General Introduction Of Practical Toxicology

By
Assist. Lec. Nawar Raad

Definitions

- Toxicology is the quantitive and qualitive study of the adverse effects of toxicants on biological organisms.
- Toxicant is a chemical or physical agent that produces adverse effects on biological organisms.
- A toxicant is a type of poison that is made by humans or introduced into the environment by human activity. This is in contrast to a toxin, which is a poison produced naturally by an organism (e.g. plant, animal, insect).
- Toxicosis, poisoning and intoxication are synonyms for the disease caused by a toxicant.

Toxicity

- Toxicity refers to the amount of a 'toxicant' which is necessary to produce a detrimental effect. On the other hand, the term 'toxicity' is the state or quality of being poisonous or capable of causing harm to the exposed humans or animals.
- Toxicity occurs when a person/animal has accumulated too much of a drug in the bloodstream, leading to the adverse effects within the body.
- Drug toxicity can occur when the dose given is too high, or the liver or kidney is unable to remove the drug from the bloodstream, allowing the drug to accumulate in the body.
- Toxic effect is the response to drug, which is harmful to the health or life of the individual.

Are all substances toxic?

- Yes!
- All are toxic to some quantifiable degree
- Sugar has an LD50 of 30,000 mg/kg.
- Ethanol has an LD50 of only 13,700 mg/kg.
- Even water has a recognized LD50 of slightly greater than 80,000 mg/kg.

Measures Of Toxicity

- Toxicity of Chemicals is determined in the laboratory.
- The normal procedure is to expose test animals
  - By ingestion, application to the skin, by inhalation, gavage/or some other method which introduces the material into the body, or
  - By placing the test material in the water or air of the test animals' environment

Measures of toxicity

- Toxicity is measured as clinical "endpoints" which include
  - ✓ Mortality
  - ✓ Teratogenicity
  - ✓ Carcinogenicity
  - ✓ Mutagenicity (ability to cause heritable change in the DNA).
- At this time we will discuss 2 measures of mortality -the LD50, and the LC50

Measures of Toxicity

The Median Lethal Dose

LD50

The amount (dose) of a chemical which produces death in 50% of a population of test animals to which it is administered by any of a variety of methods

mg/kg

Normally expressed as milligrams of substance per kilogram of animal body weight mg/kg

- Other terms used for prediction of 'lethality' are- 'no observed effect level' (NOEL), 'maximum nontoxic dose' (MNTD) and 'maximum tolerated dose' or 'minimum toxic dose' (MTD).
- Therapeutic index' or 'therapeutic ratio' is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount which causes 'death' (in animal studies) or 'toxicity' (in human studies).

Measures of Toxicity

The Median Lethal Concentration

LC50

The concentration of a chemical in an environment (generally air or water) which produces death in 50% of an exposed population of test animals in a specified time frame

mg/L

Normally expressed as milligrams of substance per liter of air or water.

Duration of Exposure:

Three terms are commonly used to describe the duration of dose(s)

1- Acute Exposure

Application of a single or short-term (generally less than a day) dosing by a chemical

If toxic symptoms are expressed, they are referred to as symptoms of "acute toxicity"

Acute toxicosis means the effects during first 24 hr.

Duration of Exposure:

2-Chronic Exposure

Expression of toxic symptoms only after repeated exposure to a chemical in doses regularly applied to the organism for a time greater than half of its life-expectancy (The life span of a mouse is about nine to 12 months).

If toxic symptoms are expressed, they are referred to as symptoms of "chronic toxicity"

Chronic toxicosis the effects produced by prolonged exposure

Duration of Exposure:

3. Subchronic Exposure

- Toxic symptoms are expressed after repeated applications for a timeframe less than half the life expectancy of the organism - but more often than a single dose or multiple doses applied for only a short time
- If toxic symptoms are expressed, they are referred to as symptoms of "subchronic toxicity"
- Subchronic are used to cover the large gap between the acute and chronic.

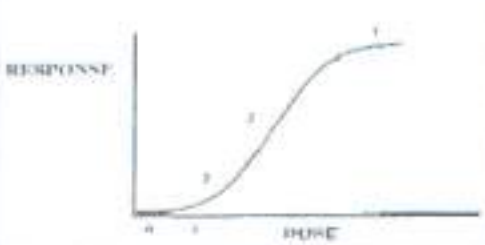
Dose-Response Relationship:

- As the dose of a toxicant increases, so does the response.

0-1 NOEL

2-3 Linear range

4 Maximum response



Dose determines the biological response

* NOEL / no observed adverse effect level

Absorption, Distribution, Metabolism and Excretion of Poisons

I. Absorption:

The toxic effects may be local, but the toxicant must be dissolved and absorbed to some extent to affect the cell.

Solubility is the primary factor affecting the absorption.

The insoluble salts and ionized compounds are poorly absorbed, while the lipid-soluble substances are usually readily absorbed even through the intact skin; e.g., barium (Ba) is toxic, but barium sulphate can be used for intestinal contrast radiography because of its low absorption.

Absorption, Distribution, Metabolism and Excretion of Poisons

II. Distribution:

Distribution (or translocation) of a toxicant occurs via bloodstream to reactive sites, including storage depots.

Liver receives portal circulation, and is mostly involved with 'intoxication' (and 'detoxification'). The selective deposit of foreign chemicals in various tissues depends on the receptor sites.

The ease of chemical translocation depends largely on its water solubility. Polar- or aqueous-soluble agents tend to be excreted by the kidney; lipid-soluble chemicals are more likely to be excreted via the bile and accumulate in fat depots.

Absorption, Distribution, Metabolism and Excretion of Poisons

III. Metabolism:

Metabolism (or biotransformation) of toxicant by the body is an attempt to detoxify.

In some cases, the metabolized xenobiotic agents are more toxic than the original compound. This is called 'lethal synthesis'.

The biotransformation of many organophosphorus insecticides (OPIs) produces metabolites more toxic than the initial (or parent) compounds (e.g., parathion to paroxan).

Absorption, Distribution, Metabolism and Excretion of Poisons

IV. Excretion:

Excretion of most toxicants and their metabolites is by way of the kidney.

The excretion rate may be of primary concern because some toxicants can cause violative residues in food-producing animals.

The route of administration, dose and condition of the animal may have a profound effect on the excretion rates.

The toxicants are removed in the kidney by glomerular filtration, tubular excretion by passive diffusion and active tubular secretion. The damage to kidney from the excretion of xenobiotics is specific to the anatomic location where the excretion occurs.

The excretion sites are proximal tubules, glomeruli, medulla, papilla and loop of Henle. The proximal convoluted tubule is the most common site of toxicant induced injury.

Factors affecting poisoning

1. **Exposure-related Factors:**
   - Duration and frequency of exposure
   - Route of exposure
   - Exposure of a poison relative to periods of stress or food intake
   - Environmental factors like temperature, humidity and barometric pressure

Factors affecting poisoning

2. **Biologic Factors:**
   - The age and size of animal
   - The distribution and metabolism of xenobiotic agents
   - The membrane permeability, and hepatic and renal clearance capability
   - The body surface area
   - Nutritional and dietary factors, hormonal and health status, organ pathology

Factors affecting poisoning

3. **Chemical Factors:**
   - Chemical nature of a poison determines the solubility
   - The vehicle or carrier of the toxic compound
   - The isomers, including optical isomers, vary in toxicity
   - The adjuvants are formulation factors used to alter the toxicologic effect of the active constituent
   - The binding agents, enteric coating and sustained-release preparations.
   - The flavoring agents affect the palatability, and thus the excess amount of toxic drugs is ingested.

Difficulties in Toxicological studies

1. No ethical way to get human volunteers, hence need to use "model" systems of rats, cats, dogs, rabbits, etc.
2. Baseline study required (control group)
3. Response not necessarily numerical
4. Variations of individual response:
   a) Allergy or immunity
   b) Organism specific response, not applicable to humans
   c) Dosage response
   d) Response time, latency, acute versus chronic
   e) Difficulty in measuring intended variable (lead in liver measured by lead in blood)

Nicotine Toxicity

By

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NICOTINE

- Nicotine is a potent parasympathomimetic stimulant and an alkaloid found in the nightshade family of plants
- Nicotine is a toxic substance found in the tobacco plant (Nicotiana tabacum).
- The commercial preparation of the plant involves drying the leaves for the production of chewing tobacco, cigars, cigarettes, & snuff.
- Nicotine is easily isolated from the plant for use in nicotine replacement products (gum, patches, & nasal spray).
- Nicotine constitutes approximately 0.6-3.0% of the dry weight of tobacco
- Nicotine acts as a receptor agonist at most nicotinic acetylcholine receptors.

NICOTINE

- Nicotine is highly addictive, an average cigarette yields about 2.5 mg of absorbed nicotine, the substance acts as a stimulant in mammals, While high amounts (50-100 mg) can be harmful.
- this stimulant effect is a contributing factor to the addictive properties of tobacco smoking. Nicotine's addictive nature includes psychoactive effects, drug reinforced behavior, compulsive use, relapse after abstinence, physical dependence and tolerance
- Reinforcement refers to the response that is probable after a stimulus can be positive or negative.
  - ✓ Positive reinforcement means that the activity or situation have beneficial outcomes such as pleasure or reward.
  - ✓ Negative reinforcement refers to the removal or cessation of negative feelings or behaviors when an activity or situation occurs.
- In relation to drugs, positive and negative reinforcement are both required to instill a certain behavior in a person such as an addiction
- Beyond addiction, both short and long-term nicotine exposure have not been established as dangerous to adults, at high-enough doses, nicotine is associated with poisonings and is potentially lethal

Therapeutic uses

- **Primary TU of nicotine is intreating nicotine dependence in order to eliminate smoking**
- "NICORETTE GUM" used to treat nicotine addiction .
- Cognitive enhancements?

