Clinical Toxicology

CANNABINOIDS TOXICITY

Cannabis is a collective term referring to the bioactive substances from *Cannabis sativa.* The *C. sativa* plant contains a group of more than 60 chemicals called cannabinoids. The major cannabinoids are cannabinol, cannabidiol, and tetrahydrocannabinol. The principal psychoactive cannabinoid is Δ^9-tetrahydrocannabinol (THC). Marijuana is the common name for a mixture of dried leaves and flowers of the *C. sativa* plant. Hashish and hashish oil are the pressed resin and the oil expressed from the pressed resin, respectively. The concentration of THC varies from 1% in low-grade marijuana up to 50% in hash oil. Pure THC and a synthetic cannabinoid are available by prescription with the generic names of dronabinol and nabilone, respectively. Currently, marijuana is the most commonly used illicit xenobiotic in the United States.

MEDICAL USES

Cannabinoids are proposed for use in the management of many clinical conditions (Table 1), but have generally only been approved for the control of chemotherapy-related nausea and vomiting that are resistant to conventional antiemetics, for breakthrough postoperative nausea and vomiting, and for appetite stimulation in human immunodeficiency virus (HIV) patients with anorexia-cachexia syndrome. The claims of benefit in the other medical conditions in Table 1 are not supported by evidence.

Table 1: *Medical Conditions Proposed for Cannabinoid Use*

Anorexia-cachexia syndrome secondary to HIV infection[a]
Anxiety
Asthma
Depression
Epilepsy
Glaucoma
Head injury
Insomnia
Migraine headaches
Multiple sclerosis
Muscle spasticity and spasms
Nausea and vomiting (resistant)[a]
Neurologic disorders
Pain
Parkinson disease
Tourette syndrome

[a] FDA approved use.

Δ^9-THC (sometimes referred to in the literature as Δ^1-THC) was isolated in 1964. After that, two specific G protein–coupled cannabinoid-binding receptors were identified: CB1 (or *Cnr1)* and CB2 (or *Cnr).*

Both receptors inhibit adenylyl cyclase and stimulate potassium channel conductance. CB1 receptors are distributed throughout the brain. CB1 receptors are located presynaptically and their activation inhibits the release of acetylcholine, L-glutamate, γ-aminobutyric acid, noradrenaline, dopamine, and 5-hydroxytryptamine. CB2 receptors are located peripherally in immune system tissues (splenic macrophages), B lymphocytes, peripheral nerve terminals, and the vas deferens. Other brain regions in which the CB1 receptors are found include areas responsible for anxiety, pain, sensory perception, motor coordination, and endocrine function. This distribution is consistent with the clinical effects elicited by cannabinoids. CB2 receptors are believed to participate in the regulation of immune responses and inflammatory reactions.

Activity at the CB1 receptors is believed to be responsible for the clinical effects of cannabinoids, including the regulation of cognition, memory, motor activities, nociception, and nausea and vomiting. Chronic administration of a cannabinoid agonist reduces CB1 receptor density in several regions of the rat brain.

Cannabis is available in several forms:

1. Marijuana is a combination of the *C sativa* flowering tops and leaves. The THC content is 0.5-5%.
2. Hashish is dried resin collected from the flowering tops. The THC concentration is 2-20%. Hash oil is a liquid extract; it contains 15% THC.

Absorption:

The route of administration determines the absorption of the cannabis product, as follows:

- Smoking – Onset of action is rapid (within minutes); it results in 10-35% absorption of the available THC; peak plasma concentrations occur within 8 minutes.
- Ingestion – Onset occurs within 1-3 hours (unpredictable); 5-20% is absorbed due to stomach acid content and metabolism; peak plasma levels occur 2-6 hours after ingestion.

Absorption of synthetic forms is as follows:

- Dronabinol (Marinol) – 10% absorption; peak concentration 2-3 hours after ingestion.
- Nabilone (Cesanet) – Up to 90% absorption; peak concentration in 2 hours after ingestion.

Distribution:

THC has a steady-state volume of distribution of approximately 2.5 to 3.5 L/kg. Cannabinoids are lipid soluble and accumulate in fatty tissue in a biphasic pattern. Initially, THC is distributed to highly vascularized tissues such as the liver, kidneys, heart, and muscle. Following smoking or intravenous administration, the distribution half-life is less than 10 minutes. After the initial distribution phase, THC accumulates more slowly in less vascularized tissues and body fat. Once administration of Δ^8-THC

stopped, the cannabinoids were slowly released from fat stores as adipose tissue turned over.

THC crosses the placenta and enters the breast milk. Concentrations in fetal serum are 10% to 30% of maternal concentrations. Daily marijuana smoking by a nursing mother resulted in concentrations of THC in breast milk that are eightfold higher than concomitant maternal serum concentrations.

Metabolism:

THC is nearly completely metabolized by hepatic microsomal hydroxylation and oxidation by the cytochrome P450 system (primarily CYP2C9 and CYP3A4). The primary metabolite (11-hydroxy-Δ^9-THC or 11-OH-THC) is active and is subsequently oxidized to the inactive 11-nor-Δ^9-THC carboxylic acid metabolite (THC-COOH) and many other metabolites.

Clinical Manifestation:

The clinical effects of THC use, including time of onset and duration of effect, vary with the dose, the route of administration (ingestion is slower in onset than inhalation), the experience of the user, the user's vulnerability to psychoactive effects, and the setting in which the drug is used. The concomitant use of central nervous system depressants such as ethanol, or stimulants such as cocaine, alters the psychological and physiologic effects of cannabis.

ACUTE TOXICITY:

Acute toxicity may include decreases in coordination, muscle strength, and hand steadiness. Lethargy, sedation, postural hypotension, inability to concentrate, decreased psychomotor activity, slurred speech, and slow reaction time also may occur.

In young children, the acute ingestion of cannabis is potentially life threatening. Ingestion of estimated amounts of 250 to 1000 mg of hashish resulted in obtundation in 30 to 75 minutes. Tachycardia (>150 beats/min) was found in one-third of the children. Less commonly reported findings include apnea, cyanosis, bradycardia, hypotonia, and opisthotonus.

ACUTE ADVERSE REACTIONS

Cannabis users occasionally may experience distrust, dysphoria, fear, or panic reactions. Transient psychotic episodes are associated with cannabis use. Commonly reported adverse reactions at the prescribed dose of dronabinol or nabilone include postural hypotension, dizziness, sedation, xerostomia, abdominal discomfort, nausea, and vomiting. Life-threatening ventricular tachycardia (200 beats/min) has been reported.

Large doses of THC may produce confusion, amnesia, delusions, hallucinations, anxiety, and agitation. Most episodes remit rapidly.

However, a clear relationship exists between long-term cannabis use and mental health problems. Substance-abusing adolescents commonly suffer one or more comorbid health or behavioral problems. Several studies have demonstrated marijuana abuse to coexist with attention deficit hyperactivity disorder, other learning disabilities, depression, and anxiety. Cohort and well-designed cross-sectional studies suggest a modest association between early, regular, or heavy cannabis use and depression

CHRONIC USE ADVERSE EFFECTS

Long-term use of cannabis is associated with a number of adverse effects.

Cardiovascular effects
These include the following:

- Naive users may experience a sudden 20-100% rise in heart rate, lasting up to 2-3 hours
- Peripheral vasodilatation causes postural hypotension, which may lead to dizziness or syncope
- Cardiac output increases by as much as 30%, and cardiac oxygen demand is also increased; tolerance to these effects can develop within a few days of use
- Naive users can experience angina; in addition, users with preexisting coronary artery disease or cerebrovascular disease may experience myocardial infarctions, congestive heart failure, and strokes

Respiratory effects:
Respiratory effects include the following:

- Transient broncho-dilatation may occur after an acute exposure.

- With chronic heavy smoking, users experience increased cough, sputum production, and wheezing. These complaints are augmented by concurrent tobacco use.

- One study sites that the rate of decline of respiratory function in an 8-year period was greater among marijuana smokers than among tobacco smokers.

- Aside from nicotine, marijuana cigarettes contain some of the same components as tobacco smoke, including bronchial irritants, tumor initiators (mutagens), and tumor promoters. The amount of tar in a marijuana cigarette is 3 times the amount in a tobacco cigarette when smoked, with one-third greater deposition in the respiratory tract.
- Chronic cannabis use is associated with bronchitis, and emphysema.

- Several case reports strongly suggest a link between cannabis smoking and cancer of the aerodigestive system, including the oropharynx and tongue, nasal and sinus epithelium, and larynx.

Most illegally obtained marijuana is contaminated with *Aspergillus* species, which can cause invasive pulmonary aspergillosis in immunocompromised users.

Reproductive effects

These include the following:

- High-dose THC in animals causes a drop in testosterone levels, decreased sperm production, and compromised sperm motility and viability.
- THC alters the normal ovulatory cycle.

Cannabis administration during pregnancy reduces birth-weight in animals. However, studies are equivocal in humans. No evidence exists that cannabis increases the risk of birth defects.

Management:

Gastrointestinal decontamination is not recommended for patients who ingest cannabis products, nabilone, or dronabinol because clinical toxicity is rarely serious and responds to supportive care. In addition, a patient with a significantly altered mental status, such as somnolence, agitation, or anxiety, has risks associated with gastrointestinal decontamination that outweigh the potential benefits of the intervention.

Agitation, anxiety, or transient psychotic episodes should be treated with quiet reassurance and benzodiazepines (lorazepam 1–2 mg intramuscularly or diazepam 5–10 mg intravenously) or antipsychotics (haloperidol, ziprasidone) as needed. There are no specific antidotes for cannabis. Coingestants, such as cocaine or ethanol, should be identified and their effects anticipated and treated as indicated.

Lysergic Acid Diethylamide (LSD)

LSD was first synthesized on November 16, 1938 by Swiss chemist Albert Hofmann at the Sandoz Laboratories in Basel, Switzerland as part of a large research program searching for medically useful ergot alkaloid derivatives.

Lysergic acid diethylamide (LSD) is the synthetic diethylamide derivative of ergot alkaloids, and was originally synthesized exclusively from these alkaloids produced by the fungus *Claviceps purpurea*, which is a contaminant of rye and certain other grains. Today, most LSD is synthesized entirely in the laboratory, and typically sold to addicts as liquid-impregnated blotting paper or sugar cubes, tiny tablets (“microdots”), gelatin squares (“window panes”), liquid, or powder. LSD is said to be the most powerful of all hallucinogens, and is active in doses of 50 to 100 mg. It occurs as a water-soluble, colorless, tasteless and odorless powder.

Drugs related to LSD (lysergamides) also occur naturally in plants such as “Morning glory” (*Rivea corymbosa*) and “Hawaiian baby woodrose” (*Ipomoea violacea*). Seeds of morning glory contain lysergic acid hydroxyethylamide, which is 1/10th as powerful as LSD. At least 200 to 300 seeds have to be pulverized—intact seed coat resists digestion—and ingested, for inducing hallucinogenic effects.

Mode of Intake

The LSD is almost always ingested. Other less common routes of intake include intranasal, sublingual, smoking, conjuctival instillation, and very rarely injection.

Mode of Action

The LSD is structurally related to serotonin (5-hydroxy- tryptamine) and is an agonist at the 5-HT_1 receptor. Serotonin modulates many psychological and physiological processes including mood, personality, affect, appetite, sexual desire, motor function, temperature regulation, pain perception, and sleep induction. LSD inhibits central raphe neurons of brainstem through stimulation of 5-HT_{1A} receptors, which are coupled to adenylcyclase. LSD is also an agonist at 5-$HT_{2A,\ 2C}$ receptors, which are not located presynaptically on serotonergic cell bodies but on certain subpopulations of neurons in postsynaptic regions. The majority of 5-HT_2 receptors in the brain are located in the cerebral cortex. Animal experiments have shown that LSD is anatomically distributed maximally in the visual and auditory cortex, and the limbic cortex (besides the pituitary, pineal, and hypothalamic areas), which parallels the finding of high concentration of 5-HT_2 receptors in human cerebral cortex. Recent studies also suggest that activation of D_1 (dopamine) receptors may contribute to the neurochemical effects of LSD.

The LSD has a half-life of 2.5 hours, while the duration of effects lasts for up to 8 hours. But psychotropic effects can occur for several days, and urine-screen is usually positive for 100 to 120 hours. The route of metabolism is hepatic hydroxylation. The usual dose of abuse is 100 to 300 mcg. Doses over 0.2 mg/kg are potentially lethal.

Clinical (Toxic) Features

- **Acute Poisoning:**

A.Physical :

Mydriasis, hippus. – Vertigo. – Tachycardia, hypertension. – Sweating, piloerection. – Hyperthermia. – Tachypnoea. – Muscle weakness, ataxia. – Hyperactivity. – Coma.

B. Psychological :

Euphoria or dysphoria,

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Bizarre perceptual changes: People's faces and body parts appear distorted, objects undulate, sounds may be magnified and distorted, colors seem brighter with halos around objects. Occasionally there is depersonalisation, and the hallucinating person may feel as if he is observing an event instead of being involved in it.

- **Chronic Poisoning:**

a. Prolonged psychotic reactions, which are mainly schizophrenic in nature.

b. Severe depression.

c. Flashback phenomena: The person relives the LSD experience periodically in the absence of drug intake for months or years.

d. Post-hallucinogen perception disorder: A persistent perceptual disorder often described by the person as if he is residing in a bubble under water in a "purple haze", with trailing of lights and images. Associated anxiety, panic, and depression are common.

Diagnosis

- Radioimmunoassay of serum or urine (limit of detection 0.1ng/ml).
- HPTLC (high performance thin layer chromatography) can detect LSD in urine in concentrations less than 1 mcg/litre.
    - HPLC (high pressure/performance liquid chromatography) of serum and urine.
    - GC-MS (gas chromatography–mass spectrometry) can confirm positive LSD urine levels to a lower limit of 5 pg/ml.

Treatment

- Avoid gut decontamination as LSD is ingested in micro- quantities and rapidly absorbed, rendering decontamination procedures totally redundant.
- Do not use restraints in agitated patients; it will only exacerbate the condition.
- Because of the short half-life and few serious medical reactions, elimination enhancement procedures such as haemodialysis, haemoperfusion, etc. are not warranted.
- Treat acute panic attacks with quiet environment, reassurance, supportive care, and administration of diazepam (5–10 mg IV) or haloperidol (in severe cases).
- Treat acute psychotic reactions with cautious administration of neuroleptics such as haloperidol. Avoid phenothiazine, which can cause hypotension, sedation, extrapyramidal reactions, lowered seizure threshold, and potentiation of anticholinergic effects.
- Treat flashbacks with psychotherapy, anti-anxiety agents, and neuroleptics.
- Treat post-hallucinogen perception disorder with long- lasting benzodiazepines such as clonazepam, and to lesser extent anticonvulsants such as valproic acid and carbamazepine. This approach must be combined with behavioral therapy. The patient must be instructed not to consume alcohol, cannabis, caffeine, and other drugs, which can intensify the disorder.

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- Radioimmunoassay of serum or urine (limit of detection 0.1ng/ml).
- HPTLC (high performance thin layer chromatography) can detect LSD in urine in concentrations less than 1 mcg/litre.
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Treatment

- Avoid gut decontamination as LSD is ingested in micro- quantities and rapidly absorbed, rendering decontamination procedures totally redundant.
- Do not use restraints in agitated patients; it will only exacerbate the condition.
- Because of the short half-life and few serious medical reactions, elimination enhancement procedures such as haemodialysis, haemoperfusion, etc. are not warranted.
- Treat acute panic attacks with quiet environment, reassurance, supportive care, and administration of diazepam (5–10 mg IV) or haloperidol (in severe cases).
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Clinical Toxicology

CAUSTICS

Exposure to caustic agents may occur via the dermal, ocular, respiratory, and gastrointestinal routes with the most significant of these, by far, resulting from ingestion. Morbidity and mortality from exposures to caustics is a worldwide problem.

Caustics cause both histologic and clinical damage on contact with tissues. Table 1 lists common caustics and the commercial products that contain them. Many are available for home use, in both solid and liquid forms, with variations in viscosity, concentration, and pH. Usually, children are unintentionally exposed to household products. Adults may be exposed to household or industrial products that result from occupational exposure or are suicide attempts.

PATHOPHYSIOLOGY

A caustic is a xenobiotic that causes both functional and histologic damage on contact with tissue surfaces. Although there are many ways to categorize caustics, they are most typically classified as acids or alkalis. An acid is a proton donator and causes significant injury, generally at a pH below 3. An alkali is a proton acceptor and causes significant injury, generally at a pH above 11. The extent of injury is modulated by duration of contact; ability of the caustic to penetrate tissues; volume, pH, and concentration; the presence or absence of food in the stomach; and a property known as *titratable acid*/*alkaline reserve* (TAR). TAR quantifies the amount of neutralizing xenobiotic needed to bring the pH of a caustic to that of physiologic tissues. Neutralization of caustics takes place at the expense of the tissues, resulting in the release of thermal energy, producing burns. Generally, as the TAR of caustics increases, so does their ability to produce tissue damage. Some xenobiotics, such as zinc chloride and phenol, have a high TAR and are capable of producing severe burns even though their pH is near physiologic.

ALKALIS

Following exposure to an alkaline xenobiotic, dissociated hydroxide (OH^-) ions penetrate tissue surfaces producing what is histologically described as liquefactive necrosis. This process includes protein dissolution, collagen destruction, fat saponification, cell membrane emulsification, transmural thrombosis, and cell death.

The alkali, such as sodium hydroxide ("liquid lye"), then continues to penetrate until the OH^- concentration is sufficiently neutralized by the tissues.

Although federal regulations have lowered the maximal available house- hold concentration of many caustics, there are two industrial strength products that seem to be readily available and therefore warrant special mention: ammonium hydroxide and sodium hypochlorite. Ammonia (ammonium hydroxide) products are weak bases—

partially dissociated in water—that can cause significant esophageal burns, depending on the concentration and volume ingested. Household ammonium hydroxide ranges in concentration from 3% to 10%. Strictures have formed in patients who ingested 28% solutions. Sodium hypochlorite is the major component in most industrial and household bleaches. Large case series and reports have found that severe injuries occur only in patients with large-volume ingestions of concentrated products and that most other patients do well with supportive care.

Table 1:

Xenobiotic	Applications
Acetic acid	Permanent wave neutralizers, photographic stop bath
Ammonia (ammonium hydroxide)	Toilet bowl cleaners, metal cleaners and polishes, hair dyes and tints, antirust products, jewelry cleaners, floor strippers, glass cleaners, wax removers
Benzalkonium chloride	Detergents
Boric acid	Roach powders, water softeners, germicide
Formaldehyde, formic acid	Deodorizing tablets, plastic menders, fumigant, embalming agent
Hydrochloric acid (muriatic acid)	Metal and toilet bowl cleaners
Hydrofluoric acid	Antirust products, glass etching, microchip etching
Iodine	Antiseptics
Mercuric chloride ($HgCl_2$)	Preservative
Methylethyl ketone peroxide	Industrial synthetic agent
Oxalic acid	Disinfectants, household bleach, metal polish, antirust products, furniture refinisher
Phenol (creosol, creosote)	Antiseptics, preservatives
Phosphoric acid	Toilet bowl cleaners
Phosphorus	Matches, fireworks, rodenticides, methamphetamine synthesis
Potassium permanganate	Illicit abortifacient, antiseptic solution
Selenious acid	Gun bluing agent
Sodium hydroxide	Detergents, paint removers, drain cleaners and openers, oven cleaners
Sodium borates, carbonates, phosphates, and silicates	Detergents, electric dishwasher preparations, water softeners
Sodium hypochlorite	Bleaches, cleansers
Sulfuric acid	Automobile batteries, drain cleaners
Zinc chloride	Soldering flux

Ingestion of button batteries were once considered a unique caustic exposure. Composed of metal salts and a variety of alkaline xenobiotics, such as sodium and potassium hydroxide, leakage of battery contents was a legitimate concern. In recent years, however, new techniques used in the production of button batteries that effectively prevent leakage have shifted the concern following their ingestion from caustic to foreign-body exposure. Household detergents, such as laundry powders and dishwasher detergents, contain silicates, carbonates, and phosphates, and have the potential to induce caustic burns and strictures even when ingested unintentionally.

ACIDS

In contrast to alkaline exposures, following exposure to an acid, hydrogen (H^+) ions desiccate epithelial cells, producing an eschar and resulting in what is histologically referred to as *coagulation necrosis*. This process leads to edema, erythema, mucosal sloughing, ulceration, and necrosis of tissues. Dissociated anions of the acid (Cl^-, SO_4^{2-}, PO_4^{3-}) also act as reducing agents further injuring tissue.

Ophthalmic exposure to acids results in coagulative necrosis that tends to prevent further penetration into deeper layers of the eye. In most series, following an acid ingestion, both the gastric and esophageal mucosa are equally affected. On occasion, the esophagus may be spared damage while severe injury is noted in the stomach. Skip lesions from acid ingestions may be a function of viscosity and contact time.

CLASSIFICATION AND PROGRESSION OF CAUSTIC INJURY

Esophageal burns, secondary to both alkali and acid exposures, are classified based on endoscopic visualization that employs a grading system similar to that used with burns of the skin. Grade I burns are generally described as hyperemia or edema of the mucosa without evidence of ulcer formation. Grade II burns include submucosal lesions, ulcerations, and exudates. Some authors further divide grade II lesions into grade IIa, non-circumferential lesions, and grade IIb, near circumferential injuries. Grade III burns are defined as deep ulcers and necrosis into the periesophageal tissues.

Human case reports, postmortem studies, histologic inspection of surgical specimens, and experimental animal models reveal a consistent pattern of injury and repair following caustic injury. As wound healing of gastrointestinal tract tissue occurs, neovascularization and fibroblast proliferation take place, laying down new collagen and replacing the damaged tissue with granulation tissue. A similar pattern of repair occurs following caustic injuries of the eye.

Burns of the esophagus may persist for up to 8 weeks as remodeling takes place, and may be followed by esophageal shortening. If the initial injury penetrates deeply enough, there is progressive narrowing of the esophageal lumen. The dense scar formation presents clinically as a stricture. Strictures can evolve over a period of weeks to months, leading to dysphagia and significant nutritional deficits. Grade I burns carry no risk of stricture formation. Grade II circumferential burns lead to stricture formation in approximately 75% of cases. Grade III burns invariably progress to stricture formation and are also at a

high risk of perforation.

DIAGNOSTIC TESTING

LABORATORY

All patients with presumed serious caustic exposure should have an evaluation of serum pH, blood type and cross-match, hemoglobin, coagulation parameters, electrolytes, and urinalysis. Elevated prothrombin time (PT) and partial thromboplastin times, as well as an arterial pH lower than 7.22 are associated with severe caustic injury.

Absorption of nonionized acid from the stomach mucosa may result in acidemia. Following ingestion of hydrochloric acid, hydrogen and chloride ions (both of which are accounted for in the measurement of the anion gap) dissociate in the serum resulting in a hyperchloremic normal anion gap metabolic acidosis. Although alkalis are not absorbed systemically, necrosis of tissue may result in a metabolic acidosis with an elevated lactate concentration.

RADIOLOGY

Chest and abdominal radiographs are useful in the initial stages of assessment to detect gross signs of esophageal or gastric perforation. Signs of alimentary tract perforation that may be present on plain radiographs. However, these studies have a limited sensitivity, and an absence of findings does not preclude perforation.

CT scanning is considerably more sensitive than radiography for detecting viscus perforation and should be obtained in patients with potentially serious caustic ingestions as soon as is feasible.

A contrast esophagram is useful for defining the extent of esophageal injury. Late after the ingestion, it can detect stricture formation. In patients for whom there is a high suspicion for esophageal perforation and in whom adequate visualization of the upper gastrointestinal tract by endoscopy is not possible (grade IIb circumferential burns or grade III burns), an enteric contrast study can be obtained 24 hours after the ingestion. Extravasation of contrast outside of the gastrointestinal tract is diagnostic of perforation. Water-soluble contrast should be used when perforation is suspected as it is less irritating to mediastinal and peritoneal tissues if extravasated. However, barium contrast agents are more radiopaque than water-soluble agents and offer greater radiographic detail. Consequently, some authors recommend barium swallow if the water-soluble contrast study is nondiagnostic but demonstrates no leak. In addition, if there is risk of aspiration, barium is preferred because water-soluble contrast material can cause a severe chemical pneumonitis.

CT has great sensitivity at detecting extraluminal air in the mediastinum or peritoneal cavity as a sign of perforation. In addition, CT can visualize the esophagus and stomach distal to severe caustic burns that cannot be safely seen using endoscopy or an esophagram. CT may therefore replace enteric contrast radiography for detection of perforation in the acute stage (within 24 hours) of a caustic ingestion.

ENDOSCOPY

Endoscopy should be performed within 12 hours and generally not later than 24 hours postingestion. Numerous case series demonstrate that the procedure is safe during this period. Early endoscopy serves multiple purposes in that it allows patients with minimal or no evidence of gastrointestinal injury to be discharged. It also offers a rapid means of obtaining diagnostic and prognostic information while shortening the period of time that patients forego nutritional support, permitting more precise treatment regimens. The use of endoscopic assessment from the 2nd or 3rd day postingestion is discouraged and should be avoided between 5 days and 2 weeks postingestion as it is at this time that wound strength is least and the risk of perforation is greatest.

The choice of rigid versus flexible endoscopy is dependent on the comfort and experience of the endoscopist.

MANAGEMENT

- ACUTE MANAGEMENT

As in the case of any patient presenting with a toxicologic emergency, the healthcare provider must adhere to universal precautions. Initial stabilization should include airway inspection and protection, basic resuscitation principles, and decontamination. Examination of the oropharynx for signs of injury, drooling, and vomitus, as well as careful auscultation of the neck and chest for stridor, may reveal signs of airway edema that should prompt immediate airway protection. Careful and constant attention to signs and symptoms of respiratory distress and airway edema, such as a change in voice, are essential and should prompt intubation as airway edema may rapidly progress over minutes to hours.

A delay in prophylactic airway protection may make subsequent attempts at intubation or bag-valve-mask ventilation difficult or impossible.

Direct visual inspection of the vocal cords with a fiberoptic laryngoscope may also reveal signs of impending airway compromise. Patients necessitating intubation are best served by direct visualization of the airway either via direct laryngoscopy or fiberoptic endoscope, as perforation of edematous tissues of the pharynx and larynx is a grave complication that may occur during blind nasotracheal intubation attempts.

Following control of the airway, large-bore intravenous access should be secured and volume resuscitation initiated.

DECONTAMINATION, DILUTION, AND NEUTRALIZATION

Decontamination should begin with careful, copious irrigation of the patient’s skin and eyes when indicated to remove any residual caustic and to prevent contamination of other patients and staff.

Gastrointestinal decontamination is usually limited in patients with a caustic ingestion. Induced emesis is contraindicated, as it may cause reintroduction of the caustic to the upper gastrointestinal tract and airway. Activated charcoal is also contraindicated, as it will interfere with tissue evaluation by endoscopy and preclude a subsequent

management plan. Additionally, most caustics are not adsorbed to activated charcoal.

Gastric emptying via cautious placement of a narrow nasogastric tube with gentle suction may be attempted to remove the remaining acid in the stomach only in patients with large life-threatening intentional ingestions of acid who present within 30 minutes.

Therefore, preventing absorption of some portion of the ingested acid may have potential benefit in reducing systemic toxicity. Although the procedure has the potential to induce injury, a risk-to-benefit analysis favors gastric emptying following a presumed lethal ingestion.

In contrast, gastric emptying should be avoided with alkaline and unknown caustic ingestions as blind passage of a nasogastric tube carries the risk of perforation of damaged tissues; a risk that outweighs the benefit.

Exceptions to the general rules of gastrointestinal decontamination of caustic agents exist in the management of zinc chloride ($ZnCl_2$) and mercuric chloride ($HgCl_2$). Both are caustics with severe systemic toxicity. Ingestion of these xenobiotics causes life-threatening illness from cationic metal exposure.

The local caustic effects, though of great concern, are less consequential than the manifestations of systemic absorption. Therefore, prevention of systemic absorption should be addressed primarily, followed by the direct assessment and management of the local effects of these xenobiotics. Initial management to prevent systemic absorption includes aggressive decontamination with gentle nasogastric tube aspiration and administration of activated charcoal. In vitro data exist to suggest adequate charcoal adsorption of Hg^{2+}ion.

The use of dilutional therapy has been examined using in vitro, ex vivo, and in vivo models in an attempt to assess its efficacy in caustic ingestions. An early in vitro model demonstrated a dramatic increase in temperature when either water or milk was added.

Another in vitro model found less consequential increases in temperature despite large volumes of diluent. Results of both studies suggested that dilutional therapy was of limited benefit.

Additionally, the usefulness of dilution appeared to be inversely related to the length of time from exposure, with minimal efficacy noted in as little as 30 minutes.

The extrapolation of these variable results to humans with caustic ingestions is limited, and suggests that histologic damage can only be attenuated by milk or water when administered within the first seconds to minutes following ingestion.

Caution should be used in advising patients or family members about the use of dilutional agents. A child who refuses to swallow or take oral liquids should never be forced to do so. In general, dilutional therapy should be limited to patients within the first few minutes after ingestion who have no airway compromise, who are not complaining of significant

pharyngeal, chest, or abdominal pain, who are not vomiting, and who are alert. Dilutional therapy should be avoided in patients with nausea, drooling, stridor, or abdominal distension as it may stimulate vomiting and result in reintroduction of the caustic into the upper gastrointestinal tract.

Attempts at neutralization of ingested caustics should likewise be avoided. This technique has the potential to worsen tissue damage by forming gas and generating an exothermic reaction.

SURGICAL MANAGEMENT

The decision to perform surgery in patients with caustic ingestions is obvious in the presence of either endoscopic or diagnostic imaging evidence of perforation, severe abdominal rigidity, or persistent hypotension. Hypotension is a grave finding and often indicates perforation or significant blood loss. Additionally, elevated prothrombin time (PT) and partial thromboplastin times, as well as an arterial pH lower than 7.22, are associated with severe caustic injury.

- SUBACUTE MANAGEMENT

The extent of tissue injury dictates the subsequent management and disposition of patients with caustic ingestions.

Grade I Esophageal Injuries Patients with isolated grade I injuries of the esophagus do not develop strictures and are not at increased risk of carcinoma. Their diet can be resumed as tolerated. No further therapy is required. These patients can be discharged from the hospital as long as they are able to eat and drink and their psychiatric status is stable.

Grade IIa Esophageal Injuries If endoscopy reveals grade IIa lesions of the esophagus and sparing of the stomach, a soft diet can be resumed as tolerated, or a nasogastric tube can be passed under direct visualization. If oral intake is contraindicated because of the risk of perforation, feeding via gastrostomy, jejunostomy, or total parenteral nutrition should be instituted as rapidly as possible.

Grades IIb and III Esophageal Injuries Patients with grades IIb and III lesions must be followed for the complications of perforation, infection, and stricture development. Strictures are a debilitating complication of both acid and alkaline ingestions that can evolve over a period of weeks or months.

Although steroid therapy is theorized to arrest the process of inflammatory repair and potentially prevent stricture formation, there is some evidence that grade III burns, in particular, will progress to stricture formation regardless of therapy. In addition to stricture formation, patients with grade III burns are also at high risk for other complications, including fistula formation, infection, and perforation with associated mediastinitis and peritonitis. The use of corticosteroids in the management of grade III burns may mask infection and make the friable, necrotic esophageal tissue more prone to perforation. For these reasons, steroid therapy is not a recommended therapy for grade III

esophageal burns. When required in these patients for other indications such as caustic-induced airway inflammation, short-term steroids should be administered in conjunction with antibiotics.

A variety of other management strategies have been used in an attempt to prevent strictures and esophageal obstruction. In both animal models and in human case series, intraluminal stents and nasogastric tubes made of silicone rubber tubing can successfully maintain the patency of the esophageal lumen. These tubes are left in place for 3 weeks and are often used with concomitant corticosteroid and antibiotic therapy

Additionally, multiple therapies have been studied in various animal models in an attempt to identify agents that either inhibit synthesis or stimulate breakdown of collagen and thereby prevent stricture formation. □-Amino propionitrile (BAPN), penicillamine, *N*-acetylcysteine (NAC), halofuginone, vitamin E, and colchicine are some of these agents.

- CHRONIC TREATMENT OF STRICTURES

Commonly, the management of esophageal strictures includes early endoscopic dilation for which a variety of types of dilators are available. Contrast CT can be used to determine maximal esophageal wall thickness, which can then be used to predict response, as well as the number of sessions required to achieve adequate dilation. Multiple dilations are often necessary.

Measurement of maximal wall thickness may be also be useful in determining long-term follow up, type of nutritional support, and the potential need for surgical repair as an alternative to dilations. It may also provide an indication for those who should undergo dilations under fluoroscopy to limit the risk of perforation.

The risk of perforation from esophageal dilation is decreased if the initial procedure is delayed beyond 4 weeks postingestion, when healing, remodeling, and potential stricture formation in the esophagus have already taken place.

Patients with stricture formation require long-term endoscopic follow up for the presence of neoplastic changes of the esophagus that may occur with a delay of several decades.

Clinical Toxicology

CAUSTICS

Exposure to caustic agents may occur via the dermal, ocular, respiratory, and gastrointestinal routes with the most significant of these, by far, resulting from ingestion. Morbidity and mortality from exposures to caustics is a worldwide problem.

Caustics cause both histologic and clinical damage on contact with tissues. Table 1 lists common caustics and the commercial products that contain them. Many are available for home use, in both solid and liquid forms, with variations in viscosity, concentration, and pH. Usually, children are unintentionally exposed to household products. Adults may be exposed to household or industrial products that result from occupational exposure or are suicide attempts.

PATHOPHYSIOLOGY

A caustic is a xenobiotic that causes both functional and histologic damage on contact with tissue surfaces. Although there are many ways to categorize caustics, they are most typically classified as acids or alkalis. An acid is a proton donator and causes significant injury, generally at a pH below 3. An alkali is a proton acceptor and causes significant injury, generally at a pH above 11. The extent of injury is modulated by duration of contact; ability of the caustic to penetrate tissues; volume, pH, and concentration; the presence or absence of food in the stomach; and a property known as *titratable acid*/*alkaline reserve* (TAR). TAR quantifies the amount of neutralizing xenobiotic needed to bring the pH of a caustic to that of physiologic tissues. Neutralization of caustics takes place at the expense of the tissues, resulting in the release of thermal energy, producing burns. Generally, as the TAR of caustics increases, so does their ability to produce tissue damage. Some xenobiotics, such as zinc chloride and phenol, have a high TAR and are capable of producing severe burns even though their pH is near physiologic.

ALKALIS

Following exposure to an alkaline xenobiotic, dissociated hydroxide (OH^-) ions penetrate tissue surfaces producing what is histologically described as liquefactive necrosis. This process includes protein dissolution, collagen destruction, fat saponification, cell membrane emulsification, transmural thrombosis, and cell death.

The alkali, such as sodium hydroxide ("liquid lye"), then continues to penetrate until the OH^- concentration is sufficiently neutralized by the tissues.

Although federal regulations have lowered the maximal available house- hold concentration of many caustics, there are two industrial strength products that seem to be readily available and therefore warrant special mention: ammonium hydroxide and sodium hypochlorite. Ammonia (ammonium hydroxide) products are weak bases—

partially dissociated in water—that can cause significant esophageal burns, depending on the concentration and volume ingested. Household ammonium hydroxide ranges in concentration from 3% to 10%. Strictures have formed in patients who ingested 28% solutions. Sodium hypochlorite is the major component in most industrial and household bleaches. Large case series and reports have found that severe injuries occur only in patients with large-volume ingestions of concentrated products and that most other patients do well with supportive care.

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Sulfuric acid	Automobile batteries, drain cleaners
Zinc chloride	Soldering flux

Ingestion of button batteries were once considered a unique caustic exposure. Composed of metal salts and a variety of alkaline xenobiotics, such as sodium and potassium hydroxide, leakage of battery contents was a legitimate concern. In recent years, however, new techniques used in the production of button batteries that effectively prevent leakage have shifted the concern following their ingestion from caustic to foreign-body exposure. Household detergents, such as laundry powders and dishwasher detergents, contain silicates, carbonates, and phosphates, and have the potential to induce caustic burns and strictures even when ingested unintentionally.

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DIAGNOSTIC TESTING

LABORATORY

All patients with presumed serious caustic exposure should have an evaluation of serum pH, blood type and cross-match, hemoglobin, coagulation parameters, electrolytes, and urinalysis. Elevated prothrombin time (PT) and partial thromboplastin times, as well as an arterial pH lower than 7.22 are associated with severe caustic injury.

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RADIOLOGY

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CT scanning is considerably more sensitive than radiography for detecting viscus perforation and should be obtained in patients with potentially serious caustic ingestions as soon as is feasible.

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ENDOSCOPY

Endoscopy should be performed within 12 hours and generally not later than 24 hours postingestion. Numerous case series demonstrate that the procedure is safe during this period. Early endoscopy serves multiple purposes in that it allows patients with minimal or no evidence of gastrointestinal injury to be discharged. It also offers a rapid means of obtaining diagnostic and prognostic information while shortening the period of time that patients forego nutritional support, permitting more precise treatment regimens. The use of endoscopic assessment from the 2nd or 3rd day postingestion is discouraged and should be avoided between 5 days and 2 weeks postingestion as it is at this time that wound strength is least and the risk of perforation is greatest.

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MANAGEMENT

- ACUTE MANAGEMENT

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Decontamination should begin with careful, copious irrigation of the patient’s skin and eyes when indicated to remove any residual caustic and to prevent contamination of other patients and staff.

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The use of dilutional therapy has been examined using in vitro, ex vivo, and in vivo models in an attempt to assess its efficacy in caustic ingestions. An early in vitro model demonstrated a dramatic increase in temperature when either water or milk was added.

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SURGICAL MANAGEMENT

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- SUBACUTE MANAGEMENT

The extent of tissue injury dictates the subsequent management and disposition of patients with caustic ingestions.

Grade I Esophageal Injuries Patients with isolated grade I injuries of the esophagus do not develop strictures and are not at increased risk of carcinoma. Their diet can be resumed as tolerated. No further therapy is required. These patients can be discharged from the hospital as long as they are able to eat and drink and their psychiatric status is stable.

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Although steroid therapy is theorized to arrest the process of inflammatory repair and potentially prevent stricture formation, there is some evidence that grade III burns, in particular, will progress to stricture formation regardless of therapy. In addition to stricture formation, patients with grade III burns are also at high risk for other complications, including fistula formation, infection, and perforation with associated mediastinitis and peritonitis. The use of corticosteroids in the management of grade III burns may mask infection and make the friable, necrotic esophageal tissue more prone to perforation. For these reasons, steroid therapy is not a recommended therapy for grade III

esophageal burns. When required in these patients for other indications such as caustic-induced airway inflammation, short-term steroids should be administered in conjunction with antibiotics.

A variety of other management strategies have been used in an attempt to prevent strictures and esophageal obstruction. In both animal models and in human case series, intraluminal stents and nasogastric tubes made of silicone rubber tubing can successfully maintain the patency of the esophageal lumen. These tubes are left in place for 3 weeks and are often used with concomitant corticosteroid and antibiotic therapy

Additionally, multiple therapies have been studied in various animal models in an attempt to identify agents that either inhibit synthesis or stimulate breakdown of collagen and thereby prevent stricture formation. □-Amino propionitrile (BAPN), penicillamine, *N*-acetylcysteine (NAC), halofuginone, vitamin E, and colchicine are some of these agents.

- CHRONIC TREATMENT OF STRICTURES

Commonly, the management of esophageal strictures includes early endoscopic dilation for which a variety of types of dilators are available. Contrast CT can be used to determine maximal esophageal wall thickness, which can then be used to predict response, as well as the number of sessions required to achieve adequate dilation. Multiple dilations are often necessary.

Measurement of maximal wall thickness may be also be useful in determining long-term follow up, type of nutritional support, and the potential need for surgical repair as an alternative to dilations. It may also provide an indication for those who should undergo dilations under fluoroscopy to limit the risk of perforation.

The risk of perforation from esophageal dilation is decreased if the initial procedure is delayed beyond 4 weeks postingestion, when healing, remodeling, and potential stricture formation in the esophagus have already taken place.

Patients with stricture formation require long-term endoscopic follow up for the presence of neoplastic changes of the esophagus that may occur with a delay of several decades.

Clinical Toxicology Lecture 1

Initial evaluation of the patient: Vital signs and toxic syndromes

In the practice of medical toxicology, vital signs play an important role beyond assessing and monitoring the overall status of a patient, as they frequently provide valuable physiologic clues to the toxicologic etiology and severity of an illness. The vital signs also are a valuable parameter, which are used to assess and monitor a patient's response to supportive treatment and antidotal therapy

Pulse rate, respiratory rate and temperature were incorporated into the bedside chart and called "vital signs. It was not until the early part of the 20th century, however, that blood pressure determination also became routine. Additional components of the standard emergency assessment, such as oxygen saturation by pulse oximetry, capillary blood glucose, and pain severity, are now also beginning to be considered vital signs.

Table 1 presents the normal vital signs for various age groups. However, this broad range of values considered normal should serve merely as a guide. Only a complete assessment of a patient can determine whether or not a particular vital sign is truly clinically normal. This table of normal vital signs is useful in assessing children because normal values for children vary considerably with age, and knowing the range of normal variation is essential. Normal temperature is defined as 95° to 100.4°F (35° to 38°C).

Table 1: Normal Vital Signs by Age[a]

Age	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse (beats/min)	Respirations (breaths/min)[b]
Adult	≤120	<80	60–100	16–24
16 years	≤120	<80	80	16–30
12 years	119	76	85	16–30
10 years	115	74	90	16–30
6 years	107	69	100	20–30
4 years	104	65	110	20–30
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[a] The normal rectal temperature is defined as 95°F to 100.4°F (35°C–38°C) for all ages. For children 1 year of age or younger, these values are the mean values for the 50th percentile. For older children, these values represent the 90th percentile at a specific age for the 50th percentile of weight in that age group.

[b] These values were determined in the emergency department and may be environment and situation dependent.

Many xenobiotics affect the autonomic nervous system, which, in turn, affects the vital

signs via the sympathetic pathway, the parasympathetic pathway, or both. Meticulous attention to both the initial and repeated determinations of vital signs is of extreme importance in identifying a pattern of changes suggesting a particular xenobiotic or group of xenobiotics. The value of serial monitoring of the vital signs is demonstrated by the patient who presents with an anticholinergic overdose who is then given the antidote, physostigmine. In this situation, it is important to recognize when tachycardia becomes bradycardia (i.e., anticholinergic syndrome followed by physostigmine excess). Meticulous attention to these changes ensures that the therapeutic interventions can be modified or adjusted accordingly.

