Classification and properties of toxic substances

- SOME EFFECTS ARE DELETERIOUS AND OTHERS ARE NOT
- FOR EXAMPLE EACH DRUG PRODUCES A NUMBER OF EFFECTS BUT USUALLY ONLY ONE EFFECT IS ASSOCIATED WITH PRIMARY OBJECTIVE OF THE THERAPY
- ALL THE OTHER EFFECTS ARE REFERRED TO AS UNDESIRABLE OR SIDE EFFECTS OF THAT DRUG FOR THAT THERAPEUTIC INDICATION.
- FOR EXAMPLE; FIRST GENERATION ANTIHISTAMINIE DIPHENYDRAMINE (BENADRYI) IS EFFECTING IN REDUCING HISTAMINE RESPONSE WITH ALLERGIES BUT IT ENTERS THE BRAIN AND CAUSES MILD CENTRAL NERVOUS SYSTEM DEPRESSION.
- NEWER AND SELECTIVE HISTAMINES DO NOT CROSS THE BLOOD –BRAIN BARRIER.

ALLERGIC REACTIONS;

- *Chemical allergy* is an immunologically mediated adverse reaction to a chemical resulting from sensitization to that chemical or to a structurally similar one
- The term *hypersensitivity* is most often used to describe this allergic state, but *allergic reaction* and *sensitization reaction* are also used to describe this situation when pre-exposure of the chemical is required to produce the toxic effect

An **antigen** is any substance that causes your immune system to produce antibodies against it. An **antigen** may be a foreign substance from the environment, such as chemicals, bacteria, viruses, or pollen. An **antigen** may also be formed inside the body, as with bacterial toxins or tissue cells.

An **antibody** (AB), also known as an immunoglobulin (Ig), is a large Y-shape protein produced by plasma cells that is used by the immune system to identify and neutralize pathogens such as bacteria and viruses. The **antibody** recognizes a unique molecule of the harmful agent, called an antigen

- Because of this omission, some people assumed that allergic reactions are not dose-related.
- Thus, they do not consider the allergic reaction to be a true toxic response.
- However, for a given allergic individual, allergic reactions are dose-related.
- For example, it is well known that the allergic response to pollen in sensitized individuals is related to the concentration of pollen in the air. In addition, because the allergic response is an undesirable, adverse, deleterious effect, it

obviously is also a toxic response.

- Sensitization reactions are sometimes very severe and may be fatal.
- Most chemicals and their metabolic products are not sufficiently large to be recognized by the immune system as a foreign substance and thus must first combine with an endogenous protein to form an antigen (or immunogen).
- A molecule that must combine with an endogenous protein to elicit an allergic reaction is called a *hapten.*
- The hapten-protein complex (antigen) is then capable of eliciting the formation of antibodies, and usually at least 1or 2 weeks is required for the synthesis of significant amounts of antibodies.
- Subsequent exposure to the chemical results in an antigen-antibody interaction, which provokes the typical manifestations of allergy.
- The manifestations of allergy are numerous.
- They may involve various organ systems and range in severity from minor skin disturbance to fatal anaphylactic shock.
- The pattern of allergic response differs in various species. In humans, involvement of the skin (e.g., dermatitis, urticaria, and itching) and involvement of the eyes (e.g., conjunctivitis) are most common, whereas in guinea pigs, bronchiolar constriction leading to asphyxia is the most common.
- However, chemically induced asthma (characterized by bronchiolar constriction) certainly does occur in some humans, and the incidence of allergic asthma has increased substantially in recent years.

IDIOSYNCRIATIC REACTIONS

- *Chemical idiosyncrasy* refers to a genetically determined abnormal reactivity to a chemical.
- The response observed is usually qualitatively similar to that observed in all individuals but may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of the chemical.
- A classic example of an idiosyncratic reaction is provided by patients who exhibit prolonged muscular relaxation and apnea (inability to breathe) lasting several hours after a standard dose of succinylcholine.
- Succinyl- choline usually produces skeletal muscle relaxation of only short duration because of its very rapid metabolic degradation by an enzyme that is present normally in the bloodstream called plasma butyryl- cholinesterase (also referred to as pseudocholinesterase).

- Patients exhibiting this idiosyncratic reaction have a genetic polymorphism in the gene for the enzyme butyrylcholinesterase, which is less active in breaking down succinylcholine.
- Family pedigree and molecular genetic analyses have demonstrated that the presence of low plasma butyrylcholinesterase activity is due to the presence of one or more single nucleotide polymorphisms in this gene .
- Similarly, there is a group of people who are abnormally sensitive to nitrites and certain other chemicals that have in common the ability to oxidize the iron in hemoglobin to produce *methemoglobin,* which is incapable of carrying oxygen to the tissues.
- The unusual phenotype is inherited as an autosomal recessive trait and is characterized by a deficiency in NADH-cytochrome b5 reductase activity.
- The consequence of this genetic deficiency is that these individuals may suffer from a serious lack of oxygen delivery to tissues after exposure to doses of methemoglobin-producing chemicals that would be harmless to individuals with normal NADH-cytochrome b5 reductase activity.

