Lecture #	Lecture	Page #
Toxicology		
1	Principles of clinical toxicology	1
2	Alcohol & glycols	6
3	CO , CN & sulfide	21
4	Pesticide	30
5	Opioids	43
6	Acetaminophen	55
7	Substance abuse	62
8	Poisonous plants	68
9	Stimulants	74
10	Sports doping	86
11	ملخص (فرح عامر)	93
Forensics		
1	Death & postmortem changes	128
2	Sudden death	162
3	Child abuse	170
4	Wounds	176
5	ملخص (فرح عامر)	213

- الملخصات التي كتبتها زميلتنا فرح عامر ، كانت من المحاضرات بمادة ال Toxicologyمع زيادات من دوسية 2015\2014 ، بالنسبة لمادة ال forensicكانت من المحاضرات 2015\2014
- لم يتم التغيير على هذه الدوسية ، فقط تم إضافة الملخصات
- في فهرس 2015\2014 كان يوجد محاضرة burnsلكنها لم تكن موجودة في الدوسية

بسم الله الرحمن الرحيم

Principals Of Clinical Toxicology

DONE 22/7 : ABDULHAY AL-QAWASMY

A toxin is any substance, chemical or physical, once enters the biological system causes a harmful effect:

Toxicology: science of poisons and toxins.

Forensic toxicology: application of science of toxicology for service of law.

Any substance can be a poison depending on the dose (even water), and thus we must have a value that tells about the toxicity of each substance, of these values are:

1. LD50 : the dose that is able to kill *50%* of the experimental animals. It is a rough index as it changes according to the route of administration and the species being tested
2. Therapeutic index : LD50/ED50 : more accurate
3. Safety margin : LD1/ED99 : more accurate, the bigger the better

Not all the drugs follow the dose-response relationship[1], examples are sensitivity reactions, anaphylaxis, favism, scoline apnea ... etc

The relation between any 2 chemical substances can be : synergism, addition, potentiation, or antagonism. Antagonists can be:

Chemical : which react with the poisonous chemical to produce a compound of lesser toxicity or a one that is absorbed to a lesser extent. Eg are chelating agents (heparin and protamine sulfate) and calcium salts with oxalic acid.

Competitive (receptor) . compete with the poison for receptor site. Eg naloxone and morphine, atropine and physotigmine.

Functional (physiological) : eg a drug causing tachycardia and the other bradycardia

Dispositional : involves alteration of absorption, metabolism, distribution, or excretion of a toxic agent. eg N-acetylcysteine and acetaminophen poisoning.

[1] Dose-response means that the response depends on the dose, the higher the dose the more likely a response to occur and the bigger the response.

Epidemiology:

Leading cause of all poisons in USA is plants, but approximately 40% of all serious intoxications are caused by various household products. 70% of poisoning occur under age of 5 years

Methods to reduce or prevent

A. Absorption:

1. **Dilution** : water is the best and only fluid that should be used, it reduces gastric irritation and adds a bulk to the stomach for later ipecac emesis. Milk must not be used as it delays the onset of ipecac emesis.

Contraindications: unconscious patient, absent gag reflex, and relatively in cases of solid dosage poisoning as it causes dissolution[2].

TABLE 3. *Conditions in which emesis should not be attempted*

Do not induce vomiting if the poison is a:
- convulsant
- hydrocarbon
- corrosive acid or alkali

Do not induce vomiting if the patient:
- is unconscious or comatose
- does not have a gag reflex
- has severe cardiovascular disease or emphysema, or extremely weakened blood vessels
- is under 6 months of age

TABLE 4. *Recommended doses of syrup of ipecac*

Age	Quantity
6–12 months	6–10 mL
1–12 yr	15 mL
Adults	30 mL

2. **Emesis** : vomiting should be induced only if there is sufficient bulk, therefore adequate dilution with water increases the efficacy of emetics.

Emetics can be:

a) **Syrup of ipecac**: the active alkaloids are emetine and cephaeline. It causes vomiting by early and late phases; early within 30 minutes and due to direct stimulation of CHT, late due to stimulation of chemoreceptor trigger zone

S/E : safe, rarely causes protracted vomiting, diarrhea, lethatgy, diaphoresis, and fever.

On chronic abuse it causes peripheral myopathy, and fatal cardiomyopathy.

b) **Apomorphine** : a morphine derivative[3] with rapid emesis *(3-5)* minutes through direct stimulation to chemoreceptor trigger zone, thus can be given with charcoal whereas ipecac must be given 30 minutes before charcoal. A disadvantage is that it needs special preparation and thus cannot be given at home.

S/E: *CNS* depression, respiratory depression, and hypotension.

c) **Soap Solution**: 3-4 tablespoonfuls of a dishwashing liquid detergent should be mixed with 6-8 ounces of water, emesis will occur in less than 10 minutes by direct stimulation to trigger zone.

[2] According to the doc dilution is only beneficial in acid or alkali poisoning

[3] as it is a morphine derivative some physicians advocate administration of a narcotic antagonist (naloxone) following emesis

d) **Mechanical stimulation** : fingers are not advised and due to lack of effectiveness it is not recommended to induce vomiting.

3. **Lavage** : Usually we use tap water or normal saline[4], but may use also sodium bicarbonate, calcium salts, tannic acid, or potassium permanganate. Patient is placed on the left side to permit pooling of gastric contents and to reduce the risks of aspiration, and the patient's head should be lower than the rest of the body. The largest diameter tube should be used and the role is to lavage until clear.
There is a possibility that even if the lavage is clear there is clumps of chemicals (concretion) remaining in the Stomach.

TABLE 5. *Lavage*

Indications
Semiconscious
Unconscious child or adult
Loss of gag reflex
Ipecac-induced emesis is ineffective or contraindicated
Conscious patient ingesting large quantity highly toxic substance, repeated charcoal administration is useful
Contraindicated
Corrosives
Petroleum distillates; Aerosol patient, unless distillate is vehicle for toxic substance
Seizures
Complications/hazards
Aspiration pneumonia secondary to emesis with unprotected airway
Laryngospasm with cyanosis
Factors determining effectiveness
Physical characteristics of toxic agent (e.g., plants, capsules, tablets, liquids)
Delayed absorption of toxic agent
Diameter of lavage tube
Volume and rate of instillation of lavage solution

From refs. 72, 74.

4. Adsorbents: Either non-specific as charcoal or Specific as Fuller's earth and cholestyramine

activated charcoal

A black powder that is mixed immediately before use with sufficient water and upon reaching stomach and intestines poisons diffuse through the numerous pores on the charcoal surface forming a tight chemical bonds, the charcoal chemical complex then passes out the GIT.
Charcoal leaves a gritty sensation in the mouth, discolors the gum and mouth, and sticks to the throat, for these reasons children any refuse taking it. Addition of sorbitol gives it a sweet taste and also has a cathartic action.
For a maximal effectiveness it should be administered within 30 minutes of poison ingestion. However, when used to adsorb drugs that slow gastric emptying (eg anticholinergics) good results where obtained when it was used 6-8 hrs after poison ingestion
Dose: optimal dose is unknown, the recommended dose is 50-100g for an adult and 15-20g for a child. Relative dose ratio of at least 10:1, charcoal:drug. Larger doses occasionally causes constipation but may be used safely and multiple doses can be used.

TABLE 6. *Chemicals that are poorly absorbed or not absorbed by activated charcoal*

Alkali
Boric acid
Cyanide
DDT
Electrolytes
Ferrous sulfate
Lithium salts
Malathion
Mercury
Mineral acids
N-methyl carbamate
Tolbutamide
Water-insoluble compounds

From refs. 29, 41, 83.

special precaution : activated charcoal should not be given within 30 min of ipecac

[4] normal saline is preferred in children not to induce electrolyte imbalance

administration unless the patient has vomited, also it is not recommended for concurrent use when N-acetylcystein is indicated as antidote for acetaminophen poisoning.

5. **Cathartics** : saline cathartics are preferred. Magnesium containing cathartics should not be used in renal failure patient because of CNS depression, and sodium containing cathartics are best avoided in heart failure patient. Metabolic disturbances are the most common consequences of acute cathartic use.
Contraindications: 1. poison is strongly corrosive 2. Pt has electrolyte imbalance 3. bowel sounds are absent.

TABLE 7. *Cathartics used in poison treatment*

Cathartic	Dose	
	Child	Adult
Magnesium sulfate (Epsom Salts)	250 mg/kg	5–10 g
Magnesium citrate (Citrate of Magnesia)	4 mL/kg	300 mL
Sodium sulfate	250 mg/kg	15 g
Sodium sulfate/sodium phosphate (Fleet Phospho-Soda)	20 mL[a]	40 mL[a]
Sorbitol	1.5 g/kg[a]	1.5 g/kg (50 mL)

[a]Diluted with water.
[a]Use with caution.

B. Metabolism

Using ethanol as an antidote for methanol Poisoning as it competes with methanol metabolism and thus reduces production of its toxic metabolites

C. Excretion

1. **Forced diuresis** : by using mannitol or furosemide dangers may include water intoxication, cerebral and pulmonary edema, and electrolyte imbalance At best, forced diuresis may increase excretion by 2 folds. A better procedure is to couple this with 1. acidification of urine for basic poison by using ascorbic acid or ammonium chloride 2. alkalanization of urine for acidic poisons by using sodium bicarbonate alone or with acetazolamide
2. **Dialysis and hemperfusion:** for severely intoxicated patients.

Principles of management

5-10% of Poisoning cases have specific antidote so management is primarily supportive.
steps of management:
1. Stabilize the patient (ABC): antidote may be given at this step, eg for CO poisoning O_2 is the antidote

2. Complete assessment: Hx, P/E, Ix.
3. Decontamination: skin: wash, stomach: emesis[5] is good in most of the time and other methods can be used,
4. Enhancement of elimination: forced diuresis, acidification, alkalanization
5. Antidote
6. Continuous patient care: be aware of hypo and hyperthermia, convulsions . . etc.

THE END

[5] ipecac is the best way to induce emesis if not use soap solution

Alcohols and Glycols

INTRODUCTION

Ethyl alcohol is a serious and ubiquitous fact of life. Alcohol determination is the most frequently performed medicolegal test and remains the most common single drug taken by patients visiting emergency departments. In one study, positive blood alcohol levels were found in over one-third of male victims involved in fatal single automobile accidents. Alcohol misuse is the leading killer of persons aged 15 to 451 years and is associated with 67% of drownings, 70% of fire deaths, 67% of murders, 35% of suicides, and the vast majority of deaths from hepatic failure.

Nationally, between 40% and 55% of all divers involved in fatal crashes have blood ethanol concentration greater than or equal to 100 mg/ dL (100 mg/ dL = 0.10%). In 1983, there were 37,971 reported fatal motor vehicle accident in the United States resulting in 42,584 fatalities. Alcohol was an important contributing factor in 17,847 (42%) of these deaths. more than 200,000 Americans die annually from alcohol related disorders, and alcohol dependency afflicts 5% to 10% of the American population. For untreated alcoholics, normal life expectancy decreases 12 to 15 years compared with population norms.

ETHANOL

Ethanol is a central nervous system (CNS) depressant, Neurologic impairment depends on a number of variables, including genetic factors, amount ingested, prior alcohol use, rate and direction of blood ethanol elevation, co ingestion of other drugs and alcohol products, trauma, nutritional status and complications of chronic ethanolism. In nontolerant individuals, decrements in cognitive ability, motor coordination, and sensory perception may begin at ethanol concentrations as low as 50 mg / dL.

Alcoholism is a chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. The disease is often progressive and fatal. It is characterized by impaired control over drinking, preoccupation with alcohol, use of alcohol despite adverse consequences, and distortions in thinking, most notably denial, Each of these symptoms may be continuous or periodic.

While late in the course of illness, its medical and social consequences become obvious; early detection may be less apparent and generally requires a careful medical and psychosocial evaluation. The "Brief Michigan Alcoholism Screening Test" and "CAGE Questionnaire" (CAGE indicates a mnemonic for questions about Cutting down on drinking, Annoyance at others' concern about drinking, feeling Guilty about drinking, and using alcohol as an Eye-opener in the morning) are useful, well known, screening measures to detect occult alcoholics in hospitalized populations, but are much less sensitive in the general community.

Alcoholism tends to appear in families, and studies in twins indicate that genetic factors partly control normal alcohol use. Recent research on alcoholism has focused on metabolic factors, individual CNS responses to alcohol, and a possible genetic association with depression and personality disorders. Alcohol sensitivity may be related to an atypical isoenzyme of hepatic alcohol dehydrogenase that causes rapid formation of acetaldehyde after ethanol use.

Ethyl alcohol is a clear, colorless, aliphatic hydrocarbon. Ethanol is a "universal diluent" that is mildly polar and easily crosses cell membranes. Commercial products containing ethyl alcohol include beverages; solvents for perfumes, aftershaves, and colognes; medicinal liquids (e.g., cold preparations may contain up to 20% ethanol); mouthwashes; liniments; and some rubbing alcohols. Distilled spirits typically contain ethanol volumes of 40% to 50% (80 to 100 proof) that reliably are displayed on labels.

Wines vary more widely in ethanol content, ranging from 10% to 20% (20 to 40 proof) and average 12% ethanol by volume. The greatest variation occurs in beers, which contain from 2% to 6% ethanol (4 to 12 proof); with regular domestic American beers averaging 4% to 5% ethanol by volume. Mouthwashes may contain up to 75% ethanol, and colognes, up to 40% to 60% ethanol. More than 700 American medicinal preparations contain ethanol, apparently as an inert diluent or solvent, in concentrations ranging from 0.3% to 68%.

Pathophysiology

Ethanol is a CNS depressant that selectively depresses the reticular activating system (RAS). The mechanism of action probably involves interference with ion transport (i.e., sodium flux) at the cell membrane rather than at synapses, similar to the action of anesthetic agents. The frontal lobes are sensitive to a low concentration, resulting in alteration of thought and mood before changes in vision (occipital lobe) and coordination (cerebellum).

CHRONIC EFFECTS

Chronic ethanolism leads to multiple metabolic changes caused, at least in part, by alterations in a cellular redox, which results from a decreased oxidized to reduced nicotinamide adenine dinucleotide (NAD+ /NADH) ratio. Among other biochemical effects, there is a shift from pyruvate to lactate that results in acidosis, and an elevation of serum uric acid, which results from reduced clearance. Lipid metabolism is altered with accumulation of fat in the liver, and there is a possible increase of collagen disposition and depressed protein synthesis.

HYPOGLYCEMIA

Alcohol impairs hepatic gluconeogenesis in the presence of significant hepatic glycogen store depletion, generally secondary to starvation or fasting. It probably

does this by reducing the intracellular NAD+ /NADH ratio. Hypoglycemia occurs more commonly in children in whom small amounts of ethanol may cause hypoglycemic seizures or even death. The majority of these children are under 5 years of age. Children may drink large amounts in relation to their body weight and quickly produce high blood-alcohol concentrations. In a child under 5 years, hepatic alcohol dehydrogenase activity is not mature and the ability to metabolize any alcohol load is limited. The hypoglycemia appears to be related primarily to the inhibition of hepatic gluconeogenesis.

Pharmacokinetics

ABSORPTION

- Both gastrointestinal and respiratory tracts are effective routes of toxicity. The small intestine extracts about 80% of an oral ethanol dose; the stomach absorbs the remainder.
- Factors that delay gastric emptying may decrease absorption of alcohol.
- The rate of increase in blood ethanol depends on the type of beverage and ethanol concentration (beer slows absorption), gastric contents (high protein and high volumes decrease absorption), and gastrointestinal motility (trauma, prior gastric surgery, all reduce motility). Such factors may delay peak blood-ethanol levels several hours after consumption.
- In healthy adults, 80% to 90% of absorption occurs within 30 to 60 minutes, but food may delay complete absorption for 4 to 6 hours.

DISTRIBUTION

- Because it is both water and lipid soluble, ethanol distributes into total body water and easily penetrates the blood-brain barrier and placenta.
- The approximate volume of distribution is 0.6 L/kg in adults and 0.7 L/kg in children.
- Women have a slightly smaller volume of distribution than men do because women have relatively less water and more fat.
- Acetaldehyde, produced by all known oxidative pathways of ethanol metabolism, is converted to acetate by aldehyde dehydrogenase. Asians often harbor an inactive aldehyde dehydrogenase variant that causes them to experience high blood-acetaldehyde levels when they drink, with subsequent development of ethanol intolerance and flushing.

ELIMINATION

- The hepatic metabolism of ethanol is characterized by zero-order kinetics (i.e., the elimination rate is concentration independent) except at very low or very high concentrations. Some authors believe ethanol metabolism follows Michaelis- Menten kinetics.
- Blood ethanol decreases more rapidly at concentrations over 300 mg / dL, perhaps because of oxidation by the microsomal ethanol-oxidizing system. The kidney and lungs excrete only 5% to 10% of an absorbed dose unchanged.
- The maximum rate of metabolism is 100 to 125 mg/kg/hour, although, by enzymatic induction, tolerant individuals can increase their metabolic rates to 175 mg/kg/hour.

- The average adult metabolizes 7 to 10 g/h and reduces the ethanol level 15 to 20 mg/ dL/h. Chronic alcoholics, in contrast, may have metabolic rates as high as 30 to 40 mg/dL/ h.
- Hepatocytes contain three main ethanol metabolic pathways. The alcohol dehydrogenase pathway (in the cytosol) is the major pathway of ethanol oxidation in the body. Conversion of ethanol to acetaldehyde by alcohol dehydrogenase is the rate-limiting step. Both alcohol and aldehyde dehydrogenase require NAD, which reduces the hepatic NAD/NADH ratio. The shift in this ratio causes profound metabolic abnormalities in chronic alcoholics.
- A microsomal ethanol-oxidizing system (MEOS), represents the second major metabolic pathway and is located in the endoplasmic reticulum. The MEOS is separate from the cytochrome P450 system. This pathway becomes more important as ethanol concentration rises.
- A peroxidase-catalase system is a minor pathway located in peroxisomes.

Clinical Presentations

Ethanol is a selective central nervous system depressant in low doses and a generalized depressant in high doses. Comparison of cognitive and psychomotor skills at blood-ethanol levels of 90 and 135 mg / dL indicates that attention, concentration, motor coordination, and reaction time are significantly more affected at the higher level. Initially, ethanol produces exhilaration, which progresses to loss of restraint, behavioral abnormalities, loquaciousness, slurred speech, ataxia, gait disturbances, irritability, drowsiness, stupor, and coma.

A flushed face, dilated pupils, excessive sweating, and gastrointestinal distress (manifested as pancreatitis, gastritis, esophagitis, and/ or alcoholic hepatitis) may accompany CNS symptoms. Ethanol can produce dysrhythmias (e.g., atrial fibrillation) in nontolerant binge drinkers, as well as in chronic alcoholics. Ethanol is a vasodilator that produces decreased preload, after load, and systemic vascular resistance in healthy adults after ingestion. Ingestion of ethanol also has a myocardial depressant effect.

Chronic Effects

NEUROLOGIC EFFECTS

Diminished fine motor skills, diminished cognition, peripheral motor / sensory neuropathy. Heavy consumption (over 400 grams per week) of alcohol appears to predispose to both hemorrhagic and nonhemorrhagic strokes.

NUTRITIONAL EFFECTS

Vitamin deficiencies of Bl, B6, B12, zinc, and magnesium occur with nutritional neglect. Alcoholism probably is the most important cause of magnesium deficiency. Alcoholics ingest low levels of magnesium in their diet and excrete more in their urine. Hypomagnesemia may be present, but serum levels of magnesium do not predict body deficits accurately.

PEDIATRIC ISSUES

Alcohol abuse may occur in very young children. Percutaneous alcohol intoxication has been described in young children after use of alcohol-soaked gauze pads. In juvenile alcohol intoxication, metabolic acidosis may be correlated with blood-alcohol concentration and loss of consciousness. Hypoglycemia is the

most common reported symptom in children under 5 years of age. The hypoglycemic effects of ethanol are not dose dependent. The fasting state may predispose a child to ethanol-induced hypoglycemia. Hypokalemia is an important concomitant finding.

Withdrawal Syndromes

The withdrawal of ethanol may lead to unopposed compensatory mechanisms, which are clinically manifested as autonomic hyperexcitability. The exact mechanism of withdrawal is not known. Hypomagnesemia and hypokalemia may contribute to withdrawal effects. Sharply decreased consumption of alcohol or intercurrent illness may cause a hyperadrenergic state ranging from minor tremor and anxiety to hallucinations and convulsions. Withdrawal syndromes develop more often in regular heavy drinkers than in binge drinkers.

COMMON ABSTINENCE SYNDROME

Symptoms typically develop 6 to 8 hours after cessation of drinking. Although most patients are asymptomatic at 72 hours, some symptoms may continue for over 1 week. Symptoms may include tremor, agitation, sleep disturbance, hyperexcitability, and preoccupation with personal misery. Nausea, vomiting, weakness, headache, insomnia, flushed face,also may occur. Prognosis is excellent with appropriate management. benzodiazepines are safe and most effective in this setting.

ALCOHOLIC HALLUCINOSIS

Symptoms develop 24 to 36 hours after cessation of alcohol intake. This disorder of perception ranges from delusions to visual and auditory hallucinations. The patient often remains fully oriented. This syndrome is managed effectively with benzodiazepines, Haldol® when necessary, and by protecting individuals from harm in a supportive environment.

Toxic Dosage/Death

Death may occur from respiratory depression at ethanol levels exceeding 500mg/dL. However, chronic alcoholic may exhibit few clinical sings of intoxication at levels between 300 and 450mg/dL and may survive levels exceeding 500mg/dL. One patient survived acute alcohol intoxication with a blood ethanol level of 1,500 mg/dL. Although the reported lethal ethanol dose is 5 to 8 grams/kg for adults and 3 grams/kg for children, variation in toxicity occurs as a result of the concurrent presence of hypoglycemia and drug interactions. The American Academy of Pediatrics has established a blood level of 25mg/ dL as the maximum concentration of ethanol a single dose of alcohol-containing medication should be able to produce in a child.

Drug Interactions

Certain drugs produce a disulfiram-like reaction when taken with alcohol, possibly by inhibiting the enzyme aldehyde dehydrogenase. These include metronidazole, sulfonamides, hypoglycemia agents. Common direct interactions involve either

central nervous system depression, when there is a concomitant ingestion of sedative-hypnotics, or prolonged bleeding times, when normal subjects ingest at least five drinks and a single aspirin tablet. In ordinary doses, neither amphetamines nor caffeine significantly improves ethanol-impaired performance. The interaction of central nervous system stimulants and ethanol is unpredictable.

Laboratory

ANALYTICAL METHODS

Gas chromatography is the method of choice. This procedure is highly specific for ethanol.

Within 24 hours of death, little ethanol is formed by decomposition, even at room temperature. No blood specimen from bodies refrigerated within 4 hours of death an stored up to 28 hours contained more than 10 mg ethanol per deciliter. Blood ethanol produced by postmortem decomposition rarely exceeds 50 mg / dL. Fluoride ion, mercuric ion, and cold storage inhibit the tissue formation of ethanol by microorganism. Femoral and jugular veins are the best postmortem blood sampling sites.

BLOOD LEVELS

Ethanol blood levels roughly correlate with clinical signs. One must treat the patient however, and not the blood level, because tolerance, trauma, hypoglycemia, drug interactions, and disease factors may complicate the clinical picture. The clinical presentation of a tolerant patient at a given blood-ethanol level is less predictable for example, as clinical evidence of intoxication may be minimal in chronic alcoholics at significantly elevated blood ethanol levels. Most states accept a BAC of 0.8% to 0.10% (i.e., 80 to 100 mg/ dl) as evidence of impairment.

The American Medical Association's Council on Scientific Affairs believes that deterioration of driving skills begins at a BAC of 0.05% and progresses to more serious impairment as levels rise. Psychomotor testing indicates early impairment in processing and acquisition of information, performance on divided-attention tasks, and judgment; however, biological differences between individuals cause substantial differences in ethanol effects.

Caution should be exercised when correlating blood ethanol levels to presumed dose. One glass of wine, one shot of whiskey, or one can of beer generally raises the blood ethanol level about 25 mg/dl. The average elimination rate in nontolerant individuals is 15 to 20 mg/dl/h. Pitfalls in correlating blood-ethanol levels with consumption include exact time of consumption, peak ethanol time, accuracy of test method, appropriate marking of sample, time between incident and withdrawal of sample, time between sample withdrawal and analysis, storage methods, collection methods, variability in volume of distribution, and sampling site. Proper collection technique involves the use of nonalcoholic skin antiseptics, although at least one study found no significant difference between alcoholic and nonalcoholic preps in measurement of the blood ethanol level. Another study also showed that performing venipuncture through a pool of 100% ethanol on skin does not affect ethanol results.

Treatment

GUT DECONTAMINATION

Rapid absorption of alcohol makes decontamination unhelpful more than a few minutes after ingestion. Even the administration of charcoal before ethanol consumption does not produce different peak concentrations or time-to-peak concentrations in human volunteers. Cathartics are probably not helpful as well.

ELIMINATION ENHANCEMENT

Fructose may accelerate metabolism by 25%, but the modest reduction in alcohol levels is outweighed by the serious side effects of fructose, including vomiting, abdominal pain, pruritus, lactic acidosis, and shock. Hemodialysis increases ethanol clearance by three to four times, but supportive care usually suffices. Comatose, unstable patients with ethanol levels exceeding 500 mg / dl may indicate the need for dialysis if supportive care fails.

SUPPORTIVE MEASURES

- In all acutely inebriated patients, search for concurrent trauma, underlying disease, and coingestion of drugs and toxic alcohol substitutes (i.e., methanol, ethylene glycol).
- Evidence of trauma in the alcoholic patient indicates the need for cervical immobilization, cervical x-rays, and a careful search for cervical and cerebral injury.
- Acute ingestions in nontolerant patients usually respond to supportive care with special attention to prevention of aspiration and replacement of fluid and electrolytes.
- Comatose patients should be treated with initial attention to airway, breathing, circulation, and! a 'coma cocktail" to potentially correct easily reversible conditions (i.e., 1 amp of D50 for hypoglycemia, 2.0 mg of naloxone for possibly opiate intoxication, and 100 mg of thiamine for potential Wernicke- Korsakoff syndrome).
- Replace nutritional deficiencies in the chronic alcoholic (2 grams of magnesium sulfate, 100 mg of thiamine, 5 mg of folate, 1 ampule of multivitamins).
- Watch for development of withdrawal syndromes.
- Asymptomatic children who ingest ethanol and remain symptom free for 2 hours can safely be managed at home.

Antidotes

The efficacy of naloxone in ethanol-induced coma is questionable. There are some case studies, which describe the reversal of ethanol-induced coma by naloxone, however, no substantive series or well-controlled study confirms the usefulness of naloxone. A study on alcohol intoxication failed to show the effectiveness of naloxone in reversing ethanol-induced central nervous system depression. Flumazenil may aid in reversing the respiratory depression associated with ethanol ingestion, but this observation has not been clinically validated. Analeptic agents should not be used.

METHANOL

Methanol, methyl alcohol, or "wood alcohol" is produced from the destructive distillation of wood. Methanol toxicity may result from methanol-contaminated whiskey, or more commonly, from the ingestion of antifreeze, windshield wiper fluids, deicing solutions, paints, and paint thinners. In 996, a report of the American Association of Poison Control enters reported 2,589 exposures.

Elimination of methanol depends on the folate pool, a variable among species. Methanol is a colorless, volatile liquid with the structural formula CH3OH. Methanol has distinctive odor that may be masked by impurities added during the production process. Methanol is widely available as a solvent and antifreeze. Formulations include antifreeze (95% concentration), windshield washer fluid (35% to 95%), Sterno canned heat (4%), shellacs, various paints, paint removers, varnishes, duplicating fluids, gasoline additives, ethanol denaturants, and rarely, nail polish removers.

Pathophysiology

Methanol toxicity results from the accumulation of two metabolites, formaldehyde and formic acid. Marked species variation in toxicty occurs as a result of differential rates of formate metabolism. Formaldehyde is rapidly metabolized to formic acid. The accumulation of formic acid accounts for most of the metabolic acidosis that follows methanol ingestion and probably correlates better with clinical toxicity than methanol levels.

Lactate may appear late in the course of severe methanol poisoning as a result of both formate-induced inhibition of mitochondrial respiration and of tissue hypoxia. Serum lactate can increase after methanol intoxication despite no ventilation and perfusion and accounts for a significant bicarbonate deficit in severe poisoning. Methanol has inherent centr nervous sys- tem depressant effects similar to those of ethanol.

Pharmacokinetics

ABSORPTION

- Methanol is well absorbed from the gastrointestinal tract, with peak levels reached within 30 to 90 minutes.
- Skin and lung absorption may be significant enough to cause methanol toxicity in the home environment and' the industrial setting (e.g., a painter may develop blindness after working in methanol-soaked clothes).

DISTRIBUTION

- Methanol is distributed like ethanol, with an apparent volume of distribution of 0.6 to 0.7 L/kg.
- The highest concentrations are found in the kidney, liver, and gastrointestinal tract, with smaller concentrations in the brain, muscle,

and adipose tissue. Concentrations in the vitreous humor and optic nerve are high.

ELIMINATION

- Hepatic metabolism in humans accounts for most elimination (90% to 95%).
- Unchanged renal excretion accounts for 2% to 5 f methanol elimination.
- Pulmonary excretion accounts for small amounts ethanol elimination in human oral ingestions.
- Elimination in overdose follows saturation (zero order) kinetics.
- Alcohol dehydrogenase oxidizes methanol to formaldehyde, which is converted rapidly to formic acid by aldehyde dehydrogenase.
- The folate-dependent pathway oxidizes formic acid to carbon dioxide, and a rate constant determines variation in toxicity among species.
- Methanol is oxidized 10 times more slowly than ethanol and has a longer elimination half-life.
- Ethanol has a 10 to 20 times greater affinity for alcohol dehydrogenase than methanol. Therefore, ethanol is metabolized preferentially by alcohol dehydrogenase.
- The serum half-life of methanol after mild toxicity is 14 to 20 hours and, after severe toxicity, 24 to 30 hours.
- Concurrent administration of ethanol increases the serum half- life to 30 to 35 hours.

Clinical Presentations

The onset of symptoms varies between 40 minutes and 72 hours. Co ingestion of alcohol delays symptoms and the absence of symptoms on initial presentation does not exclude serious toxicity. The usual latent period is 12 to 24 hours. Symptoms and signs usually are limited to the central nervous system, eyes, and gastrointestinal tract. Inhalation may result in conjunctival and respiratory tract irritation. Severe metabolic acidosis may produce dyspnea and shock. Coma, seizure, and severe metabolic acidosis are serious prognostic signs. Death generally is from respiratory arrest.

NEUROLOGIC EFFECTS

Headache, vertigo, lethargy, and confusion occur commonly in mild to moderate intoxications. Coma and seizures may occur in severe cases, probably as a result of cerebral edema. Methanol produces little euphoria compared with ethanol.

OPHTHALMOLOGIC EFFECTS

Blurred vision, decreased visual acuity, photophobia, and "feeling of being in a snowfield" are common complaints. Signs include constricted visual fields, fixed and dilated pupils, retinal edema, and hyperemia of the optic disk. Prompt initiation of therapy is necessary to reverse symptoms, but even when treated appropriately, visual defects may persist in 25% of severe cases.

Toxic Dosage/Death

Generally, 1 ml/kg is considered lethal. Fatalities have been reported after ingestion of 15 ml of a 40% solution, although 30 mL generally is considered a minimal lethal dose. Adults have survived ingestions of 500 to 600 ml with aggressive medical care. Consumption of as little as 0.1 ml/kg, or 6 to 10 ml, may cause blindness, but wide individual variation exists.

Laboratory

BLOOD LEVELS

Reports correlating blood methanol to clinic effects show variation of toxicity because of differences in sample timing, individual variation, concentration of toxic metabolites, and co ingestion of ethanol. Peak methanol levels below 20 g / dl usually are associated with asymptomatic individuals Generally, central nervous system symptoms appear above 20 mg / dl, ocular symptoms appear above 100 mg/ dl (however, ocular toxicity may correlate better with formate concentration than with methanol concentration), and fatalities in untreated patients occur at 150 to 200 mg / dl. Peak methanol leaves guide treatment, but levels must be correlated to the presence of symptoms, since time of ingestion often is unknown. Co ingestion of ethanol reduces methanol toxicity.

METABOLIC ACIDOSIS

A profound metabolic acidosis occurs in severe methanol poisoning. Most patients with a serum bicarbonate level under 18 mEq/L have a methanol level over 50 mg/ .All symptomatic patients should have an arterial pH measured. Mortality correlates best with severity *of* acidosis rather with blood methanol levels.

Treatment

GUT DECONTAMINATION

Lavage is recommended for patients presenting within 2 hours of ingestion and may be useful up to 4 hrs after ingestion if coma or co ingested drugs reduce gastrointestinal motility. Charcoal does not adsorb methanol well and probably is not efficacious. There is no scientific evidence to substantiate the usefulness of cathartics in methanol poisoning.

ELIMINATION ENHANCEMENT

Forced diuresis is not effective, but hemodialysis effectively removes methanol as well as formaldehyde and formic acid. Hemodialysis is about eight times more effective than peritoneal dialysis. Dialysis does reduce the intensive care time required for ethanol therapy at methanol levels above 50 mg / dl. Dialysis may be stopped when the methanol level falls below 25 mg / dl. Ethanol also is dialyzed and maintenance levels must be increased during dialysis. Hemoperfusion is ineffective.

Indications for dialysis are somewhat controversial. A peak methanol level over 50 mg/ dl is recommended in the medical literature, but the exact level is debatable. Similarly, formate levels over 20 mg / dl have been recommended as a cut-off.

Refractory metabolic acidosis, any visual impairment, and renal failure are other indications for dialysis.

Antidotes

ETHANOL

Administration of ethanol blocks the formation of formaldehyde and formic acid because of the preferential affinity of ethanol for alcohol dehydrogenase. Ethanol levels should be maintained between 100 and 150 mg/ dl to completely inhibit toxic metabolite formation. Intravenous administration is more reliable than oral administration, but ethyl alcohol is irritating to veins. Blood must be drawn frequently before, during, and after dialysis until a steady-state ethanol level is confirmed. Continue ethanol infusion until the methanol level falls below 20 to 25 mg/ dl. As ethanol prolongs the elimination half-life of methanol to 24 to 30 hours, several days may be required to reduce the methanol level below 25 mg / dl when hemodialysis is not used.

Indications for ethanol include peak methanol levels over 20 mg/ dl. Ethanol should be considered in any patient with a history of ingestion of 0.4 ml/kg of methanol. Any symptomatic patient should receive ethanol pending confirmatory blood methanol levels. Patients who are being considered for hemodialysis and all patients with metabolic acidosis due to methanol poisoning should be considered for ethanol therapy.

FOLATE

Administration of folate provides increased cofactor for the oxidation of formic acid to carbon dioxide. Folic acid, 50 mg intravenously every 4 hours for several days, has been recommended as a large but safe dose. The use of folate is especially important in alcoholics, who may be folate depleted. Folate efficacy in humans has not been proven. Leucovorin is the active form of folate and may be substituted for folic acid.

4-METHYLPYRAZOLE

4-Methylpyrazole (4-MP) or fomepizole decreases methanol toxicity by inhibiting alcohol dehydrogenase. In most cases, administration of 20 mg / kg 4-MP adequately inhibits formate formation for 24 hours.

ETHYLENE GLYCOL

Ethylene glycol is a colorless, odorless, sweet-tasting compound that is used as an antifreeze, coolant, hydraulic brake fluid, glass cleaner, preservative, and glycerine substitute. Ethylene glycol has intoxicating properties similar to those of ethanol. Its metabolites yield central nervous system, cardiopulmonary, and renal dysfunction, as well as severe metabolic acidosis.

Pathophysiology

Ethylene glycol produces roughly the same central nervous system depression as ethanol, but ethylene glycol produces toxic metabolites, which may prove deadly. The metabolic acidosis and anion gap seen with ethylene glycol ingestion result from glycolic (primarily) and lactic acid formation. The citric acid cycle is inhibited

as a result of a reduced NAD/NADH ratio. This results in some oxalic acid formation, which contributes to the metabolic acidosis. Oxalate formation produces myocardial depression and acute tubular necrosis. Glycoaldehydes, glycolic acid, and glyoxylic acid may contribute to central nervous system depression and may contribute to renal toxicity by producing renal edema.

Pharmacokinetics

ABSORPTION

- Ethylene glycol is rapidly absorbed orally, but not by lung or dermal routes.
- Peak levels occur 1 to 4 hours after ingestion.

DISTRIBUTION

- Because ethylene glycol is highly water soluble, it distributes evenly throughout body tissue.
- The volume of distribution of ethylene glycol is 0.83 L/kg.

ELIMINATION

- Approximately 20% of a 1mg/kg dose of ethylene glycol are excreted unchanged. Less than 1% of ethylene glycol is metabolized to oxalic acid at this dose.
- The liver oxidizes ethylene glycol primarily to glycoaldehyde, glycolate, and then glyoxylate.
- The metabolism of glyoxylate follows several pathways that depend on the cofactors thiamine and pyridoxine.
- The oxidation of ethylene glycol to glyoxylate and subsequently to oxalate requires the conversion of NAD to NADH. The altered NAD /NADH ratio shifts pyruvat to lactate and thereby helps produce lactic acidosis.
- The acidic metabolites are more toxic than the parent compound. The order of toxicity appears to be glyoxylate > glycoaldehyde > ethylene glycol.
- The plasma half-life of ethylene glycol is approximately 3 to 5 hours.
- At ethanol levels of 100 to 200 mg/ dl, the half life of ethylene glycol is prolonged to 17 hours because of the 100-times greater affinity of ethanol for alcohol dehydrogenase.

Clinical Presentations

ETHYLENE GLYCOL

Ethylene glycol toxicity may be assumed with an ethanol like intoxication with no odor, a large anion-gap acidosis, coma, osmolal gap, calcium oxalate crystals, and mental status changes. The presentation of ethylene glycol poisoning is classically divided into three stages, and depends on the severity of ingestion.

Stage 1

This "Central Nervous System (CNS) Depression" stage occurs 1 to 12 hours postingestion. Transient exhilaration occurs without the odor of ethanol. Gastrointestinal complaints include nausea and vomiting. Acidosis, coma, convulsions, and myoclonic jerks may be present. The optic fundus usually is normal, although the occasional presence of papilledema may confuse the clinical presentation with that of methanol. Nystagmus and ophthalmoplegia may occur. Cerebral edema secondary to cytotoxic damage and calcium oxalate deposition synergistically depresses central nervous system activity in severe poisoning.

Stage 2

Cardiopulmonary symptoms occur 12 to 24 hours after ingestion. Tachycardia, tachypnea, and mild hypertension often occur. Congestive heart failure and circulatory collapse are seen in severe ingestions.

Stage 3

This renal stage occurs 24 to 72 hours post ingestion. This stage is characterized by oliguria, flank pain, acute bular necrosis, and renal failure. Renal damage may be transient or permanent.

Toxic Dosage/Death

A minimum lethal dose of ethylene glycol in humans is approximately 1.0 to 1.5mL/kg or 100mL in an average adult, however doses as little as 30 mL may be fatal. Levels greater than 85mg/dl generally are fatal. Patients have survived 1- and 2-L ingestions that were treated within 1 hour of their suicide attempts.

Laboratory

URINE

Although oxalate normally is a minor metabolic product of ethylene glycol metabolism, urinary oxalate crystals are a common, but not invariable, feature of ethylene glycol intoxication. Two forms of calcium oxalate crystal are noted in urine: a tent shaped form or dihydrate crystal, and a prism or dumbbell shaped monohydrate form.

Treatment

GUT DECONTAMINATION

Lavage may be effective only for a few hours, unless co ingested drugs or coma delay the generally rapid absorption of ethylene glycol. Reducing absorption is important in massive, recent overdose. Charcoal and cathartics probably are not effective.

ELIMINATION ENHANCEMENT

Deteriorating vital signs, significant metabolic acidosis not amenable to correction with hydration and sodium bicarbonate, crystalluria, and serum ethylene glycol

levels over 50mg/dl are indications for early dialysis. The endpoint for dialysis is a serum ethylene glycol level of 10 mg / dL. During hemodialysis, there is no need for ethanol administration intravenously or in the dialysate because glycolate is effectively eliminated. For clearance of ethylene glycol and its metabolites, hemodialysis is superior to peritoneal dialysis. Continuous arterioenous hemofiltration dialysis may be an alternative when hemodialysis and fomepizole therapy is not available.

SUPPORTIVE CARE

- Correct acidosis, fluid and electrolyte imbalance, and respiratory depression aggressively. Renal clearance of ethylene glycol is inversely related to water absorption. Maintenance of good urine output is necessary to enhance urinary elimination.
- Anion gap metabolic acidosis indicates the production of organic acids. Systemic acidosis below 7.2 may be treated with sodium bicarbonate. The serum bicarbonate concentration also may be increased when bicarbonate dialysate is used during hemodialysis.
- Toxicity may occur without significant elevation f the osmolal gap. Serious ethylene glycol toxicity (50mg/dL) produces an approximate rise in the osmolal gap of 1 mosm.
- Propylene glycol is osmotically active and produces a concen tration-dependent increase in serum osmolality.
- Osmolal and anion gaps may remain elevated d spite low ethylene glycol levels because of the accumulation of glycolate.
- Check the urine each hour for at least 5 hours after presumed ethylene glycol ingestion before significant intoxication is ruled out. If urine oxalate crystals are seen and confirmed by a second urine specimen in 1 hour, begin intravenous (IV) alcohol or fomepizole, and hemodialyze.
- Check urine under Wood's lamp. If antifreeze ha been ingested, the urine may fluoresce from fluorescein dye included in the product. If urine fluoresces, begin IV alcohol or fomepizole, and hemodialyze.
- Hypocalcemia secondary to calcium oxalate deposition may occur, and may be manifested by QT prolongation on electrocardiogram. Replace as indicated with 10% calcium gluconate intravenously.
- Tetany, myalgias, elevated creatinine levels, and increased creatine phosphokinase (CPK) levels may be seen in ethylene glycol poisoning and should all be monitored.
- In diethylene glycol poisoning, decontamination is recommended within 1 to 2 hours of an acute oral ingestion. Syrup of ipecac is not advised because of the potential for early seizures. Ethanol therapy has not been subjected to controlled clinical studies. Seizures are treated with standard anticonvulsants. Hemodialysis is indicated in unstable and acidotic patients.

I i

Antidotes

4-METHYLPYRAZOLE

4-MP or fomepizole is a competitive inhibitor of alcohol dehydrogenase and effectively blocks the formation of toxic metabolites from ethylene glycol. A 15-mg/kg IV loading dose is followed by 10 mg/kg IV every 12 hours for 4 doses, then 15mg/kg IV every 12 hours until the ethylene glycol level falls below

20mg/dL. In all suspected cases, do not wait for syptoms to appear or for a serum level to return before treatment. Fomepizole is dialyzable and must be given every 4 hours during dialysis.