Similarly, consider the course of a patient who has opioid-induced bradypnea (a decreased rate of breathing) and then develops tachypnea (an increased rate of breathing) after the administration of the opioid antagonist naloxone. The analysis becomes exceedingly complicated when that patient may have been exposed to two or more substances.

Table 2 describes the most typical toxic syndromes. This table includes only vital signs that are thought to be characteristically abnormal or pathognomonic and directly related to the toxicologic effect of the xenobiotic.

Table 2: Toxic Syndromes

	Vital Signs								
Group	BP	P	R	T	Mental Status	Pupil Size	Peristalsis	Diaphoresis	Other
Anticholinergics	–/↑	↑	±	↑	Delirium	↑	↓	↓	Dry mucous membranes, flush, urinary retention
Cholinergics	±	±	–/↑	–	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative–hypnotics	↓	↓	↓	–/↓	Depressed, agitated	±	↓	–	Hyporeflexia, ataxia
Opioids	↓	↓	↓	↓	Depressed	↓	↓	–	Hyporeflexia
Sympathomimetics	↑	↑	↑	↑	Agitated	↑	–/↑	↑	Tremor, seizures
Withdrawal from ethanol or sedative–hypnotics	↑	↑	↑	↑	Agitated, disoriented hallucinations	↑	↑	↑	Tremor, seizures
Withdrawal from opioids	↑	↑	–	–	Normal, anxious	↑	↑	↑	Vomiting, rhinorrhea, piloerection, diarrhea, yawning

↑ = increases; ↓ = decreases; ± = variable; – = change unlikely; BP, blood pressure; P, pulse; R, respirations; T, temperature.

In some instances, an unexpected combination of findings may be particularly helpful in identifying a xenobiotic or a combination of xenobiotics. For example, an increase in pulse with a decrease in blood pressure (cyclic antidepressants or phenothiazines), or the presentation of a decrease in pulse with an increase in blood pressure (ergot alkaloids) may be extremely helpful in diagnosing a toxic etiology.

BLOOD PRESSURE

Xenobiotics cause hypotension by four major mechanisms: decreased peripheral vascular resistance, decreased myocardial contractility, dysrhythmias, and depletion of intravascular volume. Many xenobiotics can initially cause orthostatic hypotension, and

any xenobiotic that affects autonomic control of the heart or peripheral capacitance vessels may lead to orthostatic hypotension. Hypertension from xenobiotics may be caused by CNS sympathetic overactivity, increased myocardial contractility or increased peripheral vascular resistance, or a combination of these.

PULSE RATE

Extremely useful clinical information can be obtained by evaluating the pulse rate. The normal heart rate for adults was defined by consensus more than 50 years ago as a regular rate greater than 60 beats/min and less than 100 beats/min.

Because pulse rate is the net result of a balance between sympathetic (adrenergic) and parasympathetic (muscarinic and nicotinic) tone, many xenobiotics that exert therapeutic or toxic effects or cause pain syndromes, hyperthermia, or volume depletion also affect the pulse rate. With respect to temperature, there is a direct correlation between pulse rate and temperature in that pulse rate increases approximately 8 beats/min for each 1.8°F (1°C) elevation in temperature.[4]

The inability to differentiate easily between sympathomimetic and anticholinergic xenobiotic effects by vital signs alone illustrates the principle that no single vital sign abnormality can definitively establish a toxicologic diagnosis. In trying to differentiate between a sympathomimetic and anticholinergic toxic syndrome, it should be understood that although tachycardia commonly results from both sympathomimetic and anticholinergic xenobiotics, when tachycardia is accompanied by diaphoresis or increased bowel sounds, adrenergic toxicity is suggested, but when tachycardia is accompanied by decreased sweating, absent bowel sounds, and urinary retention, anticholinergic toxicity is likely.

RESPIRATIONS

Establishment of an airway and evaluation of respiratory status are the initial priorities in patient stabilization. Although respirations are typically assessed initially for rate alone, careful observation of the depth and pattern is essential for establishing the etiology of a systemic illness or toxicity.

The term *hyperventilation* may mean tachypnea (an increase in ventilatory rate), hyperpnea (an increase in tidal volume), or both. Hyperventilation may result from the direct effect of a CNS stimulant, such as the direct effect of salicylates, on the brainstem. Bradypnea may occur when a CNS depressant acts on the brainstem. A progression from fast to slow breathing may also occur in a patient exposed to increasing concentrations of cyanide or carbon monoxide.

TEMPERATURE

Temperature evaluation and control are critical. However, temperature assessment can be done only if safe and reliable equipment is used. The risks of inaccuracy are substantial when an oral temperature is taken in a tachypneic patient, an axillary temperature or a temporal artery temperature is taken in any patient (especially those found outdoors), or a tympanic temperature is taken in a patient with cerumen impaction. Obtaining rectal temperatures using a nonglass probe is essential for safe and accurate temperature determinations in agitated individuals and is considered the standard method of temperature determination in this text.

The core temperature or deep internal temperature (T) is relatively stable (98.6° ± 1.08°F; 37° ± 0.6°C) under normal physiologic circumstances. Hypothermia (T <95°F; <35°C) and hyperthermia (T >100.4°F; >38°C) are common manifestations of toxicity.

PRINCIPLES OF MANAGING THE ACUTELY POISONED OR OVERDOSED PATIENT

Similar to the management of any seriously compromised patient, the clinical approach to the patient potentially exposed to a xenobiotic begins with the recognition and treatment of life-threatening conditions, including airway compromise, breathing difficulties, and circulatory problems such as hemodynamic instability and serious dysrhythmias. After the "ABCs" (airway, breathing, and circulation) have been addressed, the patient's level of consciousness should be assessed because this helps determine the techniques to be used for further management of the exposure.

Management of patients with altered mental status:

Altered mental status (AMS) is defined as the deviation of a patient's sensorium from normal. Although it is commonly construed as a depression in the patient's level of consciousness, a patient with agitation, delirium, psychosis, and other deviations from normal is also considered to have an AMS. After airway patency is established or secured, an initial bedside assessment should be made regarding the adequacy of breathing. If it is not possible to assess the depth and rate of ventilation, then at least the presence or absence of regular breathing should be determined. In this setting, any irregular or slow breathing pattern should be considered a possible sign of the incipient apnea, requiring ventilation with 100% oxygen by bag–valve–mask followed as soon as possible by endotracheal intubation and mechanical ventilation. Endotracheal intubation may be indicated for some cases of coma resulting from a toxic exposure to ensure and maintain control of the airway and to enable safe performance of procedures to prevent GI absorption or eliminate previously absorbed xenobiotics.

Although in many instances, the widespread availability of pulse oximetry to determine O_2 saturation has made arterial blood gas (ABG) analysis less of an immediate priority; pulse oximetry has not eliminated the importance of blood gas analysis entirely. An ABG determination will more accurately define the adequacy not only of oxygenation (PO_2, O_2 saturation) and ventilation (PCO_2) but may also alert the physician to possible toxic-

metabolic etiologies of coma characterized by acid–base disturbances (pH, PCO_2)

After the patient's respiratory status has been assessed and managed appropriately, the strength, rate, and regularity of the pulse should be evaluated, the blood pressure determined, and a rectal temperature obtained. Both a 12-lead electrocardiogram (ECG) and continuous rhythm monitoring are essential.

For a hypotensive patient with clear lungs and an unknown over- dose, a fluid challenge with IV 0.9% sodium chloride or lactated Ringer's solution may be started. If the patient remains hypotensive or cannot tolerate fluids, a vasopressor or an inotropic agent may be indicated, as may more invasive monitoring.

At the time that the IV catheter is inserted, blood samples for glucose, electrolytes, blood urea nitrogen (BUN), a complete blood count (CBC), and any indicated toxicologic analysis can be obtained. A pregnancy test should be obtained in any woman with childbearing potential. If the patient has an AMS, there may be a temptation to send blood and urine specimens to identify any central nervous system (CNS) depressants or so-called drugs of abuse along with other medications.

Within the first 5 minutes of managing a patient with an AMS, four therapeutic interventions should be *considered*, and if indicated, administered:

1. High-flow oxygen (8–10 L/min) to treat a variety of xenobiotic- induced hypoxic conditions

2. Hypertonic dextrose: 0.5–1.0 g/kg of $D_{50}W$ for an adult or a more dilute dextrose solution ($D_{10}W$ or $D_{25}W$) for a child; the dextrose is administered as an IV bolus to diagnose and treat or exclude hypoglycemia

3. Thiamine (100 mg IV for an adult; usually unnecessary for a child) to prevent or treat Wernicke encephalopathy

4. Naloxone (0.05 mg IV with upward titration) for an adult or child with opioid-induced respiratory compromise.

The clinician must consider that hypoglycemia may be the sole or contributing cause of coma even when the patient manifests focal neurologic findings; therefore, dextrose administration should only be omitted when hypoglycemia can be definitely excluded by accurate rapid bedside testing. Also, while examining a patient for clues to the etiology of a presumably toxic-metabolic form of AMS, it is important to search for any indication that trauma may have caused, contributed to, or resulted from the patient's condition.

Characteristic breath or skin odors may identify the etiology of coma. The fruity odor of ketones on the breath suggests diabetic or alcoholic ketoacidosis but also the possible ingestion of acetone or isopropyl alcohol, which is metabolized to acetone. The pungent, minty odor of oil of wintergreen on the breath or skin suggests methyl salicylate poisoning. The odors of other substances such as cyanide ("bitter almonds"), hydrogen

sulfide (“rotten eggs”), and organic phosphorus compounds (“garlic”) are summarized in Table 3.

Figure 3: *Odors Suggestive of a Xenobiotic.* **(You have to memorize this table)**

Odor	Xenobiotic
Bitter almond	Cyanide
Carrots	Cicutoxin (water hemlock)
Disinfectants	Creosote, phenol
Eggs (rotten)	Carbon disulfide, disulfiram, hydrogen sulfide, mercaptans, *N*-acetylcysteine
Fish or raw liver (musty)	Aluminum phosphide, zinc phosphide
Fruit	Nitrites (amyl, butyl)
Garlic	Arsenic, dimethyl sulfoxide (DMSO), organic phosphorus compounds, phosphorus, selenium, tellurium, thallium,
Hay	Phosgene
Mothballs	Camphor, naphthalene, *p*-dichlorobenzene,
Pepper	*O*-chlorobenzylidene malonitrile
Rope (burnt)	Marijuana, opium
Shoe polish	Nitrobenzene
Sweet fruity	Acetone, chloral hydrate, chloroform, ethanol, isopropanol, lacquer, methylbromide, paraldehyde, trichloroethane
Tobacco	Nicotine
Vinegar	Acetic acid
Violets	Turpentine (metabolites excreted in urine)
Wintergreen	Methyl salicylate

The role of gastrointestinal evacuation:

A series of highly individualized treatment decisions must now be made. The decision to evacuate the GI tract or administer AC can no longer be considered standard or routine toxicologic care for most patients. Instead, the decision should be based on the type of ingestion, estimated quantity and size of pill or tablet, time since ingestion, concurrent ingestions, ancillary medical conditions, and age and size of the patient.

After deciding whether or not an intervention to try to *prevent* absorption of a xenobiotic is indicated, the clinician must next consider the applicability of techniques available to eliminate xenobiotics already absorbed. The followings are most useful procedures for elimination of absorbed xenobiotics: manipulating urinary pH (ion trapping), diuresis, hemodialysis, hemoperfusion, hemofiltration, and exchange transfusion. Alkalinization of the urinary pH for acidic xenobiotics has only limited applicability. Commonly, sodium bicarbonate can be used to alkalinize the urine (as well as the blood) and enhance salicylate elimination (phenobarbital and chlorpropamide are less common indications), and sodium bicarbonate also prevents toxicity from methotrexate. If extracorporeal elimination is contemplated, hemodialysis should be considered for overdoses of salicylates, methanol, ethylene glycol, lithium, and xenobiotics that are both dialyzable and cause fluid and electrolyte problems. If available, hemoperfusion or high-flux

hemodialysis should be considered for overdoses of theophylline, phenobarbital, and carbamazepine.

Table 4: *Antidotes and Therapeutics for the Treatment of Poisonings and Overdoses* **(You have to memorize this table)**.

Therapeutics[b]	Uses	Therapeutics[b]	Uses
Activated charcoal (p. 108)	Adsorbs xenobiotics in the GI tract	Ipecac, syrup of (p. 104)	Induces emesis
Antivenom (*Crotalinae*) (p. 1608)	Crotaline snake envenomations	Magnesium sulfate or magnesium citrate (p. 114)	Induces catharsis
Antivenom (*Elapidae*) (p. 1308)	Coral snake envenomations	Magnesium sulfate injection	Cardioactive steroids, hydrofluoric acid, hypomagnesemia, ethanol withdrawal, torsades de pointes
Antivenom (*Latrodectus mactans*) (p. 1582)	Black widow spider envenomations	Methylene blue (1% solution) (p. 1708)	Methemoglobinemia
Atropine (p. 1473)	Bradydysrhythmias, cholinesterase inhibitors (organic phosphorus compounds, physostigmine) muscarinic mushrooms (*Clitocybe, Inocybe*) ingestions	*N*-acetylcysteine (Acetadote) (p. 500)	Acetaminophen and other causes of hepatotoxicity
Benzodiazepines (p1109)	Seizures, agitation, stimulants, ethanol and sedative–hypnotic withdrawal, cocaine, chloroquine, organic phosphorus compounds	Naloxone hydrochloride (Narcan) (p. 579)	Opioids, clonidine
		Norepinephrine (Levophed)	Hypotension (preferred for cyclic antidepressants)
Botulinum antitoxin (ABE-trivalent) (p. 695)	Botulism	Octreotide (Sandostatin) (p. 734)	Oral hypoglycemic induced hypoglycemia
Calcium chloride, calcium gluconate (p. 1381)	Fluoride, hydrofluoric acid, ethylene glycol, CCBs, hypomagnesemia, β-adrenergic antagonists	Oxygen (Hyperbaric) (p. 1671)	Carbon monoxide, cyanide, hydrogen sulfide
		D-Penicillamine (Cuprimine) (p. 1261)	Copper
L-Carnitine (p. 711)	Valproic acid	Phenobarbital	Seizures, agitation, stimulants, ethanol and sedative–hypnotic withdrawal
Cyanide kit (nitrites, p. 1689; sodium thiosulfate, p. 1692)	Cyanide		
Dantrolene (p. 1001)	Malignant hyperthermia	Phentolamine (p. 1096)	Cocaine, MAOI interactions, epinephrine, and ergot alkaloids
Deferoxamine mesylate (Desferal) (p. 604)	Iron	Physostigmine salicylate (Antilirium) (p. 759)	Anticholinergics
Dextrose in water (50% adults; 20% pediatrics; 10% neonates) (p. 728)	Hypoglycemia	Polyethylene glycol electrolyte solution (p. 114)	Decontaminates GI tract
Digoxin-specific antibody fragments (Digibind and Digifab) (p. 946)	Cardioactive steroids	Pralidoxime chloride, (2-PAM-chloride; Protopam) (p. 1467)	Acetylcholinesterase inhibitors (organic phosphorus agents and carbamates)
Dimercaprol (BAL, British anti-Lewisite) (p. 1229)	Arsenic, mercury, gold, lead	Protamine sulfate (p. 880)	Heparin anticoagulation
		Prussian blue (Radiogardase) (p. 1334)	Thallium, cesium
Diphenhydramine	Dystonic reactions, allergic reactions	Pyridoxine hydrochloride (Vitamin B_6) (p. 845)	Isoniazid, ethylene glycol, gyromitrin-containing mushrooms
DTPA (p. 1779)	Radioactive isotopes		
Edetate calcium disodium (calcium disodium versenate, $CaNa_2$ EDTA) (p. 1290)	Lead, other selected metals	Sodium bicarbonate (p. 520)	Ethylene glycol, methanol, salicylates, cyclic antidepressants, methotrexate, phenobarbital, quinidine, chlorpropamide, type 1 antidysrhythmics, chlorphenoxy herbicides
Ethanol (oral and parenteral dosage forms) (p. 1419)	Methanol, ethylene glycol		
Fat emulsion (Intralipid 20% (p. 976)	Cardiac arrest, local anesthetics		
Flumazenil (Romazicon) (p. 1072)	Benzodiazepines		
Folinic acid (Leucovorin) (p. 783)	Methotrexate, methanol	Sorbitol (p. 114)	Induces catharsis
Fomepizole (Antizole) (p. 1414)	Ethylene glycol, methanol	Starch (p. 1349)	Iodine
Glucagon (p. 910)	β-Adrenergic antagonists, CCBs	Succimer (Chemet) (p. 1284)	Lead, mercury, arsenic
Glucarpidase (p. 787)	Methotrexate	Thiamine hydrochloride (Vitamin B_1.) (p. 1129)	Thiamine deficiency, ethylene glycol, chronic ethanol consumption ("alcoholism")
Hydroxocobalamin (Cyanokit) (p. 1695)	Cyanide		
Insulin (p. 893)	β-Adrenergic antagonists, CCBs, hyperglycemia	Vitamin K_1 (Aquamephyton) (p. 876)	Warfarin or rodenticide anticoagulants
Iodide, potassium (SSKI) (p. 1775)	Radioactive iodine (I^{131})		

[a] Each emergency department should have the vast majority of these antidotes immediately available, some of these antidotes may be stored in the pharmacy, and others may be available from the Centers for Disease Control and Prevention, but the precise mechanism for locating each one must be known by each staff member.
[b] A detailed analysis of each of these agents is found in the text in the Antidotes in Depth section on the page cited to the right of each antidote or therapeutic listed.
CCB, calcium channel blocker; DTPA, diethylenetriaminepentaacetic acid; EDTA, ethylenediamine tetraacetic acid; GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; SSKI, saturated solution of potassium iodide.

AVOIDING PITFALLS

The history alone may not be a reliable indicator of which patients require naloxone, hypertonic dextrose, thiamine, and oxygen. Instead, these therapies should be *considered* (unless specifically contraindicated) only after a clinical assessment for all patients with AMS. The physical examination should be used to guide the use of naloxone. If dextrose or naloxone is indicated, sufficient amounts should be administered to exclude or treat hypoglycemia or opioid toxicity, respectively.

In a patient with a suspected but unknown overdose, the use of vasopressors should be avoided in the initial management of hypotension before administering fluids or assessing filling pressures.

Attributing an AMS to alcohol because of its odor on a patient's breath is potentially dangerous and misleading. Small amounts of alcohol and its congeners generally produce the same breath odor as do intoxicating amounts. Conversely, even when an extremely high blood ethanol concentration is *confirmed* by the laboratory, it is dangerous to ignore other possible causes of an AMS. The metabolism of ethanol is fairly constant at 15 to 30 mg/dL/h. Therefore, as a general rule, regardless of the initial blood alcohol concentration, a presumably "inebriated" comatose patient who is still unarousable 3 to 4 hours after initial assessment should be considered to have head trauma, a cerebrovascular accident, CNS infection, or other toxic-metabolic etiology for the alteration in consciousness.

MANAGEMENT OF PATIENTS WITH CUTANEOUS EXPOSURE

The xenobiotics that people are commonly exposed to externally include household cleaning materials; organic phosphorus or carbamate insecticides from crop dusting, gardening, or pest extermination; acids from leaking or exploding batteries; alkalis, such as lye; and lacrimating agents that are used in crowd control. In all of these cases, the principles of management are as follows:

1. Avoid secondary exposures by wearing protective (rubber or plastic) gowns, gloves, and shoe covers. Cases of serious secondary poisoning have occurred in emergency personnel after contact with xenobiotics such as organic phosphorus compounds on the victim's skin or clothing.

2. Remove the patient's clothing, place it in plastic bags, and then seal the bags.

3. Wash the patient with soap and copious amounts of water *twice* regardless of how much time has elapsed since the exposure.

4. Make no attempt to neutralize an acid with a base or a base with an acid. Further tissue damage may result from the heat generated by this reaction.

5. Avoid using any greases or creams because they will only keep the xenobiotic in close contact with the skin and ultimately make removal more difficult.

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Cholinergics	±	±	–/↑	–	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol or sedative–hypnotics	↓	↓	↓	–/↓	Depressed, agitated	±	↓	–	Hyporeflexia, ataxia
Opioids	↓	↓	↓	↓	Depressed	↓	↓	–	Hyporeflexia
Sympathomimetics	↑	↑	↑	↑	Agitated	↑	–/↑	↑	Tremor, seizures
Withdrawal from ethanol or sedative–hypnotics	↑	↑	↑	↑	Agitated, disoriented hallucinations	↑	↑	↑	Tremor, seizures
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PULSE RATE

Extremely useful clinical information can be obtained by evaluating the pulse rate. The normal heart rate for adults was defined by consensus more than 50 years ago as a regular rate greater than 60 beats/min and less than 100 beats/min.

Because pulse rate is the net result of a balance between sympathetic (adrenergic) and parasympathetic (muscarinic and nicotinic) tone, many xenobiotics that exert therapeutic or toxic effects or cause pain syndromes, hyperthermia, or volume depletion also affect the pulse rate. With respect to temperature, there is a direct correlation between pulse rate and temperature in that pulse rate increases approximately 8 beats/min for each 1.8°F (1°C) elevation in temperature.[4]

The inability to differentiate easily between sympathomimetic and anticholinergic xenobiotic effects by vital signs alone illustrates the principle that no single vital sign abnormality can definitively establish a toxicologic diagnosis. In trying to differentiate between a sympathomimetic and anticholinergic toxic syndrome, it should be understood that although tachycardia commonly results from both sympathomimetic and anticholinergic xenobiotics, when tachycardia is accompanied by diaphoresis or increased bowel sounds, adrenergic toxicity is suggested, but when tachycardia is accompanied by decreased sweating, absent bowel sounds, and urinary retention, anticholinergic toxicity is likely.

RESPIRATIONS

Establishment of an airway and evaluation of respiratory status are the initial priorities in patient stabilization. Although respirations are typically assessed initially for rate alone, careful observation of the depth and pattern is essential for establishing the etiology of a systemic illness or toxicity.

The term *hyperventilation* may mean tachypnea (an increase in ventilatory rate), hyperpnea (an increase in tidal volume), or both. Hyperventilation may result from the direct effect of a CNS stimulant, such as the direct effect of salicylates, on the brainstem. Bradypnea may occur when a CNS depressant acts on the brainstem. A progression from fast to slow breathing may also occur in a patient exposed to increasing concentrations of cyanide or carbon monoxide.

TEMPERATURE

Temperature evaluation and control are critical. However, temperature assessment can be done only if safe and reliable equipment is used. The risks of inaccuracy are substantial when an oral temperature is taken in a tachypneic patient, an axillary temperature or a temporal artery temperature is taken in any patient (especially those found outdoors), or a tympanic temperature is taken in a patient with cerumen impaction. Obtaining rectal temperatures using a nonglass probe is essential for safe and accurate temperature determinations in agitated individuals and is considered the standard method of temperature determination in this text.

The core temperature or deep internal temperature (T) is relatively stable (98.6° ± 1.08°F; 37° ± 0.6°C) under normal physiologic circumstances. Hypothermia (T <95°F; <35°C) and hyperthermia (T >100.4°F; >38°C) are common manifestations of toxicity.

PRINCIPLES OF MANAGING THE ACUTELY POISONED OR OVERDOSED PATIENT

Similar to the management of any seriously compromised patient, the clinical approach to the patient potentially exposed to a xenobiotic begins with the recognition and treatment of life-threatening conditions, including airway compromise, breathing difficulties, and circulatory problems such as hemodynamic instability and serious dysrhythmias. After the "ABCs" (airway, breathing, and circulation) have been addressed, the patient's level of consciousness should be assessed because this helps determine the techniques to be used for further management of the exposure.

Management of patients with altered mental status:

Altered mental status (AMS) is defined as the deviation of a patient's sensorium from normal. Although it is commonly construed as a depression in the patient's level of consciousness, a patient with agitation, delirium, psychosis, and other deviations from normal is also considered to have an AMS. After airway patency is established or secured, an initial bedside assessment should be made regarding the adequacy of breathing. If it is not possible to assess the depth and rate of ventilation, then at least the presence or absence of regular breathing should be determined. In this setting, any irregular or slow breathing pattern should be considered a possible sign of the incipient apnea, requiring ventilation with 100% oxygen by bag–valve–mask followed as soon as possible by endotracheal intubation and mechanical ventilation. Endotracheal intubation may be indicated for some cases of coma resulting from a toxic exposure to ensure and maintain control of the airway and to enable safe performance of procedures to prevent GI absorption or eliminate previously absorbed xenobiotics.

Although in many instances, the widespread availability of pulse oximetry to determine O_2 saturation has made arterial blood gas (ABG) analysis less of an immediate priority; pulse oximetry has not eliminated the importance of blood gas analysis entirely. An ABG determination will more accurately define the adequacy not only of oxygenation (PO_2, O_2 saturation) and ventilation (PCO_2) but may also alert the physician to possible toxic-

metabolic etiologies of coma characterized by acid–base disturbances (pH, PCO_2)

After the patient's respiratory status has been assessed and managed appropriately, the strength, rate, and regularity of the pulse should be evaluated, the blood pressure determined, and a rectal temperature obtained. Both a 12-lead electrocardiogram (ECG) and continuous rhythm monitoring are essential.

For a hypotensive patient with clear lungs and an unknown over- dose, a fluid challenge with IV 0.9% sodium chloride or lactated Ringer's solution may be started. If the patient remains hypotensive or cannot tolerate fluids, a vasopressor or an inotropic agent may be indicated, as may more invasive monitoring.

At the time that the IV catheter is inserted, blood samples for glucose, electrolytes, blood urea nitrogen (BUN), a complete blood count (CBC), and any indicated toxicologic analysis can be obtained. A pregnancy test should be obtained in any woman with childbearing potential. If the patient has an AMS, there may be a temptation to send blood and urine specimens to identify any central nervous system (CNS) depressants or so-called drugs of abuse along with other medications.

Within the first 5 minutes of managing a patient with an AMS, four therapeutic interventions should be *considered*, and if indicated, administered:

1. High-flow oxygen (8–10 L/min) to treat a variety of xenobiotic- induced hypoxic conditions

2. Hypertonic dextrose: 0.5–1.0 g/kg of $D_{50}W$ for an adult or a more dilute dextrose solution ($D_{10}W$ or $D_{25}W$) for a child; the dextrose is administered as an IV bolus to diagnose and treat or exclude hypoglycemia

3. Thiamine (100 mg IV for an adult; usually unnecessary for a child) to prevent or treat Wernicke encephalopathy

4. Naloxone (0.05 mg IV with upward titration) for an adult or child with opioid-induced respiratory compromise.

The clinician must consider that hypoglycemia may be the sole or contributing cause of coma even when the patient manifests focal neurologic findings; therefore, dextrose administration should only be omitted when hypoglycemia can be definitely excluded by accurate rapid bedside testing. Also, while examining a patient for clues to the etiology of a presumably toxic-metabolic form of AMS, it is important to search for any indication that trauma may have caused, contributed to, or resulted from the patient's condition.

Characteristic breath or skin odors may identify the etiology of coma. The fruity odor of ketones on the breath suggests diabetic or alcoholic ketoacidosis but also the possible ingestion of acetone or isopropyl alcohol, which is metabolized to acetone. The pungent, minty odor of oil of wintergreen on the breath or skin suggests methyl salicylate poisoning. The odors of other substances such as cyanide ("bitter almonds"), hydrogen

sulfide (“rotten eggs”), and organic phosphorus compounds (“garlic”) are summarized in Table 3.

Figure 3: *Odors Suggestive of a Xenobiotic.* **(You have to memorize this table)**

Odor	Xenobiotic
Bitter almond	Cyanide
Carrots	Cicutoxin (water hemlock)
Disinfectants	Creosote, phenol
Eggs (rotten)	Carbon disulfide, disulfiram, hydrogen sulfide, mercaptans, *N*-acetylcysteine
Fish or raw liver (musty)	Aluminum phosphide, zinc phosphide
Fruit	Nitrites (amyl, butyl)
Garlic	Arsenic, dimethyl sulfoxide (DMSO), organic phosphorus compounds, phosphorus, selenium, tellurium, thallium,
Hay	Phosgene
Mothballs	Camphor, naphthalene, *p*-dichlorobenzene,
Pepper	*O*-chlorobenzylidene malonitrile
Rope (burnt)	Marijuana, opium
Shoe polish	Nitrobenzene
Sweet fruity	Acetone, chloral hydrate, chloroform, ethanol, isopropanol, lacquer, methylbromide, paraldehyde, trichloroethane
Tobacco	Nicotine
Vinegar	Acetic acid
Violets	Turpentine (metabolites excreted in urine)
Wintergreen	Methyl salicylate

The role of gastrointestinal evacuation:

A series of highly individualized treatment decisions must now be made. The decision to evacuate the GI tract or administer AC can no longer be considered standard or routine toxicologic care for most patients. Instead, the decision should be based on the type of ingestion, estimated quantity and size of pill or tablet, time since ingestion, concurrent ingestions, ancillary medical conditions, and age and size of the patient.

After deciding whether or not an intervention to try to *prevent* absorption of a xenobiotic is indicated, the clinician must next consider the applicability of techniques available to eliminate xenobiotics already absorbed. The followings are most useful procedures for elimination of absorbed xenobiotics: manipulating urinary pH (ion trapping), diuresis, hemodialysis, hemoperfusion, hemofiltration, and exchange transfusion. Alkalinization of the urinary pH for acidic xenobiotics has only limited applicability. Commonly, sodium bicarbonate can be used to alkalinize the urine (as well as the blood) and enhance salicylate elimination (phenobarbital and chlorpropamide are less common indications), and sodium bicarbonate also prevents toxicity from methotrexate. If extracorporeal elimination is contemplated, hemodialysis should be considered for overdoses of salicylates, methanol, ethylene glycol, lithium, and xenobiotics that are both dialyzable and cause fluid and electrolyte problems. If available, hemoperfusion or high-flux

hemodialysis should be considered for overdoses of theophylline, phenobarbital, and carbamazepine.

Table 4: *Antidotes and Therapeutics for the Treatment of Poisonings and Overdoses* **(You have to memorize this table)**.

Therapeutics[b]	Uses	Therapeutics[b]	Uses
Activated charcoal (p. 108)	Adsorbs xenobiotics in the GI tract	Ipecac, syrup of (p. 104)	Induces emesis
Antivenom (*Crotalinae*) (p. 1608)	Crotaline snake envenomations	Magnesium sulfate or magnesium citrate (p. 114)	Induces catharsis
Antivenom (*Elapidae*) (p. 1308)	Coral snake envenomations	Magnesium sulfate injection	Cardioactive steroids, hydrofluoric acid, hypomagnesemia, ethanol withdrawal, torsades de pointes
Antivenom (*Latrodectus mactans*) (p. 1582)	Black widow spider envenomations	Methylene blue (1% solution) (p. 1708)	Methemoglobinemia
Atropine (p. 1473)	Bradydysrhythmias, cholinesterase inhibitors (organic phosphorus compounds, physostigmine) muscarinic mushrooms (*Clitocybe, Inocybe*) ingestions	*N*-acetylcysteine (Acetadote) (p. 500)	Acetaminophen and other causes of hepatotoxicity
Benzodiazepines (p1109)	Seizures, agitation, stimulants, ethanol and sedative–hypnotic withdrawal, cocaine, chloroquine, organic phosphorus compounds	Naloxone hydrochloride (Narcan) (p. 579)	Opioids, clonidine
		Norepinephrine (Levophed)	Hypotension (preferred for cyclic antidepressants)
Botulinum antitoxin (ABE-trivalent) (p. 695)	Botulism	Octreotide (Sandostatin) (p. 734)	Oral hypoglycemic induced hypoglycemia
Calcium chloride, calcium gluconate (p. 1381)	Fluoride, hydrofluoric acid, ethylene glycol, CCBs, hypomagnesemia, β-adrenergic antagonists	Oxygen (Hyperbaric) (p. 1671)	Carbon monoxide, cyanide, hydrogen sulfide
		D-Penicillamine (Cuprimine) (p. 1261)	Copper
L-Carnitine (p. 711)	Valproic acid	Phenobarbital	Seizures, agitation, stimulants, ethanol and sedative–hypnotic withdrawal
Cyanide kit (nitrites, p. 1689; sodium thiosulfate, p. 1692)	Cyanide		
Dantrolene (p. 1001)	Malignant hyperthermia	Phentolamine (p. 1096)	Cocaine, MAOI interactions, epinephrine, and ergot alkaloids
Deferoxamine mesylate (Desferal) (p. 604)	Iron	Physostigmine salicylate (Antilirium) (p. 759)	Anticholinergics
Dextrose in water (50% adults; 20% pediatrics; 10% neonates) (p. 728)	Hypoglycemia	Polyethylene glycol electrolyte solution (p. 114)	Decontaminates GI tract
Digoxin-specific antibody fragments (Digibind and Digifab) (p. 946)	Cardioactive steroids	Pralidoxime chloride, (2-PAM-chloride; Protopam) (p. 1467)	Acetylcholinesterase inhibitors (organic phosphorus agents and carbamates)
Dimercaprol (BAL, British anti-Lewisite) (p. 1229)	Arsenic, mercury, gold, lead	Protamine sulfate (p. 880)	Heparin anticoagulation
		Prussian blue (Radiogardase) (p. 1334)	Thallium, cesium
Diphenhydramine	Dystonic reactions, allergic reactions	Pyridoxine hydrochloride (Vitamin B_6) (p. 845)	Isoniazid, ethylene glycol, gyromitrin-containing mushrooms
DTPA (p. 1779)	Radioactive isotopes		
Edetate calcium disodium (calcium disodium versenate, $CaNa_2$ EDTA) (p. 1290)	Lead, other selected metals	Sodium bicarbonate (p. 520)	Ethylene glycol, methanol, salicylates, cyclic antidepressants, methotrexate, phenobarbital, quinidine, chlorpropamide, type 1 antidysrhythmics, chlorphenoxy herbicides
Ethanol (oral and parenteral dosage forms) (p. 1419)	Methanol, ethylene glycol		
Fat emulsion (Intralipid 20% (p. 976)	Cardiac arrest, local anesthetics		
Flumazenil (Romazicon) (p. 1072)	Benzodiazepines		
Folinic acid (Leucovorin) (p. 783)	Methotrexate, methanol	Sorbitol (p. 114)	Induces catharsis
Fomepizole (Antizole) (p. 1414)	Ethylene glycol, methanol	Starch (p. 1349)	Iodine
Glucagon (p. 910)	β-Adrenergic antagonists, CCBs	Succimer (Chemet) (p. 1284)	Lead, mercury, arsenic
Glucarpidase (p. 787)	Methotrexate	Thiamine hydrochloride (Vitamin B_1.) (p. 1129)	Thiamine deficiency, ethylene glycol, chronic ethanol consumption ("alcoholism")
Hydroxocobalamin (Cyanokit) (p. 1695)	Cyanide		
Insulin (p. 893)	β-Adrenergic antagonists, CCBs, hyperglycemia	Vitamin K_1 (Aquamephyton) (p. 876)	Warfarin or rodenticide anticoagulants
Iodide, potassium (SSKI) (p. 1775)	Radioactive iodine (I^{131})		

[a] Each emergency department should have the vast majority of these antidotes immediately available, some of these antidotes may be stored in the pharmacy, and others may be available from the Centers for Disease Control and Prevention, but the precise mechanism for locating each one must be known by each staff member.
[b] A detailed analysis of each of these agents is found in the text in the Antidotes in Depth section on the page cited to the right of each antidote or therapeutic listed.
CCB, calcium channel blocker; DTPA, diethylenetriaminepentaacetic acid; EDTA, ethylenediamine tetraacetic acid; GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; SSKI, saturated solution of potassium iodide.

AVOIDING PITFALLS

The history alone may not be a reliable indicator of which patients require naloxone, hypertonic dextrose, thiamine, and oxygen. Instead, these therapies should be *considered* (unless specifically contraindicated) only after a clinical assessment for all patients with AMS. The physical examination should be used to guide the use of naloxone. If dextrose or naloxone is indicated, sufficient amounts should be administered to exclude or treat hypoglycemia or opioid toxicity, respectively.

In a patient with a suspected but unknown overdose, the use of vasopressors should be avoided in the initial management of hypotension before administering fluids or assessing filling pressures.

Attributing an AMS to alcohol because of its odor on a patient's breath is potentially dangerous and misleading. Small amounts of alcohol and its congeners generally produce the same breath odor as do intoxicating amounts. Conversely, even when an extremely high blood ethanol concentration is *confirmed* by the laboratory, it is dangerous to ignore other possible causes of an AMS. The metabolism of ethanol is fairly constant at 15 to 30 mg/dL/h. Therefore, as a general rule, regardless of the initial blood alcohol concentration, a presumably "inebriated" comatose patient who is still unarousable 3 to 4 hours after initial assessment should be considered to have head trauma, a cerebrovascular accident, CNS infection, or other toxic-metabolic etiology for the alteration in consciousness.

MANAGEMENT OF PATIENTS WITH CUTANEOUS EXPOSURE

The xenobiotics that people are commonly exposed to externally include household cleaning materials; organic phosphorus or carbamate insecticides from crop dusting, gardening, or pest extermination; acids from leaking or exploding batteries; alkalis, such as lye; and lacrimating agents that are used in crowd control. In all of these cases, the principles of management are as follows:

1. Avoid secondary exposures by wearing protective (rubber or plastic) gowns, gloves, and shoe covers. Cases of serious secondary poisoning have occurred in emergency personnel after contact with xenobiotics such as organic phosphorus compounds on the victim's skin or clothing.

2. Remove the patient's clothing, place it in plastic bags, and then seal the bags.

3. Wash the patient with soap and copious amounts of water *twice* regardless of how much time has elapsed since the exposure.

4. Make no attempt to neutralize an acid with a base or a base with an acid. Further tissue damage may result from the heat generated by this reaction.

5. Avoid using any greases or creams because they will only keep the xenobiotic in close contact with the skin and ultimately make removal more difficult.

Clinical Toxicology

Opioid Toxicity

Opioids are substances derived from the opium poppy, or synthetic analogues with similar effects. Examples are morphine, heroin, tramadol, oxycodone and methadone. Although opioids enjoy widespread use as potent analgesics, they have the potential for abuse because of their psychoactive properties. Although the therapeutic and toxic doses are difficult to predict because of the development of tolerance with chronic use, the primary adverse event from excessive dosing is respiratory depression.

Currently, the widest clinical application of opioids is for acute or chronic pain relief. Opioids are available in various formulations that allow administration by virtually any route: epidural, inhalational, intranasal, intrathecal, oral, parenteral (ie, subcutaneous [SC], intravenous [IV], intramuscular [IM]), rectal, transdermal, and transmucosal. Patients also may benefit from several of the nonanalgesic effects engendered by certain opioids. For example, codeine and hydrocodone are widely used as antitussives, and diphenoxylate as an antidiarrheal.

The term *opiate* specifically refers to the relevant alkaloids naturally derived directly from the opium poppy: morphine; codeine. *Opioids* are a much broader class of xenobiotics that are capable of either producing opium-like effects or binding to opioid receptors. A *semisynthetic opioid*, such as heroin or oxycodone, is created by chemical modification of an opiate. A *synthetic opioid* is a chemical, not derived from an opiate that is capable of binding to an opioid receptor and producing opioid effects clinically. Synthetic opioids, such as methadone and meperidine, bear little structural similarity to the opiates. The term *narcotic* refers to sleep-inducing xenobiotics and initially was used to connote the opioids.

PHARMACOLOGY

OPIOID-RECEPTOR SUBTYPES

All three major opioid receptors have been cloned and sequenced. Each consists of seven transmembrane segments, an amino terminus, and a carboxy terminus. Because multiple opioid receptors exist and each elicits a different effect, determining the receptor to which an opioid preferentially

binds should allow prediction of the clinical effect of the opioid. However, binding typically is not limited to one receptor type, and the relative affinity of an opioid for differing receptors accounts for the clinical effects (Table 1).

Mu Receptor (μ, MOP, OP_3): The early identification of the μ receptor as the morphine-binding site gave this receptor its designation. Although many exogenous xenobiotics produce supraspinal analgesia via μ receptors, the endogenous ligand is elusive. Experimentally, two subtypes (μ_1 and μ_2) are well defined. The μ_1 subtype appears to be responsible for supraspinal (brain) analgesia and for the euphoria sometimes engendered by these xenobiotics. Although stimulation of the μ_2 subtype produces spinal-level analgesia, it also produces respiratory depression.

Kappa Receptor (k, KOP, OP_2): Although dynorphins now are known to be the endogenous ligands for these receptors, originally they were identified by their ability to bind ketocyclazocine and thus were labeled k. k receptors exist predominantly in the spinal cords of higher animals, but they also are found in the antinociceptive regions of the brain and the substantia nigra. Stimulation is responsible for spinal analgesia, miosis, and diuresis (via inhibition of antidiuretic hormone release). Unlike m-receptor stimulation, k-receptor stimulation is not associated with significant respiratory depression or constipation. The receptor currently is subclassified into three subtypes. The k_1 receptor subtype is responsible for spinal analgesia. This analgesia is not reversed by μ-selective antagonists, supporting the role of k receptors as independent media- tors of analgesia. Although the function of the k_2 receptor subtype is largely unknown, stimulation of cerebral k_2 receptors by xenobiotics such as pentazocine and salvinorin A produces psychotomimesis in distinction to the euphoria evoked by k agonists. The k_3 receptor subtype is found throughout the brain and participates in supraspinal analgesia.

Delta Receptor (δ, DOP, OP_1): Little is known about **δ** receptors, although the enkephalins are known to be their endogenous ligands.

δ receptors may be important in spinal and supraspinal analgesia (probably via a noncompetitive interaction with the m receptor) and in cough suppression.

THERAPEUTIC EFFECTS

Analgesia:

Although classic teaching attributes opioid analgesia solely to the brain, opioids actually appear to modulate cerebral cortical pain perception at supraspinal, spinal, and peripheral levels. The regional distribution of the opioid receptors confirms that μ receptors are responsible for most of the analgesic effects of morphine within the brain. They are found in highest concentration within areas of the brain classically associated with analgesia. **δ** and κ receptors also are responsible for mediation of analgesia, but they exert their analgesic effect predominantly in the spinal cord.

Xenobiotics with strong binding affinity for **δ** receptors in humans produce significantly more analgesia than morphine administered intrathecally. Indeed, the use of spinal and epidural opioid analgesia is predicated on the direct administration of opioid near the κ and **δ** receptors in the spinal cord.

Euphoria:

The pleasurable effects of many xenobiotics used by humans are mediated by the release of dopamine in the mesolimbic system. This final common pathway is shared by all opioids that activate the μ– **δ** receptor complex in the ventral tegmental area, which, in turn, indirectly promotes dopamine release in the mesolimbic region. Opioids also may have a direct reinforcing effect on their self-administration through μ receptors within the mesolimbic system. The sense of well-being and euphoria associated with strenuous exercise appears to be mediated by endogenous opioid peptides and μ receptors.

