DRUG

Drug definition:

Drug; Natural or synthetic substance which (when taken into a living body) affects its functioning or structure, and is used in the diagnosis, mitigation, treatment, or prevention of a disease or relief of discomfort.

The most important features expected from drugs are **selectivity** and **originality**.

An ideal drug, should be effective only in biological events related with target organs and tissues, should not affect the other biological processes or the body's constituents. This is called ***"Safe drug application"***.

But there are few drugs suitable for this ideal situation. Lots of drugs, can not show the expected effect, beside of it they can exert various different and severe effects.

Toxic effect (toxicity)

Even in ancient times, human beings comprehended the reality that the drugs they used for remedy can have some unexpected toxic effects in the same time.

For example, in Mesopotamia's famous **THE CODE OF HAMMURABI** (B.C. 6200) there are several punishmnets for the doctors who gave harm to their patients.

The drugs used above the therapeutic doses, unexpected effects can ocur, and they can cause poisonings.

In sometimes, because of the individual differences or the sensitivities toxic effects can ocur even in therapeutic doses of the drugs.

Side effects: The accustomed expression of the unexpected effects of the drugs is **side** effects. It is defined as; the unwanted effects that ocur during the therapy even in therapeutic doses.

CAN BE PREDICTED BUT UNDESIRABLE

Adverse Drug Reactions(ADR):

It can be defined as the enhanced/decreased unexpected pharmacological or toxicological effects of the drug. Also the unhealthy and undesirable responses developed in humans against the drug in prophylactic, diagnostic and therapeutic doses.

UNPREDICTABLE AND UNDESIRABLE

ADR definition of WHO: The unhealthy and undesirable responses developed in humans against the drug in prophylactic, diagnostic and therapeutic doses.
Therapeutic faults, voluntary or accidentally poisonings and drug abuse situations are not included to this definition.

Severe Adverse Drug Effect or Event

- Can cause deaths
- Can threaten the life of the patient
- Cause to be hospitalized or if the patient is hospitalized enhancing the stay duration in hospital
- Can cause a persistent or distinct disability
- Can lead to congenital abnormalities.

Therapeutic index is very impotant in drug use. It is the majör quantitative index determining the safety or harmlessness grade.

I-REACTIONS RELATED WITH DOSE

a- EXCESSIVE THERAPEUTIC EFFECTS

It is the excessive form of normal therapeutic effect.
In this situation, toxic effect gets severe due to dose or the hypersensitivity of patient.

EX. 1: Sedative and tranquilizing drugs:
- in low doses simmering and sedation;
- in moderae doses sloth and sleeping mode;
- in high doses coma following respiratory depression

EX 2: Oral anticoagulants:
- in low doses, extending of the prothrombin duration can not be adequate.
- in high doses, bleeding risk

EX 3: Insulin and oral hypoglycaemic agents:

- in high doses excessive hypoglycemia can develop

b- SIDE EFFECTS

Most of the drugs' effects are not spesific. They can change the predicted physiological function that should be fixed or the other physiological functions by affecting the different receptors in the body. So that several "**side effects**" can be occur with the desired therapeutic effect.

Pharmacological side effects

They are originated from the normal pharmacological effects of the drug. This effect can be the extension of the majör therapeutic effect.

EX: Desert mouth effect and vision blurring with propantheline used in peptic ulcer therapy

It can arise from the differnt pharmacological effect of the drug apart from the drug's aiming effect.

EX: Nausea with digoxin

EX: Desert mouth effect and vision blurring with chlorpromazine or tricyclic antidepressants

Therapeutic effect and side effects can occur after the interaction of the drugs with same receptors.

EX: Atropine inhibits the muscarinic receptors.

• Can cause constipation by loosening the smooth muscle in stomach-intestine duct. At the same time it can cause urine retention in urinary bladder.

In some situations, there can be no relation between therapeutic and toxic effects of a drug. This can be due to the drug's effect on the different receptors or different mechanisms.

Conversely, in some cases a side effect can be used as a therapeutic effect.

EX: If isoprenaline is used as a bronchodilator tachicardia, cardiac stimulation and arrhythmia can occur as unwanted effects. On the other side this effect can be used in treatment of heart block as a therapeutic effect.

The side effect of which of the functional effects of a drug is related with the place of use.

EX: The desert mouth effect of an anticholinergic drug is not accepted as a side effect in dentistry or premedication in anesthesiology, while it is accepted as a side effect in peptic ulcer treatment.