Working memory

Visual perception

visual attention

Motor function

Smoke tobacco

Snuff

Green Tobacco Sickness (GTS)

A set of symptoms caused by nicotine poisoning, often due to exposure during tobacco harvesting.

Management

If the skin exposed to wet tobacco leaves, conc. nicotine liquid, or nicotine pesticide compound ;

the pt's clothing ⇨promptly removed & the skin thoroughly washed with soap & water.

Absorption of nicotine

- The most common way to get nicotine into your bloodstream is through inhalation
- Your lungs are lined by millions of alveoli, which are the tiny air sacs where gas exchange occurs
- Nicotine taken in by cigarette or cigar smoking takes only 10-15 seconds to reach the brain but has a direct effect on the body for only -30 minutes
- Nicotine has pKa value of 7.9, its well absorbed through the buccal mucosa, respiratory tract, intestinal tract, and skin.
- Absorption of nicotine across biological membranes depends on pH (hyperacidity reduce absorption since it become in ionized form which is less absorbable).

$$BH^+ \leftrightarrow B + H^+$$

Distribution of nicotine

- Nicotine generally achieves a volume of distribution of 1 L/kg. reaches the brain in approximately 8 seconds, with CNS levels of nicotine rising rapidly & then declining rapidly as the drug is redistributed to other tissues.
- Nicotine readily cross the placenta & also transmitted in small concentrations in breast milk.
- Nicotine in smoke peaks in brain very rapidly, despite relatively slow increase in blood concentration
- A typical cigarette contains 8-20 mg of nicotine.
- 2.5 mg of nicotine is absorbed

Metabolism of nicotine

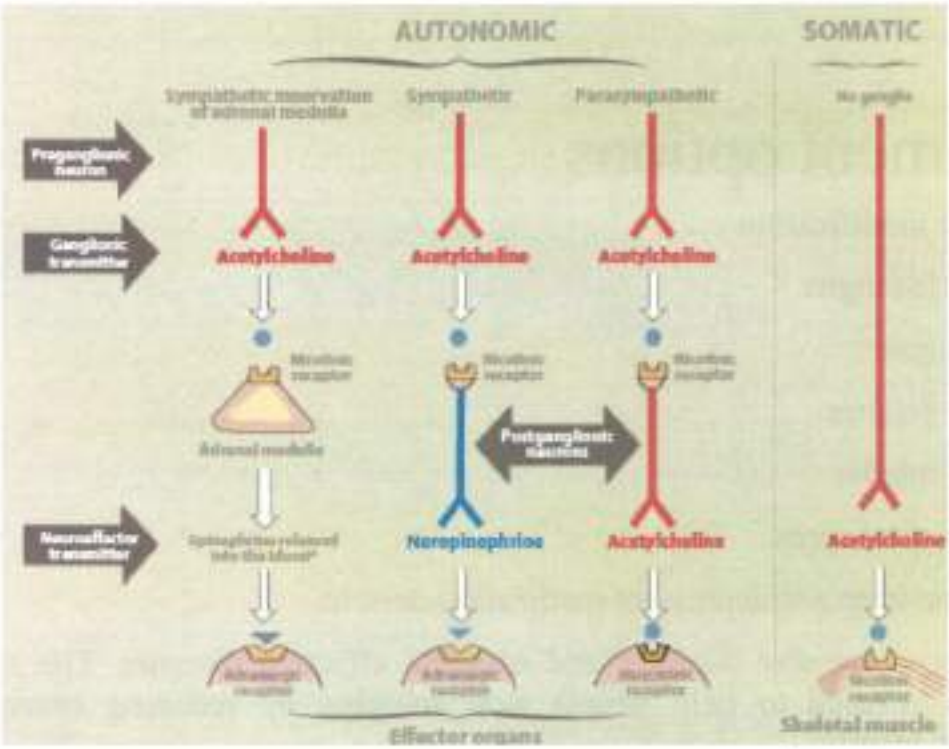
- Metabolism takes place primarily in CP450 system of the liver (80-90%), but also, to lesser extent, in the kidney & lung.
- About 80 percent of nicotine is broken down to cotinine by enzymes in your liver (e.g., CYP2A6)
- Nicotine t1/2 is 1-4 hrs., shorten in smokers to 2 hrs. & the main oxidative metabolites of nicotine are:

  1-Cotinine (major) ---t1/2 is 9 hrs.

  2-Nicotine–1-*N*-oxide(minor)

Execration of nicotine

- Cotinine and the remaining nicotine is filtered from the blood by your kidneys and excreted in the urine
- In Breast milk (in heavy smoker about 0.5 mg/L of milk), & this is large dose since infant is small.



Addiction

Nicotine meets both the psychological and physiological measures of addiction

- Psychological - people who are addicted to something will use it compulsively, without regard for its negative effects on their health or their life
- Physiological - anything that turns on the reward pathway in the brain is addictive. Because stimulating this neural circuitry makes you feel so good, you will continue to do it again and again to get those feelings back

Treatment options

- Behavior modification
- Nicotine lozenges
- Nicotine gum
- Nicotine patches
- Nicotine inhaler
- Nicotine nasal spray
- Bupropion is an antidepressant medication used to

treat major depressive disorder and seasonal affective disorder. The zyban brand of bupropion is used to help people stop smoking by reducing cravings and other withdrawal effects.

Acute effects

- Classic stimulant effects of arousal (e.g. Increased heart rate and blood pressure, alertness, appetite suppression)
- Carbon monoxide (in smoked form) reduces oxygen transport to heart and other organs
- Vasoconstriction
- Can have calming (anxiolytic) effects in some individuals
- Mild euphoria
- Cognitive enhancements
- Antidepressant effects

Chronic effects: cancer

Tobacco use accounts for one-third of all cancers • cancers relating to tobacco include:

Mouth
Pharynx
Larynx
Esophagus
Stomach
Lang
Cervix
Kidney
Bladder
Throat
Pancreas

- ❑ Cigarette smoking has been linked to about 90 percent of all lung cancer cases
- ❑ 430,000 annual deaths are attributed to cigarette smoking

More chronic effects

- ✓ Emphysema (chronic bronchitis)
- ✓ Stroke
- ✓ Vascular disease
- ✓ Esophageal reflux
- ✓ Heart disease
  - ❖ It is estimated that nearly one-fifth of deaths from heart disease are attributable to smoking
- ✓ Many of these are actually caused by other chemicals in cigarette smoke or in smokeless tobacco products
- ✓ Secondary smoke also increases the risk for many diseases
- ✓ Secondhand smoke is estimated to cause approximately 3,000 lung cancer deaths per year among nonsmokers and contributes to as many as 40,000 deaths related to cardiovascular disease
- ✓ Exposure to tobacco smoke in the home increases the severity of asthma for children and is a risk factor for new cases of childhood asthma
- ✓ Environmental tobacco smoke(ETS) exposure has been linked also with sudden infant death syndrome

Mechanism of toxicity

In adrenal medulla:

•By binding to ganglion type nicotinic receptors in the adrenal medulla nicotine increases flow of (epinephrine), a stimulating hormone & neurotransmitter.

•By binding to the receptors, it causes cell depolarization & influx of Ca through voltage-gated Ca+ channels. Calcium triggers the exocytosis of chromaffin granules & thus the release of epinephrine (& NE) into bloodstream. The release of epinephrine(adrenaline) causes an increase in heart rate, blood pressure& respiration, as well as higher blood glucose levels.

Mechanism of toxicity

In CNS:

- By binding to nicotinic Ach receptors, nicotine increases the levels of several NT, It is thought that increased levels of dopamine in the brain are responsible for the euphoria & relaxation and eventual addiction caused by nicotine consumption.
- Nicotine has higher affinity for Ach receptors in brain than those in skeletal muscle, though at toxic doses it can induce contractions & respiratory paralysis.

Acute nicotine toxicity

The biphasic pattern, started as initial stimulation (↑H.R., ↑B.P.,↑R.R, hyperactivity)

followed quickly by inhibition (↓H.R.,↓B.P.,↓R.R, hyperactivity) & the death if occur, which attributed to respiratory paralysis.

- Acute nicotine exposure

(From –insecticide sprays or tobacco)

Nausea, vomiting, salivation, diarrhea, dizziness, mental confusion, weakness.

- Fatal exposure(60 mg fatal for adult)

Decreased blood pressure, difficult breathing, irregular pulse, convulsions, respiratory failure & death.

Sign of nicotine toxicity

Extremely RARE IN SMOKERS & thus even more rare in Nicotine replacement therapy (NRT) use.

Nausea and/or vomiting

Sweating

Vertigo and/or light-headedness

Tremors

Confusion

Weakness

Racing heart

Management

♦ Orogastric lavage ⇨ if pt with oral exposure but not vomited prior to presentation.

♦ Activated charcoal ⇨ effectively binds nicotine & should be used to ↓absorption in GI exposures also in IV exposures.

