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Overview Of Drug Toxicity In Humans

Introduction

- **Humans take a number of drugs for health reasons, it is practically guaranteed that all useful drugs will produce unwanted effects, but some can produce positively dangerous effects.**

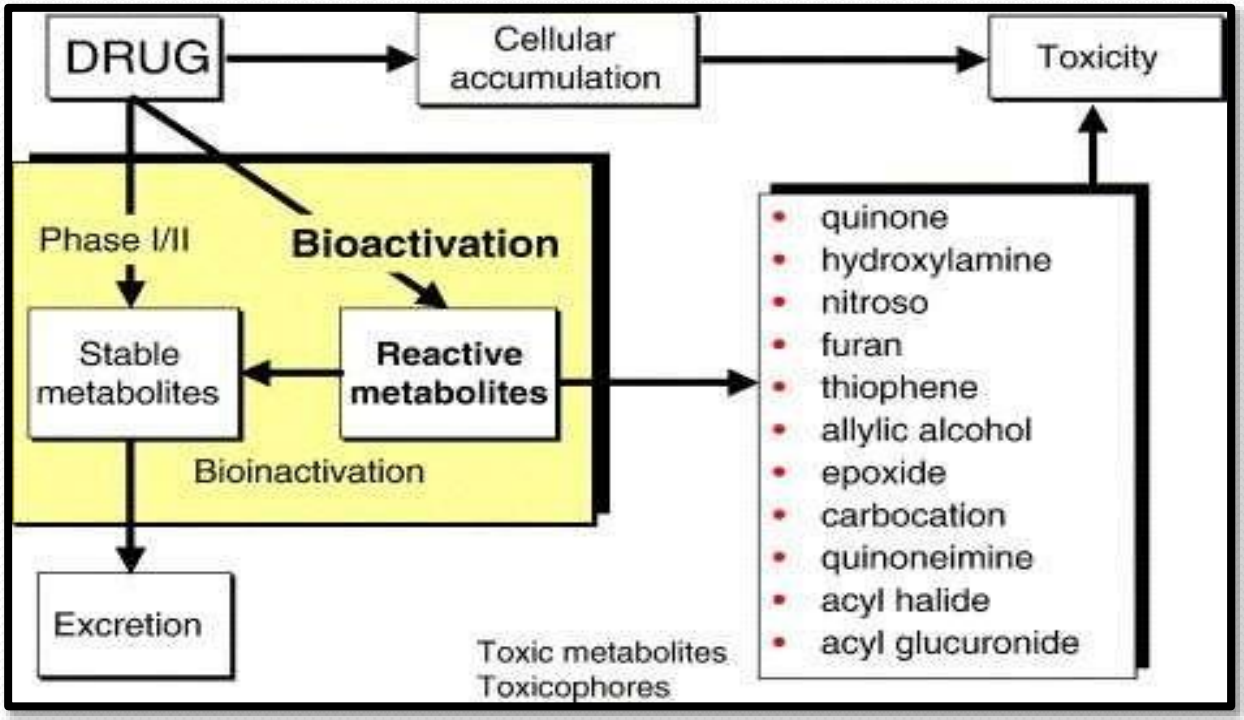
- **Toxicity refers to these sometimes deadly effects: Though all drugs have adverse effects at normal doses, it is only the dangerous ones which are referred to as toxic.**

- **These are the result of excessive pharmacological action of the drug due to overdosing or prolonged use.**

- **After a lot a R&D potential drug candidates fail because of toxicity.**

➢**Toxicity may result from extension of the therapeutic effect of the drug, e.g. Coma by barbiturates, complete A-V block by digitoxin, bleeding due to heparin, etc.**

➢**The CNS, CVS, kidney, liver, lung, skin and blood forming organs are most commonly involved in drug toxicity.**



- **Thus, drug toxicity, also called adverse drug reaction(ADR) or adverse drug event (ADE), is defined as the "manifestations of the adverse effects of drugs administered therapeutically or in the course of diagnostic techniques. It does not include accidental or intentional poisoning...”**

Explanations

Given By WHO:

- Noxious and unintended response to medicinal product if a medicine is properly prescribed and administered.
- Casual reaction between medicinal product and adverse event cannot be ruled out.
- Medicinal errors are not included in this definition.

Given By MHRA:

- An unwanted or harmful reaction experienced following the administration of drugs.
- Suspected to be related to the drugs.
- The reaction may be a known side effect of the drug or it may be new and previously unrecognised.

History of Drug Toxicity

1937 → **Elixir sulphanilamide** was an improperly prepared sulphanilamide medicine that caused mass poisoning in the United States in 1937. It caused the deaths of more than 100 people.

1957 → **Thalidomide:** West Germany- giving birth to deformed children with shortened limbs and no external ears. Later withdrawn.

1967 → **Clioquinol's** use as an antiprotozoal drug was restricted or discontinued in some countries due to an event in Japan where over 10,000 people developed SMON (subacute myelo-optic neuropathy)

1990 → **Pemoline**, for ADHD (attention deficit hyperactivity disorder), and **troglitazone**, for type-2 diabetes, were both shown to damage the liver.

