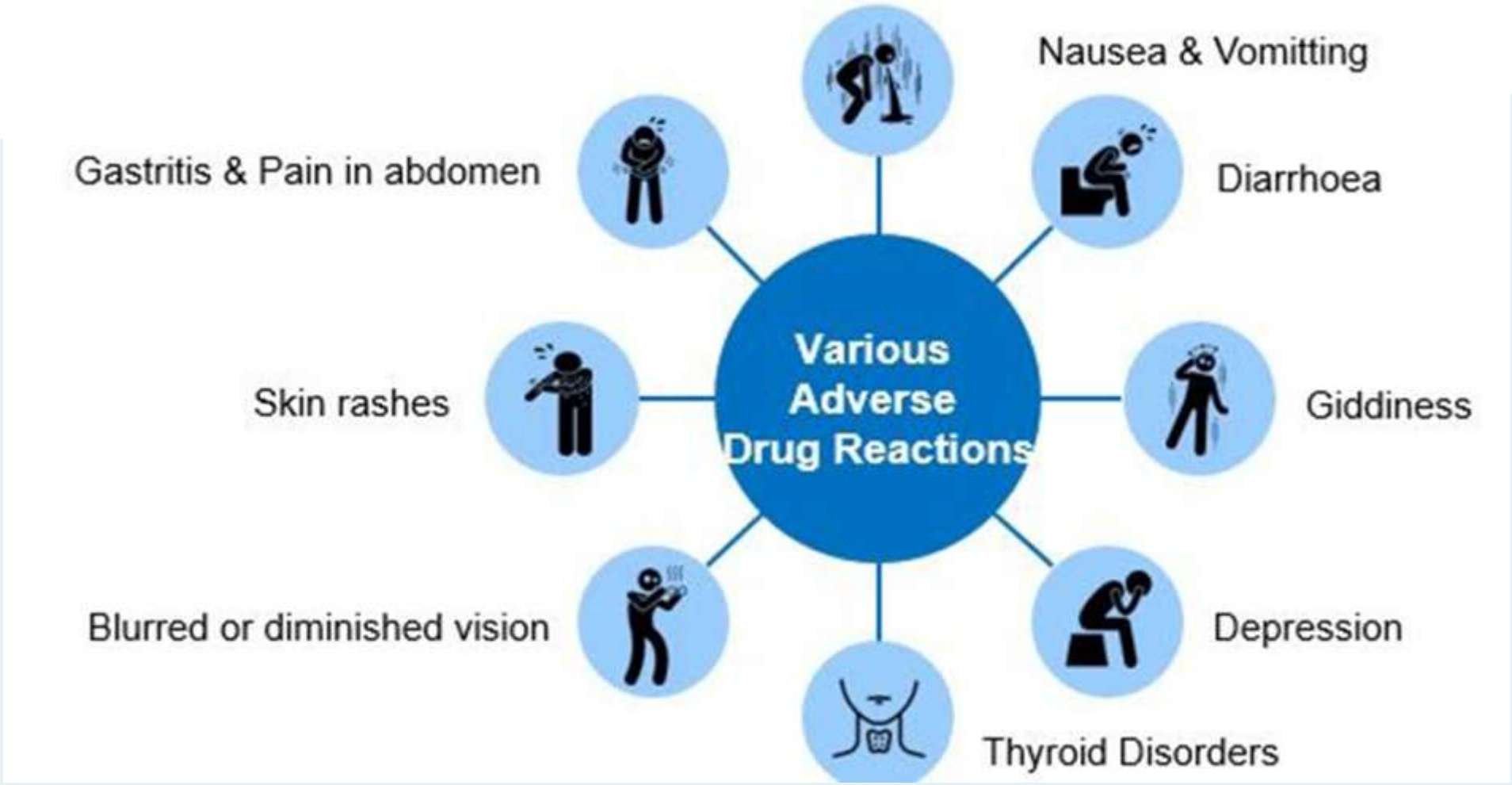
# Adverse Drug Reactions



By,
Vetri selvan P

# DEFINITION

- Any undesirable or unintended consequence of drug administration.
- Any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, for treatment, prophylaxis, diagnosis of disease.
- Adverse effects are more common with multiple drug therapy, after prolonged medication or even after stoppage of the drug and in the elderly patients.
- An incidence of 10-25% has been documented.


Various Adverse Drug Reactions
Nausea & Vomitting
Diarrhoea
Giddiness
Depression
Thyroid Disorders
Blurred or diminished vision
Skin rashes
Gastritis & Pain in abdomen

# Reason for adverse drug reaction

Dispensing and medication error

Failure to set therapeutic endpoint

Bioavailability differences

Patients factors

# Classification

**Predictable (Type A or Augmented) reactions**

- Reactions which can be predicted from the known pharmacology of the drug
- Dose dependent
- Can be alleviated by a dose reduction

**E.g.**

- Anticoagulants → Bleeding
- Beta blockers → Bradycardia
- Nitrates → Headache
- Prazosin → Postural hypotension.