♦ Symptomatic treatment :

- Seizures ⇨ benzodiazepines.
- Cardiovascular compromise ⇨ atropine for symptomatic bradycardia , Fluids for hypotension. dopamine or nor epinephrine. If hypotension does not respond to fluids.
- Respiratory compromise ⇨ oxygen

Not recommended management

- Syrup of ipecac or apomorphine induced emesis ⇨not recommended Because nicotine poisoning may cause unexpected seizures or respiratory depression.
- Urine acidification: for enhancing elimination un necessary since it may cause complications of metabolic acidosis.

Nicotine is a weak base & excretion can theoretically be enhanced by urine acidification, but it's unnecessary because the potential risks of acidification in patient with seizures outweigh any of the theoretical benefits. Furthermore, because of the symptoms are generally short-lived.

- nicotine toxicity is a complex therapeutic problem & based on symptom analysis with primary emphasis on respiratory support
- Antidotes ⇨ there is no specific antidote, only for animals we can use mecamylamine, hexamethonium& pimpedine.

Procedure

- 5 cigarettes macerated in 50 ml hot D.W. overnight then filtered by filter paper after 15 min. the resulting solution contain 1.6mg/ml nicotine.
- 5 mice given 15, 18, 20, 22, 25 units IP. respectively of nicotine solution.
- Observe the biphasic pattern of nicotine toxicity that started as stimulation followed by depression then death if it occur , and we notice in this experiment salivation, hyperpnea, prostration, clonic and tonic convulsions, piloerection are usually followed respiratory and cardiac arrest
- LD50% of nicotine for mice is 3 mg/kg

Acute toxicity study, determination of LD50

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LD50 : Median Lethal Dose

- The amount of the chemical or a toxic agent (such as a poison, virus, or radiation) that is sufficient to kill 50 percent of a population of animals usually within a certain time.
- Also called median lethal dose.
- Expressed as milligrams of substance per kilogram of body mass.
- The LD50 is one way to measure a material's short-term poisoning (acute toxicity).

ED50 : Effective dose

- ED50 is a medical term that stands for "effective dose."
- The 50 stands for 50 percent, which is the amount of people who experience a positive, therapeutic effect of the treatment in order for it to be deemed to be effective.
- While ED50 is occasionally used to describe the effectiveness of drugs, most often it's used in radiology to describe the effects of radiation treatment.

Drug variability toxicity & assessment

- ED50: Effective dose for 50% of the subject
- LD50 : Lethal Dose for 50% of subject
- The Therapeutic Index:

  TI: LD50/ED50

- No drug is 100% safe.

Why to study LD50

- To compare toxic potency or intensity of different chemicals.
- To measure how much of a Chemical required to cause death (lethality testing).
- Measure of the immediate or acute toxicity of a chemical in a particular of being tested animals.

How to determine ED50

- total no. of people undergone treatment.
- total no. of people experienced therapeutic effect.
- divide 2 over 1 and multiply by 100 to get %

Determination of LD50

- At least 3-4 dose levels where used to produce test groups with a range of toxic effects, data should be sufficient to produce dose-response curve for estimation of LD50.
- Volume of dose administered depend on the size of the test animal,

  In rodents it should not exceed 1ml/100g of body weight.
- LD50 values depend on the routs of administration, value increasing in the following sequence

IV < IP < SC < Oral

Signs recorded during acute toxicity studies

- These are increased motor activity, anesthesia, tremors, arching and rolling, clonic convulsions, tonic extension,
- lacrimation, **Straub reaction,** salivation, muscle spasm, **writhing**, hyperesthesia, **loss of righting reflex**, depression, ataxia,
- stimulation, sedation, blanching, hypnosis, cyanosis and analgesia

Experimental apparatus

- mice cage
- animal's equi-arm-balance,
- 1ml injection syringe,
- and electronic calculator

How to choose and divide the experimental animals

Principle of choice: We should choose the animals sensitive to the trial agents. Considering about source, economic value, convenient handling to the animals, we often choose mice for our experiment.

The number of every group should be more than the number of groups.

Ex. divide the animals into 7 groups in this experiment, and there are 10 animals in each group.

How to group animals

- We divide these animals into different groups according to their weight this time. Their weight of each group must be almost the same, and the different of the sum of weight in each group must be less than 5g.

Common steps performed in all tests

- The test substance was administered in graduated doses to several groups of experimental animals.
- Two Species were selected-one rodent & other non-rodent, because species differ in their response to toxic agents.
- At least 5 rodents were used at each dose level. They were all of the same sex & animals are caged individually.
- The substance used in toxicity tests should be as pure as the material eventually to be given to humans
- The test substance is dissolved in suitable solvent if necessary,

Methods to determine LD50

- Different methods used to determine LD50 are as follows:
- Karber's method.
- Up & down procedure.
- Fixed dose method.
- Reed-Muench method
- Miller & Tainter method
- Lorke's method

Different Methods For The Determination Of LD50

- **Graphical method, arithmetical method and statistical approach**
  - For routine practical class work; Reed-Muench, Miller-Tainter and Karber's Method
  - Arithmetical method: Karber method
  - Graphical method: Miller and Tainter

Contents	Method Karber [7]	Method of Miller and Tainter [7]	Method of Lorke [8]
No. of rodents used	More than necessary	More than necessary	Appropriate
Expenditure	High	High	Average
Accuracy of results	Inaccurate	Inaccurate	Doubtful

Different methods for the determination of LD50

- For calculating LD50 by any one method:
  - Find out the least tolerated (smallest) dose (100% mortality) and most tolerated (highest) dose (0% mortality) by hit and trial method
  - Once these two doses are determined, select at least 5 doses in between them, and observe mortality due to these doses
  - Apply correction factor to 0% and 100% mortality group [for 0% dead = 100 (0.25/n) and for 100% dead = 100x (n-0.25/n), where n = number of death]

Karber's method.

- The interval mean of the no, dead in each group of animals was used as well as the difference between doses for the same interval.
- The product of interval mean & dose difference was obtained.
- The sum of the product was divided by the no. of animals in a group & the resulting quotient was subtracted from the least tolerated dose in order to obtain LD50 value

$$LD50 = \text{Least tolerated dose} - \Sigma\,(a \times b) / N$$

- Where N is the no. of animals in each group,

  a is the dose difference

  b is the mean mortality

- DISADVANTAGE: Too many animals are sacrificed by this methods.

Karber's method.

Group	Dose(mg/kg)	Dose difference (mg/kg) a	Dead	Mean B	Product a * b
1	330	-	8	-	-
2	300	30	7	7.5	225
3	280	20	5	6	120
4	250	30	3	4	120
5	220	30	1	2	60
6	120	100	0	0.6	60
					T=585

LD50 = 330 - (585/8) =256.88 mg/kg

Lorke's method

- **PHASE 1**: 3 groups of 3 mice are prepared. One dose was given to each group intraperitoneally. The treated mice were monitored for 24 hr for mortality & general behavior.
- **PHASE 2**: After 24 hr 3-4 groups of one mouse were given doses based on the findings of phase 1, intraperitoneally. The mice were again monitored for 24 hr. The geographic mean of the least dose that killed mice & the highest dose that did not kill mice was taken as the median lethal dose.
- Advantage: fewer animals were sacrificed.
- Disadvantage: Accuracy, reproducibility & reliability are questionable.

Limitations of LD50

- The LD50 gives a measure of the immediate or acute toxicity
- Results may vary greatly
- LD50 is not tested on humans
- All relation to humans are only a guess
- The LD50 test is neither reliable nor useful Because the human lethal dose is difficult to be predicted from animal studies

Drug toxicity on liver

By
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Introduction

The liver is the main organ where chemicals are metabolized and excreted. so, the liver cells are exposed to these chemicals which can results in liver dysfunction, cell injury and liver failure.

toxic hepatitis occurs when your liver develops inflammation because of exposure to a toxic substance.

Toxic hepatitis may also develop when you take too much of a prescription or over the-counter medication.

Liver toxicity define as implies chemical driven liver damage

One of the liver's roles involves removing and breaking down most drugs and chemicals from your bloodstream. Breaking down toxins creates by products that can damage the liver. Although the liver has a great capacity for regeneration, constant exposure to toxic substances can cause serious, sometimes irreversible harm

Toxic hepatitis can be caused by :

- Alcohol : Heavy drinking over many to alcoholic hepatitis-inflammation in the liver due to alcohol.)
- Over-the-counter pain relievers : Nonprescription pain relievers such as acetaminophen (Tylenol, others). aspirin, ibuprofen (Advil, Motrin IB, others) and naproxen (Aleve, others) can damage your liver, especially if taken frequently or combined with alcohol.