2013

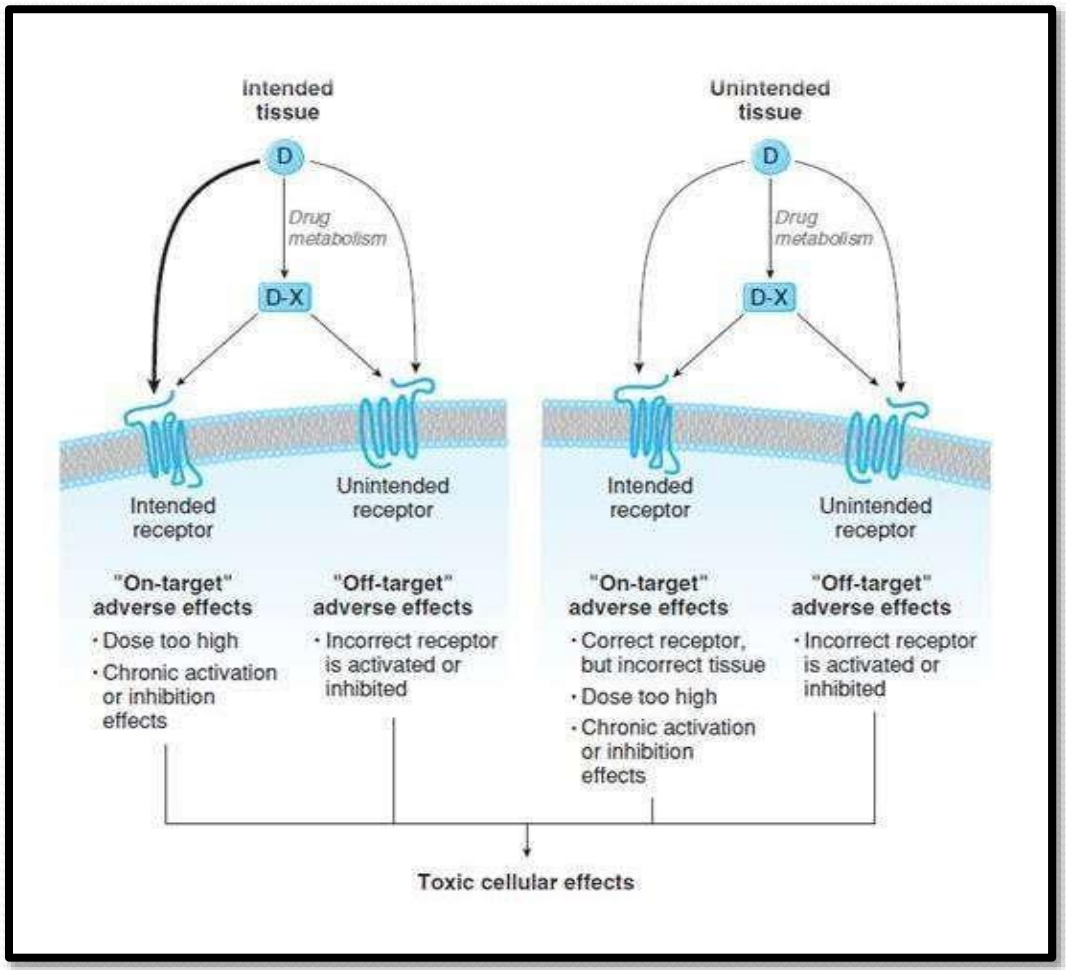
Pioglitazone was withdrawn as it caused cadiotoxicity.

Mechanism of Drug Toxicity

- **Drug will do more harm than good in an individual patient depending on many factors, including the patient's age, genetic makeup and preexisting conditions, the dose of the drug administered, and other drugs the patient may be taking.**
- **On-target adverse effects, which are the result of the drug binding to its intended receptor, but at an inappropriate concentration, with suboptimal kinetics, or in the incorrect tissue**
- **Off-target adverse effects, which are caused by the drug binding to a target or receptor for which it was not intended**

- **Production of harmful immune responses.**

- **Idiosyncratic responses.**



D is intended to modulate the function of a specific receptor (*Intended receptor*) in a particular tissue (*Intended tissue*). On-target adverse effects in the intended tissue could be caused by a supratherapeutic dose of the drug or by chronic activation or inhibition of the intended receptor by Drug D or its metabolite D–X. The same on-target effects could occur in a second tissue (*Unintended tissue*); in addition, the intended receptor could mediate an adverse effect because the drug is acting in a tissue for which it was not designed. Off-target effects occur when the drug and/or its metabolites modulate the function of a target (*Unintended receptor*) for which it was not intended.