ETHANOL

Alcohol competitively inhibits alcohol dehydrogenase and blocks the metabolism of ethylene glycol. Ethanol therapy prolongs the half-life of ethylene glycol and reduces the formation of toxic metabolites. In severe ethylene glycol intoxication, acidemia, glycolic acid production, and serum ethylene glycol levels may persist despite ethanol infusions.

Indications for ethanol therapy include a strong suspicion of significant ethylene glycol ingestion pending determination of serum levels, peak serum ethylene glycol levels over 20 mg / dL (with or without symptoms), and acidemia, regardless of ethylene glycol levels. The ethanol must be administered as soon as possible as the elimination half-life of ethylene glycol is 3 hours at low concentrations. The dosage is the same as that for methanol poisoning and may be given intravenously or orally.

After termination of hemodialysis, ethanol may be administered in IV boluses of 500 mL 5% glucose with 10% ethanol over 20 to 30 minutes, followed by a continuous infusion of 70 to 100 mL/hour. Serum ethanol level is monitored every hour until a constant level of 90 to 130 mg / dL is maintained. For severe adult poisoning in which medical care may be delayed, four 1-oz "shots" of whiskey before or during transport may be used.

COFACTORS

Pyridoxine (50 mg 1M per dose) and thiamine (100 mg 1M per dose) are cofactors in the metabolism of ethylene glycol and should be given four times each day for two days. Magnesium also is a cofactor and should be replenished aggressively, guided by serum magnesium levels, particularly in alcoholic patients.

23.5 LACRIMATING AGENTS (TEAR GAS)

23.5.1 Introduction

Before World War I, the mechanisms of biological and chemical alkylating agents were surfacing. The search for less toxic, yet severely irritating compounds was already progressing. Law enforcement and governing bodies were convinced that such chemicals could be used in domestic (personal protection, crowd control) or in military situations (war). This understanding prompted the effort to develop agents that could be effective tools for law enforcement while avoiding life-threatening force. Thus spawned the introduction of lacrimating agents, popularly referred to as tear gas or pepper spray. Unlike the pulmonary irritants or asphyxiants that have practical industrial and commercial applications, lacrimating agents were developed specifically to cause irritation.

23.5.2 Chemical Agents

The compounds consist mostly of chemically invariable groups of brominated or chlorinated, simple or aromatic hydrocarbons that cause severe local, upper respiratory, and lower respiratory illness. Most of the agents are highly lipid-soluble powders. They are dissolved in organic solvents to effect aerosol delivery, or burned and exploded for military use. Table 23.5 summarizes the properties, chemistry, and clinical effects of popular lacrimating agents currently used for domestic and military use. Today, the compounds are all organically synthesized and have otherwise limited commercial or industrial utility.

23.6 CHEMICAL ASPHYXIANTS

As noted above, chemical asphyxiants produce toxicity through induction of cellular hypoxia or anoxia. The agents alter the oxygen-carrying capacity of hemoglobin (such as with carbon monoxide) or inhibit cellular metabolic enzymes (cyanide, hydrogen sulfide), ultimately interfering with normal physiologic respiration. Among the chemical asphyxiants, carbon monoxide, cyanide, and hydrogen sulfide are the most frequently encountered chemical asphyxiants and are discussed below.

23.7 CARBON MONOXIDE (CO)

23.7.1 Incidence

Each year, nearly 500 unintentional deaths, and more than 1,700 suicides are related to carbon monoxide poisoning in the U.S. An estimated 3,000 to 5,000 people are treated annually for CO poisoning in emergency departments (EDs). Thousands more are either misdiagnosed or do not seek medical care. The statistics support the conclusion that CO poisoning is a serious public health issue.

TABLE 23.5
Lacrimating Agents: Chemical and Clinical Properties

Agent	Chemical (or *Common Name*)	Chemical Properties[a]	Uses	Acute Clinical Effects
Benzyl bromide	bromomethyl-benzene	Liquid, decomposed by water	Chemical war gas	Intense local irritation; large doses cause CNS depression
Bromoacetone	1-bromo-2-propanone	Liquid, turns violet in air	Chemical war gas	Intense local irritation
□-Bromobenzyl cyanide	□-bromobenzene acetonitrile; *camite*	Crystalline powder, odor of soured fruit	Chemical war gas	Intense local irritation
Chloroacetone	1-chloro-2-propanone	Liquid, pungent odor, turns dark with light	Tear gas component for police and military use; insecticide; lead, perfume and drug manufacturing	Intense local irritation
ω-Chloroaceto-phenone	2-chloro-1-phenylethanone; *chemical mace*	Crystalline powder	Riot control agent	Intense local irritation; URT and LRT irritation, pulmonary edema
o-Chlorobenzyl-idenemalononitrile	[(2-chloro-phenyl)methylene] propanedinitrile	Crystalline solid	Riot control agent, chemical warfare agent	Intense local irritation; URT and LRT irritation plus erythema, chest constriction, vesiculation
Chloropicrin	trichloronitro-methane; *acquinite*	Oily liquid	War gas, insecticide, disinfectant, fumigant	URT irritation and lacrimation, potent skin irritant, NVD (orally)

Note: NVD = nausea, vomiting, diarrhea, URT = upper respiratory tract, LRT = lower respiratory tract.

[a] At standard temperature and pressure (STP); All of the compounds are miscible or soluble in acetone, alcohol, chloroform or ether, and are poorly or slightly soluble in water; URT and LRT symptoms are as described in Table 23.2.

23.7.2 Chemical Characteristics and Sources of Exposure

CO is odorless, colorless, and nonirritating, and an abundant product of industrial combustion,* thus appropriately labeled as the *silent killer.*

Principal sources of the gas include commercial and passenger motor vehicle exhaust fumes (1% from new automobiles, above 10% in older models) as well as other gasoline, diesel, and propane-powered engines. Smoke from charcoal fires and organic materials, tobacco smoke (3 to 6% CO), and methylene chloride, account for the majority of sources. Methylene chloride is a useful industrial solvent in paint, cleaning, and food processing industries, as well as an aerosol propellant and insecticide. In fact, upon ingestion, methylene chloride is metabolized by hepatic mixed function oxidases (MFO) to carbon monoxide and carbon dioxide. Because of the wide distribution of the pollutant, it is not surprising to detect normal adult blood CO levels between 0.40% and 0.55%.

23.7.3 Toxicokinetics

Although CO has low aqueous (plasma) solubility, its binding affinity, particularly for hemoglobin (Hb), is high. Like other toxic gases, absorption and binding of CO to hemoglobin depends on the same factors that increase exposure to the substance — i.e., percent CO in ambient air, duration of exposure, and RMV. The degree of binding is estimated according to the following formula:

$$\% \text{ COHb} = \text{RMV} \times [\text{CO}] \times \text{time}$$

where % COHb is the percent carboxyhemoglobin formed, RMV is the respiratory minute volume (described above and equals about 6 l/min in average adults), [CO] is the CO concentration in ambient air, and time of exposure is in minutes. According to this formula, inhaling 500 ppm CO from exhaust fumes (0.05% in a typical open garage with a running motor vehicle engine) for 30 min yields a percent COHb concentration in blood equal to 15%. The compound is not metabolized, and its half-life is approximately 4 to 5 h.

23.7.4 Mechanism of Toxicity

The net effect of CO toxicity is tissue hypoxia. This is mediated through its reversible but high affinity for ferrous ion (Fe^{+2}) in hemoglobin in the red blood cell. The binding is estimated to range from 200 to 250 times that of molecular oxygen for Hb. The strength of the binding results in the formation of a stable carboxyhemoglobin (COHb) moiety. COHb then displaces the oxygen-carrying capacity of Hb, and shifts the *oxygen-Hb dissociation curve* leftward (Figure 23.1). The diagram illustrates the normal sigmoidal relationship between Hb saturation and the partial pressure of oxygen (PO_2, mmHg) dissolved in blood at normal body temperature.** At normal atmospheric pressure, the higher the PO_2, the more oxygen combines

*It is the most abundant pollutant, accounting for 0.001% atmospheric gases.
**The percent saturation expresses the average saturation of Hb with oxygen.

Pg. 23

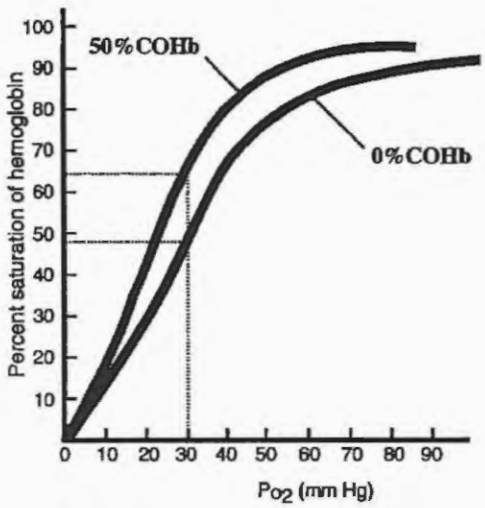


FIGURE 23.1 Oxygen-hemoglobin and carboxyhemoglobin dissociation curves.

with Hb. The curve reaches a plateau at 100 mmHg PO_2, where Hb is almost completely saturated (98%). In the presence of CO, oxygen is displaced from Hb binding sites, rendering less oxygen available for delivery to tissues. The oxygen remaining within the Hb molecule combines more tightly with Hb. At any given PO_2, in the presence of CO, Hb is more saturated with oxygen. This phenomenon is known as the *Bohr effect* (the *Bohr effect* also occurs in metabolic alkalosis, and is stimulated by high blood pH or low blood PCO_2). In addition, CO also binds myoglobin and cytochrome oxidase enzymes with high intensity.

23.7.5 Signs and Symptoms of Acute Toxicity

Clinical presentation of CO poisoning depends on the time of exposure and the concentration of CO in the area, as noted above. Acute, high-concentration exposure, such as might occur in an enclosed space (automobile exhaust in a closed garage) will produce more severe signs and symptoms than chronic, low-concentration exposure (as with faulty heating systems). The latter scenario may be misdiagnosed as mimicking a bacterial or viral infection. Symptoms from acute, mild exposure range from asymptomatic to headache, dizziness, malaise, and fatigue. Moderate exposure may present with confusion, lethargy, ataxia, syncope, and nystagmus.* Severe intoxication manifests as seizures, pulmonary edema, myocardial infarction, and coma. The classic cherry-red discoloration of the face and extremities, due to uncompensated peripheral vasodilation, is evident only in severe poisoning. Blood samples for gas analysis must be obtained immediately after exposure (using blood gas CO-oximetry). Calculation of percentage of arterial

*Pendular or jerky rhythmical oscillation of the eyeballs.

Pg. 24

blood oxyhemoglobin (SaO_2), based on blood gas analysis, is often falsely elevated because of COHb high affinity binding. Other routine clinical laboratory values may also lead to inaccurate conclusions.

Although recovery following nonfatal acute exposure is often complete within several days, subacute complications develop, depending on the severity of exposure. The complications include persistent neurologic and myocardial dysfunction, peripheral neuropathy, aspiration pneumonitis, and ischemic skin. Approximately 10 to 30% of victims of severe acute poisoning will display delayed-onset neurobehavioral dysfunction, also known as *CO-induced delayed neuropsychiatric syndrome* (CO-DNS). The condition is characterized by impaired cognitive function, personality changes, dementia, and symptoms resembling Parkinson's disease. Individuals at greater risk for development of complications are patients with a history of heart disease, anemia, and chronic obstructive pulmonary disease (COPD), and patients exposed in the presence of alcohol or respiratory depressants. Infants are also at greater risk for CO-DNS.

23.7.6 Treatment of Acute Poisoning

As with any agent suspected of causing CNS depression or disrupting cardiovascular function, clinical history and evaluation should determine other etiologies, such as intoxication with alcohol or other CNS depressants. Presence of concurrent cyanide poisoning (particularly in burn victims) may aggravate the complications. The goal of treatment of CO inhalation victims, then, is to reduce the development of cerebral and cardiovascular ischemia and to increase the dissociation of COHb. Initial management includes removal of the individual from the source (while minimizing muscle and spinal movement, if possible), followed by administration of supplemental humidified oxygen soon after. Maintenance of respiration, fluid and electrolyte replacement, and clinical chemistry determination are largely supportive. Administration of 100% normobaric* oxygen reduces the half-life of 50% COHb level from about 4 h in room air to approximately 50 to 60 min,** although longer periods may be required in high-risk patients. Treatment continues until COHb levels drop to within normal range.

23.8 CYANIDE

23.8.1 Chemical Characteristics, Occurrence, and Uses

Cyanic acid (hydrogen cyanate, HCNO) is the starting chemical principle for the various salt forms of cyanide, including the sodium (cyanogran, NaCN), potassium (KCN), and calcium (CaCN) salts. Hydrogen cyanide (HCN, hydrocyanic acid, prussic acid) is a gas and a catalyst and is prepared from the cyanate salts. In addition, the compounds occur naturally as cyanogenic glycosides. The compounds are found

---

*At 1 atm of pressure.

**Although some studies have demonstrated a further reduction of the half-life to less than 40 min with hyperbaric oxygen (i.e., 100% oxygen at 3 atm of pressure), the results from this mode of therapy are equivocal. As noted above, hyperbaric oxygen is associated with signs and symptoms of oxygen toxicity.

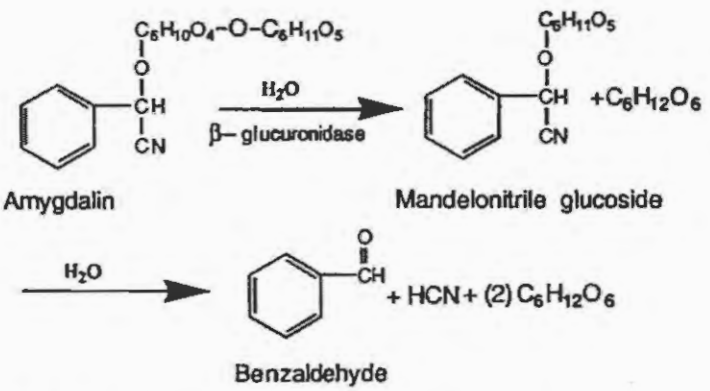


FIGURE 23.2 Cyanogenic glycosides and hydrolysis of amygdalin.

from 0.01 to 14% in the seeds of various nuts, including almonds (highest concentration, 2 to 14%), cherries, plums, apples, peaches, apricots, pears, plums, and rosaceous plants, as well as in bamboo sprouts and cassava. Figure 23.2 illustrates the hydrolysis of amygdalin, the most widely distributed cyanogenic glycoside. Most hydrolyzing agents, in the presence of the enzyme □-glucuronidase, are capable of producing the hydrolysis products of amygdalin, i.e., mandelonitrile glucoside (an intermediate) plus glucose, benzaldehyde, and hydrocyanic acid.

Cyanide compounds are also valuable industrial chemicals used in electroplating and electropolishing, manufacturing of plastics, extraction of gold and silver from ores, as fumigants, in fertilizer, and in artificial nail glue removers. Therapeutically, sodium nitroprusside, a direct arterial vasodilator used in the treatment of emergency hypertension, releases five molecules of CN when metabolized, which also accumulates with fast infusion rates (see Chapter 18, "Cardiovascular Drugs"). As with CO poisoning, fire victims are also prone to CN intoxication.

23.8.2 Mechanism of Toxicity

Cyanide produces histotoxic anoxia by inhibiting oxidative phosphorylation, resulting in arrest of cellular respiration (see Figure 16.3, Chapter 16). By binding to cytochrome a/a3, CN forms a CN–cytochrome oxidase–Fe^{+3} complex. The complex interferes with the transfer of electrons to O_2, the final electron acceptor. Ultimately, CN blocks the electron transport chain and inhibits metabolic respiration. It provokes a decrease in cellular oxygen utilization, prevents oxidative phosphorylation of ADP to ATP, and prompts an increase in venous PO_2 (arterialization of venous blood).* The decrease in aerobic respiration forces the cell to revert to anaerobic metabolism, which generates excess lactic acid, triggering metabolic acidosis.

* Interestingly, the patient is not cyanotic, and availability and binding of oxygen are not compromised. In fact, arterial PO_2 appears normal (100 mmHg).

Pg. 26

23.8.3 Toxicokinetics

Acute lethal toxicity results within 1 h from an oral dose of 100 to 200 mg, while inhalation of 150 to 200 ppm of HCN gas is fatal (approximately only 60% of the population can smell 0.2 to 5.0 ppm). Trace amounts of CN are generally detoxified slowly by binding to circulating methemoglobin (methHb). The resulting cyanomethemoglobin complex prevents access to the cytochrome enzymes. Normally circulating rhodanese enzyme (thiosulfate cyanide sulfur transferase) transfers a sulfur group to the cyanomethemoglobin complex, forming a relatively nontoxic thiocyanate ion that is eventually eliminated by renal excretion. Chronic, low dose intoxication is more insidious.

23.8.4 Signs and Symptoms of Acute Toxicity

Signs and symptoms precipitate rapidly with exposure to HCN vapors. Initially symptoms of neurological toxicity appear, including headache, nausea, vomiting, weakness, and dizziness. The chemical stimulates chemoreceptors in the carotid artery, triggering reflex hyperpnea (increase in respirations), tachypnea (gasping for air), and pulmonary edema. Hypotension with reflex tachycardia completes the cardiovascular presentation. With high doses, the victim is stuporous yet responsive, where the condition may deteriorate to hypoxic convulsions, hypotension, coma, and death.

23.8.5 Treatment of Acute Poisoning

As with CO poisoning, initial management of patients with CN intoxication includes removal of the individual from the source, decontamination (removal of clothes, flushing with water, if necessary), and administration of activated charcoal or gastric lavage if the victim is encountered soon after ingestion. The goal of treatment is to immediately decrease CN binding to cytochrome enzymes with the specific antidote available. The Cyanide Antidote Package (various manufacturers) consists of three major components:

1. Amyl nitrite inhalant, 0.3 ml (12 aspirols)
2. Sodium nitrite, 300 mg in 10 ml (2 ampoules)
3. Sodium thiosulfate, 12.5 g in 50 ml (25% solution, 2 ampoules)

plus disposable syringes, stomach tube, tourniquet, and instructions. The primary mechanism of detoxification involves conversion of CN to the nontoxic thiocyanate ion, in preparation for renal elimination. Initially, either i.v. sodium nitrite (300 mg over 3 to 5 min)* or amyl nitrite inhalant (1 or 2 crushed aspirols every 2 to 3 min, if i.v. route is not accessible) are administered. Thus, the nitrites induce formation of cyanomethemoglobin-Fe^{+3} (CN–Hb–Fe^{+3}) complex in preference to CN–cytochrome oxidase–Fe^{+3}. Nitrites convert reduced Hb–Fe^{+2} ([H]) to oxidized methHb

* In children, initial dose of sodium nitrite (mg/kg) is calculated according to the patient's Hb level (Pg. 27

([O]), freeing cytochrome oxidase enzyme to resume oxidative phosphorylation. The sequence is outlined in Reaction 1:

$$Hb\text{-}Fe^{+2} + NO_2 \rightarrow Hb\text{-}Fe^{+3} + NO \quad (23.1)$$

Since methHb has a greater affinity for CN than cytochrome oxidase, it induces the transfer of CN from the cytochrome enzyme complex to methHb, forming cyanomethemoglobin (CN–Hb–Fe^{+3}) according to Reaction 2:

$$Hb\text{-}Fe^{+3} + CN\text{–cytochrome–}Fe^{+3} \rightarrow CN\text{–}Hb\text{–}Fe^{+3} + \text{cytochrome–}Fe^{+3} \quad (23.2)$$

Peak methHb levels are reached within 30 min of i.v. administration in adults. Since cyanomethemoglobin is relatively unstable and reversible, the subsequent step is to force renal excretion of the CN moiety by administration of sodium thiosulfate. As mentioned above, this requires the rhodanase enzyme reaction that naturally detoxifies trace amounts of circulating CN ions. This reaction (3, below) is accelerated by supplying exogenous sulfur from the administration of sodium thiosulfate ($Na_2S_2O_3$). $Na_2S_2O_3$ (12.5 g i.v. over 10 min) is administered immediately after sodium nitrite (400 mg/kg, up to 12.5 g total in children). The treatment results in the formation of thiocyanate, sodium sulfite, and regenerated methemoglobin, respectively.

$$CN\text{-}Hb\text{-}Fe^{+3} + Na_2S_2O_3 \rightarrow CN\text{-}S + Na_2SO_3 + Hb\text{–}Fe^{+3} \quad (23.3)$$

Adverse reactions associated with nitrites involve hypotension and the risk of production of excess, life-threatening amounts of methemoglobin. In excess, methemoglobin decreases availability of oxyhemoglobin (reduced form) necessary for oxygen transport. Other antidotes for CN poisoning, such as 4-methylaminophenol (4-DMAP), hydroxycobalamin, dicobalt-EDTA, and hyperbaric oxygen, are not FDA approved or recommended.

Permanent neurological damage (Parkinson-like syndrome) is a complication of severe CN toxicity. Higher levels of thiocyanate are also implicated in the development of tobacco amblyopia (in chronic smokers) and tropical ataxic neuropathy (in diets rich in cassava).

23.9 METHODS OF DETECTION

Clinical chemistry analysis, hematology assays (including hemoglobin and hematocrit tests) and arterial blood gas determinations are not clinically useful indicators for CO poisoning. Routine blood gas analysis (pulse oximetry), used to measure changes in oxyhemoglobin content, may not be sensitive enough, due to the high affinity COHb complex. Carboxyhemoglobin blood levels are useful if performed soon after acute exposure. Automated spectrophotometric devices (CO-oximeters) provide valuable measures of carboxyhemoglobin, oxyhemoglobin, and methemoglobin, the levels of which are correlated with severity of CO exposure. The tech-

nique estimates simultaneously total hemoglobin, percent oxyhemoglobin, and percent carboxyhemoglobin. The procedures are recommended for most clinical purposes. For the investigation of low-level exposure and the detection of increased hemolysis in neonates, more sensitive methods involving the release of CO and its measurement by gas chromatography are required.

As with CO, pulse oximetry may not be suitable for therapeutic management of CN poisoning. In fact, the onset and rate of CN toxicity is often too rapid to allow CN blood levels to be of any utility. Consequently, determination of hemoglobin levels is a better indicator of the progress of CN poisoning, and can be used to manage initial treatment with sodium nitrite. Elevated plasma lactate, associated with cardiovascular collapse, should also suggest cyanide intoxication. Other clinical chemistry and hematology tests can be of value as indicators of supportive measures.

REFERENCES

Suggested Readings

Bui, L., Cyanide and hydrogen sulfide, in *Toxicology Secrets*, Ling, L.J. et al., Eds., Hanley & Belfus, Inc., Philadelphia, 2001, chap. 53.

Budavari, S., Ed., *The Merck Index*, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ, 1996.

Fung, F., Simple asphyxiants and pulmonary irritants, in *Toxicology Secrets*, Ling, L.J. et al., Eds., Hanley & Belfus, Inc., Philadelphia, 2001, chap. 50.

Holmes, H.N., Ed., Respiratory System, in *Handbook of Pathophysiology*, Corwin, E.I., Ed., Springhouse Corp., PA, 2001, chap. 7.

Wallace, K.L., Carbon monoxide, in *Toxicology Secrets*, Ling, L.J. et al., Eds., Hanley & Belfus, Inc., Philadelphia, 2001, chap. 52.

Review Articles

Beasley, D.M. and Glass, W.I., Cyanide poisoning: pathophysiology and treatment recommendations, *Occup. Med. (Lond).* 48, 427, 1998.

Borron, S.W. and Baud, F.J., Acute cyanide poisoning: clinical spectrum, diagnosis, and treatment, *Arh. Hig. Rada. Toksikol.*, 47, 307, 1996.

Choi, A.M. and Otterbein, L.E., Emerging role of carbon monoxide in physiologic and pathophysiologic states, *Antioxid. Redox. Signa*, 4, 227, 2002.

Friederich, J.A. and Butterworth, J.F., IV, Sodium nitroprusside: twenty years and counting, *Anesth. Analg.*, 81, 152, 1995.

Gonzales, J. and Sabatini, S., Cyanide poisoning: pathophysiology and current approaches to therapy, *Int. J. Artif Organs*, 12, 347, 1989.

Hartzell, G.E., Overview of combustion toxicology, *Toxicology*, 115, 7, 1996.

Holland, M.A. and Kozlowski, L.M., Clinical features and management of cyanide poisoning, *Clin. Pharm.*, 5, 737, 1986.

Jones, J., McMullen, M.J., and Dougherty, J., Toxic smoke inhalation: cyanide poisoning in fire victims, *Am. J. Emerg. Med.*, 5, 317, 1987.

Medinsky, M.A. and Bond, J.A., Sites and mechanisms for uptake of gases and vapors in the respiratory tract, *Toxicology*, 160, 165, 2001.

Olajos, E.J. and Salem, H., Riot control agents: pharmacology, toxicology, biochemistry and chemistry, *J. Appl. Toxicol.*, 21, 355, 2001.

Pg. 29

Pesticides

INTRODUCTION

Pesticide poisoning is an important cause of worldwide morbidity and mortality. It has been estimated that there are 3 million severe cases of acute pesticide poisoning each year with some 220,000 deaths. 95% of fatal pesticide poisonings occur in developing countries. Serious cases of pesticide poisoning are more likely to occur in adults than in children. More than 1,000 biocides and 25,000 formulations currently are in use. California leads the United States in both volume of pesticides used and pesticide-related illnesses. Both severe accidental and intentional illness results from the misapplication of these potent compounds.

Well-publicized epidemics in Iraq, Morocco [tri-o-cresyl phosphate (TOCP)], and in the United States (TOCP in alcoholic beverages) have resulted from ingestion of contaminated food and beverage products. When pesticide ranks for all age groups were combined, the east south central and west south central states of the United States were the highest ranked regions. A general trend of increasing pesticide concentrations with increasing age appears to exist, indicating that continued exposure results in higher levels of toxins in human adipose tissue because of bioaccumulation. The ultimate correlation of this data with scientific proof that toxic chemicals in the environment pose significant threats to humans has not yet been defined.

INSECTICIDES

ORGANOPHOSPHATES

Although phosphates and phosphonates were synthesized over 75 years ago, commercial interest in organophosphate com pounds did not develop until late in World War II when German scientists developed tetraethyl pyrophosphate (TEPP) as a nicotine insecticide substitute. Soon thereafter, the German group developed dimefox, sarin, tabun, and parathion. In the United States, organophosphates cause numerous poisonings each year. In California, four out of five systemic poisonings from agricultural chemicals result from exposure to organophosphate compounds. Organophosphates have relatively high acute toxicity but low chronic toxicity.

Farmhands can acquire a chronic low-level exposure known as "orange-picker's flu" characterized by nausea, weakness, and headache. Several well-recorded epidemics of severe extremity motor weakness and mild sensory impairment resulted from TOCP

contamination, and cooking oil containing TOCP (Morocco, 1959). Mass intoxication occurred in the southern United States during the 1930s when TOCP was employed as an adulterant of Jamaica Ginger ("Jake"), a popular alcohol-containing drink of the Prohibition Era. The resulting neurologic syndrome was known as Ginger "Jake" Paralysis or "Jack-Leg" because of its predilection for paralysis of the lower extremity. Gastrointestinal (GI) complaints were followed by the resolution of symptoms, and then by delayed neuropathic change often with permanent sequelae.

Diagnosis of acute organophosphate toxicity includes a reliable history, evidence of exposure to organophosphate (garlic odor), signs or symptoms of cholinergic excess, improvement with atropine or pralidoxime, and inhibition of cholinesterase in blood. A diagnosis of mild-to-moderate acute organophosphate poisoning rarely is justified unless a number of conditions are present. These include a reliable history of exposure to an organophosphate pesticide, a latent interval of not more than a few hours between the last exposure and the onset of illness, a clinical picture in which typical signs and symptoms are present, reduction of plasma and red blood cell (RBC) cholinesterase activity to a level substantially below 50% of baseline values, and an acute illness that is not substantially longer than 48 hours.

Pathophysiology

Organophosphates complex with acetylcholinesterase enzymes, leading to their deactivation. The resultant accumulation of large amounts of acetylcholine causes initial stimulation, then exhaustion of cholinergic synapses. Gamma-aminobutyric acid (GABA) and dopamine pathways provide compensatory inhibition to counteract the excessive cholinergic activity produced by these agents.

Pharmacokinetics

ABSORPTION

- Most organophosphate compounds are rapidly and well absorbed from the skin, conjunctiva, GI tract, and lungs.

DISTRIBUTION

- Most organophosphates are polar, water-soluble chemicals, but a few compounds possess high-partition coefficients (e.g., dichlofenthion), which may lead to delayed, prolonged symptoms.

ELIMINATION

- These chemicals are detoxified by cytochrome P450-mediated monooxygenases in the liver, but some metabolites are more toxic than parent compounds (i.e., conversion of the thiono groups on parathion, diazinon, and malathion to oxons).
- Metabolites usually are detected from 12 to 48 hours post exposure.

Clinical Presentations

Neurologic effects of organophosphate poisoning primarily depend on the balance between muscarinic and nicotinic receptors, and contributions of the central nervous system. Miosis is the most constant sign, but its absence does not exclude organophosphate poisoning. Muscle fasciculations are a highly reliable sign of organophosphate poisoning. The presence of excessive secretions (e.g., lacrimation and bronchorrhea) is also helpful in confirming the diagnosis.

Symptoms develop several hours post exposure, but symptoms can occur 5 minutes after massive ingestions. Another etiology should be considered if symptoms appear more than 12 hours post exposure, and the diagnosis of acute organophosphate poisoning is equivocal if symptoms begin after more than 24 hours. The exceptions are highly lipid-soluble compounds, which can cause mild initial symptoms followed by cholinergic crisis in 40 to 48 hours.

The duration of illness depends on the severity of poisoning, because several months may be required for cholinesterase activity to return to normal levels. Symptoms of mild to moderate organophosphate poisoning usually resolve within a month. Episodes of headache, visual disturbances, nausea, and vomiting may persist 10 weeks after an acute exposure.

NEUROLOGIC EFFECTS

Numerous central nervous system symptoms have been associated with organophosphate poisoning. These include giddiness, tension, anxiety, restlessness, emotional liability, excessive dreaming, insomnia, nightmares, headache, tremor, apathy, depression, drowsiness, difficulty in concentrating, confusion, slurred speech, ataxia, weakness, coma with absence of reflexes, Cheyne-Stokes respirations, convulsions, and depression of respiratory and circulatory centers with dyspnea, cyanosis, and hypotension.

MUSCARINIC EFFECTS

Muscarinic effects result from potentiation of post-ganglionic parasympathetic activity on smooth muscle. Physiological effects include intestinal, bronchial, and bladder smooth muscle contraction, pupillary constriction and decreased reactivity, secretory gland stimulation, slowing of the sinus node and atrioventricular conduction, and ventricular dysrhythmias.

NICOTINIC EFFECTS

Nicotinic effects result from accumulation of acetylcholine at the motor end plate and autonomic ganglia, leading to persistent depolarization of skeletal muscles.

CHOLINERGIC EFFECTS

The mnemonic DUMBELS describes signs of cholinergic excess: Diarrhea, Urination, Miosis, Bronchospasm, Emesis, Lacrimation, and Salivation.

ODOR

A garlic-like odor emanating from the patient or involved container may aid in the diagnosis. The organic solvent in which the organophosphate is dissolved may mask the odor.

DERMATOIOGIC EFFECTS

Organophosphate compounds can produce dermal irritation, but most are weak sensitizers. Malathion in a 10% concentration induces contact sensitization in almost one-half of those exposed.

PULMONARY EFFECTS

Bronchorrhea may be a predominant and life-threatening sign of cholinergic excess. Organophosphates may cause non-cardiogenic pulmonary edema or adult respiratory distress syndrome (ARDS). The differential diagnosis of toxin-induced ARDS includes phosgene, nitrogen dioxide, narcotics, phenothiazines, salicylates, and paraquat exposure.

RENAL EFFECTS

Immune complex nephropathy with renal dysfunction and massive proteinuria may occur several weeks after malathion exposure.

PANCREATIC EFFECTS

Pancreatitis after ingestion of organophosphates may terminate fatally. Pancreatic enzyme estimation in serum or urine, as well as imaging procedures such as ultrasound or computed tomography, should be performed in cases of parathion ingestions.

MUSCULOSKELETAL EFFECTS

Organophosphate compounds produce muscle weakness by cholinergic excess initially. Fasciculations progress to paralysis resulting from depolarization and desensitization blocks at the neuromuscular junction.

CARDIOVASCULAR EFFECTS

Depending on the agent, absorption, and amount employed, patients may have elevated blood pressure and tachycardia (e.g., nicotinic) rather than bradycardia or hypotension (e.g., muscarinic effects). Fatal dysrhythmias may develop 24 to 48 hours after ingestion.

DELAYED NEUROTOXICITY

"dying-back" of axons may occur, rather than demyelination. The process begins as a focal lesion, primarily in large myelinated fibers, and leads to axon death distal to the lesion. Polyneuropathy has been described in those exposed to organophosphates. Suggested diagnostic criteria for an organophosphate delayed syndrome include a history of severe acute organophosphate poisoning about 1 to 6 weeks prior to the onset, symptoms and signs of polyneuropathy, slow recovery, and reasonable exclusion of other nervous disease. The cerebrospinal fluid is usually normal with the exception of a slight rise in protein.

PSYCHIATRIC EFFECTS

Persistent neurobehavioral symptoms may develop. Persistent neurological and behavioral abnormalities attributed to organophosphate exposure include drowsiness, mental confusion, anxiety, emotional liability, depression, fatigue, and irritability. Most of the persistent symptoms that develop after acute organophosphate exposure resolve within 1 year.

Toxic Dosage/Death

Full recovery from most organophosphate exposures generally occurs within 10 days when optimum treatment has been quickly instituted. Fatality usually occurs in untreated, severely intoxicated patients within 24 hours.

Drug Interactions

Patients who develop low plasma cholinesterase activity after organophosphates exposure may develop apnea after administration of succinylcholine. Phenothiazines and

antihistamines have anticholinesterase activity and may potentiate organophosphate toxicity. Central nervous system depressants, such as opiates, may increase the likelihood of respiratory arrest.

Pregnancy/Lactation

Patients who ingest organophosphorous insecticides during the second or third trimesters of pregnancy have been treated successfully with atropine and pralidoxime and later delivered healthy newborns with no significant abnormalities. During early pregnancy, plasma cholinesterase levels fall but they return to normal levels by the third trimester.

Laboratory

ANALYTIC METHODS

Gas chromatographic techniques are available to identify organic phosphate metabolites of malathion, diazinon, and parathion in both blood and urine. Urine screens are qualitative tests that indicate exposure but do not correlate with symptoms or cholinesterase activity.

BLOOD LEVELS

While blood levels are available, proof of significant exposure relies more on the inhibition of cholinesterases.

RED BLOOD CELL CHOLINESTERASE

Inhibition of acetylcholinesterase is a confirmatory test for organophosphate poisoning but is not diagnostic when used alone. The RBC cholinesterase level is the preferred index of toxic exposure, because it measures the same enzyme active in nervous tissue and is less labile than the plasma cholinesterase level. RBC cholinesterase regenerates slowly (0.5% to 1% per day) and, in severe poisoning, may be depressed up to 3 months after acute exposure. In mild-to-moderate toxicity, these levels typically return to baseline values within several weeks. Pre exposure baseline levels should be established for any worker frequently exposed to organophosphates.

PLASMA (PSEUDO) CHOLINESTERASE

The liver produces most of the plasma (pseudo) cholinesterase, but this enzyme also is found in nervous tissue, pancreas, heart, and white matter. Greater daily variations in plasma cholinesterase occur compared with RBC cholinesterase. Plasma cholinesterase levels both decline and regenerate more quickly than RBC cholinesterase levels, with an initial rapid increase followed by slower recovery. Typically, plasma cholinesterase levels

are depressed for a maximum of 1 to 3 weeks after organophosphate poisoning. The rate of decline may be more important in mild- to-moderate poisoning than the amount of depression. Acute symptoms develop after a 50% decrease in baseline cholinesterase levels.

Because of the wide range of normal values for RBC and plasma cholinesterase, these levels maybe normal in symptomatic patients exposed to organophosphates. Both plasma and RBC cholinesterase levels should be drawn in all patients with suspected organophosphate toxicity. A 15% to 20% or greater increase in the plasma cholinesterase level drawn 3 to 5 days later indicates a high likelihood of organophosphate poisoning. In equivocal cases, a baseline RBC cholinesterase level should be established by serial measurements and compared with immediate post exposure values. RBC cholinesterase levels rather than plasma levels are recommended as an endpoint, because the RBC levels more closely reflect physiological effects in the nervous tissue. Generally, acute exposures are classified as mild (20% to 50% of baseline), moderate (10% to 20% of baseline), and severe (10% or less of baseline).

Treatment

GUT DECONTAMINATION

Most organophosphate insecticides contain hydrocarbon solvents, which are severe aspiration hazards. The usual measures of gastric decontamination such as activated charcoal and cathartics may be used when the patient presents within 4 hours after exposure, however extreme caution must be exercised to avoid aspiration.

ELIMINATION ENHANCEMENT

Because effective antidotes are available, methods to enhance removal are seldom necessary. Charcoal hemoperfusion may be helpful in malathion poisoning, however its effectiveness is limited by a short duration of effective removal afforded by the hemoperfusion column, and by the wide distribution of malathion in the body. Over a prolonged time in severe, acute malathion poisoning, the column must be changed as it becomes saturated.

SUPPORTIVE MEASURES

Immediate life-threatening symptoms usually are respiratory problems resulting from weakness of respiratory muscles, central depression of respiration, bronchospasm,

bronchial secretions, and pulmonary edema, which all result in hypoxemia. Frequent suctioning, endotracheal Intubation, and / or assisted ventilation may be necessary to maintain adequate oxygen- ation. Monitor PaO2 carefully with arterial blood gases in an intensive care setting.

Although cardiovascular function generally is maintained, the use of atropine and the presence of hypoxemia require continuous cardiac monitoring and an intravenous (IV) line for at least 48 hours in serious poisonings. Patients with QT prolongation should be monitored until the QT interval returns to normal.

Because organophosphates may be absorbed through intact skin, be sure to remove all contaminated clothing. Wash contaminated skin with water and then mild soap. Tincture of green soap, which contains alcohol, is an effective means of removing fat-soluble compounds. The entire area, including the nails, intertriginous areas, and groin area, should be re- washed with soap and water.

Diazepam is the drug of choice for convulsions. Avoid para sympathomimetic agents such as physostigmine or succinylcholine, as these may potentiate anticholinesterase activity.

Persistent central nervous system effects such as irritability, nervousness, fatigue, lethargy, impaired memory, depression, psychosis, and peripheral neuropathies have been reported. Serial examinations and exclusion of other possible etiologies must be entertained.

The patient must avoid re-exposure until cholinesterase activity is over 75% of normal.

Reported laboratory abnormalities include leukocytosis with a left shift, reduced eosinophil, lymphocyte, and monocyte counts, hyperglycemia, glycosuria, albuminuria, acetonuria, ketoacidosis, and hyperamylasemia. No prolonged effect on liver function, coagulation, skin, or respiratory tract has been documented.

Antidotes

ATROPINE

Atropine antagonizes both muscarinic and central nervous system effects of organophosphate poisoning by alleviating excessive bronchial secretions, salivation, sweating, anorexia, nausea, chest tightness, abdominal cramps, vomiting, and bradycardia. Atropine has no effect on muscle weakness or respiratory failure seen in severe poisoning, because this drug does not reactivate cholinesterase enzymes. For symptomatic patients, 2 to 4 mg is used intravenously in adults or 0.015 to 0.05 mg/kg in children every 15 minutes as needed.

Atropinization may be needed for up to 48 hours in cases of moderate toxicity. Atropine is metabolized rapidly, and large doses often are needed within the first 24 hours. Seriously poisoned patients develop marked resistance to the usual doses of atropine and may even require grams of antidote for many days. The drying of secretions, rather than dilated pupils, is the effective endpoint of atropine titration.

Do not wait for the return of cholinesterase levels before treating significantly symptomatic patients with atropine. Alternate routes for atropine administration (when rapid IV access cannot be achieved) include the intraosseous route in children and nebulized atropine by inhalation in adults. During antidote administration, the patient should be followed closely for signs of respiratory failure and atropinization in an intensive care setting. The patient should be observed at least 48 hours after the last dose of atropine.

PRALIDOXIME

Pralidoxime (2-P AM) is a specific antidote that effectively reverses phosphorylation of the cholinesterase when given within 24 hours and perhaps up to 36 to 48 hours postexposure. 2-P AM ameliorates muscle weakness, fasciculations, and alterations of consciousness (e.g., coma in parathion poisoning). It does not relieve bronchospasm or bronchorrhea and must be given concurrently with atropine. The indication for 2-P AM use in organophosphate poisonings is respiratory depression or muscle weakness.

The dosage is 1 to 2 g in adults or 25 to 50 mg/kg in children, given over 3 to 5 minutes. Rapid injection may cause tachycardia, laryngeal spasm, muscle rigidity, or transient neuromuscular blockade. If symptoms recur, a constant 2.5% pralidoxime IV infusion may be started in adults at 500 mg/hour, or repeat bolus doses (0.5 to 1 g or 10 to 25 mg/kg every 8 hours) may be given. It may take days until residual insecticide is cleared from body stores. Adverse reactions to 2-P AM may mimic both atropine and organophosphate poisoning. The kidney rapidly excretes 2-P AM in the urine and toxic levels of 2-P AM may accumulate in the presence of renal dysfunction.

CARBAMATES

Carbamate pesticides, like organophosphates, cause a decrease in cholinesterase activity. These poisonings are less severe than organophosphates however, because they bind reversibly to the active site on the cholinesterase enzyme, in contrast to the organophosphate pesticides which, over time, bind irreversibly. Carbamates cause the same excess in muscarinic stimulation and nicotinic stimulation, followed by weakness, as seen in organophosphate poisonings, but for a relatively shorter duration. Examples include methomyl, carbaryl, and aldicarb. Methomyl is a broad-spectrum carbamate insecticide used on various vegetable crops (e.g., cabbage and broccoli).

Hexapropymate is a carbamate sedative-hypnotic drug that, in overdose, resembles meprobamate or barbiturate intoxication and may lead to fatalities. Hypothermia, severe respiratory depression, and prolonged coma may require a long period of assisted ventilation.

Pathophysiology

Carbamylation of acetylcholinesterase produces accumulation of acetylcholine and the picture of muscarinic and nicotinic poisoning. Spontaneous hydrolysis of the carbamate-cholinesterase complex occurs *in vivo*, leading to disappearance of clinical effects within 24 hours.

Pharmacokinetics

ABSORPTION

- Carbamates are absorbed readily through the lungs, gastrointestinal tract, and skin.
- Absorption by the respiratory tract depends on the vapor pressure of individual insecticides. Carbaryl and aldicarb display low inhalation toxicity because of their high vapor pressures.

