Introduction to Toxicology

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What is Toxicology?

- Poisoning and knowledge of poisons have long been known to humans
- But as a branch of science or distinct discipline ‘Toxicology’ is very young
- Even the cave dwellers had the knowledge of substances that can cause harm…
- ‘Socrates’ & ‘Cleopatra’ are two famous victims of poisoning in history

History

- **Socrates** was forced to drink **Hemlock** for corrupting the youth of Athens
- **Cleopatra** committed suicide through the **bite of an asp;** a poisonous snake
- In 15th Century in Italy, **Cesar** and **Lucrezia Borgia** assassinated many of their political rivals by poisoning with **arsenic, copper and phosphorus**
- **Lead** caused poisoning in hundreds of thousands from the time of Roman era till 17th and 18th century as it was used in pottery, cosmetics, paints and in automobile fuels

History

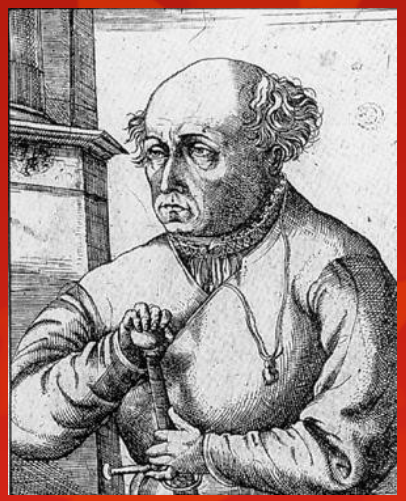
- **Mustard Gas** and other poisonous gases were used in many wars started from WW-I in 1914 by Germans
- Newer versions are **Neurotoxins, Sarin, Tabun and VX**
- Chemical toxicities has caused disasters too, like in Bhopal, India in 1984 where release of **methyl isocyanate** killed many thousands

History

Swiss physician **Paracelsus** (1493-1541) credited with being -

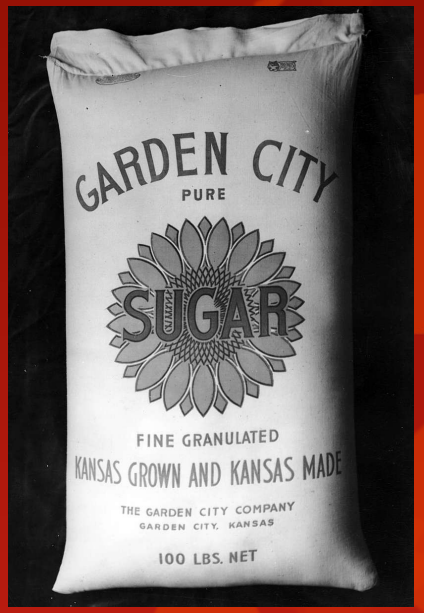
"the father of modern toxicology"

"All substances are poisons: there is none which is not a poison. The right dose differentiates a poison from a remedy"



The Dose Makes the Poison

- An apparently nontoxic chemical can be toxic at high doses
- Too much of a good thing can be bad
- Highly toxic chemicals can be life saving when given in appropriate doses
- Poisons are not harmful at a sufficiently low dose



General considerations

Definition:

- **Toxicology** is the science dealing with properties, actions, toxicity, fatal dose, detection of, interpretation of the result of toxicological analysis and treatment of poisons
- In other words- "It is the study of the adverse physicochemical effects of chemical, physical or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects"

General considerations

- **Forensic Toxicology** is the study of the chemical and physical properties of toxic substances and their physiological effect on living organisms
- Forensic toxicology deals with the medico-legal aspects of the harmful effects of chemicals on human beings
- **Clinical toxicology** deals with diagnosis and treatment of human poisoning

General considerations

- **Poison** is a substance (solid, liquid or gas), which if introduced in the living body, or brought into contact with any part thereof, will **produce ill health or death,** by its constitutional or local effects or both

General considerations

- **Toxinology** refers to toxins produced by living organisms which are dangerous to man viz., poisonous plants, snake venoms, spiders etc.