Mechanism: On Target Effects

- **On-target adverse effects, which are the result of the drug binding to its intended receptor, but at an inappropriate concentration, with suboptimal kinetics, or in the incorrect tissue**
- **An adverse effect may be an exaggeration of the desired pharmacologic action due to alterations in exposure to the drug.**
  - **Deliberate or accidental dosing error.**
  - **Alterations in the pharmacokinetics of the drug.**
  - **By changes in the pharmacodynamics of the drug-receptor interaction that alter the pharmacologic response.**
- **All this causes an increase in the effective concentration of the drug and thus to an increased biological response.**

- **An important class of on-target adverse effects may occur because the drug, or one of its metabolites, interacts with the appropriate receptor but in the incorrect tissue. Many drug targets are expressed in more than one cell type or tissue.**

Example:

- **The antihistamine diphenhydramine hydrochloride is an H1 receptor antagonist used to reduce the unpleasant symptoms of histamine release in allergic conditions.**
- **Diphenhydramine also crosses the blood-brain barrier to antagonize H1 receptors in the central nervous system, leading to somnolence.**
- **This adverse effect led to the design of second-generation H1 receptor antagonists that do not cross the blood-brain barrier, and so do not induce drowsiness.**

- **Sometimes on-target side effects unmask important and previously unknown functions of the biologic target.**

- **Example:**
  - **The administration of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (so-called *statins*), which are used clinically to decrease cholesterol levels.**
  - **A rare adverse effect of statin therapy is muscle toxicity, including rhabdomyolysis and myositis; this side effect is due to the physiologic role of HMG CoA reductase in regulating the post translational modification of several muscle proteins through a lipidation process called *geranyl-geranylation*.**

Mechanism: Off target Effects

- **The drug interacts with unintended targets. Indeed, few drugs are so selective that they interact with only one molecular target.**
- **Example:**
  - **The antihistamine terfenadine, which also inhibits a cardiac potassium channel (hERG).**
  - **The unintended inhibition of the ion channel unfortunately led to fatal cardiac arrhythmias in some patients, and terfenadine was withdrawn from the market for this reason.**
  - **The active metabolite of terfenadine, fexofenadine, was later discovered to inhibits the hERG channel only weakly, and fexofenadine is now marketed as a safer antihistamine.**

Mechanism: Harmful Metabolites

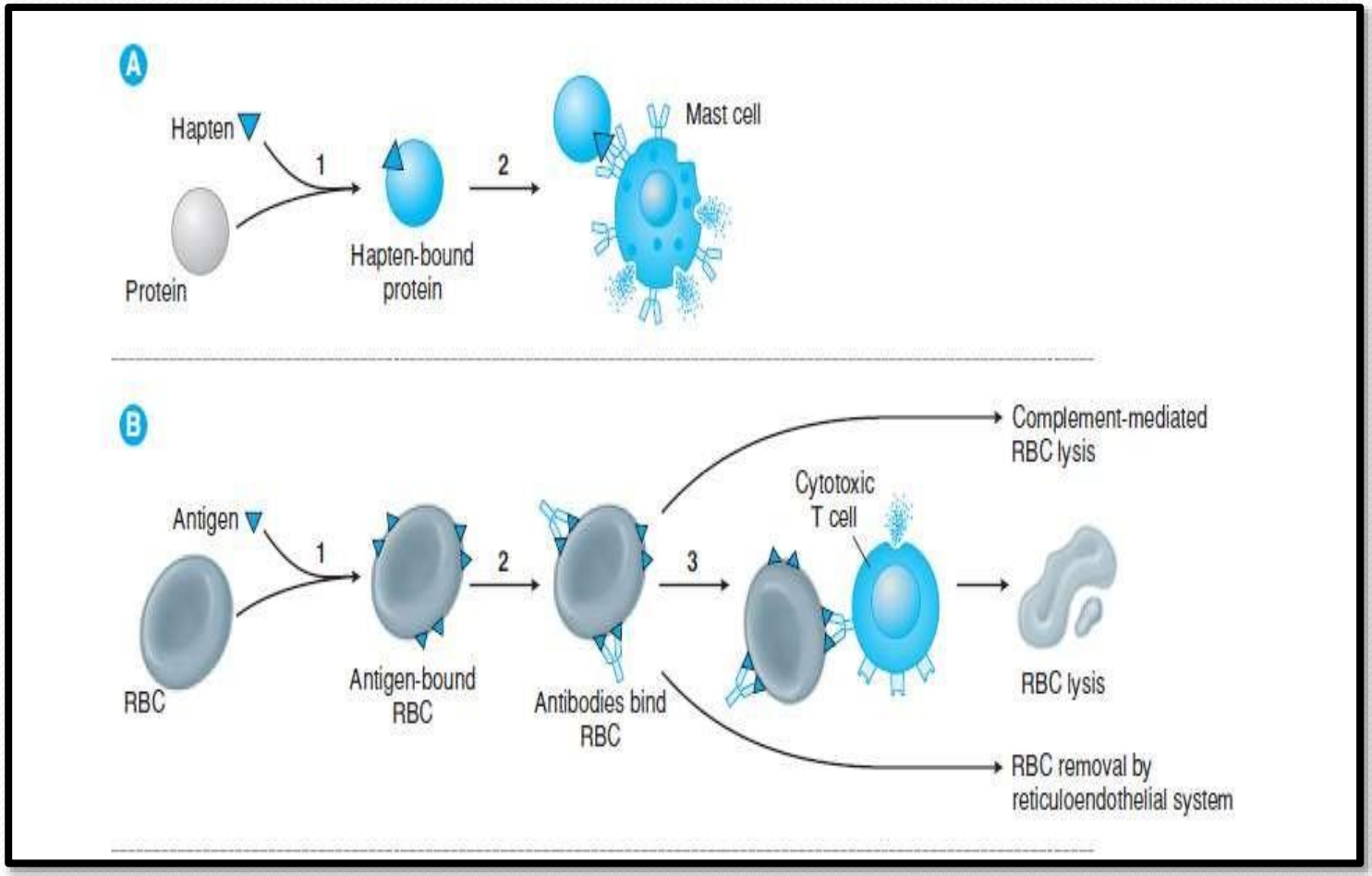
- **Virtually all drug molecules are metabolized by the liver and/or other tissues. Sometimes metabolism produces a pharmacologically active metabolite, a drug metabolite can have an adverse effect. A clinically significant example is that of acetaminophen, a commonly used analgesic and antipyretic.**
- **In therapeutic dose range, acetaminophen is metabolized Predominantly by glucuronidation and sulfation, and these conjugated products account for approximately 95% of the total excreted metabolites. P450 enzymes oxidize a small percentage of acetaminophen to a reactive intermediate, which is *N*-acetyl-benzoquinoneimine, immediately conjugated to glutathione.**