Prescription medications. Some medications. linked to serious liver injury include the combination drug amoxicillin-clavulanate (Augmentin), halothane, isoniazid, valproic acid (Depakene), phenytoin (Dilantin, Phenytek). azathioprine (Azasan, Imuran), niacin (Niaspan), atorvastatin (Lipitor), lovastatin (Mevacor), pravastatin (Pravachol) simvastatin Zocor). Fluvastatin (Lescol), rosuvastatin (Crestor), ketoconazole certain antibiotics, certain antivirals and anabolic

Industrial chemicals. Chemicals you may be exposed to an the job can cause liver injury. Common chemicals that can cause liver damage include the dry cleaning solvent carbon tetrachloride, a substance used to make plastics called vinyl chloride, the herbicide paraquat and a group of industrial chemicals called polychlorinated .biphenyls

Liver injury

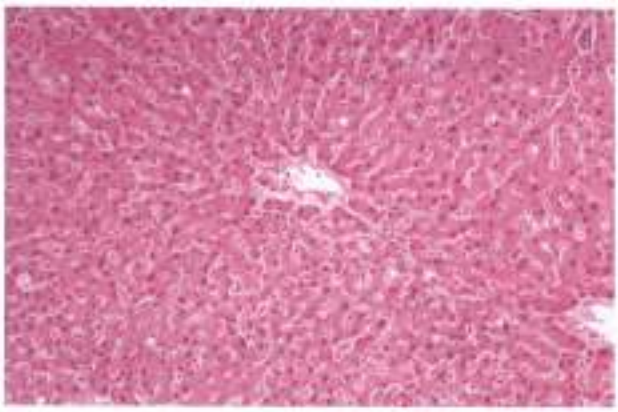
When drugs injure the liver and disrupt its normal function, symptoms, signs, and abnormal blood tests of liver

Disease develop: Abnormalities of drug induced liver diseases are similar to those of liver diseases caused by other agents such as viruses and immunologic diseases

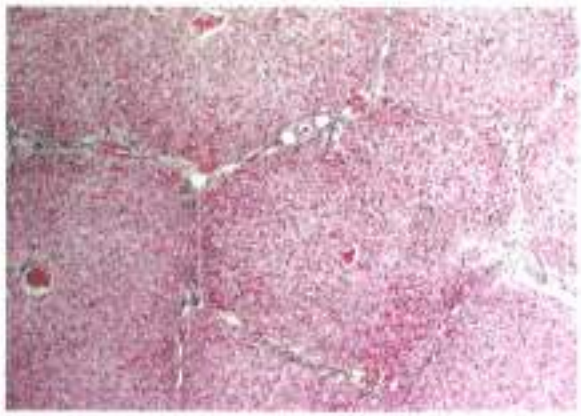
For example, drug-induced hepatitis (inflammation of the liver cells) is similar to viral hepatitis; they both can cause elevations in blood levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (enzymes that leak from the injured liver and into the blood) as well as anorexia (loss of appetite), fatigue, and nausea.

Drug-induced cholestasis (interference with the flow of bile that is caused by injury to the bile ducts) can mimic the cholestasis of autoimmune liver disease (e.g. primary biliary cirrhosis or PBC) and can lead to elevations in blood levels of bilirubin (causing jaundice), alkaline phosphatase.

Normal liver section



Hexagonal lobule



Types of the liver injury:

The liver injury caused by chemicals (hepatotoxicity) is not a single entity, thus the lesion observed does not depend only on the chemical agent involved, but also on the nature of exposure (acute or chronic, reversible or irreversible), mechanism of toxicity, number & type of the cells affected & localization within liver (periportal, mid or transient & centrilobular zones).

Accordingly, injuries divided into the following major types:

Steatosis (fatty liver),

Necrosis,

Apoptosis,

Fibrosis,

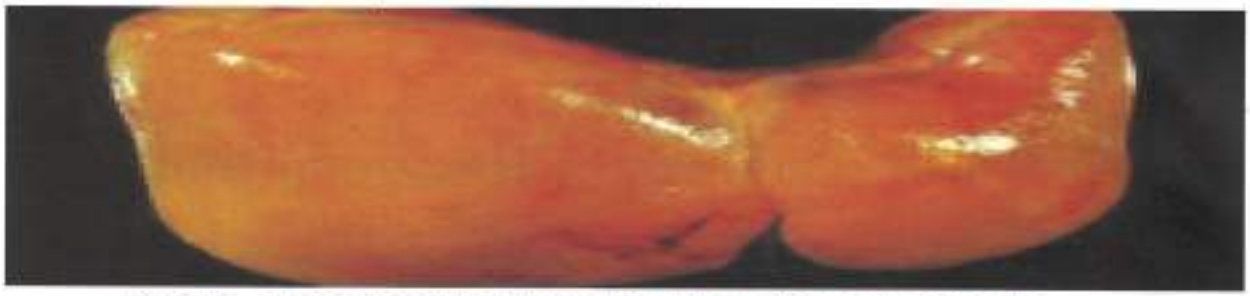
Cirrhosis,

Cholestasis,

Hepatitis,

Carcinogenesis.

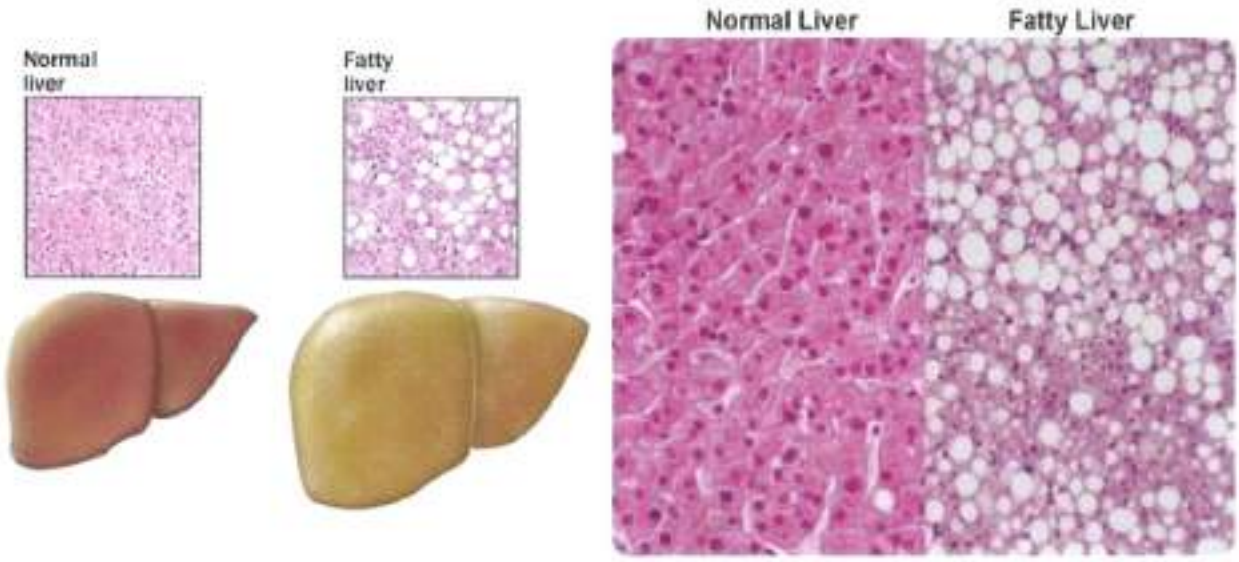
1. Steatosis (fatty liver):



Non-alcoholic fatty liver disease is estimated to affect up to 27% of the world's population

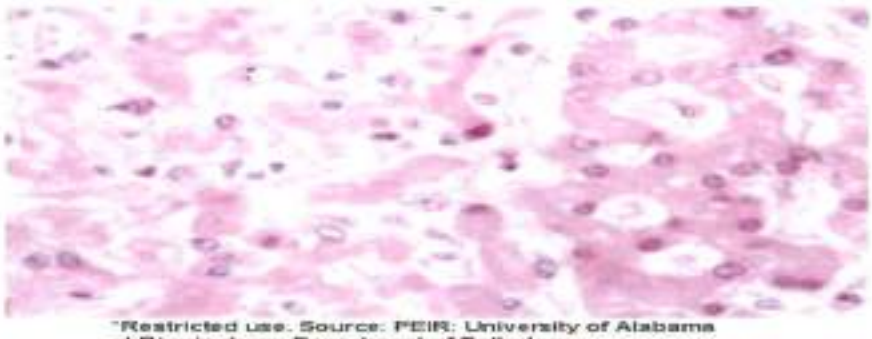
Is accumulation of abnormal amount of lipids (mainly triglycerides) as vacuoles & droplets within hepatocytes; as a result of imbalance between rate of synthesis & release of these lipids by liver cells into circulation.

In general, chemicals-induced steatosis is often reversible & doesn't necessary lead to hepatocytes death and it is an acute response to many but not all hepatotoxicants.



2. Necrosis (cell death):

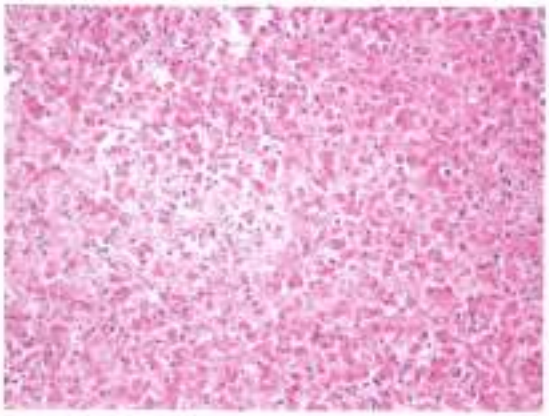
Liver Cell Necrosis – Councilman Body



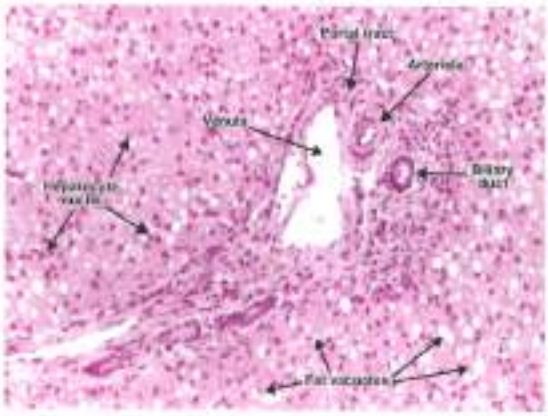
"Restricted use. Source: PEIR: University of Alabama at Birmingham, Department of Pathology

Is an acute response of liver injury associated with cell swelling, leakage of nuclear material and influx of inflammatory cells as a result of plasma membrane damage, alteration in calcium homeostasis, lipid peroxidation, disruption to cytoskeleton and damage to cell organelles.