Exogenous opioids do not induce uniform psychological effects. Some of the exogenous opioids, particularly those that are highly lipophilic such as heroin, are euphorigenic, but morphine is largely devoid of such pleasurable effects. However, morphine administration results in analgesia, anxiolysis, and sedation.

Table 1:Clinical effects related to opioid receptors:

1996 Conventional Name	Proposed IUPHAR Name	IUPHAR Name	Important Clinical Effects of Receptor Agonists
μ_1	OP_{3a}	MOP	Supraspinal analgesia Peripheral analgesia Sedation Euphoria Prolactin release
μ_2	OP_{3b}		Spinal analgesia Respiratory depression Physical dependence GI dysmotility Pruritus Bradycardia Growth hormone release
κ_1	OP_{2a}	KOP	Spinal analgesia Miosis Diuresis
κ_2	OP_{2b}		Psychotomimesis Dysphoria
κ_3	OP_{2b}		Supraspinal analgesia
δ	OP_1	DOP	Spinal and supraspinal analgesia Modulation of μ-receptor function Inhibit release of dopamine
Nociceptin/ orphanin FQ	OP_4	NOP	Anxiolysis Analgesia

Antitussive:

Codeine and dextromethorphan are two opioids with cough-suppressant activity. Cough suppression is not likely mediated via the μ_1 opioid receptor because the ability of other opioids to suppress the medullary cough centers is not correlated with their analgesic effect.

TOXIC EFFECTS

When used appropriately for medical purposes, opioids are remarkably safe and effective. However, excessive dosing for any reason may result in serious toxicity. Most adverse or toxic effects are predictable based on "opioid" pharmacodynamics. Mental status depression, hypoventilation, miosis, and hypoperistalsis are the classic symptoms.

Respiratory Depression:

Experimental use of various opioid agonists and antagonists consistently implicates u_2 receptors in the respiratory depressant effects of morphine. Through these receptors, opioid agonists reduce ventilation by diminishing

the sensitivity of the medullary chemoreceptors to hypercapnea. In addition to loss of hypercarbic stimulation, opioids depress the ventilatory response to hypoxia. Equianalgesic doses of the available opioid agonists produce approximately the same degree of respiratory depression. Patients chronically exposed to opioid agonists, such as those on methadone maintenance, experience chronic hypoventilation.

It is important to recognize that ventilatory depression may be secondary to a reduction in either respiratory rate or tidal volume. Thus, although respiratory rate is more accessible for clinical measurement, it is not an ideal index of ventilatory depression. In fact, morphine- induced respiratory depression in humans initially is related more closely to changes in tidal volume. Large doses of opioids also result in a reduction of respiratory rate.

Acute Lung Injury:

Reports linking opioids with the development of acute pulmonary abnormalities became common in the 1960s, although the first report was made by William Osler in 1880. Almost all opioids are implicated, and opioid-related acute lung injury (ALI) is reported in diverse clinical situations. Typically, the patient regains normal ventilation after a period of profound respiratory depression, either spontaneously or after the administration of an opioid antagonist, and over the subsequent several minutes to hours develops hypoxemia and pulmonary crackles. No single mechanism can be consistently invoked in the genesis of opioid-associated ALI.

Cardiovascular:

Arteriolar and venous dilation secondary to opioid use may result in a mild reduction in blood pressure. Bradycardia is unusual, although a reduction in heart rate is common as a result of the associated reduction in CNS stimulation. Opioid-induced hypotension appears to be mediated by histamine release, although induction of histamine release does not appear to occur through interaction with an opioid receptor. It may be related to the nonspecific ability of certain xenobiotics to activate mast cell G proteins, which induce degranulation of histamine-containing vesicles.
Accordingly, not all opioids are equivalent in their ability to release histamine. After administration of one of four different opioids to 60 healthy patients, meperidine produced the most hypotension and elevation of serum histamine concentrations; fentanyl produced the least. The combination of

H_1 and H_2 antagonists is effective in ameliorating the hemodynamic effects of opioids in humans.

Cardiovascular toxicity may occur with use of propoxyphene, which causes wide-complex dysrhythmias and negative contractility through sodium channel antagonism similar to that of type IA antidysrhythmics. Adulterants or co-ingestants may also produce significant cardiovascular toxicity. For example, quinine- adulterated heroin is associated with dysrhythmias. Cocaine, surreptitiously added to heroin, may cause significant myocardial ischemia or infarction. Similarly, concern that naloxone administration may "unmask" cocaine toxicity in patients simultaneously using cocaine and heroin ("speedball") probably is warranted but rarely is demonstrated unequivocally. Certain opioids at therapeutic concentrations, particularly methadone, may interfere with normal cardiac repolarization and produce QT interval prolongation.

Miosis "pinpoint pupil":

The mechanisms by which opioids induce miosis remain controversial. Support for each of several mechanisms can be found in the literature. Stimulation of parasympathetic pupilloconstrictor neurons by morphine produces miosis. Additionally, morphine increases firing of pupilloconstrictor neurons to light, which increases the sensitivity of the light reflex through central reinforcement. Not all patients using opioids present with miosis. Meperidine has a lesser miotic effect than other conventional opioids, and propoxyphene use does not result in miosis. Use of opioids with predominantly μ-agonist effects, such as pentazocine, may not result in miosis.

Seizures:

Seizures are a rare complication of therapeutic use of most opioids. In patients with acute opioid overdose, seizures most likely are caused by hypoxia. However, experimental models demonstrate a proconvulsant effect of morphine in that it potentiates the convulsant effect of other xenobiotics. These effects are variably inhibited by naloxone, suggesting the involvement of a mechanism other than opioid receptor binding. In humans, morphine-induced seizures are reported in neonates and are reversed by naloxone, although opioid withdrawal seizures in neonates are more common.

Gastrointestinal Effects:

Historically, the morphine analog apomorphine was used as a rapidly acting emetic whose clinical use was limited by its tendency to depress the patient's level of consciousness. Emesis induced by apomorphine is mediated through agonism at D_2 receptor subtypes within the chemoreceptor trigger zone of the medulla. Many opioids, particularly morphine, produce significant nausea and vomiting when used therapeutically. Whether these effects are inhibited by naloxone is not clearly established, but they likely are not. Although diphenoxylate and loperamide are widely used therapeutically to manage diarrhea, opioid-induced constipation is most frequently a bothersome side effect of both medical and nonmedical use of opioids. Constipation, mediated by μ_2 receptors within the smooth muscle of the intestinal wall, is ameliorated by oral naloxone.

MANAGEMENT

The consequential effects of acute opioid poisoning are CNS and respiratory depression. Although early support of ventilation and oxygenation is generally sufficient to prevent the death. Opioid antagonists, such as naloxone, competitively inhibit binding of opioid agonists to opioid receptors, allowing the patient to resume spontaneous respiration. Naloxone competes at all receptor subtypes, although not equally, and is effective at reversing almost all adverse effects mediated through opioid receptors.

ANTIDOTE ADMINISTRATION

The goal of naloxone therapy is not necessarily complete arousal; rather, the goal is reinstitution of adequate spontaneous ventilation. Because precipitation of withdrawal is potentially detrimental and often unpredictable, the lowest practical naloxone dose should be administered initially, with rapid escalation as warranted by the clinical situation. Most patients respond to 0.04 to 0.05 mg of naloxone administered IV, although the requirement for ventilatory assistance may be slightly prolonged because the onset may be slower than with larger doses.

SC administration may allow for smoother arousal than the high-dose IV route but is unpredictable in onset and likely prolonged in offset. Prolonged effectiveness of naloxone by the SC route can be a considerable disadvantage if the therapeutic goal is exceeded and the withdrawal syndrome develops.

Naloxone, even at extremely high doses, has an excellent safety profile in

opioid-naïve patients receiving the medication for nonopioid-related indications, such as spinal cord injury or acute ischemic stroke. However, administration of naloxone to opioid-dependent patients may result in adverse effects; specifically, precipitation of an acute withdrawal syndrome should be anticipated. The resultant agitation, hypertension, and tachycardia may produce significant distress for the patient and complicate management for the clinical staff and occasionally may be life threatening. Additionally, emesis, a common feature of acute opioid withdrawal, may be particularly hazardous in patients who do not rapidly regain consciousness after naloxone administration.

The decision to discharge a patient who awakens appropriately after naloxone administration is based on practical considerations. Patients presenting with profound hypoventilation or hypoxia are at risk for development of ALI or posthypoxic encephalopathy. Thus, it seems prudent to observe these patients for at least 24 hours in a medical setting. Patients manifesting only moderate signs of poisoning who remain normal for at least several hours after parenteral naloxone likely are safe to discharge. However, the need for psychosocial intervention in patients with uncontrolled drug use or after a suicide attempt may prevent discharge from the emergency department (ED).

Patients with recurrent or profound poisoning by long-acting opioids, such as methadone, or patients with large GI burdens (eg, “body packers” or those taking sustained-release preparations), may require continuous infusion of naloxone to ensure continued adequate ventilation. Despite the availability of long-acting opioid antagonists (eg, naltrexone and nalmefene) that theoretically permit single-dose reversal of methadone poisoning, the attendant risk of precipitating an unrelenting withdrawal syndrome hinders their use as antidotes for initial opioid reversal. However, these opioid antagonists may have a clinical role in the maintenance of consciousness and ventilation in opioid-poisoned patients already awakened by naloxone.

SPECIFIC OPIOIDS

MORPHINE AND CODEINE

Morphine is poorly bioavailable by the oral route because of extensive first-pass elimination. Morphine is hepatically metabolized primarily to morphine-3-glucuronide (M3G) and, to a lesser extent, to morphine- 6-glucuronide (M6G), both of which are cleared renally. Unlike M3G, which

is essentially devoid of activity, M6G has μ-agonist effects in the CNS. However, M6G administered peripherally is significantly less potent as an analgesic than is morphine. The polar glucuronide has a limited ability to cross the blood–brain barrier. Codeine itself is an inactive opioid agonist, and it requires metabolic activation by *O*-demethylation to morphine by CYP2D6 (Fig. 1). This typically represents a minor metabolic pathway for codeine metabolism. *N*-demethylation into norcodeine by CYP3A4 and glucuronidation are more prevalent but produce inactive metabolites.

HEROIN

Heroin is 3,6-diacetylmorphine, and its exogenous synthesis is per- formed relatively easily from morphine and acetic anhydride. Heroin has a lower affinity for the receptor than does morphine, but it is rapidly metabolized by plasma cholinesterase and liver human carboxylesterase (hCE)-2 to 6-monoacetylmorphine, a more potent μ agonist than morphine.

Heroin can be obtained in two distinct chemical forms: base or salt. The hydrochloride salt form typically is a white or beige powder and was the common form of heroin available before the 1980s. Its high water solubility allows simple IV administration. Heroin base, on the other hand, now is the more prevalent form of heroin in most regions of the world.

Because heroin base is virtually insoluble in water, IV administration requires either heating the heroin until it liquefies or mixing it with acid. Alternatively, because the alkaloidal form is heat stable, smoking or "chasing the dragon" is sometimes used as an alternative route. Street- level heroin base frequently contains caffeine or barbiturates, which improves the sublimation of heroin and enhances the yield.

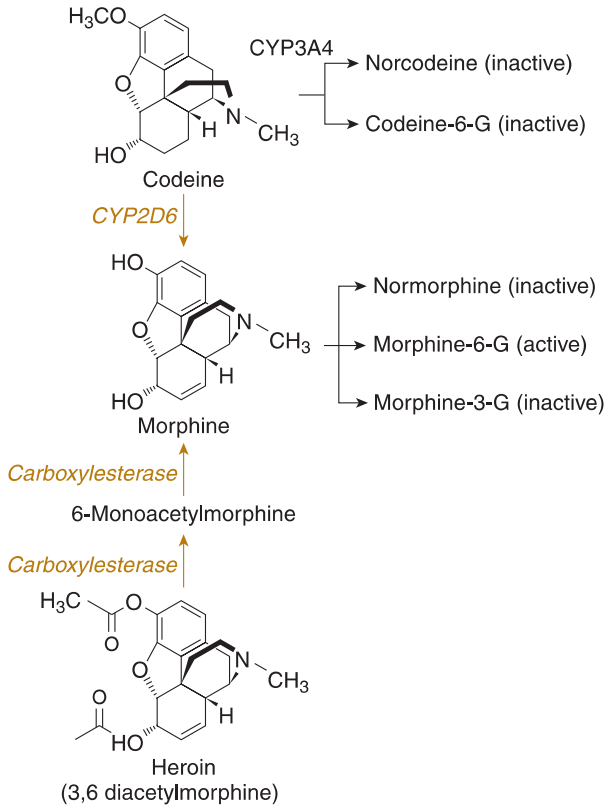

Figure 1:

Fentanyl and Its Analogs:

Fentanyl is a short-acting, highly potent opioid agonist that is widely used in clinical medicine. Fentanyl has approximately 50 to 100 times the potency of morphine. It is well absorbed by the transmucosal route. Fentanyl is widely abused as a heroin substitute and is the controlled substance most often abused by anesthesiologists.

Transdermal fentanyl in the form of a patch (Duragesic) was approved in 1991 and is widely used by patients with chronic pain syndromes. Fentanyl has adequate solubility in both lipid and water for transdermal delivery. Fentanyl patch misuse and abuse occur either by application of one or more patches to the skin or by withdrawal or extraction of the fentanyl from the reservoir for subsequent administration.

Although fentanyl is a more potent opioid agonist than heroin, the dose of naloxone required to reverse respiratory depression appears to be similar to that of other common opioids. This is because the binding affinity (K_d) of fentanyl at the μ opioid receptor is similar to that of both morphine and naloxone. In a typical overdose, the quantity of fentanyl is likely to be

equipotent to typical heroin. However, if large quantities of fentanyl are involved in the poisoning, higher than normal doses of naloxone may be required for reversal. Use of other opioids, such as sufentanil and buprenorphine, which have higher affinity for opioid receptors (lower K_d') may lead to the need for larger doses of naloxone to reverse the patient's respiratory depression.

Oxycodone and Hydrocodone:

Although media reports highlight the abuse of these and other prescription opioids by sports figures and other personalities, this trend has reached epidemic levels in regions of the country where heroin is difficult to obtain (thus the term "hillbilly heroin"). The abuse liabilities of these semisynthetic opioids based on their subjective profile are similar. Although many users initially receive oxycodone or hydrocodone as analgesics, the majority of abusers obtain the drugs illicitly or from friends. Physicians have been charged criminally with complicity for inappropriate prescriptions for patients with the intent to sell or abuse these drugs. Many of these opioids are sold in fixed combination with acetaminophen (eg, Percocet [oxycodone 5 mg], Vicodin [hydrocodone]), raising concerns about the complications of acetaminophen hepatotoxicity.

Abusers typically crush the tablet, which destroys the sustained-release matrix and liberates large amounts of insufflatable or injectable oxycodone. The psychoactive effects of these opioids are similar to other μ-receptor agonists and often are used as a substitute for heroin.

Clinical Toxicology

Opioid Toxicity

Opioids are substances derived from the opium poppy, or synthetic analogues with similar effects. Examples are morphine, heroin, tramadol, oxycodone and methadone. Although opioids enjoy widespread use as potent analgesics, they have the potential for abuse because of their psychoactive properties. Although the therapeutic and toxic doses are difficult to predict because of the development of tolerance with chronic use, the primary adverse event from excessive dosing is respiratory depression.

Currently, the widest clinical application of opioids is for acute or chronic pain relief. Opioids are available in various formulations that allow administration by virtually any route: epidural, inhalational, intranasal, intrathecal, oral, parenteral (ie, subcutaneous [SC], intravenous [IV], intramuscular [IM]), rectal, transdermal, and transmucosal. Patients also may benefit from several of the nonanalgesic effects engendered by certain opioids. For example, codeine and hydrocodone are widely used as antitussives, and diphenoxylate as an antidiarrheal.

The term *opiate* specifically refers to the relevant alkaloids naturally derived directly from the opium poppy: morphine; codeine. *Opioids* are a much broader class of xenobiotics that are capable of either producing opium-like effects or binding to opioid receptors. A *semisynthetic opioid*, such as heroin or oxycodone, is created by chemical modification of an opiate. A *synthetic opioid* is a chemical, not derived from an opiate that is capable of binding to an opioid receptor and producing opioid effects clinically. Synthetic opioids, such as methadone and meperidine, bear little structural similarity to the opiates. The term *narcotic* refers to sleep-inducing xenobiotics and initially was used to connote the opioids.

PHARMACOLOGY

OPIOID-RECEPTOR SUBTYPES

All three major opioid receptors have been cloned and sequenced. Each consists of seven transmembrane segments, an amino terminus, and a carboxy terminus. Because multiple opioid receptors exist and each elicits a different effect, determining the receptor to which an opioid preferentially

binds should allow prediction of the clinical effect of the opioid. However, binding typically is not limited to one receptor type, and the relative affinity of an opioid for differing receptors accounts for the clinical effects (Table 1).

Mu Receptor (μ, MOP, OP_3): The early identification of the μ receptor as the morphine-binding site gave this receptor its designation. Although many exogenous xenobiotics produce supraspinal analgesia via μ receptors, the endogenous ligand is elusive. Experimentally, two subtypes (μ_1 and μ_2) are well defined. The μ_1 subtype appears to be responsible for supraspinal (brain) analgesia and for the euphoria sometimes engendered by these xenobiotics. Although stimulation of the μ_2 subtype produces spinal-level analgesia, it also produces respiratory depression.

Kappa Receptor (k, KOP, OP_2): Although dynorphins now are known to be the endogenous ligands for these receptors, originally they were identified by their ability to bind ketocyclazocine and thus were labeled k. k receptors exist predominantly in the spinal cords of higher animals, but they also are found in the antinociceptive regions of the brain and the substantia nigra. Stimulation is responsible for spinal analgesia, miosis, and diuresis (via inhibition of antidiuretic hormone release). Unlike m-receptor stimulation, k-receptor stimulation is not associated with significant respiratory depression or constipation. The receptor currently is subclassified into three subtypes. The k_1 receptor subtype is responsible for spinal analgesia. This analgesia is not reversed by μ-selective antagonists, supporting the role of k receptors as independent media- tors of analgesia. Although the function of the k_2 receptor subtype is largely unknown, stimulation of cerebral k_2 receptors by xenobiotics such as pentazocine and salvinorin A produces psychotomimesis in distinction to the euphoria evoked by k agonists. The k_3 receptor subtype is found throughout the brain and participates in supraspinal analgesia.

Delta Receptor (δ, DOP, OP_1): Little is known about **δ** receptors, although the enkephalins are known to be their endogenous ligands.

δ receptors may be important in spinal and supraspinal analgesia (probably via a noncompetitive interaction with the m receptor) and in cough suppression.

THERAPEUTIC EFFECTS

Analgesia:

Although classic teaching attributes opioid analgesia solely to the brain, opioids actually appear to modulate cerebral cortical pain perception at supraspinal, spinal, and peripheral levels. The regional distribution of the opioid receptors confirms that μ receptors are responsible for most of the analgesic effects of morphine within the brain. They are found in highest concentration within areas of the brain classically associated with analgesia. **δ** and κ receptors also are responsible for mediation of analgesia, but they exert their analgesic effect predominantly in the spinal cord.

Xenobiotics with strong binding affinity for **δ** receptors in humans produce significantly more analgesia than morphine administered intrathecally. Indeed, the use of spinal and epidural opioid analgesia is predicated on the direct administration of opioid near the κ and **δ** receptors in the spinal cord.

Euphoria:

The pleasurable effects of many xenobiotics used by humans are mediated by the release of dopamine in the mesolimbic system. This final common pathway is shared by all opioids that activate the μ– **δ** receptor complex in the ventral tegmental area, which, in turn, indirectly promotes dopamine release in the mesolimbic region. Opioids also may have a direct reinforcing effect on their self-administration through μ receptors within the mesolimbic system. The sense of well-being and euphoria associated with strenuous exercise appears to be mediated by endogenous opioid peptides and μ receptors.

Exogenous opioids do not induce uniform psychological effects. Some of the exogenous opioids, particularly those that are highly lipophilic such as heroin, are euphorigenic, but morphine is largely devoid of such pleasurable effects. However, morphine administration results in analgesia, anxiolysis, and sedation.

Table 1:Clinical effects related to opioid receptors:

1996 Conventional Name	Proposed IUPHAR Name	IUPHAR Name	Important Clinical Effects of Receptor Agonists
μ_1	OP_{3a}	MOP	Supraspinal analgesia Peripheral analgesia Sedation Euphoria Prolactin release
μ_2	OP_{3b}		Spinal analgesia Respiratory depression Physical dependence GI dysmotility Pruritus Bradycardia Growth hormone release
κ_1	OP_{2a}	KOP	Spinal analgesia Miosis Diuresis
κ_2	OP_{2b}		Psychotomimesis Dysphoria
κ_3	OP_{2b}		Supraspinal analgesia
δ	OP_1	DOP	Spinal and supraspinal analgesia Modulation of μ-receptor function Inhibit release of dopamine
Nociceptin/ orphanin FQ	OP_4	NOP	Anxiolysis Analgesia

Antitussive:

Codeine and dextromethorphan are two opioids with cough-suppressant activity. Cough suppression is not likely mediated via the μ_1 opioid receptor because the ability of other opioids to suppress the medullary cough centers is not correlated with their analgesic effect.

TOXIC EFFECTS

When used appropriately for medical purposes, opioids are remarkably safe and effective. However, excessive dosing for any reason may result in serious toxicity. Most adverse or toxic effects are predictable based on "opioid" pharmacodynamics. Mental status depression, hypoventilation, miosis, and hypoperistalsis are the classic symptoms.

Respiratory Depression:

Experimental use of various opioid agonists and antagonists consistently implicates u_2 receptors in the respiratory depressant effects of morphine. Through these receptors, opioid agonists reduce ventilation by diminishing

the sensitivity of the medullary chemoreceptors to hypercapnea. In addition to loss of hypercarbic stimulation, opioids depress the ventilatory response to hypoxia. Equianalgesic doses of the available opioid agonists produce approximately the same degree of respiratory depression. Patients chronically exposed to opioid agonists, such as those on methadone maintenance, experience chronic hypoventilation.

It is important to recognize that ventilatory depression may be secondary to a reduction in either respiratory rate or tidal volume. Thus, although respiratory rate is more accessible for clinical measurement, it is not an ideal index of ventilatory depression. In fact, morphine- induced respiratory depression in humans initially is related more closely to changes in tidal volume. Large doses of opioids also result in a reduction of respiratory rate.

Acute Lung Injury:

Reports linking opioids with the development of acute pulmonary abnormalities became common in the 1960s, although the first report was made by William Osler in 1880. Almost all opioids are implicated, and opioid-related acute lung injury (ALI) is reported in diverse clinical situations. Typically, the patient regains normal ventilation after a period of profound respiratory depression, either spontaneously or after the administration of an opioid antagonist, and over the subsequent several minutes to hours develops hypoxemia and pulmonary crackles. No single mechanism can be consistently invoked in the genesis of opioid-associated ALI.

Cardiovascular:

Arteriolar and venous dilation secondary to opioid use may result in a mild reduction in blood pressure. Bradycardia is unusual, although a reduction in heart rate is common as a result of the associated reduction in CNS stimulation. Opioid-induced hypotension appears to be mediated by histamine release, although induction of histamine release does not appear to occur through interaction with an opioid receptor. It may be related to the nonspecific ability of certain xenobiotics to activate mast cell G proteins, which induce degranulation of histamine-containing vesicles.
Accordingly, not all opioids are equivalent in their ability to release histamine. After administration of one of four different opioids to 60 healthy patients, meperidine produced the most hypotension and elevation of serum histamine concentrations; fentanyl produced the least. The combination of

H_1 and H_2 antagonists is effective in ameliorating the hemodynamic effects of opioids in humans.

Cardiovascular toxicity may occur with use of propoxyphene, which causes wide-complex dysrhythmias and negative contractility through sodium channel antagonism similar to that of type IA antidysrhythmics. Adulterants or co-ingestants may also produce significant cardiovascular toxicity. For example, quinine- adulterated heroin is associated with dysrhythmias. Cocaine, surreptitiously added to heroin, may cause significant myocardial ischemia or infarction. Similarly, concern that naloxone administration may "unmask" cocaine toxicity in patients simultaneously using cocaine and heroin ("speedball") probably is warranted but rarely is demonstrated unequivocally. Certain opioids at therapeutic concentrations, particularly methadone, may interfere with normal cardiac repolarization and produce QT interval prolongation.

Miosis "pinpoint pupil":

The mechanisms by which opioids induce miosis remain controversial. Support for each of several mechanisms can be found in the literature. Stimulation of parasympathetic pupilloconstrictor neurons by morphine produces miosis. Additionally, morphine increases firing of pupilloconstrictor neurons to light, which increases the sensitivity of the light reflex through central reinforcement. Not all patients using opioids present with miosis. Meperidine has a lesser miotic effect than other conventional opioids, and propoxyphene use does not result in miosis. Use of opioids with predominantly μ-agonist effects, such as pentazocine, may not result in miosis.

Seizures:

Seizures are a rare complication of therapeutic use of most opioids. In patients with acute opioid overdose, seizures most likely are caused by hypoxia. However, experimental models demonstrate a proconvulsant effect of morphine in that it potentiates the convulsant effect of other xenobiotics. These effects are variably inhibited by naloxone, suggesting the involvement of a mechanism other than opioid receptor binding. In humans, morphine-induced seizures are reported in neonates and are reversed by naloxone, although opioid withdrawal seizures in neonates are more common.

Gastrointestinal Effects:

Historically, the morphine analog apomorphine was used as a rapidly acting emetic whose clinical use was limited by its tendency to depress the patient's level of consciousness. Emesis induced by apomorphine is mediated through agonism at D_2 receptor subtypes within the chemoreceptor trigger zone of the medulla. Many opioids, particularly morphine, produce significant nausea and vomiting when used therapeutically. Whether these effects are inhibited by naloxone is not clearly established, but they likely are not. Although diphenoxylate and loperamide are widely used therapeutically to manage diarrhea, opioid-induced constipation is most frequently a bothersome side effect of both medical and nonmedical use of opioids. Constipation, mediated by μ_2 receptors within the smooth muscle of the intestinal wall, is ameliorated by oral naloxone.

MANAGEMENT

The consequential effects of acute opioid poisoning are CNS and respiratory depression. Although early support of ventilation and oxygenation is generally sufficient to prevent the death. Opioid antagonists, such as naloxone, competitively inhibit binding of opioid agonists to opioid receptors, allowing the patient to resume spontaneous respiration. Naloxone competes at all receptor subtypes, although not equally, and is effective at reversing almost all adverse effects mediated through opioid receptors.

ANTIDOTE ADMINISTRATION

The goal of naloxone therapy is not necessarily complete arousal; rather, the goal is reinstitution of adequate spontaneous ventilation. Because precipitation of withdrawal is potentially detrimental and often unpredictable, the lowest practical naloxone dose should be administered initially, with rapid escalation as warranted by the clinical situation. Most patients respond to 0.04 to 0.05 mg of naloxone administered IV, although the requirement for ventilatory assistance may be slightly prolonged because the onset may be slower than with larger doses.

SC administration may allow for smoother arousal than the high-dose IV route but is unpredictable in onset and likely prolonged in offset. Prolonged effectiveness of naloxone by the SC route can be a considerable disadvantage if the therapeutic goal is exceeded and the withdrawal syndrome develops.

Naloxone, even at extremely high doses, has an excellent safety profile in

opioid-naïve patients receiving the medication for nonopioid-related indications, such as spinal cord injury or acute ischemic stroke. However, administration of naloxone to opioid-dependent patients may result in adverse effects; specifically, precipitation of an acute withdrawal syndrome should be anticipated. The resultant agitation, hypertension, and tachycardia may produce significant distress for the patient and complicate management for the clinical staff and occasionally may be life threatening. Additionally, emesis, a common feature of acute opioid withdrawal, may be particularly hazardous in patients who do not rapidly regain consciousness after naloxone administration.

The decision to discharge a patient who awakens appropriately after naloxone administration is based on practical considerations. Patients presenting with profound hypoventilation or hypoxia are at risk for development of ALI or posthypoxic encephalopathy. Thus, it seems prudent to observe these patients for at least 24 hours in a medical setting. Patients manifesting only moderate signs of poisoning who remain normal for at least several hours after parenteral naloxone likely are safe to discharge. However, the need for psychosocial intervention in patients with uncontrolled drug use or after a suicide attempt may prevent discharge from the emergency department (ED).

Patients with recurrent or profound poisoning by long-acting opioids, such as methadone, or patients with large GI burdens (eg, “body packers” or those taking sustained-release preparations), may require continuous infusion of naloxone to ensure continued adequate ventilation. Despite the availability of long-acting opioid antagonists (eg, naltrexone and nalmefene) that theoretically permit single-dose reversal of methadone poisoning, the attendant risk of precipitating an unrelenting withdrawal syndrome hinders their use as antidotes for initial opioid reversal. However, these opioid antagonists may have a clinical role in the maintenance of consciousness and ventilation in opioid-poisoned patients already awakened by naloxone.

SPECIFIC OPIOIDS

MORPHINE AND CODEINE

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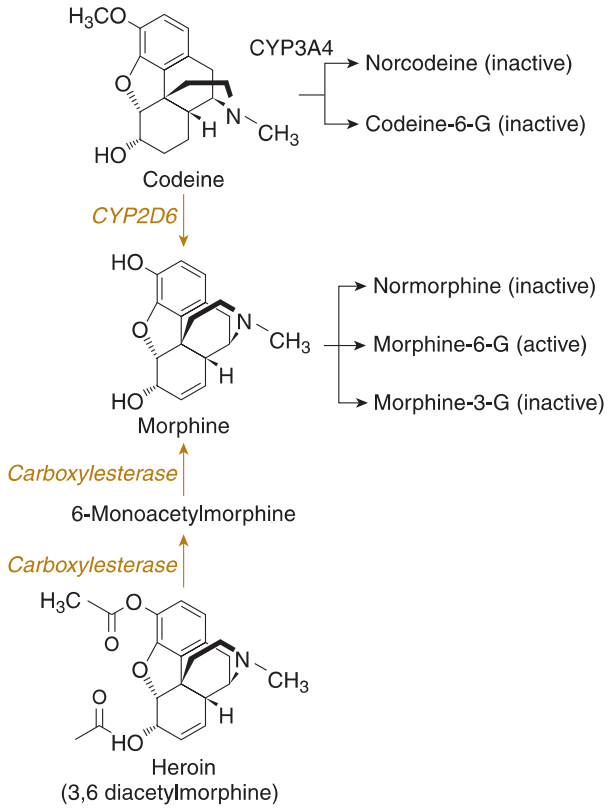

Figure 1:

Fentanyl and Its Analogs:

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Oxycodone and Hydrocodone:

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Abusers typically crush the tablet, which destroys the sustained-release matrix and liberates large amounts of insufflatable or injectable oxycodone. The psychoactive effects of these opioids are similar to other μ-receptor agonists and often are used as a substitute for heroin.

Clinical Toxicology

Cocaine Toxicity

Cocaine is a naturally occurring alkaloid with unique local anesthetic and sympathomimetic activity, which served as the prototype for the synthesis of local anesthetics. Cocaine is contained in the leaves of *Erythroxylum coca*, a shrub that grows abundantly in Colombia, Peru, Bolivia, the West Indies, and Indonesia.

The alkaloid form of cocaine (benzoylmethylecgonine) is extracted from the leaf by mechanical degradation in the presence of a hydrocarbon. The resulting product is converted into a hydrochloride salt to yield a white powder (cocaine hydrochloride). Cocaine hydrochloride can be insufflated, applied topically to mucous membranes, dissolved in water and injected, or ingested; however, it degrades rapidly when pyrolyzed. Smokeable cocaine (crack) is formed by dissolving cocaine hydrochloride in water and adding a strong base. A hydrocarbon solvent is added, the cocaine base is extracted into the organic phase, and then evaporated. The term free-base refers to the use of cocaine base in solution.

Cocaine is usually abused by either chewing coca leaves, smoking coca paste, or "snorting" cocaine hydrochloride. The last mentioned is the most popular form of cocaine intake, i.e. the drug is inhaled in powder form through the nostrils . Occasionally, cocaine hydrochloride is injected intravenously.

Today, a smokable form of cocaine ("*crack*" or *"rock*") has virtually become a rage in the West. Pure alkaloidal cocaine ("*free-base*" or *"baseball"*) can also be smoked.

Cocaine freebase is prepared from cocaine hydrochloride by extracting the cocaine with an alkaline solution (buffered ammonia) and adding a solvent such as ether or acetone. The mixture separates into two layers, the top solvent layer containing the dissolved cocaine. The solvent is then evaporated leaving almost pure cocaine crystals. *Free-base* is a colourless, odourless, transparent, crystalline substance that makes a popping or cracking sound when heated (hence the term "*crack*").

Both free-base and crack are more stable to pyrolysis than the hydrochloride salt, and therefore can be smoked either using a "coke pipe" or mixed into a cigarette ("*joint*").

A solution of cocaine hydrochloride can also be heated in a pan with baking soda added until a solid "*rock*" is formed, pieces of which can be smoked directly.

Street cocaine is often impure. The content of pure cocaine ranges from 10 to 50 percent (most commonly 15 to 20 percent). Cocaine, which is available on the street, is often adulterated with one or more of the following compounds: talc, lactose, sucrose, glucose, mannitol, inositol, caffeine, procaine, phencyclidine, lignocaine, strychnine, amphetamine, or heroin ("*speed ball*").

NEUROTRANSMITTER EFFECTS

Cocaine blocks the reuptake of biogenic amines. Specifically, these effects are described on serotonin and the catecholamines dopamine, norepinephrine, and epinephrine.

The CNS stimulant effects of cocaine are mediated through inhibition of dopamine reuptake in the nucleus accumbens. The dopamine-reuptake trans- porter controls the levels of dopamine in the synapse by rapidly carrying the neurotransmitter back into nerve terminals after its release. Cocaine, which binds strongly to the dopamine-reuptake transporter, is a classic blocker of such reuptake after normal neuronal activity. Because of this blocking effect, dopamine remains at high concentrations in the synapse and continues to affect adjacent neurons producing the characteristic cocaine "high".

Cocaine also increases the concentrations of the excitatory amino acids, aspartate and glutamate. These excitatory amino acids increase the extracellular concentrations of dopamine. Excitatory amino acid antagonists attenuate the effects of cocaine induced convulsions and death. Dopamine$_2$ (D_2) receptor agonists accentuate cocaine craving, while dopamine$_1$ (D_1) agonists diminish such craving. Cocaine also inhibits reuptake of noradrenaline and serotonin. Increase in the concentrations of the former plays an important role in the toxic effects of cocaine.

Concerning Peripheral nerves, through direct blockade of fast sodium channels, cocaine stabilize the axonal membrane, producing a local anaesthetic effect. Cocaine is the only local anaesthetic that interferes with the uptake of neurotransmitter by the nerve terminals and simultaneously functions as a vasoconstrictor.

CARDIOVASCULAR EFFECTS

Initial effect of cocaine on the CVS is bradycardia, secondary to stimulation of vagal nuclei. However, the bradycardia is too transient to be clinically evident, and tachycardia becomes the prominent effect resulting from central sympathetic stimulation. The cardiostimulatory effect of cocaine is due in large part to sensitisation to adrenaline and noradrenaline, preventing neuronal reuptake of these catecholamines, as well as due to increased release of noradrenaline from adrenergic nerve terminals. The increased concentrations and persistence of catecholamines near the receptors of the effecter organ lead to exaggerated sympathetic effects. The sympathomimetic effects of cocaine increase myocardial oxygen demand and the alpha-adrenergic mediated coronary vasoconstriction limits coronary artery blood flow.

Cocaine inhibits endogenous fibrinolysis, increases thrombogenicity, and enhances platelet aggregation.

Toxicokinetics

- Absorption:
Ingestion and insufflation: Cocaine is well-absorbed from oral, nasal, and pulmonary routes. Onset of action on insufflation is within 1 to 3 minutes, and peak effects are seen

in 20 to 30 minutes.
Intravenous injection: Onset of action is within seconds, and peak action occurs in 3 to 5 minutes.
Inhalation: Smoking produces effects as rapidly as IV injection.
Table1 lists the typical onsets and durations of action for various uses of cocaine.

- Metabolism:
Cocaine is metabolised by liver esterases and plasma cholinesterase to ecgonine methylester (EME), one of the major metabolites, while non-enzymatic hydrolysis results in the formation of the other major metabolite, benzoylecgonine (BE). Patients with lower plasma cholinesterase levels may be predisposed to more severe cocaine toxicity. Since children have lower plasma cholinesterase levels, they may be affected by smaller amounts of cocaine. In addition, the metabolic half-life of cocaine may be increased by lower plasma cholinesterase concentrations.

Route of Exposure	Onset of Action (min)	Peak Action (min)	Duration of Action (min)
Intravenous	<1	3–5	30–60
Nasal insufflation	1–5	20–30	60–120
Smoking	<1	3–5	30–60
Gastrointestinal	30–60	60–90	Unknown

Clinical Features

Acute Poisoning:

a. Hyperthermia—This results from:

- Augmentation of heat production due to increased psychomotor activity.

- Diminution of heat dissipation due to vasoconstriction.

- Direct pyrogenic effect due to action on thermoregulatory centers in the hypothalamus.

- Stimulation of calorigenic activity of liver.

Body temperature often soars to 42.2 to 44.4°C, and does not respond to conventional antipyretics. It is often associated with rhabdomyolysis, seizures, and renal failure.

b. CNS effects—

Headache, Anxiety, agitation. Hyperactivity, restlessness, non-intentional Tremor, hyperreflexia and Convulsions (Generalised tonic-clonic, partial motor, and partial complex seizure have all been reported), and pseudohallucinations (eg, cocaine bugs).

Seizures may be recurrent and status epilepticus has been reported, particularly in children. Sometimes there is lethargy and decreased level of consciousness which can persist up to 24 hours ("*cocaine washed out syndrome*"). Cerebrovascular accidents are not uncommon, and include subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, transient ischaemic attacks, migraine-type headache syndrome, cerebral vasculitis, and anterior spinal artery syndrome. Infarction of the brainstem/spinal cord has also occurred.

c. Ophthalmologic effects:

- Mydriasis and/or loss of eyebrow and eyelash hair from smoking crack cocaine may occur.
- Corneal abrasions/ulcerations due to particulate matter in smoke ("*crack eye*").
- Central retinal artery occlusion and bilateral blindness due to diffuse vasospasm. Retinal foreign body granuloma may occur with IV abuse.

d. CVS effects:

- Tachycardia.
- Systemic arterial hypertension.
- Coronary artery vasoconstriction with myocardial ischaemia and infarction.
- Tachyarrhythmias.
- Chronic dilated cardiomyopathy has been reported.
- Aortic dissection and rupture.
- Coronary artery dissection.
- Sudden cardiac death can occur.

e. Pulmonary effects:

- Thermal injuries to the upper airway leading to epiglottitis, laryngeal injury, and mucosal necrosis have been reported after smoking "crack" or free base cocaine.
- Exacerbation of asthma.
- Non-cardiogenic pulmonary edema.
- Diffuse alveolar hemorrhage.

f. Musculoskeletal effects:

- Rhabdomyolysis with hyperthermia, massive elevation of creatine phosphokinase, and acute renal failure: Although the mechanism of cocaine-associated rhabdomyolysis is unclear, it is postulated that it may result from ischaemia due to vasoconstriction, direct toxicity, hyperpyrexia, and increased muscle activity from agitation or seizure activity.

DIAGNOSTIC TESTING

Cocaine and benzoylecgonine, its principle metabolite, can be detected in blood, urine, saliva, hair, and meconium. Routine drug-of-abuse testing relies on urine testing using a variety of immunologic techniques. Although cocaine is rapidly eliminated within just a few hours of use, benzoylecgonine is easily detected in the urine for 2–3 days following last use. When more sophisticated testing methodology is applied to chronic users, cocaine metabolites can be identified for several weeks following last use.

Urine testing, even using rapid point-of-care assays, offers little to clinicians managing patients with presumed cocaine toxicity because it cannot distinguish recent from remote cocaine use. In addition, false-negative testing can result when there is a large quantity of urine in the bladder with very recent cocaine use or when the urine is intentionally diluted by increased fluid intake leading to a urine cocaine concentration below the cut-off value and interpretation of the test as negative. Under these circumstances, repeat testing is almost always positive. While false-positive tests do occur, they are more common with hair testing than urine or blood because of the increased risk of external contamination. Because of the very low rate of false-positive results, confirmation of positive urine is unnecessary for medical indications.

There may be some usefulness for urine testing of body packers, especially when the concealed xenobiotic is unknown. While many body packers will have negative urine throughout their hospitalization, a positive urine test is suggestive of the concealed drug but obviously not confirmatory. More importantly, a conversion from a negative study on admission to a positive study not only confirms the substance ingested, but also suggests packet leakage, which could be a harbinger of life-threatening toxicity. Another indication for urine testing for cocaine occurs in young patients with chest pain syndromes where the history of drug uses, specifically cocaine, is not forthcoming. Routine diagnostic tests such as a bedside rapid reagent glucose, electrolytes, renal function tests, and markers of muscle and cardiac muscle injury are more likely to be useful than urine drug screening. An ECG may show signs of ischemia or infarction, or dysrhythmias that require specific therapy. Unfortunately, in the setting of cocaine-associated chest pain, the ECG has neither the sensitivity nor the specificity necessary to permit exclusion or confirmation of cardiac injury. Cardiac markers are therefore always-required adjuncts when considering myocardial ischemia or infarction. Because cocaine use is associated with diffuse muscle injury, assays for troponin are preferred over myoglobin or myocardial band enzymes of creatine phosphokinase (CPK-MB).

MANAGEMENT

■ GENERAL SUPPORTIVE CARE

As in the case of all poisoned patients, the initial emphasis must be on stabilization and control of the patient’s airway, breathing, and circulation. If tracheal intubation is required, it is important to recognize that cocaine toxicity may be a relative

contraindication to the use of succinylcholine. Specifically, in the setting of rhabdomyolysis, hyperkalemia may be exacerbated by succinylcholine administration, and life-threatening dysrhythmias may result.

If hypotension is present, the initial approach should be infusion of intravenous 0.9% sodium chloride solution as many patients are volume depleted as a result of poor oral intake and excessive fluid losses from uncontrolled agitation, diaphoresis, and hyperthermia.