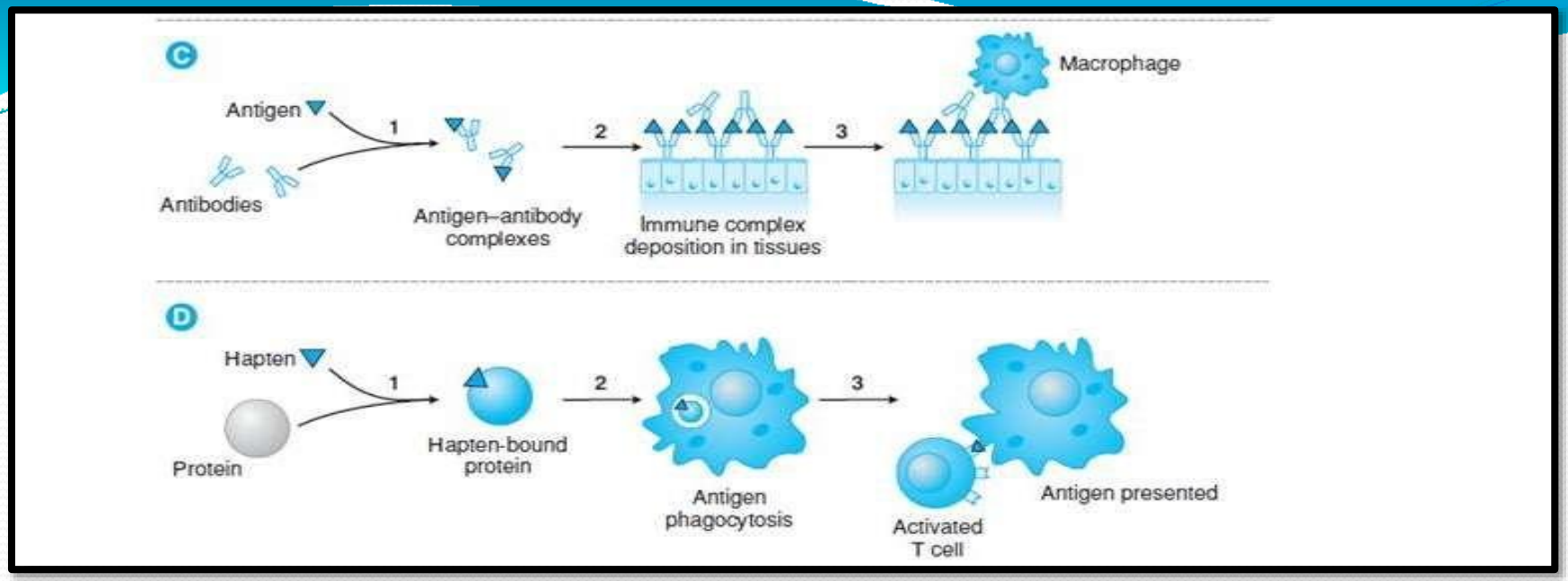
- **However, when the level of acetaminophe exceeds the therapeutic range,glucuronidation and sulfation pathways the**

become saturated and the stores of glutathione in the liver become depleted. This results in excessive accumulation of *N*-acetyl- benzoquinoneimine, an electrophile that reacts with nucleophilic groups on proteins to produce covalent protein derivatives.

