Spectrum of Undesired Effects(Lecture_2)

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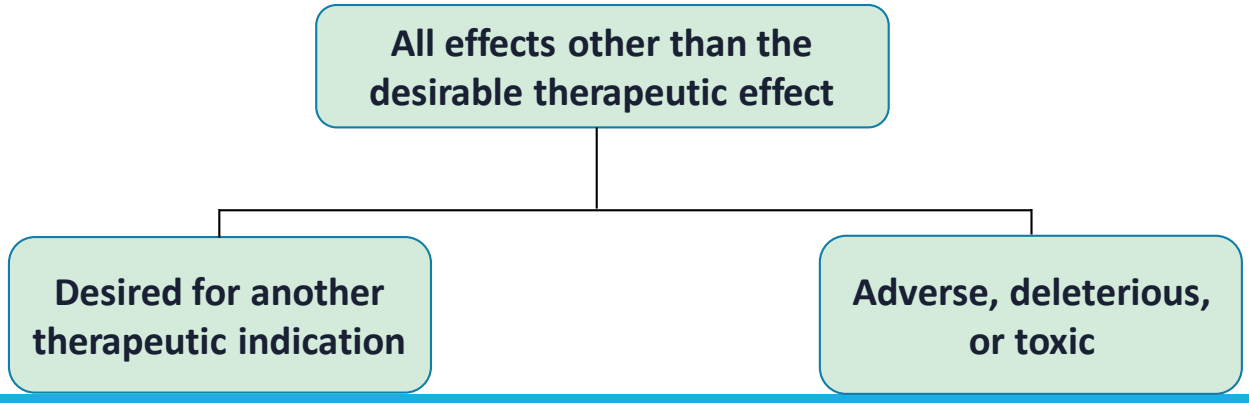
Learning outcomes:

By the end of this lecture, you should know the following:

- Understand the terminology related to undesired toxic effects.
- Differentiate between allergic and idiosyncratic reactions, immediate and delayed effects, reversible and irreversible effects, local and systemic toxic effects.
- Memorize examples about each toxic effects.
- Understand the types of interactions between chemicals.
- Understand tolerance and its mechanism.

SPECTRUM OF UNDESIRED EFFECTS:

- The spectrum of undesired effects of chemicals is often broad. Some effects are toxic, and others are not. In therapeutics, for example, each drug produces a number of effects, but usually only one effect is associated with the primary objective of the therapy; all the other effects are referred to as undesirable or side effects of that drug for that therapeutic indication. However, some of these side effects may be desired for another therapeutic indication.



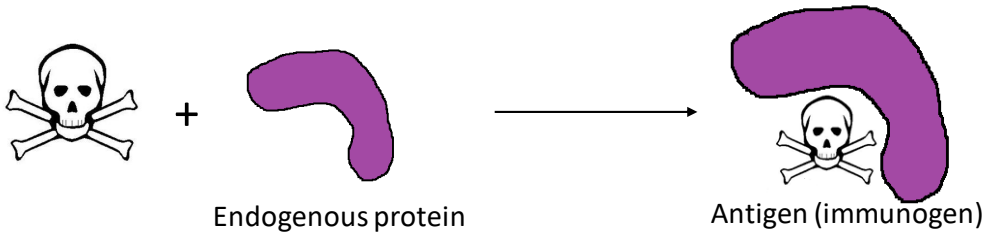
- For example, the “first-generation” antihistamine diphenhydramine is effective in reducing histamine responses associated with allergies, but it readily enters the brain and causes mild central nervous system (CNS) depression (drowsiness, delayed reaction time). With the advent of selective histamine receptor antagonists that do not cross the blood–brain barrier and thus do not have this CNS-depressant side effect, diphenhydramine is used less commonly today as an antihistamine. However, it is widely used as an “over-the-counter” sleep remedy.
- Can give other examples??