DISTRIBUTION

- Carbamates poorly penetrate the blood-brain barrier, producing minimal effects on brain cholinesterase activity and few central nervous system symptoms.
- The volume of distribution of carbaryl is 32.9 L/kg.

ELIMINATION I

- Most of these insecticides undergo hydroxylation, hydrolysis, and conjugation by the liver and are then excreted the urine within several days.
- Following first-order kinetics, the half-life of carbaryl is 1.30 hours and the half-life of α-naphthol is 1.13 hours.

Clinical Presentations

Clinical symptoms after exposure to methomyl and other carbamates are similar to those produced by organophosphates, although of lesser intensity and duration. Symptoms usually develop within 15 minutes to 2 hours and last several hours unless continued absorption occurs from clothing. Typical manifestations of cholinesterase inhibition include nausea, miosis, headache, lacrimation, salivation, vomiting, and abdominal pain. Dyspnea, tremors, muscle twitching, ataxia, and headache also may appear. Symptoms beyond 24 hours probably do not result from carbamate intoxication. The electrocardiogram (ECG) after methomyl exposure may exhibit sinus tachycardia or T - wave changes. Such changes may revert to pre-exposure status within 1 week.

Toxic Dosage/Death

Fatalities have followed ingestions of methomyl. Patients ingesting large doses, from 2 to 16 g of methomyl have developed symptoms of cholinesterase inhibition and survived. However, a lethal dose may be as low as 12 to 15mg/kg.

Laboratory

ANALYTIC METHODS

High-pressure liquid chromatography, gas chromatography, and gas chromatography/mass spectrometry methods are available.

BLOOD LEVELS

Measuring RBC and plasma cholinesterase are often not helpful as carbamates have only a transient effect (1 to 2 hours) on these levels.

Treatment

GUT DECONTAMINATION

Methods for elimination are not recommended in view of the short action of the carbamates and the effectiveness of atropine. Container identification is important to determine appropriate therapeutic measures, as the vehicle (e.g., hydrocarbon) may be as toxic as the insecticide.

ELIMINATION ENHANCEMENT

Again, no methods are recommended, because of the short clinical effect of carbamates and the presence of an effective antidote (i.e., atropine).

SUPPORTIVE MEASURES

- Immediate life-threatening symptoms usually result from weakness of the respiratory muscles, central respiratory depression/ bronchospasm, bronchial secretions, and pulmonary edema, all of which may result in hypoxemia. Frequent suctioning/ endotracheal intubation, and ventilatory assistance may be required.
- Patients should be admitted to an intensive care facility where access to a central line, oxygen, and cardiac monitoring is available. Administer fluids to replace losses.
- Be sure to remove contaminated clothing and wash the contaminated skin/ as in organophosphate treatment. Exposure after spraying will require careful washing of the entire (e.g., nails, intertriginous areas) body with tincture of green soap. Health personnel should use rubber gloves and avoid direct contact with contaminated material.
- Avoid central nervous system depressants (e.g., opiates); they may increase the possibility of respiratory arrest. Monitor the PaO_2 with repeat arterial blood gases.
- There may be a decrease in plasma cholinesterase concentrations but no decrease in RBC cholinesterase levels. Cholinesterase determination should be done within 4 hours of exposure. Such determinations generally are not important as carbamates only have a transient effect on cholinesterase

Antidotes

ATROPINE

Atropine is the antidote of choice in carbamate poisoning. Although the total amount of required atropine usually is less than in organophosphate exposures, the same initial doses are recommended. Patients generally require approximately 6 to 12 hours of

atropine treatment, but all significantly poisoned patients should be observed at least 24 hours after the last atropine dose. Atropine (0.6 mg IV in adults and 0.05 mg/kg in children) may be useful without reaching complete atropinization (e.g., dilated pupils, dry or red skin, confusion, tachycardia, fever ileus). It can be administered every 15 minutes as needed. Significant poisoning may require at least 21 hours of observation after the last atropine dose.

PRALIDOXIME

The use of 2-P AM is indicated as an adjunct to atropine in serious, potentially fatal poisonings with unknown cholinesterase inhibitors. 2-P AM is indicated in poisoning involving both organophosphates and carbamate compounds together, and if a patient with known carbamate poisoning does not respond to atropinization.

12 Opioids and Derivatives

12.1 OPIOIDS

12.1.1 History and Classification

There has been no greater disruption of modern civilizations than the insidious havoc brought upon them by the addictive potential of opioid compounds and their derivatives. From the introduction of opium into China in the seventeenth century, resulting in the undermining of its organized system, to the modern-day pharmaceutical production of synthetic narcotic analgesics, these compounds have infiltrated urban and rural societies alike. Today, narcotic addiction permeates all socioeconomic classes, from economically underserved communities, to affluent neighborhoods, to the U.S. armed forces. The number of emergency department (ED) visits involving heroin/morphine increased 15% in 2000, from 84,409 to 97,287, accounting for 15% of all hospital admissions related to drug use. Opioid analgesics are readily and easily available. These compounds are not necessarily obtained only through illicit drug dealing (street drugs), but their supply is also abundant through fraudulent and illegitimate prescriptions, as well as in the course of overprescribing practices. Health care professionals are also particularly vulnerable to the addictive potential of narcotics, principally due to easy accessibility.

The variety of opioid derivatives encountered in the twentieth century reflects the cyclical appearance and disappearance of individual compounds, mostly because of popularity among users and availability. In the 1980s, opioid addicts inadvertently ingested what they thought was a designer derivative of meperidine (4'-methyl-α-pyrrolidinopropiophenone, MPPP). Instead, synthesis and contamination with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lead to the development of an idiopathic Parkinson-like state in these patients. In the same decade, a new more potent form of heroin from Mexico (Black tar heroin) made its appearance, resulting in an increase in acute overdose fatalities. Simultaneously during this period, heroin usage began to wane, only to be replaced with the more versatile forms of cocaine. Despite the counter-effects of narcotic law enforcement efforts to remove or dissuade its nontherapeutic use, opioid use is still a major public health problem.

Initial narcotic ingestion is often an unpleasant experience. Patients usually complain of nausea, dizziness, and muscular weakness. With continued use, individuals build tolerance to the unpleasant adverse reactions in preference to the euphoric effects. Opioid compounds are ingested orally in tablet or capsule form, the most common method of administration (considering both therapeutic and illicit drug use). As greater tolerance develops, ingesting the same amount of drug does not produce euphoria as initially experienced, necessitating either higher doses or an alternate, more immediate method of administration. This includes rendering the tablets to a powder, or using a preformulated powder form, for nasal insufflation (*snorting*), for injection subcutaneously (*skin popping*) or intravenously (*mainlining*).

Rg. 43

12.1.2 Classification

By definition opioids, as a class, exert their pharmacological effects at opioid receptors, whereas opiates are alkaloid extracts of the opium poppy. The opioids are traditionally classified according to their source, as summarized in Table 12.1. Opium, the parent crude form of the naturally-occurring compounds, is derived from the milky exudates of the unripe capsule of *Papaver somniferum L.* (opium poppy). The plant is cultivated in the Mediterranean and Middle East regions, India, and China. About two dozen alkaloids, of which morphine occupies about 10%, are formed primarily in various cells of the poppy plant and excreted into the lactiferous ducts. Depending on diurnal variations, the isolated latex undergoes alkaloid biosynthesis and metabolic destruction, which contribute to the variability in alkaloid composition of crude opium samples.* The narcotic, antispasmodic, sedative, hypnotic, and analgesic properties of the extract have been recognized for centuries. Interestingly, the numerous and very small seeds of the plant do not contain opium.

Few pharmacological and toxicological differences exist between the classes. Some pharmacokinetic properties, however, distinguish the compounds, especially among the many narcotic derivatives (listed below).

12.1.3 Medicinal Chemistry

Table 12.1 illustrates the structure of morphine and side chains of the derivatives. The opioids are composed of six-membered saturated heterocyclic rings forming the phenanthrene nucleus (in bold) to which is attached a piperidine ring. The structure represents the prototype for all opioids except methadone and meperidine (Table 12.2). Although the more important opiate alkaloids exhibit a phenanthrene nucleus, the majority of the derivatives have the isoquinoline ring structure. Esterification of the phenolic functions, such as in the formation of diacetylmorphine, results in a compound with increased lipid solubility and increased potency and toxicity.

12.1.4 Mechanism of Toxicity

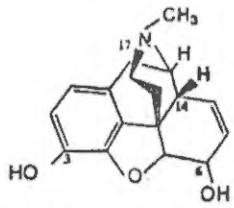
The mechanism of opiate toxicity is an extension of its pharmacology and is directly related to interaction with stereospecific and saturable binding sites or receptors in the CNS and other tissues. These receptors are classified according to the empirical observations noted for the variety of opioid effects. The opioid receptors are biologically active sites of several endogenous ligands, including the two pentapeptides, methionine-enkephalin and leucine-enkephalin. Several larger polypeptides that bind to opioid receptors, such as []-endorphin, are the most potent of the endogenous opioid-like substances.** In addition, three receptor classes have been identified:

---

* In non-Western medicine, opium refers to the dried capsule from which the latex has been extracted.

** Collectively, the term *endorphin* refers to the three families of endogenous opioid peptides: the enkephalins, the dynorphins, and the []-endorphins.

TABLE 12.1
Categories, Structure (of Morphine), and Proprietary Names of Opiate Analgesics, Derivatives, and Narcotic Antagonists Currently Available



Category	Compound	Proprietary Name	3[a]	6[a]	14[a]	N17[a]	Other[d]
Naturally occurring	Morphine	Various	OH	OH	H	CH_3	—
	Codeine (methylmorphine)	Various	O–CH_3	OH	H	CH_3	—
Semisynthetic	Diacetylmorphine	Heroin[b]	OCO–CH_3	OCO–CH_3	H	CH_3	—
	Oxymorphone	Numorphan	OH	=O	OH	CH_3	Single bond
	Hydromorphone	Dilaudid	OH	=O	H	CH_3	Single bond
Synthetic	Oxycodon	Percodan,[c] Percocet,[c] Oxycontin	O–CH_3	=O	OH	CH_3	Single bond
	Levorphanol	Levo-dromoran	OH	H	H	CH_3	Single bond no O
	Hydrocodone	Vicodin, Lorcet, Hycodan[c]	O–CH_3	=O	H	CH_3	Single bond
Narcotic antagonists	Naloxone	Narcan	OH	=O	OH	$CH_2CH{=}CH_2$	Single bond
	Naltrexone	Trexan	OH	=O	OH	CH_2–Δ	Single bond
	Nalmefene	Revex	OH	$=CH_2$	OH	CH_2–Δ	Single bond

[a] Numbers 3, 6, 14 and 17 refer to the positions in the phenanthrene nucleus; only morphine and diacetylmorphine have the C7-C8 double bond.
[b] Street name.
[c] Component of a formulation.
[d] Other = single bond between C7-C8, no O between C4-C5.

TABLE 12.2
Categories, Structural Features, and Proprietary Names of Meperidine and Methadone Congeners Currently Available

Meperidine

Methadone

Category[a]	Compound	Proprietary Name	R1	R2
Phenylpiperidine analgesics	Meperidine	Demerol	CH_3	$COOCH_2CH_3$
	Fentanyl	Sublimaze Duragesic	CH_2CH_2–phenyl	N-(phenyl)-$COCH_2CH_3$[b]
	Diphenoxylate	Lomotil[c]	CH_2CH_2C–(phenyl)$_2$–CN	$COOCH_2CH_3$
Methadone congeners	Methadone	Dolophine	Substituted diphenyl pseudopiperidine derivative	
	Pentazocine	Talwin-NX[c]	Benzazocin derivative	
	Propoxyphene	Darvon, Darvocet-N[c]	Substituted diphenyl pseudopiperidine derivative	

[a] All synthetic compounds.
[b] Sole *para*-substitution on piperidine ring.
[c] Component of a formulation.

1. Compounds that selectively bind to the **mu-receptor (μ)** exhibit morphine-like analgesia, euphoria, respiratory depression, miosis, partial gastrointestinal (GI) inhibition, and sedative effects.
2. Narcotic antagonists such as pentazocine, nalorphine, and levorphanol appear to bind to the **kappa-receptor (κ)**, although analgesia, sedation, delusion, hallucinations (psychotomimesis), GI inhibition, and miotic effects still persist.
3. Pentazocine and nalorphine are also described as having affinity for the **delta-receptors (δ)**, although this binding is primarily associated with dysphoria and mood changes (inhibition of dopamine release). The role of epsilon and zeta receptors have yet to be delineated in humans. The sigma receptor (σ), purported to have affinity for pentazocine, was once understood to represent an opioid receptor.

12.1.5 Toxicokinetics

Morphine is rapidly absorbed from an oral dose and from i.m. and s.c. injections. Peak plasma levels occur at 15 to 60 min and 15 min, respectively. Morphine is metabolized extensively, with only 2 to 12% excreted as the parent molecule, while 60 to 80% is excreted in the urine as the conjugated glucuronide. Heroin is rapidly biotransformed, first to monoacetylmorphine and then to morphine. Both heroin and monoacetylmorphine disappear rapidly from the blood ($t_{1/2}$ = 3 min, 5 to 10 min, respectively). Thus, morphine levels rise slowly, persist longer, and decline slowly. Codeine is extensively metabolized, primarily to the 6-glucuronide conjugate. About 10 to 15% of a dose is demethylated to form morphine and norcodeine conjugates. Therefore, codeine, norcodeine, and morphine in free and conjugated form appear in the urine after codeine ingestion.

12.1.6 Signs and Symptoms of Clinical Toxicity

Clinical signs and symptoms correlate with the highest concentrations of binding sites in CNS and other tissues. In particular, the limbic system (frontal and temporal cortex, amygdala, and hippocampus), thalamus, corpus striatum, hypothalamus, midbrain, and spinal cord have the highest concentrations. Analgesia appears to affect spinal ascending and descending tracts, extending up to the medullary raphe nuclei (midbrain). Effect on mood, movement, and behavior correlate with interaction with receptors in the globus pallidus (basal ganglia) and locus ceruleus, while mental confusion and euphoria (or dysphoria) alter neuronal activity in the limbic system. Hypothalamic effects are responsible for hypothermia. Miosis (pinpoint pupils) is thought to occur from μ-receptor stimulation at the Edinger-Westphal nucleus of the oculomotor nerve.

The clinical presentation of the opioid toxidrome (triad) is characterized by CNS depression (coma), miosis, and respiratory depression. Miosis is generally an encouraging sign, since it suggests that the patient is still responsive. Respiratory depression is a result of depressed brain stem and medullary respiratory centers responsible for maintenance of normal rhythm. Mu-receptor agonists depress respiration in a dose-dependent manner and can lead to respiratory arrest within minutes. Fifty percent

of acute opioid overdose is accompanied by a frothy, noncardiogenic, pulmonary edema, responsible for the majority of fatalities. The condition involves loss of consciousness and hypoventilation, probably resulting from hypoxic, stress-induced, pulmonary capillary fluid leakage. Peripheral effects include bradycardia, hypotension, and decreased GI motility. Urine output also diminishes as a consequence of increased antidiuretic hormone (ADH) secretion.

12.1.7 Clinical Management of Acute Overdose

Maintenance of vital functions, including respiratory and cardiovascular integrity, is of paramount importance in the clinical management of acute opioid toxicity. Gastric lavage and induction of emesis are effective if treatment is instituted soon after ingestion. It is possible to reverse the respiratory depression with opioid antagonists. **Naloxone** (Narcan®) is a pure opioid antagonist available as an injectable only. A 2-mg bolus repeated every 5 min, followed by 0.4 mg every 2 to 3 min as needed (up to 24 mg total), dramatically reverses the CNS and respiratory depression (in this capacity, naloxone is also indicated in the diagnosis of suspected acute opioid overdose). Depending on the extent of narcotic overdose, a continuous infusion of naloxone may be required, especially in the presence of opioids with longer half-lives, such as propoxyphene or methadone. As respiration improves, naloxone, which has a half-life of 60 to 90 min, may be discontinued and resumed as necessary. If there is no response after 10 mg of naloxone, concomitant ingestion with other depressants is likely. It should be noted that naloxone is of little benefit in reversing noncardiogenic pulmonary edema.

Naltrexone (Revia®) is also a pure opioid antagonist available as oral tablet dosage form only. A 50-mg dose of naltrexone blocks the pharmacological effects of opioids by competitive binding at opioid receptors. It is also indicated in the treatment of alcohol dependence. Naltrexone has been noted to induce hepatocellular injury when given in excess.

Nalmefene (Revex®), available in 100 μg/ml and 1 mg/ml ampules, is indicated for the complete or partial reversal of natural or synthetic opioid effects. It is a 6-methylene analog of naltrexone. Nalmefene has been associated with cardiac instability, although this reaction appears to be the result of abrupt reversal of opioid toxicity.

Several drugs have agonist activity at some receptors (κ) and antagonist activity at other (μ) receptors. Nalbuphine (Nubain®) is a potent analgesic with narcotic agonist and antagonist actions. Other mixed agonist-antagonist compounds are designated as partial agonists, such as butorphanol (Stadol®), buprenorphine (Buprenex®), and pentazocine (Talwin® and various tablet combinations). These compounds are potent analgesics and weakly antagonize the effects of opioids at the μ-receptor, while maintaining some agonist properties at the κ- and δ-receptors.

Drug enforcement personnel and customs officials respond to different conditions of opioid overdose, especially those involving *body packers* and *body stuffers*. The drug carriers, who differ only in the apparent manner of sealing and concealing illicit drug packets, run into problems when the packets leak or burst. The overall clinical response to the situation requires rapid detection with body cavity searches

and abdominal radiographs. Decontamination with activated charcoal, gastric lavage, high-dose continuous infusion with naloxone, and attention to the ABCs of emergency management of toxicity in anticipation of a developing opioid syndrome are also warranted.

12.1.8 Tolerance and Withdrawal

The Department of Mental Health and Substance Dependence at the World Health Organization (WHO), in collaboration with the U.S. National Institute on Drug Abuse (NIDA), defines several terms important in understanding drug abuse and the phenomena of tolerance and withdrawal. **Addiction** involves compulsive psychoactive drug use with an overwhelming involvement in the securing and using of such drugs. As described below, the withdrawal syndrome occurs as a result of sudden or abrupt discontinuation of the substance. **Compulsive drug use** involves the psychological need to procure and use drugs, often referred to as "craving." In this case, the uncontrollable drive to obtain the drugs is necessary to maintain an optimum state of well-being. **Habituation** refers to psychological dependence. **Physical (physiological) dependence** involves the need for repeated administration in order to prevent withdrawal (abstinence) syndrome. In fact, with repeated chronic dosing, seizure threshold for opiate narcotics is elevated, threatening the precipitation of seizure upon withdrawal (rebound effect). Cross-dependence occurs with all opioids, regardless of category.

The more complex phenomenon of **tolerance** requires the satisfaction of several criteria. With repeated administration, addicted individuals necessitate greater amounts of drug in order to achieve the desired effect. Conversely, the effect is markedly diminished with continued use of the same amount of drug. Since various pharmacological effects on different organ systems are not uniformly distributed, tolerance is not evenly demonstrated. While a diminished euphoric effect continues with progressive tolerance, the increasing doses threaten induction of respiratory depression. Increased metabolism, adjustment to the sedative, analgesic, and euphoric effects, are proposed as possible mechanisms for the development of tolerance — i.e., the physiological drive to achieve homeostasis.

Depending on the drug, the withdrawal syndrome is precipitated hours after the last narcotic dose with peak intensity occurring at about 72 h (Table 12.3). The intensity of the syndrome is greatest with heroin, followed by morphine, and methadone. Heroin withdrawal is characterized by acute, sudden symptoms of greater vigor while methadone withdrawal is distributed over 7 to 10 days and of lower intensity. The development of muscle spasms has come to define the syndrome, commonly known as "kicking the habit." Although the syndrome is rarely fatal, administration of an opioid at any time during withdrawal alleviates the condition.

12.1.9 Clinical Management of Addiction

The NIDA publishes *The Principles of Drug Addiction Treatment — A Research Based Guide*. The Guide outlines the social and clinical approach associated with

TABLE 12.3
Characterization of the Opioid Withdrawal Syndrome

Stage	Time after Last Dose	Signs and Symptoms
Anticipatory	3–4 h	Withdrawal, fear, craving, compulsive drug seeking behavior
Early withdrawal	8–12 h	Lacrimation, sweating, listless behavior, anxiety, restlessness, stomach cramps
	12–16 h	Restless sleep, nausea, vomiting, mydriasis, anorexia, tremors, cold clammy skin, fever, chills, compulsive drug seeking behavior
	48–72 h	Peak intensity; tachycardia, hypertension, hypothermia, piloerection (goose-flesh appearance of skin, "cold turkey"), muscle spasms, continued nausea, vomiting, dehydration, compulsive drug seeking behavior, risk of cardiovascular collapse
Protracted abstinence	6 months	Stimulus-driven cravings, anorexia, fatigue, bradycardia, hypotension

drug addiction treatment in the U.S. Outpatient drug-free treatment, long- and short-term residential treatment, scientifically based counseling, psychotherapeutic and community-based programs are discussed as approaches to drug addiction treatment. Among these modalities, the risks and benefits of medical detoxification associated with the use of methadone and narcotic antagonists are presented.

12.2 SPECIFIC OPIOID DERIVATIVES

12.2.1 Codeine

Codeine (methylmorphine) is available in combination with other ingredients as an analgesic (Tylenol with Codeine®) and as an antitussive in prescription cough, cold, antihistaminic, and expectorant formulas. The usual dosage form contains 15 to 60 mg/tablet or 10 mg/5 ml liquid. About 120 mg of codeine is equivalent to 10 mg of morphine. The compound produces the same triad of signs and symptoms with high doses, although tolerance and toxicity are less severe. Interestingly, in the 1950s and early 1960s, codeine cough and cold preparations (such as Cheracol Syrup®) could be purchased without a prescription, quantities of which were monitored with only a signature.

12.2.2 Diphenoxylate

A synthetic opiate chemically related to meperidine, diphenoxylate is combined with atropine (Lomotil®) for the treatment of diarrhea. The toxicity of this combination, therefore, is primarily due to the presence of the anticholinergic. Children are

especially sensitive to the effects of atropine, including production of tachycardia, flushing, hallucinations, and urinary retention. The narcotic toxicity demonstrates as miosis, respiratory depression, and in severe cases, coma.

12.2.3 Fentanyl

In the 1990s, fentanyl enjoyed increasing popularity as the narcotic of choice among illicit drug users, principally because of its enhanced potency (*China white*). At 200 times and 7000 times greater potency than morphine, α-methylfentanyl and 3-methylfentanyl also display greater potential for toxicity, respectively. The median lethal dose is about 125 μg for the former and 5 μg for the latter.* Therapeutically, fentanyl is marketed in the form of medicated patches (Duragesic Transdermal System®) for the management of chronic pain. Depending on the size of the patch and the amount of fentanyl delivered (10–40 cm^2 containing 2.5–20 mg total per patch), the transdermal system can release up to 200 μg/h.

12.2.4 Meperidine

The first synthetic opioid (1939), meperidine is equianalgesic with morphine. In the liver, the compound is hydrolyzed to meperidinic acid and normeperidine by carboxyesterases and by N-demethylation and microsomal enzymes, respectively. Both of the metabolites are active, although they possess half of the analgesic effects and twice the neurotoxic activity. Consequently, chronic oral ingestion of meperidine tablets is associated with CNS stimulation resulting in tremors, muscle twitching, nystagmus, and convulsions. Neurotoxicity correlates directly with opioid plasma concentrations and requires several days before onset. Benzodiazepines are recommended for treatment of CNS excitation. Use of naloxone is cautioned with chronic meperidine use, since the antagonist may decrease seizure threshold (increased potential for convulsions).

12.2.5 Pentazocine

Pentazocine is a benzomorphan derivative of morphine with 3- to 4-times its analgesic potency and the same addictive potential. It is presumed to exert its agonistic actions at the κ- and δ-receptors and may precipitate withdrawal symptoms in patients taking narcotic analgesics regularly. Intravenous injection of oral preparations of pentazocine and tripelenamine, an H_1-blocking antihistamine, was a common form of drug abuse.** The tablets were crushed, dissolved in tap water, heated over a flame, and injected. The combination purportedly produced an effect similar to heroin at much lower cost. Because the method of sterilization was less than optimal, and the solution contained undissolved pieces of tablet binders and fillers, addicted individuals often developed skin decubiti, abscesses, and cellulites. Continued injection resulted in serious pulmonary artery occlusion, pulmonary hypertension, and

* In October 2002, Russian commandos pumped an aerosol derivative of fentanyl into a Moscow theater to end a hostage crisis. All but two of 120 deaths occurred as a result of the effects of the opioid (Russian Health Ministry).

** The combination of the crushed tablets were known as *Ts and Blues*, *T* for Talwin® and *Blues* for the large blue color of the antihistamine tablet.

neurologic complications. As a consequence, oral pentazocine tablets were replaced with Talwin-NX® (pentazocine plus naloxone) in order to decrease this practice. The inhibitory action of naloxone on pentazocine's analgesic effect is experienced only when the tablets are crushed and injected, since naloxone is not absorbed orally.*

12.2.6 Propoxyphene

A methadone analog, propoxyphene is implicated in cardiotoxicity. The parent compound and its metabolite, norpropoxyphene, cause dose-dependent widening of the QRS complex similar to tricyclic antidepressants (see Chapter 18, Figure 18.2 for an explanation of the QRS complex). This quinidine-like effect results from inhibition of cardiac fast sodium channels, causing tachydysrhythmias. In addition, propoxyphene is frequently used as the napsylate salt in combination with acetaminophen (Darvocet-N®). The unique salt form stimulates hepatic mixed function oxidase (MFO) enzymes, increasing the presence of toxic metabolites of acetaminophen. Consequently, in chronic repeated administration, it often masks acetaminophen toxicity.

12.2.7 Hydrocodone/Oxycodone

Hydrocodone and oxycodone are powerful μ-receptor agonists with addictive and analgesic potential equivalent to morphine and heroine, respectively.

Hydrocodone is used as an analgesic in oral dosage forms (Vicodin®, Lorcet®, Lortabs®, Tylox®) for mild to moderate pain associated with minor surgical procedures, chronic joint and muscle pain, and inflammatory conditions. It is also used as an antitussive (in Hycodan®). Consequently, its addictive potential is significant when administered chronically.

Oxycodone, in combination with aspirin or acetaminophen (Percodan®, Percocet®, respectively, 2.5-mg per tablet) has enjoyed popularity as an effective analgesic for the relief of moderate to severe pain of chronic inflammation and surgery. It is particularly useful in the alleviation of chronic pain of many cancers. In 1985, MS Contin® was introduced as a delayed-release morphine tablet, with the advantage of decreasing the frequency of dosing in patients with chronic pain. This formulation was especially convenient for elderly individuals. By 1994, morphine consumption in the U.S. had risen by 75%. Based on this success, Oxycontin® was introduced in 1995 as a delayed-release oral dosage form of the more powerful oxycodone. Revenues from Oxycontin® rose from $55 million in 1996 to $1.14 billion in 2000, at which time it became the number one opioid analgesic, with 6.5 million prescriptions in 2000. By 1995, the first cases of Oxycontin® abuse ("oxys") appeared in rural Missouri and spread throughout the rust belt states of Pennsylvania, Ohio, West Virginia, Virginia, and Appalachian Kentucky. Increasing unemployment rates in these states, the large numbers of chronically ill and disabled elderly unable to relocate, coupled with the remoteness of the regions, created an environment conducive to illicit drug distribution (the

*By itself, high doses of pentazocine increase plasma epinephrine concentrations, risking the development of hypertension and increased heart rate.

drug became known as "hillbilly heroin"). Economically poor, the elderly would readily sell their Oxycontin® medication to young teens offering money, producing a captive market of nontraditional drug abusers. Unlike heroin, "oxys" are regarded as legal compounds, more easily available, and with less ambiguity associated with "copping dope" on the street. The allure of the substance was not in the potency of the tablet form but in the large quantities of active ingredient immediately accessible when a 10- to 40-mg delayed release tablet is crushed, and either "snorted" or injected.

By 1998, Oxycontin® abuse had spread to suburban and urban metropolitan areas. Since 2000, several hundred fatalities due to injected Oxycontin® overdose have been reported. Its relative purity and abundance in crushed form have created an immensely desirable compound.

12.2.8 Tramadol

Tramadol is a centrally acting synthetic analog of codeine with low affinity for the μ-receptor. It is used for moderate to severe pain control. Currently, it is not on any federal controlled substance list. Much of its effects appear to be through modulation of central monoamine pathways by inhibiting reuptake of 5-hydroxytryptamine and norepinephrine. In overdose, the effects are similar to those of other opioids, with convulsions predominating in susceptible individuals.

12.2.9 Clonidine

Clonidine (Catapres®) primarily stimulates central postsynaptic α_2-receptors that inhibit neuronal activity and decrease sympathetic overtone. Clonidine shares some pharmacological properties (μ-receptors) and clinical features with the opioids. Overdose with clonidine occurs within 60- to 90-min after ingestion, producing bradycardia, hypotension, arrhythmias, CNS depression, decreased respiration, and miosis. Although the mechanism is poorly understood, it is believed to involve antagonism of the μ-receptors. Patients who demonstrate opioid-like toxicity with clonidine respond to naloxone administration, particularly the reversal of hypoventilation and CNS depression.

12.3 METHODS OF DETECTION

Opioids are detected using a radioactive or enzyme-linked immunoassay technique (EMIT, KIMS).* The principle of the assays is the reaction of morphine in an aliquot of the urine sample with its corresponding antibody. Significant cross-reactivity occurs with opioid derivatives (as well as with components of poppy seeds) because of the reaction of the antibody with the common phenanthrene structure. Radioimmunoassays (RIAs) are also very sensitive and can detect opioids at levels of 0.5 to 10 ng/ml. RIA, however, requires tritiated (radioactive) ligands as indicators.

* These methods have supplanted the traditional GC-MS and TLC methods used for urine and blood screening.

Other immunoassays for specific opioid derivatives, such as fentanyl, methadone, and meperidine, are also available.

Both EMIT and the Abuscreen® RIA detect codeine and morphine in free and conjugated forms but do not distinguish between them. Based on the toxicokinetics of the opioids noted above, distinguishing morphine from heroin or codeine is difficult but clinically and forensically important. The presence of morphine alone or its conjugate can indicate either clinical morphine use or illicit morphine or heroin use (within the previous 1 to 2 days). The distinction is possible when the test is employed 2 to 4 days after the last dose. Other narcotics identified by the immunoassays for morphine include dihydrocodeine, dihydromorphine, and hydromorphone. Confirmation of positive results, and distinction between them are accomplished with TLC, HPLC, and GLC. Acid or enzyme hydrolysis of the urine sample, however, is necessary when the latter testing techniques are used, since approximately 90% of codeine and morphine are found in urine in the conjugated glucuronide form.

REFERENCES

Suggested Readings

Cone, E.J. et al., Oxycodone involvement in drug abuse deaths: a DAWN-based classification scheme applied to an oxycodone postmortem database containing over 1000 cases, *J. Anal. Toxicol.*, 27, 57, 2003.

Wax, P.M., Becker, C.E. and Curry, S.C., Unexpected "gas" casualties in Moscow: A medical toxicology perspective, *Ann. Emerg. Med.* 41, 700, 2003.

Wines, M., The Aftermath in Moscow: Post-Mortem in Moscow; Russia Names Drug in Raid, Defending Use, Foreign Desk, *New York Times*, Oct. 31, 2002.

Review Articles

Budd, K., Buprenorphine and the transdermal system: the ideal match in pain management, *Int. J. Clin. Pract. Suppl.* 133, 9, 2003.

Choi, Y.S. and Billings, J.A., Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation, *J. Pain Symptom Manage.*, 24, 71, 2002.

Cohen, G., The 'poor man's heroin.' An Ohio surgeon helps feed a growing addiction to OxyContin, *U.S. News World Rep.*, 130, 27, 2001.

Cone, E.J. and Preston, K.L., Toxicologic aspects of heroin substitution treatment, *Ther. Drug Monit.*, 24, 193, 2002.

Cruz, R. et al., Pulmonary manifestations of inhaled street drugs. *Heart Lung*, 27, 297, 1998.

Drug Abuse Warning Network (DAWN), Substance Abuse and Mental Health Services Administration (SAMHSA), National Institute on Drug Abuse, DHHS, U.S. Public Health Service, 2000; http://www.drugabuse.gov.

Frost, D.M., Chemical dependency and the heart, *S.D.J. Med.*, 44, 149, 1991.

Green, H. et al., Methadone maintenance programs — a two-edged sword? *Am. J. Forensic Med. Pathol.*, 21, 359, 2000.

Acetaminophen

INTRODUCTION

Acetaminophen (Paracetamol, Tylenol®) was discovered at Johns Hopkins University in 1877. In 1950, it was marketed in the United States as an analgesic to replace its nephrotoxic analogue, phenacetin. Acetaminophen is a synthetic, nonopiate derivative of p-aminophenol. It has analgesic and antipyretic properties, but lacks anti inflammatory properties. In 1966, Davidson and Eastham reported the first case of hepatic necrosis following massive acetaminophen overdose.

In 1993, about 60,000 inquiries involving acetaminophen were reported by the Toxic Exposure Surveillance System of the American Association of Poison Control Centers. Only a small minority of patients is at risk of severe liver damage. Recovery from even severe damage usually is rapid and complete, and the overall mortality rate is low. Synonyms include APAP, paracetamol, and n-acetyl-p-aminophenol.

Pathophysiology

Acetaminophen shares analgesic and antipyretic properties with its analogues, phenacetin and acetanilid. It acts by inhibiting prostaglandin synthesis. Advantages over salicylates include relative lack of sensitization, absence of gastrointestinal irritation, lack of effect on coagulation, and absence of association with Reye's disease. Risk factors that enhance the development of liver toxicity after an overdose of acetaminophen include chronic ingestion of agents that induce hepatic microsomal enzymes (e.g., isoniazid, anticonvulsants). Starvation depletes glutathione stores and is a risk factor. Patients who consume excessive quantities of acetaminophen in multiple doses may present with acetaminophen levels in the toxic range.

Pharmacokinetics

ABSORPTION

- Usually rapid and complete and occurs at a rate that depends on gastric emptying.
- Peak therapeutic concentration occurs within 1 hour.

DISTRIBUTION

- Plasma protein binding is 25% to 50% and volume of distribution is 0.75 to 1.0 L/kg.
- The half-life is about 2-3 hours, and in overdose the elimination half-life increases.

ELIMINATION

- The liver biotransforms 90% of acetaminophen by conversion to sulfate or glucuronide.
- The sulfate pathway predominates in children under 12 years old, whereas adults primarily use the glucuronide pathway (60%). Unchanged renal excretion accounts for less than 5% of elimination.

1 Pg. 55

- A small portion of the therapeutic dose is metabolized by the P450 mixed-function oxidase pathway to a reactive, toxic intermediary [N-acetyl-p-benzoquinoneimine (NAPQI)].

Clinical Presentations

When first seen, the severity of intoxication with acetaminophen cannot be determined on clinical grounds alone. Consciousness generally is not depressed, even in the presence of high serum levels of acetaminophen, unless other drugs have also been taken.

HEPATIC EFFECTS

Nausea and vomiting usually develop within a few hours of ingestion of a hepatotoxic dose of acetaminophen. At this stage, liver function tests may be normal. From about 18 to 72 hours after ingestion, there may be hepatic tenderness and abdominal pain. Unless hepatic failure develops, there usually is rapid improvement after the third day with eventual complete recovery. The maximum abnormality of liver function tests usually is delayed until the third day. Most hepatotoxicity probably results from a toxic intermediary (NAPQI) that binds covalently to hepatocytes and causes a centrilobular hepatic necrosis. The liver metabolizes most therapeutic doses of acetaminophen by glucuronide and sulfate conjugation. Only small amounts of acetaminophen are converted to NAPQI by the cytochrome P450 mixed-function oxidase system. Glutathione rapidly detoxifies this intermediate. When glutathione stores are depleted below a critical value (about 30% of normal stores) NAPQI binds with hepatic cell macromolecules, producing tissue necrosis.

There is significant individual susceptibility to the toxic effects of acetaminophen, as 20% or more of patients with toxic acetaminophen plasma levels do not develop hepatotoxicity. Severe liver damage develops in about 8% of all acetaminophen overdose patients who do not receive antidotal therapy, despite the fact that about 15% may display plasma acetaminophen levels in the toxic range. Fatal hepatic failure occurs in about 1 % to 2% of these patients who have received no specific therapy. Age, diet, nutritional status, metabolic state, and concomitant drug ingestion affect individual changes in cytochrome P450 mixed-function oxidase activity and susceptibility to hepatotoxicity.

Fulminant hepatic failure may develop in severely poisoned patients from the third to the sixth day. It is characterized by jaundice, encephalopathy, increased intracranial pressure, disseminated intravascular coagulation (DIC), hemorrhage, hyperventilation, acidosis, hypoglycemia, and renal failure. Fulminant hepatic failure after acetaminophen overdose has a mortality of 50%. The survival rate for hepatic failure following acetaminophen overdose depends on age, use of N-acetylcysteine (NAC), and degree of encephalopathy on presentation. Delay in performing liver transplantation adversely affects the chances of survival by increasing the risk of cerebral edema, hemorrhage, hypotension, and renal failure. Candidates for liver transplantation should be identified early.

RENAL EFFECTS

Renal impairment has been reported in about 1% of patients who have ingested an acetaminophen overdose. The kidney also metabolizes acetaminophen to a toxic intermediate, which binds to renal macromolecules, leading to cell death. Oliguric renal failure may become apparent within 24 to 48 hours of acetaminophen overdose, and it usually is associated with back pain, microscopic hematuria, and proteinuria. Acetaminophen may cause analgesic nephropathy

and end-stage renal disease. Renal papillary necrosis has been reported following consumption of acetaminophen.

CARDIOVASCULAR EFFECTS

Myocardial changes may include fatty degeneration of myocytes, focal myocardial muscle necrosis, left ventricular dilation, subendocardial necrosis, and focal infiltration of neutrophils into the myocardium. Cardiomyopathy and myocarditis have been reported. Acetaminophen-induced cardiotoxicity rarely is clinically significant. Dysrhythmias and other electrocardiographic abnormalities occur frequently in patients with acetaminophen-induced hepatic coma, but ST -T wave changes develop rarely in nonencephalopathic patients.

PANCREATIC EFFECTS

Doses of acetaminophen as low as 9.75 grams have been associated with pancreatitis. Hyperamylasemia may be observed in significant overdoses.

ALCOHOLIC PATIENTS

The alcoholic patient may be more susceptible to the hepatic effects of an overdose of acetaminophen. In chronic alcoholics, glutathione depletion is probably a more important risk factor for hepatotoxicity than increased metabolic activation of acetaminophen. Liver toxicity and acute renal tubular necrosis in alcoholics have been associated with daily doses of only 4 to 6 g of acetaminophen for 3 to 4 days. However, definitive proof linking alcoholism with an increased risk of hepatotoxicity at therapeutic doses has not been clearly established. Most reports of acetaminophen-induced hepatotoxicity in alcoholics involve excessive doses of acetaminophen.

CHRONIC EFFECTS

Chronic acetaminophen poisoning in adults is uncommon but often results in an encephalopathy together with other clinical and laboratory manifestations of hepatic failure. Chronic excessive use by adults who seek pain relief and fever control may lead to a toxic hepatitis.

Toxic Dosage/Death

In adults, the single acute threshold dose for severe liver damage is 150 to 250 mg / kg. Children younger than 10 years old appear to be more resistant than adults.

Pregnancy/Lactation

Both the mother and the fetus are at risk for hepatotoxicity following an overdose of acetaminophen because acetaminophen, but not the conjugated metabolites, freely diffuses across the placenta. There is no clear evidence, however, that either acetaminophen or NAC (the antidote for acetaminophen toxicity) is teratogenic. Treatment of pregnant patients should follow standard protocols. Acetaminophen is classified as pregnancy risk factor B.

Neonates whose mothers have taken an overdose of acetaminophen experience a relatively lower degree of hepatic damage than adults and older children. However, the fetus remains at risk if a large dose of acetaminophen crosses the placental barrier, because the fetal liver forms a toxic metabolite through oxidation.

Laboratory

ANALYTIC METHODS

Acetaminophen is measured by immunoassay.

BLOOD LEVELS

Therapeutic concentration ranges from 5-20 µg/mL. Some feel that a serum acetaminophen level in all cases of drug overdose can be cost-effective. Acetaminophen is widely available, is usually an initially silent overdose, is a drug that has the potential for significant morbidity or mortality, and effective-treatment is available if the diagnosis is confirmed. A standard approach to toxicity based on quantitative levels, and the Rumack nomogram, has been widely accepted (Fig. 1).

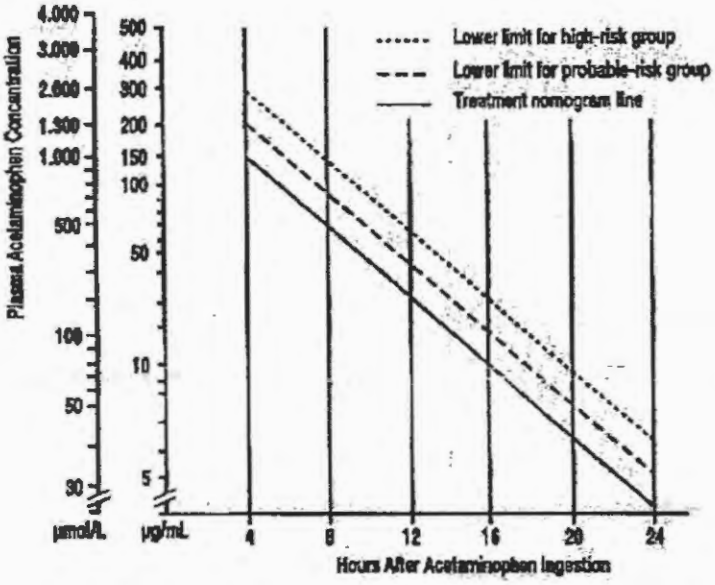


Figure 1. Nomogram lines used to define risk groups, according to initial plasma acetaminophen concentration, (From Smilkstein MJ, Bronstein AC, linden C, et al. Acetaminophen overdose: A 48-hour intravenous N-acetylcysteine treatment protocol. Ann Emerg Med 1991; 20:1 058- 1063)

Treatment

GUT DECONTAMINATION

Activated charcoal should be given within the first several hours of ingestion of acetaminophen. Activated charcoal may reduce the serum level of acetaminophen even after absorption is complete. Activated charcoal adsorbs some of the antidote NAC *in vitro;* however, there is no clinical evidence that the administration of activated charcoal inhibits the efficacy of oral NAC. There also is little evidence to support the practice of increasing the dose of oral NAC therapy after the administration of activated charcoal. There is no contraindication to the administration of activated charcoal and intravenous NAC. NAC dosing is not

based on acetaminophen blood levels. The optimal dose of activated charcoal has not been determined. An acceptable standard dose for adults is 1 gram/kg. If a patient presents within 1 to 2 hours of an acetaminophen overdose, emesis or activated charcoal therapy may reduce the availability of acetaminophen and result in lower blood levels. For the patient who presents more than 1 to 2 hours after a pure acetaminophen overdose, it is unlikely that gastrointestinal decontamination will be useful. It seems reasonable to give activated charcoal and to wait for a 4-hour acetaminophen level, as NAC is most effective when it is started within 8 hours of ingestion. If the level is in a potentially toxic range according to the nomogram, NAC therapy should be initiated. In significant acetaminophen overdoses, which present 8 hours after ingestion, NAC is still recommended, however its efficacy may be less pronounced. Gastric emptying procedures and activated charcoal administration are of limited value, if any, in chronic cases.