- **An antidote for acetaminophen overdose is *N*-acetylcysteine, which reacts directly with (and thereby detoxifies) the iminoquinone. Administered within 8 to 16 hours of an overdose of acetaminophen, *N*-acetylcysteine can be lifesaving.**

Mechanism: Harmful Immune Responses





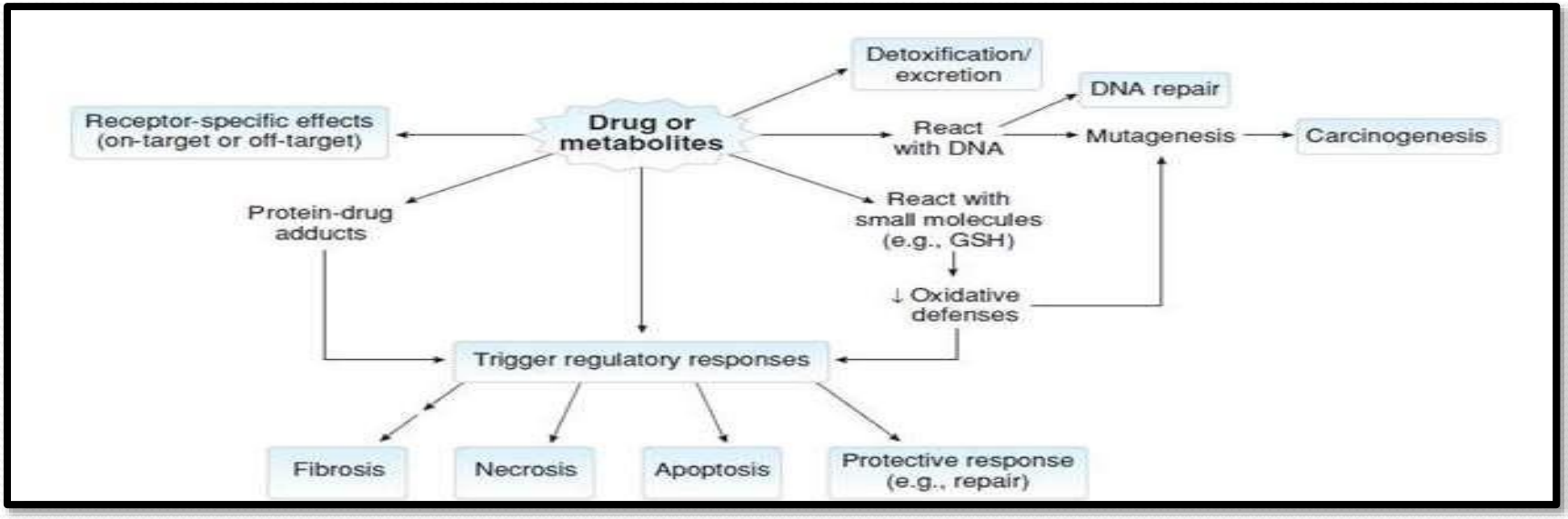
Mechanism of hypersensitivity reactions.A.Type I hypersensitivity reactions occur when hapten binds to a protein(1).The antigen crosslinks IgE antibodies on the surface of mast cell degranlation (2).Mast cells release histamine and other inflammatory mediators.B. Type II hypersentivity reactions occur when an antigen binds to the surface of a circulating blood cell, usually a red blood cell (RBC) (1).Antibodies to the antigen then bind surface of the RBC (2), attracting cytotoxic T cells (3), which release mediators that lyse the RBC binding of Ab to EBCs can also directly stimulate complement –mediated RBC lysis & RBC removal by the reticuloendothelial system. C. Type III hypersensitivity reactions occur when Ab bind to a soluble toxin, acting as an antigen (1).The antigen-antibody complexes are then deposited in the tissues (2), attracting macrophages (3) and starting a complement-mediated reaction sequence (not shown).D. Type IV hypersensitivity reactions occur when a hapten binds to a protein (1) and the hapten-bound protein is phagocytosed by a Langerhans cell (2).The Langerhans cell migrates to a regional lymph node ,where it presents the antigen to a T cell ,thereby activating T cell(3)

CLASSIFICATION	PRIMARY TRIGGERS	PRIMARY MEDIATORS	EXAMPLES OF SIGNS AND SYMPTOMS	EXAMPLES OF DRUGS
Type I or immediate-type hypersensitivity (humoral)	Antigen-binding IgE on mast cells	Histamine and serotonin	Hives and urticaria, bronchoconstriction, hypotension, and shock	Penicillin
Type II or antibody-dependent cellular cytotoxicity (humoral)	IgG and complement-binding cell-bound antigen	Neutrophils, macrophages, and natural killer cells	Hemolysis	Cefotetan
Type III or immune-complex disease (humoral)	IgG and complement-binding soluble antigen	Neutrophils, macrophages, and natural killer cells; reactive oxygen species and chemokines	Cutaneous vasculitis	Mitomycin C
Type IV or delayed-type hypersensitivity (cell-mediated)	Antigen in association with major histocompatibility complex (MHC) protein on the surface of antigen-presenting cells	Cytotoxic T lymphocytes, macrophages, and cytokines	Macular rashes and organ failure	Sulfamethoxazole

