Lecture 1

INTRODUCTION TO GENERAL TOXICOLOGYY

Introduction to General Toxicology

- **The term toxicology derives the Greek toxicon, meaning poison, and logos, meaning science.**

Introduction to General Toxicology

- **Toxicology is the study of the adverse effects of chemical, physical, or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects.**
- **Toxicology studies the agents responsible for adverse effects, the mechanisms involved, the damage that may ensue, testing methodologies to determine the extent of damage, and ways to avoid or repair it.**

Introduction to General Toxicology

- **Toxicology is largely concerned with the interaction of toxicants and biological organisms.**
- **While toxicodynamics investigates the effect of the toxicant on the organism,**
- **Toxicokinetics looks at how the organism affects the toxicant (e.g., absorption, biotransformation, distribution, and elimination).**

Introduction to General Toxicology

Toxin it formally should be used to refer to toxic substances produced biologically.

Thus, technically, chemicals such as formaldehyde or asbestos, say, would not be considered toxins.

Introduction to General Toxicology

There are any number of other terms which could be used to delineate the broader category of substances which are toxic, regardless of origin. Examples are toxicant, toxic agent, and toxic substance.

Xenobiotics is a term referring to substances, whether toxic or not, foreign to a given organism.

Introduction to General Toxicology

- **One needs to clarify the use of the words poisonous and venomous when used as animal adjectives. Though often used interchangeably, they are, in fact, rather distinct.**
- **A venom requires a delivery mechanism. Thus, because a snake, for example, injects its venom (or toxin) into its victim, it is considered a venomous animal.**
- **Instead, a toxic mushroom must be ingested to make its effect felt. Thus, it should instead be deemed poisonous.**

Introduction to General Toxicology

- **Toxins are poisons that originate from plants and microbial organisms and also include venoms released by animals in order to injure predators.**
- **Aflatoxin is an example of a toxin; it is produced and released from the fungus Aspergillus that grows on foods such as corn and nuts. Exposure to aflatoxin is associated with an increased risk of liver cancer.**

Introduction to General Toxicology

- By comparison, xenobiotics include a variety of synthetic chemicals with different intended purposes. Pharmaceuticals are xenobiotics developed to treat disease, whereas pesticides are used to deter pests.
- For example, the chemical "dioxin" [TCDD]) is generated during the production and/or combustion of certain chlorinated organic chemicals.
- A unique skin toxicity, called chloracne, has been observed in individuals exposed to dioxin.