ELIMINATION ENHANCEMENT

Exchange transfusion has been used in neonates following acetaminophen ingestion by the mother shortly before birth. Arteriovenous hemofiltration has been employed for treatment of the associated hepatic encephalopathy, but there is little evidence that this procedure removes significant amounts of acetaminophen. The primary use of hemodialysis in overdoses of acetaminophen is for the treatment of renal failure. There is little clinical evidence at present that supports the effectiveness of early hemodialysis for overdose therapy. Peritoneal dialysis is ineffective. Hemoperfusion does not have a well-defined role in the treatment of acetaminophen overdose.

SUPPORTIVE MEASURES

- Basline blood tests for hospitalized patients should include complete blood count, liver function tests, glucose, electrolytes, and creatinine. Repeat liver function tests daily for 3 days, then as indicated by the appearance of hepatic encephalopathy. No further tests are necessary for those patients whose acetaminophen levels fall below the "toxic line" on the Rumack nomogram.
- Hepatotoxicity is characterized by elevated serum levels of alanine and aspartate transaminase, lactic dehydrogenase, and total bilirubin levels; long prothrombin and partial thromboplastin times; hypoalbuminemia; hypoglycemia; and elevated serum ammonia levels. Early signs of hepatotoxicity include hypoglycemia and metabolic acidosis. The severity of the liver function abnormality is not a reliable predictor of outcome.
- The prothrombin time is the best laboratory guide to the severity of hepatic encephalopathy. The development of an encephalopathy is likely when the prothrombin time exceeds 25 seconds at 48 hours postingestion, or 40 seconds at 72 hours. A peak prothrombin time exceeding 100 seconds or a prothrombin time that continues to increase 4 days after an overdose indicates a poor prognosis (8% chance of survival) and suggests the need for a liver transplant.
- Administer vitamin K1 for elevated prothrombin time (1.5x normal). Fresh frozen plasma should be used for severe prolongation (3x normal). Follow serial hemoglobin and stool guaiac tests for evidence of gastrointestinal bleeding.
- Elevated amylase and lipase may occur in pancreatitis and DIC may yield consumption of fibrinogen. Hyperlactatemia may occur in severely poisoned patients. Thrombocytopenia may occur as well. A moderate reduction in the platelet count may occur during acute liver failure, but severe thrombocytopenia with a nadir in the platelet count 2 days postingestion may occur in the absence of hepatic encephalopathy.
- Repeat acetaminophen levels are unnecessary once serial levels indicate that peak levels have occurred and the last level is below the toxic line.

5 Pg. 59

- Maintain normal hydration and electrolyte balance and avoid forced diuresis.
- Regular lactulose and enemas assist the elimination of nitrogenous substances and endotoxins from the bowel in encephalopathic patients.
- Cerebral edema is a major cause of death following the development of hepatic encephalopathy and may be treated with mannitol and fluid restriction.

Antidotes

N-ACETYLCYSTEINE

A nomogram developed by Rumack and Matthew in 1975 relates plasma levels of acetaminophen, at specific times postingestion, to potential hepatotoxicity. Acetaminophen levels *"above the lower line"* have about a 60% chance of developing severe liver abnormalities (as defined by elevation of alanine and aspartate transaminase activities above 1,000 IU/L). Levels above a second, higher line increase this probability to 90%. Patients With values above either line often do not develop liver damage~ whereas severe liver damage may rarely occur in patients with relatively low acetaminophen concentrations.

NAC is the N-acetyl derivative of L-cysteine, a naturally occurring amino acid. It helps replenish diminished glutathione stores in acetaminophen overdoses. In the United States, oral NAC is suggested in patients whose acetaminophen level (at given times) exceeds the lower lines on the Rumack-Matthew nomogram.

It should be noted that treatment lines initially were developed from observations of untreated patients. The usefulness of the nomogram lines in young children, and after 15 hours postingestion, has never been validated. They do not, in themselves, predict life or death.

Oral NAC is the only antidote currently approved for general use in acetaminophen poisoning in the United States, but intravenous NAC is available under a restricted investigational drug protocol. NAC provides maximum protection against hepatotoxicity when administered within 8 to 12 hours of an acetaminophen overdose. The efficacy of NAC decreases after this period, but few deaths in treated cases occur when NAC is administered by 16 hours postingestion. The effectiveness of NAC beyond 14 to 36 hours is controversial. Late therapy with NAC is not associated with an increased incidence of adverse effects. NAC administration would appear justified in the presence of hepatotoxicity caused by acetaminophen, no matter what the time course or interval since the last dose.

Once NAC therapy begins, a full course of NAC should be administered regardless of the location of subsequent levels of acetaminophen on this nomogram. Subsequent plasma levels of acetaminophen that fall below the treatment line are not an indication to stop NAC therapy. A 5% solution of NAC should be given as an oral loading dose of 140 mg/kg. The available commercial preparations of NAC are 10% and 20% solutions and need to be diluted. This can be done using water or a commercial carbonated or flavored drink. Seventeen further doses of 70 mg/kg NAC should be given as a 5% solution in diluent every 4 hours. The total dose given is 1,330 mg/kg over 72 hours. NAC has no hepatotoxic effects. Drinking NAC through a straw minimizes its unpleasant odor.

Alternatives in patients unable to retain oral NAC include placement of a nasogastric or duodenal tube and intravenous administration of metoclopramide to reduce nausea. Ondanestron, another antiemetic, improves tolerance to oral NAC in intravenous doses of 0.15 mg/kg repeated every 8 hours for three doses.

The acetaminophen nomogram has not been validated for chronic prolonged ingestions. Hepatic damage may occur despite acetaminophen concentrations the "nontoxic" range on the nomogram if the time when ingestion was completed rather than the time ingestion commenced is used to plot the results. Chronic excessive, continuous, or prolonged ingestions do not provide 'easy predictors, unlike overdose at a single point.

An initial nontoxic acetaminophen blood level at 4 hours after ingestion may be followed by a delayed toxic concentration.

METHIONINE

Methionine is an oral antidote used in Great Britain. Evidence in the United States has not been sufficient for adequate evaluation of its safety or efficacy. Methionine acts as a glutathione precursor and protects against acetaminophen-induced hepatic and renal toxicity if it is administered within 8 to 10 hours of overdose.

CIMETIDINE

Cimetidine reduces acetaminophen-induced liver toxicity in animal models, but the amount of cimetidine required to inhibit the formation of toxic metabolites substantially following an overdose of acetaminophen probably is beyond a clinically acceptable dose. The role of cimetidine as adjunctive therapy to NAC is unproved.

SELECTED READINGS Acetaminophen

1. Davidson DGD, Eastham WN: Acute liver necrosis following overdose of paracetamol. Br Med J 1966; 2:497-499.

2.Prescott LF: Paracetamol overdosage. Pharmacological considerations and clinical management. Drugs 1983;25:290-314.

3. Rumack BH, Peterson RC, Koch GG, et al.: Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. Arch Intern Med

SUBSTANCE ABUSE: AN INTRODUCTION

Many illicit drugs and chemicals, including medications, produce addiction and dependence when used, and withdrawal symptoms when their use is discontinued

They are divided into:

- **Stimulators** like amphetamines, cocaine, and caffeine.
- **Sedatives** like alcohol and benzodiazepines.
- **Narcotics** (depressants) like morphine, codeine, and heroine.
- **Hallucinogens** like cannabis, *amanita muscaria* (mushrooms), and LSD.

DEFINITIONS

Drug abuse: an intense desire to obtain increasing amounts of a particular substance for their pharmacological effects without medical purposes or cultural limits.

Drug dependence: the body's physical need or addiction, to a specific agent. Over the long term it may lead to physical harm, behavioral problems, and association with people who abuse drugs.

Tolerance: occurs when long-term use of a substance produces adaptive changes so that increasing amounts of the substance are needed to produce the same effect.

Withdrawal: unpleasant symptoms that occur when drug use is decreased or discontinued, though adaptive changes persist. The mechanism of withdrawal may involve interaction with membrane proteins and various neurotransmitters and neuroreceptors in the brain, including those interacting with gamma-aminobutyric acid (GABA), glutamate (NMDA), and opiates).

GENERAL CONSIDERATIONS

Different people will be affected by drugs in different ways. Some people are more prone to addiction than others.

Substances can be taken into the body in several ways:

1. Oral ingestion (swallowing)
2. Inhalation or smoking

3. Injection intravenously (shooting up)
4. Depositing onto the mucosa of the mouth or nose (snorting)

The most common reason why abuse takes place is to get high. Children and adolescents may experiment with drugs, yet only a small percentage grows up to become abusers.

Drug abuse by pregnant women poses a danger to the fetus. It may develop birth defects, may be born with an addiction and go into withdrawal symptoms, or may be born with a disease associated with drug abuse (e.g. HIV/AIDS).

People with chronic pain may become dependent on drugs. Psychiatric illnesses may be complicated with drug abuse, and similarly drug abuse may be a sign of a mental condition. It should also be noted that drug abuse may be visible among athletes, especially concerning steroids.

The signs and symptoms displayed by a person due to the drug depend on what the person is taking. an addict who has not abused drugs for some time may go into withdrawal, and those who are chronic abusers would expect this and act through their own experience to relieve themselves.

HALLUCINOGNS: CANNABIS

Hallucinogens comprise a wide array of substances, these include:

- Lysergic acid diethylamide (LSD).
- Cannabis (tetrahydrocannabinol) which will be discussed below.
- Psilocybin (mushrooms)
- Mescaline (from *amantia muscaria,* also a mushroom)
- Phencyclidine

CANNABIS: SOURCE AND CHEMISTRY

Cannabis refers to hallucinogens (psychoactive substances) that are derived from the dried leaves and flowers of the plant *cannabis sativa.* It comes in two major forms:

1. Marijuana: dried leaves and flowering tops of the plant. It is usually rolled into cigarettes, smoked by pipes, or added to baked goods.
2. Hashish: solid, black resinous material from dried leaves. Usually smoked by pipes.

Cannabis contains several pharmacologically active substances, of which, the most powerful psychoactive member is delta-I-tetrahydrocannabinol (THC). Another less active substance is cannabinol, which is 10 times less potent than THC.

PHARMACOKINETICS

The route of ingestion of cannabis determines its absorption and thus the speed of onset. Inhalation causes faster absorption than ingestion.. If smoked, onset of effects occurs within a few minutes lasting 2-3 hours. If eaten, onset takes place within 30 minutes and lasts about 5-8 hours.

Blood concentration peaks before the onset of its effects. Its plasma half life ranges from 18 hours to 4 days. It is a fat soluble substance, and thus it accumulates in tissue with high lipid content, and may remain in adipose tissue for as long as 30 days.

CLINICAL MANIFESTATIONS

Very little is known about how cannabis exerts its effects, though it's believed it works through benzodiazepine and cannabinoid receptors.

A distinctive feature of a patient on cannabis is his/her bloodshot eyes. The patient appears high. Symptoms due to acute intoxication differ according to the dose of the drug:

Low dose (~ 2mg THC):
- Relaxation
- Mild euphoria
- Increased visual, auditory, and gustatory perception

Moderate dose *(5-7mg):*
- Disturbances in thought process and time perception
- Short term memory impairment
- Ataxia

High dose (>15mg):
- Depersonalization
- Disorientation
- hallucinations

- Paranoia
- Tachycardia
- Sensory disturbances
- Decreased libido

IV misuse of the crude extract of cannabis:
- Nausea and vomiting
- Diarrhea
- Abdominal pain
- Fever
- Hypotension
- Pulmonary edema
- Acute renal failure
- Disseminated intravascular coagulation
- Death

Acute poisoning by inhalation or ingestion is very rare.

Cannabis shows neither physical dependence nor any withdrawal symptoms.

MANAGEMENT

In case of drug induced psychosis reassurance may be all that is needed but IV diazepam could be given for sedation. If needed, emesis or gastric lavage could also be performed.

All patients who have injected themselves with cannabis should be admitted and carefully managed for fluid and electrolyte maintenance to prevent risk of ARF and pulmonary edema.

By: Emil S. Oweis
5th year medical student
Toxicology Department

Poisonous Plants

Poison

Any substance, chemical or physical, once enter the biological system causes a harmful effect.

Acute - A rapid, severe onset of signs

Chronic - Over a period of time. Can refer to prolonged or repeated exposure to toxins or to the progression of clinical signs.

Epidemiology

American Association of Poison Control Centers indicated that plants were the 16th most commonly reported substance involved in human toxic exposure .

> 70% in children 5 years of age or younger.

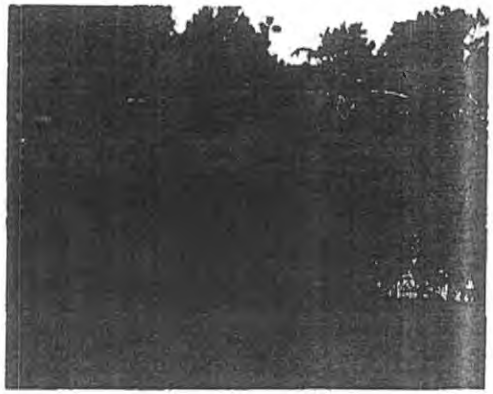
Examples

1.Castor plants

2.Datura

3.Defla

Castor plants



Continued

*Castor plants are indigenous to temperate and tropical India, Africa, and South America, but are widely grown

*The potent cholinergic properties of the oil have rendered it useful for decades as an "over-the-counter" laxative.

*A toxin called ricin is found throughout the plant, but is concentrated in the seeds

*Ricin is derived from the processing of the castor bean and its seeds in the extraction of castor oil

*One raw seed is enough to kill a human in 2 days, which makes for a long, agonizing and unstoppable death.

P67

Pathophysiology

*Ricin is composed of two lectins found in the seeds, ricin I and II.

*The compounds, especially ricin II, bind to and inactivate the 60S ribosomal subunit in somatic cells, thus blocking protein synthesis.

Ricin→ impair chain elongation→ cell death

→ tissue damage

Exposure

1. Ingestion
2. Inhalation
3. Injection

Ingestion

*Ingestion of intact castor bean seeds is unlikely to cause deleterious effects for several days, although ingestion of chewed castor beans rarely results in significant morbidity.

*Gradually, however, it produces nausea, vomiting, dyspnea,and diarrhea

* Gastroenteritis follows and is characterized by severe bloody diarrhea, vomiting, and dehydration

*Mental confusion, seizures, and hyperthermia complicate the scenario.

Inhalation

*Inhalation of ricin powder likely produces a cough, dyspnea, nausea, and vomiting within a few hours.

*Pulmonary congestion and cyanosis could soon follow.

Injection

*Injection of a lethal amount of ricin (estimated to be about 500 mg) at first would cause local muscle paralysis and lymph node necrosis near the injection site

*Massive stomach and intestinal hemorrhaging would ensue, followed by multiple organ failure.

*Death occurs within 36 to 48 h and is due to focal necrosis of liver, spleen, lymph nodes, intestine, and stomach

*Ricin is not an environmental metabolic product, and unintentional ricin poisoning is highly unlikely.

*Its presence suggests deliberate contamination.

*Antidotes are not available for ricin poisoning.

*Treatment necessitates supportive emergency measures, including maintenance of respiration and renal perfusion, and gastric decontamination.

Datura

A.k.a angel's trumpets.

Continued

* Toxic part of the plant: all parts.
* Main toxic constituents: Tropane alkaloids
* leaves/flowers: atropine
  Seeds/roots: hyoscyamine
  Fruits: scopolamine
* Accidentally(or intentionally) ingesting even a leaf could lead to severe side effects

P69

Symptoms (Anticholinergic)

* Xerostomia
* Eyes: blurred vision, photophobia& fixed dilated pupils.
* Urinary retention
*CVS: tachycardia, hypertension & arrhythmias.
*CNS: disorientation, agitation, convulsions, delirium, hallucinations, ataxia & coma
* Death may occur within 4-24 hrs (Rs failure)

Mode of action

*Peripheral effects are predominant and result from anticholinergic action. Central effect involve initial stimulation of the cns with excitement and restlessness followed by depression, delirium and coma.

* It does not block nicotinic receptors so there is little or no action at skeletal muscular junctions or autonomic ganglia.

Treatment of poisoning

* Ipecac to induce emesis or gastric lavage.
* Activated charcoal to reduce absorption
* Catheterization to empty the bladder if necessary
* Diazepam for hallucinations and delirium

Defla

Nerium oleander

Continued

* This plant grows outdoors in warmer regions, and in sometime is grown as a house plant
* All parts of the plant both green and dry are considered toxic
* The toxic principles are two potent cardiac glycosides (cardenolides), oleanderin and neriine, and can be isolated from all parts of the plants
* Exposure: Ingestion & inhalation

Continued

Symptoms of toxicity after ingestion or inhalation of smoke:

- Blurred vision
- Vomiting, nausea, Diarrhea(may be bloody) , excess salivation & abdominal pain.
- Bradyarrythmias or tachyarrythmias
- Extremities may become pale and cold due to poor or - irregular circulation
- Confusion, drowsiness, tremors or shaking of the muscles, seizures, collapse, and even coma that can lead to death.
- Death usually by heart attack

Mode of action (cardiac glycoside)

Inhibits Na+/K+ ATPase pump causing:

-intracellular Na+ increase

-Ca ions increase in muscles cells of the heart

-irregular muscle contraction

-may have an effect on the signaling pathways

-may inhibit protein assembly

P71

Thank You

Treatment

* Gastric decontamination: activated charcoal
* Hydration via IV saline
* Electrolytes
* treatment of arrythmias:
  - Brady: atropine or isoprenaline
  - Tachy: usually poor prognosis, digoxin-specific Ab fragments, lidocaine
* Same treatment for inhalation of smoke, except charcoal.

Stimulants

General Notes

What Are They?

- Stimulants are a class of drugs that elevate mood, increase feelings of well-being, and increase energy and alertness.

- Examples include:
  - Cocaine,
  - Methamphetamine,
  - Amphetamines,
  - Methylphenidate, (Ritalin)
  - Caffeine
  - Nicotine,
  - MDMA (3,4-methylenedioxymethamphetamine), better known as "Ecstasy."

Cocaine

- Cocaine comes in two forms:
  - Powder cocaine is a hydrochloride salt, made from the leaf of the coca plant.
  - "Crack" is a smokeable form of cocaine that is processed with ammonia or baking soda and water, and heated to remove the hydrochloride.

Methamphetamine

- Methamphetamine is a powerful stimulant, originally derived from amphetamine.
- It comes in clear crystals or powder and easily dissolves in water or alcohol.
- Although most of the methamphetamine used in the United States comes from "superlabs," it is also made in small laboratories using inexpensive over-the-counter and often toxic ingredients (such as drain cleaner, battery acid, and antifreeze).

Amphetamines

- Amphetamines, such as Adderall, are stimulants that often come in pill form and are sometimes prescribed by doctors for medical problems, most commonly attention deficit hyperactivity disorder (ADHD).
- Amphetamines can also be abused—that is, used in a way other than as prescribed (e.g., crushed and snorted) or used by someone without a prescription.

Methylphenidate

- Methylphenidate, such as Concerta or Ritalin, is another medication prescribed for people with ADHD.
- As seen with amphetamines, including Adderall, numerous studies have shown its effectiveness when used as prescribed.
- When it is abused, however, methylphenidate can lead to many of the same problems seen with other stimulants.

What Are the Common Street Names?

- Cocaine is generally sold on the street as a fine, white, crystalline powder, known as "coke," "C," "snow," "flake," "blow," "bump," "candy," "Charlie," "rock," and "toot."
- "Crack," the street name for the smokeable form of cocaine, got its name from the crackling sound made when it's smoked.
- A "speedball" is cocaine or crack combined with heroin, or crack and heroin smoked together.

What Are the Common Street Names?

- Methamphetamine is commonly known as "speed," "meth," "chalk," and "tina."
- In its smokeable form, it's often called "ice," "crystal," "crank," "glass," "fire," and "go fast."
- Street names for amphetamines include "speed," "bennies," "black beauties," "crosses," "hearts," "LA turnaround," "truck drivers," and "uppers."
- Street names for methylphenidate include "rits," "vitamin R," and "west coast."

How Are They Abused?

- Powder cocaine is usually snorted or injected (also called "mainlining"), or it can be rubbed onto mucous tissues, such as the gums.
- Street dealers generally dilute cocaine with other substances (such as cornstarch, talcum powder, or sugar), with active drugs (such as procaine, a chemical that produces local anesthesia), or with other stimulants (such as amphetamines).
- Crack cocaine is often smoked in a glass pipe.

How Are They Abused?

- Stimulants are abused in several ways, depending on the drug. They can be:
  - Swallowed in pill form.
  - Snorted in powder form through the nostrils, where the drug is absorbed into the bloodstream through the nasal tissues.
  - Injected, using a needle and syringe, to release the drug directly into a vein.
  - Heated in crystal form and smoked (inhaled into the lungs).
- Injecting or smoking a stimulant produces a rapid high—or rush—because the drug is absorbed into the bloodstream quickly, intensifying its effects.
- Snorting or swallowing stimulants produces a high that is less intense but lasts longer.
- Some abusers dissolve the tablets in water and inject the mixture
- Complications from this method of use can arise because insoluble materials in the tablets can block small blood vessels!!!

How Are They Abused?

- Methamphetamine is swallowed, snorted, injected, or smoked. "Ice," a smokeable form of methamphetamine, is a large, usually clear crystal of high purity that is smoked, like crack, in a glass pipe.
- Amphetamines and methylphenidate are usually swallowed in pill form.

How Many Teens Use Them?

- In 2011, a NIDA-funded study reported that the following percentages of 8th, 10th, and 12th graders had abused these drugs at least once in the past year:
  - Powder cocaine: 1.1 percent of 8th graders, 1.7 percent of 10th graders, and 2.6 percent of 12th graders
  - Crack cocaine: 0.9 percent of 8th graders, 0.9 percent of 10th graders, and 1.0 percent of 12th graders
  - Methamphetamine: 0.8 percent of 8th graders, 1.4 percent of 10th graders, and 1.4 percent of 12th graders
  - Amphetamines: 3.5 percent of 8th graders, 6.6 percent of 10th graders, and 8.2 percent of 12th graders
  - Nonmedical use of Ritalin: 1.3 percent of 8th graders, 2.6 percent of 10th graders, and 2.6 percent of 12th graders
  - Nonmedical use of Adderall: 1.7 percent of 8th graders, 4.6 percent of 10th graders, and 6.5 percent of 12th graders

How Do Stimulants Produce Euphoria?

- Stimulants change the way the brain works by changing the way nerve cells communicate.
- Nerve cells, called neurons, send messages to each other by releasing chemicals called neurotransmitters.
- Neurotransmitters work by attaching to key sites on neurons called receptors.

How Do Stimulants Produce Euphoria?

- There are many neurotransmitters, but dopamine is the main one that makes people feel good when they do something they enjoy, like eating a piece of chocolate cake or riding a roller coaster.
- Dopamine is a brain chemical (or neurotransmitter) associated with pleasure, movement, and attention.
- Stimulants cause a buildup of dopamine in the brain, which can make people who abuse stimulants feel intense pleasure and increased energy.

How Do Stimulants Produce Euphoria?

- They can also make people feel anxious and paranoid. And with repeated use, stimulants can disrupt the functioning of the brain's dopamine system, dampening users' ability to feel any pleasure at all.
- People may try to compensate by taking more and more of the drug to experience the same pleasure.
- Stimulants have been abused for both "performance enhancement" and recreational purposes (i.e. to get high).
- For the former, they suppress appetite (to facilitate weight loss), increase alertness ,focus and attention.

What Are the Short-Term Effects?

- In the short term, stimulants can produce feelings of tremendous joy, increased wakefulness, and decreased appetite.
- People who abuse them can become more talkative, energetic, or anxious and irritable.
- Other short-term effects of stimulants can include increased body temperature, heart rate, and blood pressure; dilated pupils; nausea; blurred vision; muscle spasms; and confusion.

What Are the Long-Term Effects?

- As with many other drugs of abuse, repeated stimulant abuse can cause addiction.
- That means that someone repeatedly seeks out and uses the drug despite its harmful effects.
- Repeated drug use changes the brain in ways that contribute to the drug craving and continued drug seeking and use that characterizes addiction.
- Other effects of long-term stimulant abuse can include paranoia, aggressiveness, extreme anorexia, thinking problems, visual and auditory hallucinations, delusions, and severe dental problems.

What Are the Short-Term Effects?

- Stimulants can also cause the body's blood vessels to narrow, constricting the flow of blood, which forces the heart to work harder to pump blood through the body.
- The heart may work so hard that it temporarily loses its natural rhythm.
- This is called fibrillation and can be very dangerous because it stops the flow of blood through the body.

What Are the Long-Term Effects?

- Repeated use of cocaine can lead to tolerance of its euphoric effects, causing the person to take greater amounts or to use the drug more frequently (e.g., binge use) to get the same effects.
- Such use can lead to bizarre, erratic behavior. Some people who abuse cocaine experience panic attacks or episodes of full-blown paranoid psychosis, in which the individual loses touch with reality and hears sounds that aren't there (auditory hallucinations).
- Different ways of using cocaine can produce different adverse effects. For example, regularly snorting cocaine can lead to hoarseness, loss of the sense of smell, nosebleeds, and a chronically runny nose. Cocaine taken orally can cause reduced blood flow, leading to bowel problems.

What Are the Long-Term Effects?

- Repeated use of methamphetamine can cause violent behavior, mood disturbances, and psychosis, which can include paranoia, auditory hallucinations, and delusions (e.g., the sensation of insects creeping on the skin, called "formication").
- The paranoia can result in homicidal and suicidal thoughts. Methamphetamine can increase a person's sex drive and is linked to risky sexual behaviors and the transmission of infectious diseases, such as HIV.
- However, research also indicates that long-term methamphetamine use may be associated with decreased sexual function, at least in men.

What Treatments Are Available for Stimulant Abuse?

- These programs reward patients who refrain from using drugs by offering vouchers or other small rewards. MI may be particularly useful for helping patients to initially stop taking the drug and for helping them to stay in treatment.
- Currently, there are no medications approved by the U.S. Food and Drug Administration to treat people who are addicted to stimulants, although that is an active area of research for NIDA.

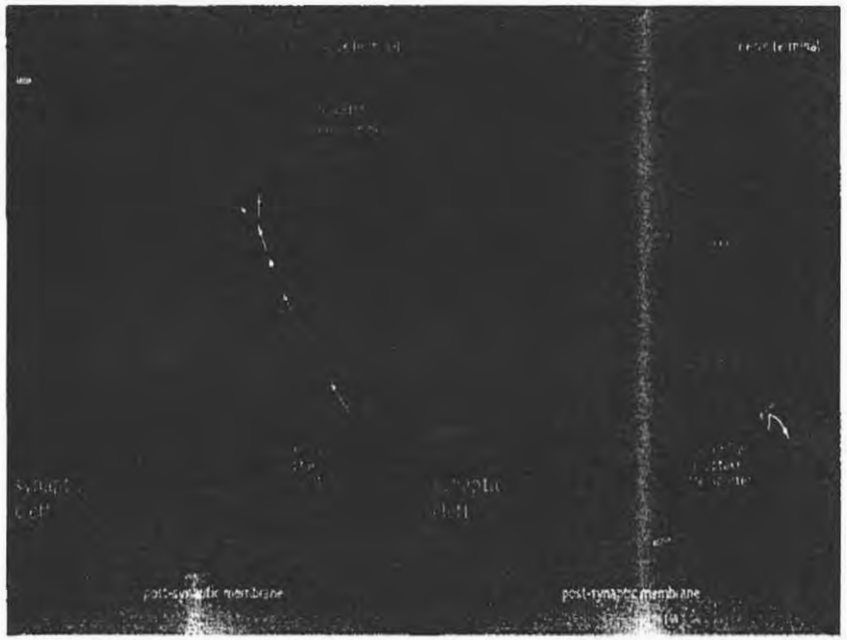
What Treatments Are Available for Stimulant Abuse?

- Several behavioral therapies are effective in treating addiction to stimulants.
- These approaches are designed to help the person think differently, change their expectations and behaviors, and increase their skills in coping with various stresses in life.
- One form that is showing positive results in people addicted to either cocaine or methamphetamine is called contingency management, or motivational incentives (MI).

Specific Notes

Cocaine

- Alkaloid extracted from the leaves of the coca plant
- Serotonin-dopamine-NE reuptake inhibitor
- **Target organs** : CNS , CVS
- ***Psychological dependence*** not physical (affect mesolimbic reward pathway)



Pathophysiology

- Normally, once dopamine has attached to a nerve cell's receptor and caused a change in the cell, it's pumped back to the neuron that released it. But cocaine blocks the pump, called the dopamine transporter. Dopamine then builds up in the gap (synapse) between neurons.
- The result: dopamine keeps affecting a nerve cell after it should have stopped. That's why someone who uses cocaine feels an extra sense of pleasure for a short time.
- Cocaine disappears from the brain quickly!

Cocaine

- **Uses** :
  - Local anaesthesia for URT
- **Forms of cocaine :**
  - **Salts :** Soluble in water
  - **Basic :** Insoluble in water
  - **Crack cocaine :** Lower purity-form of free base
  - **Coca leaf infusions**

Cocaine

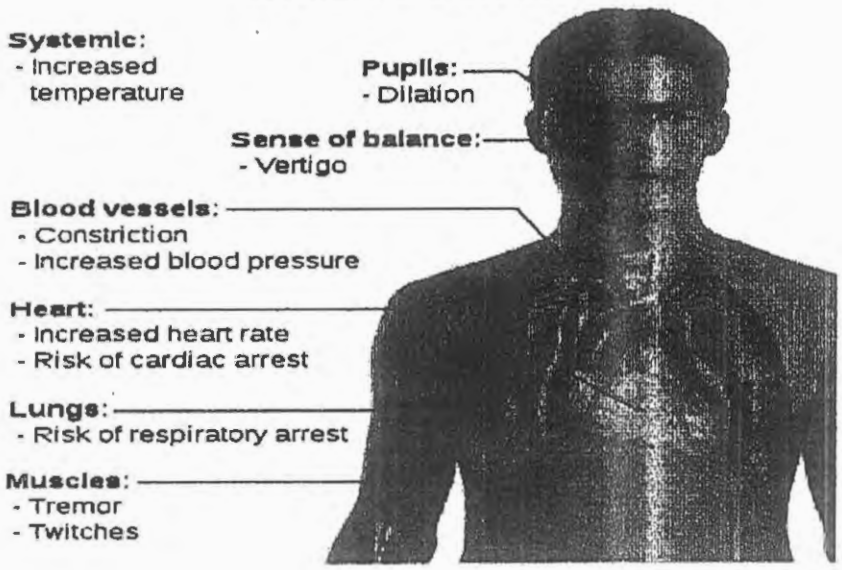
- **Routes of administration**
  - **Oral:**
    - 30 minutes to enter the bloodstream
    - Effects are attained approximately 60 minutes after cocaine is administered by ingestion
  - **Insufflation:**
    - Absorbed through the mucous membranes lining the sinuses
  - **Injection: Most rapid and most dangerous**

- Cocaine Intoxication :
  - Tachyarrhythmia
  - Marked elevation of blood pressure
  - Respiratory failure
  - Stroke
  - Cerebral hemorrhage
  - Heart-failure

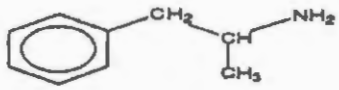
Cocaine

- Management:
  - ABCs
  - Administer Benzodiazepines to manage seizures
  - There is <u>NO</u> officially approved specific antidote for cocaine overdose

Main physiological effects of
Crack cocaine



Amphetamine



- Prepared from phenylethylamine
- Sympathomimetic

- <u>Target organs</u>:
  - CNS → stimulation 'euphoria, agitation, convulsion, tremor
  - CVS → tachycardia, HTN, arrhythmia, collapse
  - Other systems to be affected: endocrine, GI, skin, genitourinary
  - Pregnancy → Spontaneous Abortion, Teratogenic

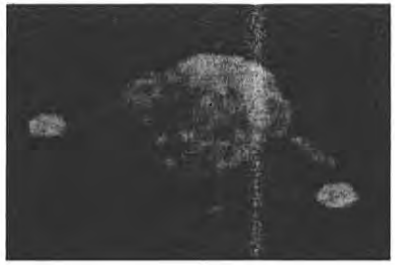
- <u>Indications for use</u> :
  - Attention-deficit hyperactivity disorder (ADHD).
  - Narcolepsy
- Previous indications not currently recommended:
  - Appetite suppressants
  - Relief of fatigue

Pathophysiology

- Methamphetamine interferes with this recycling process, and causes too much dopamine to be released.

- Methamphetamine has a much longer duration of action than cocaine. The long presence in the brain ultimately makes methamphetamine very harmful to brain cells.

Amphetamine



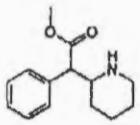
- **Routes of intake** :
  - Oral
  - Inhalation
  - Parenteral
- **Distribution** :
  - Concentrated in lung, kidney, CSF, brain (high Lipid soluble)
- **Elimination** :
  - Urinary excretion 'unchanged'
  - De-amination 'CYT-P450'

Amphetamine

- Withdrawal symptoms :' fairly mild'
- Depression, increased appetite, abdominal cramping, diarrhea, headache

- Management:
  - Reduce toxic effect of the drug
  - Reduce morbidity
  - Prevent complications
  - GI decontamination is performed by the administration of activated charcoal, Benzodiazepam, Haloperidol, CVS agents 'labetolol

Methylphenidate

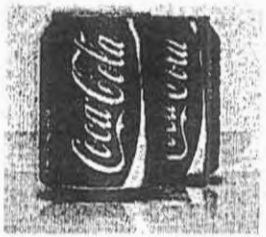


- Incorporates Phenylethylamine
- Sympathomimetic
- Very similar to cocaine

- <u>Overdose :</u>
  - mostly asymptomatic
  - if symptomatic : agitation, hallucinations, psychosis, lethargy, seizures, tachycardia, dysrhythmias, hypertension, and hyperthermia

Caffeine

- White crystalline xanthine alkaloid
- Acetyl-cholinesterase inhibitor
- Increase neural activity level through antagonizing adenosine



Caffeine

- *caffeine intoxication :*
- <u>CNS features</u>
- ✓ Headache
- ✓ Anxiety, agitation
- ✓ Tremulousness, perioral and extremity tingling (resulting from tachypnea-induced respiratory alkalosis)
- ✓ Seizures

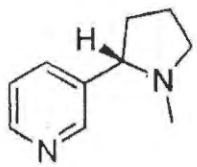
- <u>Cardiovascular features</u>
- ✓ Palpitations or racing heart rate
- ✓ Chest pain

- <u>GI features</u>
- ✓ Nausea and vomiting
- ✓ Abdominal pain
- ✓ Diarrhea, bowel incontinence
- ✓ Anorexia

Caffeine

- Management:
- ✓ ABCs
- ✓ Check blood glucose level.
- ✓ Patients with anxiety, severe agitation, or seizures may require a short-acting benzodiazepine (eg, lorazepam) given intravenously or intramuscularly.

Nicotine



- Bitter-tasting compound
- From the leaves of tobacco plants
- Acute nicotine poisoning usually occurs in young children who accidentally chew on nicotine gum or patches

Nicotine

- Management:

✓ Do not induce vomiting

✓ Activated charcoal

✓ Gastric lavage

✓ If the chemical is on the skin, wash with soap and lots of water for at least 15 minutes

Nicotine

o Toxicity signs & symptoms :

- Abdominal cramps
- Agitation, restlessness, or excitement
- Muscular twitching
- Breathing – rapid
- Burning sensation in mouth
- Coma
- Confusion
- Convulsions
- Depression
- Drooling (increased salivation)
- Fainting
- Headache
- High blood pressure, which then drops
- Vomiting
- Weakness

Thank You

Sports Doping

MOHAMMAD AL-FAQIH

History

- Ancient Greeks ingested certain plants before races believing it would give them an edge in competition.
- In 1976 International Olympic Committee started widespread drug testing and penalized athletes for positive testing.
- Even with present more rigorous testing, drug use has continued to grow among both the world's best and less elite athletes.

Doping

- the administration to or use by a healthy individual of any agent or substance, nor normally present in the body, and/or of any physiological agent or substance , when introduced in abnormal additional quantities and/or by an abnormal route and/or in an abnormal manner, with the purpose and effect of increasing artificially and in an unfair manner the performance of that individual during the period of competition.

Categories of drugs used

- Performance-enhancing drugs:
  - Intent is to improve performance.
  - E.g., anabolic steroids, narcotic analgesics, beta blockers.
- Recreational drugs:
  - Alter the state of mind with no intention of improving performance.
  - E.g., marijuana, cocaine, heroin.

Doping categories banned by International Olympic Committee

1. Anabolic androgenic steroids.
2. Stimulants (including hallucinogens).
3. Narcotic analgesics.
4. Beta-adrenergic blockers.
5. Diuretics.

- The technique of blood doping.
- Recently banned: creatine, human growth hormone and tetrahydrogesterinone (THG).

Legal substances

1. Depressants.
2. Nicotine.
3. Diet regimens (e.g., carbohydrate loading).
4. Amino acids.
5. Vitamins.
6. Creatine (except banned).

Anabolic steroids

- Best known doping category.
- Increases male hormone androgen and decreases female hormone estrogen.
- Benefits:
- Depends on type of skill and physical demands of the sport.
- Increase strength and power:
- Intensify training program - steroids enhance recovery, build skeletal muscle tissue.
- Increase strength occurs because steroids promote synthesis of proteins that help build skeletal muscle tissue.
- Used for medical purposes to promote muscle growth and tissue repair as part of injury rehabilitation (legal).

Harmful effects of steroids

- Females: masculinizing effect - increase facial and body hair, lowered voice, temporary sterility, increase muscular bulk/strength, reproductive problems.
- Males: increase feminine characteristics – decrease facial and body hair, decrease sperm production, sterility, impotence.
- Increase injuries to muscles, tendons, ligaments.
- Adolescents: stunted growth due to premature fusion of epiphysis of long bones.

Harmful effects of steroids

- Liver cancer, increase blood pressure, premature heart disease, stroke.
- "Roid Rage" (heightened, uncontrolled aggression, e.g., increase domestic violence, suicide, murder, sport violations).
- Clinical depression when stop use.

Stimulants

- Increase the rate of heart, nervous, and respiratory system.
- Enhance performance by increase alertness or weight loss (amphetamines) to compete at a lower weight.
- Psychomotor: amphetamines and diet supplements.
- Sympathomimetic amines: stimulate sympathetic and autonomic nervous system.
- Hallucinogens: recreational and mind altering drugs.
- Central nervous system:
- Ephedrine, and many over the counter stimulants.
- Caffeine in high amounts.

Narcotic analgesics

- Used by athletes during soreness to reduce fever or swelling - anti-inflammatory effect.
- Can also slow performance due to a sedative effect.
- Examples: codeine, heroin, opium, morphine.
- Produce dependence very commonly.

Beta-blockers

- Aid performance by slowing the heart rate, decreasing anxiety, and steadying natural body tremors - good for rifle/pistol shooting, archery, bowling, golf.
- Adverse effects: bronchospasms, CNS disturbances, hypotension, impotence.
- Sport adverse effects: interfere with high intensity, longer endurance tasks.
- More difficult to induce dependence.

Diuretics

- Increase the rate at which water and salt leave the body as urine.
- Used for weight loss - for boxers and wrestlers to compete at a lower weight.
- Can cause nausea, stroke, heat exhaustion, impairs thermoregulatory control, blood clotting, reduced blood volume, and muscle cramps.

Caffeine

- Central nervous system stimulant is banned with more than 18 ounces consumption.
- Prolongs endurance performance and high-intensity short-duration exercise, creating an unfair advantage.
- Combined with insufficient water intake, athletes internal body temperature rises inducing premature fatigue and dangerous heat-related illnesses.

P87

Blood doping

- Remove one liter of the athlete's blood 1-2 months before competition and freeze it.
- Inject red blood cells back into the athlete before competition.
- Benefits: increase oxygen carrying capacity and thus aerobic (endurance) performance.
- Dangers might include hepatitis B or C as well as the HIV virus if blood samples get mixed up.

Erythropoietin (Epo)

- Naturally secreted by the kidneys in response to hypoxia that stimulates production of red blood cells.
- Enhances the body's ability to transport oxygen to peripheral exercising muscles.
- Reduces onset of muscular fatigue and improves regulation of internal body temperature, thus providing an unfair advantage.

Creatine

- Regarded as both a nutritional and physiological ergogenic aid.
- Popular for 3 reasons:
- Not considered a steroid.
- Assumed safe in reasonable amounts.
- Legally available in health stores and fitness clubs.
- May increase lean body mass and performance in repetitive, high-intensity, very short-term tasks with brief recovery periods.

Human Growth Hormone (HGH)

- Naturally secreted through the pituitary gland, but has also been created through DNA technology.
- It increases body mass while reducing fat mass.
- Mixed evidence on performance enhancement.
- Could cause distorted physical characteristics - Frankenstein's syndrome.

Rationale for anti-drug policy in sports

- Medical, legal, and ethical issues:
- May cause athletes' physical and psychological harm.
- Violates state and federal laws if use for non-medical purposes.
- Cheating: violates team rules and organizational policies.
- Contaminates performance results.

How widespread is drug abuse in sports?

- Studies with specific sport populations (strength or endurance) report higher drug use.
- Users believed steroid used in moderation were safe.
- Asking athletes to honestly self-report drugs use is very difficult.

Likely causes of drug abuse in sports

- Physical causes:
- Enhance sport performance.
- Cope with pain and injury rehabilitation.
- Weight control.
- Psychological causes:
- Stress and anxiety.
- Boredom.
- Personal turmoil(a state of severe confusion or agitation).
- Low self-confidence and self-esteem.
- Negative perfectionism.

Likely causes of drug abuse in sports

- Social causes:
- Peer pressure and acceptance.
- Models (particularly with adolescents).
- Social support (approval among peers and coaches).

P89

Thank you

Toxicology

Index

- principals of Toxicology
- CO
- Cyanide
- Drugs in Sports
- pesticides
- Alcohol & Glycols.
- Important Antidotes.