- **Orfila** is regarded as the father of modern toxicology because of his historical contribution to this subject

Drug laws in Malaysia:

- Dangerous Drugs Act 1952, which regulates control of raw & prepared opium, cannabis, certain dangerous drugs & external trade & provisions to deal with them

- Poisons Act 1952, which was formulated to regulate the import, storage, transport, labelling, coloring of poisons and supply of poisons to outpatients, for use in hospital

Drug laws in Malaysia:

- Drug Dependents (Treatment & Rehabilitation) Act 1983, to provide for the treatment and rehabilitation of drug dependents and for matters connected therewith

- Dangerous Drugs (Special Preventive Measures) Act 1985, to provide for the preventive detention of persons associated with any activity relating to or involving the trafficking in dangerous drugs

Drug laws in Malaysia:

- Dangerous Drugs (Forfeiture of Property) Act 1988, to make provisions for the offences in relation to the property, and for the seizure and forfeiture of property, connected with activity related to offences under this Act, the Dangerous Drugs Act 1952, or any foreign law corresponding to these Acts or to the provisions for offences under these Acts; for assistance to foreign countries

Medico-Legal Aspects of Poisons

- Administration of any substances with the intention of causing injury or death and which cause injury or death as a result, is legally sufficient for awarding punishment similar to homicide or attempted murder

Medico-Legal Aspects of Poisons

- Section 326 of penal code: voluntarily causing grievous hurt by dangerous weapons or means – punished with imprisonment for a term which may extend to twenty years, and shall also be liable to fine or to whipping

Medico-Legal Aspects of Poisons

- Section 328 of penal code: causing hurt by means of poison, etc., with intent to commit offence - punished with imprisonment for a term which may extend to ten years, and shall also be liable to fine

Ideal Homicidal Poison:

- Should be cheap and easily available
- Should be colorless, odorless and tasteless
- Capable of being administered with food materials without being detected
- Should be highly toxic and capable of sure shot death
- Signs & symptoms should resemble a natural disease
- Least Postmortem changes and not to be detected by any chemical tests
- e.g. Fluorine and Thallium, but commonly used are Arsenic and Aconite

- **Ideal Suicidal Poison:**
  - Should be cheap and easily available
  - Should be tasteless or be of pleasant taste
  - Capable of being administered with food materials
  - Should be highly toxic and capable of sure shot death
  - Should be capable of producing painless death
  - e.g. Opium and Barbiturates, but commonly used are Organophosphorus compounds and Endrin

- Stupefying Poisons:
  - Dathura, Cannabis indica, Chloral Hydrate.
- Abortificient Poisons:
  - Calotropis, Oleanders, Aconite, Croton, Semecarpus, Cantharides, Ergot, Lead, Arsenic, Mercury, and Potassium permanganate.
- Cattle Poisons:
  - Abrus precatorius, Oleanders, Calotropis, Organophosphorus, Arsenic, Aconite, Strychnine, etc.
- Arrow Poisons:
  - Abrus, Croton, Aconite, Strychnine, Curare and Snake venom etc.

CLASSIFICATION OF POISONS

- CORROSIVES:
  - Strong Acids:
    - Mineral / Organic Acids:
      - Sulphuric acid, Hydrochloric acid & Nitric acid
    - Organic Acids:
      - Carbolic acid, Oxalic acid, Acetic acid, etc.
  - Strong Alkalis:
    - Hydrates and Carbonates of Na, K, NH_4
  - Metallic Salts:
    - $ZnCl_2$, $FeCl_2$, $CuSO_4$, $AgNO_3$, KCN, etc.

IRRITANTS:

Agricultural

- Inorganic:
  - Non-metallic:
    - P, I, Cl, Br, CCl4
  - Metallic:
    - As, An, Cu, Pb, Hg, Ag, Zn, etc.
  - Mechanical:
    - Powdered glass, Diamond dust, Hair etc.

- Organic:
  - Vegetable:
    - Abrus precatorius, Castor, Croton, Calotropis, etc.
  - Animal:
    - Snake and insect venom, Cantharides, Ptomaine

SYSTEMIC POISONS:

- Cerebral:
  - CNS Depressants:
    - Alcohol, GA, Opioid analgesics, Hypnotics and Sedatives.
  - CNS Stimulants:
    - Cyclic Antidepressants, Amphetamine, Caffeine.
  - Deliriant poisons:
    - Dhatura, Belladonna, Hyoscyamus, Cannabis, Cocaine, etc.
- Spinal Poisons:
  - Nux vomica and Gelsemium
- Peripheral poisons:
  - Conium and Curare.
- Cardiovascular:
  - Aconite, Quinine, Oleander, Tobacco, HCN.
- Asphyxiants:
  - CO, CO_2, H_2S