Mechanism: Idiosyncratic Toxicity

- **Idiosyncratic drug reactions are rare adverse effects for which no obvious mechanism is apparent.**
- **These idiosyncratic reactions are often thought to reflect unique individual genetic differences in the response to the drug molecule, possibly through variations in drug metabolism or immune response.**
- **Idiosyncratic reactions are difficult to explain and often difficult to study in animal models, precisely because the genetic variation that may be causing the adverse response is not known.**
- **It is believed that the systematic study of patient variations in response to different drugs (pharmacogenomics) may help to elucidate the mechanisms that underlie idiosyncratic drug reactions.**

Drug Toxicity: Pathology



Mechanism of drug toxicity: **A drug or its metabolites or both interact with specific receptors to mediate ON-TARGET or OFF-TARGET adverse effects .In addition, metabolites can be detoxified & excreted , or can react with a variety of macromolecules including DNA, small antioxidants such as glutathione (GSH), or cellular or plasma proteins. The formation of unpaired DNA adduct is often mutagenic & may lead to cancer. The impairement of oxidative defences can lead to inflammation & cell death. The formation of drug-protein adducts can trigger immune responses that can damage cells & tissues. Regardless of the mechanism of damage, a gradation of acute responses from protective to apoptosis & necrosis can result, depending on the extent of damage & the temporal & dose relationship. Chronic inflammation & repair can lead to tissue fibrosis**

Drug Toxicity: Types

- Cytotoxicity.
- Carcinogenicity.
- Mutagenicity.
- Teratogenicity.

Cytotoxicity

- This is the simplest form of drug toxicity, where the drug or an active metabolite causes serious damage to the cells. Often, the cells of a specific organ are affected, causing a potentially fatal loss of function of the liver or kidney, damage to the eyes or ears, or abnormal clotting of the blood.