Best of luck :)
Farah Amer

Principals of Toxicology

Emesis → Ipecac (the best way to induce emesis)

Gastric Lavage → usually we use Tap water or ½ Saline (preffered in children)
(may use Sodium Bicarb, Ca^{+2} Salts, Tannic acid)
→ pt. is placed on Lt. side → ↓ risk of aspiration pooling of gastric contents
→ Head is lower than the rest of Body
→ largest diameter Tube should be used.

Adsorbents → non-specific as Charcoal.
→ specific

Activated Charcoal → Black powder mixed w water Before use
(Suspended in the Solution)
→ it forms tight Chemical bonds w the poison (adsorption) then the Charcol Chemical complexes pass out the GIT
→ Maximal effectiveness:
- administered within 30 mins of poison ingestion.
- substance should be non-ionized + Molecular wt (100-1000) to be absorbed.

→ Dose: 50-100 g - adult
15-20 g - Child
(Ratio) [charcoal:drug 10:1]
- large doses → constipation
- Multiple ↓ → Safe to use.

→ Should Not be given within 30 mins of ipecac unless the pt has vomited.

Cathartics & laxatives

- Saline Cathartics are preferred.
  - Mg^{+2}-Containing → ~~Mg salt~~ used in RF.
  - ~~Na^{+}~~-Containing → avoided in HF.
- (Metabolic disturbances) are mc. SE of acute cathartic
- Contraindications: ① poison is Strongly corrosive.
  ② pt. has e^- imbalance.
  ③ Bowel Sounds are absent.
- ↑ motility of intestine or ↑ Bulk of feces.
- Types:
  - Stimulant Cathartics → Emodin (irritant glycoside)
    Vegetable oils (ex. Castor oil)
  - Hyperosmotic Cathartics → Mg-Salts
    Sodium Salts
    Sugar alcohol
    polyethylene glycol
  - Hydrophilic Colloids (Bulk laxatives)
    - use fibers to draw water into the Bowel.
  - Lubricant laxatives.
  - Fecal Softeners (Surfactants)

Metabolism → ex. using Ethanol as an Antidote for Methanol Poisoning
(it competes w Methanol Metabolism → ↓ production of Toxic metabolites)

Excretion

- ① Forced diuresis (using mannitol or Furosemide)
  - May ↑ excretion by 2 folds.
  - a better procedure → acidification of urine for Basic poison by Ascorbic acid or Ammonium Chloride.
    → alkalinization of urine for acidic poison. by Sodium Bicarb ± Acetazolamide.
- ② Dialysis & Hemiperfusion.

• Principles of Management

- (5-10%) of poisoning have specific antidote.
- ABCD ← detoxification

① ABC, stabilize the pt.
② Complete pt. assessment ((Hx. , P/E , Iox))
③ Decontamination of poison ((skin → wash , stomach → enesis))
④ Enchancement of elimination ((forced diuresis, acidification, alkalization
⑤ Antidote
⑥ Continuous pt. Care.

The End
Farahtmeh

CO

- odorless, colorless & tasteless gas also nonirritating. ((silent killer))
- It is produced by incomplete combustion of carbonaceous materials
- **Sources**:
(ex. fires, gasoline/diesel incomplete combustion, Heaters, ovens, smoking, work sites, charcol fires, wood burning stoves, motor vehicles ...)
- anything that contain Carbon & had incomplete combustion -

- lighter than air
- ✻1 poisoning in industrial countries
- **Normal Values**:
in adult body ≤ 0.5 % (from Hb metabolism)
in air ((atmosphere)) ~ 0.001 %

* COHb ↑ hemolytic anemi
* Smoking ↑ CO up to 3-6 %

- CO intoxication can occur by inhalation of Methylene Chloride (used in industrie
- Methylene Chloride is metabolised by liver to CO (15%) & CO_2, it is stored in the tissues & continues the release of CO for at least twice as long as direct CO inhalation. ((~ present ∵ late manifestations of CO poisening))

- motor vehicle exhaust fumes can lead to CO intoxication in a Closed garage. But this depends on how efficient the burning is.

- **Mechanism of toxicity**:
((Tissue Hypoxia)) mediated by:
Reversible binding of CO to Hb → formation of stable Carboxy-Hb (COHb) → displaces the (O_2-carrying capacity) of Hb → Shift the (O_2-Hb dissociation curve to the Left → O_2 on Hb molecule Binding more tightly ∵ Hb → less O_2 available to tissues ⇝ tissue Hypoxia.
((at any given pO_2, ∵ the presence of CO Hb is more saturated ⊖ O_2))

Recall:

- CO has higher affinity to Hb ((200-250 times))
- Clinical presentation doesn't correlate w/ COHb level But sx typically begin w/ Headaches at level around (10%).
- It binds to Cardiac Myoglobin → myocardial depression
- CO intoxication has its most effect on organs w/ higher O_2 requirments ((Brain & Heart))
- It is Not necessary that CO occupy all 4 Binding sites on Hb.

Signs & Symptoms:

- mainly affect CNS & CNS.
- Headache, dizziness, malaise, fatigue, confusion, lethargy, ataxia, Syncope & coma.
- Tachycardia, Hyperthermia, (MI) mcc of death.
- "Cherry-Red" discoloration in Cadaver
- The pt. doesn't look cyanosed, he is "plethoric" (O_2 still present in Bld But doesn't reach tissues)
- The more severe the initial poisoning the more the residual damage will result ((depending on severity of exposure))
- complications include persistent Neurologic & Myocardial dysfunction.

- CO-induced delayed neuropsychiatric syndrome (CO-DNS): impaired cognitive function, personality changes, dementia & Sx resemble Parkinson's disease.

- individuals at greater risk for complications development:
  - infants (Fetal Hb) - Elderly - pregnants
  - anyone w/ a disease ↓ O_2 carrying capacity (ex. anemia ...)

- CDC criteria is
  ① suspected ② probable ③ Confirmed.

Investigations:

- venous or Arterial Blood Sample. (sample shouldn't be open)
- If you are taking the ABGs take a venous sample easier.
- In ABG → Resp. Acidosis [acidosis shifts the curve to the Rt. So it stimulates O_2 Release.]

Hx:

① To relieve Cerebral & Cardiac ischemia
② dissociation of COHb & ↑ CO elimination Rate.

- calm the pt. as much as possible, the pt should be resting (in order Not to ↑ O_2 demand)

- COHb < 15% → fresh air & Rest
- COHb > 15% → 100% O_2
- COHb > 40% → Hyperbaric O_2

- addition of (5-7%) of CO_2 is indicated since CO_2 stimulates Breathing that is why we don't Hx resp. acidosis.

* Hyperbaric O_2:
- (100%) O_2 at 3 atm. of pressure in a special Chamber
- ↓ half life of COHb > 50% 4 hrs → < 40 mins

The End
Farah Amer

Cyanide

- Cyanide compounds used in electroplating & electropolishing, manifacturing of plastics, extraction of gold & silver ....
- In Seeds of various nut, apples, apricots .etc there is a compound called (Amygdalin) that is hydrolyzed into Hydrogen Cyanide (HCN)
  But this can't Cause acute poisoning Because the amount is very little.
- Cyanide gas could be found in pesticides as fumigant, fires & gas chamber [used for
- In NL Body → Metabolism of vit. B12 (Cyanocobalamine) can give CN
  - cobalamine itself could be used as antidote for CN by binding to it & ↓ toxicity
- Which drug can (↑ CN) in our Bodies?
  Nitroprusside (vasodilater) when given faster & higher than the recommended dose could ↑ CN.

HCN
- Hydrocyanic acid
- Prussic acid

Mechanism of Toxicity:

(Histotoxic anoxia)

CN Binds to cytochrome a/a3 ((oxidase system)) → (CN-cytochrome Oxidase - Fe^{+3} Complex) →
The complex interferes w/ the Transfere of e^- to O_2 (final e^- acceptor) →
CN Blocks (e⁻ Transport Chain) & inhibits Metabolic Respiration →
↓ Cellular O_2 Utilization → prevents ATP production & ↑ venous PO_2
The ↓ in Aerobic Respiration forces the cells to revert to Anaerobic metabolism → ↑ lactic acid → Triggers Metabolic Acidosis.

* CO poisoning → O_2 is Not released to the tissues.
  CN poisoning → O_2 is released But Not utilized.

* Majority of CN is Metabolised in liver.

Signs & symptoms :

- No cyanosis ((O_2 present in Blood , Both arterial & venous))
- The gas is irritant can cause pulmonary edema , Tachypnea , ↑ Tearing , ↑ salivation , ..
- CNS & CVS are affected mainly ((similar to CO))
- Headache , N/V , weakness , dizziness , dilated pupils , coma , death ,
- Hypotension ∵ reflex Tachycardia , Tachypnea , hyperpnea [stimulation of Chemoreceptors on Carotid Body] ∵ ↑ dose hypo-apnea occurs . ((↑ stimulation of Breathing , ↑ Toxicity))
- Time Since exposure & dose → affects Toxicity ((mild , moderate , severe))
- HCN gases are rapidly acting , whereas HCN salts → delayed action → ((need time to be absorbed))

Hb : to ↓ HCN Binding to Cytochrome oxidase .

- Endogenous detoxification to HCN to be excreted by kidneys :

$$HCN + \text{Thiosulfate} \longrightarrow \text{Thiocyanate} + \text{sulfite}$$

(↓ thiosulfate leads to CN toxicity - rate-limiting step) ((non-toxic))

- We can give (Nitrates) that convert reduced $Hb-Fe^{+2}$ to oxidized metHb :

$$Hb-Fe^{+2} + NO_2 \longrightarrow Hb-Fe^{+3} + NO$$

- metHb (↑) affinity for CN than cytochrome oxidase :

$$Hb-Fe^{+3} + CN\text{-cytochrome-}Fe^{+3} \longrightarrow CN-Hb-Fe^{+3} + \text{Cytochrome-}Fe^{+3}$$

[free cytochrome ∴ No CN :)]

* How to produce metHb ($Hb\text{-}Fe^{+3}$) ?

we can give :

1. Amyl Nitrate (inhalation) , Na^+-Nitrate (IV)
   - MetHb should not ↑ more than 40%.

→ $Hb\text{-}Fe^{+2}$ + Na^+ Nitrate → Met-Hb ($Hb\text{-}Fe^{+3}$)

Amyl Nitrate

* Nitrates can cause :
  - Hypotension
  - risk of production of excess metHb.

2. Sodium Thiosulfate can be given in the presence of Sulfar Transferase.

$CN\text{-}Hb\text{-}Fe^{+3}$ + $Na_2S_2O_3$ (N=Thiosulfate) → $CN\text{-}S$ (Thiocyanate) + Na_2SO_3 + $Hb\text{-}Fe^{+3}$

if too much met-Hb this will shift the curve to the left → ↓ O_2 utilization

* so only 40% met Hb Not more is needed.

- O_2 is Not specific antidote
- Activated Charcoal is Not useful → HCN is ionized
  - MW. (not from 100-1000)

The End

Farah Amer

Drugs in Sports

- Sports Doping -

Categories of Drugs Used

- Performance-inhancing (ex. anabolic Steroids, B-Blocker.)
- Recreational (ex. Marijuana, cocaine, Heroin)

Drugs used & substances

Banned	Legal
- Anabolic Steroids	- Vitamins
- Stimulants	- Diet regimen ((carbs loading))
- B-Blockers	- Amino Acids
- Diuretics	- Depressants
- Narcotics	- Creatine (expect Banned)
- Creatine	
- GH	
- Tetrahydrogesterinone (THG)	

Anabolic Steroids

- ↑ Male Androgens ↓ Female Estogen.
- Benifits : ① ↑ Strength ((↑ Body protein Synthesis))
  ② Enhance recovery.
  ③ Build Skeletal Muscle Tissue
  (legal) → ④ Used in Medical cases where muscle growth & tissue repair is required
- Harmful effects :
  ① ♀ → Musculanizing effects, Hirsutism, Reproductive problems, lowered voice

② ♂ → ↓ facial+Body hair , ↓ sperm production , Sterility & Impotence.
③ Adolescents → Stunted Growth (premature Closure of long Bone epiphysis)
④ ↑ injuries to Tendons , ligaments & Muscles.
⑤ ↑ BP , ↑ premature Heart Diseases & Stroke
⑥ Liver disease & Cancer.
⑦ Clinical depression
⑧ Roid Rage → Aggression & Violence.

Amphetamines-like substance → Fat Burners.

Stimulants

- effect : ↑ HR ; Enhance performance → ↑ Alertness , ↓ wt , Stimulate sympathetic ANS , Mind Alerting drugs.
- ex : Amphetamines , Sympathomimetic amines , Hallucinogens , Caffeine (high dose).

Human Growth Hormone

- effect : ↑ Body Mass , ↓ Body fat Mass
  can Cause distorted physical Characteristics → (Frankenstein's Syndrome)

Creatine

- popular for 3 reasons : ① Not Considered Steroid.
  ② Safe in Reasonable amounts.
  ③ legally available in fitness Clubs.
- effect : ↑ lean Body Mass , high intensity , very Short term tasks w/ brief recovery periods.

B-Blockers

- ↑ performance → ↓ HR , ↓ Anxiety , Steadying Natural Body Tremors.
  (good for Rifle / pistol Shooting , Bowing , golf players)
- effects : Bronchospasm , CNS disturbance , Hypotension , Impotence.
- sport SE : interfere w/ high intensity , longer duration Tasks.
- Difficult to produce Dependence.

Caffeine

- CNS stimulant, Banned in Sports (>18 once).
- prolongs endurance performance → Unfair.
- ⓘ intake w/ insufficient water intake → ↑ internal Body Temp. → premature fatigue + Heat-Related illness.

Erythropoietin

- ⓘ production of RBCs, ⓘ Ability to transport O_2, ⓘ onset of Muscle fatigue & improves Regulation of internal Body Temp.

Narcotic Analgesic

- ⓘ fever & inflammation, Slow the performance (Sedative effect).
- produce Dependence very Commonly.

(ex: codeine, Heroin, opium, morphine..)

Diuretics

- used for wt. loss → for Boxers & Wrestlers (compete at lower wt.)
- SE: Nausea, impair Thermoregularity control, Blood Clotting, Stroke, ↓ Blood Volume, Muscle Cramps.

Blood Doping

- Remove 1 l of Blood (1-2 months) prior to Competition & freeze it → inject RBCs Back to Athlete Before competition (↑ O_2 Carrying Capacity & enhance performance)

---

* Decatrolin (Deca) → Anabolic Steroid, Injectable, could be detected in Body up to 18mnt In Urine ~12 month

* Dianabol → Orally effective anabolic Steroids.

* Mixing More than one Type Together "Stacking":

Decatrolin + Dianabol + AA + B-HCG (prevent Testis Shrinkage) + Tamoxifen (prevent gynecomastia)

The End

Pesticides

- pesticides poisoning can cause mortility & morbidity worldwide
- mortality depend on: Type, amounts, time of discovery & General Health.

Organophosphates

- In General have higher acute toxicity But low chronic toxicity
- most of them are Polar & water soluble.
- **Mechanism of Toxicity:**

organophosphates complex with AcetylCholinesterase enzyme leading to deactivation of the enzyme inreversibly, this results in Accumulation of Acetyl Choline in synapses → excess Cholinergic stimulation.

- elimination: detoxification by cytochrome P450-monoxygenases in the lives.
- usually metabolites are detected from 12-24 hrs post exposure.

- **Signs & symptoms:**

symptoms develop several hrs after exposure But Can occur after 5 mins after Massive ingestion.

* CNS Effects → Anxiety, Tension, Headaches, Confusions, convulsions..
* Muscarinic effects → (post-ganglionic parasymp. activity)
  → Miosis, ↑salivation (frothy secretions), Bronchial & Bladder smooth muscles contraction
* Nicotinic effects → Muscles fasiculations (cramping) / diaphragm pralysis..
* Cholinergic effects → (DUMBELS)
  - D → diarrhea
  - U → Urination
  - M → Miosis
  - B → Bronchospasm, Broncharrhea,
  - E → Emesis
  - L → Lacrimation
  - S → Salivation

* muscarinic effects:
  - Salivation
  - Lacrimation
  - Urination
  - Diarrhea
  - GI upset
  - Emesis

(SLUDGE)

- CVS → Bradycardia / Hypotension.

* The most concern ☺ toxicity is Resp. Faliure from excessive airway secretions.

- Resp → Rhinorrhea, Bronchorrhea, Bronchospasm, Cough, severe Resp distress..

* full recovery from most organophosphates exposure generally within 10days when optimum ttt is given.
* Death if untreated within 24 hrs.

- dx: ① hx.
② "Garlic odor", evidence of exposure.
③ S&S of Cholinergic effect.
④ improvement ☺ Atropine ((non-specific antidote)) or Pralidoxime.
⑤ labs: ↓↓ levels of Cholinesterase [RBC cholinesterase not plasma ① more stable ② more accurate.

ttt: [1] Gut decontamination → activated Charcol within 4hrs.

[2] Atropine → ((competitive inhibitor for post-synaptic Cholinergic Receptors))
- Muscarinic effect.
- has No effect on Muscle Weakness or Resp. Faliure (↔ Thats why we should give Pralidoxime))
- Dose: [2-4 mg (IV) → adults
  [0.015 - 0.05 mg/kg (IV) → children.
  * might be needed up to 48 hrs ((moderate toxicity))
- SE: may cause arrhythmias (ABC then give it)

[3] Pralidoxime → Specific antidote, reverse phosphorylation of the Cholinesterase
- ameliorates: m. weakness, fasiculations, LOC.
- Dose: 1-2 g → adult
  25-50 mg/kg → children.
- SE: rapid injection may cause Tachycardia, laryngeal Spasm, muscle rigidity or neuromuscular Blockade.

Carbamates

- mechanism of Toxicity :
- Reversibly Bind to Cholinesterase enzyme & inhibits it → - muscarinic - Nicotinic - CNS
- ((unlike organophosphate ~ irreversible Binding))
- less severe poisoning

- follows 1st-order kinetics , half-life = 1.30 hrs , excreted in Urine [within few days]
- Examples of Carbamates : Methomyl , Carbaryl & Aldicarb.

Signs & Symptoms :

- similar to Organophosphates ((lesser intensity & duration))

labs :

- Measuring RBC & plasma Cholinesterase are Not helpful.
((carbamates have transient effect 1-2hrs on these levels)).

- Rx :
  1. Activated Charcol...
  2. Atropine
  3. pralidoxime.

The End
Farah Amer

Alcohol & Glycols

- Alcohol is the most common single drug taken by patients visiting ER departments.
- Alcohol misuse is the leading killer of people aged 15-45 yrs.
- Neurological impairment from alcoholism depends on:
  1. Genetics
  2. Coingestion with other drugs.
  3. Trauma
  4. Amount ingested.
  5. prior Alcohol use; in non-tolerant individuals impairment might occur at concentrations as low as 50 mg/dl.
  6. Nutritional status.
  7. presence of complications from chronic Alcoholism.

- For early detection use the (CAGE) questionaire:
  1. Have you ever tried to Cutdown on drinking?
  2. Do you get annoyed about others concerns about Alcohol?
  3. Do you feel guilty when you drink alcohol?
  4. Do you use alcohol as an Eye-opener in the morning?

- spirit → 40-50% Ethanol.
  Wine → 10-20% Ethanol.
  Beer → 2-6% Ethanol.

Mechanism of Action

- Alcohol is a CNS depressant; it depresses the Reticular Activating System
  Frontal lobe → disorders of thought & Mood.
  Occipital lobe → Abnormalities in Vision
  Cerebellum → ~ In Coordination.

Absorption

- 80% in Small intestine
- 20% in Stomach.
- Anything that delay gastric emptying → Delay Absorption
  "Fatty food"
- 80-90% → occurs within 30-60 mins with food → needs 4-8 hrs.

Distribution

- water & lipid soluble.
- Can Cross the BBB, placenta & Body fluids.
- Distribution is lower in ♀ than in ♂.
- 0.6 L/kg → Adult.
- 0.7 L/kg → Child.

Elimination

- follows Zero-order kinetics
  → elimination rate is concentration dependent.
  "Hepatic Metabolism"

elimination Rates
- metabolites (7-10 g/hr)
- ↓ level (15-20 mg/dl/hr)
- chronic Alcoholics (30-40 mg/dl/hr)
  ↳ more active dehydrogen

Metabolic pathways (3 pathways)

1. Alcohol dehydrogenase

Alcohol —(alcohol dehydrogenase)→ Acetaldehyde —(Aldehyde Acetate)→ Acetic Acid.

2. Microsomal peroxidizing system
   → imp. in alcohol Metabolism at ↑↑ Concentration.

3. peroxidase - catalase system.

Bld ethanol level decreases more Rapidly at conc over 300 mg/dl → microsomal system.

Numbers that are imp.

- 1 Unit = 10 g → elevate Bld Conc of ethanol by 25 mg/dl
- Lethal dose : Adults → 5-8 g/kg
  Children → 3 g/kg
- Intoxication : 100-150 mg/dl
  (بالقياس) 80 mg/dl [>80 مخمور، <80 هادي]

* Deaths occur from Resp depression

Symptoms

- Slurred speech, ataxia, impaired cognition, dilated pupils, ..
- peds : metabolic acidosis, Hypoglycemia, hypokalemia.
- withdrawal : Autonomic Hyperexcitability, hypo K^+, hypo Mg^+
- Abstinence syndrome : . (6-8 hrs) post-drinking stops
  . But most pts are asymptomatic until 72hr
- Alcohol Hallucinosis : . develops (24-36 hrs) after cessation
  - delusions + visual, auditory hallucinations
  - give BDZ + Haloperidol.

Drug Interactions

- Drugs that can cause (Disulfiram like reaction) when taken with alcohol :
  - Metronidazol.
  - Sulfonamides & hypoglycemic agents.

- This reaction occurs due to ↑ serum levels of acetaldehyde ((acetaldehyde normally converted to acetate by the action of aldehyde dehydrogenase & the Disulfiram Blocks this enzyme)).

- CNS Depression → ((Alcohol + Sedative Hypnotics))

- prolonged Bleeding time → ((5 drinks Alcohol + Tablet of Aspirin))

- Neither Amphetamines nor Caffeine significantly improves ethanol impaired performance.

Labs

- Gas Chromatography is the method of Choice. [Specific for Ethanol]
- (Femoral) & (Jugular veins) are the Best postmortem Blood Sampling Sites.
- Blood Ethanol levels correlate with Clinical Signs.

Chronic effects of alcohol

(1 ↑ NAD+ / NADH ratio
(2 Hypoglycemia
(3 ↑ Uric acid serum conc.
(4 Acidosis (lactate accumulation → Alcohol switches metabolism from pyruvate to lactate.)
(5 Accumulation of fat in the liver.
(6 vit. deficiencies → B_1, B_6, B_{12} + Zinc, Mg
(7 predispose to Both hemorrhagic & Non-hemorrhagic Strokes.

Mgx

- ABC + Supportive care + O_2
- In Comatosed pt → give "Coma Cocktail"
  Naloxone, Thiamine, Dextrose 50.
- Chronic Alcoholics → $MgSO_4$, Thiamine, Folate, Multivitamins.
- No antidote, No Role for gut decontamination.
- Hemodialysis if ethanol levels > 500 mg/dl.

The End
Farah Amer

Note: Alcoholism
- No Control over drinking
- physically dependent.
- pre-occupation w drinking
- impaired thinking, denial.
- Taking Alcohol although adverse consequences.

Important Antidotes

* Warfarin → vit. K.
* Heparin → Protamine Sulfate.
* B-Blockers, Ca^{2+} Channel Blockers → Glucagon.
* Opioids, Narcotics → Naloxone.

* Anticholinergics → Neostigmine.
* Benzodiazepines → Flumazenil.
* Methanol → Ethanol.
* paracetamol → Acetylcysteine.
* Digoxin → digoxin immune fab
* Iron → Deferoxamine
* Ethylene Glycol → Fomepizole, Ethanol.

Forensic

Postmortem changes

Death:

The absence of the 7 vital life processes(growth,reproduction,sensitivity , movement,nutrition ,execretion and respiration).

Medically and scientifically, death is not an event, it is a process.
♂ legally defined as the ***irreversible*** cessation of function
of 3 systems:
(1) CNS
(2) RS
(3) CVS.

Types of deaths:

• There are many types of death, and it's good to know some definitions:

- **Somatic death.**
- **Clinical Death.**
- **Brain Death.**
- **Cellular death.**

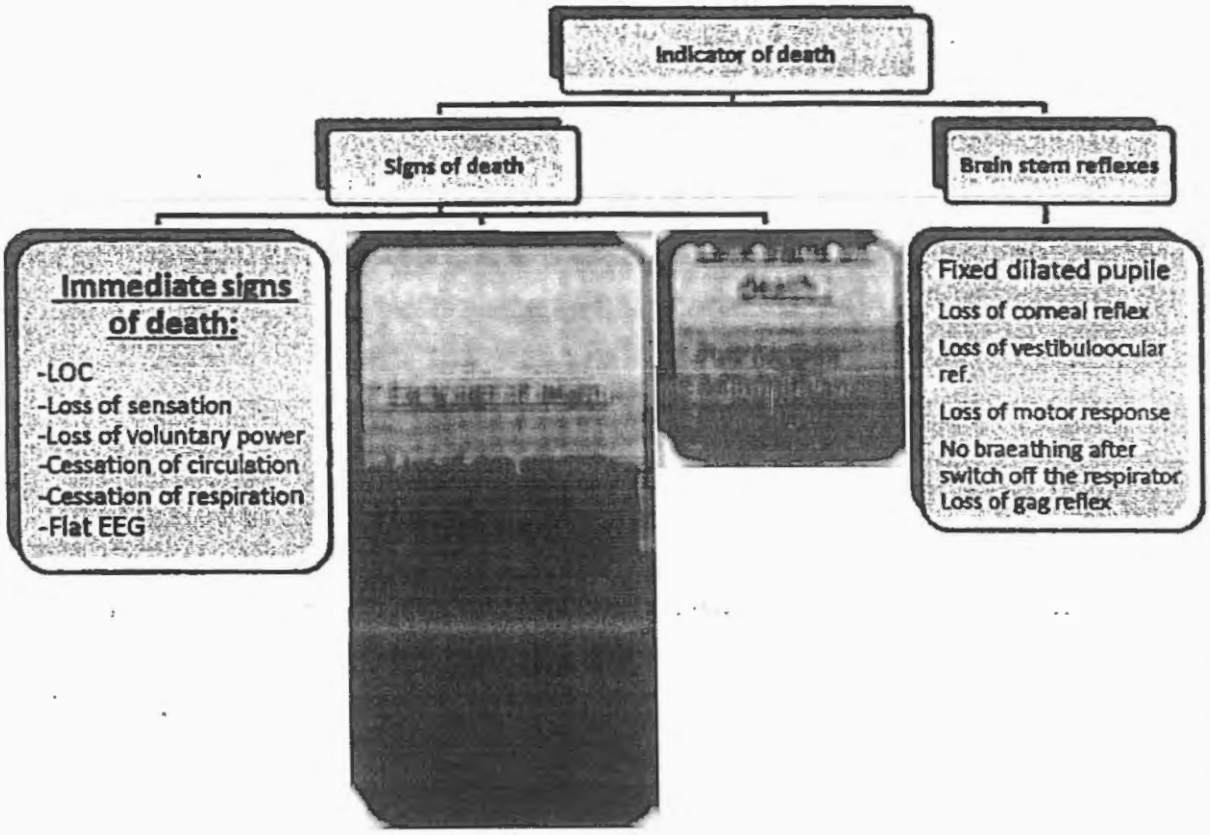
Type of death	Functional systems	Reversibility
Somatic death	No functional system	irreversible
Clinical Death	**No functional system**	**life can be brought back through CPR(4 mins)**
Brain Death	**Only brain /others systems are resuscitated**	**Somatic death occur if resuscitation has been ceased**
Cellular death	**Cessation of respiration(cellular oxidation) is followed by autolysis and decay**	

*Skin and bone will remain metabolically active and thus 'alive' for many hours and these cells can be successfully cultured days after somatic death.

* Apparent Death

• A state of ***suspended animation*** that mimics death; it occurs in:

– Electrocution
– Hypothermia
– Sun stroke
– Drowning
– Drug overdose (e.g. barbiturates)
– Head injury.



Definitions:

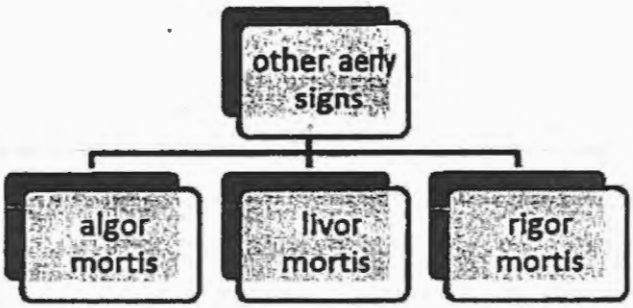
1. **mode** of death : an abnormal physiological state that pertained at the time of death: for example, 'coma', 'congestive cardiac failure', 'cardiac arrest' and 'pulmonary oedema'.

2.cause: electrolyte abnormality as a cause for cardiac arrest .

P91

3. Manner refers to the circumstantial events (suicidal ,homicidal and accident).

EARLY CHANGES			
eye	**muscles**	**skin**	**stomach**
1.Loss of reflexes. 2.mid-dilated pupils. 3.aniscoria. 4.Tache noire. 5.Incomplet closure of eyelid. 6.loss of IO tension 7.shunting and trunking of retinal vessels.	1.Primary flaccidity with complete loss of tone. 2.mild activity 2nd to release of NT from dying neurons. 3.loss of sphincter tone .	Become pale No growth of hair follicles but it become more prominent against pale skin .	Gastric contents are identified in the mouth or airways In up to 25 % of all autopsies. لكن ما بتكون هي السبب في الوفاة (اختناق).



BODY COOLING/ ALGOR MORTIS:

The **most useful indicator of time of death** during the **first 24 hours** post-ortem.

The body surface begins cooling immediately after death, followed by delay in deep organs cooling, until a heat gradient is set up between the core of the body and the surface. Delay ♉ "Temperature plateau"

Plateau = Variable: from minutes to 2-3 hours.

In practice the temperature is either measured per rectum or intra-hepatic via an abdominal stab.

P92

HYPOSTASIS / LIVOR MORTIS

Purple or reddish purple discoloration of the skin 2nd to accumulation of blood within capillaries

Starts **immediately** after death become Apparent after **2 hrs** and fixed after 8 hrs.

- May not appear at all especially in **infants, old** and **anemic** or in those who have died from **severe blood loss.**

*Sites of hypostasis Depends on the position of the body before death(1.vertical as in hanging 2. Upper limbs /chest as in drowning 3.face down with whitening around lips and mouth as in epilepsy .)

*Color of Hypostasis

- The color of hypostasis is variable and depends on the state of oxygenation at death.
- It may be masked by dark skin colours, by jaundice or by some dermatological conditions.
- Colour changes that may act as indicators of possible causes of death:

_Cherry-pink: CO poisoning.
_Dark blue-pink: Cyanide poisoning.
_Brown: Methahemoglobinemia.
_Pallor: Anemia, hemorrhage (or normal in extremes of age).

Hypostasis	bruises
Dependant areas	Any where
Well defined	Ill defined edges
Blood is retained in intact capillaries	Blood escapes through ruptured capillaries
Same level on surface	Raised
Pale over pressure areas	Red
Incision: blood flows from the cut vessel (washable)	Incision: blood coagulates in tissue

RIGOR MORTIS

Death ♉ Cessation of respiration ♉ Depletion of oxygen ♉ Less ATP ♉ Secondary anoxic process ♉ Lactic acid cell cytoplasm becomes increasingly acidic ♉ With low ATP and high acidity, the actin and myosin fibres bind together and form a gel ♉ But Unlike normal muscle contractions, the body is unable to complete the cycle and release the coupling between the myosin and actin, creating a perpetual state of muscular contraction, until the breakdown of muscle tissue by digestive enzymes during decomposition.

- It starts to develop about 2-3 hrs after death.

It is first detected in smaller muscle groups such as those around the ***eyes, mouth, jaw & fingers.***

Factors affecting timing of R.M

♉ *Environmental temperature*:

_Cold and wet ♉ onset slow, duration longer.

_Hot and dry ♉ onset fast, duration shorter.

♉ *Muscular activity before death*:

_Muscles healthy and robust, at rest before death ♉ Slow onset, duration longer.

_Muscles exhausted/ fatigued ♉ Onset rapid, esp. in those limbs being used (E.g. in someone running at time of death, lower limbs develop RM faster than upper limbs).

_Increase activity (convulsions, electrocution, lightning) ♉ Rapid onset & short duration.

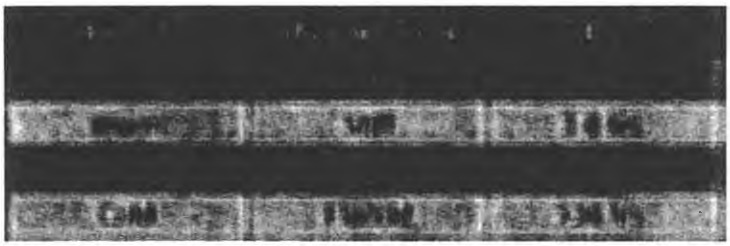
♉ *Age*:

_Extremes of age ♉ Rapid onset.

♉ *Health.*

Estimated time of death

- A crude but useful aide-memoire.



RM site	RM in iris	In heart	in Dartos muscle of scrotum:	Erector Pilli muscles attached to hair follicles
effect	Aniscoria(unequal Dilation)	Mistaken with hypertrophy	Expulsion of semen	Goose bumps اله دور بالاعتقاد باستمرارية نمو الشعر بعد الوفاة!!

Conditions Mistaken as R.M:

1.heat stiffness (electrical shock).

2.cold stiffness(freezing!!)

3.cadaveric spasm .

Rigor Mortis vs. Cadaveric Spasm

Rigor Mortis	Cadaveric Spasm
Onset delayed after death (2-3 hrs.). Duration up to 36 hrs.	Onset is instantaneous. Duration is a few hours, until it is replaced by rigor mortis.
Intensity comparatively moderate.	Intensity comparatively very strong.
Mechanism of formation: Breakdown of ATP below critical level.	Mechanism of formation unknown, but predisposing factors: Excitement, fear, fatigue, exhaustion, nervous tension, contraction of M's at time of death.
All muscles of the body are affected gradually.	Selected muscles, which were in a state of contraction at the time of death, are affected.

POST-MORTEM DECOMPOSITION

process	putrefaction	adipocere	mummification	skeletilization
definition	destruction of the soft tissues of the body by the action of bacteria and enzymes	transformation of fatty t a yellowish-white greasy, (but friable when dry wax-like substance, with a sweetish rancid odour	the dehydration or dessication of the tissues.	
period	**Starts 48-72hrs Post mortem**	**3-4wks____5/6mnths**	The time cannot be precisely stated but usually takes few weeks.	12-18 months
Criteria to occur	**1.humidity. 2.temp (21-38).retarded If <21 or >38.**	**warm, moist, anaerobic environment.** هو شرط بضل مغمور في الماء	dry heat, especially when there are air current	
Factors ↑	**1.obesity. 2.edematous decedent. 3.child except if unfed due To lack of commensal Bacteria. 4.injury__>portals of entry For bacteria.**	**Extreme moist and Anaerobic enviroment**		
Gross appearance	**1.greenish discolouration of the the anterior abdominal wall. This most commonly begins in the right iliac fossa 2.marbling_>RBC hemolysis Within capillaries. 3. skin blisters**	**Waxy with preservation Of facial features and Even injuries.**	1.leathery or parchment-like mass and tendons surrounding the bone. 2.Skin shrinkage may produce large artefactual splits mimmicking injuries.	

*** The gases produced include hydrogen sulphide, methane ،co2, NH3 and H2. The offensive odour is caused by some of these gases and by small quantities of mercaptans.**

*** adipocere develops as the result of hydrolysis of fat with the release of fatty acids which, being acidic, then inhibit putrefactive bacteria.**

***The medico-legal importance of adipocere lies not in establishing time of death but rather in its ability to preserve the body to an extent which can aid in personal identification and the recognition of injuries. The presence of adipocere indicates that the post mortem interval is at least weeks and probably several months.**

P96

DEATH

One hundred years ago, it was priests who declared a person dead. Now, doctors have taken that role.

The 7 Life Processes

(1) Movement
(2) Reproduction
(3) Growth
(4) Respiration
(5) Nutrition
(6) Excretion
(7) Sensitivity

Death

The absence of the 7 vital life processes!

Death

- Medically and scientifically, death is not an event, it is a **process .**
- **The irreversible cessation of all integrated functioning of the human organism as a whole, mental or physical**
- legally defined as the ***irreversible*** cessation of function of 3 systems:

(1) CNS
(2) RS
(3) CVS

Before the 1960's, death was diagnosed only by *cardio-pulmonary* criteria: CNS criteria are new to the list.

Types of deaths:

- There are many types of death, and it's good to know some definitions:

- **Somatic death.**
- **Clinical Death.**
- **Brain Death.**
- **Cellular death.**

Somatic death

- Somatic death is the death-- the permanent, irreversible death-- of an organism as a whole.
- In humen it is usually after brain death, as the other vital organs are unable to function without the brain. With modern technology, though, one can be brain dead but still have circulation and respiration artificially. In such a case one isn't somatically dead because other organs are still alive. Once artificial support is removed somatic death occurs, because the person is then entirely and completely inactive with regard to brain, circulation, and respiration.

Clinical Death

- **No breathing, no circulation, and no brain activity** characterize clinical death. But that's only half. The other side, the most integral part which separates clinical death from somatic death, is that clinical death begins at the very onset of the symptoms of death, say right after cardiac arrest has cause the heart to stop.
- It lasts for about four minutes, and it is the interval in which life can be brought back through CPR. After a short few minutes, death is permanent.

P99

Brain Death

- A brain deprived of oxygen survives for 3 to 7 minutes, making it the first organ to die when circulation or respiration ceases or is impeded, whatever the cause of trouble may be.
- After a few minutes, the brain can't be brought back to life by any means available today.
- This is brain death, and it's the reason why clinical death, the period in which a person can be resuscitated, is so short. Once the brain goes, the heart doesn't know how to pump and the lungs don't know how to breath.

Cellular death

- Cessation of respiration (The utilization of oxygen) and the normal metabolic activity in the body tissues and cells.
- Cessation of respiration is soon followed by autolysis and decay, which, if it affects the whole body, is indisputable evidence of true death.
- The differences in cellular metabolism determine the rate with which cells die and this can be very variable – except, perhaps, in the synchronous death of all of the cells following a nearby nuclear explosion.

- Skin and bone will remain metabolically active and thus 'alive' for many hours and these cells can be successfully cultured days after somatic death.
- White blood cells are capable of movement for up to 12 hours after cardiac arrest – a fact that makes the concept of microscopic identification of a 'vital reaction' to injury of doubtful reliability. The cortical neuron, on the other hand, will die after only 3–7 minutes of complete oxygen deprivation.
- **A body dies cell by cell and the complete process may take many hours.**

Apparent Death

- A state of ***suspended animation*** that mimics death; it occurs in:
  - Electrocution
  - Hypothermia
  - Sun stroke
  - Drowning
  - Drug overdose (e.g. barbiturates)
  - Head injury
- Suspended animation is the slowing of life processes by external means ***without*** termination!

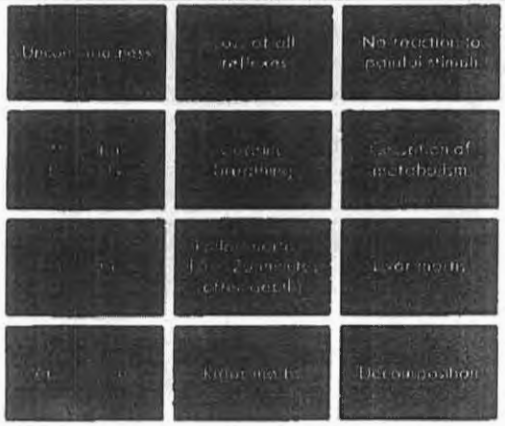
Indicators of cerebral death

1. Unconsciousness (coma)
2. Absence of spontaneous breathing.
3. Maximally dilated pupils which do not react to light.
4. Absence of vestibulo-ocular reflex
5. Absence of corneal reflex
6. Absence of motor response to painful stimuli
7. Absence of gag reflex

Diagnosing Death Is Important Medico-Legally :

- ☐ To detect the cause of death.
- ☐ To know the time of death
- ☐ For social reasons
- ☐ For organ donation
- ☐ For recognizing apparent death
- ☐ For statistical reasons
- ☐ For heritage reasons

Signs of death



The mode versus the cause of death

- **This is particularly important in** relation to the documentary certification of deaths
- The mode of death : an abnormal physiological state that pertained at the time of death: for example, 'coma', 'congestive cardiac failure', 'cardiac arrest' and 'pulmonary oedema'.
  - These offer no information as to the underlying pathological condition and should not be used as the definitive cause of death unless further qualified by the more fundamental aetiological process.

P101

Manner of death

- In addition to the mode and cause of death, here is also the **manner of death, which is not really a medical decision.** Manner refers to the circumstantial events and is a legal categorization:

1. Natural
2. Accident
3. Homicide
4. Suicide
5. Undetermined (2-5%)
6. Pending investigation

Body changes after death

- Initially these changes can only be detected biochemically as the metabolism in the cells alters to autolytic pathways. Eventually the changes become visible and these visible changes are important for two reasons:

1. Because a doctor needs to know the normal progress of decomposition so that he does not misinterpret these normal changes for signs of an unnatural death.
2. Because they can be used in determining how long the individual has been dead.

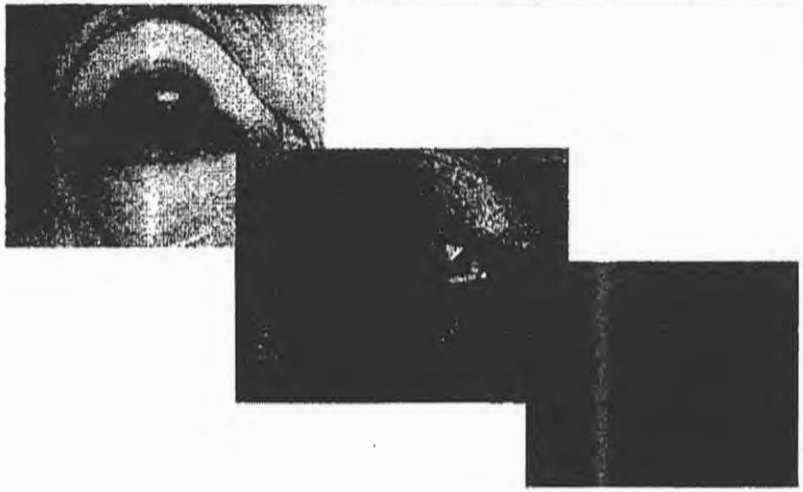
To summarize, post-mortem signs of death can be roughly estimated by:

- Early
  - Eye Changes
  - Skin changes
  - Muscles
  - Gastric
- Late
  - Algor Mortis (cooling)
  - Livor Mortis (hypostasis)
  - Rigor Mortis
- Very late
  - Decomposition
- Chemical Changes in Body Fluids (electrolytes)
- Insect Activity

EARLY CHANGES - Eye

- Loss of corneal and light ***reflexes.***
- ***Mid-dilated*** pupils.
- Irregular size and shape of the pupils (***anisocoria***).
- Eyelids usually closed ***incompletely.***
- loss of intraocular tension.
- The retinal vessels show the break up or fragmentation of the columns of blood, which is called '**trucking**' or '**shunting**'
- ***Tache noire:*** Where the sclera remains exposed to air, two black triangular spots appear at each side of the cornea (due to drying).