Toxic side effects

The most of the drugs shows toxic effects when they are used in excessive doses. The drugs with wide therapeutic index rarely show toxicity in normal doses while the toxicity risk of the drugs with narrow is high.

EX: Aminoglycoside antibiotics including streptomycine, gentamicine can cause damage in internal ear and deafness, even when therapeutic doses are exceeded in small amounts.

EX: Cytotoxic drugs used in cancer treatment, can lead to bone marrow depression and damage in divided all cells.
The toxic side effects of the drugs can be divided into 3 groups:

a- Functional Toxic Effects
When the drug is used to fix the damaged physiological function of the patient, this effect can be occurred due to the effect on this function realted with excessive amounts or individual hypersensitivity.

This effect is reversible.

EX: Atropine and similar drugs can cause desert mouth; midriasis, constipation and tachycardia. When they are not used these side effects can not be seen.

EX: Sedation occurred during the treatment with antihistaminics is a side effect. The workers working in jobs with high attention should be careful in using this drug.

EX: The drugs belonging to quinidine group, can cause the cardiac arrythmia.

b- Biochemical Toxic Effects
Some of the drugs can exert toxic effects by changing the biochemical parameters. It is the premise of mild structural toxic effect generally.

EX: Some drugs can change the electrolyte levels (Na^+, K^+). They can cause hyperglycemia and hyperuricemia.

EX: Aminoglycoside antibiotics can accumulate in kidney cortex and then they damage the lysosomes of the proximal tubulus cells and they trigger the lysosomal enzymes in urine.

This effect is reversible.

c- Structural Toxic Effects
The toxic effects that cause morphological damages on tissues and cells.

This effect can be seen only onder electron microscope.

It is an irreversible effect.
Structural toxic effect can be categorized into 3 groups:

I. Irreversible defects related to chemical factor:
Alkylating antineoplastic drugs, mustard gases used as war gases and heavy metals inhibiting the sulphydryl groups of proteins Show this type of effect.

Furthermore, drugs can cause structural changes in several organs and tissues such as bone marrow, blood cells, collagen tissues and thyroid gland.

EX: Chloroform anesthesia		fatty liver
	Aminopyrine	anemia
	Phenothiazines	cataract

II. Metabolites:
In formation of structural toxic effects, not only the drug itself, the reactive metabolites of it can be the factors.

Reaktive metabolites, can bind with macromoşecules in cells with covalent bonds causing some persistent changes. This can lead to functional, biochemical and structural changes in cells.

The organs in which the structural toxic effects generally occur are **liver** and **kidneys**.
In liver cells, the reactive metabolites can detoxified by conjugation with reduced glutation (GSH) (Glutation conjugation). GSH-transferase enzyme catalize this reaction.

In acute poisonings with hepatotoxic drugs, the excessive amounts of reactive metabolites arised can bring the cells and tissues into defenseless position by depleting the glutation sources of the liver cells. For treatment, the drugs enhancing cysteine and glutation formation are used in order to increase the durability of the cells against the reactive metabolites.

III. Indirect structural defects due to the joining of the chemical into the reaction forming the free radicals in cells:
This type of xenobiotics themselves or their metabolites can not Show direct toxic effects but the free radicals (ROS) occuring in the reactions activated by these are responsible from the toxicity.

Free radicals arise from the molecular oxygen (O_2):

- ☹ Superoxide anion ($O_2^{\bullet -}$)
- ☹ Hydroxyl radical ($OH^{\bullet}$) ➔ ***The most reactive, therefore most toxic.***
- ☹ Hydrogen peroxide (H_2O_2)
- ☹ Single oxygen

Reactive oxygen species (ROS) arise from normal physiological processes. In pathological situations they form in excessive amounts leading to "**oxidative stress**" in cells.

This imbalance the oxidant-antioxidant balance on behalf of oxidant.

These radicals cause irreversible changes by attacking to the macromolecules of the cells and cell membrane mainly.