IMMEDIATE VERSUS DELAYED REACTIONS

- Immediate toxic effects can be defined as those that occur or develop rapidly after a single administration of a substance, whereas delayed toxic effects are those that occur after the lapse of some time.
- Carcinogenic effects of chemicals usually have a long latency period, often 20 to 30 years after the initial exposure, before tumors are observed in humans.
- For example, daughters of mothers who took diethylstilbestrol (DES) during pregnancy have a greatly increased risk of developing vaginal cancer, but not other types of cancer, in young adulthood, some 20 to 30 years after their in utero exposure to DES.
- Also, delayed neurotoxicity is observed after exposure to some organophosphorus insecticides that act by covalent modification of an enzyme referred to as *neuropathy target esterase* (NTE), a neuronal protein with serine esterase activity.
- Binding of certain organophosphates (OP) to this protein initiates degeneration of long axons in the peripheral and central nervous system.
- The most notorious of the compounds that produce this type of neurotoxic effect is triorthocresylphos- phate (TOCP).
- The effect is not observed until at least several days after exposure to the toxic compound.
- In contrast, most substances produce immediate toxic effects but do not produce delayed effects.

REVERSIBLE VERSUS IRREVERSIBLE REACTIONS

- Some toxic effects of chemicals are reversible, and others are irreversible.
- If a chemical produces pathological injury to a tissue, the ability of that tissue to

regenerate largely determines whether the effect is reversible or irreversible.

- Thus, for a tissue such as liver, which has a high ability to regenerate, most injuries are reversible, whereas injury to the CNS is largely irreversible because differentiated cells of the CNS cannot divide and be replaced.
- Carcinogenic and teratogenic effects of chemicals, once they occur, are usually considered irreversible toxic effects.

LOCAL VERSUS SYSTEMIC TOXICITY

- Another distinction between types of effects is made on the basis of the general site of action.
- Local effects are those that occur at the site of first contact between the biological system and the toxicant.
- Such effects are produced by the ingestion of caustic substances or the inhalation of irritant materials.
- For example, **chlorine gas** reacts with lung tissue at the site of contact, causing damage and swelling of the tissue, with possibly fatal consequences, even though very little of the chemical is absorbed into the bloodstream.
- The alternative to local effects is systemic effects. Systemic effects require absorption and distribution of a toxicant from its entry point to a distant site, at which deleterious effects are produced.
- Most substances except highly reactive materials produce systemic effects.
- For some materials, both effects can be demonstrated.
- For example, **Tetra Ethyl Lead** produces effects on skin at the site of absorption and then is transported systemically to produce its typical effects on the CNS and other organs.
- If the local effect is marked, there may also be indirect systemic effects.
- For example, **kidney** damage after a severe acid burn is an indirect systemic effect because the toxicant does not reach the kidney.
- Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs; instead, they usually elicit their major toxicity in only one or two organs.
- These sites are referred to as the **target organs** of toxicity of a particular chemical.
- The target organ of toxicity is often not the site of the highest concentration of the chemical.
- For example, **lead** is concentrated in bone, but its toxicity is due to its effects in soft tissues, particularly the brain.
- **DDT** is concentrated in adipose tissue but produces no known toxic effects in that tissue.
- The target organ of toxicity most frequently involved in systemic toxicity is the CNS (brain and spinal cord).
- Even with many compounds having a prominent effect elsewhere, damage to the CNS can be demonstrated by the use of appropriate and sensitive methods.

- Next in order of frequency of involvement in systemic toxicity are the;
  - ✓ circulatory system; the blood and hematopoietic system;
  - ✓ visceral organs such as the liver, kidney, and lung; and the skin.
  - ✓ Muscle and bone are least often the target tissues for systemic effects.
- With substances that have a predominantly local effect, the frequency with which tissues react depends largely on the portal of entry (skin, gastrointestinal tract, or respiratory tract).

INTERACTION OF CHEMICALS

- Because of the large number of different chemicals an individual may come in contact with at any given time (workplace, drugs, diet, hobbies, etc.), it is necessary, in assessing the spectrum of responses, to consider how different chemicals may interact with each other.
- Interactions can occur in a variety of ways.
- Chemical interactions are known to occur by a number of mechanisms, such as alterations in absorption, protein binding, and the biotransformation and excretion of one or both of the interacting toxicants.
- In addition to these modes of interaction, the response of the organism to combinations of toxicants may be increased or decreased because of toxicologic responses at the site of action.
- The effects of two chemicals given simultaneously produce a response that may simply be additive of their individual responses or may be greater or less than that expected by addition of their individual responses.
- The study of these interactions often leads to a better understanding of the mechanism of toxicity of the chemicals involved.
- A number of terms have been used to describe pharmacologic and toxicological interactions.
  1. An *additive* effect occurs when the combined effect of two chemicals is equal to the sum of the effects of each agent given alone (example: 2 + 3 = 5).
  - ➢ The effect most commonly observed when two chemicals are' given together is an additive effect. For example, when two **organophosphate insecticides** are given together, the cholinesterase inhibition is usually additive.
  2. A *synergistic* effect occurs when the combined effects of two chemicals are much greater than the sum of the effects of each agent given alone (2+2=20).