Tache Noire



Muscles

- The muscles rapidly become flaccid (**primary flaccidity**), with complete loss of tone, but they may retain their reactivity and may respond to touch and other forms of stimulation for some hours after cardiac arrest.
- Discharges of the dying motor neurons may stimulate small groups of muscle cells and lead to focal twitching, although these decrease with time.
- Loss of muscle tone in the sphincters may result in voiding of urine.

Skin

- The fall in blood pressure and cessation of circulation of the blood usually render the skin, conjunctivae and mucous membranes pale.
- The skin of the face and the lips may remain red or blue in colour in hypoxic/congestive deaths. The hair follicles die at the same time as the rest of the skin and there is no truth in the belief that hair continues to grow after death, although the beard may appear more prominent against a pale skin.

Stomach

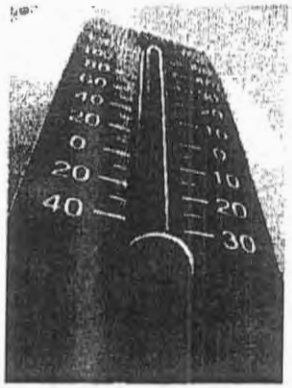
- Regurgitation is a very common feature of terminal collapse and it is a common complication of resuscitation.
- Gastric contents are identified in the mouth or airways in up to 25 % of all autopsies. The presence of this material cannot be used to indicate that inhalation was the cause of death unless it is supported by eyewitness accounts or by the microscopic identification of food debris in the peripheral airways.

P103

BODY COOLING/ ALGOR MORTIS

- **The most useful indicator of time of death** during **the first 24 hours** post-mortem.
- After death all metabolic activity ceases rapidly (muscles, liver) & circulation stops → Heat production ceases soon after death.
- The body surface begins cooling immediately after death, followed by delay in deep organs cooling, until a heat gradient is set up between the core of the body and the surface.
  - Delay → "Temperature plateau"
  - Plateau = Variable: from minutes to 2-3 hours.

- In practice the temperature is either measured per rectum or intra-hepatic via an abdominal stab.
- *The rate of body cooling:*
  - *1C/hr in summer.*
  - *1.5C/hr in winter.*



Factors affecting rate of cooling:

Body surface area	• larger surface area → speeds up cooling rate. • Children large surface area gives rapid heat loss
Edema	• slower cooling rate
Body weight	• Larger bwt slower cooling • Smaller bwt faster cooling
Clothing, posture	
Environm. Temp.	• Higher humidity: rapid cooling rate • Rapid air velocity: rapid cooling rate
Water	• rapid cooling rate • More rapid in flowing water than still water
Fulminating INFXN	• e.g. septicaemia, the body temperature may continue to rise for some hours after death.

HYPOSTASIS / LIVOR MORTIS

- After death occurs, circulation of blood ceases & subsequent movement of blood is by gravity.
- Blood accumulates in the capillaries in the dependent parts of the body → ***Purple or reddish purple*** discoloration of the adjacent skin.
- Within pressure areas such as the *shoulder blades, buttock & calves* → Discoloration will be ***pale***.
- Starts **immediately** after death.
- Apparent after **2 hrs.** and fixed after 8 hrs.
- May not appear at all especially in **infants, old** and **anemic** or in those who have died from **severe blood loss.**

P104

Sites of hypostasis

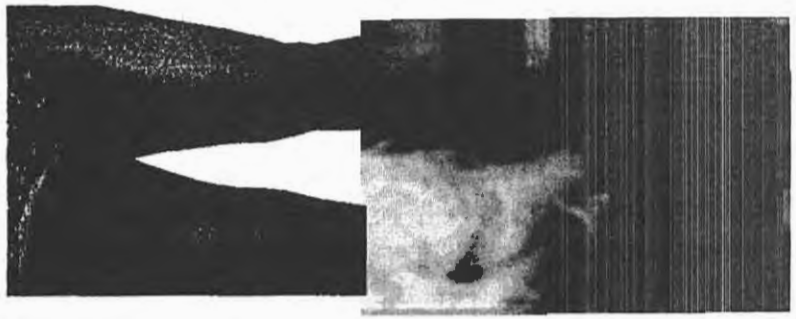
- **Depends on the position of the body before death:**

Supine

- **Shoulders, buttocks.**
- **Heels pressing against surface giving a white color (pale).**

Vertical

- Hanging Position.
- Distally in legs & feet.

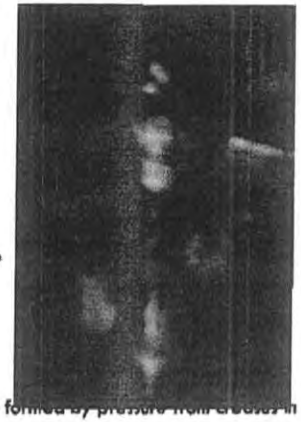


Drowning

- Chest, upper chest and upper limbs.

Face-down

- As in *epilepsy, drunken victims.*
- Whitening around nose & lips.



The linear marks are formed by pressure from creases in the blanket. The pale areas around the mouth and nose are not necessarily signs of suffocation.

Other sites

- **Heart:** Mistaken for MI
- **Lungs:** Mistaken for pneumonia
- **Intestine:** Mistaken for hemorrhagic infarction

- Once hypostasis is established it has ability to undergo subsequent gravitational shift if the body is moved into a different posture.
- This is important because changes in the position of a body after the initial development of hypostasis will result in redistribution of the hypostasis and examination of the body may reveal <u>*two overlapping patterns*</u>.

- It can also be used by forensic investigators to determine whether or not a body has been moved (For instance, if the body is found lying face down but the pooling is present on the deceased's back, investigators can determine that the body was originally positioned face up).

Color of Hypostasis

- The color of hypostasis is variable and depends on the state of oxygenation at death.
- It may be masked by dark skin colours, by jaundice or by some dermatological conditions.
- Colour changes that may act as indicators of possible causes of death:
  - Cherry-pink: CO poisoning.
  - Dark blue-pink: Cyanide poisoning.
  - Brown: Methahemoglobinemia.
  - Pallor: Anemia, hemorrhage (or normal in extremes of age).

Timing and Permanence of Hypostasis

- Hypostasis Starts from1/2 hr to many hrs after death.
- The time is so variable that it has no significant role in determining the time of death.

Medico-legal Importance of Hypostasis

- Sure sign of death.
- Cause of death.
- Position before / after death.
- Indicate if the body was moved or not after death.

Hypostasis vs. bruises

Hypostasis	Bruises (Ecchymosis)
Dependent areas	Any where
Well defined edges	Ill defined edges
Blood is retained in intact capillaries	Blood escapes through ruptured capillaries
Same level on surface	Raised
Pale over pressure areas	Red
Incision: blood flows from the cut vessel (washable)	Incision: blood coagulates in tissue

RIGOR MORTIS

- Temperature-dependent, physico-chemical change that occurs within muscle cells as a result of lack of oxygen causing the limbs of the corpse to become stiff and difficult to move or manipulate.

- Death → Cessation of respiration → Depletion of oxygen → Less ATP → Secondary anoxic process → Lactic acid cell cytoplasm becomes increasingly acidic → With low ATP and high acidity, the actin and myosin fibres bind together and form a gel → But Unlike normal muscle contractions, the body is unable to complete the cycle and release the coupling between the myosin and actin, creating a perpetual state of muscular contraction, until the breakdown of muscle tissue by digestive enzymes during decomposition.

Rigor Mortis (cont'd)

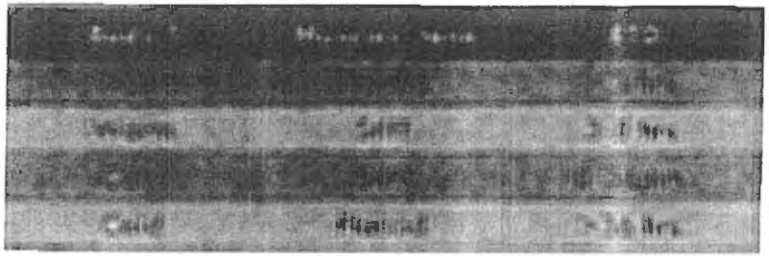
- R.M initiated when the ATP concentration falls to 85% of normal.
- It starts to develop about 2-3 hrs after death.
- Rigor develops uniformly throughout the body but it is first detected in smaller muscle groups such as those around the ***eyes, mouth, jaw & fingers.***
- Peaks in the next 6-12 hrs.
- It concludes around 36-48 hrs. after death.
- It resolves in the same order in which it develops.

Factors affecting timing of R.M

- *Environmental temperature:*
  - Cold and wet → onset slow, duration longer.
  - Hot and dry → onset fast, duration shorter.
- *Muscular activity before death:*
  - Muscles healthy and robust, at rest before death → Slow onset, duration longer.
  - Muscles exhausted/ fatigued → Onset rapid, esp. in those limbs being used (E.g. in someone running at time of death, lower limbs develop RM faster than upper limbs).
  - Increase activity (convulsions, electrocution, lightning) → Rapid onset & short duration.
- *Age:*
  - Extremes of age → Rapid onset.
- *Health.*

Estimated time of death

- A crude but useful aide-memoire.



Rigor Mortis (cont'd)

- R.M in **Iris:**
  - May affect the eyes unequal, making the pupils unequal.
- R.M in the **Heart:**
  - Contracted, stiff LV may be mistaken for LV hypertrophy.
- R.M in **Dartos muscle of scrotum:**
  - Rigor in Dartos → constricts testes and epididymis expulsion of semen.
- R.M in **Erector Pilli muscles attached to hair follicles:**
  - Goose bumps, hair stands up.

How to test for Rigor?

- It is best to test for rigor across a joint using very gentle pressure from one or two fingers only; the aim is to detect the presence and extent of the stiffness, not to 'break' it.
- If rigor is broken by applying too much force, those muscle groups cannot reliably be tested again.

Cadaveric Spasm

- Also known as **instantaneous rigor or rigidity**, or **cataleptic rigidity.**
- Rare form of muscular stiffening that occurs at the moment of death, persists into the period of rigor mortis and can be mistaken for rigor mortis.
- The cause is unknown, but usually associated with violent deaths happening with intense emotion.
- May affect all muscles in the body, but typically only groups, such as the forearms, or hands.
- Maybe seen in cases of drowning victims when grass, weeds, roots or other materials are clutched, and provides proof of life at the time of entry into the water.
- Often demonstrates the last activity one did prior to death and is therefore significant in forensic investigations, e.g. clinging on a knife tightly.

Cadaveric Spasm

Cadaveric spasm in a drowning victim: This victim grasped at some ivy as he fell into water.

Victim of suicide: The cadaveric spasm has maintained the position of his arms after the shotgun has been removed.

Rigor Mortis vs. Cadaveric Spasm

Rigor Mortis	Cadaveric Spasm
Onset delayed after death (2–3 h). Duration up to 36 hrs.	Occurs instantly. Duration unknown.
Intensity comparatively moderate.	Intensity comparatively very strong.
Mechanism of formation: Breakdown of ATP below critical level.	Mechanism of formation: Coagulation of muscle tonus (contraction) without relaxation death.
All muscles of the body are affected gradually.	Selected muscles, which were in a state of contraction at the time of death, are affected.

Conditions Mistaken as R.M

- ***Heat stiffness:***
  - Exposure of a body to intense heat (burning, high voltage electrocution, etc.) → Coagulation of muscular proteins → Muscular **shortening.**
- ***Cold stiffness:***
  - Exposure of the body to extreme cold (<-5°C) → Solidification of subcutaneous fat and muscles, freezing of synovial fluid in joints.
  - Rigor mortis halted until thawing occurs, after which it develops very rapidly.

Medico-legal Importance of R.M

- May help in time estimation.
- May help in finding the cause of death.
- May help to know the position.
- Sure sign of death.

P109

POST-MORTEM DECOMPOSITION

- In the cycle of life, dead bodies are usually returned, through reduction into their various components, to the chemical pool that is the earth.
- Some components will do this by entering the food chain at almost any level – from ant to tiger – whereas others will be reduced to simple chemicals by the autolytic enzymic processes built into the lysosomes of each cell.

- Putrefaction.
- Mummification.
- Adipocere.
- Skeletelization.

Putrefaction

- The normal **final sign** of death.
- Starts immediately after death at the **cellular level.**
- Becomes **visible** in 48-72 hrs.
- Two phenomena for putrefaction:
  - **Autolysis:** Occurs by digestive enzymes released from the cells after death.
  - **Bacterial action:** Most of them come from the bowel and Clostridium predominates (same bacteria that causes gas gangrene).
- The 1st visible sign of putrefaction is green or greenish red discoloration of the skin of the anterior abdominal wall.
  - Normally starts in the right iliac fossa.

Putrefaction

- The blood vessels provide an excellent channel for bacterial spread throughout the body ➡ Decomposition of Hb which, when present in the superficial vessels, results in linear branching patterns of brown discoloration of the skin that is called '***marbling***'.
- As the superficial layers of the skin lose cohesions, **blisters** full of red or brown fluid form in many areas. When the blisters burst, the skin sloughs off.
- Considerable **gas formation** is common and the body begins to swell, with bloating of the face, abdomen, breasts and genitals.

Marbling

P110

Putrefaction

- The increased internal pressure causes the eyes and tongue to protrude and forces bloody fluid up from the lungs and it will often leak out of the mouth and nose as 'purge'.
- In general terms, within a week or so the body cavities will burst and the tissues will liquefy and drain away into the underlying ground.
  - **Brain & epithelial tissues** are the 1st to be affected by putrefaction.
  - **Heart, uterus & prostate** may survive for longer periods.

Influences on Putrefaction

- A high environmental **humidity** will enhance putrefaction.
- **Bodily habits** of the decedent; <u>obese</u> individuals putrefy more rapidly than those who are lean.
- Putrefaction will be delayed in deaths from **exsanguination** (bleeding to death) because blood provides a channel for the spread of putrefactive organisms within the body.
- Conversely, putrefaction is more rapid in persons dying with widespread infection, congestive cardiac failure or retention of sodium and salts.

Influences on Putrefaction

- **Age:** more rapid in children than in adults, but the onset is relatively slow in unfed new-born infants because of the lack of commensal bacteria.
- **Heavy clothing** and other coverings, by retaining body heat, will speed up putrefaction.
- Rapid putrefactive changes may been seen in corpses left in a room which is well heated, or in a bed with an electric blanket.
- **Injuries** to the body surface promote putrefaction by providing portals of entry for bacteria and the associated blood provides an excellent medium for bacterial growth.

Mummification

- A body lying in **dry and warm** conditions, either climatic or in the microenvironment, may desiccate instead of putrefying.
  - **Drying & shriveling** of the tissues.
  - **Brown** in color.
- Also seen in newborn infants (sterile) whose bodies are placed in cool dry environments.
- No growth of micro-organisms

- The time required for complete mummification can't be precisely stated but it takes several weeks to months, depending on the **size** of the body (More likely in the thin individual) and **atmospheric conditions.**
- Once the changes are complete, the body will remain in that condition **indefinitely.**
- Mummification is **partial**

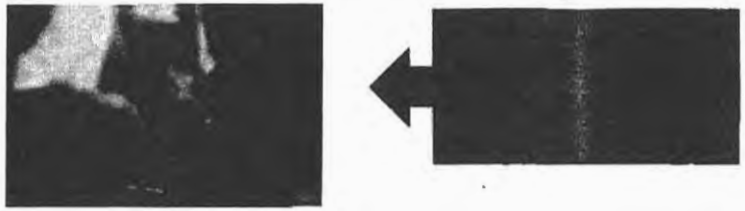
Medicolegal Importance of Mummification

- Cause of Death.
- Can detect abnormal pathology inside **deep** organs.

Adipocere

- Chemical change in the body fat, which is hydrolyzed to a waxy compound not unlike soap.
- Moisture is necessary.
- The optimum conditions for the formation of adipocere:
  - Wet, warm environment (Sometimes original body water being sufficient for adipocere).
  - Bacterial activity (C. perfiringes).
- It occurs in:
  - **Subcutaneous** fat of the *cheeks ,breast, buttocks.*
  - ***May occur*** in internal organs such as *liver, kidney & heart.*
- It needs **months** to occur, and occurs **partially.**

- 3 stages
  - In early stages: Adipocere is a pale, rancid, greasy semi-fluid material with a most unpleasant smell.
  - Later: Becomes more brittle and whiter.
  - When fully formed, adipocere is a grey, firm, waxy compound which maintains the shape of the body.



Immersion and burial

- Immersion in water or burial will slow the process of decomposition.
- Body in air will decompose twice as fast as a body in water and four times as fast as a body under the ground.
- The first change that affects the body in water is the loss of epidermis. Gaseous decomposition progresses and the bloated body is often lifted to the surface by these gases, most commonly at about 1 week but this time is extremely variable.

Medico-legal Importance of Adipocere

- Preserve the body which can permit identification after death.
- It may give conclusions about the cause of death.
- It indicates that the time interval since death was at least weeks to several months.

Skeletelization

- The environment is more important than the time in this process.
- 12-18 months: Soft tissues will be absent.
  - Tendons, ligaments, hair and nails will be identifiable for some time after that.
- After 3 yrs: the bones will be bare and disarticulated.
- In temperate zones the bones will remain solid & heavy with the preservation of bone marrow in long bones for a number of years, that can sometimes be suitable for specialist DNA analysis.
- After 40-50 years:
  - Bone surface becomes dry & brittle.
  - Marrow cavity will be empty.

ESTIMATING THE TIME OF DEATH

- Unfortunately, all methods now in use to determine the time of death are to a degree unreliable and inaccurate. They usually give vague or answers.
- The longer the postmortem interval, the less precise the estimate of the interval.

Estimating the Time of Death (cont'd)

- **Gastric emptying:**
  - Depend on type of meal and emotional status.
- **The entomology of dead:**
  - Studying insects & their maggots which infest the dead body for estimating the probable time of death.
  - Different types of insects infest the dead body at different stages after death occurs.
- **Scene markers**
  - Though unscientific, is often more accurate than determinations made by scientific means.

Estimating the Time of Death

- **Core body temperature:**
  - The best and the most commonly used.
- **Rigor mortis.**
- **Hypostasis:**
  - Complete after 6 hrs.
- **Chemical changes in vitreous.**
  - As time since death increases, so does the K conc.
- **Eye pressure:**
  - Eye balls become softer, and less fluid pressure in the first 3 hrs.

THANK YOU

Sudden death

Death that occurs within1- 24 hours from the onset of symptoms... not due to disaster

يعني ما يكون السبب حادث سير أو نتيجة كوارث طبيعية !!

- If death could not be certified by the treating physician, then it is described as sudden, unexpected or unexplained and Must be reported for medicolegal investigation.

MCC is cardiovascular disease (حتى لو ما وجدنا دليل ع ذلك في التشريح يعني negative biobsy).

Causes of sudden death

CVS	Pulmonary causes	Genitourinary Cause	Epilepsy	Fatal abdominal catastrophes
1HD (mcc)	1PE	= Ectopic pregnancy	- Status epilepticus	1. Bleeding (varices PUD CA)
ATH /HTN				Mesenteric Infarction
Aortic valve disease (ischemia of the inner zone)	2. Chest infections/ Respiratory obstruction	-Induced abortions. > hemorrhage or embolus (uterus perforation)	Fits in bed, while driving falls	3. Strangulated intestine hernia
cardiomyopathy	3.TB_>hemoptysis (rare)			4. Fulminating peritonitis: appendicitis
Sentinel changes	4Bronchial asthma			

disease	Autopsy findings	Causes of death /notes
coronary atheroma	• Lumen patency is lost • myocardial fibrosis (due to ischemia) • Recent infarcts. *Most sudden deaths from coronary insufficiency don't have MI.	

P115

	Most common sites: - first 1/3 of the LAD - Distal 1/3 of Right coronary artery - Proximal part of circumflex artery.	
2. Hypertensive Heart Disease	1.Concentric hypertrophy(lt ventricle) 2. No valvular disease or cardiomyopathies. 3. Changes in the blood vessels and organs (kidney). 4. Heart: 500-700 gm (NL: 320-380 gm). أحيانا الوزن طبيعي بس بيضل في تثخن !	1.Renal failure 2. Ruptured aneurysm 3. Cerebral hemorrhage
3. Aortic Valve Disease	d left ventricle (weighing up to 800	– lowers perfusion pressure in the coronaries esp. if associated with regurge
4. Cardiomyopathies	• Most important feature: BIG heart without HTN or valvular problems – Heart weight >700 gm	• Most common cause of sudden death in an apparently healthy athlete is (HOCM)
5.death in old age	– No specific lesions – Atrophy: tortuous coronary vessels on the epicardium – Heart size: small (HTN may have caused ventricular enlargement keeping the weight normal; 250-300gm) -brown, muscles are flabby and soft	
6. Ruptured Aortic Aneurysm	1. Atheromatous aneurysm • Most common • Site: abdominal aorta 2. Dissecting aortic aneurysm	

	• Site: whole aorta.. thoracic part • Medionecrosis causes dissection of aortic wall_ hemopericardium_ tamponade_ death 3. Syphilitic aneurysm • Site: thoracic aorta • Uncommon nowadays	
7. Ruptured Cerebral Aneurysm	In case of SAH look for the site of aneurysm : 1. at site of bifurcation. 2.anterior circulation >post.one . 3.MCA more than other due to larger diameter .	• Spontaneous rupture (circle of Willis A.) – Young-middle aged adults • The rupture of a Berry aneurysm causes of death in young child bearing f>m • Vascular malformation (children)

*Bridging

• Frequent cause of sudden death among **young age**

•def : Presence of coronary blood vessels deep in the myocardium (NL: epicardium)

• Myocardial contraction compromises the coronary blood flow resulting in sudden death.

. Chest infections

• H. influenza:

– Fulminating epiglottitis (– Pediatric age group)

• Diptheria:

– Laryngeal obstruction.

Bronchial asthma :

May die suddenly without being in an acute attack with unknown mechanism !!

*suspected cause of death in **negative biopsy** :

1.electrolytes abnormality

2.arrythmia.

3.epilepsy.

4.Poisoning/toxins.

Sudden Death

WHO definition

- Death that occurs within 24 hours from the onset of symptoms
- Due to natural causes
  - Death within 24 hrs from an RTA is NOT considered to be sudden death

- Some physicians accept sudden death to be within 1 hr from the onset of symptoms
- Many jurisdictions believe that death may only be certified by an attending physician who has been treating the deceased within the past 14 days and is satisfied that the death was caused by a potentially lethal disease which he was aware of

- If death could not be certified by the treating physician, then it is described as sudden, unexpected or unexplained
- Must be reported for medicolegal investigation

Immediate Cause of Death

- Almost always found in the **cardiovascular system**
- Although topographically the actual lesion may not be found in the heart or great vessels
- Heart disease; aortic aneurysm
- Massive cerebral hemorrhage, SAH
- Ruptured ectopic pregnancies
- Hemoptysis, hematemesis, PE

Causes of sudden death

- Cardiovascular causes
- Pulmonary causes
- Fatal abdominal catastrophes
- Genitourinary system causes
- Epilepsy

P121

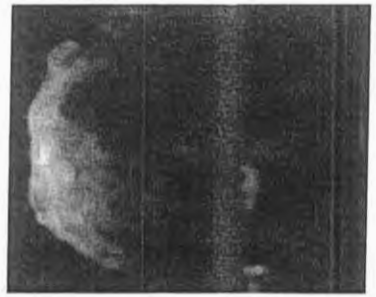
Cardiovascular

Ischemic Heart Disease (IHD)

- The most common cause (West)
  - Coronary ATH
  - HTN
  - Aortic valve disease
  - Cardiomyopathies
  - Death in old age

1.Coronary atherosclerosis

- The most common cause of IHD
  - Mechanism: Stenosis of one or more major branches of the coronary arteries by atheromas



Coronary Atheromas

- Complications:
- Ulcerated plaques may rupture→
  - Open end may face upstream: valve - like obstruction
  - Open end may face downstream: obstructing smaller branches or bifurcation sites
- Hemorrhage:
  - Subintimal hemorrhage→ sudden reduction in coronary blood flow
- Coronary thrombosis

Sites of predilection

- Most common sites:

  - first 1/3 of the LAD

  - Distal 1/3 of Right coronary artery

  - Proximal part of circumflex artery

Autopsy Findings

- Lumen patency is lost
- Areas of myocardial fibrosis (due to ischemia)
- Recent infarcts

Causes of death in Coronary Insufficiency

- Autopsy: severe, long-standing stenosis sometimes with foci from a ruptured plaque or subintimal hemorrhage
- Most sudden deaths from coronary insufficiency don't have MI
- Most common cause of death post MI is arrhythmias (due to ischemia of pacemakers and conducting system of the heart) ⇨Vfib, Afib, cardiac arrest and ectopic beats

2. Hypertensive Heart Disease

- The silent killer
- Usually coexists with coronary stenosis, but may be pure
- Autopsy:
  - Concentric hypertrophy (systemic HTN→ left ventricular hypertrophy)
    - × No valvular disease or cardiomyopathies
  - Changes in the blood vessels and organs (kidney)
  - Heart: 500-700 gm (NL: 320-380 gm)
    - × Sometimes overall weight is normal yet there is relative Lt. ventricular thickening

Causes of Death in HTN

- Causes death due to:
  1. Renal failure
  2. Ruptured aneurysm
  3. Cerebral hemorrhage
- Relative ischemia of the inner zone of the myocardium is the cause of death in HTN and aortic valve disease

3. Aortic Valve Disease

- Most common: Idiopathic calcific aortic stenosis
- Rheumatic heart disease (mitral valve) ⇨ rare
- Usually elderly men
- Mechanism:
  - lowers perfusion pressure in the coronaries esp. if associated with regurge
- Autopsy:
  - Enlarged left ventricle (weighing up to 800 gm)

4. Cardiomyopathies

- Most important feature: BIG heart without HTN or valvular problems
  - Heart weight >700 gm
- 4 types: Dilated, Hypertrophic, Constrictive, Obstructive
- Most common cause of sudden death in an apparently healthy athlete is Hypertrophic Obstructive Cardiomyopathy (HOCM)
- In old athletes: Atherosclerosis

5. Death in old age

١٧

- Autopsy:
  - o No specific lesions
  - o Atrophy: tortuous coronary vessels on the epicardium
  - o Heart size: small (HTN may have caused ventricular enlargement keeping the weight normal; 250-300gm)
  - o Heart: brown, muscles are flabby and soft

Bridging

١٨

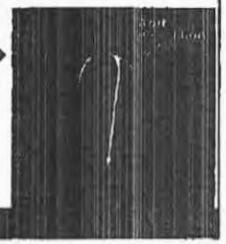
- Frequent cause of sudden death
- Presence of coronary blood vessels deep in the myocardium (NL: epicardium)
- Myocardial contraction compromises the coronary blood flow ⇨ sudden death

Figure 3.2 "Bridging" of left anterior descending coronary artery.

6. Ruptured Aortic Aneurysm

٢٠

- The most frequent extracardiac cause arising in the CVS (aorta or cerebral vessel)
- 3 types of AA:
  1. Atheromatous aneurysm
     - Most common
     - Site: abdominal aorta
  2. Dissecting aortic aneurysm
     - Site: whole aorta.. thoracic part
     - Medionecrosis causes dissection of aortic wall→ hemopericardium→ tamponade→ death
  3. Syphilitic aneurysm
     - Site: thoracic aorta
     - Uncommon nowadays



7. Ruptured Cerebral Aneurysm

- Spontaneous rupture (circle of Willis A.)
  - Young-middle aged adults
- The rupture of a Berry aneurysm causes of death in young child bearing females more than males

Autopsy Findings

- Subarachnoid hemorrhage
- Aneurysm location:
  - Anterior circulation > Post.
  - Bifurcation sites (mostly)
    - MCA & post. Communicating artery
    - Bifurcation of basilar arteries
    - On the MCA in sylvian fissure
    - On the anterior communicating artery
    - Where post. Communicating artery joins the posterior vessels
  - Usually multiple with usual diameter of 3-8 mm
- Vascular malformation (children)
  - Angioma
  - AV anastomosis

- Usual point of bleeding is in the Circle of Willis
- Hemorrhage is more dense over the base of the brain

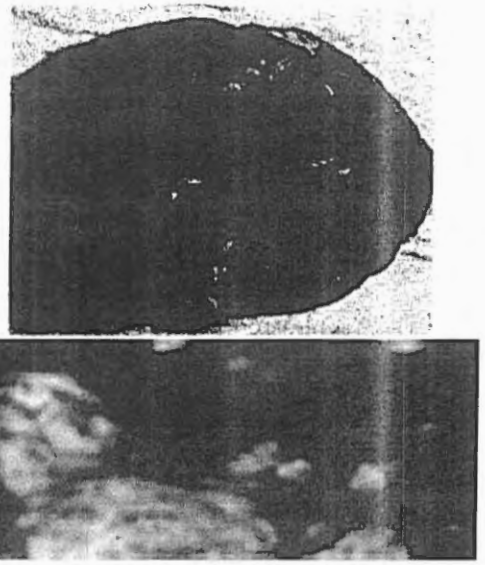


Figure 3.9 (A) Massive subarachnoid hemorrhage from ruptured aneurysm of right middle cerebral artery. (B) Berry aneurysm

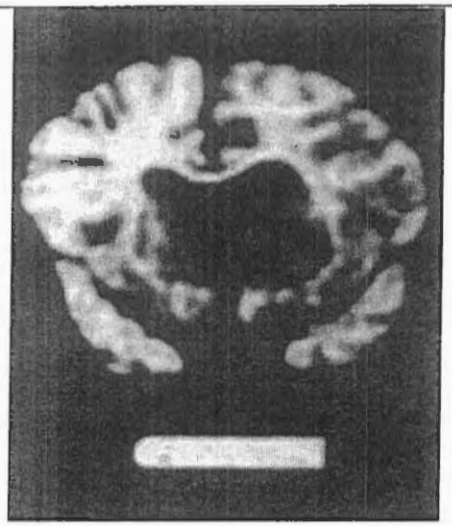


Figure 3.10 Primary intracerebral hemorrhages involving (A) basal ganglia with rupture into ventricular system (*continued*).

Pulmonary

٢٥

1. Pulmonary embolism
2. Chest infections/ Respiratory obstruction
3. TB (hemoptysis) ⇨ rare
4. Bronchial asthma

1. Pulmonary Embolism

٢٦

- Old age
- Immobility
- Surgical operations
- Obese
- DVT

2. Chest infections

٢٧

- H. influenza:
  - Fulminating epiglottitis
  - Pediatric age group
- Diptheria:
  - Laryngeal obstruction

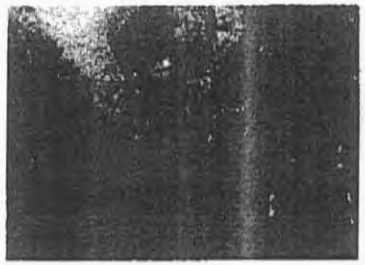
3. Bronchial Asthma

٢٨

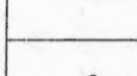
- May die suddenly without being in an acute attack
- Mechanism (unknown):
  - Hypoxia & respiratory acidosis→ Increases myocardial irritability
  - Drugs (theophylline)→ VFib

Fatal Abdominal Catastrophes

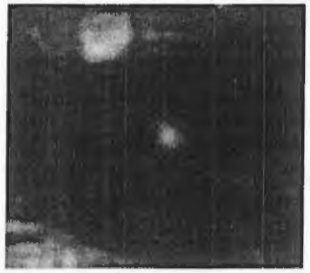
1. Bleeding
   - Esophageal varices
   - Duodenal ulcers
   - CA stomach or esophagus→ erosion of blood vessel
2. Mesenteric infarction
   - By emboli originating from the aorta and its branches or in situ formation of thrombi



Fatal Abdominal Catastrophes



3. Strangulated intestine: hernia



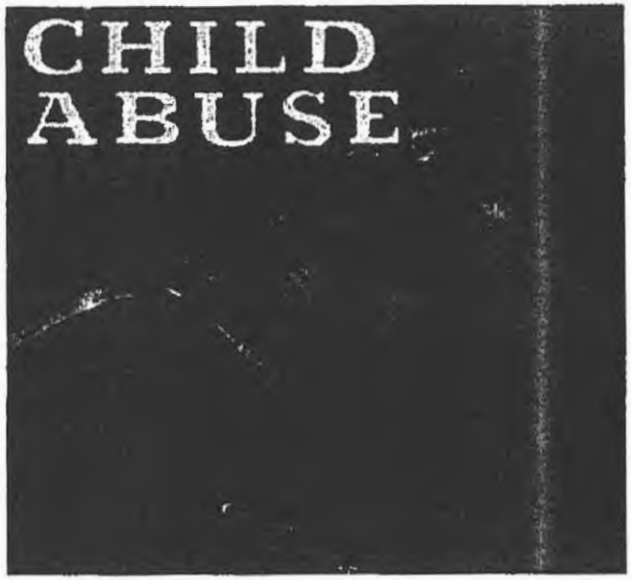
4. Fulminating peritonitis: appendicitis

Genitourinary system

- Mostly related to pregnancy
  - Ectopic pregnancy
  - Induced abortions→ hemorrhage, air embolus, tract perforation

Epilepsy

- Status epilepticus
- Fits in bed, while driving, falls
- Autopsy: search for bites
- Negative autopsy: epilepsy is an acceptable cause of death

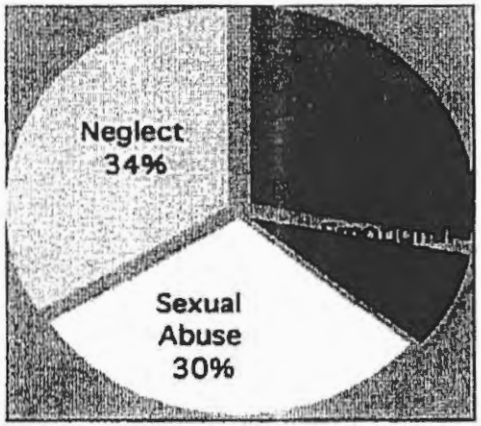


Definition of Child Abuse

"The physical or mental injury, sexual abuse or exploitation, negligent treatment, or maltreatment of a child under the age of 18 by a person who is responsible for the child's welfare under circumstances which indicate that the child's health or welfare is harmed or threatened."

Types of Child Abuse

- physical abuse
- sexual abuse
- emotional abuse
- neglect



Physical Abuse

Physical abuse is any non-accidental injury to a child under the age of 18 by a parent or caretaker. These injuries may include beatings, shaking, burns, human bites, strangulation, or immersion in scalding water or others, with resulting bruises and welts, fractures, scars, burns, internal injuries or any other injuries.

Corporal Punishment

• **Corporal punishment of children --- in the form of hitting, punching, kicking or beating --- is socially and legally accepted in most countries. In many, it is a significant phenomenon in schools and other institutions and in penal systems for young offenders.**

PSYCHOLOGICAL MALTREATMENT
Definition

- **Psychological Neglect** - the consistent failure of a parent or caretaker to provide a child with appropriate support, attention, and affection.

- **Psychological Abuse** - a chronic pattern of behaviors such as belittling, humiliating, and ridiculing a child.

Emotional Abuse

- **Emotional abuse includes the failure of a caregiver to provide an appropriate and supportive environment, and includes acts that have an adverse effect on the emotional health and development of a child.**

- **Such acts include restricting a child's movements, denigration, ridicule, threats and intimidation, discrimination, rejection and other nonphysical forms of hostile treatment.**

Neglect

- **Neglect refers to the failure of a parent to provide for the development of the child – where the parent is in a position to do so – in one or more of the following areas: health, education, emotional development, nutrition, shelter and safe living conditions.**

- **Neglect is thus distingulshed from circumstances of poverty in that neglect can occur only in cases where reasonable resources are available to the family or caregiver.**

CHILD SEXUAL ABUSE
Definition

Child sexual abuse is the exploitation of a child or adolescent for the sexual gratification of another person.

Goals.....

- To assess the child's safety
- To reassure the child and family
- To obtain or refer for counseling if indicated
- To document findings in such a way that information can be effectively and accurately presented in legal settings, if required
- To help to ensure the well being of the child

CHILD SEXUAL ABUSE

- All children who are suspected victims of child sexual abuse should be offered a medical evaluation. The timing and detail of the examination should be based on specific screening criteria developed by qualified medical providers.

Forensic Examination for Victims of Sexual Violence :

consent

History

Physical Examination

general examination

genito-anal examination

Sample collection

Documentation and reporting

History

What signs to look for
What samples to take
How to interpret findings
Routine background
Medical
Gynaecological
Sexual
What happened

The victim should not be asked to describe the assault repeatedly

General Examination

Bruises and contusions (e.g. inner aspect of thighs, scalp, face, lips);

Lacerations (e.g. scalp, forearm);

Ligature marks (e.g. ankles, wrists and neck);

Pattern injuries (i.e. fingertip marks, scratch marks, bite marks, factitious self-inflicted injuries)

General Examination

General appearance
Upper arms, forearms and hands
Face, ears, lips
Scalp
Neck
Breasts
Abdomen
Thighs and Legs
Hips and Buttocks

Genito-anal Examination

Inspection, labial traction
Swabs
Speculum
Anal +/- digital +/- proctoscope

Forensic Specimens

Vulval / vaginal / endocervical swabs
Buccal swabs – for DNA profiling Other swabs (e.g. anal, oral, breasts)
Fingernail (clipping / scraping)
Pubic hair
Clothing / debris
+/- Toxicological samples (blood, urine)

Thank you

Oral swab: up to 1 day (usually few hours
Drugs and alcohol:
blood up to 4 days (usually half-day)
urine up to 7 days
Rectal swab: 3 days (usually 1 day)
Vaginal swab: up to 7 days (usually < 72 hours)
Skin swab: before washing
Dry material (panties): before washing

P133

Introduction to wounds

Medically

1.Mechanical
- **A)DUE TO BLUNT FORCE**
- Abrasion
- Contusion
- Laceration
- Fracture and dislocation
- **B)DUE TO SHARP FORCE**
- a)Incised wound
- c)Stab wound
- **C.FIREARM WOUNDS**
- a) Firearm wound

2.Thermal
- DUE TO COLD-frost bite ,immersion foot
- DUE TO HEAT-burns,scald

3.Chemical: corrosive acid ,corrosive alkali
4.physical- electricity .lightning,Xray.
5.explosions

Classification of injury

Legally

- 1.SIMPLE
- 2.GREVIOUS (offensive,intended)

Medicolegally

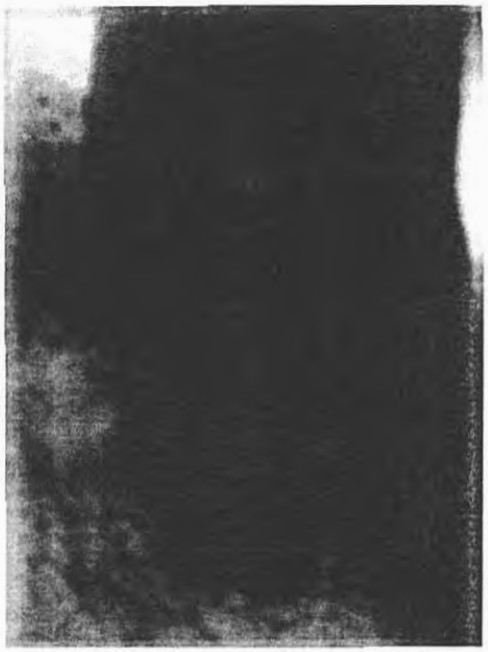
- 1.SUICIDE
- 2.HOMICIDE
- 3.ACCIDENT
- 4.FABRICATED
- 5.DEFENCE

Abrasion

- destruction of only superficial layer of epidermis,a thickness of 1.6mm.
- Bleed very slightly
- Heal very rapidly
- Leave no scar
- **Types of abrasions:**
- Scratch or linear abrasion-has length but no significant width.eg by pin, thorn, nail etc. very sharp objects
- Graze(sliding,grinding abrasion)-longitudional parallel lines. by rough surface in contact with a broader surface of skin, eg. RTA
- Patterned abrasion (pressure and impact abrasions)- thumb mark in strangulation, ligature mark in hanging, wheel mark of tyre,teethbite mark.

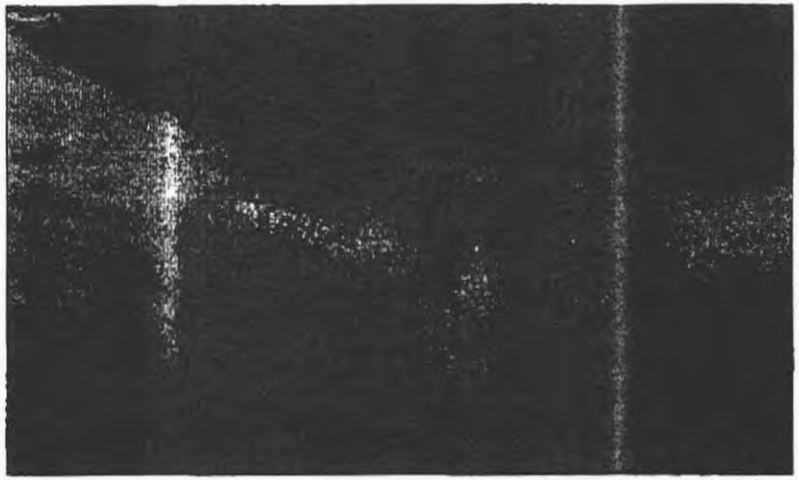
- **Age of abrasion by color change:** exact age cant be determined
- Red color- fresh
- Red scab- 12-24 hours-by drying of blood and lymph
- Reddish brown scab- 2 to 4 days
- Healing from periphery- 4 to 7 days,dark brown
- Complete healing- 10 to 14 days
- Seperation of scab- 10 to 14 days

- **Medicolegal importance:**
- Identification of object
- Direction of injury
- Time since injury
- Possibility of internal injury
- Somtime erosion by ants look like abrasion.d/d-ants produce abrasions that are brown,irregular margin,commonly at mucocutaneous junction at eyelids,nostril,mouth,axilla.By a hand lens: show multiple cresent shaped,sand like bite marks.