Routes of Poison Administration:

- Inhalation:
  - Benzene, Xylene, Acetone, Methyl Chloroform, CCl4, CO, H2S, Methane, Lead, Mercury, Asbestos, etc.
- Injection into blood vessels
- Intradermal, Subcutaneous, Intramuscular Inj.
- Application into serous membrane
- Introduction into Stomach
- Introduction into natural orifices
- Rubbing into skin:
  - Organic phosphates, Nicotine, Phenol, Mercury, and Hydro cyanic acid

Factors Modifying Poison Actions:

- Quantity:
  - Higher the quantity, more severe action
- Form of the Poisonous substance:
  - Poison acts most rapidly in gaseous form and least in liquid form
  - When the combination of chemicals is more soluble, then more is the action
  - Alteration of action or efficacy when mixed with inert substances
- Mode of Administration

Factors Modifying Poison Actions:

- Conditions of the body:
  - Age factor: Poisons have greater effects at two extremes of age
  - Idiosyncrasy: Which is inherent personal hypersensitivity
  - Habit: Effect of certain poisons decreases with habituation. It results from a decreased reaction between the chemical and the biological effectors

Factors Modifying Poison Actions:

- State of Health: A healthy person tolerates better than a diseased one
- Sleep and Intoxication: Action of some poisons get delayed if a person goes to sleep
- Cumulative Action: Those poisons which are slowly eliminated from the body, may gradually accumulate and then may produce poisonous symptoms

Types of Poisoning:

- Acute Poisoning
- Chronic Poisoning
- Sub-acute Poisoning
- Fulminant Poisoning

Diagnosis of Poisoning

- **In the Living:**
  - No single symptom and no definite group of symptoms
  - A detailed clinical history is of great importance
  - A case of poisoning should be suspected if the following things are observed:
    - Symptoms appearing suddenly in an otherwise healthy individual
    - Symptoms appearing within a short period after food or drink
    - In a group or gathering, if similar symptoms are seen in all the individuals after intake of food or drink

Diagnosis of Poisoning

- The following group of symptoms are suggestive of poisoning:
  - Sudden onset of abdominal pain, nausea, vomiting, diarrhea and collapse (Arsenic)
  - Sudden onset of coma with constriction of pupils (Organo-phosphates)
  - Sudden onset of convulsions
  - Sudden onset of delirium with dilated pupils. (Dhatura)
  - Paralysis of LMN type (Strychnine)
  - Jaundice and hepato-cellular failure (CCl_4)
  - Oliguria with proteinuria and hematuria

Diagnosis of Poisoning

- In these cases, collect:
  - Stomach washings (entire)
  - Urine (as much as possible)
  - 10ml of Blood with NaF

Diagnosis of Poisoning

- In the Dead:
  - First, collect all the relevant information from Inquest report and also from the relatives
  - Postmortem examination may show:
    - External findings:
      - STAINS on clothes, marks of vomit or poison
      - COLOR CHANGES on affected skin and mucous membrane. (black color in H_2SO_4 & HCl, brown in Nitric acid)
      - PM STAINING may be Dark brown/yellow in Phosphorus, Cherry red in CO, Chocolate color in Nitrates, Nitrobenzene etc.
      - ODOUR from nose and mouth may be GARLIC like (P, Arsine gas, Arsenic), SWEETISH (Ethanol, Chloroform), ACRID (Paraldehyde, Chloral hydrate), ROTTEN EGG (H_2S, Mercaptans)

Diagnosis of Poisoning

- In the Dead [Cont…]
  - INJECTION MARKS may be detected which may suggest route of administration.
  - SKIN may show HYPERKERATOSIS (Chr. Arsenic poisoning), JAUNDICE (P, KClO4).
  - VIOLENCE MARKS such as bruise or other injuries if seen, suggests mode of death from cause other than poisoning.

In the Dead [Cont…]

- Internal Findings:
  - SMELL: Peculiar smell seen in Cyanide, Alcohol, Phenol, Chloroform and Camphor poisoning
  - MOUTH & THROAT: To be examined thoroughly for evidence of corrosion and inflammation or staining
  - ESOPHAGUS: Marked softening seen in Corrosive alkalis.
  - UPPER RESPIRATORY TRACT: May show evidence of volatile poisons
  - STOMACH: May show hyperemia, color changes, softening, ulcers, perforation, etc. All the contents should be emptied in a jar with NaCl and the stomach preserved for chemical analysis

In the Dead [Cont…]
Internal findings…..