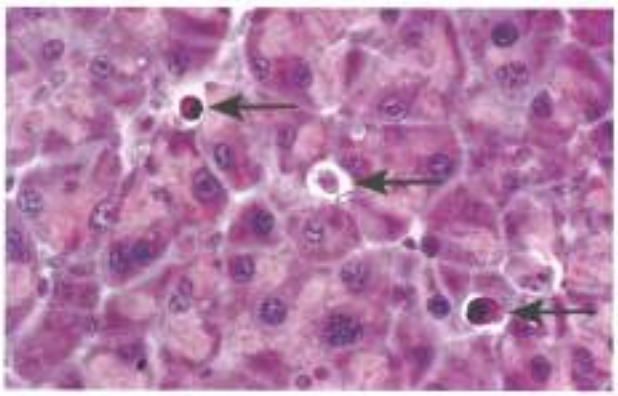
Liver necrosis



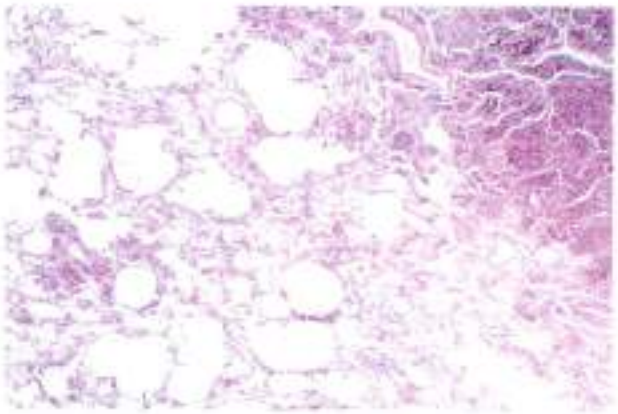
Necrosis with steatosis



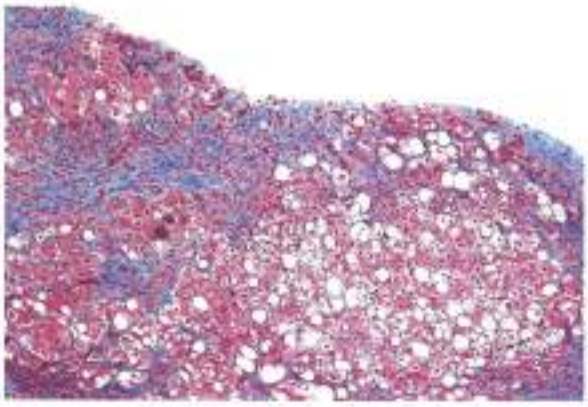
3. Apoptosis



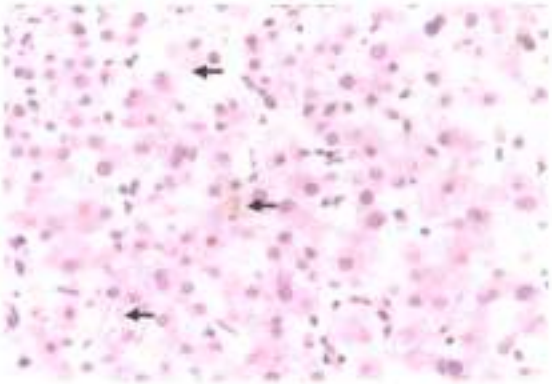
4. Fibrosis



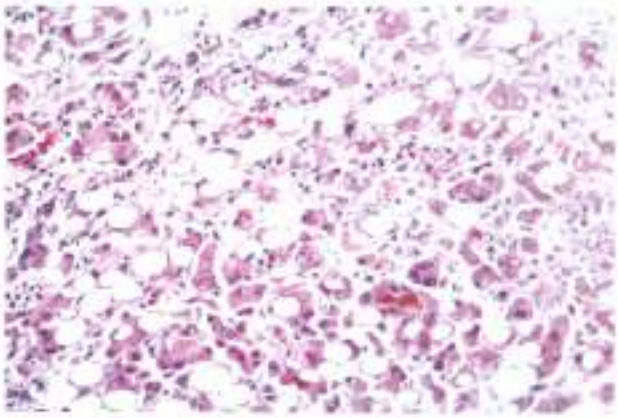
5. Cirrhosis



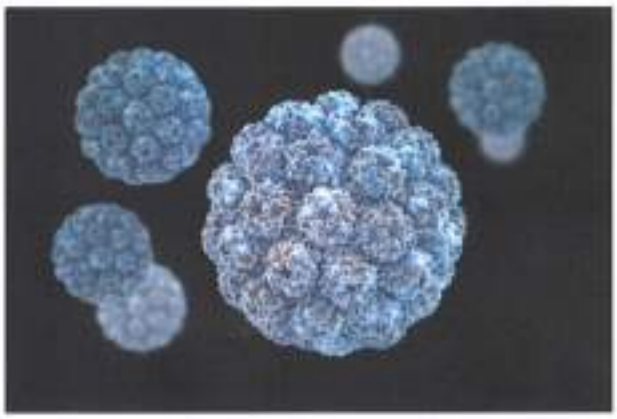
6. Cholestasis



7. Hepatitis



8. Carcinogenesis



Diazepam toxicity

Diazepam widely used orally as anxiolytic agent and muscle relaxant IV form of diazepam acute sever agitation and pre medication for anesthesia Diazepam act by stimulation for GABA that inhibit central transmission at neuromuscular junction

a sedative for minor surgery or invasive procedures, and for treatment of status epilepticus or severe recurrent seizures. Diazepam therapy has not been associated with serum aminotransferase elevations, and clinically apparent liver injury from diazepam has been reported,

Pharmacologic activity of diazepam

Centrally Acting Agents

diazepam is to be combined with other centrally acting agents careful consideration should be given to the pharmacology of the agents employed particularly with compounds that may potentiate or be potentiated by the action of Valium, such as phenothiazines, antipsychotics, anxiolytics/sedatives, hypnotics, anticonvulsants, narcotic analgesics, anesthetics, sedative antihistamines, narcotics, barbiturates, MAO inhibitors and other antidepressants.

Signs of diazepam toxicity

Cyanosis

Confusion

Depression

Dizziness

Labored breathing

Falling into a comatose state

Tiredness

Uncoordinated movement

Stomach upset

Rashes

nystagmus (rapid eye movement from side to side)

Weakness

Double vision

Death

Elimination of diazepam

Elimination The initial distribution phase is followed by a prolonged terminal elimination phase (half-life up to 48 hours).

The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours

Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates. The clearance of diazepam is 20 to 30 mL/min in young adults. Diazepam accumulates upon multiple dosing and there is some evidence that the terminal elimination half-life is slightly prolonged.

Toxic dose of diazepam

The recommended daily dose is 4.4 mg of diazepam through out the day only up to 10 mg of diazepam should be taken at on time less in someone with out a tolerance to diazepam

Toxic dose<LD50> of valium is 720 mg/kg in mice.

And 1240 mg/kg in rats.

diazepam is incredibly safe and difficult to overdose if. taken by itself

Determination of diazepam toxicity

1. By TLC estimation of RF value

Stationary phase: silica gel

Mobile phase: chloroform acetone

Reagent-DRAGENDROFF

2. Response to UV radiation

With UV 254 nm seems to be Brown colure

With UV 366 nm seems to be green colure

3. Exposure to HCL acid give yellow colure

Metal Toxicity

By
Assist. Lec. Nawar Raad

Lab objectives:

- Objectives of this lab are to determine:
- some toxic effects associated with arsenic (As), cadmium (Cd), lead (Pb), & mercury (Hg) which are major toxic metals.
- biomarkers of metal exposure.

METALS POISONING/TOXICITY

- "Toxicity" is a function of solubility. The insoluble compounds as well as the metallic forms often exhibit negligible toxicity.
- Toxicity of any metal depends on its ligands: organo-metallic forms like methylmercury and tetraethyl lead, can be extremely toxic; while organo-metallic derivatives are less toxic, e.g., cobaltocenium cation.
- 'Metal toxicity' is toxic effect of some metals in certain forms and doses. Some metals are toxic when they form poisonous soluble compounds. Some metals have no role, i.e., they are not essential minerals, or they are toxic in a certain form.
- In case of Pb, any measurable amount may have ill health effect. Often 'heavy metals' are thought as synonymous, but the 'lighter metals' may also be toxic in certain circumstances, like beryllium; and not all heavy metals are particularly toxic, and some are essential, like Fe.
- 'Trace elements' become poisonous when taken in abnormally high, toxic doses. The heavy metals like Fe, Cu, manganese (Mn) and Zn in small quantities are essential for good health.