Introduction to General Toxicology

Pictures of a chlorine rash

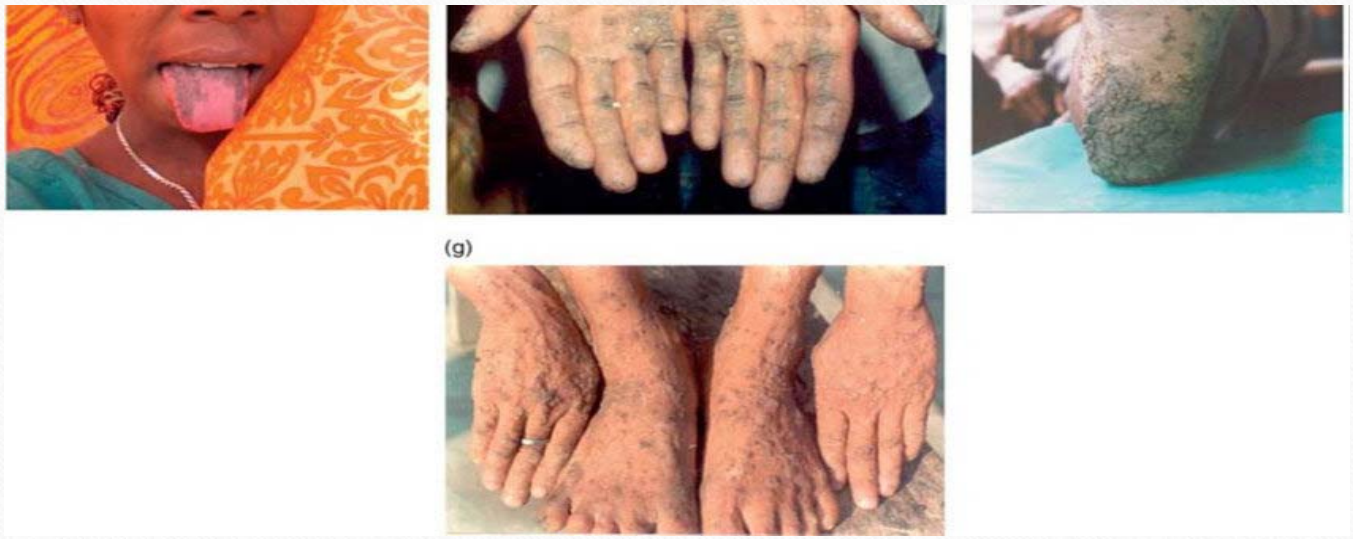
Introduction to General Toxicology

- **Some toxic substances can be produced by both natural and anthropogenic activities.**
- **For example, polyaromatic hydrocarbons are produced by the combustion of organic matter through ordinary processes (e.g., forest fires) and human activities (e.g., combustion of coal for energy production and cigarette smoking).**

Introduction to General Toxicology

- **Arsenic, a toxic metalloid, largely appears in groundwater as a natural contaminant, but also enters groundwater from other sources as well.**
- **Generally, such toxic chemicals are referred to as toxicants, rather than toxins, because, although they may be naturally produced, they are not produced by biological systems.**

Introduction to General Toxicology



Different skin symptoms due to arsenic toxicity

Classification of toxic chemicals

Toxic chemicals may also be classified in terms of:

1.Their physical state (gas, dust, liquid, size; e.g., nanoparticles);

2.Their chemical stability or reactivity (explosive, flammable, corrosive);

3.General chemical structure (aromatic amine, halogenated hydrocarbon, etc.); or

Classification of toxic chemicals

4.Ability to cause significant toxicity (extremely toxic, very toxic, slightly toxic, etc.).

5.Classification of toxic chemicals on the basis of their biochemical mechanisms of action (e.g., alkylating agent, cholinesterase inhibitor, and endocrine disruptor).

The last classification is usually more informative than classification by general terms such as irritants and oxidizers.

Chemical toxicity and LD50

- **Chemicals differ in their ability to produce serious injury or death.**
- **Side table shows the dose of chemicals needed to produce death in 50% of treated animals (lethal dose 50 [LD50]).**

Table 2-1

Approximate Acute LD_{50} Values of Some Representative Chemicals

CHEMICAL	LD_{50} (MG/KG)*
Ethyl alcohol	10,000
Glyphosate	5,600
Sodium chloride	4,000
Ferrous sulfate	1,500
Morphine sulfate	900
Phenobarbital sodium	150
Chlorpyrifos	18
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
VX nerve gas	1
D-Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

**LD_{50} is the dose (mg/kg body weight) causing death in 50% of exposed animals.*

Chemical toxicity and LD50

- **Chemicals produce death in microgram doses and are commonly denoted as extremely poisonous.**
- **Other chemicals may be relatively harmless after doses in excess of several grams.**

Classification of Toxicology

- Descriptive Toxicology
- Mechanistic Toxicology
- Clinical Toxicology
- Forensic Toxicology
- Environmental Toxicology
- Occupational Toxicology
- Regulatory Toxicology

Descriptive Toxicology

- **The emphasis is on the testing of toxicants, typically on animals.**
- **It focuses on the dose–response relationship and extrapolation to humans.**

Mechanistic Toxicology

- **Looks at how the agent induces its biochemical or physiological effect on the organism, that is, modes of action.**
- **Biochemical and Molecular Toxicology is a synonym for this branch.**

Clinical Toxicology

- **This branch's focus on the effects of drugs and other chemicals on humans, particularly, but also on other animals.**
- **Its work is often involved with drug overdoses and other poisonings, and determining the substance involved and its amount in the body.**

Forensic Toxicology

- **Concerned with the cause of death from toxic agents, often in instances of drug abuse or misuse.**
- **With a focus on homicides and suicides, this branch of toxicology goes hand in hand with the work of the police and medical examiners.**

Environmental Toxicology

- **Investigates the effects of toxicant exposures on the general environment and living organisms therein.**
- **Thus, pollution of air, water, and soil, and effects on plants and wildlife would fall within this branch.**
- **Ecotoxicology, a more specialized area, is devoted to the effects of toxic chemicals on populations, communities, and terrestrial, freshwater, and marine ecosystems.**