In the setting of cocaine toxicity it is important to recognize that both animal and human experience suggests that elevated temperature represents the most critical vital sign abnormality. Determination of the core temperature is an essential element of the initial evaluation, even when patients are severely agitated. When hyperthermia is present, preferably rapid cooling with ice water immersion, or the combined use of mist and fanning, is required to achieve a rapid return to normal core body temperature. Sedation or paralysis and intubation may be necessary to facilitate the rapid cooling process. Pharmacotherapy including antipyretics, drugs that prevent shivering (chlorpromazine or meperidine), and dantrolene are not indicated as they are ineffective and have the potential for adverse drug interactions such as serotonin syndrome (meperidine) or seizures (chloropromazine).

Sedation remains the mainstay of therapy in patients with cocaine- associated agitation. It is important to remember that cocaine use is associated with hypoglycemia and that many of the peripheral findings of hypoglycemia are the result of a catecholamine discharge. Consequently, a rapid reagent glucose test should be obtained, or hypertonic dextrose should be empirically administered if indicated, prior to or while simultaneously achieving sedation. Both animal models and extensive clinical experience in humans support the central role of benzodiazepines. Although the choice among individual benzodiazepines is not well studied, an understanding of the pharmacology of these drugs allows for rational decision-making. The goal is to use parenteral therapy with a drug that has a rapid onset and a rapid peak of action, making titration easy. Using this rationale, midazolam and diazepam are preferable to lorazepam, because significant delay to peak effect for lorazepam often results in oversedation when it is dosed rapidly, or in prolonged agitation when the appropriate dosing interval is used. Drugs should be administered in initial doses that are consistent with routine practices and increased incrementally based on an appropriate understanding of their pharmacology. For example, if using diazepam, the starting dose might be 5–10 mg, which can be repeated every 3–5 minutes and increased if necessary. Large doses of benzodiazepines may be necessary (on the order of 1 mg/kg of diazepam). This may result from cocaine-induced alterations in benzodiazepine receptor function.

On the rare occasion when benzodiazepines fail to achieve an adequate level of sedation, either a rapidly acting barbiturate or propofol should be administered. The use of phenothiazines or butyrophenones is contraindicated. In animal models, these drugs enhance toxicity (seizures), lethality, or both. Additional concerns about these drugs include interference with heat dissipation, exacerbation of tachycardia, prolongation of the QT interval, induction of torsade de pointes, and precipitation of dystonic reactions.

Once sedation is accomplished, often no additional therapy is required. Specifically, hypertension and tachycardia usually respond to sedation and volume resuscitation. In the uncommon event that hypertension and/or tachycardia persists, the use of a β-adrenergic antagonist or a mixed α- and β-adrenergic antagonist is contraindicated. Again, in both animal models and human reports, these drugs increase lethality and fail to treat the underlying problem. The resultant unopposed α-adrenergic effect may produce severe and life-threatening hypertension or vasospasm. A direct-acting vasodilator like nitroglycerin, nitroprusside or possibly nicardipine or a α-adrenergic antagonist (such as phentolamine) may be considered. Other nonspecific therapies for rhabdomyolysis such as intravenous fluid should also be considered.

DECONTAMINATION

The majority of patients who present to the hospital following cocaine use will not require gastrointestinal decontamination as the most popular methods of cocaine use are smoking, intravenous and intranasal administration. If the nares contain residual white powder presumed to be cocaine, gentle irrigation with 0.9% sodium chloride solution will help remove adherent material. Less commonly, patients may ingest cocaine unintentionally or in an attempt to conceal evidence during an arrest (body stuffing) or transport large quantities of drug across international borders (body packing). These patients may require intensive decontamination and possibly surgical removal.

■ SPECIFIC MANAGEMENT

End-organ manifestations of vasospasm that do not resolve with sedation, cooling, and volume resuscitation should be treated with vasodilatory agents (such as phentolamine). When possible, direct delivery via intra-arterial administration to the affected vascular bed is prefer- able. Because this approach is not always feasible, systemic therapy is typically indicated. Phentolamine can be dosed intravenously in increments of 1–2.5 mg, and repeated as necessary until symptoms resolve or systemic hypotension develops.

Acute Coronary Syndrome

A significant amount of animal, in vitro, and in vivo human experimentation has been directed at defining the appropriate approach to a patient with presumed cardiac ischemia or infarction. In some instances an approach that is similar to the treatment of coronary artery disease (CAD) is indicated, although there are certain notable exceptions. An overall approach to care is available in the American Heart Association guidelines and a number of reviews.

High-flow oxygen therapy is clearly indicated as it may help overcome some of the supply–demand mismatch that occurs with coronary insufficiency. Aspirin is safe in patients with cocaine-associated chest pain and is recommended for routine use. In addition, administration of morphine is likely to be effective as it relieves cocaine-induced vasoconstriction. Morphine also offers the same theoretical benefits of preload reduction and reduction of catecholamine release in response to pain that is thought to be responsible for its usefulness in patients with CAD.

Nitroglycerin is clearly beneficial as it reduces cocaine-associated coronary constriction of both normal and diseased vessels and relieves chest pain and associated symptoms. Interestingly, in several clinical trials of cocaine-associated chest pain, benzodiazepines are at least as effective or superior to nitroglycerin. Although the reasons for this are unclear, possible etiologies include blunting of central catecholamines or direct effects on cardiac benzodiazepine receptors. Either or both drugs can be used in standard dosing.

Over the last decade, the benefits of β-adrenergic antagonism have been demonstrated in patients with CAD. In contrast, β-adrenergic antagonism increases lethality in cocaine-toxic animals and in humans, exacerbates cocaine-induced coronary vasoconstriction, and produces severe paradoxical hypertension. Similarly, with regard to treatment of coronary constriction, labetalol is no better than placebo Thus, in the setting of cocaine use, β-adrenergic antagonism is absolutely contraindicated. The 2008 American Heart Association Guidelines for the treatment of cocaine-associated chest pain and MI state that use of β-adrenergic antagonists should be avoided in the acute setting. If, after the measures mentioned previously have been initiated, hypertension or vasospasm is still present and treatment is indicated, phentolamine is preferred based on its demonstrable experimental and clinical results. If tachycardia does not respond to accepted therapies above, then diltiazem can be administered and titrated to effect. Prior to the administation of any negative inotrope, it is essential to confirm that the tachycardia is not compensatory for a low cardiac output resulting from global myocardial dysfunction. Noninvasive methods of assessment of cardiac function have been used successfully in patients with cocaine-associated acute coronary syndromes.

There are no data on the use of either unfractionated or low- molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, or clopidogrel. The recent AHA guidelines recommend the administration of unfractionated heparin or low-molecular-weight heparin in patients with cocaine-associated MI. The decision to use any of these medications should be based on a risk-to-benefit analysis.

Cocaine abuse is well-known for its propensity to cause sudden death not only due to its deleterious effects on health (cerebrovascular accidents, myocardial infarction, malignant hyperthermia, renal failure), but also due to its capacity to provoke the user to commit acts of aggression and violence. Deaths due to massive overdose are especially common among those who smuggle the drug within their bodies ("cocaine packers").

Bodypacker Syndrome:

The practice of swallowing balloons, condoms, or plastic packets filled with illegal drugs for the purpose of smuggling is called "body packing", and the individual who does this is referred to as a "mule". This must be differentiated from "body stuffing" in which an individual who is on the verge of being arrested for possession of illegal drugs, swallows his illicit contraband to conceal the evidence. Leaking from these poorly wrapped packets can produce cocaine toxicity.

Sudden death due to massive overdose can occur in either a bodypacker or a bodystuffer, if one or more of the ingested packages burst within the gastrointestinal tract.

Treatment:

- Emesis, lavage, charcoal, as applicable.

- Cathartic/whole bowel irrigation to flush the packages out of the intestines. - Symptomatic patients should be considered a medical emergency, and be evaluated for surgical removal of the packets.

- Asymptomatic patients should be monitored in an intensive care unit until the cocaine packs have been eliminated. This must be confirmed by follow-up plain radiography and barium swallows.

- Bowel obstruction in asymptomatic patients may necessitate surgery. Endoscopic removal has been successful in some cases.

Drugs to be avoided in the Treatment of Cocaine Poisoning

Drug	*Adverse Effects*
Beta blockers (especially propranolol)	Coronary artery spasm (Paradoxical hypertension)
Lignocaine, procainamide, quinidine	Convulsions Arrhythmias
Haloperidol, droperidol, phenothiazines	Hyperpyrexia Convulsions
Dantrolene	Cardiac insufficiency
Bromocriptine	Coronary artery constriction

Clinical Toxicology

Cocaine Toxicity

Cocaine is a naturally occurring alkaloid with unique local anesthetic and sympathomimetic activity, which served as the prototype for the synthesis of local anesthetics. Cocaine is contained in the leaves of *Erythroxylum coca*, a shrub that grows abundantly in Colombia, Peru, Bolivia, the West Indies, and Indonesia.

The alkaloid form of cocaine (benzoylmethylecgonine) is extracted from the leaf by mechanical degradation in the presence of a hydrocarbon. The resulting product is converted into a hydrochloride salt to yield a white powder (cocaine hydrochloride). Cocaine hydrochloride can be insufflated, applied topically to mucous membranes, dissolved in water and injected, or ingested; however, it degrades rapidly when pyrolyzed. Smokeable cocaine (crack) is formed by dissolving cocaine hydrochloride in water and adding a strong base. A hydrocarbon solvent is added, the cocaine base is extracted into the organic phase, and then evaporated. The term free-base refers to the use of cocaine base in solution.

Cocaine is usually abused by either chewing coca leaves, smoking coca paste, or "snorting" cocaine hydrochloride. The last mentioned is the most popular form of cocaine intake, i.e. the drug is inhaled in powder form through the nostrils . Occasionally, cocaine hydrochloride is injected intravenously.

Today, a smokable form of cocaine ("*crack*" or *"rock*") has virtually become a rage in the West. Pure alkaloidal cocaine ("*free-base*" or *"baseball"*) can also be smoked.

Cocaine freebase is prepared from cocaine hydrochloride by extracting the cocaine with an alkaline solution (buffered ammonia) and adding a solvent such as ether or acetone. The mixture separates into two layers, the top solvent layer containing the dissolved cocaine. The solvent is then evaporated leaving almost pure cocaine crystals. *Free-base* is a colourless, odourless, transparent, crystalline substance that makes a popping or cracking sound when heated (hence the term "*crack*").

Both free-base and crack are more stable to pyrolysis than the hydrochloride salt, and therefore can be smoked either using a "coke pipe" or mixed into a cigarette ("*joint*").

A solution of cocaine hydrochloride can also be heated in a pan with baking soda added until a solid "*rock*" is formed, pieces of which can be smoked directly.

Street cocaine is often impure. The content of pure cocaine ranges from 10 to 50 percent (most commonly 15 to 20 percent). Cocaine, which is available on the street, is often adulterated with one or more of the following compounds: talc, lactose, sucrose, glucose, mannitol, inositol, caffeine, procaine, phencyclidine, lignocaine, strychnine, amphetamine, or heroin ("*speed ball*").

NEUROTRANSMITTER EFFECTS

Cocaine blocks the reuptake of biogenic amines. Specifically, these effects are described on serotonin and the catecholamines dopamine, norepinephrine, and epinephrine.

The CNS stimulant effects of cocaine are mediated through inhibition of dopamine reuptake in the nucleus accumbens. The dopamine-reuptake trans- porter controls the levels of dopamine in the synapse by rapidly carrying the neurotransmitter back into nerve terminals after its release. Cocaine, which binds strongly to the dopamine-reuptake transporter, is a classic blocker of such reuptake after normal neuronal activity. Because of this blocking effect, dopamine remains at high concentrations in the synapse and continues to affect adjacent neurons producing the characteristic cocaine "high".

Cocaine also increases the concentrations of the excitatory amino acids, aspartate and glutamate. These excitatory amino acids increase the extracellular concentrations of dopamine. Excitatory amino acid antagonists attenuate the effects of cocaine induced convulsions and death. Dopamine$_2$ (D_2) receptor agonists accentuate cocaine craving, while dopamine$_1$ (D_1) agonists diminish such craving. Cocaine also inhibits reuptake of noradrenaline and serotonin. Increase in the concentrations of the former plays an important role in the toxic effects of cocaine.

Concerning Peripheral nerves, through direct blockade of fast sodium channels, cocaine stabilize the axonal membrane, producing a local anaesthetic effect. Cocaine is the only local anaesthetic that interferes with the uptake of neurotransmitter by the nerve terminals and simultaneously functions as a vasoconstrictor.

CARDIOVASCULAR EFFECTS

Initial effect of cocaine on the CVS is bradycardia, secondary to stimulation of vagal nuclei. However, the bradycardia is too transient to be clinically evident, and tachycardia becomes the prominent effect resulting from central sympathetic stimulation. The cardiostimulatory effect of cocaine is due in large part to sensitisation to adrenaline and noradrenaline, preventing neuronal reuptake of these catecholamines, as well as due to increased release of noradrenaline from adrenergic nerve terminals. The increased concentrations and persistence of catecholamines near the receptors of the effecter organ lead to exaggerated sympathetic effects. The sympathomimetic effects of cocaine increase myocardial oxygen demand and the alpha-adrenergic mediated coronary vasoconstriction limits coronary artery blood flow.

Cocaine inhibits endogenous fibrinolysis, increases thrombogenicity, and enhances platelet aggregation.

Toxicokinetics

- Absorption:
Ingestion and insufflation: Cocaine is well-absorbed from oral, nasal, and pulmonary routes. Onset of action on insufflation is within 1 to 3 minutes, and peak effects are seen

in 20 to 30 minutes.
Intravenous injection: Onset of action is within seconds, and peak action occurs in 3 to 5 minutes.
Inhalation: Smoking produces effects as rapidly as IV injection.
Table1 lists the typical onsets and durations of action for various uses of cocaine.

- Metabolism:
Cocaine is metabolised by liver esterases and plasma cholinesterase to ecgonine methylester (EME), one of the major metabolites, while non-enzymatic hydrolysis results in the formation of the other major metabolite, benzoylecgonine (BE). Patients with lower plasma cholinesterase levels may be predisposed to more severe cocaine toxicity. Since children have lower plasma cholinesterase levels, they may be affected by smaller amounts of cocaine. In addition, the metabolic half-life of cocaine may be increased by lower plasma cholinesterase concentrations.

Route of Exposure	Onset of Action (min)	Peak Action (min)	Duration of Action (min)
Intravenous	<1	3–5	30–60
Nasal insufflation	1–5	20–30	60–120
Smoking	<1	3–5	30–60
Gastrointestinal	30–60	60–90	Unknown

Clinical Features

Acute Poisoning:

a. Hyperthermia—This results from:

- Augmentation of heat production due to increased psychomotor activity.

- Diminution of heat dissipation due to vasoconstriction.

- Direct pyrogenic effect due to action on thermoregulatory centers in the hypothalamus.

- Stimulation of calorigenic activity of liver.

Body temperature often soars to 42.2 to 44.4°C, and does not respond to conventional antipyretics. It is often associated with rhabdomyolysis, seizures, and renal failure.

b. CNS effects—

Headache, Anxiety, agitation. Hyperactivity, restlessness, non-intentional Tremor, hyperreflexia and Convulsions (Generalised tonic-clonic, partial motor, and partial complex seizure have all been reported), and pseudohallucinations (eg, cocaine bugs).

Seizures may be recurrent and status epilepticus has been reported, particularly in children. Sometimes there is lethargy and decreased level of consciousness which can persist up to 24 hours ("*cocaine washed out syndrome*"). Cerebrovascular accidents are not uncommon, and include subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, transient ischaemic attacks, migraine-type headache syndrome, cerebral vasculitis, and anterior spinal artery syndrome. Infarction of the brainstem/spinal cord has also occurred.

c. Ophthalmologic effects:

- Mydriasis and/or loss of eyebrow and eyelash hair from smoking crack cocaine may occur.
- Corneal abrasions/ulcerations due to particulate matter in smoke ("*crack eye*").
- Central retinal artery occlusion and bilateral blindness due to diffuse vasospasm. Retinal foreign body granuloma may occur with IV abuse.

d. CVS effects:

- Tachycardia.
- Systemic arterial hypertension.
- Coronary artery vasoconstriction with myocardial ischaemia and infarction.
- Tachyarrhythmias.
- Chronic dilated cardiomyopathy has been reported.
- Aortic dissection and rupture.
- Coronary artery dissection.
- Sudden cardiac death can occur.

e. Pulmonary effects:

- Thermal injuries to the upper airway leading to epiglottitis, laryngeal injury, and mucosal necrosis have been reported after smoking "crack" or free base cocaine.
- Exacerbation of asthma.
- Non-cardiogenic pulmonary edema.
- Diffuse alveolar hemorrhage.

f. Musculoskeletal effects:

- Rhabdomyolysis with hyperthermia, massive elevation of creatine phosphokinase, and acute renal failure: Although the mechanism of cocaine-associated rhabdomyolysis is unclear, it is postulated that it may result from ischaemia due to vasoconstriction, direct toxicity, hyperpyrexia, and increased muscle activity from agitation or seizure activity.

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MANAGEMENT

■ GENERAL SUPPORTIVE CARE

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DECONTAMINATION

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■ SPECIFIC MANAGEMENT

End-organ manifestations of vasospasm that do not resolve with sedation, cooling, and volume resuscitation should be treated with vasodilatory agents (such as phentolamine). When possible, direct delivery via intra-arterial administration to the affected vascular bed is prefer- able. Because this approach is not always feasible, systemic therapy is typically indicated. Phentolamine can be dosed intravenously in increments of 1–2.5 mg, and repeated as necessary until symptoms resolve or systemic hypotension develops.

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There are no data on the use of either unfractionated or low- molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, or clopidogrel. The recent AHA guidelines recommend the administration of unfractionated heparin or low-molecular-weight heparin in patients with cocaine-associated MI. The decision to use any of these medications should be based on a risk-to-benefit analysis.

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Treatment:

- Emesis, lavage, charcoal, as applicable.

- Cathartic/whole bowel irrigation to flush the packages out of the intestines. - Symptomatic patients should be considered a medical emergency, and be evaluated for surgical removal of the packets.

- Asymptomatic patients should be monitored in an intensive care unit until the cocaine packs have been eliminated. This must be confirmed by follow-up plain radiography and barium swallows.

- Bowel obstruction in asymptomatic patients may necessitate surgery. Endoscopic removal has been successful in some cases.

Drugs to be avoided in the Treatment of Cocaine Poisoning

Drug	*Adverse Effects*
Beta blockers (especially propranolol)	Coronary artery spasm (Paradoxical hypertension)
Lignocaine, procainamide, quinidine	Convulsions Arrhythmias
Haloperidol, droperidol, phenothiazines	Hyperpyrexia Convulsions
Dantrolene	Cardiac insufficiency
Bromocriptine	Coronary artery constriction

Decongestants

A **decongestant**, or **nasal decongestant**, is a type of pharmaceutical drug that is used to relieve congestion in the upper respiratory tract. The active ingredient in most decongestants are either imidazoline , pseudoephedrine ,ephedrine ,phenylephrine or phenylepropanolamine . Regular use of decongestants for long periods should be avoided because mucosal ciliary function is impaired: atrophic rhinitis and anosmia can occur due to persistent vasoconstriction

Pharmacology

The vast majority of decongestants act via enhancing norepinephrine (noradrenaline) and epinephrine (adrenaline) or adrenergic activity by stimulating the α-adrenergic receptors. This induces vasoconstriction of the blood vessels in the nose, throat, and paranasal sinuses, which results in reduced inflammation (swelling) and mucus formation in these areas.

Pseudoephedrine acts indirectly on the adrenergic receptor system, whereas phenylephrine and oxymetazoline are direct agonists. The effects are not limited to the nose, and these medicines may cause hypertension through vasoconstriction; it is for this reason that people with hypertension are advised to avoid them. Besides hypertension, common side-effects include sleeplessness, anxiety, dizziness, excitability, and nervousness.

Topical nasal or ophthalmic decongestants quickly develop tachyphylaxis (*a rapid decrease in the response to a drug after repeated doses over a short period of time*). Long-term use is not recommended, since these agents lose effectiveness after a few days

Imidazoline

The imidazoline derivatives, oxymetazoline, xylometazoline, tetrahydrozoline, and naphazoline, are found in topical ophthalmic and nasal decongestants available OTC. They are generally used as topical vasoconstrictors in the nose and eyes for

temporary relief of nasal congestion due to colds, hay fever or other upper respiratory allergies, or sinusitis.

Imidazolines are sympathomimetic agents, with primary effects on α-adrenergic receptors and little if any effect on β-adrenergic receptors. Oxymetazoline is readily absorbed orally. Effects on α-receptors from systemically absorbed oxymetazoline hydrochloride may persist for up to 7 hr after a single dose. The elimination half-life in people is 5–8 hr. It is excreted unchanged both by the kidneys (30%) and in feces (10%).

Clinical Findings:

signs of intoxication may include vomiting, bradycardia, cardiac arrhythmias, poor capillary refill time, hypotension or hypertension, panting, increased upper respiratory sounds, depression, weakness, collapse, nervousness, hyperactivity, or shaking. These signs usually appear within 30 min to 4 hr after exposure. In general, imidazoline decongestant exposure may affect the GI, cardiopulmonary, and nervous systems.

Treatment:

Decontamination (induction of emesis and administration of activated charcoal) may not be practical because of the rapid absorption and onset of clinical signs. Heart rate and rhythm and blood pressure should be assessed, and an ECG obtained if needed. IV fluids should be given, along with atropine at 0.02 mg/kg, IV, if bradycardia is present. Diazepam (0.25–0.5 mg/kg, IV) can be given if CNS signs (eg, apprehension, shaking) are present. Serum electrolytes (ie, potassium, sodium, chloride) should be assessed and corrected as needed. Yohimbine, a specific α2-adrenergic antagonist, can also be used at 0.1 mg/kg, IV, and repeated in 2–3 hr if needed. If yohimbine is not available, atipamezole can be used at 50

mcg/kg, one-fourth IV and the rest IM; it can be repeated in 30–60 min if there is no improvement.

Pseudoephedrine and Ephedrine

Pseudoephedrine is a sympathomimetic drug found naturally in plants of the genus Ephedra. Several states in the USA have limited the availability and use of pseudoephedrine as an OTC decongestant because of its use as a precursor in illegal amphetamine synthesis. It is being replaced with other decongestants such as phenylephrine.

Pseudoephedrine is a stereoisomer of ephedrine and is available as the hydrochloride or sulfate salt. Both ephedrine and pseudoephedrine have α- and β-adrenergic agonist effects. The pharmacologic effects of the drugs are due to direct stimulation of adrenergic receptors and the release of norepinephrine

pseudoephedrine is rapidly absorbed orally. The onset of action is 15–30 min, with peak effects within 30–60 min. With extended-release preparations (12–24 hr), onset of clinical signs can be delayed (2–8 hr) and duration of clinical signs can be longer than with regular preparations. It is incompletely metabolized in the liver. Approximately 90% of the drug is eliminated through the kidneys. Renal excretion is accelerated in acidic urine. Elimination half-life varies between 2–21 hr, depending on urinary pH.

Clinical Findings:

Pseudoephedrine and ephedrine overdose can result in mainly sympathomimetic effects, including agitation, hyperactivity, mydriasis, tachycardia, hypertension, sinus arrhythmias, anxiety, tremors, hyperthermia, head bobbing, hiding, and vomiting. Clinical signs can be seen at dosages of 5–6 mg/kg, and death may occur at 10–12 mg/kg.

Treatment:

Treatment of pseudoephedrine toxicosis consists of decontamination, controlling the CNS and cardiovascular effects, and supportive care. Vomiting should be induced only in asymptomatic patients, followed by administration of activated charcoal with a cathartic. If the condition contraindicates induction of emesis, a gastric lavage with a cuffed endotracheal tube should be performed. Hyperactivity, nervousness, or seizures can be controlled with acepromazine (0.05–1 mg/kg, IM, IV, or SC), chlorpromazine (0.5–1 mg/kg, IV), phenobarbital (3–4 mg/kg, IV), or pentobarbital to effect. Diazepam should be avoided, because it can exaggerate hyperactivity. Phenothiazines should be used with caution because they can lower the seizure threshold, lower blood pressure, and cause bizarre behavioral changes. Tachycardia can be controlled with propranolol at 0.02–0.04 mg/kg, IV, repeated if needed, or with esmolol at 0.2–0.5 mg/kg, given slowly IV or as a constant-rate infusion at 25–200 mcg/kg/min. IV fluids should be given. Acidifying the urine with ammonium chloride (50 mg/kg, PO, qid) or ascorbic acid (20–30 mg/kg, IM or IV, tid) may enhance urinary excretion of pseudoephedrine. Acid-base status should be monitored if ammonium chloride or ascorbic acid is given. Electrolytes, heart rate and rhythm, and blood pressure should be monitored. Excessive trembling or shaking can cause myoglobinuria; if this occurs, kidney function should be monitored. Significant and persistent hyperthermia due to severe hyperactivity and CNS excitation could result in disseminated intravascular coagulation. Clinical signs of toxicosis can last 1–4 days. The presence of pseudoephedrine in urine can support the diagnosis.

Phenylephrine

Phenylephrine is a sympathomimetic amine with mainly an α1-adrenergic receptor agonist effect, available OTC as a decongestant in oral formulations (5–10 mg tablets), nasal sprays, or eye drops (0.25%–1%). It has poor oral bioavailability (38%) in people because of a significant first-pass effect and

extensive metabolism by monoamine oxidases in the GI tract and liver. The oral LD50 in rats and mice is 350 mg/kg and 120 mg/kg, respectively. The half-life is 2–3 hr. CNS stimulation, agitation, nervousness, and hypertension are possible but less frequent with phenylephrine than with pseudoephedrine. Treatment is mainly symptomatic care and is similar to that for pseudoephedrine toxicosis

Phenylpropanolamine

PPA acts primarily as a selective norepinephrine releasing agent. It also acts as a dopamine releasing agent with around 10-fold lower potency. The stereoisomers of the drug have only weak or negligible affinity for α- and β-adrenergic receptors. Many sympathetic hormones and neurotransmitters are based on the phenethylamine skeleton, and function generally in "fight or flight" type responses, such as increasing heart rate, blood pressure, dilating the pupils, increased energy, drying of mucous membranes, increased sweating, and a significant number of additional effects.

Clinical findings :

Overdose signs and symptoms comprise hypertesion , mydriasis , arrhythmia , anxiety , chest pain , auditory and visual hallucinations , paranoid ideation , occasionally delirium and psychosis , seizures , hemorrhagic and non-hemorrhagic cerebral infarction , urine retention and renal failure .

Treatment :

Emesis is not indicated because drowsiness and coma may occur rapidly .

Emesis is contraindicated in patient with hypertension since protracted vomiting may increase intracranial pressure .

Activated charcoal and gastric lavage may be of value in phenylpropanolamine

Monitor serum CPK and renal function in severally symptomatic patient , and those with prolong seizures or coma . A CT scan is indicated in patient with severe headache , neurologic deficits or abnormal mental status (especially PPA) .

1- Seizures , agitation and psychosis should be treated with IV diazepam . refractory cases should be managed with barbiturate or neuromuscular blocking agents . monitor for respiratory depression , hypertension , arrhythmia and the need for endotracheal intubation . Evaluate for hypoxia , electrolyte disturbance and hypoglycemia .

2- Severe symptomatic palpitation , tremor and associated anxiety may respond to propranolol particularly in patient with combination overdose of PPA with other sympathomimetic agents. However , propranolol may worsen hypertension with single ingredient PPA overdose .

3- Persistent or highly elevated hypertension should be treated with nifedipine . Nitroglycerin and phentolamine are possible alternatives .

4- Hypotension can be managed with isotonic fluid , trendelenberg position and dopamine infusion .

5- Dysrhythmias usually respond to standard doses of lignocaine . Lignocaine and amiodarone are generally first line for stable monomorphic ventricular tachycardia particularly in patient with impaired cardiac function . Sotalol is an alternative for stable monomorphic ventricular tachycardia . Sinus tachycardia dose not generally require treatment unless hemodynamic compromise develops If therapy is required a short acting cardio selective agent such as esmolol is generally preferred.

6- Because the imidazoline decongestant produce sedation , hypotension and bradycardia via a central alpha-adrenoreceptor stimulation similar to clonidine the adminsration of nalaxone may be theoretically beneficial

7- Dialysis may be beneficial in PPA overdose .

Decongestants

A **decongestant**, or **nasal decongestant**, is a type of pharmaceutical drug that is used to relieve congestion in the upper respiratory tract. The active ingredient in most decongestants are either imidazoline , pseudoephedrine ,ephedrine ,phenylephrine or phenylepropanolamine . Regular use of decongestants for long periods should be avoided because mucosal ciliary function is impaired: atrophic rhinitis and anosmia can occur due to persistent vasoconstriction

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Clinical Toxicology
Hydrocarbons Toxicity

A *hydrocarbon* is an organic compound made up primarily of carbon and hydrogen atoms, typically ranging from 1 to 60 carbon atoms in length. This definition includes products derived from plants (pine oil, vegetable oil), animal fats (cod liver oil), natural gas, petroleum, or coal tar. There are two basic types of hydrocarbon molecules, *aliphatic* (straight or branched chains) and *cyclic* (closed ring), each with its own subclasses.

Solvents are a heterogenous class of xenobiotics used to dissolve and to provide a vehicle for delivery of other xenobiotics. The most common industrial solvent is water. The common solvents most familiar to toxicologists are *organic solvents* (containing one or more carbon atom), and most of these are hydrocarbons. Most are liquids in the conditions under which they are used. Specifically named solvents (Stoddard solvent, white naphtha, ligroin) represent mixtures of hydrocarbons emanating from a common petroleum distillation fraction.

Physical properties of hydrocarbons vary by the number of carbon atoms and by molecular structure. Unsubstituted, aliphatic hydrocarbons that contain up to 4 carbons are gaseous at room temperature, 5 to 19 carbon molecules are liquids, and longer-chain molecules tend to be tars or solids. Branching of chains tends to destabilize intermolecular forces, so that less energy is required to separate the molecules. The result is that, for a given molecular size, highly branched molecules have lower boiling points and tend to be more volatile.

Compound	Common Uses	Viscosity (SUS)[a]
Aliphatics		
Gasoline	Motor vehicle fuel	30
Naphtha	Charcoal lighter fluid	29
Kerosene	Heating fuel	35
Turpentine	Paint thinner	33
Mineral spirits	Paint and varnish thinner	30–35
Mineral seal oil	Furniture polish	30–35
Heavy fuel oil	Heating oil	>450
Aromatics		
Benzene	Solvent, reagent, gasoline additive	31
Toluene	Solvent, spray paint solvent	28
Xylene	Solvent, paint thinner, reagent	28
Halogenated		
Methylene chloride	Solvent, paint stripper, propellant	27
Carbon tetrachloride	Solvent, propellant, refrigerant	30
Trichloroethylene	Degreaser, spot remover	27
Tetrachloroethylene	Dry cleaning solvent, chemical intermediate	28

Table 1: *Classification and Viscosity of Common Hydrocarbons*

Gasoline is a mixture of alkanes, alkenes, naphthenes, and aromatic hydrocarbons, predominantly 5 to 10 carbon molecules in size. Gasoline is separated from crude oil in a

common distillation fraction. However, most commercially available gasolines are actually blends of up to eight component fractions from refinery processors. More than 1500 individual xenobiotics may be present in commercial grades, but most analytical methods are only able to isolate 150 to 180 compounds from gasolines. Notably, *n*-hexane is present at up to 6%, and benzene is present between 1% and 6%, depending on the grade and the place of origin of the product.

Organic halides contain one or more halogen atoms (fluorine, chlorine, bromine, iodine) usually substituted for a hydrogen atom in the parent structure. Examples include chloroform, trichloroethylene, and the freons.

Oxygenated hydrocarbons demonstrate toxicity specific to the oxidation state of the carbon, as well as to the atoms adjacent to it (the "R" groups). The *alcohols* are widely used as solvents in industry and in household products

PHARMACOLOGY

Inhalation of hydrocarbon vapor depresses consciousness. Acute central nervous (CNS) toxicity from occupational overexposure or recreational abuse parallels the effect of administering an inhaled general anesthetic. The concentration of volatile anesthetic that produces loss of nociception in 50% of patients defines the minimum alveolar concentration (MAC) required to induce anesthesia. Inhaled solvent vapor similarly produces unconsciousness in 50% of subjects when the partial pressure in the lung reaches its median effective dose (ED_{50}). The ED_{50} of occupational parlance is effectively the same as the MAC used in anesthesiology parlance. Virtually all patients will be anesthetized when the partial pressure is raised 30% above the MAC (MAC □□1.3), and death, if ventilation is not supported, typically occurs when the concentration reaches two to four times the MAC.

Occupational exposure to lipid-soluble solvents, such as aromatic, aliphatic, or chlorinated hydrocarbons, are more likely to cause acute and chronic CNS effects than exposure to water-soluble hydrocarbons such as alcohols, ketones, and esters.

Unfortunately, a single mechanism remains elusive. Halothane, isoflurane, sevoflurane, enflurane, and desflurane inhibit fast sodium channels. Toluene, trichloroethylene, perchloroethylene, and others inhibit neuronal calcium currents.

The effect of hydrocarbons on cardiac conduction remains an active arena of toxicologic research. Nearly all classes of hydrocarbons, to varying degrees, augment the dysrhythmogenic potential by "sensitizing" the myocardium.

Cardiac sensitization is incompletely understood. Halothane and isoflurane inactivate sodium channels, whereas chloroform and others attenuate potassium efflux through voltage-gated channels. Sensitization may be mediated by slowed conduction velocity through membrane gap junctions. Halocarbons, in the presence of epinephrine, cause dephosporylation of this gap junction protein, thereby increasing gap junctional resistance and slowing conduction velocity in myocardial tissue.

TOXICOKINETICS

Human toxicokinetic data are lacking for most hydrocarbons, and much of our understanding of the kinetics comes from animal studies. Hydrocarbons are variably absorbed through ingestion, inhalation, or dermal routes of exposure. Partition coefficients, in particular, are useful predictors of the rate and extent of the absorption and distribution of hydrocarbons into tissues as the higher the value the greater the potential for redistribution. A partition coefficient for a given chemical species is the ratio of concentrations achieved between two different media at equilibrium.

Table 2 lists the partition coefficients for commonly encountered hydrocarbons.

Table 2

	Partition Coefficients		$t_{1/2}$			
	Blood/Air	Fat/Air	α	β	Elimination	Relevant Metabolites
Aliphatics						
n-Hexane	2.29[a]	159[a]	11 min	99 min	10%–20% exhaled; liver metabolism by CYP 2E1	2-Hexanol, 2,5-hexanedione, γ-valerolactone
Paraffin/tar	Not absorbed or metabolized					
Aromatics						
Benzene	8.19	499[a]	8 h	90 h	12% exhaled; liver metabolism to phenol	Phenol, catechol, hydroquinone, and conjugates
Toluene	18.0[a]	1021[a]	4–5 h	15–72 h	Extensive liver extraction and metabolism	80% metabolized to benzyl alcohol; 70% renally excreted as hippuric acid
o-Xylene	34.9	1877[a]	30–60 min	20–30 h	Liver CYP 2E1 oxidation	Toluic acid, methyl hippuric acid
Halogenated						
Methylene chloride	8.94	120[a]	Apparent $t_{1/2}$ of COHb 13 h	40 min	92% exhaled unchanged. Low doses metabolized; high doses exhaled. Two liver metabolic pathways	(a) CYP 2E1 to CO and CO_2 (b) Glutathione transferase to CO_2, formaldehyde, formic acid
Carbon tetrachloride	2.73	359[a]	84–91 min[a]	91–496 min[a]	Liver CYP 2E1, some lung exhalation (dose-dependent)	Trichloromethyl radical, trichloromethyl peroxy radical, phosgene
Trichloroethylene	8.11	554[a]	3 h	30 h	Liver CYP 2E1—epoxide intermediate; trichloroethanol is glucuronidated and excreted	Chloral hydrate, trichloroethanol, trichloroacetic acid
1,1,1- Trichloroethane	2.53	263[a]	44 min	53 h	91% exhaled; liver CYP 2E1	Trichloroacetic acid, trichloroethanol
Tetrachloroethylene	10.3	1638[a]	160 min	33 h	80% exhaled; liver CYP 2E1	Trichloroacetic acid, trichloroethanol

[a] Fat/blood partition coefficient is obtained by dividing the fat/air coefficient by the blood/air coefficient, as determined in rat models. All coefficients are determined at 98.6°F (37°C).

Inhalation is a major route of exposure for most volatile hydro- carbons. The absorbed dose is determined by the air concentration, duration of exposure, minute ventilation, and the blood-to-air partition coefficient. Most hydrocarbons cross the alveolus through passive diffusion. The driving force for this is the difference in vapor concentration between the alveolus and the blood. Hydrocarbons that are highly soluble in blood and tissues are readily absorbed through inhalation, and blood concentrations rise rapidly following inhalation exposure. Aromatic hydrocarbons are generally well absorbed through inhalation, absorption of aliphatic hydrocarbons varies by molecular weight: aliphatic hydrocarbons with between 5 and 16 carbons are readily absorbed, through inhalation, whereas those with more than 16 carbons are less readily absorbed.

Absorption of aliphatic hydrocarbons through the digestive tract is inversely related to

molecular weight, ranging from complete absorption at lower molecular weights, to approximately 60% for C-14 hydro- carbons, 5% for C-28 hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with more than 32 carbons. Oral absorption of aromatic hydrocarbons with between 5 and 9 carbons ranges from 80% to 97%. Oral absorption data for aromatic hydrocarbons with more than 9 carbons are sparse.

While the skin is a common area of contact with solvents, for most hydrocarbons the dose received from dermal exposure is a small fraction of the dose received through other routes, such as inhalation. When xenobiotics have near equality in the water-to-lipid partition coefficient, their rate of skin absorption is increased. Solvents that contain both hydrophobic and hydrophilic moieties (eg, glycol ethers, dimethylformamide, dimethylsulfoxide) are particularly well absorbed dermally.

The dose received via skin absorption will also depend on the surface area of the skin exposed and the duration of contact. Though highly volatile compounds may have a short duration of skin contact because of evaporation, skin absorption can also occur from contact with hydrocarbon vapor.

Once absorbed into the central compartment, hydrocarbons are distributed to target and storage organs based on their tissue-to-blood partition coefficients and on the rate of perfusion of the tissue with blood. During the onset of systemic exposure, hydrocarbons accumulate in tissues that have tissue/blood coefficients greater than 1 (eg, for toluene, the fat-to-blood partition coefficient is 60). Table 2 lists the distribution half-lives of selected hydrocarbons.

Hydrocarbons can be eliminated from the body unchanged, for example, through expired air, or can be metabolized to more polar compounds, which are then excreted in urine or bile.

PATHOPHYSIOLOGY AND CLINICAL FINDINGS

■ RESPIRATORY

Several factors are classically associated with pulmonary toxicity after hydrocarbon ingestion. These include specific physical properties of the xenobiotics ingested, the volume ingested, and the occurrence of vomiting. Physical properties of viscosity, surface tension, and volatility are primary determinants of aspiration potential.

Hydrocarbons with low viscosities (eg, turpentine, gasoline, naphtha) have a higher tendency for aspiration in animal models.

Surface tension is a cohesive force generated by attraction (ie, Van der Waals forces) between molecules. This influences adherence of a liquid along a surface ("its ability to creep"). The lower the surface tension, the less well the liquid will creep and the higher the aspiration risk.

Volatility is the tendency for a liquid to become a gas. Hydrocarbons with high volatility tend to vaporize, displace oxygen, and potentially lead to transient hypoxia.

It is not clear which physical property is most important in predicting toxicity. Early reports conflicted in attempting to relate risk of pulmonary toxicity to the amount of hydrocarbon ingested, or to the presence or absence of vomiting. One prospective study addressed both of these variables.

It is widely held that aspiration is the main route of injury from ingested simple hydrocarbons. The mechanism of pulmonary injury, however, is not fully understood. Intratracheal instillation of 0.2 mL/kg of kerosene causes physiologic abnormalities in lung mechanics (decreased compliance and total lung capacity) and pathologic changes such as interstitial inflammation, polymorphonuclear exudates, intraalveolar edema and hemorrhage, hyperemia, brochial and bronchiolar necrosis, and vascular thrombosis. These changes most likely reflect both direct toxicity to pulmonary tissue and disruption of the lipid surfactant layer.

Most patients who go on to develop pulmonary toxicity after hydrocarbon ingestion will have an episode of coughing, gagging, or choking. This usually occurs within 30 minutes after ingestion and is presumptive evidence of aspiration. Radiographic evidence of pneumonitis develops in 40%–88% of admitted aspiration patients. Findings can develop as early as 15 minutes or as late as 24 hours after exposure

CARDIAC

The most concerning cardiac effect from hydrocarbon exposure is precipitation of a dysrhythmia by myocardial sensitization (see Pharmacology previously). These events are described with all classes of hydrocarbons, but halogenated compounds are most frequently implicated, followed by aromatic compounds.

CENTRAL NERVOUS SYSTEM

Transient CNS excitation may occur after acute hydrocarbon inhalation or ingestion. More commonly, CNS depression or anesthesia occurs. In cases of aspiration, hypoxemia from pulmonary damage may contribute to the CNS depression. Coma and seizures are reported in 1%–3% of cases. Chronic occupational exposure or volatile substance use may lead to a chronic neurobehavioral syndrome; the painter's syndrome, most notably described after toluene overexposure. The clinical features include ataxia, spasticity, dysarthria, and dementia, consistent with leukoencephalopathy.

Animal models of toluene poisoning reveal norepinephrine and dopamine depletion. The severity and reversibility of this syndrome depends on the intensity and duration of toluene exposure. Infrequent exposure may produce no clinical neurologic signs, whereas heavy (eg, daily) use can lead to significant neurologic impairment after as little as one year, but more commonly after 2–4 years of ongoing exposure. The specific cognitive and neuropsychological findings in toluene-induced dementia are termed a white matter dementia.

In the occupational setting, exposures are rarely as extensive as those that occur with volatile substance misuse. Given the significantly lesser exposures, the findings among workers overexposed to solvent concentrations above permissible exposure limits are

often subclinical, and detected primarily through neurobehavioral testing.

GASTROINTESTINAL

Hydrocarbons irritate gastrointestinal mucous membranes. Nausea and vomiting are common after ingestion.

HEPATIC

The chlorinated hydrocarbons (Table 1) and their metabolites are hepatotoxic. In most cases, activation occurs via a phase I reaction to form a reactive intermediate. In the case of carbon tetrachloride, this intermediate is the trichloromethyl radical. This radical forms covalent bonds with hepatic macromolecules, and may initiate lipid peroxidation. Carbon tetrachloride causes centrilobular necrosis after inhalational, oral ingestion, or dermal exposure.