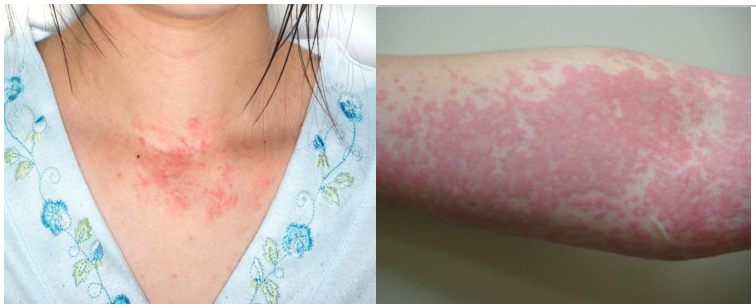
Allergic Reactions:

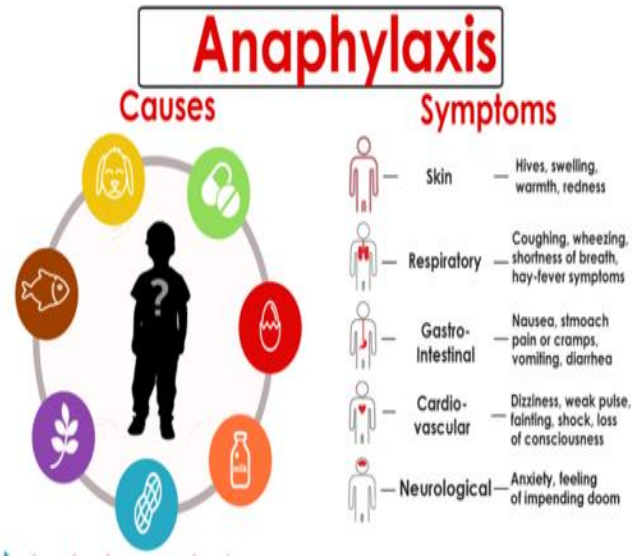
❑ Chemical allergy:

- Immunological mediated adverse reaction to a chemical resulting from previous sensitization to that chemical or a structurally similar one.
- Allergic reactions for individuals are dose-dependant (e.g. Pollen).
- Range in severity from minor skin disturbance to fatal anaphylactic shock.
- In human; involvement of skin (dermatitis, urticaria, itching) and eye (conjunctivitis) are most common.
- Sensitization reactions might 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.







Anaphylaxis causes your immune system to release a flood of chemicals that can cause **you** to **go into shock** — your blood pressure drops suddenly, and your airways narrow, blocking breathing. Signs and symptoms include a rapid, weak pulse; a skin rash; and nausea and vomiting

Idiosyncratic Reactions:

- Genetically determined abnormal reactivity to a chemical.
- The response observed is usually quantitatively like 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. e.g., succinylcholine, troglitazone

✓.Idiosycratic reacton is provided by patients who exhibited prolong muscular relaxation and apnea (in ability to breath) lasting several hour after standard dose of succinylcholine.

✓Usually succinylcholine produce skeletal muscle relaxation of only short duration because its rapid metabolic degradation by enzyme that is present in the blood stream called butylcholinesterase.

- ✓Longer muscular relaxation and apnea after standard succinylcholine dose---polymorphism in pseudocholinesterase.
- ✓ Abnormal NADH-cytochrome b5 reductase activity: 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 enzyme activity

Immediate vs. Delayed Toxicity

➢ Immediate toxicity:

✓ Immediate toxic effects occur or develop rapidly after a single administration of a substance.

✓ most substances produce immediate toxic effects but do not produce delayed effects.

➢ Delayed toxicity:

✓ Occurs after the wait of some period of time. e.g., carcinogenic effect of DES:

✓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

✓ Daughters of a mother had taken DES (diethylstilbestrol) during pregnancy – could develop vaginal cancer in young adulthood.

Reversible vs. Irreversible Toxic effects:

- The reversibility of the toxic effects of chemicals depends on the injured tissue itself; the ability of the of that tissue to regenerate.
- For example: Liver has high regeneration ability, thus most liver injuries are reversible.
- In contrast, CNS cells cannot be replaced, thus, most CNS injuries are irreversible.
- Carcinogenic and teratogenic effects of chemicals, once they occur, are usually considered irreversible toxic effects.