Occupational Toxicology

- **Deals with the study of chemical and other agents in the workplace, worker exposures, safety and health, and standard setting.**
- **Industrial Hygiene covers a very similar terrain.**

Regulatory Toxicology

- **Focuses on ways in which humans and the environment can be protected from toxic effects, through regulations and standard setting.**
- **Considers scientific decision-making within a societal and legal framework.**
- **Relies heavily upon risk assessment.**

Toxicogenomics

- **Concerned with the compilation and synthesis of information regarding gene and protein expression in order to understand molecular mechanisms involved in toxicity.**
- **Toxicogenomics calls upon proteomics, metabolomics, and transcriptomics to identify biomarkers that predict toxicity and genetic susceptibility to harmful substances.**
- **Environmental pollutants, pharmaceuticals, and other potentially toxic substances are all within the scope of toxicogenomics research.**

Selective toxicity

- **Selective toxicity means that a chemical produces injury to one kind of living matter (such as a cell or organism) without harming another form of life even though the two may exist in intimate contact.**

Selective toxicity

- **Selective toxicity results because the chemical**
- **(1) is equally toxic to both organisms but accumulates preferentially in the target or**
- **(2) alters a unique cellular or a biochemical feature that is absent or irrelevant in the unaffected species.**

Modifying Factors of toxicity

- **Not all humans respond to toxicants in the same manner and to the same degree as each other.**
- **Multiple factors modify one's susceptibility to adverse outcomes.**

Modifying Factors of toxicity

- **Particularly important modifiers include genetic variation among a population, age and life stages, sex and hormonal status, microbiome, and circadian rhythm.**
- **Other influences that can impact the extent of toxicity include the concomitant use of tobacco, alcohol, nutraceutical, pharmaceutical and illicit drugs, exercise, nutrition, and co-exposures in the workplace and at home.**

Modifying Factors of toxicity

1. Genetics:

- **Hereditary differences in a single gene that occur in more than 1% of the population are referred to as genetic polymorphisms.**

Modifying Factors of toxicity

2. **Age**

- **Life stage, and in turn age, It is an important factor that can alter susceptibility to toxicity.**
- **Metabolic processes that aid in xenobiotic clearance are often altered at juvenile and advancing ages.**

Modifying Factors of toxicity

2. **Age Life stage, and in turn age:**

- **For example, newborns have relatively low gastric emptying, gastrointestinal motility, and expression of the metabolic enzymes including CYP2D6, CYP2E1, and CYP3A4.**
- **Reduced metabolic capacity can decrease the clearance of some chemicals and increase the risk of toxicity.**

Modifying Factors of toxicity

3. **Sex:**

- **Along with genetics and age, sex can be a determinant of xenobiotic disposition and toxicity.**
- **One of the notable sex-related differences in humans is the effect of alcohol.**

Modifying Factors of toxicity

3. **Sex:**

- **Alcohol is absorbed and metabolized differently in females and males.**
- **This is in part due to the lower extent of body water in women compared to men of a similar weight.**
- **Toxicities such as liver disease and brain damage due to alcohol consumption appear to be more frequent and/or earlier in females compared to males.**

Modifying Factors of toxicity

4. **Circadian Rhythm**

- **Circadian rhythm is a 24-hour cycle that regulates a number of molecular and physiological processes.**
- **Within the 24-hour cycle, there are diurnal (light cycle), nocturnal (dark cycle), and crepuscular (transition) periods.**

Modifying Factors of toxicity

4. **Circadian Rhythm**

- **The circadian clock consists of a cellular clock with specific genes that oscillate in expression.**
- **Timing in the circadian system is affected by a number of factors including light, activity, food consumption, and social cues.**
- **While most changes in physiological processes during the 24-hour period are not readily apparent, they can still impact susceptibility to toxicity.**

Modifying Factors of toxicity

5. **Microbiome**

- **Within the body, bacteria outnumber human cells by a ratio of 10:1.**
- **Typically, anaerobic and facultative aerobic bacteria comprise the resident microflora of the intestinal tract.**
- **The influence of commensal microbes on human health, including toxicologic responses, is garnering greater attention with the advent of highly sensitive methods in metagenomics.**

THANK YOU FOR YOUR ATTENTION