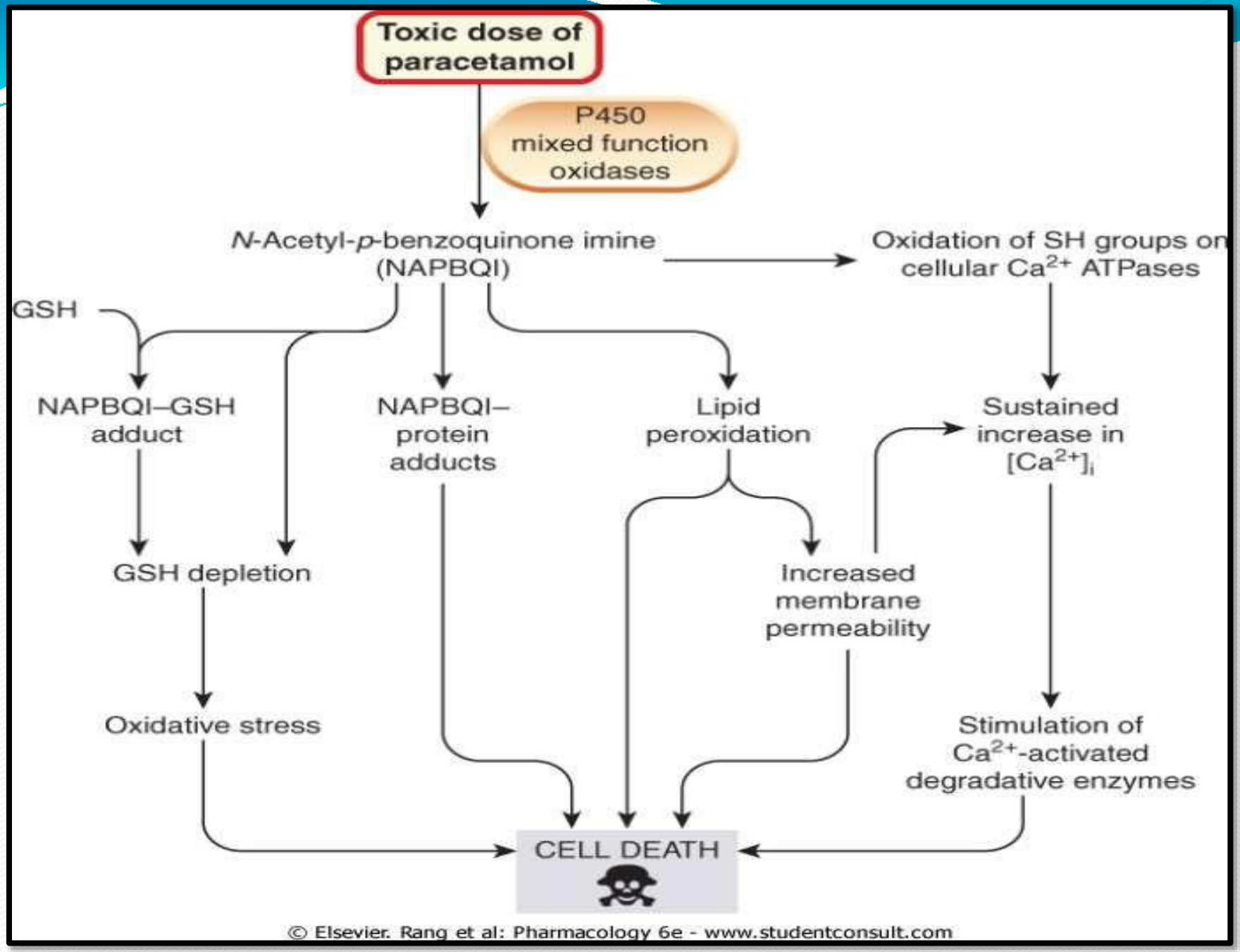
Types of cytotoxicity

Non-covalent interactions

- Lipid peroxidation
- Generation of toxic reactive oxygen species
- Reactions causing depletion of glutathione (GSH)
- Modification of sulfhydryl groups.

Covalent interactions

- Hepatotoxicity e.g. Paracetamol
- Nephrotoxicity e.g.Aminoglycosides


Toxic dose of paracetamol
P450 mixed function oxidases
N-Acetyl-p-benzoquinone imine (NAPBQI)
Oxidation of SH groups on cellular Ca2+ ATPases
GSH
NAPBQI–GSH adduct
NAPBQI–protein adducts
Lipid peroxidation
Sustained increase in [Ca2+]i
GSH depletion
Increased membrane permeability
Oxidative stress
Stimulation of Ca2+-activated degradative enzymes
CELL DEATH
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Carcinogenicity

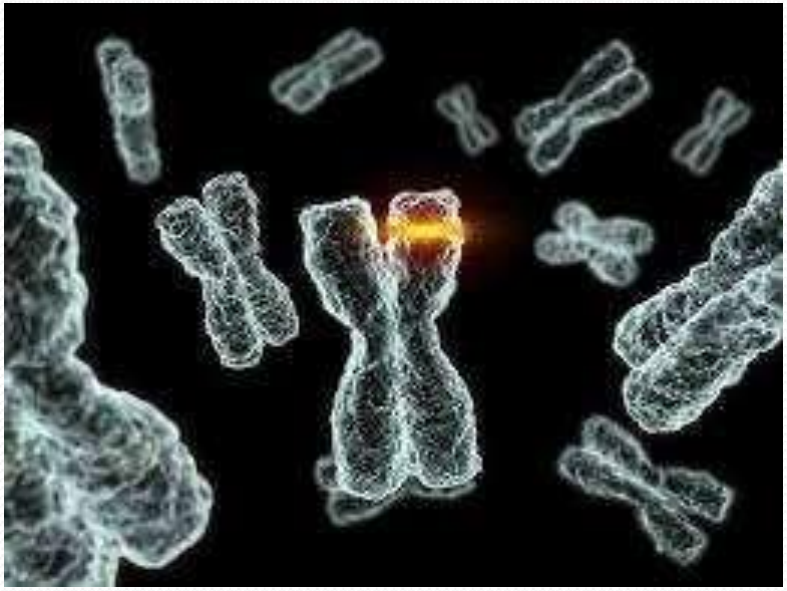
- **A carcinogen is any substance, radionuclide, or radiation that is an agent directly involved in causing cancer. This may be due to the ability to damage the genome or to the disruption of cellular metabolic processes.**
- **Several radioactive substances are considered carcinogens, but their carcinogenic activity is attributed to the radiation, for example gamma rays and alpha particles, which they emit.**
- **Examples of non-radioactive carcinogens are inhaled asbestos, certain dioxins, and tobacco smoke.**

The hazard symbol for carcinogenic chemicals in the Globally Harmonized System.

Mutagenicity

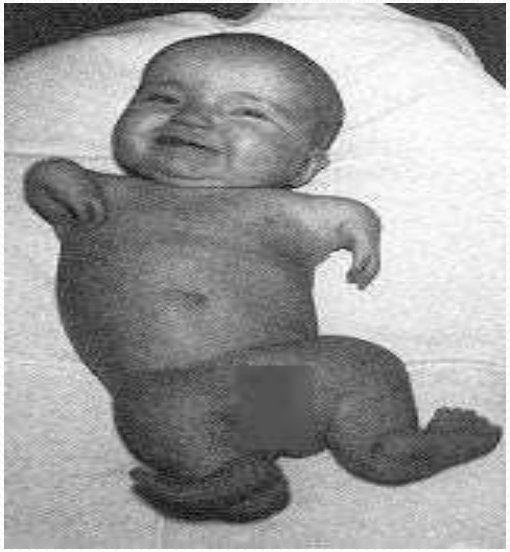
- **Some drugs can cause permanent changes to the DNA of germ cells - egg cells and sperm cells - leading to mutations which are inherited by a patient's children.**