Local vs. Systemic Toxicity:

➢ Local toxicity:

✓ The sign of sensitivity/ toxicity are localized at the site of contact with the toxicant.

✓ 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.

Systemic toxicity:

- Systemic effects require absorption and distribution of toxicant from its entry point to a distant site at which the systemic adverse effects are produced.
- ✓ For some materials, both effects can be demonstrated. For example, tetraethyl lead cause both local skin and systemic CNS effects.
- ✓ Systemic toxicity are usually observed in one or two organs, these are called target organs of toxicity of a particular 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.
- ✓ Indirect systemic effect, example kidney damage after acid burns.

Local vs. Systemic Toxicity

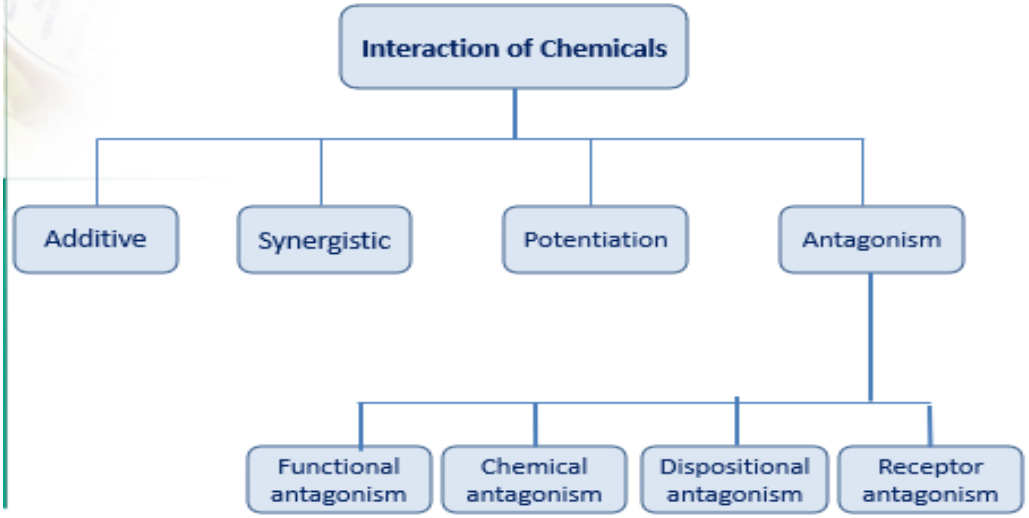
➢ **Examples of target organs:**

- ✓ CNS (main)
- ✓ Circulatory system
- ✓ Blood and hematopoietic system.
- ✓ Visceral organs such as the liver, kidney, lungs.
- ✓ The skin.
- ✓ Muscle and bone are least targeted.

Interaction of Chemicals

- 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 1 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 toxicological responses at the site of action.
- The effects of 2 chemicals given simultaneously produce a response that may simply be:

Interaction of Chemicals



Additive Effect:

- ✓ The combined effect of two chemicals is equal to the sum of the effects of each agent alone; 2+3=5. e.g., 2 OPs (organo phosphates) insecticides

- **Synergistic Effect:**

- ✓ The combined effect of two chemicals is much higher than the sum of the effects of each agent alone; 2 + 3=35, 2+2 = 40
- ✓ Example: Both carbon tetrachloride and ethanol are hepatotoxic, simultaneous exposure to both agents cause liver injury with much higher intensity of their sum.