DERMATOLOGIC

Most hydrocarbon solvents cause nonspecific irritation of skin and mucous membranes. Repeated, prolonged contact can dry and crack the skin. The mechanism of dermal injury appears to be defatting of the lipid layer of the stratum corneum. Up to 9% of workers may develop eczematous lesions from dermal contact.

Contact dermatitis and blistering may progress to partial- and even full-thickness burns. Severity is proportional to duration of exposure. Hydrocarbons are irritating to skin. Acute, prolonged exposure can cause dermatitis and even full-thickness dermal damage. Chronic dermal exposure to kerosene or diesel fuel can cause oil folliculitis. A specific skin lesion called chloracne is associated with exposure to chlorinated aromatic hydrocarbons with highly specific stereochemistry (eg, dioxins, polychlorobiphenyls).

DIAGNOSTIC TESTING

Laboratory and ancillary testing for hydrocarbon toxicity should be guided by available information regarding the specific xenobiotic, the route of exposure, and the best attempt at quantifying the exposure. Inhalation or ingestion of hydrocarbons associated with pulmonary aspiration is most likely to result in pulmonary toxicity. The use of pulse oximetry and arterial blood gas testing in this group of patients is warranted when clinically indicated. Early radiography is indicated in patients who are severely symptomatic; however, radiographs performed immediately after hydrocarbon ingestion demonstrate a low predictive value for the occurrence of aspiration pneumonitis.

Patients observed for 6 hours after an ingestion, who demonstrate no abnormal pulmonary findings, have adequate oxygenation, are not tachypneic, and have a normal chest radiograph after the 6-hour observation period, have a good medical prognosis with very low risk of subsequent deterioration.

The choice of specific diagnostic laboratory tests to assess organ sys- tem toxicity or function following exposure to a hydrocarbon depends on the type, dose, and route of

exposure, and on the assessment of the patient's clinical condition. Useful clinical tests may include pulse oximetry and an electrocardiogram (ECG). Laboratory tests include serum or urine electrolytes, arterial blood gas, complete blood counts, and creatine phosphokinase. If a hydrocarbon has specific target organ toxicities (eg, benzene/bone marrow, carbon tetrachloride/liver, or *n*-hexane/peripheral nervous system), evaluating and monitoring target organ system function is indicated.

Specific diagnostic testing for hydrocarbon poisoning can include (1) bioassays for the specific hydrocarbon or its metabolites in blood, breath, or urine, or (2) assessment of toxicity. Bioassays for a hydrocarbon are seldom necessary for diagnosis or management of hydrocarbon poisoning in the emergency setting and rarely clinically available.

When deciding whether to obtain a bioassay for a hydrocarbon, the clinician should determine the following: (1) What is the most informative biologic sample (blood, urine, breath) and how should it be collected, handled, and stored? (2) What are the kinetics of the hydrocarbon and the timing of exposure, and how should the results be interpreted in light of these kinetics? (3) What ranges of concentrations are associated with toxicity? Most hydrocarbon bioassays are performed by only a few, specialized clinical laboratories.

Chronic overexposures to hydrocarbons, as occur with volatile substance use, can result in persistent damage to the central nervous system. Damage can be detected and quantified using neuroimaging methods such as magnetic resonance imaging (MRI) or positron emission tomography (PET).

MANAGEMENT

Identification of the specific type, route, and amount of hydrocarbon exposure is rarely essential to achieve effective management.

Decontamination is one of the cardinal principles of toxicology, with priority that is second only to stabilization of the cardiopulmonary status. Safe decontamination can avoid further absorption and avoids secondary casualties in those attempting to provide care.

Exposed clothing should be removed and safely discarded as further absorption or inhalation of hydrocarbons from grossly contaminated clothing can worsen systemic toxicity. Decontamination of the skin should have a high priority in massive hydrocarbon exposures, particularly those exposures involving highly toxic hydrocarbons (Table 3). Water alone may be ineffective in decontaminating most hydrocarbons, but early decontamination with soap and water may be adequate. The caregiver should remain aware that certain hydrocarbons are highly flammable and pose a fire risk to hospital staff. Several studies have attempted to evaluate the role of gastric decontamination after hydrocarbon ingestion. Results were largely inconclusive and the level of evidence, poor.

In the absence of a contraindication, gastric emptying is potentially useful only when the hydrocarbon has inherent severe toxicity or is co-ingested with a more potent xenobiotic (Table 3). Patients who have no symptoms at home or upon initial medical evaluation are

unlikely to need gastric emptying. For patients who do undergo gastric emptying, gastric lavage is likely the superior method. If lavage is performed, a small nasogastric tube (18-French, not a large-bore tube) should be employed. If no gag reflex is present, an endotracheal tube should be placed prior to lavage.

Activated charcoal (AC) has limited ability to decrease gastrointestinal absorption of hydrocarbons and may distend the stomach and predispose patients to vomiting and aspiration. The use of AC may be justified in patients with mixed overdoses, but its role in isolated hydrocarbon ingestions appears very limited. The use of cathartics and promotility agents for hydrocarbon ingestions is also of limited importance in current management.

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Indications
Hydrocarbons with inherent systemic toxicity (CHAMP)
C: camphor
H: halogenated hydrocarbons
A: aromatic hydrocarbons
M: hydrocarbons containing metals
P: hydrocarbons containing pesticides

Table 3: *Orogastric Lavage for Hydrocarbon Ingestion.*

Antibiotics are frequently administered in the setting of hydrocarbon pneumonitis to treat possible bacterial superinfection. Despite this, animal models, including guinea pigs, dogs, and baboons, did not demonstrate any efficacy of prophylactic antibiotics.

Antibiotic administration may be justified in severely poisoned patients. Ideally, sputum cultures should direct antibiotic use. These, however, are often delayed and are not useful in critically ill patients. Most authorities do not recommend prophylactic antibiotics. Most recommend close observation of temperature and blood leukocyte count, as delayed elevation (24 hours after presentation) of temperature and/or leukocytes may signal bacterial superinfection

Corticosteroids, like antibiotics, have been prophylactically administered in the setting of hydrocarbon pulmonary toxicity. The rationale for their use is prevention and limitation of the inflammatory response in the lungs after hydrocarbon injury. Animal models do not show any benefit of corticosteroid administration. In one study, corticosteroids increased the risk for bacterial superinfection with or without concomitant antibiotics. Furthermore, two controlled human trials failed to show a benefit from corticosteroid administration.

Respiratory distress requiring mechanical ventilation in this setting may be associated with large ventilation–perfusion mismatch.

Management of dysrhythmias associated with hydrocarbon toxicity should include consideration of electrolyte and acid–base abnormalities such as hypokalemia and

acidosis result from toluene, hypoxemia, hypotension, and hypothermia.

A number of investigators have suggested protocols for determining which patients can be safely discharged. None of these protocols has been prospectively validated. However, rational guidelines for hospitalization can be recommended. Those patients, who have clinical evidence of toxicity, and most individuals with intentional ingestions, should be hospitalized. Patients, who do not have any initial symptoms, have normal chest radiographs obtained at least 6 hours after ingestion, and who do not develop symptoms during the 6-hour observation period can be safely discharged. Care should be individualized for patients who are asymptomatic but who have radiographic evidence of hydrocarbon pneumonitis, and for patients who have initial respiratory symptoms but quickly become asymptomatic during medical evaluation. Reliable patients may be considered for possible discharge with next-day follow up.

Clinical Toxicology
Hydrocarbons Toxicity

A *hydrocarbon* is an organic compound made up primarily of carbon and hydrogen atoms, typically ranging from 1 to 60 carbon atoms in length. This definition includes products derived from plants (pine oil, vegetable oil), animal fats (cod liver oil), natural gas, petroleum, or coal tar. There are two basic types of hydrocarbon molecules, *aliphatic* (straight or branched chains) and *cyclic* (closed ring), each with its own subclasses.

Solvents are a heterogenous class of xenobiotics used to dissolve and to provide a vehicle for delivery of other xenobiotics. The most common industrial solvent is water. The common solvents most familiar to toxicologists are *organic solvents* (containing one or more carbon atom), and most of these are hydrocarbons. Most are liquids in the conditions under which they are used. Specifically named solvents (Stoddard solvent, white naphtha, ligroin) represent mixtures of hydrocarbons emanating from a common petroleum distillation fraction.

Physical properties of hydrocarbons vary by the number of carbon atoms and by molecular structure. Unsubstituted, aliphatic hydrocarbons that contain up to 4 carbons are gaseous at room temperature, 5 to 19 carbon molecules are liquids, and longer-chain molecules tend to be tars or solids. Branching of chains tends to destabilize intermolecular forces, so that less energy is required to separate the molecules. The result is that, for a given molecular size, highly branched molecules have lower boiling points and tend to be more volatile.

Compound	Common Uses	Viscosity (SUS)[a]
Aliphatics		
Gasoline	Motor vehicle fuel	30
Naphtha	Charcoal lighter fluid	29
Kerosene	Heating fuel	35
Turpentine	Paint thinner	33
Mineral spirits	Paint and varnish thinner	30–35
Mineral seal oil	Furniture polish	30–35
Heavy fuel oil	Heating oil	>450
Aromatics		
Benzene	Solvent, reagent, gasoline additive	31
Toluene	Solvent, spray paint solvent	28
Xylene	Solvent, paint thinner, reagent	28
Halogenated		
Methylene chloride	Solvent, paint stripper, propellant	27
Carbon tetrachloride	Solvent, propellant, refrigerant	30
Trichloroethylene	Degreaser, spot remover	27
Tetrachloroethylene	Dry cleaning solvent, chemical intermediate	28

Table 1: *Classification and Viscosity of Common Hydrocarbons*

Gasoline is a mixture of alkanes, alkenes, naphthenes, and aromatic hydrocarbons, predominantly 5 to 10 carbon molecules in size. Gasoline is separated from crude oil in a

common distillation fraction. However, most commercially available gasolines are actually blends of up to eight component fractions from refinery processors. More than 1500 individual xenobiotics may be present in commercial grades, but most analytical methods are only able to isolate 150 to 180 compounds from gasolines. Notably, *n*-hexane is present at up to 6%, and benzene is present between 1% and 6%, depending on the grade and the place of origin of the product.

Organic halides contain one or more halogen atoms (fluorine, chlorine, bromine, iodine) usually substituted for a hydrogen atom in the parent structure. Examples include chloroform, trichloroethylene, and the freons.

Oxygenated hydrocarbons demonstrate toxicity specific to the oxidation state of the carbon, as well as to the atoms adjacent to it (the "R" groups). The *alcohols* are widely used as solvents in industry and in household products

PHARMACOLOGY

Inhalation of hydrocarbon vapor depresses consciousness. Acute central nervous (CNS) toxicity from occupational overexposure or recreational abuse parallels the effect of administering an inhaled general anesthetic. The concentration of volatile anesthetic that produces loss of nociception in 50% of patients defines the minimum alveolar concentration (MAC) required to induce anesthesia. Inhaled solvent vapor similarly produces unconsciousness in 50% of subjects when the partial pressure in the lung reaches its median effective dose (ED_{50}). The ED_{50} of occupational parlance is effectively the same as the MAC used in anesthesiology parlance. Virtually all patients will be anesthetized when the partial pressure is raised 30% above the MAC (MAC □□1.3), and death, if ventilation is not supported, typically occurs when the concentration reaches two to four times the MAC.

Occupational exposure to lipid-soluble solvents, such as aromatic, aliphatic, or chlorinated hydrocarbons, are more likely to cause acute and chronic CNS effects than exposure to water-soluble hydrocarbons such as alcohols, ketones, and esters.

Unfortunately, a single mechanism remains elusive. Halothane, isoflurane, sevoflurane, enflurane, and desflurane inhibit fast sodium channels. Toluene, trichloroethylene, perchloroethylene, and others inhibit neuronal calcium currents.

The effect of hydrocarbons on cardiac conduction remains an active arena of toxicologic research. Nearly all classes of hydrocarbons, to varying degrees, augment the dysrhythmogenic potential by "sensitizing" the myocardium.

Cardiac sensitization is incompletely understood. Halothane and isoflurane inactivate sodium channels, whereas chloroform and others attenuate potassium efflux through voltage-gated channels. Sensitization may be mediated by slowed conduction velocity through membrane gap junctions. Halocarbons, in the presence of epinephrine, cause dephosporylation of this gap junction protein, thereby increasing gap junctional resistance and slowing conduction velocity in myocardial tissue.

TOXICOKINETICS

Human toxicokinetic data are lacking for most hydrocarbons, and much of our understanding of the kinetics comes from animal studies. Hydrocarbons are variably absorbed through ingestion, inhalation, or dermal routes of exposure. Partition coefficients, in particular, are useful predictors of the rate and extent of the absorption and distribution of hydrocarbons into tissues as the higher the value the greater the potential for redistribution. A partition coefficient for a given chemical species is the ratio of concentrations achieved between two different media at equilibrium.

Table 2 lists the partition coefficients for commonly encountered hydrocarbons.

Table 2

	Partition Coefficients		$t_{1/2}$			
	Blood/Air	Fat/Air	α	β	Elimination	Relevant Metabolites
Aliphatics						
n-Hexane	2.29[a]	159[a]	11 min	99 min	10%–20% exhaled; liver metabolism by CYP 2E1	2-Hexanol, 2,5-hexanedione, γ-valerolactone
Paraffin/tar	Not absorbed or metabolized					
Aromatics						
Benzene	8.19	499[a]	8 h	90 h	12% exhaled; liver metabolism to phenol	Phenol, catechol, hydroquinone, and conjugates
Toluene	18.0[a]	1021[a]	4–5 h	15–72 h	Extensive liver extraction and metabolism	80% metabolized to benzyl alcohol; 70% renally excreted as hippuric acid
o-Xylene	34.9	1877[a]	30–60 min	20–30 h	Liver CYP 2E1 oxidation	Toluic acid, methyl hippuric acid
Halogenated						
Methylene chloride	8.94	120[a]	Apparent $t_{1/2}$ of COHb 13 h	40 min	92% exhaled unchanged. Low doses metabolized; high doses exhaled. Two liver metabolic pathways	(a) CYP 2E1 to CO and CO_2 (b) Glutathione transferase to CO_2, formaldehyde, formic acid
Carbon tetrachloride	2.73	359[a]	84–91 min[a]	91–496 min[a]	Liver CYP 2E1, some lung exhalation (dose-dependent)	Trichloromethyl radical, trichloromethyl peroxy radical, phosgene
Trichloroethylene	8.11	554[a]	3 h	30 h	Liver CYP 2E1—epoxide intermediate; trichloroethanol is glucuronidated and excreted	Chloral hydrate, trichloroethanol, trichloroacetic acid
1,1,1- Trichloroethane	2.53	263[a]	44 min	53 h	91% exhaled; liver CYP 2E1	Trichloroacetic acid, trichloroethanol
Tetrachloroethylene	10.3	1638[a]	160 min	33 h	80% exhaled; liver CYP 2E1	Trichloroacetic acid, trichloroethanol

[a] Fat/blood partition coefficient is obtained by dividing the fat/air coefficient by the blood/air coefficient, as determined in rat models. All coefficients are determined at 98.6°F (37°C).

Inhalation is a major route of exposure for most volatile hydro- carbons. The absorbed dose is determined by the air concentration, duration of exposure, minute ventilation, and the blood-to-air partition coefficient. Most hydrocarbons cross the alveolus through passive diffusion. The driving force for this is the difference in vapor concentration between the alveolus and the blood. Hydrocarbons that are highly soluble in blood and tissues are readily absorbed through inhalation, and blood concentrations rise rapidly following inhalation exposure. Aromatic hydrocarbons are generally well absorbed through inhalation, absorption of aliphatic hydrocarbons varies by molecular weight: aliphatic hydrocarbons with between 5 and 16 carbons are readily absorbed, through inhalation, whereas those with more than 16 carbons are less readily absorbed.

Absorption of aliphatic hydrocarbons through the digestive tract is inversely related to

molecular weight, ranging from complete absorption at lower molecular weights, to approximately 60% for C-14 hydro- carbons, 5% for C-28 hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with more than 32 carbons. Oral absorption of aromatic hydrocarbons with between 5 and 9 carbons ranges from 80% to 97%. Oral absorption data for aromatic hydrocarbons with more than 9 carbons are sparse.

While the skin is a common area of contact with solvents, for most hydrocarbons the dose received from dermal exposure is a small fraction of the dose received through other routes, such as inhalation. When xenobiotics have near equality in the water-to-lipid partition coefficient, their rate of skin absorption is increased. Solvents that contain both hydrophobic and hydrophilic moieties (eg, glycol ethers, dimethylformamide, dimethylsulfoxide) are particularly well absorbed dermally.

The dose received via skin absorption will also depend on the surface area of the skin exposed and the duration of contact. Though highly volatile compounds may have a short duration of skin contact because of evaporation, skin absorption can also occur from contact with hydrocarbon vapor.

Once absorbed into the central compartment, hydrocarbons are distributed to target and storage organs based on their tissue-to-blood partition coefficients and on the rate of perfusion of the tissue with blood. During the onset of systemic exposure, hydrocarbons accumulate in tissues that have tissue/blood coefficients greater than 1 (eg, for toluene, the fat-to-blood partition coefficient is 60). Table 2 lists the distribution half-lives of selected hydrocarbons.

Hydrocarbons can be eliminated from the body unchanged, for example, through expired air, or can be metabolized to more polar compounds, which are then excreted in urine or bile.

PATHOPHYSIOLOGY AND CLINICAL FINDINGS

■ RESPIRATORY

Several factors are classically associated with pulmonary toxicity after hydrocarbon ingestion. These include specific physical properties of the xenobiotics ingested, the volume ingested, and the occurrence of vomiting. Physical properties of viscosity, surface tension, and volatility are primary determinants of aspiration potential.

Hydrocarbons with low viscosities (eg, turpentine, gasoline, naphtha) have a higher tendency for aspiration in animal models.

Surface tension is a cohesive force generated by attraction (ie, Van der Waals forces) between molecules. This influences adherence of a liquid along a surface ("its ability to creep"). The lower the surface tension, the less well the liquid will creep and the higher the aspiration risk.

Volatility is the tendency for a liquid to become a gas. Hydrocarbons with high volatility tend to vaporize, displace oxygen, and potentially lead to transient hypoxia.

It is not clear which physical property is most important in predicting toxicity. Early reports conflicted in attempting to relate risk of pulmonary toxicity to the amount of hydrocarbon ingested, or to the presence or absence of vomiting. One prospective study addressed both of these variables.

It is widely held that aspiration is the main route of injury from ingested simple hydrocarbons. The mechanism of pulmonary injury, however, is not fully understood. Intratracheal instillation of 0.2 mL/kg of kerosene causes physiologic abnormalities in lung mechanics (decreased compliance and total lung capacity) and pathologic changes such as interstitial inflammation, polymorphonuclear exudates, intraalveolar edema and hemorrhage, hyperemia, brochial and bronchiolar necrosis, and vascular thrombosis. These changes most likely reflect both direct toxicity to pulmonary tissue and disruption of the lipid surfactant layer.

Most patients who go on to develop pulmonary toxicity after hydrocarbon ingestion will have an episode of coughing, gagging, or choking. This usually occurs within 30 minutes after ingestion and is presumptive evidence of aspiration. Radiographic evidence of pneumonitis develops in 40%–88% of admitted aspiration patients. Findings can develop as early as 15 minutes or as late as 24 hours after exposure

CARDIAC

The most concerning cardiac effect from hydrocarbon exposure is precipitation of a dysrhythmia by myocardial sensitization (see Pharmacology previously). These events are described with all classes of hydrocarbons, but halogenated compounds are most frequently implicated, followed by aromatic compounds.

CENTRAL NERVOUS SYSTEM

Transient CNS excitation may occur after acute hydrocarbon inhalation or ingestion. More commonly, CNS depression or anesthesia occurs. In cases of aspiration, hypoxemia from pulmonary damage may contribute to the CNS depression. Coma and seizures are reported in 1%–3% of cases. Chronic occupational exposure or volatile substance use may lead to a chronic neurobehavioral syndrome; the painter's syndrome, most notably described after toluene overexposure. The clinical features include ataxia, spasticity, dysarthria, and dementia, consistent with leukoencephalopathy.

Animal models of toluene poisoning reveal norepinephrine and dopamine depletion. The severity and reversibility of this syndrome depends on the intensity and duration of toluene exposure. Infrequent exposure may produce no clinical neurologic signs, whereas heavy (eg, daily) use can lead to significant neurologic impairment after as little as one year, but more commonly after 2–4 years of ongoing exposure. The specific cognitive and neuropsychological findings in toluene-induced dementia are termed a white matter dementia.

In the occupational setting, exposures are rarely as extensive as those that occur with volatile substance misuse. Given the significantly lesser exposures, the findings among workers overexposed to solvent concentrations above permissible exposure limits are

often subclinical, and detected primarily through neurobehavioral testing.

GASTROINTESTINAL

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Toxicology *Lecture 2*

ABSORPTION

The process by which toxicants cross body membranes to enter the bloodstream is referred to as absorption. There are no specific systems or pathways for the sole purpose of absorbing toxicants. Xenobiotics penetrate membranes during absorption by the same processes as do biologically essential substances such as oxygen, foodstuffs, and other nutrients. The main sites of absorption are the GI tract, lungs, and skin.

Absorption of Toxicants by the Gastrointestinal Tract

The GI tract is one of the most important sites where toxicants are absorbed. Many environmental toxicants enter the food chain and are absorbed together with food from the GI tract. This site of absorption is also particularly relevant to toxicologists because accidental ingestion is the most common route of unintentional exposure to a toxicant (especially for children) and intentional overdoses most frequently occur via the oral route.

Absorption of toxicants can take place along the entire GI tract, even in the mouth and the rectum. If a toxicant is an organic acid or base, it tends to be absorbed by simple diffusion in the part of the GI tract where it exists in its most lipid-soluble (nonionized) form. Because gastric juice is acidic (pH about 2) and the intestinal contents are nearly neutral, the lipid solubility of weak organic acids or bases can differ markedly in these 2 areas of the GI tract. The Henderson– Hasselbalch equations determine the fraction of a toxicant that is in the nonionized (lipid-soluble) form and estimate the rate of absorption from the stomach or intestine.

However, the Henderson–Hasselbalch calculations are not an absolute determination of absorption because other factors—including the mass action law, surface area, and blood flow rate—have to be taken into consideration in examining the absorption of weak organic acids or bases. However, the Henderson–Hasselbalch calculations are not an absolute determination of absorption because other factors—including the mass action law, surface area, and blood flow rate—have to be taken into consideration in examining the absorption of weak organic acids or bases.

The mammalian GI tract has numerous specialized transport systems (carrier-mediated) for the absorption of nutrients and electrolytes. The absorption of some of these substances is complex and depends on several additional factors. For example, iron absorption is determined by the need for iron and takes place in 2 steps.

Iron accumulates within the mucosal cells as a protein–iron complex termed ferritin. When the concentration of iron in blood drops below normal values, some iron is liberated from the mucosal stores of ferritin and transported into the blood. Calcium is also absorbed by a 2-step process: absorption from the lumen followed by exudation into the interstitial fluid. Vitamin D is required for both steps of calcium transport.

Some xenobiotics are absorbed by the same specialized transport systems for nutrients, thereby leading to potential competition or interaction. For example, 5-fluorouracil is

absorbed by the pyrimidine transport system, thallium utilizes the system that normally absorbs iron, lead can be absorbed by the calcium transporter, and cobalt and manganese compete for the iron transport system.
Numerous xenobiotic transporters are expressed in the GI tract where they function to increase or decrease absorption of xenobiotics.
In humans, Organic anion-transporting polypeptide (OATP1A2 and OATP2B1) are the most abundant and important members of this family that are expressed in the intestine, although OATP3A1 and OATP4A1 have also been identified. Organic Cation/Carnitine Transporters (OCTN1 and OCTN2) are also present in the intestine, with OCTN2 specifically involved in the uptake of carnitine. The peptide transporter, PEPT1 is highly expressed in the GI tract and mediates the transport of peptide-like drugs such as antibiotics, particularly those containing a β-lactam structure. The OCTs, particularly Organic Cation Transporter (OCT1 and OCT2), also contribute to xenobiotic uptake into enterocytes, but are expressed on the basolateral membrane.
The primary active efflux transporters such as Multi-Drug Resistance 1 (MDR1), Multidrug resistance-associated protein 2 (MRP2), and Breast Cancer Resistance Protein (BCRP) are also expressed on enterocyte brush-border membranes where they function to excrete their substrates into the lumen, thereby decreasing the net absorption of xenobiotics. MRP3 is also found in the intestine, but is localized to the basolateral membrane.
The expression of the intestinal transporters varies across the GI tract. For example, MDR1 expression increases from the duodenum to colon, whereas MRP2 and most of the uptake transporters are expressed most highly in the duodenum and decrease to in the terminal ileum and colon.

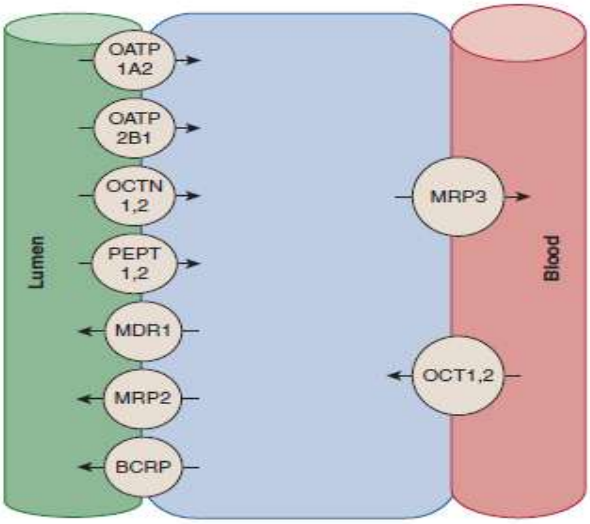

Figure: Schematic model showing the important xenobiotic transport systems present in the human gastrointestinal tract.

Particles and particulate matter can also be absorbed by the GI epithelium. In this case, particle size is a major determinant of absorption, whereas factors such as the lipid solubility or ionization characteristics are less important. For particles, size is inversely related to absorption such that absorption increases with decreasing particle diameter.

This explains why metallic mercury is relatively nontoxic when ingested orally and why powdered arsenic was found to be significantly more toxic than its coarse granular form. Large particles (greater than about 20 μm in diameter) enter intestinal cells by pinocytosis, a process that is much more prominent in newborns than in adults.

Additionally, surface characteristics of nanoparticles contributes to their absorption, with hydrophobic, nonionized particles being more extensively absorbed than those modified to possess an ionized surface as is the case with larger particles, the gut-associated lymphoid tissue appears to be the predominant absorption pathway for nanoparticles from the GI tract. Overall, the absorption of a toxicant from the GI tract depends on its physical properties, including lipid solubility and its dissolution rate.

In addition to the characteristics of the compounds themselves, there are numerous additional factors relating to the GI tract itself that influence the absorption of xenobiotics. These factors include pH, the presence of food, digestive enzymes, bile acids, and bacterial microflora in the GI tract, along with the motility and permeability of the GI tract. A toxicant may be hydrolyzed by stomach acid, biotransformed by enzymes in the GI tract or modified by the resident microflora to new compounds with a toxicity different from that of the parent compound. For example, snake venoms, which are proteinaceous moieties, are much less toxic by the oral route relative to intravenous exposure because they are degraded by digestive enzymes of the GI tract.

Intestinal microflora can also influence absorption and toxicity of compounds. For example, a variety of nitroaromatic compounds are reduced by intestinal bacteria to potentially toxic and carcinogenic aromatic amines. It has also been shown that ingestion of well water with high nitrate content produces methemoglobinemia much more frequently in infants than in adults. In this case, bacteria in the GI tract convert nitrate to nitrite, increasing the likelihood of methemoglobinemia. Infants are more susceptible to methemoglobinemia because the higher pH of the neonatal GI tract is permissive for the growth of bacteria (such as *Escherichia coli*) that convert nitrate to nitrite. One example wherein intestinal microflora reduce the potential toxicity is that of the mycotoxin, deoxynivalenol, which is found in numerous grains and foodstuffs. Strict anaerobes detoxify this compound leading to the absorption of a less toxic reductive metabolite. Agents such as the chelator, ethylenediaminetetraacetic acid (EDTA), increase absorption of some toxicants by increasing intestinal permeability. Before a chemical enters the systemic circulation, it can be biotransformed by the cells in the GI tract or extracted by the liver and excreted into bile with or without prior biotransformation. This phenomenon of the removal of chemicals before entrance into the systemic circulation is referred to as presystemic elimination or first-pass effect. Chemicals that have a high first-pass effect will appear to have a lower absorption because they are eliminated as quickly as they are absorbed. Furthermore, metal ions can affect absorption of other ions. For example, cadmium decreases the absorption of zinc and copper, calcium decreases cadmium absorption, and magnesium decreases absorption of fluoride. Consumption of grapefruit juice can also influence GI absorption through the actions of naringin, a flavonoid that inhibits the function of several transporters including MDR1 and OATP1A2. By reducing MDR1-dependent efflux, grapefruit juice increases GI absorption of numerous pharmaceutical agents (such as calcium-channel blockers and cholesterol-lowering agents), and, in some cases, this effect leads to toxic or adverse reactions resulting from increased exposure to the drugs.

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Vapor pressure is that exerted by a vapor above its own liquid in a closed system, such that liquids that have a high vapor pressure have a higher tendency to evaporate.

Therefore, the nose acts as a "scrubber" for water-soluble and highly reactive gases.

Absorption of gases in the lungs differs from intestinal and percutaneous absorption of compounds in that the dissociation of acids and bases and the lipid solubility of molecules are less important factors in pulmonary absorption because diffusion through cell membranes is not rate-limiting in the pulmonary absorption of gases. There are at least 3 reasons for this. First, ionized molecules are of very low volatility, so that they do not achieve significant concentrations in normal ambient air. Second, type I pneumocytes are very thin and the capillaries are in close contact with the pneumocytes, so that the distance for a chemical to diffuse is very short. Third, chemicals absorbed by the lungs are removed rapidly by the blood, and blood moves very quickly through the extensive capillary network in the lungs.

When a gas is inhaled into the lungs, gas molecules diffuse from the alveolar space into the blood and then dissolve. Except for some gases with a special affinity for certain body components (eg, the binding of carbon monoxide to hemoglobin), the uptake of a gas by a tissue usually involves the simple physical process of dissolving. The end result is that gas molecules partition between two media, namely air and blood during the absorptive phase and blood and other tissues during the distributive phase. As the inspired gas remains in contact with blood in the alveoli, more molecules dissolve in blood until gas molecules in blood are in equilibrium with gas molecules in the alveolar space. At this equilibrium, the ratio of the concentration of chemical in the blood and chemical in the gas phase is constant. This solubility ratio is called the blood-to-gas partition coefficient, and it is unique for each gas. Note that although the ratio is constant, the concentrations achieved vary in accordance with Henry's law, which dictates that the amount of gas dissolved in a liquid is proportional to the partial vapor pressure of the gas in the gas phase at any given concentration before or at saturation. Thus, the higher the inhaled concentration of a gas (ie, the higher the partial pressure), the higher the gas concentration in blood, but the blood:gas ratio does not change unless saturation has occurred.

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The blood carries the dissolved gas molecules to the rest of the body. In each tissue, the gas molecules are transferred from the blood to the tissue until equilibrium is reached at a tissue concentration dictated by the tissue-to-blood partition coefficient. After releasing part of the gas to tissues, blood returns to the lungs to take up more of the gas. The process continues until a gas reaches equilibrium between blood and each tissue according to the tissue- to-blood partition coefficients characteristic of each tissue. This equilibrium is referred to as steady state, and at this time, no net absorption of gas takes place as long as the exposure concentration remains constant.

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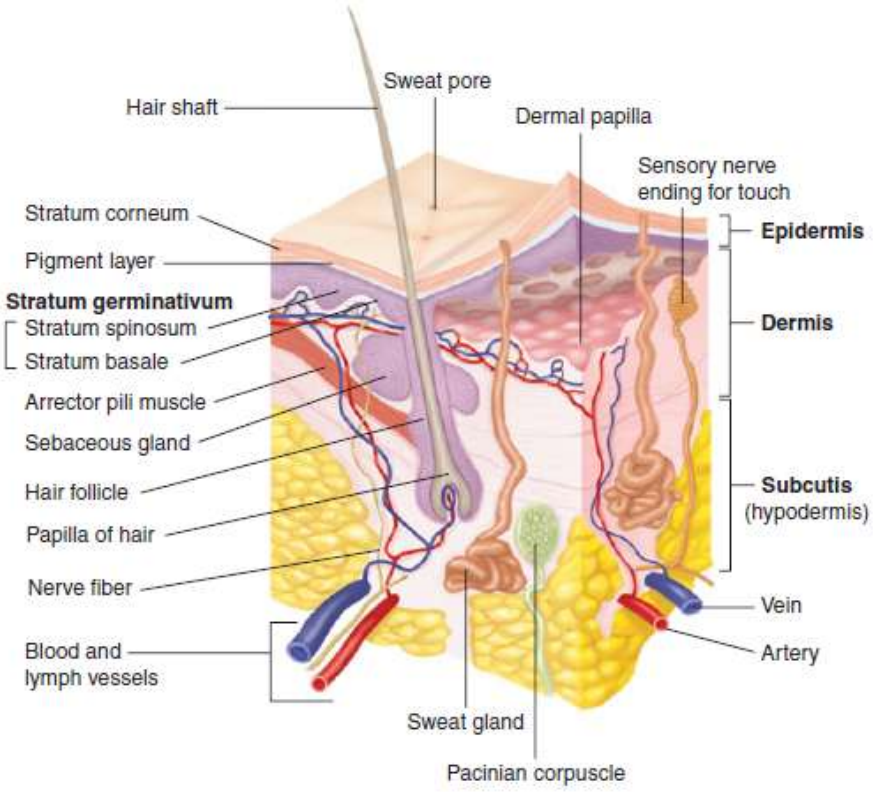
Ultimately, to be absorbed a chemical must pass the barrier of the stratum corneum and then traverse the other six layers of the skin. In contrast to the complexity of the GI tract, the skin is a simpler penetration barrier for chemicals because passage through the stratum corneum is the rate-determining step. In general, lipophilic (fat-soluble) compounds are absorbed more readily across the stratum corneum, whereas the penetration of hydrophilic (water-soluble) compounds is more limited. although lipophilic compounds may pass more readily through the stratum corneum, their passage through the dermis may become rate-limiting. Hydrophilic compounds are more likely to penetrate the skin through appendages such as hair follicles.

The permeability of the skin also depends on both the diffusivity and the thickness of the stratum corneum. There are several factors that can influence the absorption of toxicants through the skin, including (1) the integrity of the stratum corneum, (2) the hydration state of the stratum corneum, (3) temperature (4) solvents as carriers, and (5) molecular size.

Caustic agents, such as acids and alkalis, that damage the stratum corneum increase its permeability. The most frequently encountered penetration-enhancing damage to the skin results from burns and various skin diseases. Solvents used to dissolve compounds of interest can also influence dermal penetration. In general, lower absorption will be observed if a toxicant is highly soluble in the vehicle, whereas low solubility of the toxicant in the vehicle will tend to increase dermal penetration. In addition, solvents such as dimethyl sulfoxide (DMSO) facilitate the penetration of toxicants through the skin by increasing the permeability of the stratum corneum.



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Toxicology *Lecture 2*

ABSORPTION

The process by which toxicants cross body membranes to enter the bloodstream is referred to as absorption. There are no specific systems or pathways for the sole purpose of absorbing toxicants. Xenobiotics penetrate membranes during absorption by the same processes as do biologically essential substances such as oxygen, foodstuffs, and other nutrients. The main sites of absorption are the GI tract, lungs, and skin.

Absorption of Toxicants by the Gastrointestinal Tract

The GI tract is one of the most important sites where toxicants are absorbed. Many environmental toxicants enter the food chain and are absorbed together with food from the GI tract. This site of absorption is also particularly relevant to toxicologists because accidental ingestion is the most common route of unintentional exposure to a toxicant (especially for children) and intentional overdoses most frequently occur via the oral route.

Absorption of toxicants can take place along the entire GI tract, even in the mouth and the rectum. If a toxicant is an organic acid or base, it tends to be absorbed by simple diffusion in the part of the GI tract where it exists in its most lipid-soluble (nonionized) form. Because gastric juice is acidic (pH about 2) and the intestinal contents are nearly neutral, the lipid solubility of weak organic acids or bases can differ markedly in these 2 areas of the GI tract. The Henderson– Hasselbalch equations determine the fraction of a toxicant that is in the nonionized (lipid-soluble) form and estimate the rate of absorption from the stomach or intestine.

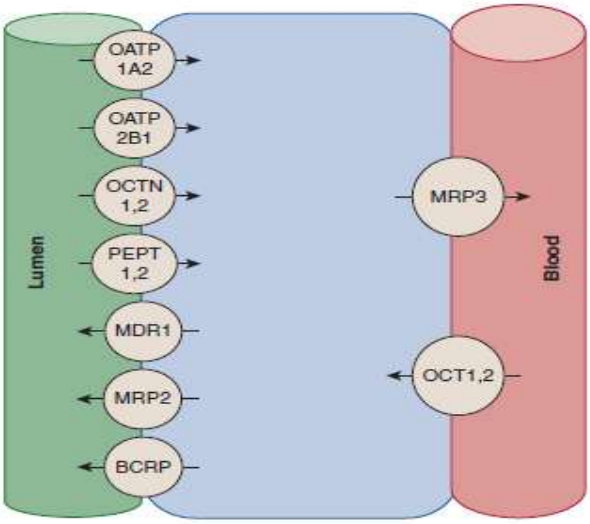
However, the Henderson–Hasselbalch calculations are not an absolute determination of absorption because other factors—including the mass action law, surface area, and blood flow rate—have to be taken into consideration in examining the absorption of weak organic acids or bases. However, the Henderson–Hasselbalch calculations are not an absolute determination of absorption because other factors—including the mass action law, surface area, and blood flow rate—have to be taken into consideration in examining the absorption of weak organic acids or bases.

The mammalian GI tract has numerous specialized transport systems (carrier-mediated) for the absorption of nutrients and electrolytes. The absorption of some of these substances is complex and depends on several additional factors. For example, iron absorption is determined by the need for iron and takes place in 2 steps.

Iron accumulates within the mucosal cells as a protein–iron complex termed ferritin. When the concentration of iron in blood drops below normal values, some iron is liberated from the mucosal stores of ferritin and transported into the blood. Calcium is also absorbed by a 2-step process: absorption from the lumen followed by exudation into the interstitial fluid. Vitamin D is required for both steps of calcium transport.

Some xenobiotics are absorbed by the same specialized transport systems for nutrients, thereby leading to potential competition or interaction. For example, 5-fluorouracil is

absorbed by the pyrimidine transport system, thallium utilizes the system that normally absorbs iron, lead can be absorbed by the calcium transporter, and cobalt and manganese compete for the iron transport system.
Numerous xenobiotic transporters are expressed in the GI tract where they function to increase or decrease absorption of xenobiotics.
In humans, Organic anion-transporting polypeptide (OATP1A2 and OATP2B1) are the most abundant and important members of this family that are expressed in the intestine, although OATP3A1 and OATP4A1 have also been identified. Organic Cation/Carnitine Transporters (OCTN1 and OCTN2) are also present in the intestine, with OCTN2 specifically involved in the uptake of carnitine. The peptide transporter, PEPT1 is highly expressed in the GI tract and mediates the transport of peptide-like drugs such as antibiotics, particularly those containing a β-lactam structure. The OCTs, particularly Organic Cation Transporter (OCT1 and OCT2), also contribute to xenobiotic uptake into enterocytes, but are expressed on the basolateral membrane.
The primary active efflux transporters such as Multi-Drug Resistance 1 (MDR1), Multidrug resistance-associated protein 2 (MRP2), and Breast Cancer Resistance Protein (BCRP) are also expressed on enterocyte brush-border membranes where they function to excrete their substrates into the lumen, thereby decreasing the net absorption of xenobiotics. MRP3 is also found in the intestine, but is localized to the basolateral membrane.
The expression of the intestinal transporters varies across the GI tract. For example, MDR1 expression increases from the duodenum to colon, whereas MRP2 and most of the uptake transporters are expressed most highly in the duodenum and decrease to in the terminal ileum and colon.



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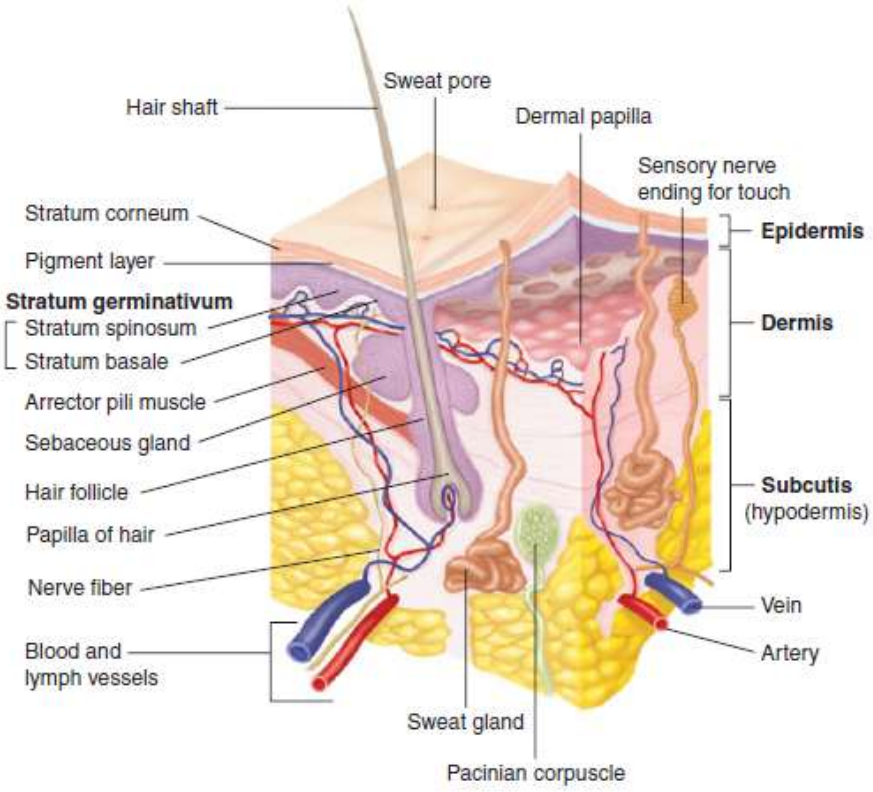

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Toxicology Lecture 1

INTRODUCTION TO TOXICOLOGY

Toxicology is the study of the adverse effects of chemical or physical agents on living organisms. A *toxicologist* is trained to examine and communicate the nature of those effects on human, animal, and environmental health. Toxicological research examines the cellular, biochemical, and molecular mechanisms of action as well as functional effects such as neurobehavioral and immunological, and assesses the probability of their occurrence. *Risk assessment* is the quantitative estimate of the potential effects on human health and environmental significance of various types of chemical exposures (eg, pesticide residues in food, contaminants in drinking water). The variety of potential adverse effects and the diversity of chemicals in the environment make toxicology a broad science, which often demands specialization in one area of toxicology.