- DUODENUM/INTESTINE: Ulceration beyond pylorus points to natural disease. Characteristic changes are seen in Hg poisoning. Normal GI tract rules out poisoning by Corrosives, Phenols, Hg and Arsenic compounds
- LIVER: Phosphorus, Chloroform, TNT, CCl_4, etc leads to Necrosis of liver. Fatty liver is seen in case of As, CCl_4, Mushroom poisoning, P_4, etc.
- RESPIRATORY SYSTEM: Corrosive poisons leads to glottic edema and congestion
- KIDNEYS: Metallic poisons, Cantharidin poison leads to degenerative changes. PCT necrosis is seen with $HgCl_2$, Phenols, Lysol, CCl_4 poisoning
- HEART: Subendocardial hemorrhages in Left Ventricle are seen in Acute Arsenic poisoning
- BLADDER / VAGINA / UTERUS: Should be specially examined in cases of Criminal abortion

Chemical Analysis & Rules

- Organs removed should be kept in clean container and contamination prevented
- Specimens of blood, urine, bile, etc. should be kept in glass container
- Specimen of choice for poison detection is Blood
- Urine is ideal choice for direct spot test in death due to delayed poisoning. It is also the only specimen to show poisonous substance in chronic poisoning death
- In advanced decomposition, thigh muscle may help in detection of poison
- It is important to keep Liver / Kidney separately from Alimentary canal contents

Analytical Procedure

- Steps involved:
  - Separation of poison from biological tissues
  - Purification of poisonous substance
  - Analytical detection and quantitative estimation by TLC, GC, UV Spectrometry and Immunoassays
  - Immunoassays includes Enzyme IA, Fluorescent IA and Radio IA
- Lethal Dose:
  - Dose of poison that can be lethal to life and can cause death
  - Minimum Lethal dose is the minimum dose that can cause death

Factors Influencing Toxicological Analysis

- Age & Weight.
- Presence of natural diseases.
- Traumatic Lesions.
- Degree of tolerance.
- Hypersensitivity reactions.

FAILURE OF DETECTION OF POISON:

- Vomiting, Diarrhea, Evaporation & Oxidation, Detoxification, Vegetable alkaloids, Biological toxins, etc.

Duties of Medical Practitioner

- Medical duty is to take care of the patient and treat the case
- Legal duties includes:
  - Police assistance and determination of manner of death
  - History collection
  - Collection of vomit, urine and preserving for analysis
  - Consultation and shifting the patient to a hospital setup
  - Suspected articles of poison to be preserved

Duties of Medical Practitioner….

- Private practitioners are bound to inform the police in case of homicidal poisoning
- If private practitioner is summoned by the investigative police officer, he is bound to divulge all information
- Duty to arrange for Dying Declaration
- On requisition by police, to perform an autopsy and furnish cause of death

General Lines of Treatment [ABCD…]

- **A**irway/**A**ntidote
- **B**reathing
- **C**irculation
- **D**econtamination/**D**extrose/**D**rugs
- Removal of unabsorbed poisons:
  - Inhaled poisons: Fresh air
  - Injected poisons: Ligature application
  - Contact poisons: Immediate removal of clothing and washing thoroughly
  - Ingested poisons: Gastric Lavage

Gastrointestinal decontamination

- Emesis:
  - It is useful within 3 hrs of ingestion
  - Done with ipecac syrup(30 ml)
- Activated charcoal:
  - It is useful within 1 hr of ingestion
  - Works by adsorbing poisons
  - Dose 50gm(adults), 1 gm/kg (children)
- Gastric lavage:
  - It is useful within 3 hrs of ingestion
  - Tube used is Boas tube or Nasogastric tube

Gastrointestinal decontamination

- Boas tube:
  - 1cm diameter & 1 ½ meter long
  - Has got lateral openings
  - Middle portion has got a suction bulb
  - Other features are Mouth gag, 50 cm mark, etc.
- 250 ml of Warm water is put over funnel of the tube and is taken out by the suction pump. This washing is preserved for analysis
- 1:5000 $KmNO_4$ sol., 5% $NaHCO_3$ sol. Or 4% Tannic acid is used for the lavage