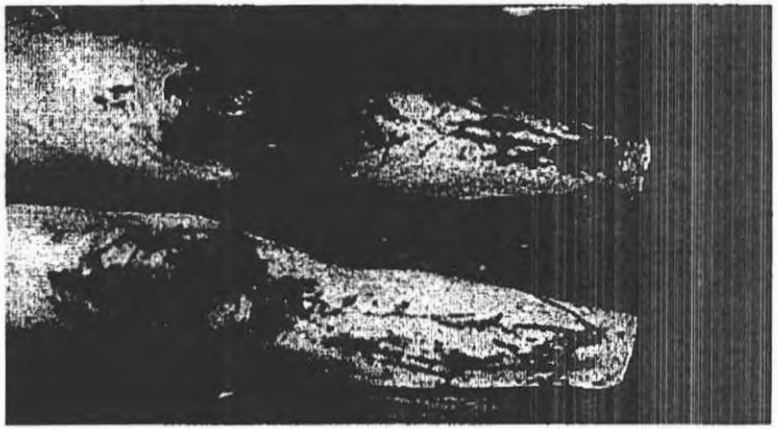


- **Difference:**
- **Antemortem abrasion**
- has Moist surface
- Bleeding present
- On drying scab formation,scab slightly raised
- Blurred margin
- Inflammation present
- Intravital reaction and congestion seen
- **Postmortem abrasion**
- Dry surface
- No bleeding
- No scab
- Sharply defined margin
- Inflammation absent
- Not seen

Abrasions from scraping against a rough surface during a fall.



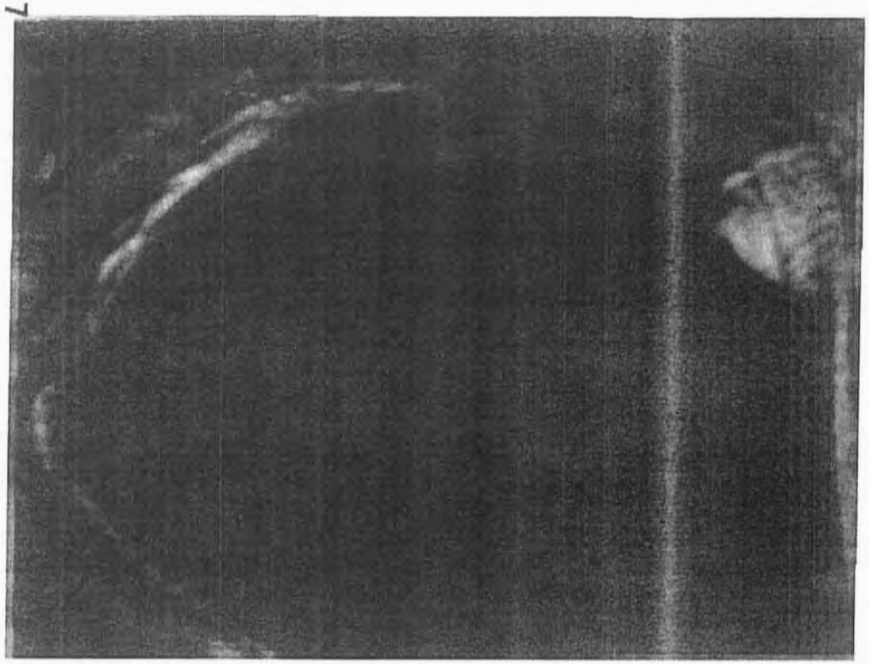
Extensive abrasions caused by stumbling, drunk and naked, against furniture. The dark leathery appearance is due to
post-mortem drying of the damaged areas of skin



Contusion

- Surface injury to the skin and sub-cutaneous which leads to an effusion of blood into tissues
- usually caused by blunt trauma.
- Appears 1-2 hours after injury.
- may take the shape of weapon eg: railway tract appearance.
- Children, old, obese women bruise easily.
- Mongolian spot shouldn't be confused with bruise.
- Contusion may be also in the internal organs and muscle.
- Gravity shifting of bruise may occur in bruises occuring late after death happens.

P137



- A **Mongolian spot**, also known as "Mongolian blue spot", "congenital dermal melanocytosis", and "dermal melanocytosis is a benign, flat,congenital birthmark with wavy borders and irregular shape.

- **Color changes in a bruise:**
- 1st day- red
- 2nd day- 3rd day -bluish
- 4th day- brown (haemosiderin)
- 5th-6th day- green(haematoidin)
- 7th-12th day- yellow(bilirubin)
- 13th-15th day ,2 weeks – normal
- Subconjunctival Hemorrhage do not undrego colour change.

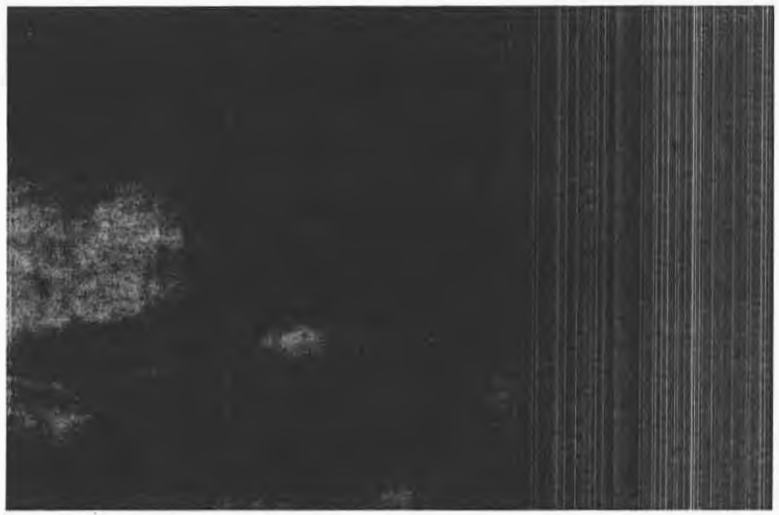
- **ML aspect of contusion:**
- Patterned bruise-Identification of weapon,ligature,vehicle
- Degree of violence from size
- Time since injury
- Purpose of injury
- Homicidal, suicidal, accidental.Position of assailant where his arms grasp the victim.

- **Difference between antemortem and postmortem bruise:**
- **Antemortem contusion**
- Swelling present
- Color changes present
- Epithelium abraded
- Clotted blood in tissue present
- **Postmortem contusion**
- Not present
- Not present
- Not present
- Not present

- **Difference b/n artificial and true bruise**
- **Artificial bruise**
- By juice of marking nut, calotropis or plumbago
- At exposed accessible site
- Dark brown colour
- Shape irregular
- Margins well defined and regular
- Itching present
- Positive chemical test
- **True bruise**
- Trauma
- Anywhere
- Typical colour changes
- Usually rounded
- Not well defined,diffuse,no vesicles
- Absent
- negative

P138

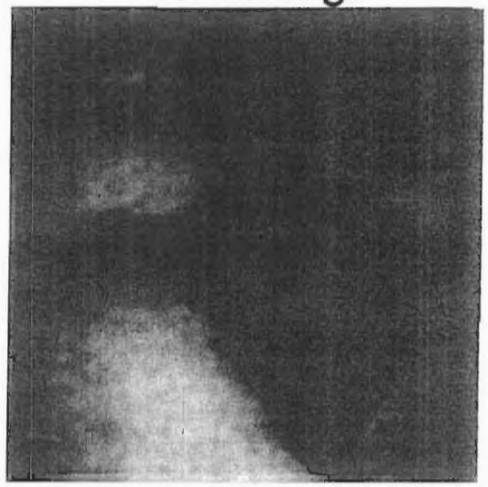
Patterned intradermal bruise on the forehead due to a
fall onto ribbed ceramic tiles.



Bruising of the upper arm. The pattern of these bruises
is typical of forceful gripping. Small abrasions from fingernails are
also seen.

P139

Recent bruising of the abdominal wall and scrotum due to kicking.



Typical 'railway-line' bruises caused by a wooden rod.
Note that the centre of the parallel contusions is unmarked.

Lacerated wound

- Lacerations are the blunt force injuries in which the skin and the underlying tissues are torn apart due to application of force.

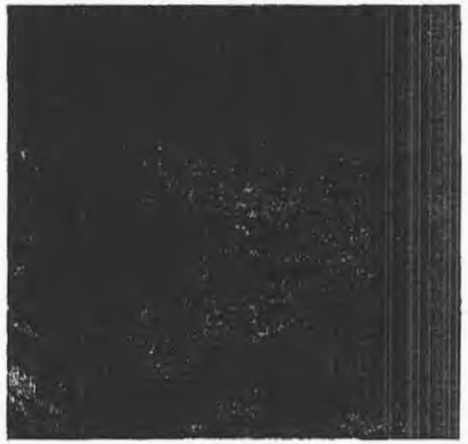
- **Characteristics**
- The edges of wound are irregular, ragged and often bruised
- Margins are often abraded due to impact of weapon
- Strands of the tissues **bridge** across the deeper parts of a laceration
- As the blood vessels are crushed usually external hemorrhages may not be marked
- Foreign material may be found as well

- **Types of Lacerations**
- **1. Split Lacerations**
- Crushing of the skin and subcutaneous tissues between two hard objects, splits them, producing split lacerations (perpendicular impact).
- Example includes on the face, scalp, hands and lower legs.
- **2. Stretch Lacerations**
- Overstretching of the skin may tear it, producing a flap of skin in the direction of injury. It results due to tangential impact.
- Example is of a laceration on scalp when it hits windscreen in an accident or a laceration due to kicks by a hard boot which raises a skin flap.
- **3. Avulsions**
- Separation of skin due to some grinding compression of the tissues, e.g. a wheel passing over a limb (de-gloving of skin).
- **4. Tears**
- Irregularly directed impact with some blunt object can cause actual tearing of the skin. It is the flaying off. E.g. blows from broken bottles.
- **5. Chop Lacerations**
- These are the lacerations produced by a weapon with sharp heavy edge, such as an axe(فأس), or a hatchet(بلطة). Margins show abrasions and bruising, these are usually homicidal.

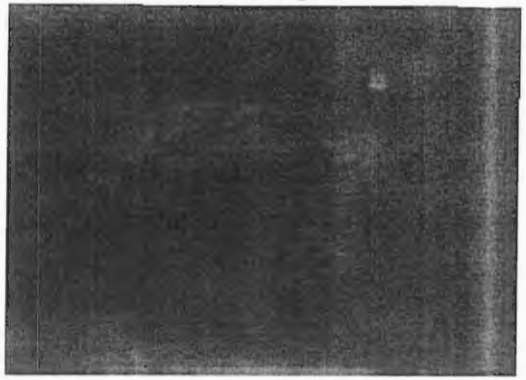
Lacerations	Incised Wounds
Hair and hair bulbs are crushed	Hair and hair bulbs are not crushed
Edges are bruised	Edges are not bruised
Base of wound has bridging across muscle fibers	No bridging

- **Forensic Importance of Lacerations**
- Lacerations are generally accidental or homicidal
- Distribution and shape may help in forensic reconstruction of events
- Trace matter may be found in lacerations

Multiple lacerations from a blunt steel bar. These were
initially mistaken by the police for axe wounds. The abraded or
crushed margins can be easily seen.



Laceration of an arm of a pedestrian struck by a car.
The impact has been oblique, causing a flap of skin to tear away to the right.



P141

- **ML importance:to find homicidal,accidental or suicidal**
- Homicidal, anywhere in the body, deep
- Suicidal- multiple, superficially, usually in the left hand
- Accidental- anywhere
- Edges of the wound indicate: antemortem or postmortem, sharp or blunt weapon.

Incised wounds

- **Incised wound**:(cut,slash,slice)
- Clean cut through tissues ,usually skin and subcut. By sharp edged or cutting weapon, eg. knife, sword, glass.
- Edges are smooth, clean cut and everted and no bruising along the edges.
- Linear wound.
- Broader than the edge of weapon
- **Length is greater than depth and breadth.**
- Edges may be inverted in case of underlying muscle attached to skin, eg. scrotum.
- All tissues are clearly divided and there **is no tissue bridging**
- As the vessels are cut, bleeding is **profuse** even in small incised wounds
- At the commencement, the tissues are more deeply cut and tails off at the end. This indicates the direction of the wound.
- If sharp weapon enters obliquely, one margin of wound is beveled and the other overhangs, indicating the direction

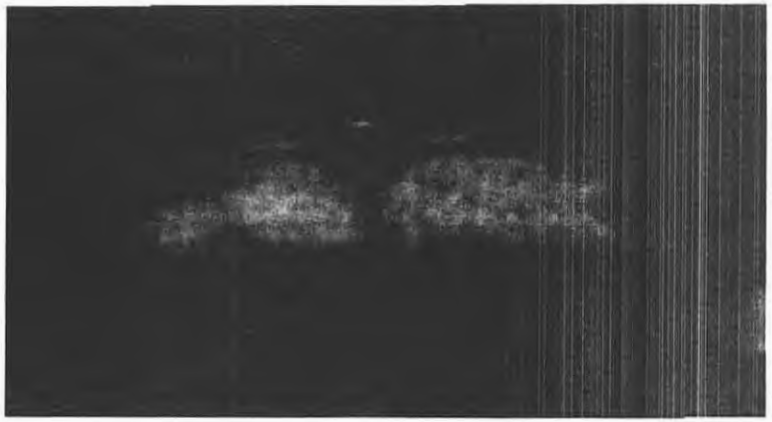
Difference between incised wound
Antemortem
Bleed freely and profusely
Arterial spouting present
Blood is clotted
Edges gape
Inflammation present
Serum serotonin and histamine increased
Postmortem
Very slight or no hemorrhage
Not present
Not clotted
Edges closely
Not present
Not raised

- **Difference between suicidal and homicidal cut-throat wounds**
- **Suicidal**
- Left side of neck,passing across the throat,usually in rt handed
- Level above thyroid cartilage
- Multiple,superficial,rarely single
- Edges usually ragged,due to overlapping
- Hesitation cuts present
- Defence wound absent
- Weapon usually present
- Clothes not torn or damaged
- Circumstancial evidence, quite place
- **Homicidal wounds**
- Usually on both sides
- On or below thyroid cartilage
- Multiple .cross each other at a deep level
- Sharp and clean cut,bevelling may be seen

Stab (puncture wounds)

- A stab wound is produced by thrusting of any pointed (sharp or blunt) object into the body so that the **depth** is the greatest dimension of the wound.
- Examples include knives, ice pick, dagger, iron bar, scissors, etc.

Incised wound to the flank; it is clearly longer than it is depth



- **Types**
- **1. Perforating Stab Wounds**
- When the stab wound also makes an exit
- **2. Penetrating Stab Wounds**
- When a body cavity, like abdomen or thorax, is penetrated
- **3. Concealed Punctured wounds**
- Especially in the cases of infanticide, i.e. by inserting needles in the anterior fontanellae or nape of neck.

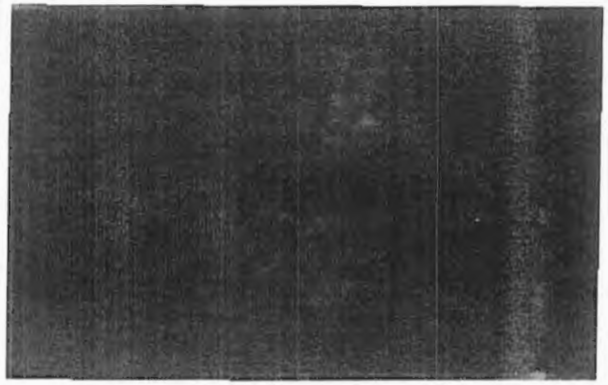
- **Characteristics of Stab Wounds**
- **1. Entry Wound**
- Generally it is bigger than the exit. It may be:
- Wedge shaped
- Elliptical
- Rounded
- Cruciate
- Irregular
- Repetition of a stab wound without complete withdrawal, may show different pattern.
- **2. Margins**
- Margins may show effects of hilt.
- **3. Depth and Direction**
  4. Exit Wound
- If any, it corresponds to the tip of the weapon

P143

- **Continue Features of stab wound:**
- Aperture is usually smaller than the weapon due to elasticity of the skin
- Depth is greater than breadth and length.
- Very little external hemorrhage but profuse internal hemorrhage
- Shape- Wedge shaped with knife, elliptical with dagger, rounded with needle, slit-like opening with screw driver,
- Margins of entry wound are clean and inverted,
- Margins of exit wound are small and everted
- Direction determined by line joining entry and exit wounds or X-ray after radio-opaque dyes.

- **5. Scissors stabs**
- Z shaped injuries are seen
- **6. Gaping of Wound**
- Wound is slightly shorter than the weapon width, only when wound is inflicted across Langer's lines.
- **7. Scrimmage Enlargement**
- Extension of the wound due to motion of the weapon or body against the cutting edge.

A complex stab wound where all three injuries are caused by a single action. The first entry is in the right breast; there is an exit wound in the middle and a re-entry wound over the centre of the chest.

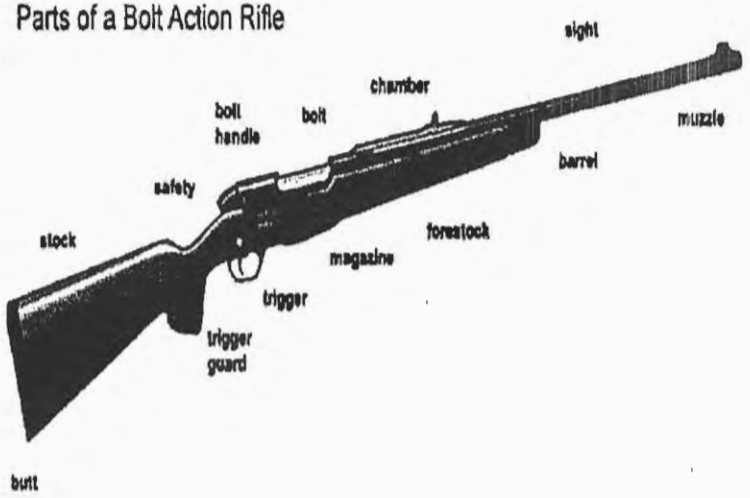


- **ML(medical legal) importance:**
- Nature of weapon
- Direction of wound
- to find Suicidal, homicidal or accidental

GUNSHOT WOUNDS

GUNSHOT WOUNDS

Parts of a Bolt Action Rifle



Type of firearms :

1. smooth barrel → shotguns

2. Grooved barrel → rifled weapons

- Firearm injuries can be classified according to range into :

1. **Firm Contact** → muzzle is pressed against the skin when fired

2. Loose **contact** → muzzle of the gun is held a short distance from the skin , approx. 0- 4 inches away from handguns)

3. **Near contact**→ defined by the presence of stippling "powder tattooing" on the skin surrounding the entry wound
4. Intermediate
5. Distant

The factors that can affect the amount and distribution of gunshot on skin include:

1. firing distance
2. length and diameter of the firearm barrel
3. characteristics of the gunpowder
4. angle between the firearm barrel and target
5. the environment (wind)
6. type of clothing
7. characteristics of the target (tissue type)

Basic features of firearm wounds

First, Entrance wound

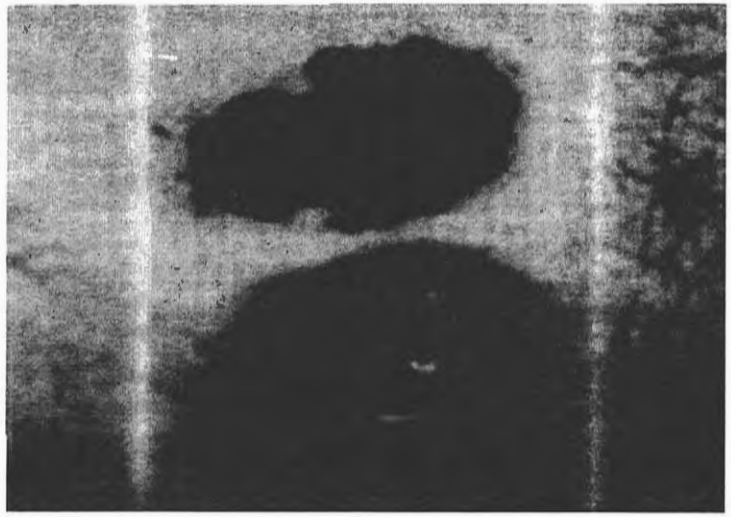
- Round or oval central defect with an abrasion collar, caused by unburned powder and small metal fragments striking the skin
  [if the bullet impact is perpendicular to the skin surface, it will be round, but if it hits at an angle, the abrasion collar will be as an eccentric hole]

- Diameter of the wound is usually smaller than the bullet. This is because the skin is elastic and it retracts after the bullet enters the skin.

- Underlying tissues will not protrude.

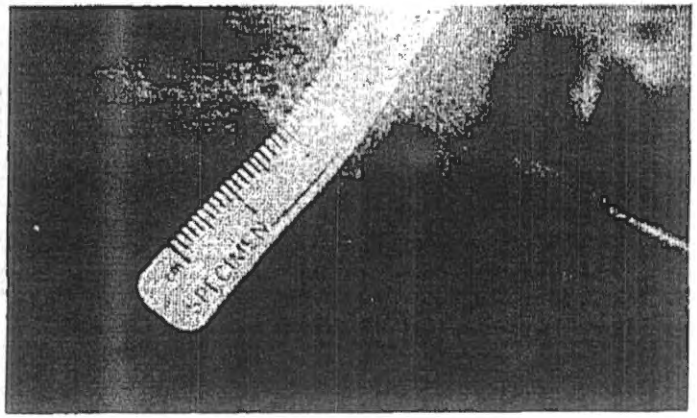
A. Firm Contact wound

- Muzzle imprint (Retrograde gas pressure forcing the skin against the muzzle)
- no powder tattoo
- cherry-red discoloration of wound track tissues caused by the release of carbon monoxide from the muzzle that causes the formation of carboxyhaemoglobin

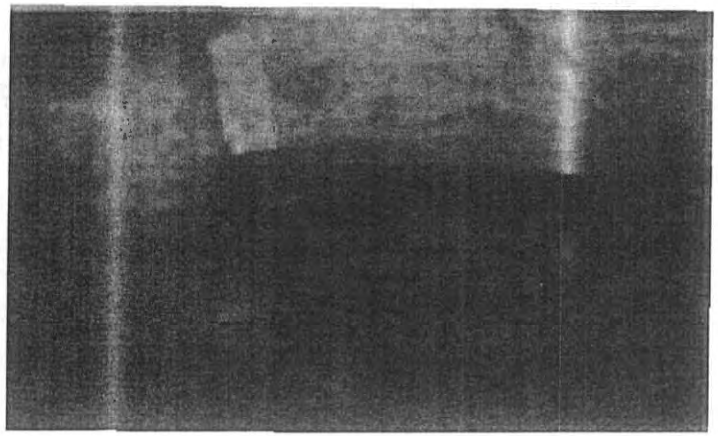


This is an contact wound.
Because the barrel contacts the skin, the gases released when firing go into the subcutaneous tissue and cause the star-shaped laceration.

GUNSHOT WOUNDS

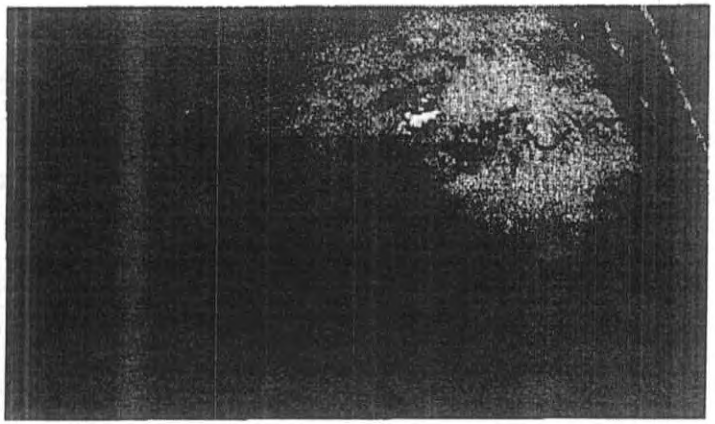


GUNSHOT WOUNDS



P147

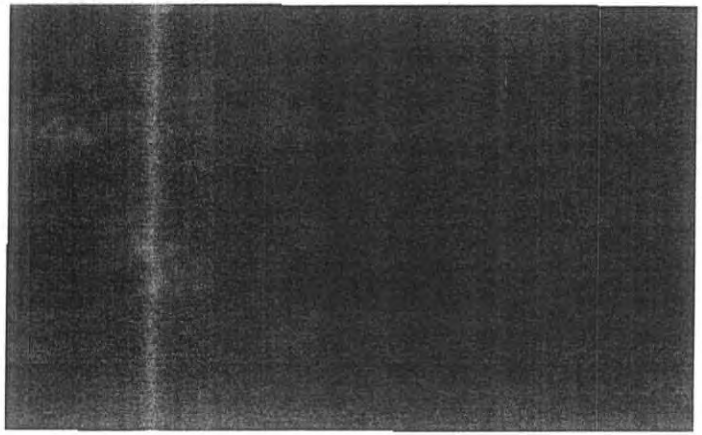
GUNSHOT WOUNDS



B. Loose contact wound

wide zone of powder stippling, but lack a muzzle imprint

entrance site is somewhat irregular



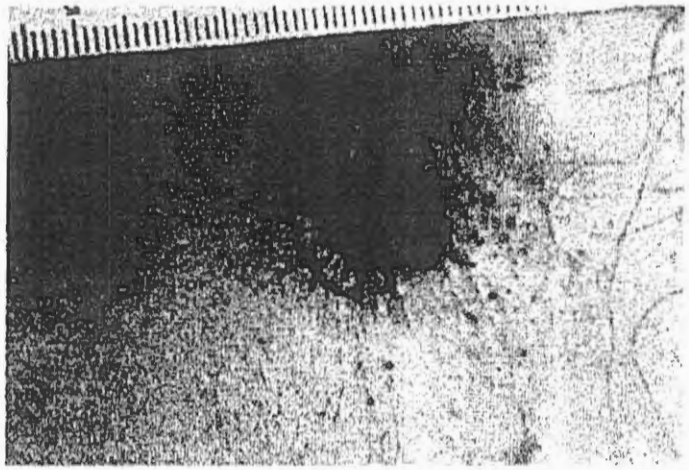
P148

GUNSHOT WOUNDS

GUNSHOT WOUNDS

GUNSHOT WOUNDS

GUNSHOT WOUNDS



C. Near wound

- Approximately 4 – 6 inches from body
- Powder Tattooing possible
- Circular pattern of powder distribution around bullet hole

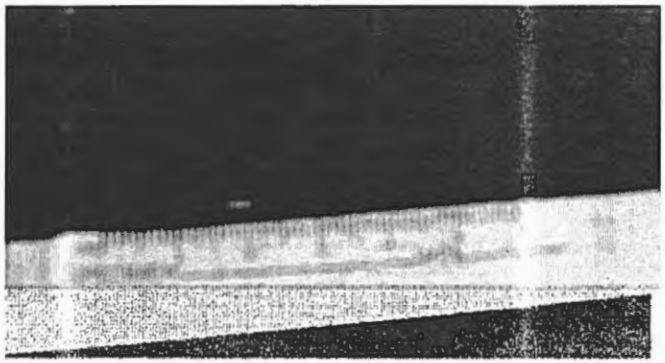
GUNSHOT WOUNDS

- D– Intermediate Range Wounds
  - Approximately 6 – 24 inches from body
  - No visible sooting
  - Dispersed powder particles
    - As soon as one sees individual tattooing marks, one is dealing with intermediate range wounds

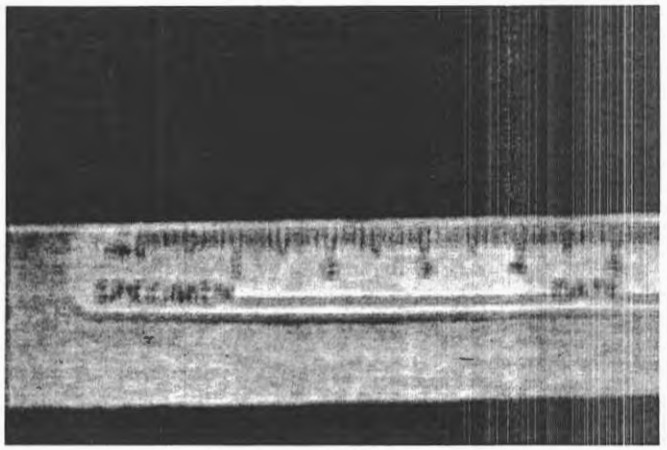
GUNSHOT WOUNDS

- Zone V: Distant Range Wounds
- Approximately 2-3 feet or greater
  - The only marks on the body are those produced by mechanical action of bullet perforating the skin

GUNSHOT WOUNDS



GUNSHOT WOUNDS

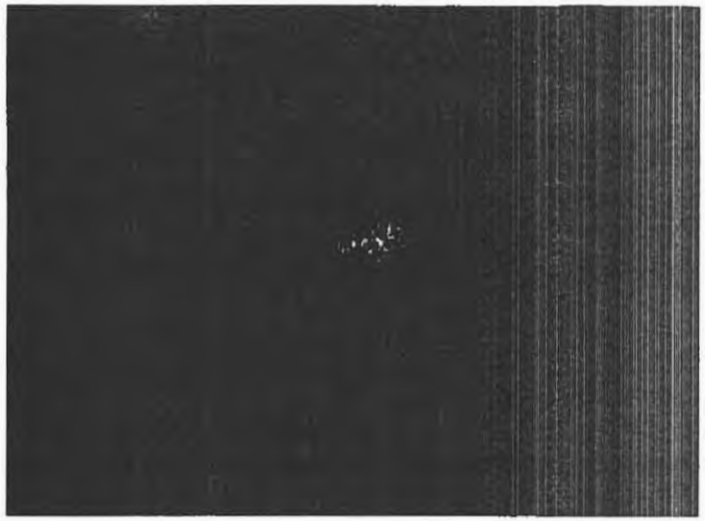


2nd, exit wound

In general;

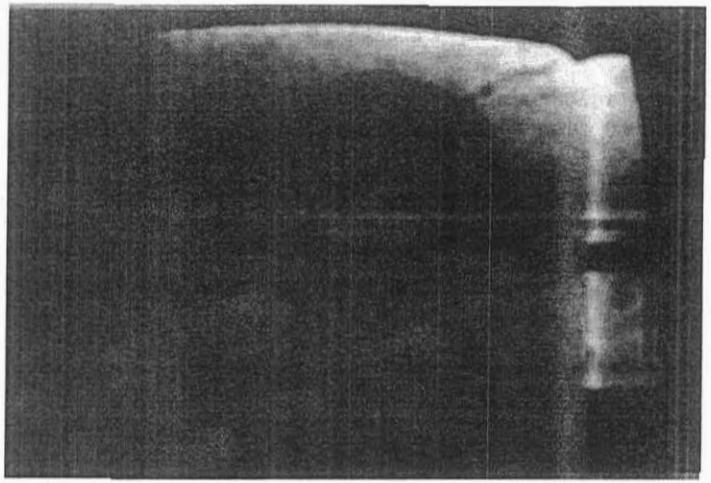
- exit wounds are larger than entrance wounds.
- irregular in outline, and their edges are everted.
- Absence of abrasion collar and powder tattooing
- Muzzle velocity is of vital importance when considering the characteristics of an exit wound

e.g. high velocity rifles can pass straight through the body unless they strike bone, and if the projectile has not been deformed, the defect can be rounded !

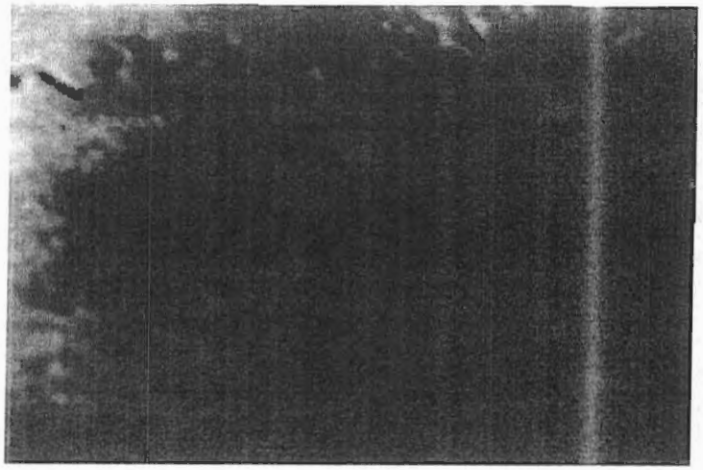


Gunshot wounds in bone

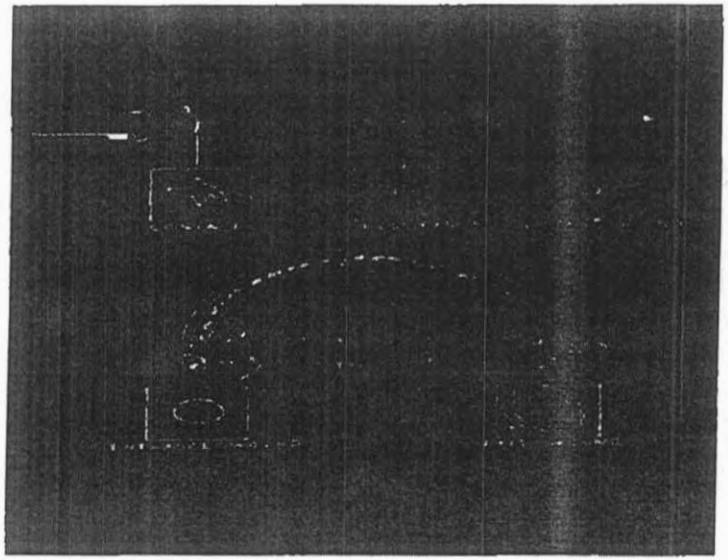
- In flat bones (i.e. skull) entrance wounds are round with sharp margins and show internal beveling: the inner table of the skull is more eroded than the outer table, producing a "cone" shape in the direction of the bullet path
- Exit wounds may be more irregular and show external beveling (outer table of the skull is more eroded than the inner table, producing a cone shape facing outward)
- In the skull, gunshot wounds often produce numerous fractures due to rapidly increasing pressure as the bullet travels through the skull



Entrance site



Exit site



P152

GUNSHOT WOUNDS

GUNSHOT WOUNDS

GUNSHOT WOUNDS

P153

أنواع الجروح و الإصابات

١. السحجات (الخدوش)

٢. الجروح الرضية (المتهتكة أو السحقية)

٣. الجروح القطعية

٤. الجروح الطعنية (النافذة و الوخزية)

٥. جروح الأسلحة النارية

٦. الكدمات و الرضوض

٧. الإصابات الأخرى

P154

١. السحجات (الخدوش)

هي نوع الطبقات الخارجية من الجلد نتيجة الارتطام أو الاحتكاك

تسمى السحجات الناتجة عن الارتطام ← السحجات المطبوعة
عن الاحتكاك ← السحجات الاحتكاكية

في الغالب ترافق السحجات باقي أنواع الجروح و الإصابات

أهميتها في تحديد :
أ. شكل و مواصفات الأداة و السلاح المستعمل
ب. اتجاه القوة المستعملة
ج. الاشتباه بأسباب معينة للوفاة أو علامات مقاومة أو تقييد المجني عليه
د. تقدير عمر الجروح و الإصابات الأخرى المرافقة، نظرا لقصر مدة شفاء السحجات

- تقدير القوة المستعملة تعتمد على :
١. طبيعة الأنسجة المصابة
٢. الأداة المستعملة
٣. سرعة انطلاقها
٤. المصاب ثابت في مكانه أو متحرك في اتجاه القوة أو عكسها

** قد تحدث الجروح الرضية في الغالب بصورة عرضية كما في حوادث السيارات أو تحدث في صورة جنائية

** تكمن خطورتها بالإصابة بالكزاز، و لكن يمكن تجنب هذه الإصابة باستئصال الأنسجة الميتة في الجرح و إعطاء المصاب جرعة منشطة من اللقاح إن كان قد سبق تطعيمه به و إلا فأنن يجب إعطاء المصل الواقي الخاص

٣. الجروح القطعية

قطع حاد في الجلد و الأنسجة الواقعة تحته نتيجة جسم صلب حاد

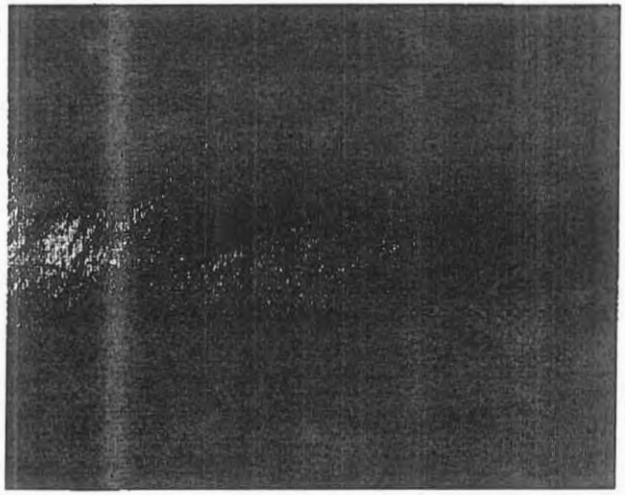
** تتميز ب :
- انتظام حافتها
- نزفها الشديد
- قطع الشعر قطعا حادا
- طولها في الجلد أكبر من عمقها في الجسم
- تكون عميقة في بدايتها و سطحيتا في نهايتها، أما عرض الجرح فيعتمد على اتجاه قطع العضلات في مسار الجرح

** قد يكون للسلاح أكثر من حافة حادة واحدة إلا انه لا يمكن معرفة أبعاد السلاح أو عدد حوافه من خلال قياسات أبعاد الجرح القطعي

٢. الجروح الرضية (المتهتكة أو السحقية)

هي تمزق الجلد و الأنسجة تحته نتيجة :
- الارتطام بجسم صلب أو وقوعها بين قوتين متعاكستين مثل وقوعها بين العظام و الجسم الصلب المسبب لها
- وقوعها بين أي جسمين صلبين آخرين
- الضغط مع الشد على الجلد
- تصادم الجلد و الأنسجة التي تقع تحته بجسم صلب غير منتظم أو جسم صلب حاد نسبيا

**تتميز بأن حوافها غير منتظمة مع وجود جسور من الجلد او من الانسجة تحته سليمة تصل بين حافتي الجرح
كما أن الحواف تكون متسحجة و متكدمة و الشعر في منطقة الإصابة مهروسا النزيف الناتج يكون بسيطا
يكون الجلد و الأنسجة تحته مرفوعا باتجاه القوة المستعملة



** الجروح الانتحارية

- تكون عادة في مكان حيوي من الجسم تؤدي إصابته إلى الوفاة السريعة مثل : عنق، الرسغ

- تكون الجروح في العادة في متناول اليد من الجسم

- وجود جروح ترددية : عبارة عن جروح قطعية سطحية عديدة متوازية عند بداية الجرح القاتل أي عند بداية اتجاه القوة المستعملة

- في بعض الحالات تكون اليد المستعملة لا تزال تمسك بشدة على السلاح المستعمل (التوتر الرمي)

١. الجروح الطعنية

جروح نافذة في أعماق الجسم نتيجة جسم صلب حاد ذو رأس مدبب أو جسم حاد غير مدبب أو جسم دائري مدبب أو غير مدبب

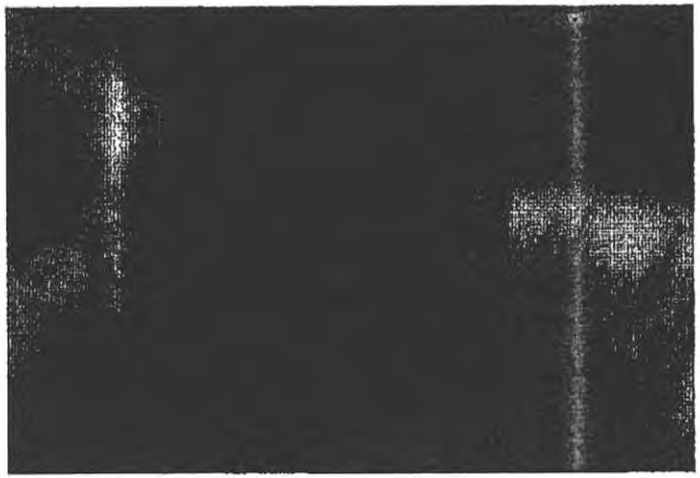
** تتميز هذه الجروح ب :
- عمق الجرح في الجسم أكبر من طول مدخل الجرح الموجود على الجلد
- غالبا ما يكمن النزيف داخلي

** تكون هذه الجروح في الغالب جنائية إلا أنه قد يحدث بصورة عرضية أو انتحارية

** أهم مضاعفات هذه الجروح :
- النزيف الدموي
- السدة الهوائية
- الاختناق نتيجة قطع الحنجرة

** تشفى غالبا خلال ٧-١٠ أيام

** غالبا تكون جروح عرضية إلا أنها قد تكون جنائية أو دفاعية أو مفتعلة



٥. جروح الأسلحة النارية

تقسم إلى نوعين :

أ. جروح الاسلحة المتفجرة

ب. جروح الاعيرة أو المقذوفات

ب. جروح الاعيرة و المقذوفات النارية

تقسم هذه الاسلحة إلى نوعين حسب ماسورة السلاح :

١. جروح بنادق الصيد (ذو ماسورة ملساء)

٢. جروح البنادق العسكرية و المسدسات (ذو ماسورة غير ملساء)

** يمكن معرفة نوع السلاح المستعمل فيما اذا كان ذو حافة واحدة أو أكثر من خلال تحديد نوع زاويتي الجرح

- اذا كانت الزاويتين حادتين ← السلاح ذا حافتين حادتين
- زاوية واحدة حادة فقط ← السلاح ذا حادة واحدة

** يمكن معرفة نفاذ السلاح بكامله داخل الجسم بوجود سحجات حول حافتي الجرح نتيجة إصابتها بجزء مقبض السلاح المتصل بالنصل

** أما معرفة اتجاه القوة المستعملة و الوضع الجسمي الذي كان عليه المصاب و موقع المعتدي عند وقوع الاعتداء فإن العوامل السابقة تساعد في ذلك

أ. جروح الأسلحة المتفجرة

- جروح و اصابات مختلفة، نافذة و غير نافذة بفعل شظايا السلاح نفسه و شظايا أي مواد في منطقة الانفجار

- حروق نتيجة اللهب و الغازات ذات الحرارة العالية

- وشم أو تمش بارودي

- التسمم بغاز اول اكسيد الكربون

- إصابات غير مباشرة ناتجة عن الانهيارات أو السقوط

** عند إطلاق النار بتماس فان جميع الغازات المتحررة عن اشتعال ملح البارود تدخل في جرح المدخل و في حالة الجلد الملتصق بشدة بالعظام تحته فان حجم الغازات المتزايد يؤدي إلى انفجار يتسبب بتشقق جرح المدخل بحيث يظهر شكل الجرح نجميا !