Different Areas of Toxicology

The professional activities of toxicologists fall into 3 main categories: descriptive, mechanistic, and regulatory. Although each has distinctive characteristics, each contributes to the other, and all are vitally important to chemical risk assessment.

A *mechanistic toxicologist* is concerned with identifying and understanding the cellular, biochemical, and molecular mechanisms by which chemicals exert toxic effects on living organisms. The results of mechanistic studies are very important in many areas of applied toxicology. In risk assessment, mechanistic data may be very useful in demonstrating that an adverse outcome (eg, cancer, birth defects) observed in laboratory animals is directly relevant to humans. For example, the relative toxic potential of organophosphorus (OP) insecticides in humans, rodents, and insects can be accurately predicted on the basis of an understanding of common mechanisms (inhibition of acetylcholinesterase) and differences in biotransformation for these insecticides among the different species.

Similarly, mechanistic data may be very useful in identifying adverse responses in experimental animals that may not be relevant to humans. For example, the propensity of the widely used artificial sweetener saccharin to cause bladder cancer in rats may not be relevant to humans at normal dietary intake rates. This is because mechanistic studies have demonstrated that bladder cancer is induced only under conditions where saccharin is at such a high concentration in the urine that it

forms a crystalline precipitate. Dose–response studies suggest that such high concentrations would not be achieved in the human bladder even after extensive dietary consumption.

Mechanistic data are also useful in the design and production of safer alternative chemicals and in rational therapy for chemical poisoning and treatment of disease. For example, the drug thalidomide was originally marketed in Europe and Australia as a sedative agent for pregnant women. However, it was banned for clinical use in 1962 because of devastating birth defects that occurred if the drug was ingested during a critical period in pregnancy. But mechanistic studies over the past several decades have demonstrated that this drug may have a unique molecular mechanism of action that interferes with the expression of certain genes responsible for blood vessel formation (angiogenesis). With an understanding of this mechanism, thalidomide has been "rediscovered" as a valuable therapeutic agent that may be highly effective in the treatment of certain infectious diseases (eg, leprosy) and multiple myeloma. This provides an interesting example of how a highly toxic drug with selectivity toward a specific population (pregnant women) can be used relatively safely with proper precautions.

A clear understanding of mechanism of action led to the development of strict prescribing guidelines and patient monitoring

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In addition to the above categories, there are other specialized areas of toxicology such as forensic, clinical, and environmental toxicology. *Forensic toxicology* is a hybrid of analytic chemistry and fundamental toxicological principles. It is concerned primarily with the medicolegal aspects of the harmful effects of chemicals on humans and animals. The expertise of forensic toxicologists is invoked primarily to aid in establishing the cause of death and determining its circumstances in a post-mortem investigation. *Clinical toxicology* designates an area of professional emphasis in the realm of medical science that is concerned with disease caused by or uniquely associated with toxic substances

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Morphine sulfate	900
Phenobarbital sodium	150
Picrotoxin	5
Strychnine sulfate	2
Nicotine	1
D-Tubocurarine	0.5
Hemicholinium-3	0.2
Tetrodotoxin	0.10
Dioxin (TCDD)	0.001
Botulinum toxin	0.00001

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

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Arsenic, a toxic metalloid, may occur as a natural contaminant of groundwater or may contaminate groundwater secondary to industrial activities. Generally, such toxic substances are referred to as toxicants, rather than toxins, because, although they are naturally produced, they are not produced by biological systems.

Toxic agents may also be classified in terms of their physical state (gas, dust, liquid, size, eg, nanotoxicology), their chemical stability or reactivity (explosive, flammable, oxidizer), general chemical structure (aromatic amine, halogenated hydrocarbon, etc), or poisoning potential (extremely toxic, very toxic, slightly toxic, etc). Classification of toxic agents on the basis of their biochemical mechanisms of action (eg, alkylating agent, cholinesterase inhibitor, endocrine disruptor).

Classifications such as air pollutants, occupation-related agents, and acute and chronic poisons can provide a useful focus on a specific problem.

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The spectrum of undesired effects of chemicals is often broad. Some effects are deleterious and others are not. In therapeutics, for example, each drug produces a number of effects, but usually only one effect is associated with the primary objective of the therapy; all the other effects are referred to as *undesirable* or *side effects* of that drug for that therapeutic indication. However, some of these side effects may be desired for another therapeutic indication. For example, the "first-generation" antihistamine diphenhydramine (Benadryl) is effective in reducing histamine responses associated with allergies, but it readily enters the brain and causes mild central nervous system (CNS) depression (drowsiness, delayed reaction time). With the advent of selective histamine receptor antagonists that do not cross the blood–brain barrier and thus do not have this CNS-depressant side effect, diphenhydramine is used less commonly today as an antihistamine. However, it is widely used as an "over-the-counter" sleep remedy, often in combination with analgesics (eg, Tylenol PM, Excedrin PM), taking advantage of the CNS-depressant effects. Some side effects of drugs are never desirable and are always deleterious to the well-being of humans. These are referred to as the *adverse, deleterious,* or *toxic* effects of the drug.

Immediate versus Delayed Toxicity

Immediate toxic effects can be defined as those that occur or develop rapidly after a single administration of a substance, whereas delayed toxic effects are those that occur after the lapse of some time. Carcinogenic effects of chemicals usually have a long latency period, often 20 to 30 years after the initial exposure, before tumors are observed in humans.

Reversible versus Irreversible Toxic Effects

Some toxic effects of chemicals are reversible, and others are irreversible. If a

chemical produces pathological injury to a tissue, the ability of that tissue to regenerate largely determines whether the effect is reversible or irreversible. Thus, for a tissue such as liver, which has a high ability to regenerate, most injuries are reversible, whereas injury to the CNS is largely irreversible because differentiated cells of the CNS cannot divide and be replaced. Carcinogenic and teratogenic effects of chemicals, once they occur, are usually considered irreversible toxic effects.

Local versus Systemic Toxicity

Another distinction between types of effects is made on the basis of the general site of action. Local effects are those that occur at the site of first contact between the biological system and the toxicant. Such effects are produced by the ingestion of caustic substances or the inhalation of irritant materials. For example, chlorine gas reacts with lung tissue at the site of contact, causing damage and swelling of the tissue, with possibly fatal consequences, even though very little of the chemical is absorbed into the bloodstream. The alternative to local effects is systemic effects. Systemic effects require absorption and distribution of a toxicant from its entry point to a distant site at which deleterious effects are produced. Most substances except highly reactive materials produce systemic effects. For some materials, both effects can be demonstrated. For example, tetraethyl lead produces effects on skin at the site of absorption and then is transported systemically to produce its typical effects on the CNS and other organs. If the local effect is marked, there may also be indirect systemic effects.

Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs; instead, they usually elicit their major toxicity in only 1 or 2 organs. These sites are referred to as the *target organs* of toxicity of a particular chemical.

Route and Site of Exposure

The major routes (pathways) by which toxic agents gain access to the body are through the gastrointestinal tract (ingestion), the lungs (inhalation), or the skin (topical, percutaneous, or dermal). Toxic agents generally produce the greatest effect and the most rapid response when given directly into the bloodstream (the intravenous route). An approximate descending order of effectiveness for the other routes would be inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and dermal. The “vehicle” (the material in which the chemical is dissolved) and other formulation factors can markedly alter absorption after ingestion, inhalation, or topical exposure. In addition, the route of administration can influence the toxicity of agents. For example, an agent that acts on the CNS,

but is efficiently detoxified in the liver, would be expected to be less toxic when given orally than when given via inhalation, because the oral route requires that nearly all of the dose pass through the liver before reaching the systemic circulation and then the CNS.

Occupational exposure to toxic agents most frequently results from breathing contaminated air (inhalation) and/or direct and prolonged contact of the skin with the substance (dermal exposure), whereas accidental and suicidal poisoning occurs most frequently by oral ingestion

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In human exposure situations, the frequency and duration of exposure are usually not as clearly defined as in controlled animal studies, but many of the same terms are used to describe general exposure situations. Thus, workplace or environmental exposures may be described as *acute* (occurring from a single incident or episode), *subchronic* (occurring repeatedly over several weeks or months), or *chronic* (occurring repeatedly for many months or years).

For many chemicals, the toxic effects that follow a single exposure are quite different from those produced by repeated exposure. For example, the primary acute toxic manifestation of benzene is CNS depression, but repeated exposures can result in bone marrow toxicity and an increased risk for leukemia.

Toxicology Lecture 1

INTRODUCTION TO TOXICOLOGY

Toxicology is the study of the adverse effects of chemical or physical agents on living organisms. A *toxicologist* is trained to examine and communicate the nature of those effects on human, animal, and environmental health. Toxicological research examines the cellular, biochemical, and molecular mechanisms of action as well as functional effects such as neurobehavioral and immunological, and assesses the probability of their occurrence. *Risk assessment* is the quantitative estimate of the potential effects on human health and environmental significance of various types of chemical exposures (eg, pesticide residues in food, contaminants in drinking water). The variety of potential adverse effects and the diversity of chemicals in the environment make toxicology a broad science, which often demands specialization in one area of toxicology.

Different Areas of Toxicology

The professional activities of toxicologists fall into 3 main categories: descriptive, mechanistic, and regulatory. Although each has distinctive characteristics, each contributes to the other, and all are vitally important to chemical risk assessment.

A *mechanistic toxicologist* is concerned with identifying and understanding the cellular, biochemical, and molecular mechanisms by which chemicals exert toxic effects on living organisms. The results of mechanistic studies are very important in many areas of applied toxicology. In risk assessment, mechanistic data may be very useful in demonstrating that an adverse outcome (eg, cancer, birth defects) observed in laboratory animals is directly relevant to humans. For example, the relative toxic potential of organophosphorus (OP) insecticides in humans, rodents, and insects can be accurately predicted on the basis of an understanding of common mechanisms (inhibition of acetylcholinesterase) and differences in biotransformation for these insecticides among the different species.

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Toxicology Lecture 3

DISTRIBUTION

The rate of distribution to organs or tissues is determined primarily by blood flow and the rate of diffusion out of the capillary bed into the cells of a particular organ or tissue, and usually occurs rapidly.

The final distribution depends largely on the affinity of a xenobiotic for various tissues. In general, the initial phase of distribution is dominated by blood flow, whereas the eventual distribution is determined largely by affinity. The penetration of toxicants into cells occurs by passive diffusion or special transport processes.

Volume of Distribution

A key concept in understanding the disposition of a toxicant is its volume of distribution (Vd), a primary determinant of the concentration of a toxicant in blood that is used to quantify distribution throughout the body. It is defined as the volume in which the amount of drug would need to be uniformly dissolved in order to produce the observed blood concentration.

Examples of Factors that Contribute to Volume of Distribution (Vd)

COMPOUND	Vd (L/kg)	FACTORS INFLUENCING DISTRIBUTION
Warfarin	0.1	High plasma protein binding with little distribution into tissues
Ethanol	0.5	Distribution in total body water
Propranolol	4.3	Distributed to peripheral tissues
Tamoxifen	50	Extensive distribution to peripheral tissues and high protein binding
Chloroquine	100	High tissue uptake and trapping in lysosomes

If a chemical distributes only to the plasma compartment (no tissue distribution), it has a high plasma concentration and hence, a low Vd. In contrast, if a chemical distributes throughout the body (total body water), the effective plasma concentration is low and hence, a high Vd. Some toxicants selectively accumulate in certain parts of the body as a result of protein binding, active transport, or high solubility in fat. In this case, it is assumed that the chemical in the storage depot is toxicologically inactive.

Storage of Toxicants in Tissues

Because only the free fraction of a chemical is in equilibrium throughout the body, binding to or dissolving in certain body constituents greatly alters the distribution of a xenobiotic. The compartment where a toxicant is concentrated is described as a storage depot. Toxicants in these depots are always in equilibrium with the free fraction in plasma.

Plasma Proteins as Storage Depot Binding to plasma proteins is the major site of protein binding, and several different plasma proteins bind xenobiotics and some endogenous constituents of the body. Albumin is the major protein in plasma and it binds many different compounds. α1 -Acid glycoprotein, although present at a much lower concentration than albumin, is also an important protein in plasma, and compounds with basic characteristics tend to bind to it. Transferrin, a β-globulin, is important for the transport of iron in the body. The other major metal-binding protein in plasma is ceruloplasmin, which carries copper.

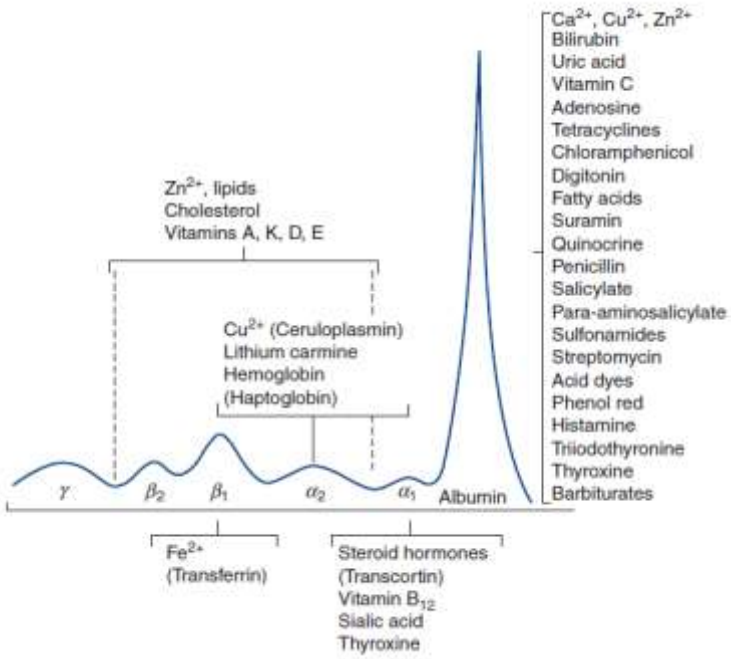

Figure 1: Schematic representation of the electrophoretic separation of plasma proteins and xenobiotics that interact with these proteins.

The α- and β-lipoproteins are very important in the transport of lipid-soluble compounds such as vitamins, cholesterol, and steroid hormones as well as xenobiotics. Plasma γ-globulins are antibodies that function specifically in immunological reactions.

Albumin, present in the plasma at a concentration of 500 to 600 μM, is the most abundant protein in plasma and serves as both a depot and multivalent transport protein for many endogenous and exogenous compounds. Protein–ligand interactions occur primarily as a result of hydrophobic forces, hydrogen bonding, and Van der Waals forces. However, the interaction of a chemical with plasma proteins is a reversible process.

In particular, severe toxic reactions can occur if a toxicant with a high degree of protein binding is displaced from plasma proteins by another chemical, increasing the free fraction of the toxicant in plasma. This interaction increases the equilibrium concentration of the toxicant in a target organ, thereby increasing the potential for toxicity. For example, if a compound is 99.9% bound to plasma protein (0.1% free), then an interaction that decreases protein binding to 99.5%, which may seem to be a minor change, is effectively a 5-fold increase in the free plasma concentration (0.5% free). For example, if a strongly bound sulfonamide is given concurrently with an antidiabetic drug, the sulfonamide may displace the antidiabetic drug and induce a hypoglycemic coma. Similarly, interactions resulting from displacement of warfarin can lead to inappropriate blood clotting and possible deleterious effects. Plasma protein binding can also give rise to species differences in the disposition of xenobiotics.

Additional factors that influence plasma protein binding across species include differences in the concentration of albumin, in binding affinity, and/or in competitive binding of endogenous substances.

Liver and Kidney as Storage Depots The liver and kidney have a high capacity for binding many chemicals. These two organs probably concentrate more toxicants than do all the other organs combined, and, in most cases, active transport or binding to tissue components are likely to be involved.

In addition, some proteins serve to sequester xenobiotics in the liver or kidney. For example, metallothionein (MT), a specialized metal-binding protein, sequesters both essential and toxic metals including zinc and cadmium (Cd) with high affinities in the kidney and liver. Another protein that sequesters certain toxicants in the kidney is α2u-globulin.

Fat as Storage Depot There are many organic compounds that are highly stable and lipophilic, leading to their accumulation in the environment. The lipophilic nature of these compounds also permits rapid penetration of cell membranes and uptake by tissues, and it is not surprising that highly lipophilic toxicants are distributed and concentrated in body fat where they

are retained for a very long time. Toxicants appear to accumulate in fat by dissolution in neutral fats, which constitute about 50% and 20% of the body weight of obese individuals and lean athletic individuals, respectively. Storage lowers the concentration of the toxicant in the target organ such that toxicity is likely to be less severe in an obese person than in a lean individual.

Bone as Storage Depot Compounds such as fluoride, lead, and strontium may be incorporated and stored in the bone matrix. For example, 90% of the lead in the body is eventually found in the skeleton.

Blood–Brain Barrier

Access to the brain is restricted by the presence of two barriers: the BBB and the blood–cerebral spinal fluid barrier (BCSFB). Although neither represents an absolute barrier to the passage of toxic chemicals into the CNS, many toxicants do not enter the brain in appreciable quantities because of these barriers.

The BBB is formed primarily by the endothelial cells of blood capillaries in the brain (Fig. 2). Each endothelial cell forms a tight junction with adjacent cells, essentially forming a tight seal between the cells and preventing diffusion of polar compounds through paracellular pathways. Diffusion of more lipophilic compounds through endothelial cell membranes is counteracted by xenobiotic efflux transporters present in the endothelial cells. Glial cells, particularly astrocytes, contribute to the BBB by secreting chemical factors that modulate endothelial cell permeability, and astrocytes and perivascular microglial cells extend processes that support the integrity of the BBB. For small- to medium-sized water-soluble molecules, the tighter junctions of the capillary endothelium and the lipid membranes of the glial cell processes represent the major barrier. Although the absorption of lipid-soluble compounds is favored in the brain, such compounds must traverse the membranes of the endothelial cells, not be substrates for xenobiotic transporters, and then traverse the glial cell processes to enter the brain.

Although the BBB is a physical structure that limits distribution to the brain, active transport processes also play a pivotal role in determining the concentration of xenobiotics in the brain. Numerous ATP-dependent transporters have been identified as part of the BBB, comprising various members of the ABC and SLC families.

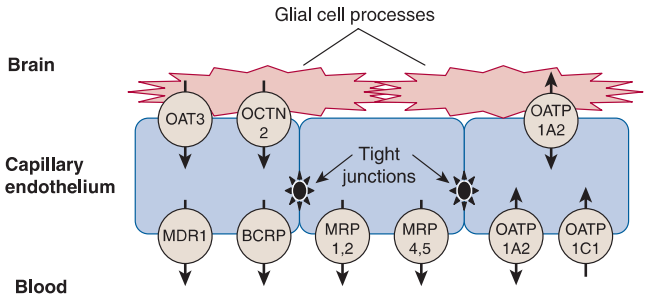

Figure 2: *Schematic model showing the xenobiotic transporting systems that contributes to the human blood–brain barrier.*

Efflux transporters, including MDR1, BCRP, MRP1, 2, 4, and 5 are located on the apical (blood side) plasma membrane and function to move xenobiotics absorbed into the capillary endothelial cells out into the blood, thereby limiting distribution into the brain. Uptake transporters, including OATP1A2 and OATP1C1 are found on both the basolateral and apical side of the endothelium, and can drive a concentrative efflux if coupled energetically to the electrical potential difference across the endothelial cell membrane. OATP1C1 is suggested to specifically transport thyroid hormone into the brain. Finally, uptake transporters on the apical membranes include OAT3 and CTN2. In combination, these transporters can efficiently efflux a wide range of anionic, cationic, uncharged, and numerous drug conjugates from the brain.

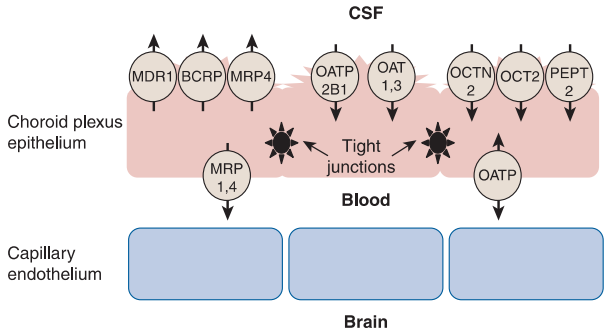

Figure 3: *Schematic model showing the xenobiotic transporting systems that contribute to the human blood–cerebral spinal fluid barrier.*

EXCRETION

Toxicants are eliminated from the body by several routes. The kidney is perhaps the most important organ for the excretion of xenobiotics because more chemicals are eliminated from the body by this route than by any

other. Biotransformation to more water-soluble products is usually a prerequisite to the excretion of xenobiotics through urine. The second important route of elimination of many xenobiotics is through feces, and the third, primarily for gases, is through the lungs. Biliary excretion of xenobiotics and/or their metabolites is most often the major source of fecal excretion.

Urinary Excretion

The kidney is a very efficient organ for the elimination of toxicants from the body.

Toxic compounds are excreted in urine by the same mechanisms the kidney uses to remove the end products of intermediary metabolism from the body, including glomerular filtration, tubular excretion by passive diffusion, and active tubular secretion. In general, the excretion of small molecular weight (<350 Da), water-soluble compounds is favored in urine.

The kidney receives about 25% of the cardiac output, about 20% of which is filtered at the glomeruli. The glomerular capillaries have large pores (approximately 70 nm), which filter compounds up to a molecular weight of about 60 kDa (smaller than albumin). Thus, the degree of plasma protein binding affects the rate of glomerular filtration because protein–xenobiotic complexes, particularly those bound to albumin, will not be filtered.

A toxicant filtered at the glomerulus may remain in the tubular lumen and be excreted in urine. Depending on the physicochemical properties of a compound, it may be reabsorbed across the tubular cells of the nephron back into the bloodstream. The pH of urine may vary but it is usually slightly acidic (approximately 6–6.5). Excretion of salicylate can be accelerated by administering sodium bicarbonate. In a similar manner, urinary acidifycation can be used to increase the excretion of a weak base such as phencyclidine (PCP) in drug abusers.

Toxic agents can also be excreted from plasma into urine by passive diffusion through the tubule.

Xenobiotics can also be excreted into urine by active secretion. This process involves the uptake of toxicants from the blood into the cells of the renal proximal tubule, with subsequent efflux from the cell into the tubular fluid from which urine is formed.

Transporters expressed on the basolateral side of the renal tubules in humans that contribute mainly to excretion include OATs, OCTs, and OATP4C1. MDR1, MRP2, and MRP4 are also found on the luminal brush border of the proximal tubule, where they contribute to the efflux of xenobiotics out of the cells and into the tubular fluid, thereby enhancing excretion.

As in all active transport systems, there is competition for renal secretion of xenobiotics. This fact was taken advantage of during World War II, when penicillin was in short supply. Penicillin is actively secreted by the organic acid systems (OATs) of the kidney.
To lengthen its half-life and duration of action, another acid was sought to compete with penicillin for renal secretion, and probenecid was successfully introduced for this purpose.

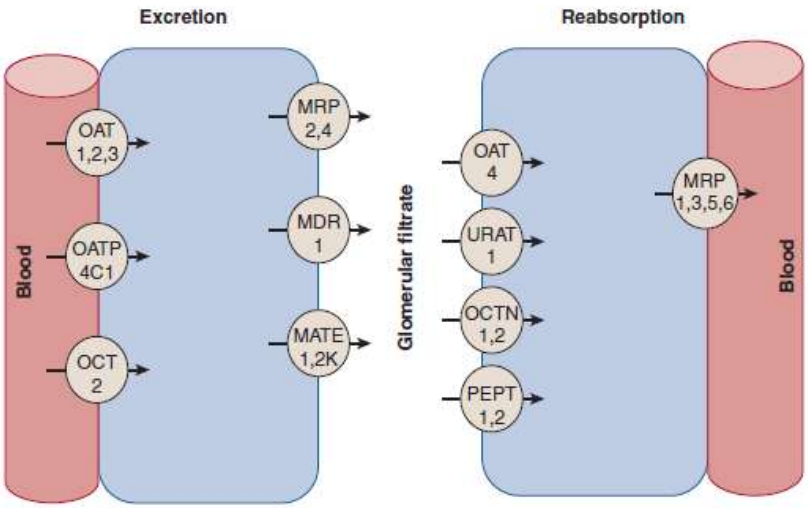

Figure 4: Schematic model showing the transport systems in the human proximal tubule of the kidney.

Fecal Excretion

Fecal excretion, the second major pathway for the elimination of xenobiotics, is a complex process that is not as well understood as urinary excretion. Excretion of toxicants via the feces can result from direct elimination of non-absorbed compounds in the GI tract, from delivery to the GI tract via the bile and from secretion into intestinal luminal contents from the enterocytes.

Non-absorbed Ingesta In addition to undigested material, varying proportions of nutrients and xenobiotics that are present in food or are ingested voluntarily (drugs) pass through the alimentary canal unabsorbed, contributing to fecal excretion.

Biliary Excretion The biliary route of elimination is a significant source contributing to the fecal excretion of xenobiotics and is even more important for the excretion of metabolites. Biliary excretion is regulated predominantly by xenobiotic transporters present on the canalicular membrane, which include MRP2, BCRP, MDR1, Multidrug and toxin extrusion protein 1 (MATE1), and BSEP (Fig. 5). MRP2 is extremely important in biliary secretion because it is largely responsible for the transport of organic anions including glucuronide and glutathione conjugates of many xenobiotics. BCRP has particular affinity for sulfated conjugates of toxicants, whereas MDR1 primarily transports a variety of substrates into bile. MATE1 is specifically involved in biliary excretion of organic cations, and BSEP is critical for the secretion of bile salts and the regulation of bile flow.

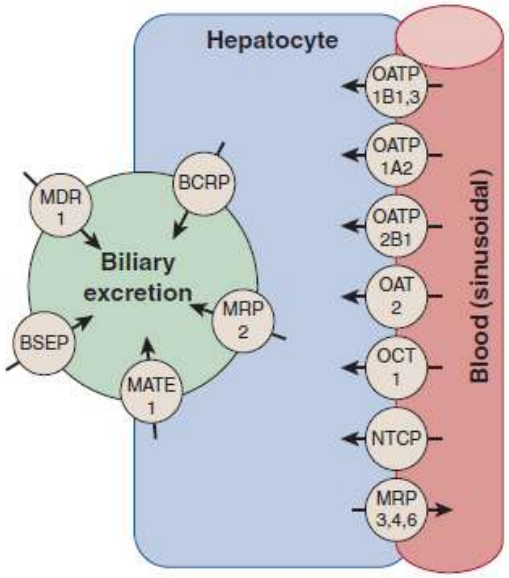

Figure 5: Schematic model showing the xenobiotic transporting systems present in the human liver.

Toxicology Lecture 3

DISTRIBUTION

The rate of distribution to organs or tissues is determined primarily by blood flow and the rate of diffusion out of the capillary bed into the cells of a particular organ or tissue, and usually occurs rapidly.

The final distribution depends largely on the affinity of a xenobiotic for various tissues. In general, the initial phase of distribution is dominated by blood flow, whereas the eventual distribution is determined largely by affinity. The penetration of toxicants into cells occurs by passive diffusion or special transport processes.

Volume of Distribution

A key concept in understanding the disposition of a toxicant is its volume of distribution (Vd), a primary determinant of the concentration of a toxicant in blood that is used to quantify distribution throughout the body. It is defined as the volume in which the amount of drug would need to be uniformly dissolved in order to produce the observed blood concentration.

Examples of Factors that Contribute to Volume of Distribution (Vd)

COMPOUND	Vd (L/kg)	FACTORS INFLUENCING DISTRIBUTION
Warfarin	0.1	High plasma protein binding with little distribution into tissues
Ethanol	0.5	Distribution in total body water
Propranolol	4.3	Distributed to peripheral tissues
Tamoxifen	50	Extensive distribution to peripheral tissues and high protein binding
Chloroquine	100	High tissue uptake and trapping in lysosomes

If a chemical distributes only to the plasma compartment (no tissue distribution), it has a high plasma concentration and hence, a low Vd. In contrast, if a chemical distributes throughout the body (total body water), the effective plasma concentration is low and hence, a high Vd. Some toxicants selectively accumulate in certain parts of the body as a result of protein binding, active transport, or high solubility in fat. In this case, it is assumed that the chemical in the storage depot is toxicologically inactive.

Storage of Toxicants in Tissues

Because only the free fraction of a chemical is in equilibrium throughout the body, binding to or dissolving in certain body constituents greatly alters the distribution of a xenobiotic. The compartment where a toxicant is concentrated is described as a storage depot. Toxicants in these depots are always in equilibrium with the free fraction in plasma.

Plasma Proteins as Storage Depot Binding to plasma proteins is the major site of protein binding, and several different plasma proteins bind xenobiotics and some endogenous constituents of the body. Albumin is the major protein in plasma and it binds many different compounds. α1 -Acid glycoprotein, although present at a much lower concentration than albumin, is also an important protein in plasma, and compounds with basic characteristics tend to bind to it. Transferrin, a β-globulin, is important for the transport of iron in the body. The other major metal-binding protein in plasma is ceruloplasmin, which carries copper.

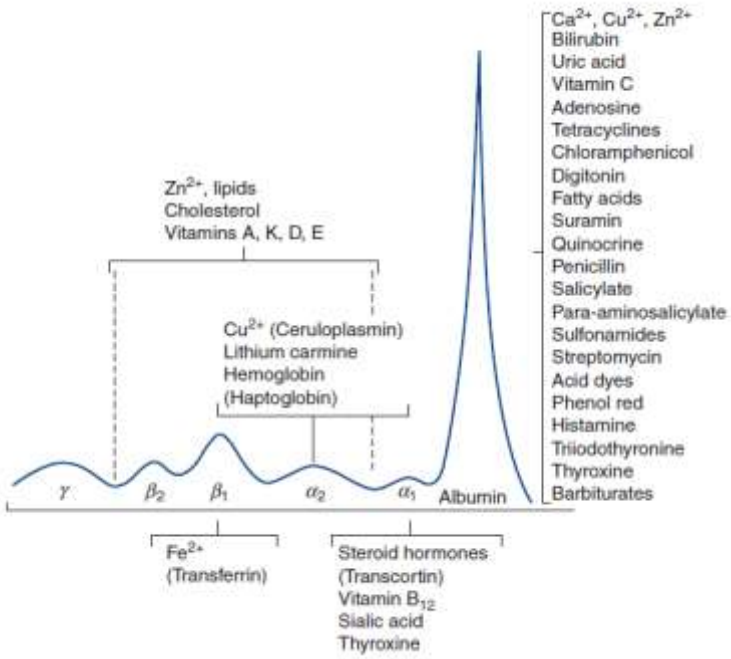

Figure 1: Schematic representation of the electrophoretic separation of plasma proteins and xenobiotics that interact with these proteins.

The α- and β-lipoproteins are very important in the transport of lipid-soluble compounds such as vitamins, cholesterol, and steroid hormones as well as xenobiotics. Plasma γ-globulins are antibodies that function specifically in immunological reactions.

Albumin, present in the plasma at a concentration of 500 to 600 μM, is the most abundant protein in plasma and serves as both a depot and multivalent transport protein for many endogenous and exogenous compounds. Protein–ligand interactions occur primarily as a result of hydrophobic forces, hydrogen bonding, and Van der Waals forces. However, the interaction of a chemical with plasma proteins is a reversible process.

In particular, severe toxic reactions can occur if a toxicant with a high degree of protein binding is displaced from plasma proteins by another chemical, increasing the free fraction of the toxicant in plasma. This interaction increases the equilibrium concentration of the toxicant in a target organ, thereby increasing the potential for toxicity. For example, if a compound is 99.9% bound to plasma protein (0.1% free), then an interaction that decreases protein binding to 99.5%, which may seem to be a minor change, is effectively a 5-fold increase in the free plasma concentration (0.5% free). For example, if a strongly bound sulfonamide is given concurrently with an antidiabetic drug, the sulfonamide may displace the antidiabetic drug and induce a hypoglycemic coma. Similarly, interactions resulting from displacement of warfarin can lead to inappropriate blood clotting and possible deleterious effects. Plasma protein binding can also give rise to species differences in the disposition of xenobiotics.

Additional factors that influence plasma protein binding across species include differences in the concentration of albumin, in binding affinity, and/or in competitive binding of endogenous substances.

Liver and Kidney as Storage Depots The liver and kidney have a high capacity for binding many chemicals. These two organs probably concentrate more toxicants than do all the other organs combined, and, in most cases, active transport or binding to tissue components are likely to be involved.

In addition, some proteins serve to sequester xenobiotics in the liver or kidney. For example, metallothionein (MT), a specialized metal-binding protein, sequesters both essential and toxic metals including zinc and cadmium (Cd) with high affinities in the kidney and liver. Another protein that sequesters certain toxicants in the kidney is α2u-globulin.

Fat as Storage Depot There are many organic compounds that are highly stable and lipophilic, leading to their accumulation in the environment. The lipophilic nature of these compounds also permits rapid penetration of cell membranes and uptake by tissues, and it is not surprising that highly lipophilic toxicants are distributed and concentrated in body fat where they

are retained for a very long time. Toxicants appear to accumulate in fat by dissolution in neutral fats, which constitute about 50% and 20% of the body weight of obese individuals and lean athletic individuals, respectively. Storage lowers the concentration of the toxicant in the target organ such that toxicity is likely to be less severe in an obese person than in a lean individual.

Bone as Storage Depot Compounds such as fluoride, lead, and strontium may be incorporated and stored in the bone matrix. For example, 90% of the lead in the body is eventually found in the skeleton.

Blood–Brain Barrier

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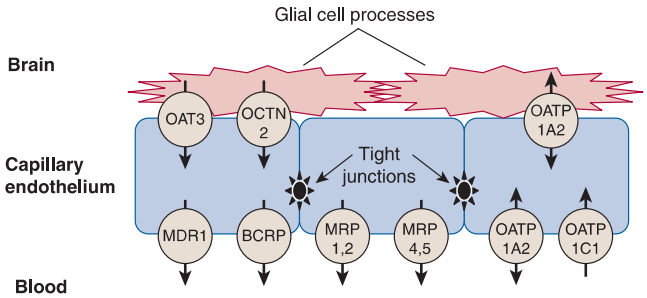

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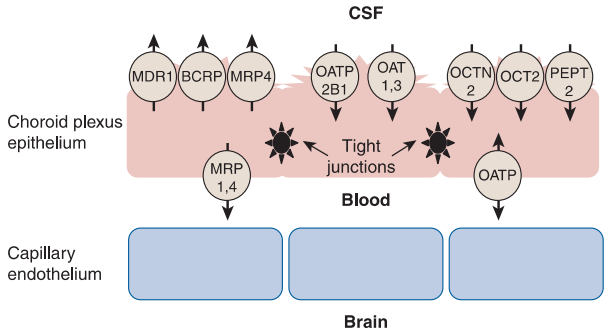

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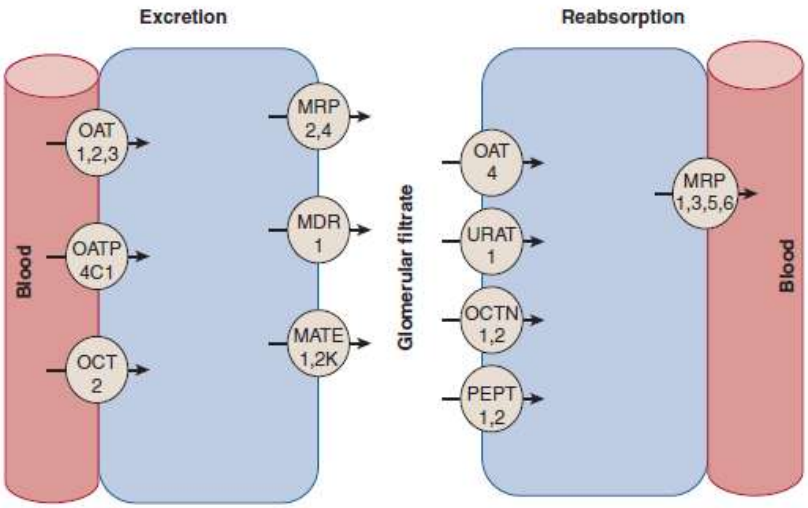

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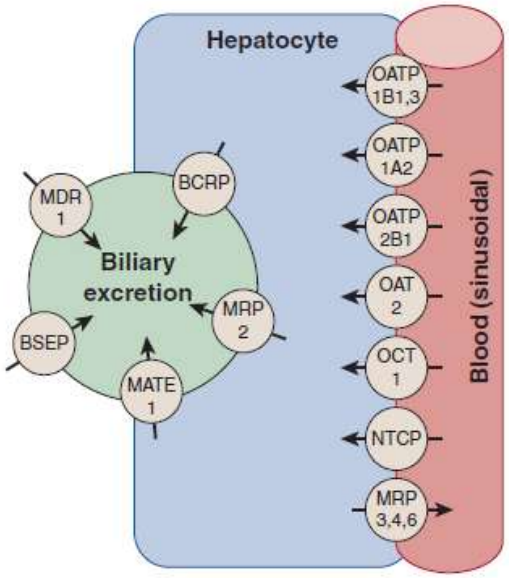

Figure 5: Schematic model showing the xenobiotic transporting systems present in the human liver.

Toxicology

Toxic Responses of the Liver

The liver is the main organ where exogenous chemicals are metabolized and eventually excreted. As a consequence, liver cells are exposed to significant concentrations of these chemicals, which can result in liver dysfunction, cell injury, and even organ failure.

Hepatic Functions:

Liver is the first organ to encounter ingested nutrients, vitamins, metals, drugs, and environmental toxicants as well as waste products of bacteria that enter portal blood. The Venous blood from the stomach and intestine flows into the portal vein and then through the liver before entering the systemic circulation.

All the major functions of the liver can be detrimentally altered by acute or chronic exposure to toxicants (Table 1).

Loss of function also occurs when toxicants kill an appreciable number of cells and when chronic insult leads to replacement of cell mass by nonfunctional scar tissue. Alcohol abuse is the major cause of liver disease in most western countries; thus ethanol provides a highly relevant example of a toxicant with multiple functional consequences. Early stages of ethanol abuse are characterized by lipid accumulation (fatty liver) due to diminished use of lipids as fuels and impaired ability to synthesize the lipoproteins that transport lipids out of the liver.

Table 1

Major Functions of Liver and Consequences of Impaired Hepatic Functions

TYPE OF FUNCTION	EXAMPLES	CONSEQUENCES OF IMPAIRED FUNCTIONS
Nutrient homeostasis	Glucose storage and synthesis Cholesterol uptake	Hypoglycemia, confusion Hypercholesterolemia
Filtration of particulates	Products of intestinal bacteria (eg, endotoxin)	Endotoxemia
Protein synthesis	Clotting factors Albumin Transport proteins (eg, very low density lipoproteins)	Excess bleeding Hypoalbuminemia, ascites Fatty liver
Bioactivation and detoxification	Bilirubin and ammonia Steroid hormones Xenobiotics	Jaundice, hyperammonemia-related coma Loss of secondary male sex characteristics Diminished drug metabolism Inadequate detoxification
Formation of bile and biliary secretion	Bile acid-dependent uptake of dietary lipids and vitamins Bilirubin and cholesterol Metals (eg, Cu and Mn) Xenobiotics	Fatty diarrhea, malnutrition, Vitamin E deficiency Jaundice, gallstones, hypercholesterolemia Mn-induced neurotoxicity Delayed drug clearance

Structural Organization

Two concepts exist for organization of the liver into operational units, namely, the lobule and the acinus. Classically, the liver was divided into hexagonal lobules oriented around terminal hepatic venules (also known as central veins).

At the corners of the lobule are the portal triads (or portal tracts), containing a branch of the portal vein, a hepatic arteriole, and a bile duct (Figure 1). Blood entering the portal tract via the portal vein and hepatic artery is mixed in the penetrating vessels, enters the sinusoids, and percolates along the cords of parenchymal cells (hepatocytes), eventually flows into terminal hepatic venules, and exits the liver via the hepatic vein. The lobule is divided into three regions known as centrilobular, midzonal, and periportal. The acinus is the preferred concept for a functional hepatic unit. The terminal branches of the portal vein and hepatic artery, which extend out from the portal tracts, form the base of the acinus. The acinus has three zones: zone 1 is closest to the entry of blood, zone 3 abuts the terminal hepatic vein, and zone 2 is intermediate. Acinar zonation is of considerable functional consequence regarding gradients of components both in blood and in hepatocytes. Blood entering the acinus consists of oxygen-depleted blood from the portal vein (60%–70% of hepatic blood flow) plus oxygenated blood from the hepatic artery (30%–40%). Enroute to the terminal hepatic venule, oxygen rapidly leaves the blood to meet the high metabolic demands of the parenchymal cells. Approximate oxygen concentrations in zone 1 are 9% to 13%, compared with only 4% to 5% in zone 3. Therefore, hepatocytes in zone 3 are exposed to substantially lower concentrations of oxygen than hepatocytes in zone 1. In comparison to other tissues, zone 3 is hypoxic. Another well-documented acinar gradient is that of bile salts. Physiological concentrations of bile salts are efficiently extracted by zone 1 hepatocytes with little bile acids left in the blood that flows past zone 3 hepatocytes.
There is difference in bile acid transporter expression between different zones.

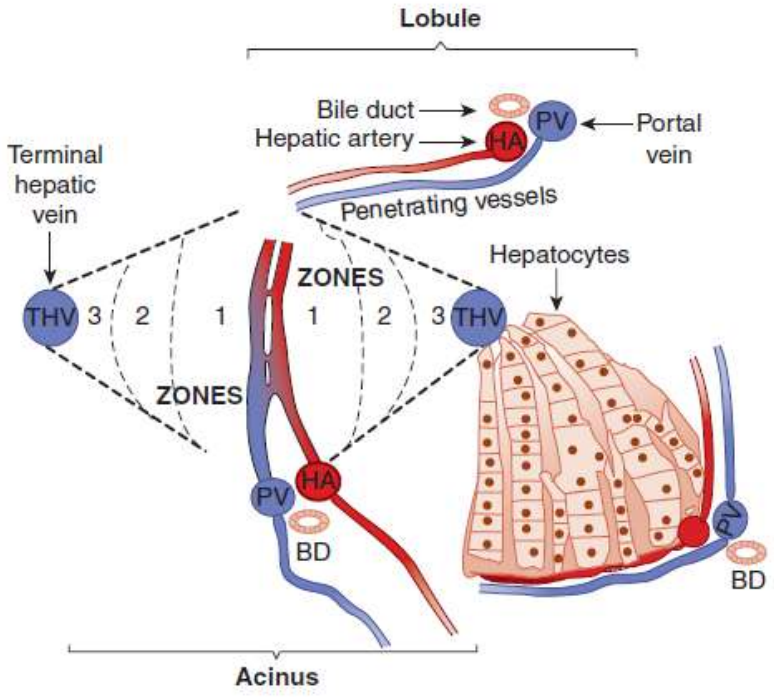

Figure 1: Schematic of liver operational units, the classic lobule and the acinus. The lobule is centered around the terminal hepatic vein (central vein), where the blood drains out of the lobule. The acinus has as its base the penetrating vessels, where blood supplied by the portal vein and hepatic artery fl ows down the acinus past the cords of hepatocytes. Zones 1, 2, and 3 of the acinus represent metabolic regions that are increasingly distant from the blood supply.