TOXIC METALS

- arsenic (As, a metalloid), cadmium (Cd), lead (Pb), mercury (Hg), barium (Ba), beryllium, osmium, thallium, vanadium, and radioactive metals (viz., actinium, thorium, uranium, radium, transuraniums- plutonium and americium, polonium, and radioactive isotopes of metallic elements not otherwise strongly toxic- cobalt (Co)-60 and strontium-90), etc.
- Aluminium (Al) has no known biological role and its classification into 'toxic metals' is controversial. Its significant toxic effects and accumulation to tissues are found in impaired renal patients. However, the individuals with healthy kidneys can be exposed to large amounts of Al with no ill effects. Thus, Al is not dangerous to persons with normal elimination capacity. Vanadium poisoning is notable as it is an anticorrosive component of automotive steel, fragments of which can be left in passengers during automobile accident

ARSENIC:

- Sources of exposure:
- Environmental arsenic exposure mainly occurs from arsenic-contaminated drinking water.
- Manufacture of pesticides, & herbicides.
- Smelting industries.

- Why arsenic accumulates in keratin rich tissues such as hair, skin & nails?

Arsenic forms covalent complex with sulfhydryl groups of cysteine & because keratin contains many cysteine residues, this makes it one of the major sites for accumulation of arsenic.

Some Effects Of Arsenic Poisoning:

- Acute poisoning:
- Hair loss
- Transverse bands of opacity in nails (Mees' lines) (Fig 1)
- Fatty degeneration of liver

- Chronic poisoning:
- Melanosis (neck, eyelids)
- Hyperkeratosis (Fig 2)
- Hyperpigmentation (rain drop pattern) (Fig 3)
- Skin cancer (Fig 4)

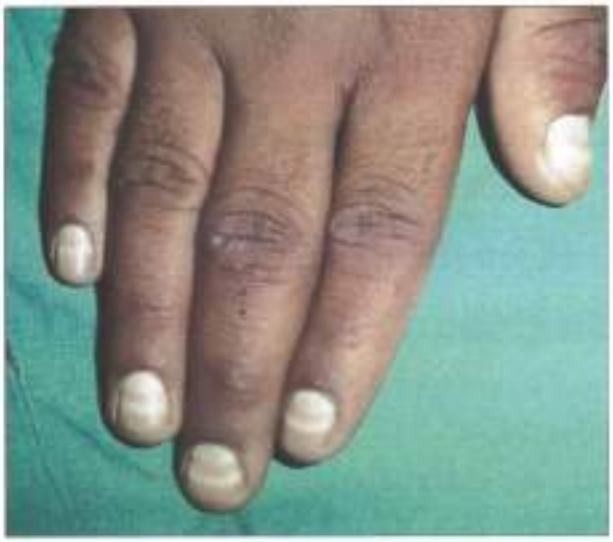


Figure 1. Mees' Lines

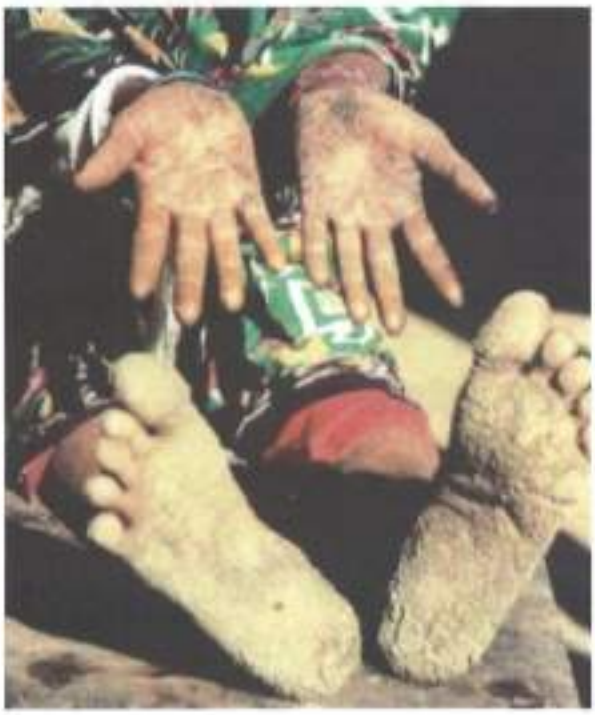


Figure 2. Hyperkeratosis—arsenic poisoning

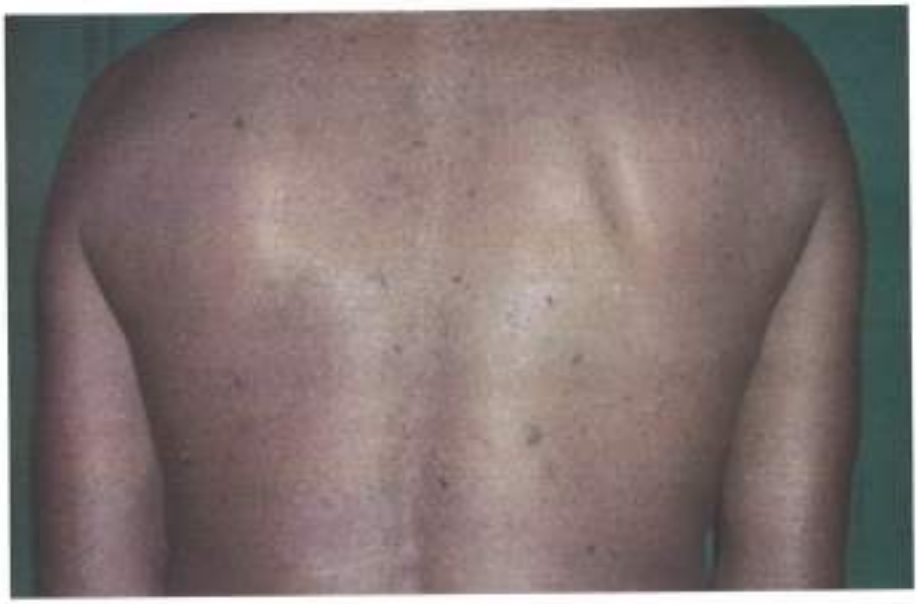


Figure 3. Raindrop pigmentation—arsenic poisoning

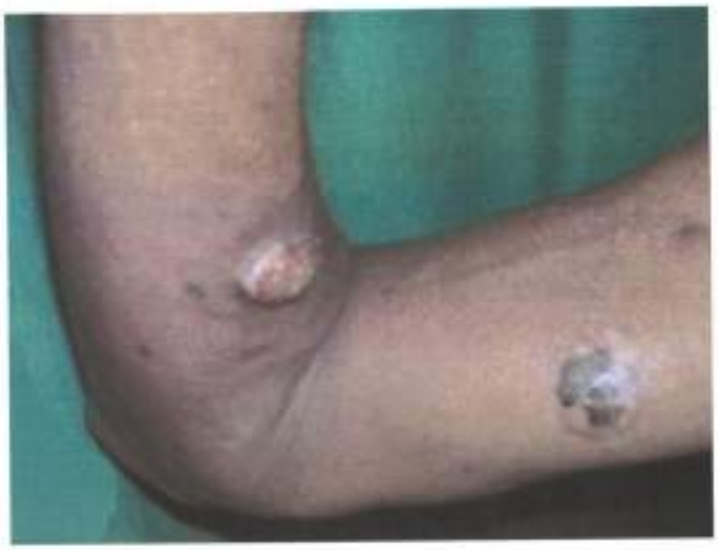


Figure 4. Skin cancers—arsenic poisoning

Cadmium :

- **Sources of exposure:**
- Food due to the use of cadmium-containing water for irrigation of plants.
- Cigarette smoking.

Some Toxic Effects Of Cadmium:

- kidney damage.
- Skeletal damage: Long-term high cadmium exposure may cause skeletal damage, first reported from Japan, where the itai-itai (ouch-ouch) disease (Fig 5) (a combination complications of osteomalacia & osteoporosis) was discovered in the 1950s. The exposure was caused by cadmium-contaminated water used for irrigation of local rice fields.
- Prostate cancer & kidney cancer.
- *Cadmium may affect bone directly through:*

1. direct interference with incorporation of calcium in bone cells, &
2. direct stimulation of bone resorption, & impairment of bone formation

Figure 5. Itai-itai disease

Rice fields

LEAD

Source of exposure:

- Young children are particularly vulnerable to the toxic effects of lead.
- Environmental sources of lead exposure in children are
- shown in (Fig 6).
- A major route of exposure for the general population is from food & water.
- Other potential sources of lead exposure are battery making, soldering, jewelry making, & pottery making.