- **Example is nitrogen mustard, that destroys cancer cells by linking their DNA strands together with a nitrogen atom, but can also link the DNA of germ cells, leading to deletions of DNA bases, thereby causing mutations.**



Teratogenicity

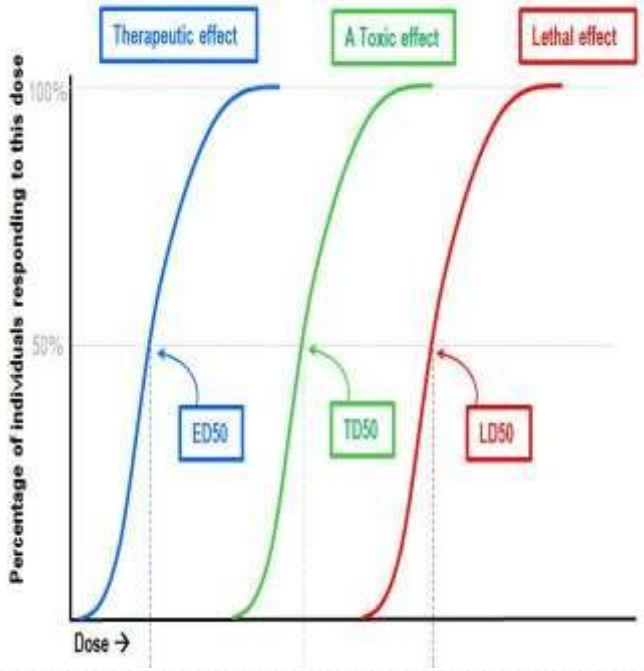
- **Some drugs can cause defects in the development of the foetus, leading to gross abnormalities of the baby: known as teratogenicity**
- **The type of abnormality seen depends on the stage at which the drug is taken, as different organs develop at different times during pregnancy.**
- **For instance, thalidomide taken after 21 days of pregnancy will often lead to lack of external ears and paralysis of the cranial nerves3, whereas thalidomid taken after 27 days will lead to limb Malformation (phocomelia).**



Measuring Toxicity

- Toxicity can be measured by the effect the substance has on an organism, a tissue or a cell.
- We know that individuals will respond differently to the same dose of a substance because of a number of factors including their gender, age and body weight.
- Therefore a population-level measure of toxicity is often used.
- The probability of an outcome for a population is then related to a given individual in a population.

Lethal dose (LD_{50})



- One such population-level measure is the median lethal dose, LD50 (lethal dose, 50%). This is defined as the dose required to kill half the members of a specific animal population when entering the animal's body by a particular route. LD_{50} is a general indicator of a substance's toxicity within a short space of time. It is a measure of acute toxicity.
- Most users of a substance will want to know the toxicity of that substance. The information for an LD_{50} must include the substance, the route of entry and the animal species. For example, table salt has an oral LD_{50} of 3 gm/kg in rats. Paracetamol has an oral LD_{50} of 1.944 gm/kg in rats.

Fixed-dose procedure

- In 1992, the fixed-dose procedure (FDP) was proposed as an alternative test to LD_{50}. It uses fewer animals, and there is less pain and suffering.
- In this procedure, the test substance is given at one of four fixed-dose levels (5, 50, 500 and 2000 milligrams per kilogram) to five male and five female rats.
- When a dose produces clear signs of toxicity but no death is identified, the chemical is then classified at that level.

Avoiding Toxicity

- **Banning dangerous drugs, or**

By strictly controlling their uses.

- **Drugs must go through both rigorous animal testing and small-scale trials on humans to detect unexpected effects**
- **To advise doctors not to prescribe their drugs to pregnant women.**
- **Child-proof containers have also been developed and clear labelling is used to warn patients of risks.**
- **Potentially fatal drugs are sold in restricted amounts in blister packs, making it difficult to take enough pills for the drug to have toxic effects.**

Toxicity Treatment

The first line of defence is to remove the drug from the patient before it is fully absorbed, and techniques include:

- **Irrigation to remove drugs applied to the eyes or skin.**
- **Gastric lavage, where the stomach is washed out and drained using tubes.**
- **Activated charcoal, which is swallowed and soaks up the drug from the gut.**
- **Ipecac syrup, which causes vomiting in order to empty the stomach.**
- **Cathartics, laxatives which purge the drug from the gut.**

A second line of defense involves the removal of the drug from the bloodstream by various methods, including:

- **Changing urine pH to increase excretion of the drug into the urine.**
- **Forced diuresis, where drugs are given to increase urine production.**
- **Haemodialysis, where the blood is passed through a machine to remove the drug.**
- **Exchange transfusion to replace the patient's drug-filled blood with fresh blood.**


اللهم عجل لولیک الفرج
عَزیزٌ عَلَيَّ اَنْ اَرَی الخَلقَ وَلا تُرَی وَلا اَسمَعُ لَكَ حَسیساً وَلا نَجوَی
سخت است برای من اینکه ببینم مردم را و تو را نبینم ، و نشنوم از تو صدایی و نجوایی