# Classification

**Unpredictable (Type B or Bizarre) reactions**

- Cannot be predicted from the pharmacology of the drug
- Not dose dependent
- Host dependent factors important in predisposition

**E.g.**

- Penicillin → Anaphylaxis
- Anticonvulsant → Hypersensitivity

PENICILLIN

# Classification

**Chemical (Type C or Chronic) reactions**

- Biological characteristics can be predicted from the chemical structure of the drug/metabolite

**E.g.**

- Paracetamol → Hepatotoxicity

# Classification

**Delayed (Type D) reactions**

- Occur after many years of treatment.
- Can be due to accumulation.

**E.g.**

- Chemotherapy → Secondary tumours
- Phenytoin during pregnancy → Teratogenic effects
- Antipsychotics → Tardive dyskinesia
- Analgesics → Nephropathy

# Classification

**End of treatment (Type E) reactions**

- Occur on withdrawal especially when drug is stopped abruptly

**E.g.**

- Phenytoin withdrawal → Seizures
- Steroid withdrawal → Adrenocortical insufficiency

| Type of reaction | Mechanism/Example |
|---|---|
| Type A (Augmented) | Predicted from the known pharmacology of the drug. These reactions are dose-dependent: examples are bleeding with anticoagulants |
| Type B (Bizarre) | Reactions are not predicted from the known pharmacology of the drug. They appear (but actually are not) relatively dose-independent, as very small doses might already elicit symptoms. They include immune-mediated side-effects like maculopapular exanthema, but also other hypersensitivity reactions, like aspirin-induced asthma |
| Type C (Chemical/Chronic) | Which are related to the chemical structure and its metabolism, e.g. paracetamol hepatotoxicity. |
| Type D (Delayed) | Which appear after many years of treatment, e.g. bladder carcinoma after treatment with cyclophosphamide |
| Type E (End of treatment) | Occur after drug withdrawal, e.g. seizures after stopping phenytoin |

# Excessive pharmacological effects (Toxic effects)

- Due to overdosage or prolonged use
- Overdosage may be absolute (accidental, homicidal, suicidal) or relative (i.e. Usual dose in presence of renal failure, age range, lower albumin level etc.,)
- **Examples**

  -Coma by barbiturates

  -Complete A-V block by digoxin

  -Bleeding due to heparin

  -Morphine (analgesic) causes respiratory failure in overdosage

  -Phenytoin (anticonvulsant) cause memory impairment after prolong used

# Classification of ADRs.... Depending on Severity

- **Minor ADRs**: No therapy, antidote or prolongation of hospitalization is required.
- **Moderate ADRs:** Requires change in drug therapy, specific treatment or prolongs hospital stay by at least 1 day.
- **Severe ADRs:** Potentially life threatening, causes permanent damage or requires intensive medical treatment.
- **Lethal:** Directly or indirectly contributes to death of the patient.

# Secondary pharmacological effects (Side effects)

- Unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses
- Can be predicted from the pharmacological profile of a drug
- Reduction is dose, usually ameliorates the symptoms
- Examples- postural hypotension caused by prazosin; promethazine produces sedation

# Rebound effect on discontinuation

- Chronic use of certain drugs produces drug dependent and addiction
- Drugs producing dependence are-opioids, barbiturates and other depressants including alcohol and benzodiazaphines
- Amphetamines, cocaine, cannabis are drugs which produce addiction

# DRUG ALLERGY

- Immunologically mediated reaction producing stereotype symptoms, unrelated to the pharmacodynamic profile of the drug
- Generally occur even with much smaller doses
- Also called Drug hypersensitivity
- Types:

Type I: Immediate, anaphylactic (IgE)

E. g: Penicillin → Anaphylaxis

Type II: Cytotoxic antibody (IgG, IgM)

E. g: Methyldopa → hemolytic anemia

Type III: Serum sickness (IgG, IgM)

Antigen-antibody complex

E. g: Procainamide-induced lupus

Type IV: Delayed hypersensitivity (T cell)

E. g: Contact dermatitis

Humoral immunity

Cell mediated immunity

**What is the synergistic effect of drugs?**

The synergistic effect of drugs is when two or more drugs are combined, their overall effect is greater than the sum of their individual effects. In most cases, this means that the combination of the drugs yields greater efficacy (the capacity of a drug to obtain its desired effect) in treating the intended illness or disease than what each drug can do if not in combination.

Potentiation or synergism occurs when a mixture of two or more drugs produces a greater response than expected (i.e., greater than the sum of their individual effects;

What is drug tolerance and tachyphylaxis?

The term tachyphylaxis is used to describe desensitization that occurs very rapidly, sometimes with the initial dose. The term tolerance is conventionally used to describe a more gradual loss of response to a drug that occurs over days or weeks.

# Acknowledgement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- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.