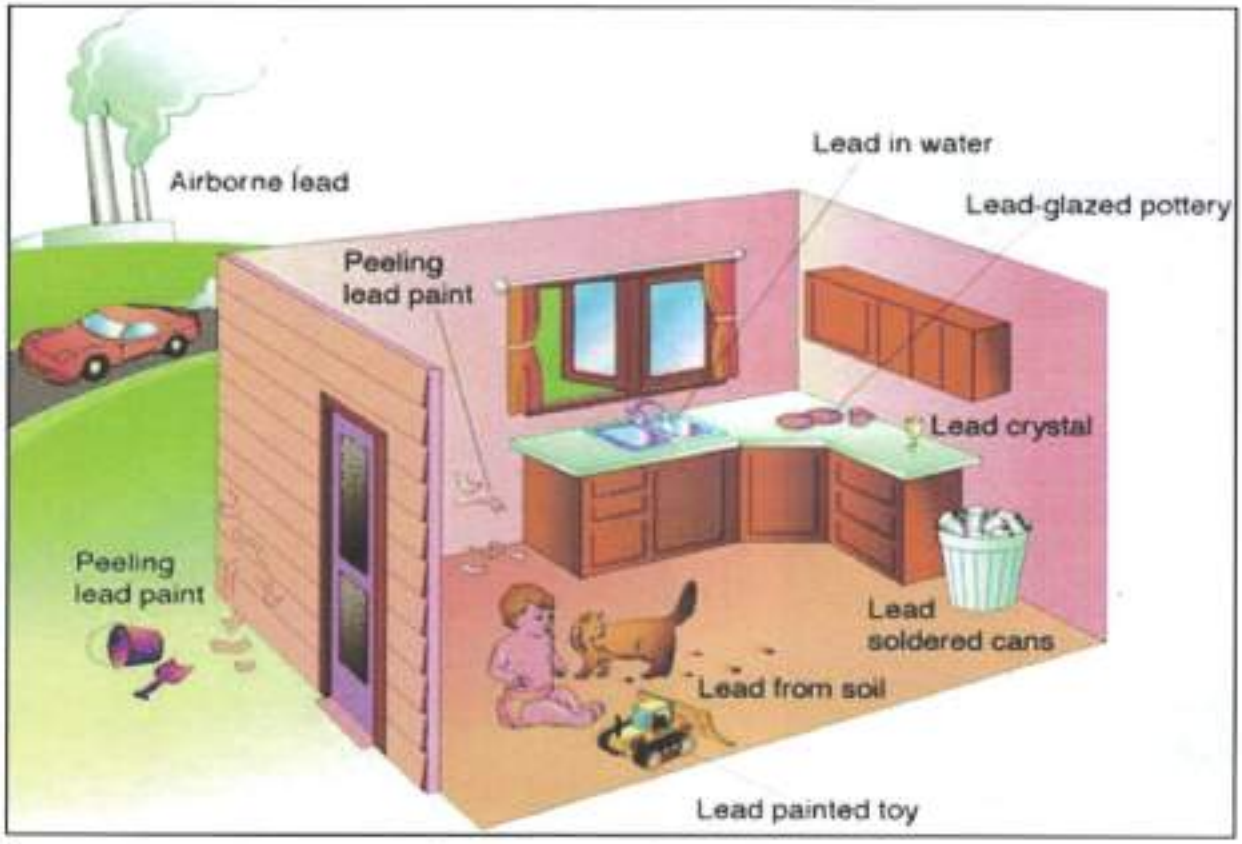


Figure 6. Environmental sources of childhood lead exposure

Some effects of lead:

- The majority of lead which is absorbed is stored in the bones and teeth. In children, about 70% of lead is distributed in this way; in adults up to 95%.
- The hypermineralisation is reflected in the form of densities which are the classic "lead lines" observed on x-ray (Fig 7).
- Hypermineralisation occurs because lead is an osteoclast poison, so bone density is increased due to unopposed action of osteoblasts

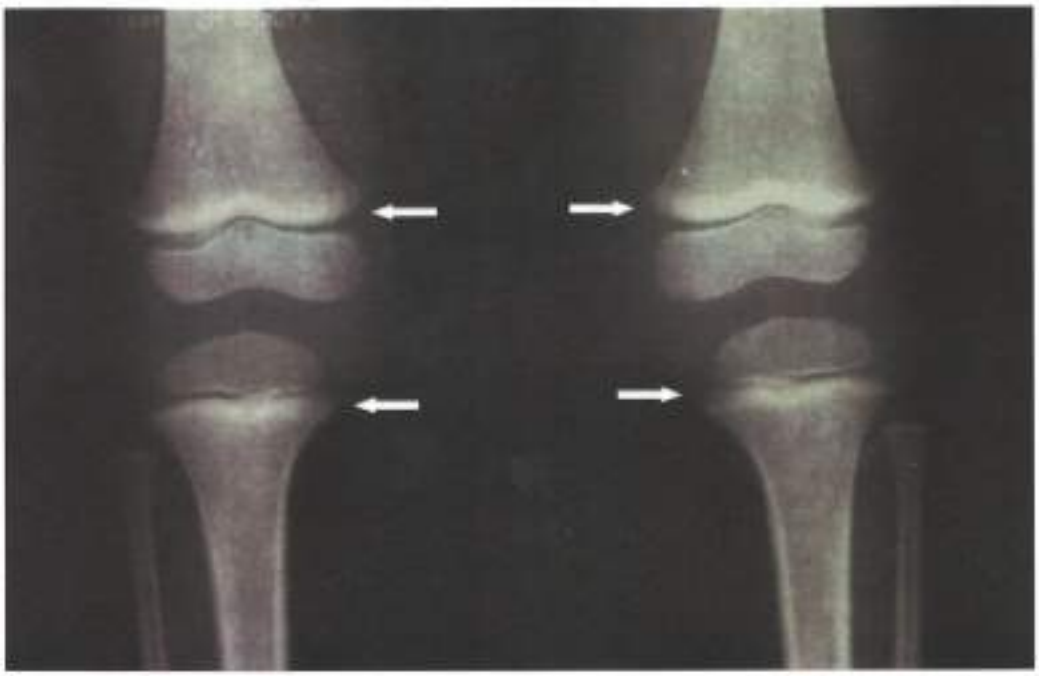
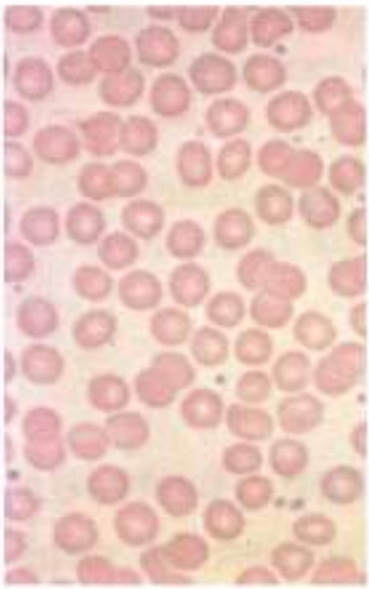
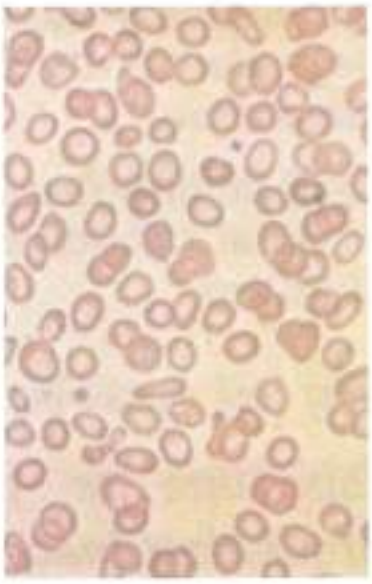


Figure 7. Longbone radiograph of knees - metaphyseal "lead band".

Microcytic & hypochromic anemia, as in iron deficiency. (Fig 8)



Normal



Hypochromic microcytic anemia

Figure 8. Normal blood smear and a smear from a patient with hypochromic microcytic anemia.

Blood film examination may reveal basophilic stippling of red blood cells (dots in red blood cells visible through a microscope) (fig 9).

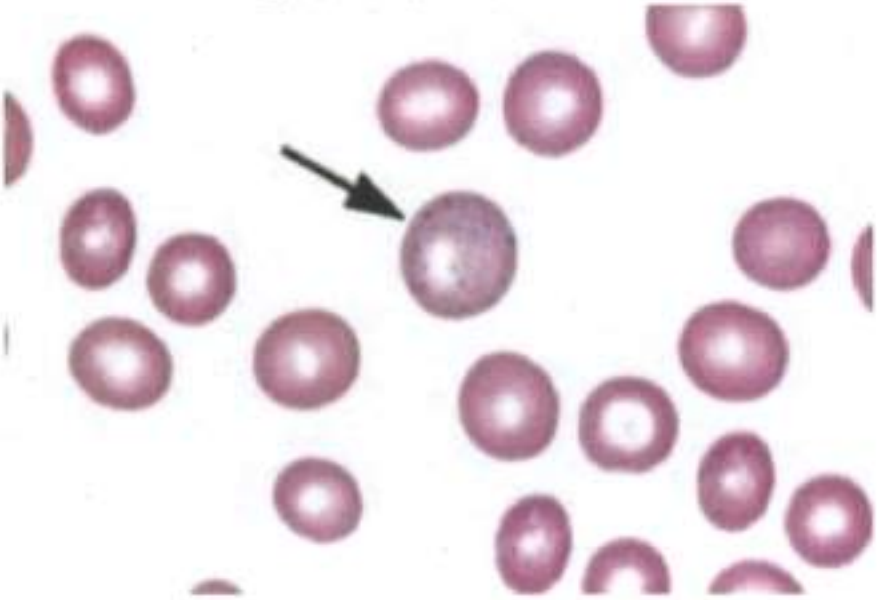


Figure 9. Basophilic stippled cell (arrowed)

Why lead causes basophilic stippling of red blood cells?