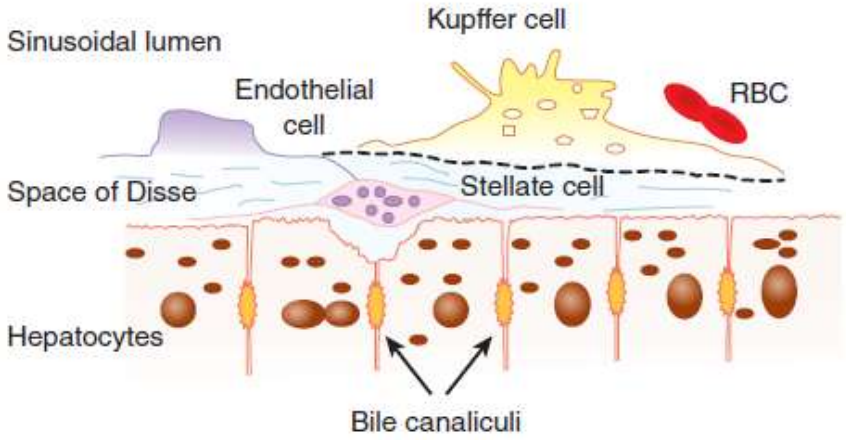

Figure 2A:Schematic of liver sinusoidal cells. Note that the Kupffer cell resides within the sinusoidal lumen. The stellate cell is located in the space of Disse between the thin, fenestrated endothelial cells, and the cord of hepatocytes.

Hepatocytes in the mitochondria-rich zone 1 are predominant in fatty acid oxidation, gluconeogenesis, and ammonia detoxification to urea. Gradients of enzymes involved in the bioactivation and detoxification of xenobiotics have been observed along the acinus by immunohistochemistry. Hepatic sinusoids are the channels between cords of hepatocytes where blood percolates on its way to the terminal hepatic vein. Sinusoids are larger and more irregular than normal capillaries.

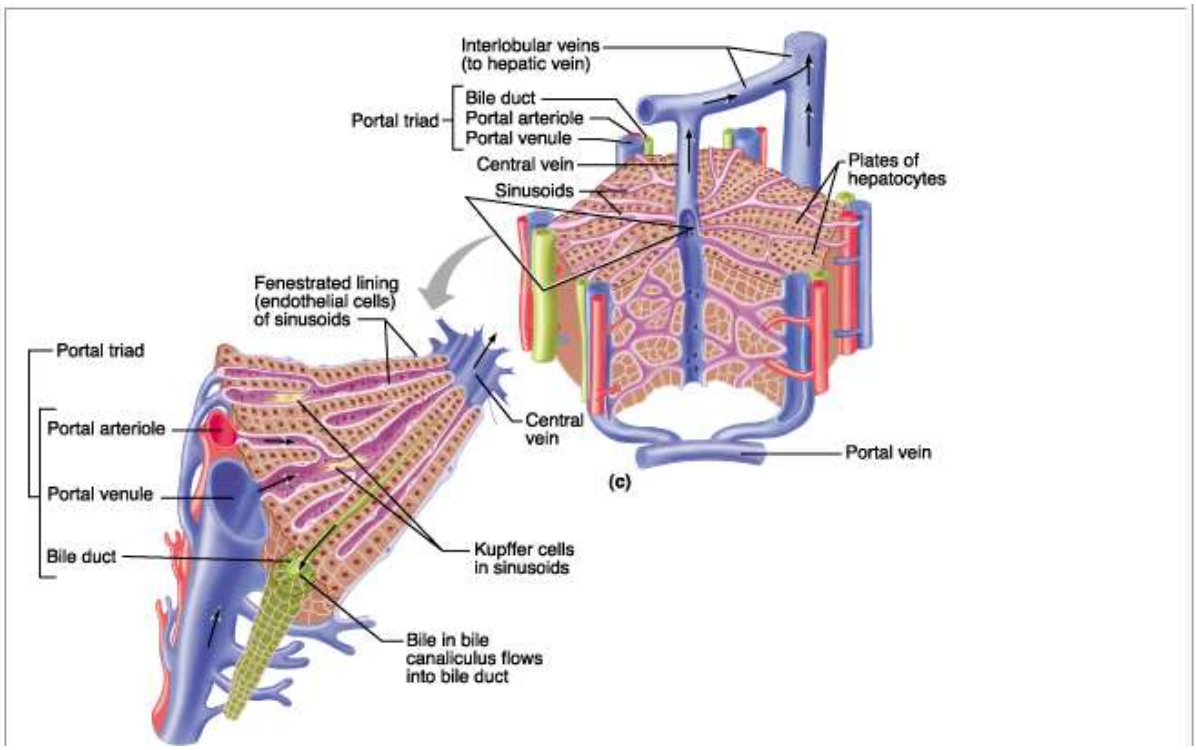

*Figure 2**B**:*

The three major types of cells in the sinusoids are endothelial cells, Kupffer cells, and stellate cells (Figure 2). Sinusoids are lined by thin, discontinuous endothelial cells with numerous fenestrae (or pores) that allow molecules smaller than 250 kDa to cross the interstitial space (known as the space of Disse) between the endothelium and hepatocytes. The numerous fenestrae and the lack of basement membrane facilitate exchanges of fluids and molecules, such as albumin, between the sinusoid and hepatocytes, but hinder movement of particles larger than chylomicron remnants. Kupffer cells are the resident macrophages of the liver and constitute approximately 80% of the fixed macrophages in the body. Kupffer cells are situated within the lumen of the sinusoid. The primary function of Kupffer cells is to ingest and degrade particulate matter. Also, Kupffer cells are a major source of cytokines and eicosanoids and can act as antigen-presenting cells. Hepatic stellate cells (HSCs; also known as Ito cells or by the more descriptive terms of *fat-storing cells*) are located between endothelial cells and hepatocytes. Stellate cells are the major sites for vitamin A storage in the body. Upon activation, these cells can synthesize and excrete collagen and other extracellular matrix proteins and express smooth muscle actin.

Bile Formation

Bile is a yellow fluid containing bile acids, GSH, phospholipids, cholesterol, bilirubin and other organic anions, proteins, metals, ions, and xenobiotics. Formation of this fluid is a specialized function of the liver. Adequate bile formation is essential for uptake of lipid nutrients from the small intestine (Table 1), for protection of the small intestine from oxidative insults, and for excretion of endogenous and xenobiotic compounds. Hepatocytes begin the process of bile formation by transporting bile acids, GSH, and other osmotically active compounds including xenobiotics and their metabolites into the canalicular lumen.

The canaliculi are separated from the intercellular space between hepatocytes by tight junctions, which form a barrier permeable only to water, electrolytes, and to some degree to small organic cations.

The large extrahepatic bile ducts merge into the common bile duct. Bile can be stored and concentrated in the gallbladder before its release into the duodenum. On the basal (sinusoidal) side of the hepatocytes, there are sodium-dependent and sodium-independent uptake systems. Most conjugated bile acids (taurine and glycine conjugates) and some of the unconjugated bile acids are transported into hepatocytes by sodium/taurocholate cotransporting polypeptide (NTCP) (Fig. 3). Sodium-independent uptake of conjugated and unconjugated bile acids is performed by members of the organic anion transporting polypeptides (OATPs). OATP1B1 and OATP1B3 are predominantly expressed in liver and are capable of transporting conjugated and unconjugated bile acids and steroids, bromosulfophthalein, and many other organic anions.

Furthermore, the OATPs are transporting numerous drugs and also some hepatotoxins, for example, phalloidin, microcystin, and amanitin.

Bile acid excretion is a major driving force of bile formation (bile salt-dependent bile flow). Other constituents of bile are transported by members of the multidrug resistance (MDR) P-glycoprotein family such as MDR3 (ABCC2), which transports phospholipids, and the heterodimeric transporters ABCG5/ABCG8, which transport cholesterol and plant sterols into bile. In addition, MRP2 (a member of the multidrug resistance-

associated proteins) transports GSH, which is the main compound responsible for the bile salt-independent bile flow, as well as sulfated and glucuronidated bile acids, glutathione disulfide and glutathione conjugates, bilirubin diglucuronide, and many other conjugated drugs and chemicals. Other transport systems of the canalicular membrane include the breast cancer resistance protein (BCRP; ABCG2), which can contribute to the biliary excretion of bile acids and xenobiotics. Biliary excretion is important in the homeostasis of multiple metals, notably copper, manganese, cadmium, selenium, gold, silver, and arsenic.

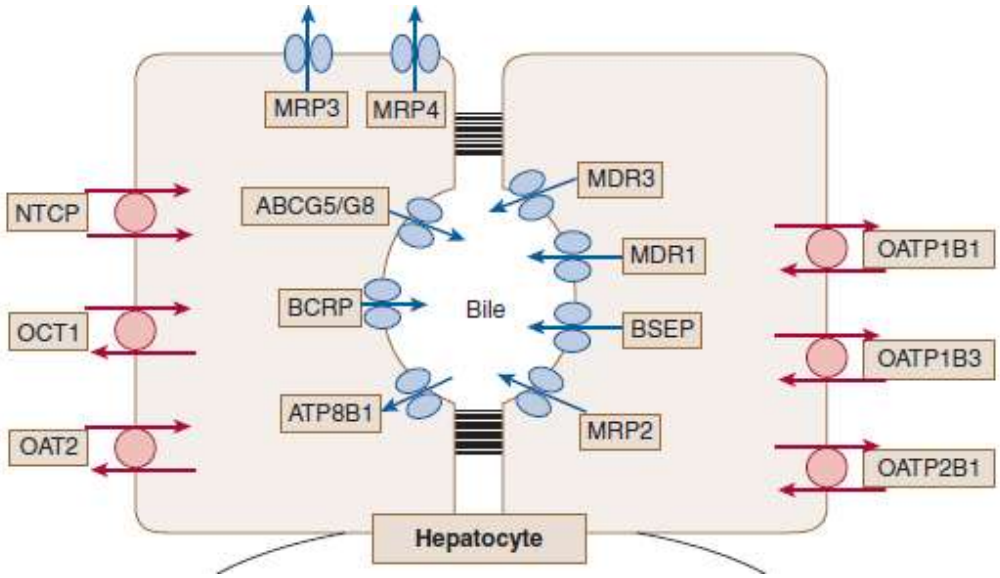

Figure 3:Transport proteins in human hepatocytes and cholangiocytes. Efflux transporters (blue symbols) and Uptake transporters (red symbols).

Mechanisms and Types of Toxicant-Induced Liver Injury

Cell Death

Based on morphology, liver cells can die by two different modes, oncotic necrosis ("necrosis") or apoptosis. Necrosis is characterized by cell swelling, leakage of cellular contents, nuclear disintegration (karyolysis), and an influx of inflammatory cells. Because necrosis is generally the result of an exposure to a toxic chemical or other traumatic conditions, for example, ischemia, large numbers of contiguous hepatocytes and nonparenchymal cells may be affected. Thus, an ongoing oncotic necrotic process can be identified by the release of liver-specific enzymes such as alanine (ALT) or aspartate (AST) aminotransferase into the plasma and by histology, where areas of necrosis with loss of nuclei and inflammatory infiltrates are easily detectable in H&E sections. In contrast, apoptosis is characterized by cell shrinkage, chromatin condensation, nuclear fragmentation, formation of apoptotic bodies, and, generally, a lack of inflammation. The characteristic morphological features of apoptosis are caused by the activation of caspases, which trigger the activation of enzymes such as caspase-activated DNase (CAD) responsible for internucleosomal DNA fragmentation. In addition, caspases can directly cleave cellular and nuclear structural proteins. Under these conditions, apoptotic bodies are phagocytosed by Kupffer cells or taken up by neighboring hepatocytes.

Canalicular Cholestasis

This form of liver dysfunction is defined physiologically as a decrease in the volume of bile formed or an impaired secretion of specific solutes into bile. Cholestasis is characterized biochemically by elevated serum levels of compounds normally concentrated in bile, particularly bile salts and bilirubin. When biliary excretion of the yellowish bilirubin pigment is impaired, this pigment accumulates in skin and eyes, producing jaundice, and spills into urine, which becomes bright yellow or dark brown. Because drug-induced jaundice reflects a more generalized liver dysfunction, it is considered a more serious warning sign in clinical trials than mild elevations of liver enzymes. Toxicant-induced cholestasis can be transient or chronic. Many different types of chemicals, including metals, hormones, and drugs, cause cholestasis (Table 2). The molecular mechanisms of cholestasis are related to expression and function of transporter systems in the basolateral and canalicular membranes.

The hepatotoxicity of phalloidin, microcystin, and amanitin is facilitated by the uptake through OATPs. Furthermore, there is a growing list of drugs including rifampicin, bosentan, and troglitazone, which are known to directly inhibit BSEP. However, estrogen and progesterone metabolites inhibit BSEP from the canalicular side after excretion by MRP2. A substantial inhibition of bile salt excretion can lead to accumulation of these compounds in hepatocytes and may directly cause cell injury. However, more recent findings indicate that most of the bile acids accumulating in the liver after obstructive cholestasis are nontoxic and instead of cell death cause pro-inflammatory gene expression in hepatocytes. Thus, liver injury after obstructive cholestasis is caused mainly by inflammatory cells.

Table 2:

Types of Hepatobiliary Injury

TYPE OF INJURY OR DAMAGE	REPRESENTATIVE TOXINS
Fatty liver	Amiodarone, CCl_4, ethanol, fialuridine, tamoxifen, valproic acid
Hepatocyte death	Acetaminophen, allyl alcohol, Cu, dimethylformamide, ethanol
Immune-mediated response	Diclofenac, ethanol, halothane, tienilic acid
Canalicular cholestasis	Chlorpromazine, cyclosporin A, 1,1-dichloroethylene, estrogens, Mn, phalloidin
Bile duct damage	Alpha-naphthylisothiocyanate, amoxicillin, methylenedianiline, sporidesmin
Sinusoidal disorders	Anabolic steroids, cyclophosphamide, microcystin, pyrrolizidine alkaloids
Fibrosis and cirrhosis	CCl_4, ethanol, thioacetamide, vitamin A, vinyl chloride
Tumors	Aflatoxin, androgens, arsenic, thorium dioxide, vinyl chloride

Sinusoidal Damage

The sinusoid is, in effect, a specialized capillary with numerous fenestrae for high permeability. The functional integrity of the sinusoid can be compromised by dilation or blockade of its lumen or by progressive destruction of its endothelial cell wall. Progressive destruction of the endothelial wall of the sinusoid will lead to gaps and then ruptures of its barrier integrity, with entrapment of red blood cells. These disruptions of the sinusoid are considered the early structural features of the vascular disorder known as

veno-occlusive disease. Well established as a cause of veno-occlusive disease are the pyrrolizidine alkaloids (eg, monocrotaline, retrorsine, and seneciphylline) found in some plants used for herbal teas and in some seeds that contaminate food grains. Numerous episodes of human and animal poisoning by pyrrolizidine alkaloids have been reported around the world, including massive problems affecting thousands of people in Afghanistan in 1976 and 1993. (1974–1976 – Afghanistan: widespread poisoning (an estimated 7800 people affected with hepatic veno-occlusive disease (liver damage) and about 1600 deaths) was attributed to wheat contaminated with weed seeds known as charmac (*Heliotropium popovii*. H Riedl) that contain pyrrolizidine alkaloids.)

Veno-occlusive disease is also a serious complication in about 15% of the patients given high doses of chemotherapy (eg, cyclophosphamide) as part of bone-marrow transplantation regimen. Selective depletion of GSH within sinusoidal endothelial cells and activation of matrix metalloproteinases are critical events in the mechanism of endothelial cell injury in the pathophysiology of veno-occlusive disease.

Fatty Liver

Fatty liver (steatosis) is defined biochemically as an appreciable increase in the hepatic lipid (mainly triglyceride) content, which is <5 wt% in the normal human liver. Currently, the most common cause of hepatic steatosis is insulin resistance due to central obesity and sedentary lifestyle.

However, acute exposure to many hepatotoxins, for example, carbon tetrachloride and drugs can induce steatosis. Compounds that produce prominent steatosis associated with lethality include the antiepileptic drug valproic acid and the antiviral drug fialuridine. Ethanol is by far the most relevant drug or chemical leading to steatosis in humans and in experimental animals. Often, drug-induced steatosis is reversible and does not lead to death of hepatocytes. Although steatosis alone may be benign, it can develop into steatohepatitis (alcoholic or nonalcoholic), which is associated with significant liver injury. Steatohepatitis can progress to fibrosis and even hepatocellular carcinoma.

Free fatty acids (FFAs) can be newly synthesized in hepatocytes (mainly from carbohydrate-derived acetyl-coenzyme A). FFAs released from adipose tissue can be taken up into hepatocytes, or they are generated in the liver from hydrolysis of absorbed fat (chylomicrons). Once in the cytosol, FFAs can be imported into mitochondria for degradation (β-oxidation), or esterified into triglycerides for incorporation into very low-density lipoproteins (VLDL), which transports the FFAs to the peripheral adipose tissue. Thus, FFA synthesis, consumption, and storage are in a state of equilibrium with no relevant accumulation of triglycerides in the liver. However, if there is chronic excess food consumption with obesity and insulin resistance, excess uptake of FFAs derived from adipose tissue and food into hepatocytes leads to an overload of FFAs, which cannot be degraded and are therefore esterified to triglycerides. One part of the excess triglycerides is incorporated into VLDL, and the other part is stored in the liver gradually leading to steatosis. The previously preferred hypothesis of nonalcoholic steatohepatitis (NASH) considered triglyceride accumulation in hepatocytes as the first hit and any additional stress (oxidant stress, lipid peroxidation) as a second hit leading to the progression from steatosis to steatohepatitis. However, more recent data have clearly demonstrated that triglyceride accumulation does neither cause insulin resistance nor cell injury. A new hypothesis postulates that nonalcoholic fatty liver disease (NAFLD) is

mainly caused by lipotoxicity of nontriglyceride fatty acid metabolites. Mechanisms of lipotoxicity elucidated in cell culture experiments include endoplasmic reticulum stress, activation of the mitochondrial cell death pathway, and lysosomal dysfunction.

Fibrosis and Cirrhosis

Hepatic fibrosis (scaring) occurs in response to chronic liver injury and is characterized by the accumulation of excessive amounts of fibrous tissue, specifically fibril forming collagens type I and III, and a decrease in normal plasma membrane collagen type IV. Fibrosis can develop around central veins and portal tracts or within the space of Disse. With continuing collagen deposition, the architecture of the liver is disrupted by interconnecting fibrous scars. When the fibrous scars subdivide the remaining liver mass into nodules of regenerating hepatocytes, fibrosis has progressed to cirrhosis and the liver has limited residual capacity to perform its essential functions. The primary cause of hepatic fibrosis/cirrhosis in humans worldwide is viral hepatitis. However, biliary obstruction and, in particular, alcoholic and NASH are of growing importance for the development of hepatic fibrosis. In addition, fibrosis can be induced by chronic exposure to drugs and chemicals including ethanol and by heavy metal overload. HSC which are the main cell type producing extracellular matrix proteins. Products formed during liver cell injury initiate HSC activation. Activating signals can be reactive oxygen species and lipid peroxidation products generated in injured hepatocytes. In addition, Kupffer cells can release reactive oxygen and pro-inflammatory cytokines during the phagocytosis of cell debris or apoptotic bodies, thereby recruiting more inflammatory cells and enhancing the injury and oxidant stress. Damaged sinusoidal endothelial cells contribute to the activation of HSC.

Tumors

Chemically induced neoplasia can involve tumors that are derived from hepatocytes, bile duct progenitor cells, the ductular “bipolar” progenitor cells, and the periductular stem cells. Hepatocellular cancer has been linked to chronic abuse of androgens, alcohol, and a high prevalence of aflatoxin-contaminated diets. In addition, viral hepatitis, metabolic diseases, and NASH are major risk factors for hepatocellular carcinoma. The synergistic effect of coexposure to aflatoxin and hepatitis virus B is well recognized.

The malignant transformation of hepatocytes occurs as a result of increased cell turnover due to chronic liver injury, persistent inflammation, regeneration, and cirrhosis. Direct DNA binding of carcinogens or their reactive metabolites (eg, aflatoxin metabolites) or indirect DNA modifications by reactive oxygen species generated during inflammation and cell injury can lead to genetic alterations in hepatocytes resulting in impaired DNA repair, the activation of cellular oncogenes, and inactivation of tumor suppressor genes. An overall imbalance between stimulation of proliferation and inhibition of apoptosis in the liver leads to the survival and expansion of these preneoplastic cells. This concept is supported by the observation that 30% of hepatocellular carcinomas show mutations in the tumor suppressor gene p53; the mutation rate is up to 70% in areas with high aflatoxin exposure. The functional inactivation of p53 by mutations prevents the induction of apoptosis.

Factors in the Site-Specific Injury of Representative Hepatotoxicants

SITE	REPRESENTATIVE TOXICANTS	POTENTIAL EXPLANATION FOR SITE-SPECIFICITY
Zone 1 hepatocytes (vs zone 3)	Fe (overload) Allyl alcohol	Preferential uptake and high oxygen levels Higher oxygen levels for oxygen-dependent bioactivation
Zone 3 hepatocytes (vs zone 1)	CCl_4 Acetaminophen Ethanol	More P450 isozyme for bioactivation More P450 isozyme for bioactivation and less GSH for detoxification More hypoxic and greater imbalance in bioactivation/detoxification reactions
Bile duct cells	Methylenedianiline, sporidesmin	Exposure to the high concentration of reactive metabolites in bile
Sinusoidal endothelium (vs hepatocytes)	Cyclophosphamide, monocrotaline	Greater vulnerability to toxic metabolites and less ability to maintain glutathione levels
Kupffer cells	Endotoxin, $GdCl_3$	Preferential uptake and then activation
Stellate cells	Vitamin A Ethanol (chronic)	Preferential site for storage and then engorgement Activation and transformation to collagen-synthesizing cell

Toxicology

Toxic Responses of the Liver

The liver is the main organ where exogenous chemicals are metabolized and eventually excreted. As a consequence, liver cells are exposed to significant concentrations of these chemicals, which can result in liver dysfunction, cell injury, and even organ failure.

Hepatic Functions:

Liver is the first organ to encounter ingested nutrients, vitamins, metals, drugs, and environmental toxicants as well as waste products of bacteria that enter portal blood. The Venous blood from the stomach and intestine flows into the portal vein and then through the liver before entering the systemic circulation.

All the major functions of the liver can be detrimentally altered by acute or chronic exposure to toxicants (Table 1).

Loss of function also occurs when toxicants kill an appreciable number of cells and when chronic insult leads to replacement of cell mass by nonfunctional scar tissue. Alcohol abuse is the major cause of liver disease in most western countries; thus ethanol provides a highly relevant example of a toxicant with multiple functional consequences. Early stages of ethanol abuse are characterized by lipid accumulation (fatty liver) due to diminished use of lipids as fuels and impaired ability to synthesize the lipoproteins that transport lipids out of the liver.

Table 1

Major Functions of Liver and Consequences of Impaired Hepatic Functions

TYPE OF FUNCTION	EXAMPLES	CONSEQUENCES OF IMPAIRED FUNCTIONS
Nutrient homeostasis	Glucose storage and synthesis Cholesterol uptake	Hypoglycemia, confusion Hypercholesterolemia
Filtration of particulates	Products of intestinal bacteria (eg, endotoxin)	Endotoxemia
Protein synthesis	Clotting factors Albumin Transport proteins (eg, very low density lipoproteins)	Excess bleeding Hypoalbuminemia, ascites Fatty liver
Bioactivation and detoxification	Bilirubin and ammonia Steroid hormones Xenobiotics	Jaundice, hyperammonemia-related coma Loss of secondary male sex characteristics Diminished drug metabolism Inadequate detoxification
Formation of bile and biliary secretion	Bile acid-dependent uptake of dietary lipids and vitamins Bilirubin and cholesterol Metals (eg, Cu and Mn) Xenobiotics	Fatty diarrhea, malnutrition, Vitamin E deficiency Jaundice, gallstones, hypercholesterolemia Mn-induced neurotoxicity Delayed drug clearance

Structural Organization

Two concepts exist for organization of the liver into operational units, namely, the lobule and the acinus. Classically, the liver was divided into hexagonal lobules oriented around terminal hepatic venules (also known as central veins).

At the corners of the lobule are the portal triads (or portal tracts), containing a branch of the portal vein, a hepatic arteriole, and a bile duct (Figure 1). Blood entering the portal tract via the portal vein and hepatic artery is mixed in the penetrating vessels, enters the sinusoids, and percolates along the cords of parenchymal cells (hepatocytes), eventually flows into terminal hepatic venules, and exits the liver via the hepatic vein. The lobule is divided into three regions known as centrilobular, midzonal, and periportal. The acinus is the preferred concept for a functional hepatic unit. The terminal branches of the portal vein and hepatic artery, which extend out from the portal tracts, form the base of the acinus. The acinus has three zones: zone 1 is closest to the entry of blood, zone 3 abuts the terminal hepatic vein, and zone 2 is intermediate. Acinar zonation is of considerable functional consequence regarding gradients of components both in blood and in hepatocytes. Blood entering the acinus consists of oxygen-depleted blood from the portal vein (60%–70% of hepatic blood flow) plus oxygenated blood from the hepatic artery (30%–40%). Enroute to the terminal hepatic venule, oxygen rapidly leaves the blood to meet the high metabolic demands of the parenchymal cells. Approximate oxygen concentrations in zone 1 are 9% to 13%, compared with only 4% to 5% in zone 3. Therefore, hepatocytes in zone 3 are exposed to substantially lower concentrations of oxygen than hepatocytes in zone 1. In comparison to other tissues, zone 3 is hypoxic. Another well-documented acinar gradient is that of bile salts. Physiological concentrations of bile salts are efficiently extracted by zone 1 hepatocytes with little bile acids left in the blood that flows past zone 3 hepatocytes.
There is difference in bile acid transporter expression between different zones.

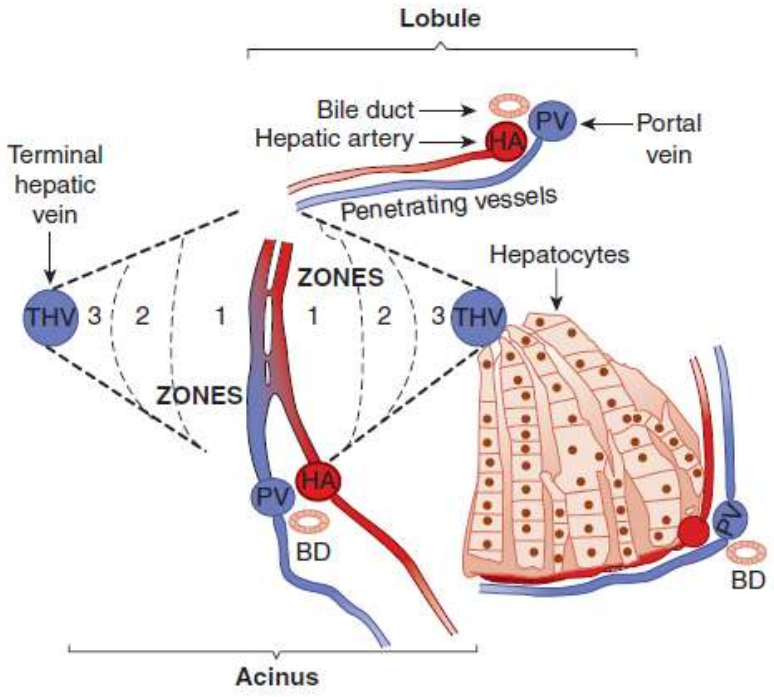

Figure 1: Schematic of liver operational units, the classic lobule and the acinus. The lobule is centered around the terminal hepatic vein (central vein), where the blood drains out of the lobule. The acinus has as its base the penetrating vessels, where blood supplied by the portal vein and hepatic artery fl ows down the acinus past the cords of hepatocytes. Zones 1, 2, and 3 of the acinus represent metabolic regions that are increasingly distant from the blood supply.

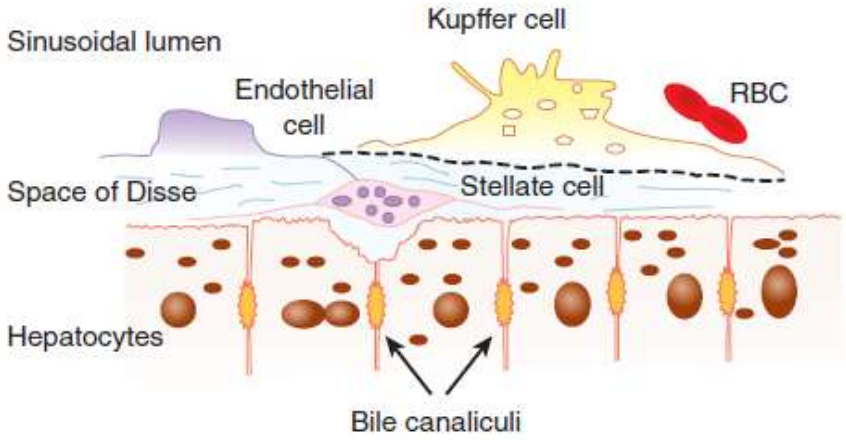

Figure 2A:Schematic of liver sinusoidal cells. Note that the Kupffer cell resides within the sinusoidal lumen. The stellate cell is located in the space of Disse between the thin, fenestrated endothelial cells, and the cord of hepatocytes.

Hepatocytes in the mitochondria-rich zone 1 are predominant in fatty acid oxidation, gluconeogenesis, and ammonia detoxification to urea. Gradients of enzymes involved in the bioactivation and detoxification of xenobiotics have been observed along the acinus by immunohistochemistry. Hepatic sinusoids are the channels between cords of hepatocytes where blood percolates on its way to the terminal hepatic vein. Sinusoids are larger and more irregular than normal capillaries.

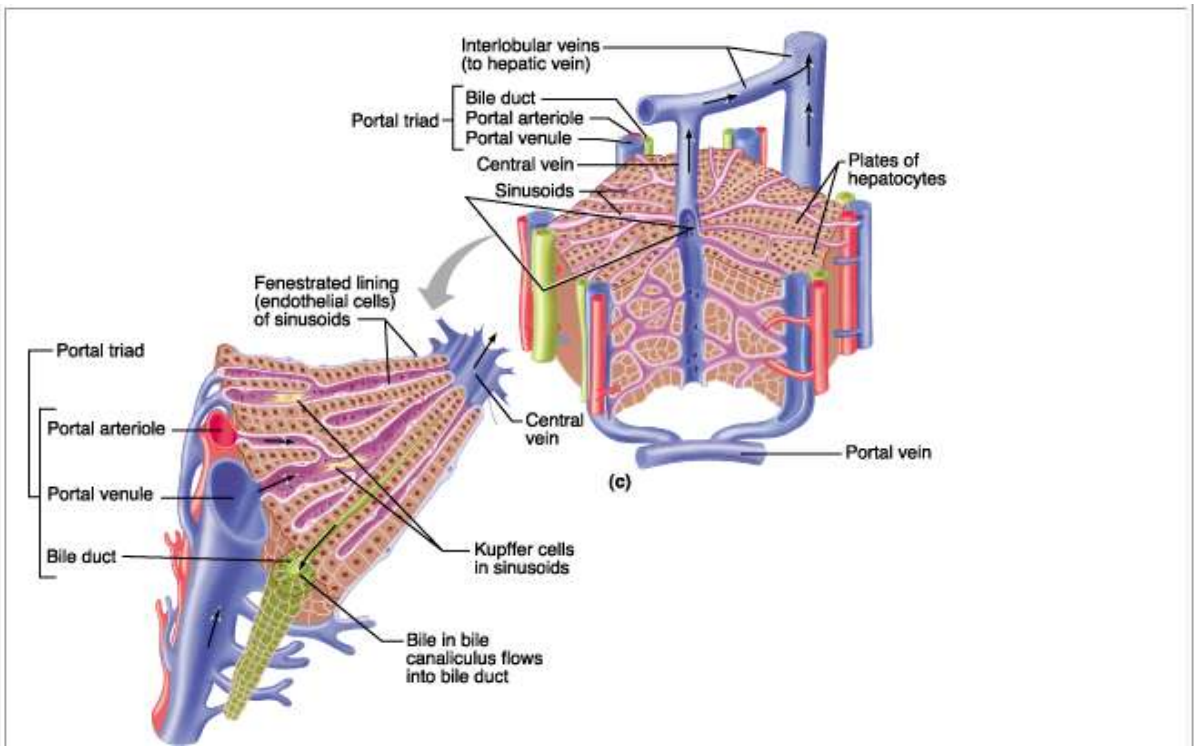

*Figure 2**B**:*

The three major types of cells in the sinusoids are endothelial cells, Kupffer cells, and stellate cells (Figure 2). Sinusoids are lined by thin, discontinuous endothelial cells with numerous fenestrae (or pores) that allow molecules smaller than 250 kDa to cross the interstitial space (known as the space of Disse) between the endothelium and hepatocytes. The numerous fenestrae and the lack of basement membrane facilitate exchanges of fluids and molecules, such as albumin, between the sinusoid and hepatocytes, but hinder movement of particles larger than chylomicron remnants. Kupffer cells are the resident macrophages of the liver and constitute approximately 80% of the fixed macrophages in the body. Kupffer cells are situated within the lumen of the sinusoid. The primary function of Kupffer cells is to ingest and degrade particulate matter. Also, Kupffer cells are a major source of cytokines and eicosanoids and can act as antigen-presenting cells. Hepatic stellate cells (HSCs; also known as Ito cells or by the more descriptive terms of *fat-storing cells*) are located between endothelial cells and hepatocytes. Stellate cells are the major sites for vitamin A storage in the body. Upon activation, these cells can synthesize and excrete collagen and other extracellular matrix proteins and express smooth muscle actin.

Bile Formation

Bile is a yellow fluid containing bile acids, GSH, phospholipids, cholesterol, bilirubin and other organic anions, proteins, metals, ions, and xenobiotics. Formation of this fluid is a specialized function of the liver. Adequate bile formation is essential for uptake of lipid nutrients from the small intestine (Table 1), for protection of the small intestine from oxidative insults, and for excretion of endogenous and xenobiotic compounds. Hepatocytes begin the process of bile formation by transporting bile acids, GSH, and other osmotically active compounds including xenobiotics and their metabolites into the canalicular lumen.

The canaliculi are separated from the intercellular space between hepatocytes by tight junctions, which form a barrier permeable only to water, electrolytes, and to some degree to small organic cations.

The large extrahepatic bile ducts merge into the common bile duct. Bile can be stored and concentrated in the gallbladder before its release into the duodenum. On the basal (sinusoidal) side of the hepatocytes, there are sodium-dependent and sodium-independent uptake systems. Most conjugated bile acids (taurine and glycine conjugates) and some of the unconjugated bile acids are transported into hepatocytes by sodium/taurocholate cotransporting polypeptide (NTCP) (Fig. 3). Sodium-independent uptake of conjugated and unconjugated bile acids is performed by members of the organic anion transporting polypeptides (OATPs). OATP1B1 and OATP1B3 are predominantly expressed in liver and are capable of transporting conjugated and unconjugated bile acids and steroids, bromosulfophthalein, and many other organic anions.

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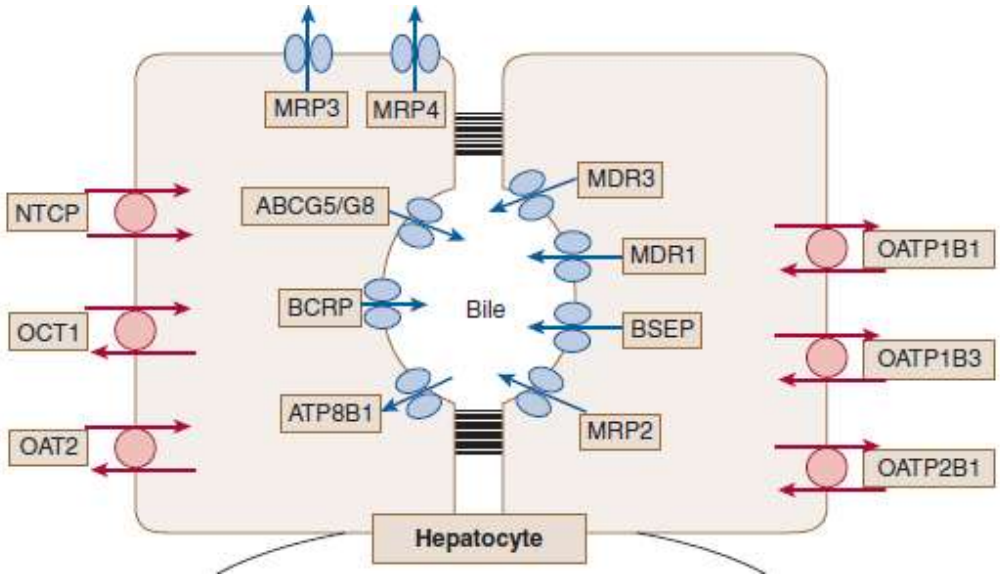

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Zone 1 hepatocytes (vs zone 3)	Fe (overload) Allyl alcohol	Preferential uptake and high oxygen levels Higher oxygen levels for oxygen-dependent bioactivation
Zone 3 hepatocytes (vs zone 1)	CCl_4 Acetaminophen Ethanol	More P450 isozyme for bioactivation More P450 isozyme for bioactivation and less GSH for detoxification More hypoxic and greater imbalance in bioactivation/detoxification reactions
Bile duct cells	Methylenedianiline, sporidesmin	Exposure to the high concentration of reactive metabolites in bile
Sinusoidal endothelium (vs hepatocytes)	Cyclophosphamide, monocrotaline	Greater vulnerability to toxic metabolites and less ability to maintain glutathione levels
Kupffer cells	Endotoxin, $GdCl_3$	Preferential uptake and then activation
Stellate cells	Vitamin A Ethanol (chronic)	Preferential site for storage and then engorgement Activation and transformation to collagen-synthesizing cell

Toxicology
Toxic Responses of the Liver

Critical Factors in Toxicant-Induced Liver Injury

Uptake and Concentration

Hepatic "first pass" uptake of ingested chemicals is facilitated by the location of the liver downstream of the portal blood flow from the gastrointestinal tract. Lipophilic compounds, particularly drugs and environmental pollutants, readily diffuse into hepatocytes because the fenestrated epithelium of the sinusoid enables close contact between circulating molecules and hepatocytes. Thus, the membrane-rich liver concentrates lipophilic compounds. Other toxins are rapidly extracted from blood because they are substrates for transporters located on the sinusoidal membrane of hepatocytes.

Phalloidin and microcystin are illustrative examples of hepatotoxins that target the liver as a consequence of extensive uptake into hepatocytes by sinusoidal transporters. Ingestion of the mushroom *Amanita phalloides* is a common cause of severe, acute hepatotoxicity in continental Europe and North America. Microcystin has produced numerous outbreaks of hepatotoxicity in sheep and cattle that drank pond water containing the blue-green alga *Microcystis aeruginosa.*

Because of its dual blood supply from both the portal vein and the hepatic artery, the liver is presented with appreciable amounts of all toxicants in the systemic circulation.

Vitamin A hepatotoxicity initially affects stellate cells, which actively extract and store this vitamin. Cadmium hepatotoxicity becomes manifest when the cells exceed their capacity to sequester cadmium as a complex with the metal-binding protein, metallothionein (MT).

Iron poisoning produces severe liver damage. Hepatocytes contribute to the homeostasis of iron by extracting this essential metal from the sinusoid by a receptor-mediated process and maintaining a reserve of iron within the storage protein ferritin. Acute Fe toxicity is most commonly observed in young children who accidentally ingest iron tablets. The cytotoxicity of free iron is attributed to its function as an electron donor for the Fenton reaction, where hydrogen peroxide is reductively cleaved to the highly reactive hydroxyl radical, an initiator of lipid peroxidation. Accumulation of excess iron beyond the capacity for its safe storage in ferritin is initially evident in the zone 1 hepatocytes, which are closest to the blood entering the sinusoid.

Bioactivation and Detoxification

One of the vital functions of the liver is to eliminate exogenous chemicals and endogenous intermediates. Therefore, hepatocytes contain high levels of phase I enzymes, which have the capacity to generate reactive electrophilic metabolites. Hepatocytes also have a wide variety of phase II enzymes, which enhance the hydrophilicity by adding polar groups to lipophilic compounds and target these

conjugates to certain carriers in the canalicular or plasma membrane for excretion. Generally, phase II reactions yield stable, non-reactive metabolites. Although electrophiles may be effectively conjugated and excreted, if the intermediate is highly reactive, some of these compounds can react with proteins and other target molecules before an interaction with a phase II enzyme is possible. In contrast, if the amount of the reactive metabolite exceeds the capacity of the hepatocyte to detoxify it, covalent binding to cellular macromolecules will occur and potentially result in cell injury. Thus, the balance between phase I reactions, which generate the electrophile, and conjugating phase II reactions determines whether a reactive intermediate is safely detoxified or may cause cell dysfunction or injury.

Regeneration

The liver has a high capacity to restore lost tissue and function by regeneration. Loss of hepatocytes due to hepatectomy or cell injury triggers proliferation of all mature liver cells. This process is capable of restoring the original liver mass.

Hepatocytes are normally quiescent, that is, they are in G0 phase of the cell cycle. In order to proliferate, they need to enter the cell cycle. The process is initiated by cytokines (TNF-α, IL-6), which prime hepatocytes to respond to essential growth factors such as HGF and TGF-α. Both cytokines and growth factors are involved in the activation of transcription factors and ultimately expression of cell cycle-regulating proteins. stimulation of repair by exposure to a moderate dose of a hepatotoxicant strongly attenuates tissue damage of a subsequent high dose of the same chemical (autoprotection) or a different hepatotoxin (heteroprotection). In addition to the dose of the hepatotoxicant, other factors such as age, nutritional status, and disease state may influence tissue repair.