Potentiation Effect:

- ✓ When one substance has no toxicity at certain organs, however, when combined with another chemical the later becomes much more toxic and/or possesses toxicity at certain organs; 0+2=10.
- ✓ Example: Isopropanol is not hepatotoxic, when administered with carbon tetrachloride, carbon tetrachloride toxicity intensifies. (much greater)

Antagonism Effect:

- ✓ When two chemicals administered together interfere with each other's actions or one interferes with the action of the other; 4+6=8, 4+(-4)=0, 4+0=1 (Antidote)

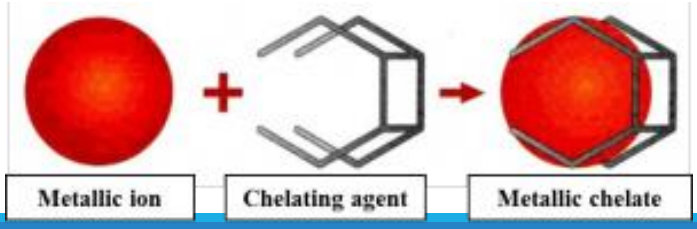
4 Major types
a:Functional Antagonism

- ✓ When two chemicals counterbalance each other by producing opposite effects on the same physiological function.
- ✓ Example: Severe barbiturates intoxication is manifested by a marked fall in blood pressure; IV administration of vasopressors such as norepinephrine or metaraminol antagonize its effect.
- ✓ Another example: convulsions and benzodiazepines.

b. Chemical Antagonism (inactivation):

- ✓ A chemical interaction between two chemicals in which a less toxic product is produced. Or is a chemical reaction between 2 chemicals that produce less toxic products
- ✓ Examples:
- Chelators (2,3-dimercaptosuccinic acid) dimercaprol with metal ions (arsenic, mercury and lead) decrease metal toxicity.

- Protamine sulfate complex with heparin prevents its anticoagulant activity.



c. Dispositional Antagonism:

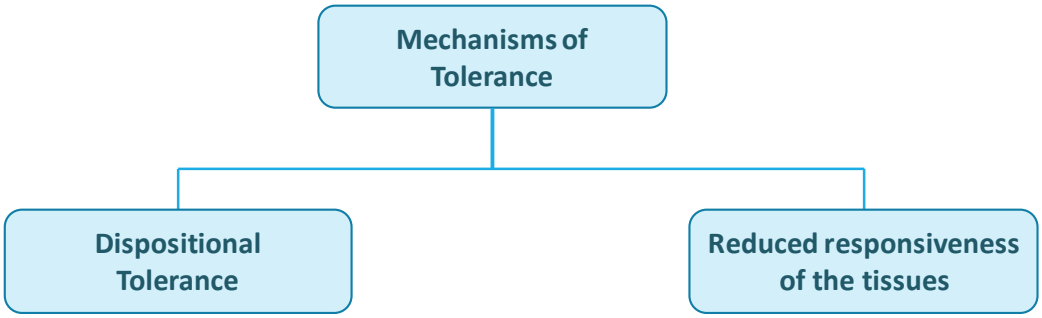
- ✓ Occurs when the absorption, biotransformation, distribution, or excretion of a chemical is altered so that the concentration and/or duration of the chemical at the target organ are diminished.
- ✓ Examples:
- Prevention of absorption of toxicants by charcoal or ipecac.
- Increase the activity of metabolizing enzymes by using enzyme inducers (phenobarbital) if parent drug is the toxic (warfarin) or by using enzyme inhibitors (SKF-525A) if metabolite is more toxic.
- Increase the excretion of a chemical by the use of osmotic diuretics or alteration of urine pH.

d. Receptor Antagonism:

- ✓ The two chemicals do not interact with each other; however, they bind to the same receptor. Hence, a less combined effect is produced compared to the sum of their separate effects or when one chemical antagonize the effect of the other one .
- ✓ Very common example of such interaction are the receptor blockers.
- E.g., naloxone blocks morphine receptors.
- Tamoxifen block estrogen receptors, lower breast cancer risk among women at high risk for estrogen related cancer
- Atropine and Ops ??

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.



- Dispositional tolerance refers to an organism's increased ability to metabolize and distribute the drug in the body. Thus, with increased dispositional tolerance, more of the drug must be taken to reach a specific concentration at the receptor sites. For example: Alcohol and barbiturates increased liver enzyme activity other example carbon tetra chloride and cadmium