- *Pyrimidine 5' nucleotidase is an enzyme needed for the degradation of ribosomal RNA during reticulocytes maturation.*
- *Lead inhibits that enzyme & that results in aggregation of residual ribosomes which are manifested by basophilic stippling*

Why lead causes Burton's line?

This line is caused by a reaction between circulating lead with sulphur ions released by oral bacterial activity which deposits lead sulphide at the junction of the teeth & gum

- Chronic lead nephrotoxicity: consists of interstitial fibrosis & progressive nephron loss, azotemia & renal failure.
- A remarkable pathogenic feature of lead poisoning is the presence of inclusion bodies composed of lead-protein complex (Fig. 10).
- Lead-induced inclusion bodies are frequently nuclear, & are common in kidney

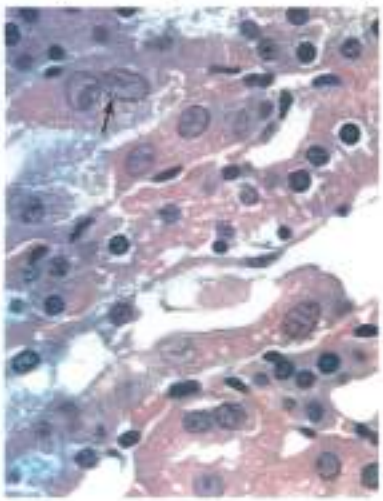


Figure 10. Lead-induced inclusion body formation in kidneys from wild-type (WT) mouse. Arrow indicates typical karyomegaly of P3 proximal tubular cell.

- In severe toxicity [Blood lead (BL) more than 100mcg/100 ml], lead results in:
- lead palsy: wrist drop (Fig. 11) or foot drop.
- a bluish black lead line on gums (Burton's line) (Fig.12).
- lead encephalopathy: It is more common in children.

Fig 11. Wrist drop

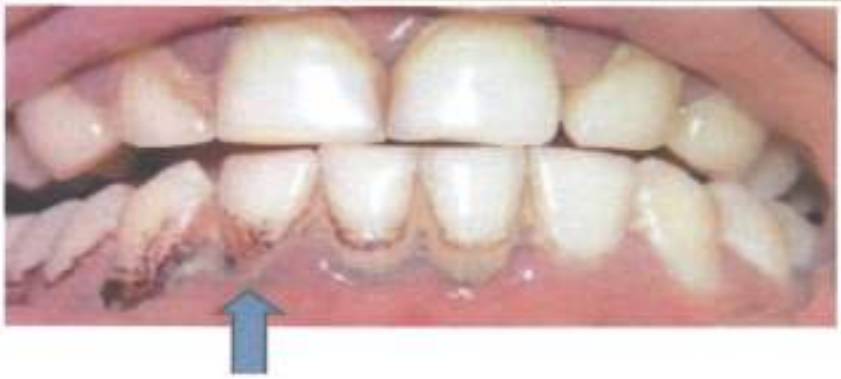
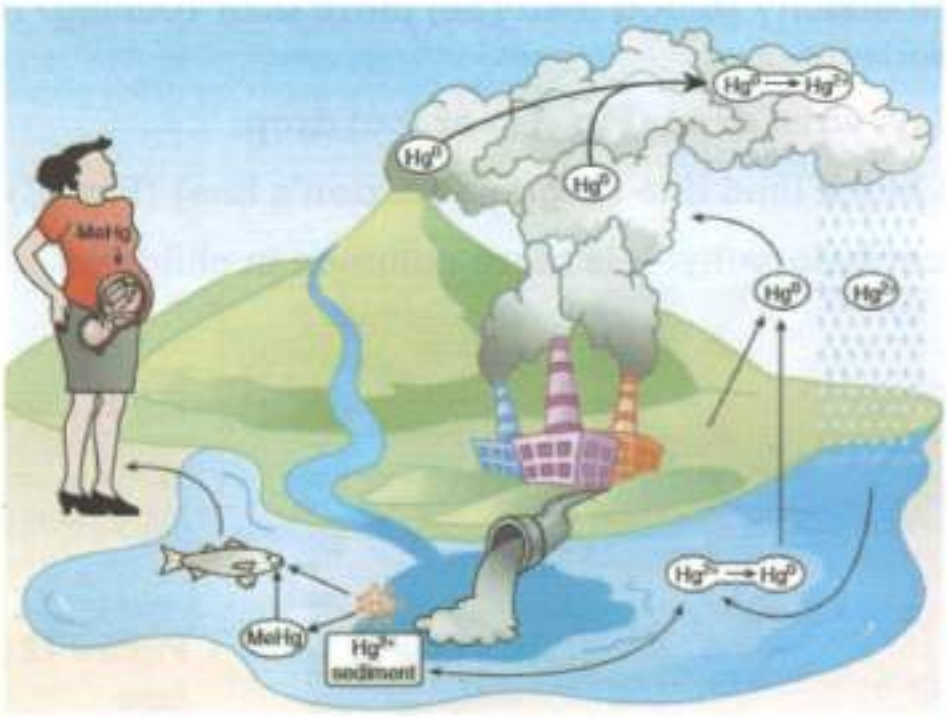


Figure 12 . Burton's Line

MERCURY

- Sources of exposure:
- Breaking of mercury fluorescent light bulbs.
- Liquid mercury following breakage of thermometers.
- Dental amalgam.
- Methyl mercury from consumption of fish



The movement of mercury in the environment

A brief human history of mercury poisoning

Qin Shi Huang,
1st emperor of China

200 BC

Mad hatters

19th-20th century

Minimata disaster

1950s

Iraq grain disaster

1971

Karen Wetterhahn,
Dartmouth professor

1997

MINIMATA DISEASE:

- Between 1953 & 1970, around Minamata Bay in Japan, more than 2000 people were diagnosed to be suffering from a curious cluster of neurological symptoms comprising paraesthesiae, narrowing of vision, dysarthria, diminution of hearing, amnesia, ataxia, staggering gait, weakness, & emotional instability.
- Some developed paralysis & became stuporous, & out of all the people afflicted nearly a hundred died. The condition has been known as the Minimata disease (Fig. 13).
- It was caused by consumption of fish contaminated with methyl mercury. The most severely affected victims were actually infants who had been exposed in utero

Figure 13 . Minamata disease

IRAQ GRAIN DISASTER:

- The shocking tragedy occurs in Iraq in 1971–72, when 500 people died out of a total of 6530 victims due to consumption of imported wheat and barley meant for sowing, treated with methyl mercury fungicide.

SOME EFFECTS OF MERCURY POISONING:

Acute poisoning from inhalation:

- Dyspnea, cough, fever, stomatitis.
- Deep red oral mucosa with "strawberry tongue" (Fig. 14)
- Skin rash (Fig. 15)

Figure 14 . Strawberry tongue

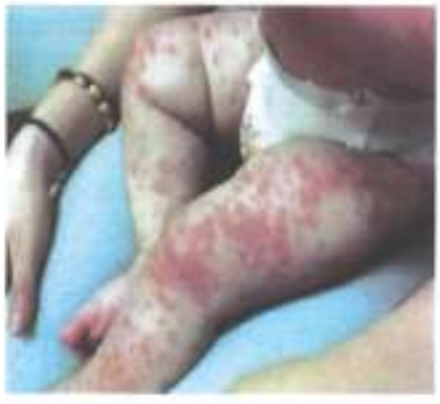


Figure 15 . Skin rash

SOME EFFECTS OF MERCURY POISONING:

Chronic poisoning by ingestion:

- Colitis
- Dementia
- Tremor
- Renal failure
- Acrodynia (Pink disease) (Fig. 16). This is seen mainly in children. The hands & feet become puffy, pinkish, painful, paraesthetic, perspiring & peeling

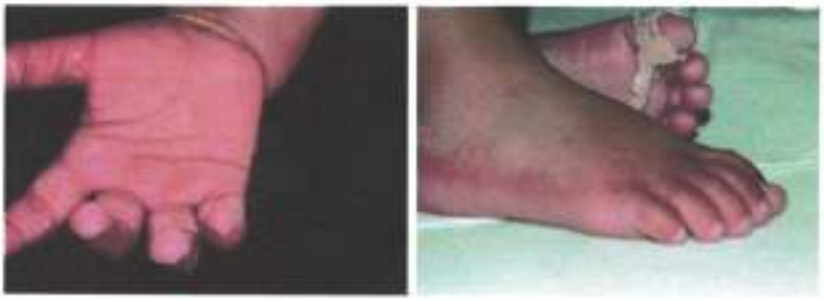


Figure 16 . Pink disease (Acrodynia)

ASSESSMENT OF METAL EXPOSURE:

- The biological half-life varies according to the metal as well as the organ or tissue. For example, the biological half-lives of cadmium in kidney & lead in bone are 20 to 30 years, whereas for some metals, such as arsenic or lithium, they are only a few hours to days.
- Blood, urine, & hair are the most accessible tissues for measuring metal exposure.
- Blood and urine concentrations usually, but not always, are reflective of more recent exposures
- Hair can be useful in assessing variations in exposure to metals over the period of its growth. Analyses can be performed on segments of the hair, so that metal content of the newest growth can be compared with past exposures.
- Note: average hair growth is around 0.4 mm/day