P158

إصابة العظام بالمقذوفات النارية

** العظام تتكون من طبقتين خارجية و داخلية و بسبب انتشار ضغط المقذوف الناري عند ارتطامه و دخوله في الصحيفة الخارجية فإن الفتحة في الصحيفة الداخلية يكون أوسع من الفتحة او الكسر في الصفيحة الخارجية = الشطف الداخلي، و هو ما يحدث دائما في جرح المدخل

و عند الخروج المقذوف يحدث الصورة المعاكسة !

** الجرح الناتج عن المقذوف أو الرصاصة

- يتصف جرح المدخل دائما بوجود فقد أو ضياع في الجلد يتناسب قطره أو مساحته مع قطر المقذوف و اتجاه دخوله

- اذا كان دخول المقذوف الناري عموديا على جرح المدخل فان قطر الجرح يتوقع ان يكون أقل من قطر المقذوف بسبب تمدد الجلد اولا ثم رجوعه الى وضعه الطبيعي

- في بعض الاحيان تكون حافة الجرح في الملابس الملوثة بما يسمى «المسحة الرصاصية» ، عبارة عن جزيئات المواد التي تلوث المقذوف من ماسورة السلاح. ولا نجد أيا من هذه العلامات في جرح المخرج و الذي يتصف بانه تمزق في الجلد فقط دون أي فقد منه

** تحديد اتجاه الاطلاق

١. تحديد اتجاه دخول المقذوف الناري في الجسم في الوضع القائم العادي من خلال السحجات في حواف جرح المدخل

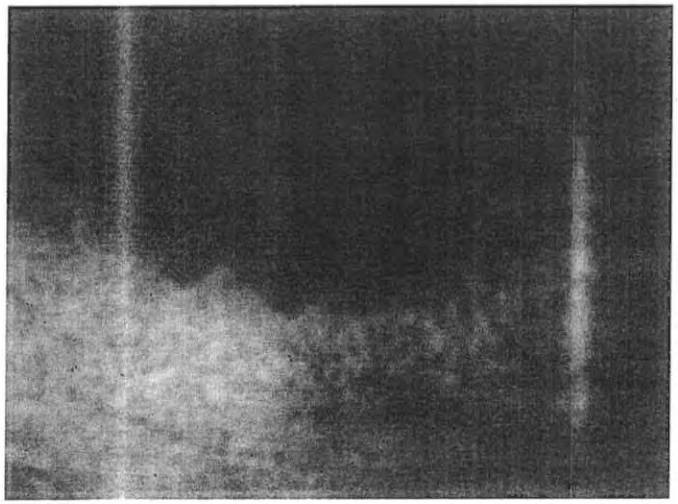
٢. يتم تصور اتجاه اطلاق النار و وضع الجاني و المجني عليه

** يجب أن لا يعتد دائما بمسار القذوف الناري في الجسم أو بالمسار بين جرح المدخل و المخرج لأن اتجاه المقذوف داخل الجسم يتغير حسب طبيعة الانسجة التي يصادفها

** سرعة تغير اللون تعتمد على :

- كمية الدم النازف في الأنسجة
- كمية الاوعية الدموية التي تغذيها

** في الغالب ترافق هذه الاصابات السحجات و تسمى بالسحجات الرضية و نظرا لسرعة التغييرات في السحجات و قصر مدة شفائها، فان تقدير عمر هذه السحجات يساعد في التقدير الدقيق لعمر الكدمات



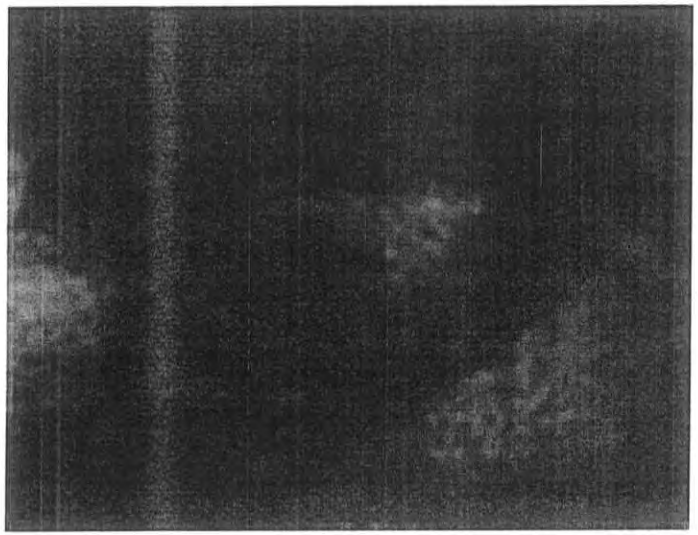
٦. الكدمات و الرضوض

عبارة عن نزيف دموي نتيجة تمزق الاوعية الدموية في الانسجة الواقعة تحت الجلد نتيجة الارتطام بجسم صلب او وقوع الانسجة بين قوتين متعاكستين

** قد تحمل الكدمات شكل و مواصفات الاداة المسببة لها اذا كانت ذات شكل هندسي مميز

** قد تتعذر ملاحظة الكدمات كلما كان لون الجلد داكنا

** أول ما يظهر الكدم يكون لونه احمر ← بعد فترة وجيزة يصبح بنفسجي ← أزرق بعد ٢-٣ أيام ← أخضر بعد ٣-٤ أيام ← اصفر ← يختفي نهائيا بعد ٦-٧ أيام



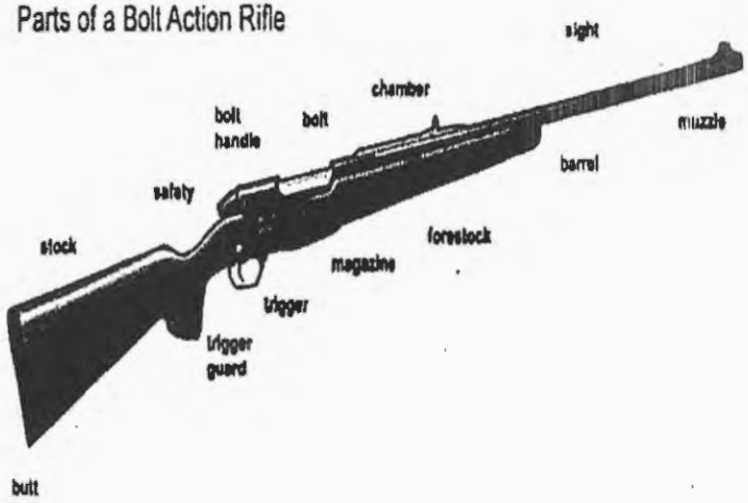
Firearm wounds

Type of firearms :

1. smooth barrel → shotguns

2. Grooved barrel → rifled weapons

Parts of a Bolt Action Rifle



The factors that can affect the amount and distribution of gunshot on skin include:

1. firing distance
2. length and diameter of the firearm barrel
3. characteristics of the gunpowder
4. angle between the firearm barrel and target
5. the environment (wind)
6. type of clothing
7. characteristics of the target (tissue type)

- Firearm injuries can be classified according to range into :

1. **Firm Contact** → muzzle is pressed against the skin when fired
2. Loose **contact** → muzzle of the gun is held a short distance from the skin (< 1 cm from skin with handguns)
3. **far** → defined by the presence of stippling "powder tattooing" on the skin surrounding the entry wound

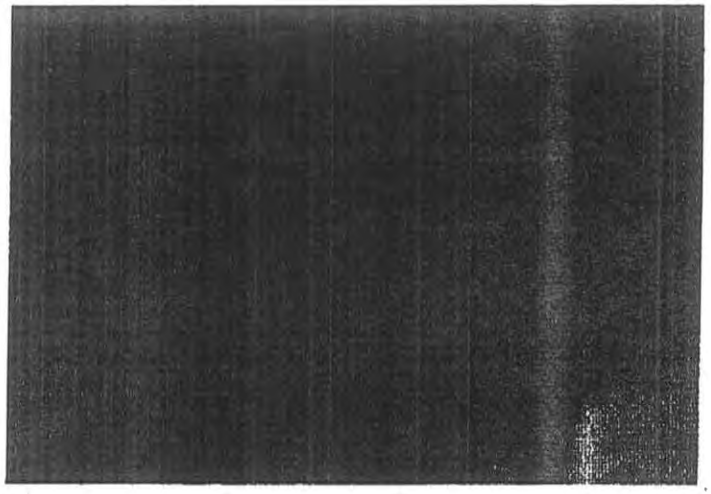
A. Firm Contact wound

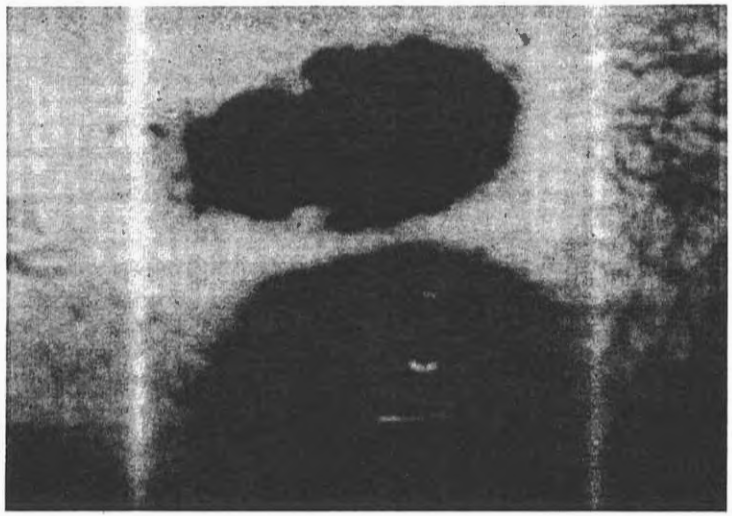
- Muzzle imprint (Retrograde gas pressure forceing the skin against the muzzle)
- no powder tattoo
- cherry-red discoloration of wound track tissues caused by the release of carbon monoxide from the muzzle that causes the formation of carboxyhaemoglobin

Basic features of firearm wounds

First, Entrance wound

- Round or oval central defect with an abrasion collar, caused by unburned powder and small metal fragments striking the skin
  [if the bullet impact is perpendicular to the skin surface, it will be round, but if it hits at an angle, the abrasion collar will be uneven]
- Diameter of the wound is usually smaller than the bullet. This is because the skin is elastic and it retracts after the bullet enters the skin.
- Underlying tissues will not protrude.

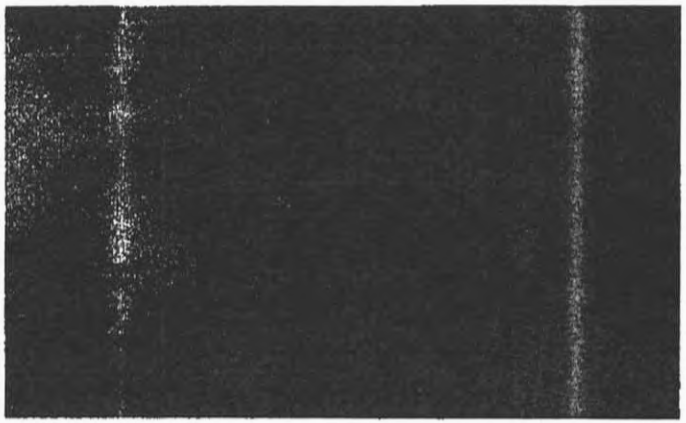


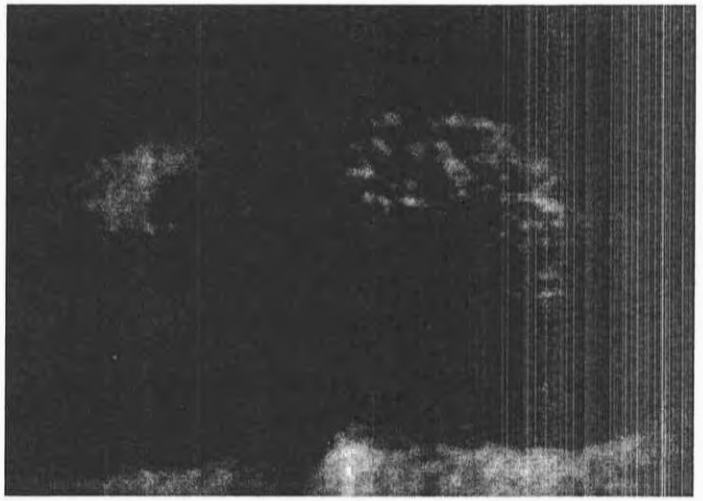


This is an contact wound.
Because the barrel contacts the skin, the gases released when firing go into the subcutaneous tissue and cause the star-shaped laceration.

B. Loose contact wound

wide zone of powder stippling, but lack a muzzle imprint
entrance site is somewhat irregular

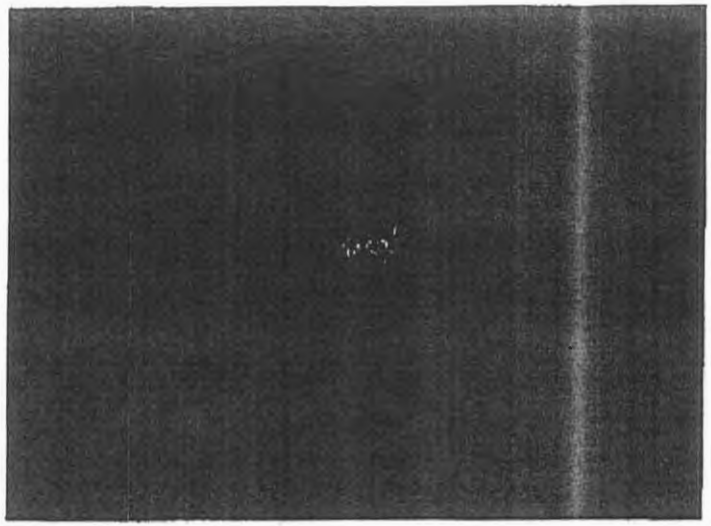




C. far wound

- Appear as a round wound with sharp margins
- abrasion ring on the surrounding skin
- no powder tattooing is noticed

P163



2nd, exit wound

In general;

- exit wounds are larger than entrance wounds.
- irregular in outline, and their edges are everted.
- Absence of abrasion collar and powder tattooing
- Muzzle velocity is of vital importance when considering the characteristics of an exit wound

e.g. high velocity rifles can pass straight through the body unless they strike bone, and if the projectile has not been deformed, the defect can be rounded !

Gunshot wounds in bone

- In flat bones (i.e. skull) entrance wounds are round with sharp margins and show internal beveling: the inner table of the skull is more eroded than the outer table, producing a "cone" shape in the direction of the bullet path
- Exit wounds may be more irregular and show external beveling (outer table of the skull is more eroded than the inner table, producing a cone shape facing outward)
- In the skull, gunshot wounds often produce numerous fractures due to rapidly increasing pressure as the bullet travels through the skull

P164

Exit site

Entrance site


Forensic

Index

- wounds
- Gun Shot Wounds
- Burns
- Child Abuse
- Summary of death & post mortem Changes
- Death & postmortem Changes (full Topic)

Good luck :)
Farah Amer

Wounds

- **Mechanical**
  - ① due to Blunt force → Abrasion, Contusion, Laceration, * & dislocation
  - ② due to Sharp force → Incised, Stab
  - ③ firearm wounds
- **Thermal**
  - ① due to Cold (FrostBite)
  - ② due to Heat (Burns, Scald)
- **Chemical**
  - Corrosive acid & alkali
- **Physical-**
  - Electricity
  - Lightening

* Medicolegally: ① Suicide ② Homicide ③ Accident ④ Fabricated ⑤ defense

Abrasions

- destruction of superficial layer.
- Bleed Slightly, Heal Rapidly, leave No Scar.
- 2 Types: ① Frictional ② patterned.

* Brush Burn
  - Sliding Abration

Contusion

- surface injury to skin & subCutaneous → effusion of Bld into Tissues
- May affect internal Organs!
- Children, Old, Obese Bruise easily.
- Healing → you see color Changes [Red - Blue - Brown - green/yellow - NL (2wks)]
- Could be: Homicidal, Suicidal, Accidental ((Rarely or Never fabricated))

* Never occur in Internal Organs:
  - incised wounds.
  - Abrasions.

Lacerated Wounds

- injury in which the Skin & the Underlying tissue are torn apart.
- Types: ① Split (Crushing of Skin + SQ tissue btwn 2 hard objects)
  ② Stretch (overstretching of Skin → flap)
  ③ Avulsions (grinding Compression)
  ④ Tears (irregularly directed impact)
  ⑤ Chop ((weapon w sharp Heavy edge ex axe, ß / Hatchet))

- Lacerated Wounds are generally Accidental or Homicidal.

* Incised wounds

- Clean Cut through tissues (usually skin & sub Q tissue)
- Fabricated Wounds are Mostly **Incised** wounds.
- It Could be Homicidal ((anywhere in Body)), Suicidal ((Multiple, superficial)) & Accidental anywhere.
- Usually → Length > depth & Breadth.
  - Broader than the edge of Weapon.

* الجروح القطعية عادة تكون accidental إلا إذا كانت homicidal

	Lacerations	Incised Wounds
edges	- irregular, ragged & Bruised	- smooth, clean cut, everted no Bruising along the edges.
Bridging	- Base of wound has Bridging across muscle fibers	- No Bridging
Bld vessels	- Blood Vessels → Crushed external Hmrg Not Marked	- Vessels are Cut → Bleeding is profuse.
Hair	- Hair & Hair Bulbs - Crushed	- Not Crushed.

* Stab wounds

- Thrusting of any pointed (sharp/Blunt) object into the Body so that Depth is the greatest Dimension.
- Types: ① perforating → stab wound also makes an Exit.
  ② penetrating → when Body Cavity (Abdomen/ Thorax) is penetrated.
  ③ Concealed (punctured) → inserting a needle in Ant. fontanellae ((Infants))
- Characteristics: [1] Entry Wound (usually > Exit) [2] Exit Wound
  - Margins → Clean & inverted → Small & everted.
- Gaping of Wound → wound is slightly Shorter than the Weapon width, only when inflicted across ((Langer's lines)).
- Direction determined by Line Joining entry & exit wounds or X-Ray after [Radio-opaque dyes]

The End

Gun Shot Wounds

- Factors that affect the amount & distribution of gunshot on skin:
  1. Firing distance
  2. Lenght & diameter of firearm Barrel.
  3. Characteristics of Gunpowder
  4. Angle Btwn firearm Barrel & Target.
  5. Wind
  6. Type of Clothing.
  7. Characteristics of the Target ((Tissue Type)).

- Basic Features:

1 Entrance Wound

- Round or Oval Central defect
- Abrasion Collar = rim.
- diameter of the wound is usually smaller than the Bullet
- Powder Tattooing (unburned soot)
- inverted edges.
- Stellate shaped in higher velocity weapons or hard Contact over a bony part

2 Exit Wounds

- usually Larger than entrance wound.
- Irregularly Shaped.
- No powder Tattooing, soot soiling, abrasion Collar.
- Everted Skin Edges
- May have abraded edges ((shored exit wounds)).

- Classification according to distance / Range:

1. Firm Contact
2. loose Contact
3. Near Contact
4. intermediate
5. Distant

1. Firm Contact → ((Muzzle is pressed against the Skin when fired))
   - Muzzle imprint (Retrograde Gas pressure → force skin against the muscle)
   - No powder Tattooing.
   - Cherry-Red discoloration of wound track tissue ((release of CO → COHb))

Muzzle → mouth of the gun

1 Loose Contact → (muzzle of gun is held in short distance from the skin)
- wide zone of powder stippling, lack Muzzle imprint.
- Entrance site → irregular.

2 Near Contact → (presence of powder tattooing on skin surrounding the entry)
- powder Tattooing
- Circular pattern of powder distribution around Bullet Hole.

3 Intermediate Range
- No visible sooting
- Dispersed powder particles.

*individual Tattooing mark, consider it's (intermediate)

4 Distant Range.
- The only Mark on Body → Mechanical action of Bullet perforating the skin.
- No soaking, no powder tattooing.

- Gunshots in Bones :
  * Flat Bones (Skull) →
    - entrance wounds : round ∞ Sharp margins + internal Beveling
    - Cone Shape in direction of Bullet path. △
    - exit wounds : irregular + external Beveling.
    - Cone shape facing outward (outerpart more eroded than inner) ▽
    - Gunshots usually produce numerous fractures.

The End
Farah Anwar.

Burns

① Thermal ② Chemical ③ Electrical ④ Radiation

Thermal → depends on: Temp. & duration of Exposure.
→ 2 Types: ① dry Heat Burn ② Scald.

*in general minimum Temp. to produce a Burn is (44°C)

① Dry Heat Burn

* local effects:
  - 1st, 2nd, 3rd degree
  - surface area (Rule of 9)

* effects of Heat on Body:
  Skin → splitting
  Muscle → stiffness, (pugilistic Attitude) Sx
  Bone → *
  Skull → * + Extradural Hematoma

Heat Hematoma	Extradural Hematoma
occur due to Burn	results from an injury Before the Burn.
contains Oxy Hemoglobin	Not present.
Bld Brown & Spongy.	—
may be ass. with *	injury Before Burn depressed skull *
Bilateral (usually)	Unilateral.

* The general Condition of any Burned person is determined by:
  ① Surface area
  ② degree & site
  ③ age & Health Status.

* Inhalational injury:
  - direct effect of Heat on Upper Airways
  - CO poisoning
  - other toxic gases

* General Complications:
  - shock, ARF, septicemia, Fat Embolism after 2nd day (Rare > 7th day)
    Pulmonary " after 7th "

* Dry Heat Burns:
  - Accidental - Homicidal - Suicidal - Fabricated

Al-Hussein Bin Ali Street - P.O. Box 6399 - Amman 11118, Jordan
Tel: +962 6 5607100 - Fax: +962 6 5665160
info@landmarkamman.com - www.landmarkamman.com

Burns :

antemortum	postmortum
- Erythema & Congestion (more pronounced)	- No / slight erythema, congestion.
- Blisters → filled w protein rich fluid (protein ↑ antemortum)	- Blisters → filled with gases or protein poor fluid
- Black Soot in Alveoli	- No Black soot in alveoli
- Carboxy hemoglobin	- No Carboxy Hemoglobin.

* Soot particles → evidence of Heat trauma.
  - if found in Nostrils & Mouth → could be passively entered.
  - if Bellow the Vocal Cords → the pt. was Breathing → significant sign of Antemortum Burn.

2 Scald Burn

* local effect :
  - 1st, 2nd degree
  - surface area.
* General Complications :
  - Shock, ARF, septicemia, fat embolism.

*Scald occur when liquid in Contact has Temp. > 60°C

Dry Heat Burn	Scald Burn
- clothes are dry	- clothes are wet.
- Burned Hair	- Wet Hair.
- affects Body (down → up)	- affects Body (up → down)
- any degree from Erythema to Charing.	- doesn't exceed erythema & Blistering
- Blisters → Border of Burn	- Blisters → on whole area of Burn.
- Black Soot in Alveoli	- No Black Soot.
- Carboxy hemoglobin in peripheral Bld.	- No Carboxy hemoglobin.

landmark
AMMAN HOTEL & CONFERENCE CENTER

* Causes of death in Thermal Burn:

(< 6 hrs) →
- Neurogenic Shock.
- CO poisoning
- Direct damage to Vital Organs (e.g Brain, Heart)
- Traumatic asphyxia

(6 - 48 hrs) →
1. Toxemic shock
2. Hypovolemic shock.
3. Fat Embolism
4. Acute laryngeal edema.

(> 48 hrs) →
- septicemia
- infxns
- Ruptured Curling Ulcer.
- Waterhouse - Friderichsin's syndrome.

2 Chemical Burns

- Acid or Alkali
- 1st or 3rd degree (Never 2nd !) due to Vasoconstriction which hinders fluid escape to form Blisters.

3 Electrical Burns

① Contact with electrical Body

2 points → entrance & exit

- Entrance → Through the Hand, usually round / oval w depressed center & Raised Margin. ((multiple vesicle under magnifying lens))
  → usually greyish in Color [sometimes take the color of electrified Body as if it was the metal metalization e.g. coin]
- Exit → usually lacerative wound.

Al-Hussein Bin Ali Street - P.O. Box 6399 - Amman 11118, Jordan
Tel: +962 6 5607100 - Fax: +962 6 5665160
info@landmarkamman.com - www.landmarkamman.com

② Burns caused by Sparks (air gap btwn Metal & Body)

③ Burn caused by flash → caused by High Voltage electrical Burns
Voltage btwn (1,000–5,000)

* which is More dangerous direct Current or Ulternating Current?

- Ulternating current is More dangerous.
- defibrilator used in ∵ Cardiac Arrest ⟹ direct Current.

* Causes of death of Electrical Burns:
  - Ventricular fibrillation (~Cardiac Arrest)
  - Diaphragmatic spasm (~ Resp. failure)
  - Brain Stem injury & Censequent loss of Resp.
  - Trauma.

④ lightening
- fern or Branch like, Streaks pattern.

The End
Farah Amer

Child Abuse

- definition of Physical Abuse :
  ① Any non-accidental injury
  ② To a Child < 18 yrs.
  ③ By a parent or Care giver ((caretaker))

- definition of Child Abuse :
  ① Physical or Mental or sexual or exploitation or Negligent ttt or Maltreatment
  ② of a Child < 18 yrs
  ③ by a person who is responsible for the Child welfare.

- Types of Abuse : physical , Sexual , Emotional , Neglect.

- **Physical Abuse**
- Shaken Baby Syndrome (Triad of) :
  ① Cerebral Edema
  ② Subdural Hematoma.
  ③ Retinal Hemorrhage
  ± Rib fractures or Bruises at sites of holding the Baby.

- * clues for physical Abuse :
  - X-Ray ✻ of different Chronological ages.
  - Hx. Not Related to P/E.
  - ✻ in Child who hasn't walking yet
  - ✻ / Trauma at unexpected Sites :
    (Frenulum (in the mouth) , inner aspect of thigh , Back , Buttocks , ears ...)

The End
For dr. Amer

Summary of Most imp. things in Death & postmortem Changes

* Types of Death:

- Somatic → permanent, irreversible death
- Clinical → No Breathing, No Circulation, No Brain Activity
- Cellular → Cessation of Resp. ((utilization of O_2)) followed by autolysis & decay
- Brain → ① coma (unconsciousness) ② Absence of Vestibulo-ocular Reflex.
  ③ Absence of Spontaneous Breathing ④ Dilated pupills. ⑤ " " Corneal " ⑥ " " Motor response to Painful stimuli ⑦ " Gag Reflex

* Postmortem Changes:

- Liver Mortis → starts within (20 mins), well-developed (4 hrs), fixation (6-8 hrs)
- Rigor Mortis → starts ((after Acidity is gone)) after 2-3 hrs, peaks after (12 hrs) & disappear after (12-36 hrs)
- Cadaveric spasm → Instantaneous: after death. (last for hrs)
- Algor Mortis → Body keep its Temp. then starts cooling after (2-3 mins)

* Body situation	Time
- warm & flaccid	(< 3 hrs)
- warm & Rigid	(3-8 hrs)
- Cold & Rigid	(8-36 hrs)
- Cold & flaccid	(> 36 hrs)

- Liver mortis color → Variable Colors: Cherry-pink → ((Co poisoning)) if Brown → Met-Hb ((Nitrates poisoning, Aniline)
- Rigor mortis develops when ATP ↓ 15%
- Cold Stiffness develops → Temp (< -5°C)
- Frost Bite " → Temp. (< -2.5°C), commonly seen → Nose.
- Heat Stiffness " → Temp (50°C) ?

- Earliest Sign of Death → loss of skin elasticity
- The early Changes include:

① Eyes → loss of Reflexes, ↓ Eye Tension, clouding of Cornea, Eyelids incomplete closure
- Tache noire : wrinkled dusty spots on Sclera
- Tracking (shunting) of Blood in Retinal Vessels

② Muscles → Muscles flaccidity develop 1st

③ Skin → loss of elasticity & pale

④ Stomach → Gastric Contents found in Airways

* Late Changes

putrefaction:

① 1st organ to putrefy → Then → Then ... Last Thing
(Larynx / Trachea) → (Heart) → (Brain) → (Uterus / prostate)

② Earliest Sign → greenish discoloration over (Rt. iliac fossa) due to (Sulfmet Hb).

③ Better in Humid media → Better in (Soil)

- postmortum Hemolysis due to Bacterial enzyme → lecithinase.
- Combustible Gas of Autolysis → Hydrogen Sulphide.

* After Death:
- CSF: lactic acid ↑
  - Amino acid ↑
  - Uric acid ↑
  - (Not Urea)
- Blood: Na^+ ↓

- Bacteria in putref. → C. welchii

Mummification:

① dehydration of Cadaver ② (Odorless) ③ Dry Heat Media

The End
Faraah Amer

Death & postmortem Changes

* Types of Death : ① Somatic death. (permenant / irreversible death)
  ② clinical Death. * توقف القلب والتنفس عن العمل وعدم مقدرتهما الذاتية للعمل. (انتهاء الحياة)
  on This Type we depend to diagnose death.
  ③ Molecular (cellular) death.
  ④ Brain death. (* يُعلن عن مماتك الموت الدماغي بعد ثاني مرة من رؤية الفريق الطبي الميت دماغياً)

→ cellular death follows Clinical death.

* The most important postmortem Changes :
  - Livor Mortis or Hypostatis (الزرقة الرمية)
  - Rigor Mortis (التيبس الرمي)
  - Heat Stiffening (التيبس الحراري)
  - Cadaveric spasm (التوتر الرمي)
  - Decomposition or putrefaction (التعفن)
  - mummification (التحنيط الطبيعي)
  - Adipocere (التشمع الرمي)

Hypostasis - Livor Mortis

* After death → circulation of Bld ceases & subsequent movement of Blood by gravity → Blood accumulates in the Capillaries in the dependent parts of the Body → purple or Reddish-purple discoloration of the Skin.
* Starts immediatly after Birth ((Within 20 minutes)).
* May Not appear in :
  - Infants , old.
  - Anemia.
  - who died from Severe Blood loss.
  - who died from Septicemia ((high change of postmortem Clotting of Blood))

* Sites of Hypostasis :

Depends on the position Before death :

① Vertical → Hanging position.
② Chest , upper limbs → Drowning.
③ Shoulder , Buttocks → Supine .
④ face down + whitening around lips & mouth → Epilepsy.

* Colors of Hypostasis :

. Variable Colors depend on State of oxygenation at Death
. Might be masked by dark skin colors , by Jaundice or some dermatological Conditions .
. Color Changes (may indicate possible Cause of Death) :

most imp.
① Cherry-pink → CO poisoning
② Chocolate-Brown → Methemoglobin ((ex. Nitrates, Aniline poisoning))
③ Dark Blue-pink → Cyanide poisoning .
④ pallor → Anemia / Hemorrhage ((الأكثر في extremities & Old ages))

* Medico-legal importance of Hypostasis :

[1] 1st Sure Sign of Death. - أول علامة أكيدة للوفاة
[2] Cause of Death. - تأثير الشبوهة لأسباب وفاة معينة .
[3] Position Before / after death - وضع الميت
[4] Indicates if the Body was Moved or Not after death (إذا تم تحريك الجثة من الوضع الذي وجدت عليه الجثة)

→ once hypostasis is established it has the ability to undergo Subsequent gravitational Shift if the Body is moved into a different posture.
→ Changes in the position of the Body after initial development of Hypostasis will result in Redistribution of the hypostasis & examination of the Body will Show → 2 overlapping patterns.
→ Hypostasis Becomes fixed after almost ((8 hrs)).

	Hypostasis	Bruises
area	- Dependent area	- Any where
Borders	- Well-defined	- ill-defined edges.
Bld distribution	- Blood is retained in intact Capillaries	- Blood escapes through ruptured Capillaries
level	- Same level on surface	- Raised.
Color on pressure	- Pale over pressure areas	- Red.
incision	- Blood flows from the Cut Vessel (washable)	- Blood Coagulates in Tissue.

→ when you put pressure ((pres)) over hypostasis → area disappear then reappear But the Bruise persist with pressure.

Rigor Mortis

* In latin → Riger: Rigidity , Mortis: Death.
* It is the period of partial / complete rigidity affecting Voluntary & Involuntary muscles, occurs after death, Usually preceded by a period of generalized Muscular Flaccidity.

* Mechanism:

After Death → ↓Resp. → ↓O_2 → ↓ATP, 2ry anoxic process → ↑ lactic Acid → high acidity + membrane permeability changes → ↑Ca^{2+} leak → Actin & Myosin fibers Bind → The Body is unable to complete the cycle & release the Coupling of Actin & Myosin Because of insufficient ATP → This Creates a perpetual State of Muscular Contraction (until Breakdown of Muscle Tissue by digestive enzymes during decomposition)

→ most imp. factors in Rigor Mortis Mechanism → ATP depletion.
- actin-myosin interaction
- Lactic acid accumulation

* Rigor Mortis starts to develop after 2-3 hrs after death.
Peaks after 12 hrs & concludes (disappears) after 12 hrs - 36 hrs

* Temporal Sequence :

1. Flaccidity period
   - Starts immediatly after death & Continues for 1-3 hrs on avg.
   - occurs due to cessation of Nerve impulses.

2. Rigor Period
   - onset is Variable . → (لا يعتمد على لمعرفة وقت الوفاة)
   - 1st Noticed in Small Muscles (Jaw, eyes, fingers ..) due to :
     ① small muscles have smaller amount of Glycogen Storage
     ② small joints are easier to be immobilized.

→ Rigor Mortis develops Uniformly throughout the Body But it is 1st detected in Small Muscles
(Seen in order Jaw, facial muscles, Neck muscles, wrist, ankle, Knee, etc.)
→ it resolves in the same order as it develops.

* Factors affect timing :

1. Environmental Temperature.
   - warm Temp → onset : Fast , ends earlier (duration Shorter).
   - Cold Temp → onset : Slow , it could be suspended (duration longer)
     - في حالة الإنجماد يتوقف التيبس الرمي نهائياً ويعود اذا عادت الحرارة طبيعية -

2. Muscular activity Before Death.
   - exhausted / fatigued muscles (deplete glycogen Stores) → Rapid onset
   - Muscles Healthy, at Rest Before Death → Slow onset.
   - ↑ Activity (convulsions, lightening) → Rapid onset.

3 Age (+ sex) (Extremes of Age → Rapid onset)

- infants, Cachectic & old people → may Not appretiate Rigor Mortis
- Females (in General less Muscle Mass) → Fast Onset.

4 Drugs

- strychine → earlier onset
- Barbiturates → delay onset.

- Gross effect :

1 Eyes → Iris is affected → pupil size change → unequal.

2 Heart → Ventricular Contraction → might be mistaken by LV Hypertrophy. (we can differentiate btwn them by Measuring Total wt. & Actual Thick

3 Dartos Muscle in Scrotum → Constricts Testes & epididymis → expulsion of Semen at urethral meatus (shouldn't be wrongly attributed to Sexual activity Before death.)

4 Erector pilli muscle attached to hair follicle → Goose bump, hair stand up. (They think that hair grow after death)

→ Testing Rigor Mortis ?

- The Best to Test it across a joint using 1 or 2 fingers only to detect the presence & extent of Stiffness
- If Rigor is Broken by applying too much force, those Muscle groups cannot reliably be Tested again. (Muscle fibers → Ruptured)

Body Situation	Time Since death
Warm & flaccid	(< 3 hrs)
Warm & Rigid	(3 – 8 hrs)
Cold & Rigid	(8 – 36 hrs)
Cold & flaccid	(> 36 hrs)

Heat & Cold Stiffness

- In Extreme Temp. muscle undergo false Rigor.

- Extreme Cold. (<0° usually -5° or Below)
  - Body fluid freeze → SQ fat will solidify → Muscles appear like in Rigor Mortis
  - Rigor Mortis is only postponed, And after warming the Body. It will supervene (will Take place).

- Heat
  - proteins will become denatured & Coagulate → appear as Rigor Mortis
  - Extent of Rigidity depend on: ① Time & ② intensity of Temp.

P/E: Muscles appear Cooked (Brownish Color)
- Skin → desiccated (dehydrated)
- Marked Shortening → flexion in UL + opisthotonos (abnormal posture due to rigidity) → giving Pugilistic attitude (Boxer) - سوداوي

Cadaveric Spasm

- Instant rigor that develops at time of death without peroid of post-mortem flaccidity.
- Usually ass. with Violent deaths happening with intense emotion.
  ((It seems that glycogen depletion has a role in it))
- Maybe seen in Cases of drowning Victims → [grass, weeds Clutched, proof of life at time of entry of water]
- Usually affects one Group of Muscles (ex. forearm, hand ....)
- often demonstrates the last activity one did prior to death & helps in forensic investigations ((ex. Clinging on a knife Tightly))

- Rigor Mortis will appear Normally even with Cadaveric Spasm.
  [one group is Rigid → After ~3 hrs Rigor Mortis Begin → Rigidity all over Body → after 36 hrs the Body Become flaccid.]

	Riger Mortis (RM)	Cadaveric Spasm
onset	- Onset delayed after 2-3 hrs (preceded by flaccidity) lasts up to 36 hrs	- Onset is instantaneous & lasts for few hours until it is Replaced by RM.
intensity	- comparatively Moderate	- comparatively v. Strong.
Mechanism	- Breakdown of ATP Below Critical level.	- unknown But predisposing factors: excitement, fear, fatigue, exhaustion, Nervous tension, contraction of Muscles at time of death.
muscles affected	- Affects the Whole Body	- affects one Group of Muscles.
death circumstance	- occurs in any death Circumstance	- Confined to death during physical or emotional Stress.

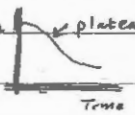
Algor Mortis / Body Cooling

- The Most usefull indicator of time of death during the first 24 hrs postmortem
- Mechanism:

Body surface begins Cooling immediatly after death → followed by delay in deep organs Cooling until a Heat gradient is setup Between the core & the skin (surface) → Temprature plateau.

(i.e. Body Cooling occurs until a difference Btwn the Core Temp. & Skin Temp. is attained)

- Plateau phase is Variable from (Minutes to 2-3 hrs).



- Body Cooling takes a place at all Times unless the Surrounding or (ambient) Temp. is At or Above 37°C
- Body Temp. Rarely Cools off to Ambient Temp. (unless it was 0°C)
- The Rate of Body Cooling: 1°C / hr → summer
  1.5°C / hr → winter

Factors affecting the Rate of Cooling

1 Initial Body Temp.

- Body Temp. Before death Should not always be assumed to be 37°C.
- Some factors should be taken into Consideration:

① oral Temp. > 0.4°C than Axillary
oral Temp. < 0.4°C than Rectal.

② diurnal Variation of almost 1°C exists in the Same individual.
highest ((4-6 pm)), lowest ((2-6 pm)).

③ Strenuous excercise may raise Temp. up to (5°C) higher than NL.
& May persist up to 30 mins after Rest.

④ Febrile illness (due to Microorganism) May raise Temp up to 5°C higher than NL. (Can also occurs in infected wounds, septic abortions, Hemorrhages →)

⑤ Hypothermia (is also common)
leaving a victim exposed for a few hrs Before death → ① 10°C Below NL

2 Body Dimensions - Body Wt -

mass & Ht of the individual affect in Cooling. Also the surface area has a role (the larger → the faster the cooling. But we should remember the role of SQ fat → acts an isolator).

- Thin → faster Cooling ((↓ fat))
  Obese → Slower ~

3 Posture

- Body - Curled up → (↓ surface area) → Slower Cooling.
- Amount of Skin resting on a surface & the Nature of the Surface.

[4] Clothings & Coverings ((① Clothes → ② Heat loss))

[5] Ambient Temp

- if ambient Temp is at or Above 37°C ((Body won't cool down it may warm up !))
- local Heating may also lead to the same result.

[6] Air movement & Humidity

- Rapid Air velocity → faster cooling
- Humidity ((damp air)) → faster cooling → faster Heat Conduction

[7] The Medium around the Body

- Body immersed in fluid / water → faster cooling
  (More Rapid in flowing Water > still water)

[8] Hemorrhage & fulminating infn.

- severe Hemorrhage (Before death) → ↑ cooling
- septicemia → Body Temp. may cont. ↑ after death.

Methods of Measuring Body Temp.

① Thermometry

- In practice Rectal (Core) Temp. is measured ((except in cases of sexual or homosexual assults are suspected))
- It helps to give an estimation of Time of death.

((ex. Temp. → 32°C / post-mortem interval is $37 - 32 + 3 = 8$ hrs $(37 - \text{Temp.} + 3)$))

- Introducting a Thermometer in a stab wound in Abdomen ((intra-hepatic)) Shouldn't be done.

② Normogram Method.

- More practical, More accurate ((Body wt, Ambient Temp.... all Factors Mentioned are taken in consideration.))

③ Multiple-site serial Measurement Method.

- Temp. is Taken from Multiple sites of the Body & estimation is made by computer system. Very accurate.

Early Changes

- early changes occur in: Eyes, Muscles, Skin & Stomach.

- Early occular Changes
  1. loss of Reflexes
  2. Mid-dilated fixed Irregular pupils (anisocoria)
  3. ↓ Eye Ball Tension
  4. Eyelids Closed incompletely
  5. Tache noire: where the sclera remains exposed to air ⇝ drying.
     2 yellow ((Become Brownish-Black after hrs)) Triangular spots appear on each side of Cornea
  6. Trucking "shunting" of Blood in the Retinal Vessels

- Muscles
  1. 1ry flaccidity ⇒ Complete loss of Tone
  2. Mild activity. 2ry to release of NT from dying Neurons.
  3. loss of Sphincter Tone

- Skin
  - Become pale.

- Stomach.
  Gastric Contents are identified in Mouth / airways in up to 25% of autopsies.

Post Mortum Decomposition (cont)

process	Putrefaction	Adipocere	Mummification
definition	destruction of Soft tissues of the body by Action of Bacteria Chief Bactoria ((C. welchii))	Body fat hydrolyzed to a waxy compound ((sweetish rancid odor))	dehydration or dessication of the tissue ((Odorless))
period	(48 - 72) hrs	3-4 wks → 5-6 maths	usually few wks
Media to occur	① Humidity ② Temp (21-38°)	Warm, Moist Anaerobic	Dry Heat ((esp. air current))
factors	① Obesity ② Child ③ Injury → (↑ entry of Bacteria)	Extreme moist & Anaerobic envir.	—
appearance	- Greenish discoloration MC Begin in ((Rt. iliac fossa)) due to : ((Sulfamet Hb)) - Marbling (RBC Hemolysis) - Skin Blisters	- Waxy. - preservation of facial features & injuries	- Parchment-like Mass & Tendons surrounds the Body - Skin Shrinkage

* Skeletilization → (12-18 maths)

The End
Farah Amer

- **This is a BLANK page for Notes**

- This is a BLANK page for Notes

- This is a BLANK page for Notes

- This is a BLANK page for Notes

- This is a BLANK page for Notes