Main defects:

#1. The peroxidation of cytoplasmic and intracell organelle membrane lipids

#2. The increase of membrane permeability

#3. The cross binding and oxidation of enzymes and cytostructural proteins' sulphydryl groups

#4. Inactivation of enzymes

#5. The activation of proteolytic enzymes and inhibition of antiptoteases follwing the inactivation of enzyme

#6. The break down of the DNA structure and the development of mutation

#7. Depolymerization of mucopolysaccharides

#8. The break down of ion transportation in cells

#9. The break down of transmembrane potential

There are severel enzymes defending the cells against free radicals:

- ✓ superoxide dismutase
- ✓ catalase
- ✓ glutathione peroxidase, glutathione reductase.

Also,

- Reduced glutathione
- Vitamin E
- Ascorbic acid
- α-lipoic acid
- Vitamin K

These antioxidant factors can also catch these radicals and inactivate them.

c- SECONDARY EFFECTS

These are the indirect results of the drug use.

EX: Wide broaded antibiotics can cause superinfection by suppressing the bacterial flora ending in formation of resistant microorganisms.

EX: Corticosteroids and immunosupressants can give damage to some defence mechanisms of the body leading up to several infections.

II-THE ADVERSE REACTINS NOT RELATED WITH DOSE

Some undesirable effects of xenobiotics developing due to the sensitivity of the biological system can be seen. The effects in which the immune system plays a majör role are called **unexpected, abnormal toxic effects**.

a- Hypersensitivity Reactions

The unwanted reactions formed due to the individual factors (patological situation, genetic differences, hypersensitivity etc.), even in therapeutic doses.

EX: Patients with brochial asthma are very sensitive to the bronchoconstructor effects of histamine, histamine inducers and cholinergic drugs. When they use these drugs asthma crisis can occur.

EX: Patients with glaucoma, can not use atropine amd similar drugs beacuse of their glaucoma crises risk. These drugs can not show any effects in normal individuals.

b- Allergy
Allergy is an immunological process which is different from the chemical or drug's pharmacological and toxic effect.

The main principle for the formation of allergy is that the drug should gain antigenic feature.

The main differences between allergy and other reactions:

Allergic reaction can not occur in the first exposure of the person against the xenobiotic: A time must be passed regarding to the formation of antibodies and sensitive lymphocytes. Allergic reactions arise in sensitive persons. In the second exposure the allergic reactions occur.

Allergic reactions are not related with dose The low dose of a xenobiotic can cause severe reactions in sensitive persons.

Summary of allergic reactions;

① **Chemical + body proteins** **ANTIGEN**
(Drug)
HAPTEN-half antigen

Antigen **Reticuloendothelial system** **ANTIBODY**

ANTIGEN + ANTIBODY

ALLERGIC reactions.
Due to scientific studies, in order to be antigen, hapten should bind to proteins with covalent bonds by some groups:

- Diazonium (- N^+ N)
- Thiol (-SH)
- Sulphonic acid(-SO_3H)
- Aldehyde (-CHO)
- Chinon groups
- Active halogen groups

Some chemicals/drugs can not make complexes with proteins but their metabolites are reactive.

EX: Penicillin

Penicillin is not so reactive to bind with protein but its metabolite pencilloic acid is a reactive substance and Show hapten effect. Because of this, penicillin is **prohapten**.

Penicillin ↻ **Penicilloic acid** + protein ↻**Peniciloilprotein**
(**prohapten**) (**hapten**) (**antijen**)

Cross Allergy:

If allergy can be seen against one of the substance any other substance which has the same chemical group allergy can also be seen. This is called cross allergy.

EX: If someone is allergic to sulphonamide he/she is also allergic to sulphonylurea, asetazolamide, furosemide.

a) **ANAPHYLACTIC REACTIONS:**

These reactions are the fastest reactions. They show general or local effects. Clinical signs can be seen as urticheria, Asthma in respiratory system.

b) **CYTOTOXIC REACTIONS:**

Drug or its metabolite can combine to certain component of blood cells or vessel endothelium making them as antig. The antibodies against them are found in blood and body fluids. Some of these antibodies can bind to antigen molecules found in surface of cells. At last, cells are cytolized and they are demolished.

c)**ARTHUS REACTION:**

Drug sensitive lymphocytes are responsible for this reactions.

←

These cells are located on tissues.

When antigen enters the body, sensitive lymphocytes are activated and by the lymphokines they secreted macrophages and monocytes accumulate in the tissue. So that, local inflammation signs arise.

These reactions are seen on the drug application site.

c- Photosensitivity

Many xenobiotics can cause dermal reactions when they expose to light.