- for example both **carbon tetrachloride and ethanol** are hepatotoxic compounds, but together they produce much more liver injury than the mathematical sum of their individual effects on liver at a given dose would suggest.

3. *Potentiation* occurs when one substance does not have a toxic effect on a certain organ or system but when added to another chemical makes that chemical much more toxic (example: 0 + 2 = 10).

- **Isopropanol**, for example, is not hepatotoxic, but when it is administered in addition to **carbon tetrachloride,** the hepatotoxicity of carbon tetrachloride is much greater than when it is given alone.

4. *Antagonism* occurs when two chemicals administered together interfere with each other's actions or one interferes with the action of the other (example: 4 + 6 = 8; 4 + (-4) = 0; 4 + 0 = I).

Antagonistic effects of chemicals are often very desirable in toxicology and are the basis of many antidotes. There are four major types of antagonism:

I. functional,
II. chemical,
III. dispositional,
IV. receptor.

Functional antagonism occurs when two chemicals counterbalance each other by producing opposite effects on the same physiologic function.

- Advantage is taken of this principle in that the blood pressure can markedly fall during severe **barbiturate intoxication**, which can be effectively antagonized by the intravenous administration of a vasopressor agent such as **norepinephrine**.
- Similarly, many chemicals, when given at toxic dose levels, produce convulsions, and the convulsions often can be controlled by giving **anticonvulsants** such as the benzodiazepines (e.g., diazepam).

Chemical antagonism or inactivation is simply a chemical reaction between two compounds that produces a less toxic product.

- For example, **dimercaptol** (British antilewisite, or BAL) chelates with metal ions such as arsenic, mercury, and lead and decreases their toxicity.
- The use of antitoxins in the treatment of various animal toxins is also an example of chemical antagonism.
- The use of the strongly basic low-molecular-weight protein protamine sulfate to form a stable complex with heparin, which abolishes its anticoagulant activity, is another example.

Dispositional antagonism occurs when the disposition that is, the absorption, distribution, biotransformation, or excretion of a chemical is altered so that the concentration and/or duration of the chemical at the target organ are diminished.

- Thus, the prevention of absorption of a toxicant by **ipecac** or **charcoal** and the increased excretion of a chemical by administration of an osmotic diuretic or alteration of the pH of the urine are examples of dispositional antagonism.
- If the parent compound is responsible for the toxicity of the chemical (such as the

anticoagulant warfarin) and its metabolic breakdown products are less toxic than the parent compound, increasing the compound's metabolism (biotransformation) by administering a drug that increases the activity of the metabolizing enzymes (e.g., a "microsomal enzyme inducer" such as phenobarbital) will decrease its toxicity.

- However, if the chemical's toxicity is largely due to a metabolic product (as in the case of the organophosphate insecticide parathion), inhibiting its biotransformation by an inhibitor of microsomal enzyme activity will decrease its toxicity.
- **Receptor antagonism** occurs when two chemicals that bind to the same receptor produce less of an effect when given together than the addition of their separate effects (4+6=8) or when chemical antagonizes the effect of the second chemical for example (0+4=1).Receptor antagonanists are often termed as BLOCKERS. This concept is used in the treatment of poisoning.

- For example, the receptor antagonist naloxone is used to treat the respiratory depressive effects of morphine and other morphine like narcotics by competitive binding to the same receptor.
- Another example of receptor antagonism is the use of the antiestrogen drug **Tamoxifen** to lower breast cancer risk among women at high risk for this estrogen related cancer. Tamoxifen competitively block estradiol from binding to its receptor.
- Treatment of organophosphate insecticide poisoning with **atropine** is an example not of the antidote competing with the poison for the receptor (cholinesterase) but involves blocking the receptor (cholinergic receptor) for the excess acetylcholine that accumulates by poisoning of the cholinesterase by the organophosphate

Tolerance

Tolerance is a state of decreased responsiveness to a toxic effect of a chemical resulting from prior exposure to that chemical or to a structurally related chemical. Two major mechanisms are responsible for tolerance:

1; one is due to a decreased amount of toxicant reaching the site where the toxic effect is produced ***(dispositional tolerance)***, and

2; the other is due to a reduced responsiveness of a tissue to the chemical. Comparatively less is known about the cellular mechanism responsible for altering the responsiveness of a tissue. Two chemicals known to produce dispositional tolerance are carbon tetrachloride and cadmium. Carbon tetrachloride produces tolerance to itself by decreasing the formation of the reactive metabolite (**trichloromethyl radical**) that produces liver injury. The mechanism of cadmium tolerance is explained by induction of **metallothionein,** a metal-binding protein. Subsequent binding of cadmium to metallothionein rather than to critical macro molecules decreases its toxicity.