Gastrointestinal decontamination

- Gastric lavage is continued till the pumped out washings are colorless. At this point a small amount of the agent is left out inside the stomach
- Contra-indications:
  - Absolute CI is Corrosive poisoning due to danger of perforation of stomach. (Exception: Carbolic Acid poisoning)
  - Can be used but by taking precautions in:
    - Convulsant poisons
    - Comatose patients
    - Volatile poisons
    - Esophageal varices
    - Hypothermia

Gastrointestinal decontamination

Catharsis

- It is known to reduce the transit time in GIT
- Two types are Ionic/saline and Saccharide cathartics

Ionic/saline cathartics:

- Magnesium citrate 4 ml/kg
- Sodium sulphate 30 gm.

Saccharide cathartics:

- Sorbitol (D - glucitol) 50 ml 0f 70% solution

Whole Bowel Irrigation

- Involves the administration of non-absorbable polyethyleneglycol which is instilled at the rate of 2L/hr. in adults and 0.5L/hr. in preschool children

Indications:

- Large ingestion of iron, lithium, sustained release or enteric coated drugs
- Also used in cases of body packers

ADMINISTRATION OF ANTIDOTES

- **Physical antidotes:** They neutralize poisons by mechanical action or prevent their absorption.
  - **Activated Charcoal:**
    - This is a fine, black, odorless powder
    - Produced by destructive distillation of various organic materials, usually from organic pulp and then treating at high temperatures. This process increases the absorptive capacity
    - Particles are small but with high absorptive capacity and it acts mechanically by adsorbing and retaining within its pores organic and some mineral poisons

Activated Charcoal [Cont….]

- Usually given mixed with water
- Helpful in Barbiturates, Atropine, Benzodiazipine, Opiates, Quinine, Strychnine, Phenothiazines, Pyrethrins, Aluminium Phosphide, etc.
- Less useful in Corrosives, Heavy metals, Cyanide, Hydrocarbon and Alcohol poisons
- Dose: 50 – 100 mg (Adults) and 15 – 30 mg (Children)

- Demulcents:
  - These are substances which form a protective coating on the gastric mucous membrane and thus do not permit the poison to cause any damage
  - Examples include Milk, Starch, Egg white, Mineral oil, Milk of Magnesia, etc.
  - Fats and oils should not be used for fat soluble poisons like, Kerosene, Phosphorus, OP compounds, DDT, Phenol, Acetone, etc.
- Bulky Foods:
  - They act as mechanical antidote to glass powder by imprisoning the particles within its meshes and thus prevents damage by the sharp glass particles

Chemical Antidotes:

- They counteract the action of poison by forming harmless or insoluble compounds by oxidizing poisons
  - Common Salt: Decomposes Silver Nitrate by direct chemical action
  - Albumen: Precipitates Mercuric Chloride
  - Dialyzed Iron: Neutralize Arsenic poison

- **Physiological Antidotes:**
  - These are substances which produce exactly the opposite actions to that of poison
  - e.g. atropine in organophosphorus poisoning and naloxone in morphine poisoning
- **Chelating agents:**
  - These agents act by forming stable and soluble complexes by the inner ring structure which can combine with the metallic poisons
  - e.g. British Anti Lewisite (BAL) and Ethylene diamine tetra-acetic acid (EDTA)

Methods for enhancing elimination of toxins

- **Urinary alkalization:**
  - This is also known as alkaline diuresis
  - IV bicarbonate 1 lit. of 1.26% over 3 hrs is given
  - Potassium levels can fall, so add 20-40 mmol. potassium to each lit. of IV fluids given
  - Aim for a Urinary pH of 7.5-8.5
- Indications: poisoning with chlorpropamide, phenobarbitone, salicylates, phenoxy acetate herbicides

Methods for enhancing elimination of toxins

- **Extracorporeal techniques:**

  Hemodialysis: can be considered for poisoning with salicylates,

  ethylene glycol, methanol, ethanol, theophylline & lithium

  Haemoperfusion: can be considered for poisoning with theophylline, phenobarbitone & carbamazepine

- **Multiple-dose activated charcoal:**

  This can increase elimination of some drugs by interrupting their enteroenteric & enterohepatic circulation

- The dose given is 50 gm (1 gm/kg in children) of activated charcoal every 4 hrs.
- Indications: poisoning with carbamazepine, dapsone, quinine, phenobarbitone, theophylline

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THANKS