PHOTOALLERGY: Sunlight (especially UV light) plays a direct role in these reactions.
In photoallergy, from the topical drug with the help of sunlight a hapten metabolite occur. This metabolite forms antigen with dermal protein. Antigen-antibody complex occurs. With the help of sunlight exposure dermal damage arise. It is not related with the dose.

EX: Tiazid, aminobenzoic acid, griseofulvin, prometazine, chlorpropamid

PHOTOTOXIC REACTIONS:

Many chemicals, can form compounds that can come up to the high energy level by absorbing light energy. When giving this energy back a radiation energy come off. This radiation energy can cause cell damage via photochemical way.

In phototoxic reactions, the severity of the lesion is related with the drug dose and the amount of exposed light.

III- LONG TERM EFFECTS

The effects seen long time after drug use. Early diagnosis is important for protection beacuse when some of them is diagnosed they become irreversible (carcinogenic effects, blindness, chronic kidney failure etc). Some of them's mechanisms are not known.

They can be divided into 2 groups:

a- Accumulation effects related with high dose
b- Delayed effects

a- ACCUMULATED EFFECTS RELATED WITH HIGH DOSE

Some adverse drug reactions can only be seen after long tern treatment. These effects are dose dependent. Some of them related with the accumulation of drug in the tissues.

EX: An antimalarial drug called **chloroquine**, is used in rheumatoid arthritis since 1965. It is a long term used drug and the elimination from the body is too slow. Generally, it can accumulate in retinal pigment cells and corna ephitelium. Accumulation in corneacan blur the vision; but when you stop using the drug, the effect is removed. Retinopathy can cause irreversibl loss of sight.

EX: Phenothiazins accumulate in retinal pigment cells causing retinopathy.

EX: Phenacetin, aspirine or aminopyrin analgesic combination abuse, cause chronic interstisiel nephrit and chronic kidney failure. Mechanism is not known but it is thought that it is related with nephropathic effect of phenacetin.

EX: Long term treatment with corticosteroids can cause osteoporosis, muscle loss, dermal atrophy and peptic ulcer.

EX: Long term used oral contraseptives can cause infertility.

b- DELAYED EFFECTS

Effects seen after months or years due to the use of the drug. They can be seen rarely.

EX: The hypothyroidism seen after ^{131}**I** (radioactive iodine) thyrotoxicozis treatment

EX: Nephropathic analgesics induced kidney pelvis cancers.
The long term use of cytotoxic drugs cause leucemia.
EX: Melphalan used in myeloma treatment can cause acute leucemia

ÖRNEK: Chloramphenicol induced acute leucemia.
The progression of some tumors are related with hormones.

EX: Pregnants who use diethylstilbesterol in early pregnancy, vaginal adenosarcomes can be seen in their daughter. **(Transplasental karsinojenezis).**

EX: The long term use of oral contraseptives can cause breast and cervix cancers.

EX: Alkylating antineoplastik drugs are used in cancer despite its risks. But some of them can be used non carcinogenic stiuations. They can cause lymphomas.

IV-TERATOGENIC EFFECTS

Some drugs used by pregnant women can cause deformations in fetus; as a result babies borns with malformations.

- Babies born with deformations is only one sight of the drug's toxicity on fetus.
- Sometimes, embryo can be destroyed by drug' strong toxic effect..
- Sometimes teratogen drug can cause a damage which gives harm to fetus.

Human embryo is very sensitive to teratogenic effect in **organogenesis period**.

The drugs that are proved to be teratogenic:

- **Folik asit antagonists (antineoplastic drugs)**
- **Androgenic hormones**
- In the early1960's in especially Germany and England thousands of babies wer born with malformations due to Thalidomide use. Thalidomide case is called as, "**Thalidomide Disaster**".

Potentially teratogenic drugs in human:

- **Some anticonvulsants**
- **Dexamphetamine**
- **Ethionamid**' dir.
- **Alcohol**
- **Smoking** can be also added to this list.
- Salycilates
- Antiacids
- Sulphonamides
- Nicotinamid
- Psychotropic drugs
- Chloroquine
- Oral hypoglycaemic agents are also suspected for their teratogenic risk

Xenobiotics are divided into A, B, C, D ve X groups.
The new drugs' teratogenic potentials must be monitored during marketing.

Pregnant women should avoid themselves from using drugs so that they can reduce the teratogenic risk to minimum. If she must use a drug the drug's benefit-harm scale should be evaluated by doctor.