Inflammation

The activation of resident macrophages (Kupffer cells), NK and NKT cells, and the migration of activated neutrophils, lymphocytes, and monocytes into regions of damaged liver is a well-recognized feature of the hepatotoxicity produced by many chemicals. The main reason for an inflammatory response is to remove dead and damaged cells. However, under certain circumstances, these inflammatory cells can aggravate the existing injury by release of directly cytotoxic mediators or by formation of pro and anti-inflammatory mediators (Figure 1).

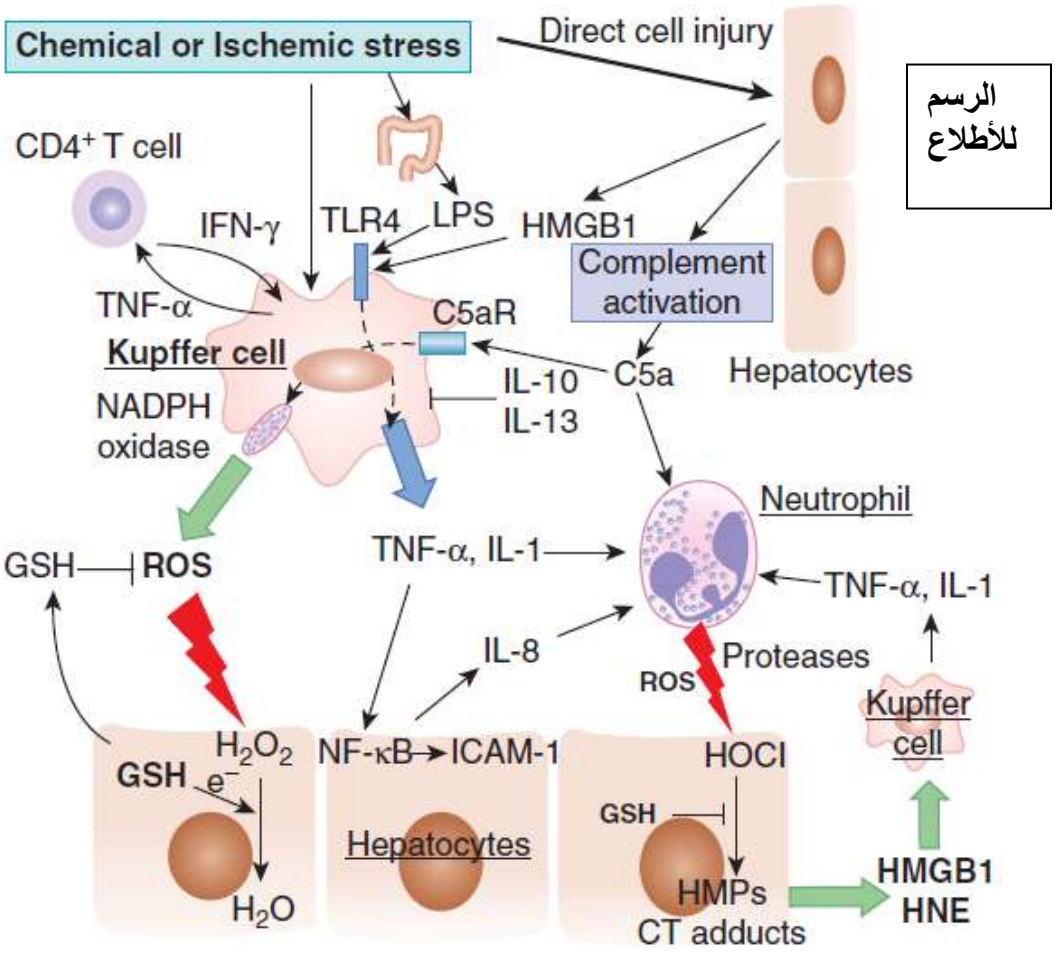

Figure 1: Self-perpetuating inflammatory response after chemical or ischemic stress. *C5aR, C5a complement receptor; CT, chlorotyrosine protein adducts; GSH, reduced glutathione; HMGB1, high-mobility group box-1; HMPs, hypochlorous acid modifi ed proteins; HNE, hydroxynonenal; HOCl, hypochlorous acid; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL-1, interleukin-1, LPS, lipopolysaccharide; NF-κB, nuclear factor-κB; ROS, reactive oxygen species; TLR4, toll-like receptor-4; TNF, tumor necrosis factor.*

Kupffer cells and neutrophils are potent phagocytes, which have a vital function in host defense and removal of cell debris. Formation of reactive oxygen species by NADPH oxidase is a critical tool for these cells. Upon activation, Kupffer cells generate mainly hydrogen peroxide, which can diffuse into neighboring liver cells and create an intracellular oxidant stress leading to cellular stress and injury. Kupffer cells can be activated by bacterial products, opsonized particles, and activated complement factors to cause oxidant stress and cell injury.

Recent evidence suggests that not only bacterial products but also intracellular proteins, for example, HMGB-1, which are released during necrotic cell death, can bind to toll-like receptors on Kupffer cells and trigger cytokine and chemokine formation. However, Kupffer cells can also generate anti-inflammatory mediators such as prostaglandin E2 and interleukin-10, which down regulate formation of proinflammatory cytokines and attenuate toxin-induced liver injury. Thus, Kupffer cells can promote or inhibit an injury

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Immune Responses

In addition to the activation of an inflammatory response, immune-mediated reactions may also lead to severe liver injury. Drugs and chemicals that have been suggested to cause immune-mediated injury mechanisms in the liver include halothane, tienilic acid, and dihydralazine. A delay in onset of the injury or the requirement for repeated exposure to the drug and the formation of antibodies against drug-modified hepatic proteins are characteristic features of immune reactions. However, the mechanisms of these immune-mediated liver injuries are not well understood. The *hapten hypothesis* assumes that a reactive metabolite covalently binds to cellular proteins and the drug-modified protein is taken up by APCs, cleaved to peptide fragments, which are then presented within the major histocompatibility complex (MHC) to T cells. In support of the hapten hypothesis, antibodies against drug-modified proteins were detected in the serum of patients with halothane hepatitis or with liver injury caused by ethanol, tienilic acid, and dihydralazine.
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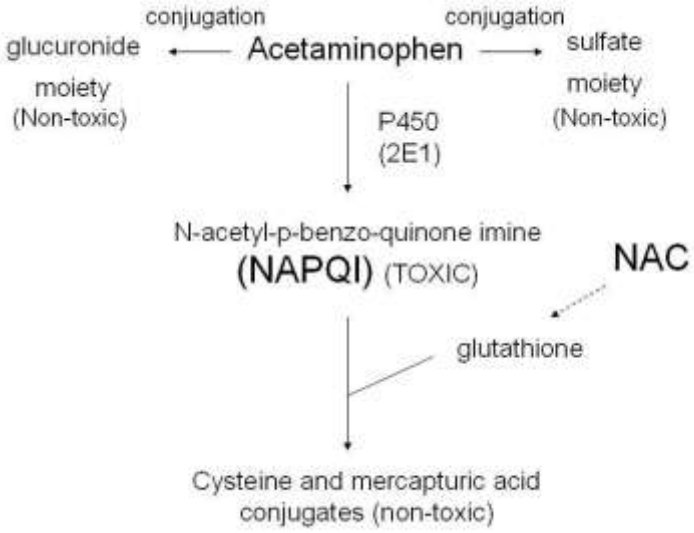

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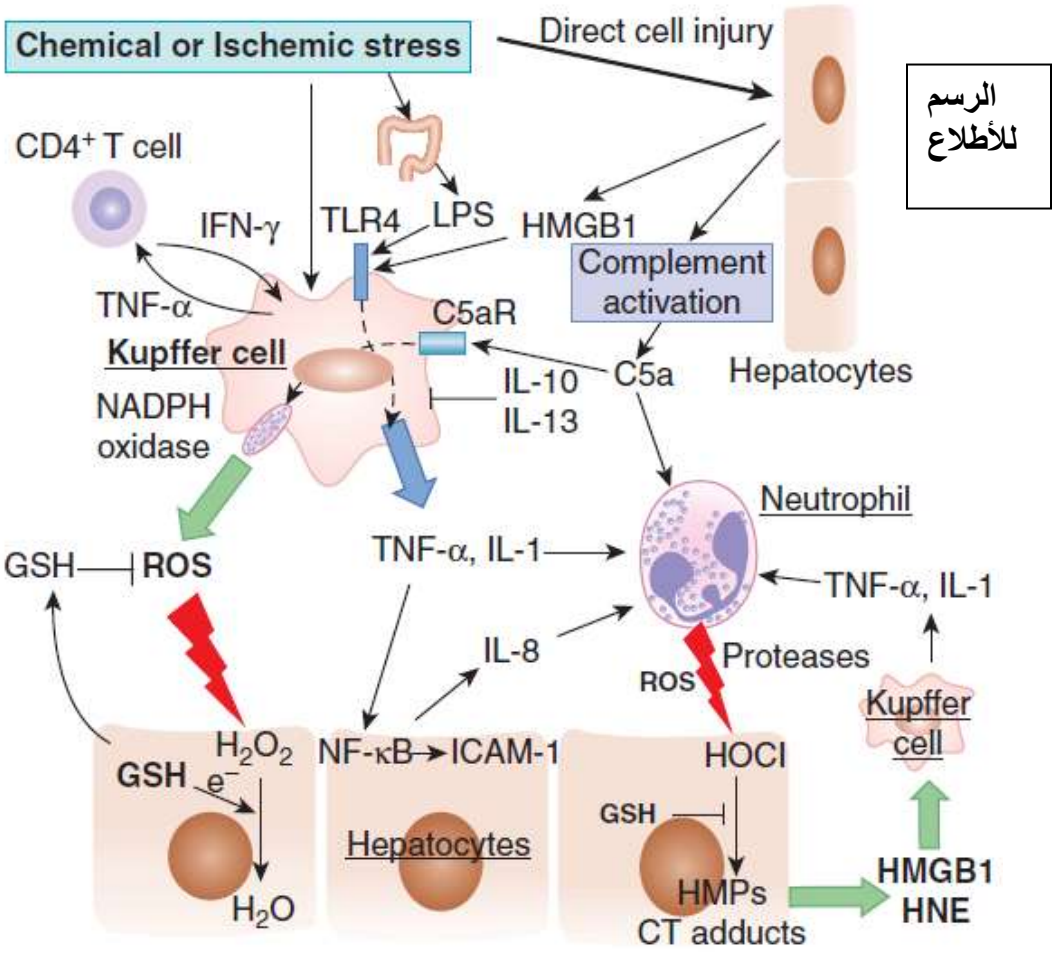

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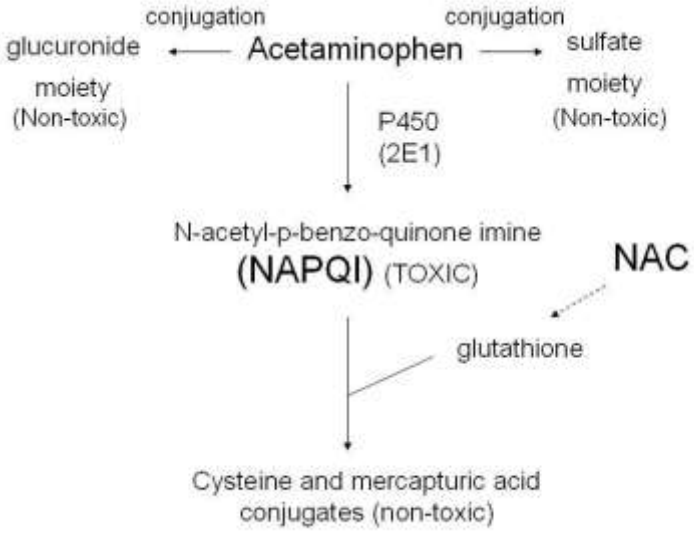

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Toxicology
Toxic Responses of the Kidney

The functional integrity of the mammalian kidney is vital to total body homeostasis because the kidney plays a principal role in the excretion of metabolic wastes and in the regulation of extracellular fluid volume, electrolyte composition, and acid–base balance.

In addition, the kidney synthesizes and releases hormones, such as renin and erythropoietin, and metabolizes vitamin D3 to the active 1,25-dihydroxy vitamin D3 form. A toxic insult to the kidney therefore could disrupt any or all of these functions and could have profound effects on total body metabolism.

FUNCTIONAL ANATOMY

Gross examination of a sagittal section of the kidney reveals three clearly demarcated anatomic areas: the cortex, medulla, and papilla (Figure 1). The cortex constitutes the major portion of the kidney and receives a disproportionately higher percentage (90%) of blood flow compared to the medulla (6%–10%) or papilla (1%–2%). The functional unit of the kidney, the nephron, may be considered in three portions: the vascular element, the glomerulus, and the tubular element.

The afferent and efferent arterioles, arranged in a series before and after the glomerular capillary tuft, respectively, are ideally situated to control glomerular capillary pressure and glomerular plasma flow rate.

Indeed, these arterioles are innervated by the sympathetic nervous system and contract in response to nerve stimulation, angiotensin II, vasopressin, endothelin, adenosine, and norepinephrine, affecting glomerular pressures and blood flow. The efferent arterioles draining the cortical glomeruli branch into a peritubular capillary network, whereas those draining the juxtamedullary glomeruli form a capillary loop, the vasa recta, supplying the medullary structures.

These post-glomerular capillary loops provide an efficient arrangement for delivery of nutrients to the post-glomerular tubular structures, delivery of wastes to the tubule for excretion, and return of reabsorbed electrolytes, nutrients, and water to the systemic circulation.

The glomerulus is a complex, specialized capillary bed composed primarily of endothelial cells that are characterized by an attenuated and fenestrated cytoplasm, visceral epithelial cells characterized by a cell body (podocyte) from which many trabeculae and pedicles (foot processes) extend, and a glomerular basement membrane (GBM), which is a trilamellar structure sandwiched between the endothelial and epithelial cells (Figure 2). A portion of the blood entering the glomerular capillary network is fractionated into a virtually protein-free and cell-free ultrafiltrate, which passes through Bowman's space and into the tubular portion of the nephron.

The formation of such an ultrafiltrate is the net result of the Starling forces that determine fluid movement across capillary beds, that is, the balance between transcapillary hydrostatic pressure and colloid oncotic pressure.

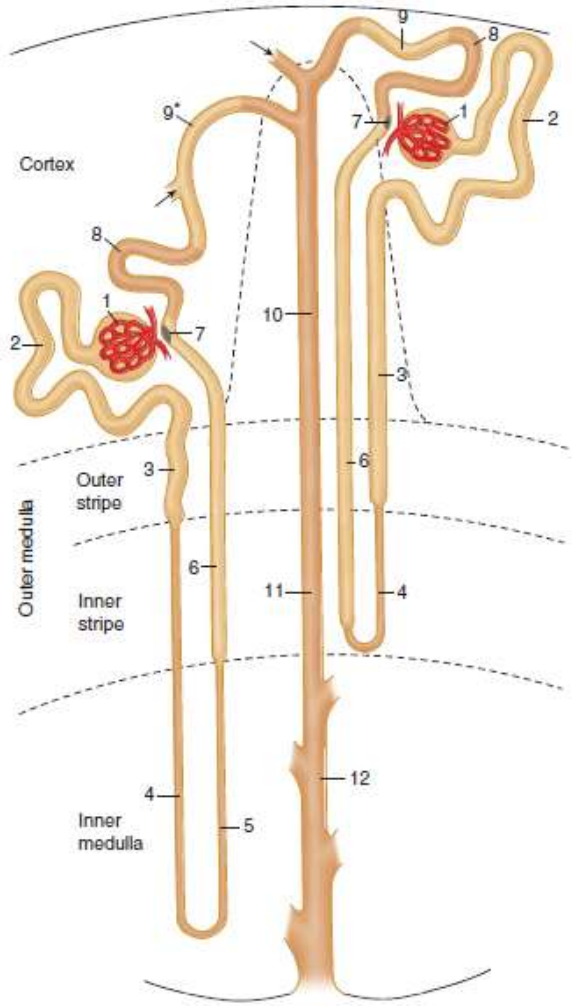

Figure 1. *Schematic of short- and long-looped nephrons and the collecting system.*

The filtration of macromolecules is inversely proportional to the molecular weight of a substance; thus, small molecules, such as inulin (molecular weight [MW] ~5,500), are freely filtered, whereas large molecules, such as albumin (MW 56,000–70,000), are restricted.

Filtration of anionic molecules tends to be restricted compared to that of neutral or cationic molecules of the same size. In particular, charge-selective properties of the glomerulus appear to be related to the anionic groups of the GBM coupled with the anionic coating of the epithelial and endothelial cells (Figure 2). These highly anionic components produce electrostatic repulsion and hinder the

circulation of polyanionic macromolecules, thereby markedly retarding passage of these molecules across the filtration barrier.

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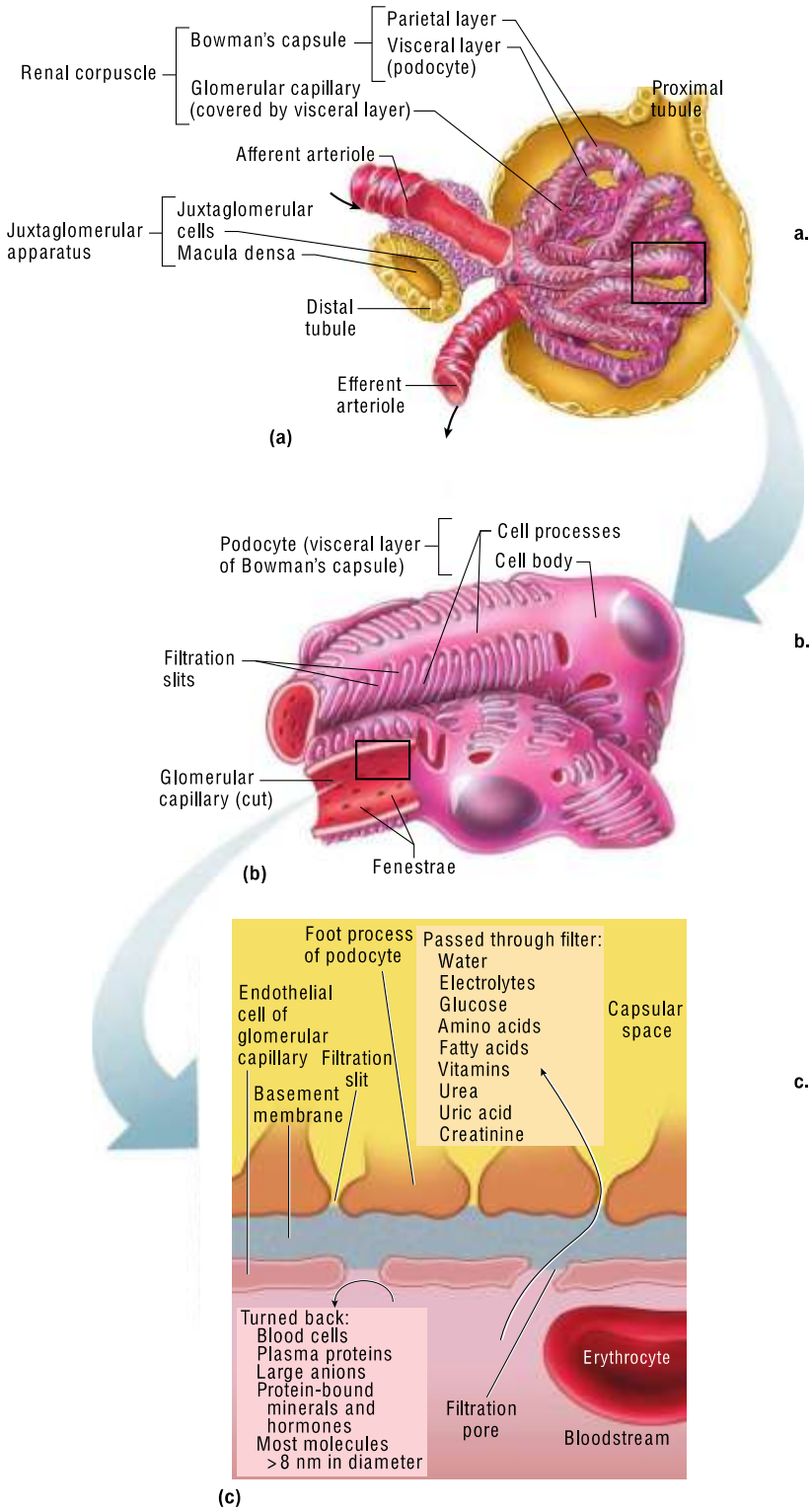

a. Blood flows into the glomerulus through the afferent arterioles and leaves the glomerulus through the efferent arterioles. The proximal tubule exits Bowman's capsule.

b. Podocytes of Bowman's capsule surround the capillaries. Filtration slits between the podocytes allow fluid to pass into Bowman's capsule. The glomerulus is composed of capillary endothelium that is fenestrated. Surrounding the endothelial cells is a basement membrane.

c. Substances in the blood are filtered through capillary pores between endothelial cells (single layer). The filtrate then passes across the basement membrane and through filtration slit between the foot processes (also called pedicels) and enters the capsular space. From here, the filtrate is transported to the lumen of the proximal convoluted tubule.

Figure 2:

Proximal Tubule

The proximal tubule consists of three discrete segments: the S 1 (pars convoluta), S 2 (transition between pars convoluta and pars recta), and S 3 (the pars recta) segments (Figure 1). The formation of urine is a highly complex and integrated process in which the volume and composition of the glomerular filtrate is progressively altered as fluid passes through each of the different tubular segments. The proximal tubule is the workhorse of the nephron, as it reabsorbs approximately 60% to 80% of solute and water filtered at the glomerulus. Toxicant-induced injury to the proximal tubule therefore will have major consequences to water and solute balance. The proximal tubule contains numerous transport systems capable of driving concentrative transport of many metabolic substrates, including amino acids, glucose, and citric acid cycle intermediates.

The proximal tubule also reabsorbs virtually all the filtered low molecular- weight proteins by specific endocytotic protein reabsorption processes. In addition, small linear peptides may be hydrolyzed by peptidases associated with the proximal tubular brush border. An important excretory function of the proximal tubule is secretion of weak organic anions and cations by specialized transporters that drive concentrative movement of these ions from post-glomerular blood into proximal tubular cells, followed by secretion into tubular fluid.

Loop of Henle, Distal Tubule and Collecting Duct

The thin descending and ascending limbs and the thick ascending limb of the loop of Henle are critical to the processes involved in urinary concentration (Figure 1). Approximately 25% of the filtered Na^+ and K^+ and 20% of the filtered water are reabsorbed by the segments of the loop of Henle.

The late distal tubule, cortical collecting tubule, and medullary collecting duct perform the final regulation and fine-tuning of urinary volume and composition. The remaining Na^+ is reabsorbed in conjunction with K+ and H+ secretion in the late distal tubule and cortical collecting tubule. The combination of medullary and papillary hypertonicity generated by countercurrent multiplication and the action of antidiuretic hormone (ADH, vasopressin) serve to enhance water permeability of the medullary collecting duct. Chemicals that interfere with ADH synthesis, secretion, or action therefore may impair concentrating ability.

PATHOPHYSIOLOGIC RESPONSES OF THE KIDNEY

Acute Kidney Injury

One of the most common manifestations of nephrotoxic damage is acute renal failure or acute kidney injury (AKI). AKI is a group of syndromes that comprises multiple causative factors and occurs in a variety of settings with varied clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure.

Any decline in GFR is complex and may result from prerenal factors (renal vasoconstriction, intravascular volume depletion, and insufficient cardiac output), postrenal factors (ureteral or bladder obstruction), and intrarenal factors (glomerulonephritis, tubular cell injury, death, and loss resulting in back leak; renal vasculature damage, interstitial nephritis) (Figure 3).

The pre- and postrenal factors can lead to decreased GFR. If a chemical causes tubular damage directly, then tubular casts can cause tubular obstruction, increased tubular pressure, and decreased GFR. The tubular damage may result in epithelial cell death/loss, leading to back leak of glomerular filtrate and a decrease in GFR.

Extensive evidence supports the idea that endothelial injury and inflammatory cells play a role in ischemia-induced AKI.

It is thought that more than 90% of AKI mediated by intrarenal factors is the result of ischemia/reperfusion injury or nephrotoxicity.

Although chemically induced AKI can be initiated by proximal tubular cell injury, nephrotoxicants may also delay the recovery of renal function by inhibiting cellular repair and regeneration. It was been demonstrated that cisplatin impaired tubular regeneration resulting in prolonged renal dysfunction, effects that were in contrast to the regenerative response and renal functional recovery following tobramycin-induced nephrotoxicity.

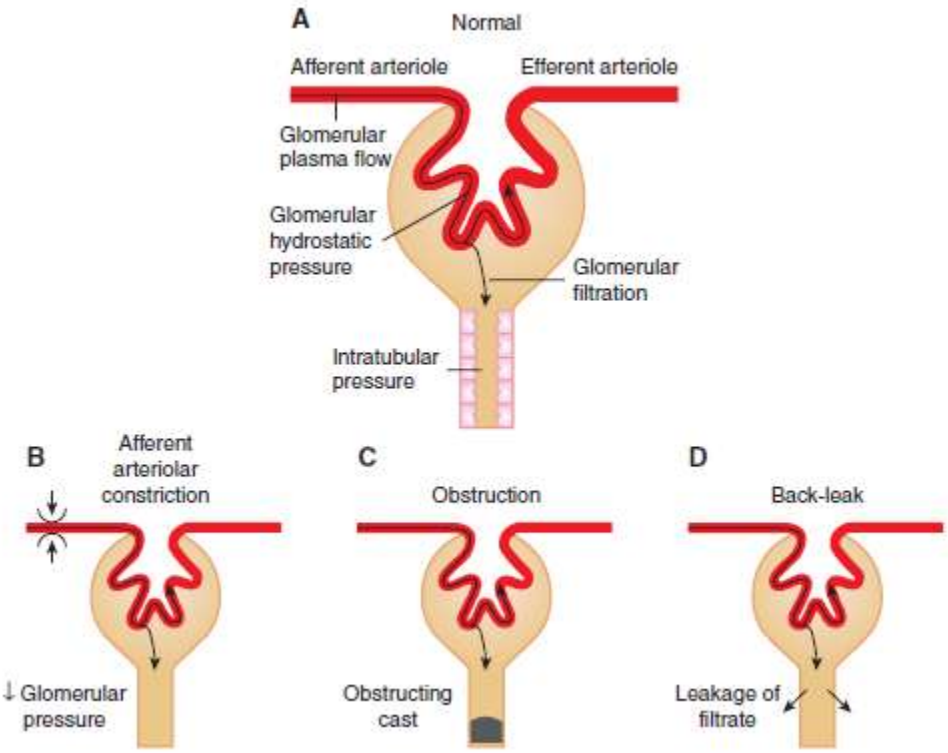

Figure 3. *Mechanisms of reduction of the GFR. (**A**), GFR depends on 4 factors: (1) adequate blood flow to the glomerulus; (2) adequate glomerular capillary pressure; (3) glomerular permeability; and (4) low intratubular pressure. (**B**), Afferent arteriolar constriction decreases GFR by reducing blood flow, resulting in diminished capillary pressure. (**C**), Obstruction of the tubular lumen by cast formation increases tubular pressure; when tubular pressure exceeds glomerular capillary pressure, filtration*

*decreases or ceases. (**D**), Back-leak occurs when the paracellular space between cells increases and the glomerular filtrate leaks into the extracellular space and bloodstream.*

Chronic Kidney Disease

It is generally believed that progression to chronic kidney disease (CKD) and end-stage renal failure is not simply a function of a primary renal insult per se but rather is related to secondary pathophysiologic processes triggered by the initial injury.

A low level of injury or inflammation may exist following AKI that ultimately leads to CKD and/or may sensitize the kidney to a second insult.

Progressive deterioration of renal function may occur with long-term exposure to a variety of chemicals (eg, analgesics, lithium, and cyclosporine). The progression of chronic renal disease, for example, has been postulated to be a consequence of the glomerular hemodynamic response to renal injury.

That is, following nephron loss, there are adaptive increases in glomerular pressures and flows that increase the single-nephron GFR of remnant viable nephrons. Although these compensatory mechanisms serve to maintain whole-kidney GFR, evidence has accumulated to suggest that, with time, these alterations are mal-adaptive and foster the progression of renal failure.

The compensatory increases in glomerular pressures and flows of the remnant glomeruli may result in mechanical damage to the capillaries due to increased shear stress on the endothelium and damage to the glomerular capillary wall, leading to altered permeabilities, and mesangial thickening due to increased transcapillary flux and local deposition of macromolecules. Other factors likely to play a role in the pathogenesis of chronic renal failure include growth promoters and inhibitors, increased

extracellular matrix deposition, reactive oxygen species (ROS), lipid accumulation, and tubulointerstitial injury.

Reasons for the Susceptibility of the Kidney to Toxicity

The unusual susceptibility of the mammalian kidney to the toxic effects of noxious chemicals can be attributed in part to the unique physiologic and anatomic features of this organ. Although the kidneys constitute only 0.5% of total body mass, they receive about 20% to 25% of the resting cardiac output. Consequently, any drug or chemical in the systemic circulation will be delivered to these organs in relatively high amounts. The processes involved in forming concentrated urine also serve to concentrate potential toxicants in the tubular fluid. As water and electrolytes are reabsorbed from the glomerular filtrate, chemicals in the tubular fluid may be concentrated, thereby driving passive diffusion of toxicants into tubular cells. Therefore, a nontoxic concentration of a chemical in the plasma may reach toxic concentrations in the kidney.

Finally, renal transport, accumulation, and metabolism of xenobiotics contribute significantly to the susceptibility of the kidney (and specific nephron segments) to toxic injury.

In addition to intrarenal factors, the incidence and/or severity of chemically induced nephrotoxicity may be related to the sensitivity of the kidney to circulating vasoactive substances. Under these conditions, vasoconstrictors such as angiotensin II or vasopressin are increased. Normally, the actions of high circulating levels of vasoconstrictor hormones are counterbalanced by the actions of increased vasodilatory prostaglandins; thus, renal blood flow (RBF) and GFR are maintained. However, when prostaglandin synthesis is suppressed by NSAIDs, RBF declines markedly and AKI ensues, due to the unopposed actions of vasoconstrictors.

Site-Selective Injury

Many nephrotoxicants have their primary effects on discrete segments or regions of the nephron. For example, the proximal tubule is the primary target for most nephrotoxic antibiotics, antineoplastics, halogenated hydrocarbons, mycotoxins, and heavy metals, whereas the glomerulus is the primary site for immune complexes, the loop of Henle/collecting ducts for fluoride ions, and the medulla/papilla for chronically consumed analgesic mixtures. The reasons underlying this site-selective injury are complex but can be attributed in part to site-specific differences in blood flow, transport and accumulation of chemicals, physicochemical properties of the epithelium, reactivity of cellular/molecular targets, balance of bioactivation/detoxification reactions, cellular energetics, and/ or regenerative/repair mechanisms.

Glomerular Injury

The glomerulus is the initial site of chemical exposure within the nephron, and a number of nephrotoxicants produce structural injury to this segment. In certain instances, chemicals alter glomerular permeability to proteins by altering the size- and charge-selective functions.

The decrease in charge selectivity is thought to result from a decrease in negatively charged sites, while the loss of size selectivity is thought to result from focal detachment of podocytes from the GBM. Cyclosporine, amphotericin B, and gentamicin are examples of chemicals that impair glomerular ultrafiltration without significant loss of structural integrity and decrease GFR.

A chemical may function as a hapten attached to some native protein (eg, tubular antigens released secondary to toxicity) or as a complete antigen and elicit an antibody response.

Proximal Tubular Injury

The proximal tubule is the most common site of toxicant-induced renal injury. The reasons for this relate in part to the selective

accumulation of xenobiotics into this segment of the nephron. For example, in contrast to the distal tubule, which is characterized by a relatively tight epithelium with high electrical resistance, the proximal tubule has a leaky epithelium, favoring the flux of compounds into proximal tubular cells. More importantly, tubular transport of organic anions and cations, low-molecular-weight proteins and peptides, GSH conjugates, and heavy metals is localized primarily if not exclusively to the proximal tubule. Thus, transport of these molecules will be greater in the proximal tubule than in other segments, resulting in proximal tubular accumulation and toxicity.

In addition to segmental differences in transport, segmental differences in cytochrome P450 and cysteine conjugate β-lyase activity also are contributing factors to the enhanced susceptibility of the proximal tubule. Both enzyme systems are localized almost exclusively in the proximal tubule, with negligible activity in the glomerulus, distal tubules, or collecting ducts. Thus, nephrotoxicity requiring P450 and β-lyase-mediated bioactivation will most certainly be localized in the proximal tubule. Indeed, the site of proximal tubular bioactivation contributes at least in part to the proximal tubular lesions produced by chloroform (via cytochrome P450) and by haloalkene *S*-conjugates (via cysteine β-lyase).

Finally, proximal tubular cells appear to be more susceptible to ischemic injury than distal tubular cells. Therefore, the proximal tubule will likely be the primary site of toxicity for chemicals that interfere with RBF, cellular energetics, and/or mitochondrial function.

Loop of Henle/Distal Tubule/ Collecting Duct Injury

Chemically induced injury to the more distal tubular structures, compared to the proximal tubule, is an infrequent occurrence.

Functional abnormalities at these sites manifest primarily as impaired concentrating ability and/or acidification defects. Drugs that have been associated with acute injury to the more distal tubular structures include amphotericin B, cisplatin, and methoxyflurane. Each of these drugs induces an ADH-resistant polyuria, suggesting that the concentrating defect occurs at the level of the medullary thick ascending limb and/or the collecting duct.

Fluoride inhibits sodium chloride reabsorption in the thick ascending limb and inhibits ADH-mediated reabsorption of water, possibly due to disruption in adenylate cyclase.

Toxicology
Toxic Responses of the Kidney

The functional integrity of the mammalian kidney is vital to total body homeostasis because the kidney plays a principal role in the excretion of metabolic wastes and in the regulation of extracellular fluid volume, electrolyte composition, and acid–base balance.

In addition, the kidney synthesizes and releases hormones, such as renin and erythropoietin, and metabolizes vitamin D3 to the active 1,25-dihydroxy vitamin D3 form. A toxic insult to the kidney therefore could disrupt any or all of these functions and could have profound effects on total body metabolism.

FUNCTIONAL ANATOMY

Gross examination of a sagittal section of the kidney reveals three clearly demarcated anatomic areas: the cortex, medulla, and papilla (Figure 1). The cortex constitutes the major portion of the kidney and receives a disproportionately higher percentage (90%) of blood flow compared to the medulla (6%–10%) or papilla (1%–2%). The functional unit of the kidney, the nephron, may be considered in three portions: the vascular element, the glomerulus, and the tubular element.

The afferent and efferent arterioles, arranged in a series before and after the glomerular capillary tuft, respectively, are ideally situated to control glomerular capillary pressure and glomerular plasma flow rate.

Indeed, these arterioles are innervated by the sympathetic nervous system and contract in response to nerve stimulation, angiotensin II, vasopressin, endothelin, adenosine, and norepinephrine, affecting glomerular pressures and blood flow. The efferent arterioles draining the cortical glomeruli branch into a peritubular capillary network, whereas those draining the juxtamedullary glomeruli form a capillary loop, the vasa recta, supplying the medullary structures.

These post-glomerular capillary loops provide an efficient arrangement for delivery of nutrients to the post-glomerular tubular structures, delivery of wastes to the tubule for excretion, and return of reabsorbed electrolytes, nutrients, and water to the systemic circulation.

The glomerulus is a complex, specialized capillary bed composed primarily of endothelial cells that are characterized by an attenuated and fenestrated cytoplasm, visceral epithelial cells characterized by a cell body (podocyte) from which many trabeculae and pedicles (foot processes) extend, and a glomerular basement membrane (GBM), which is a trilamellar structure sandwiched between the endothelial and epithelial cells (Figure 2). A portion of the blood entering the glomerular capillary network is fractionated into a virtually protein-free and cell-free ultrafiltrate, which passes through Bowman's space and into the tubular portion of the nephron.

The formation of such an ultrafiltrate is the net result of the Starling forces that determine fluid movement across capillary beds, that is, the balance between transcapillary hydrostatic pressure and colloid oncotic pressure.

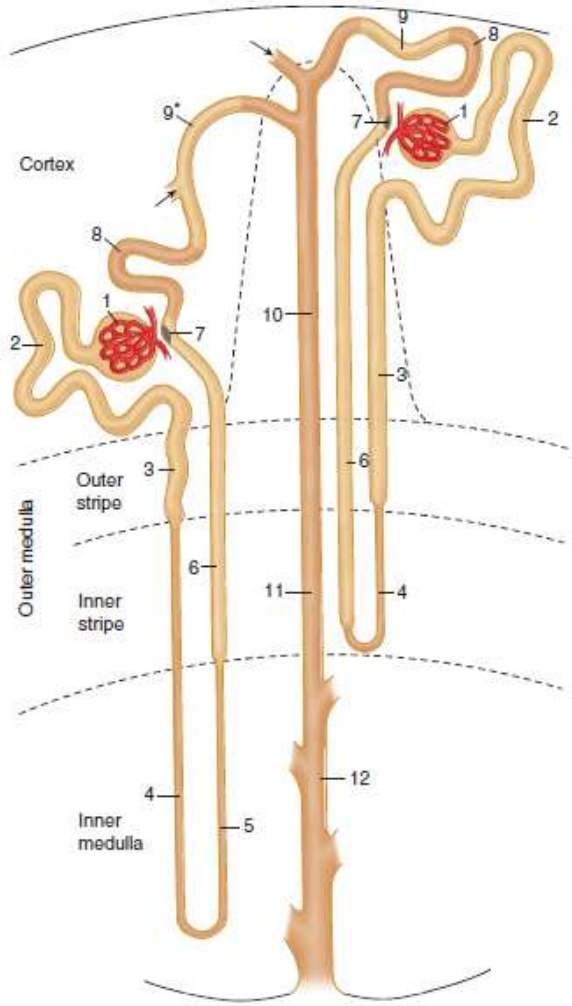

Figure 1. *Schematic of short- and long-looped nephrons and the collecting system.*

The filtration of macromolecules is inversely proportional to the molecular weight of a substance; thus, small molecules, such as inulin (molecular weight [MW] ~5,500), are freely filtered, whereas large molecules, such as albumin (MW 56,000–70,000), are restricted.

Filtration of anionic molecules tends to be restricted compared to that of neutral or cationic molecules of the same size. In particular, charge-selective properties of the glomerulus appear to be related to the anionic groups of the GBM coupled with the anionic coating of the epithelial and endothelial cells (Figure 2). These highly anionic components produce electrostatic repulsion and hinder the

circulation of polyanionic macromolecules, thereby markedly retarding passage of these molecules across the filtration barrier.

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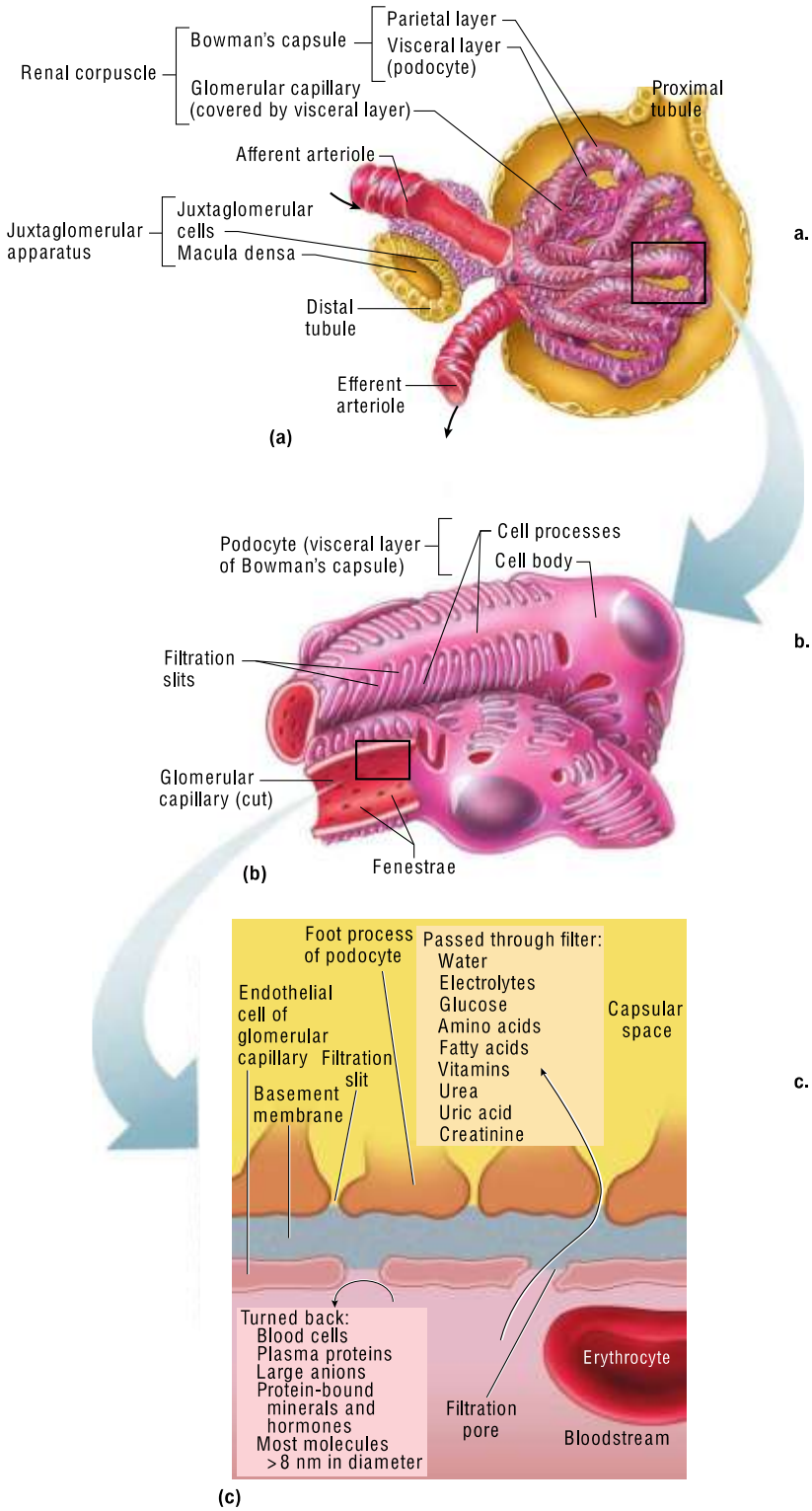

a. Blood flows into the glomerulus through the afferent arterioles and leaves the glomerulus through the efferent arterioles. The proximal tubule exits Bowman's capsule.

b. Podocytes of Bowman's capsule surround the capillaries. Filtration slits between the podocytes allow fluid to pass into Bowman's capsule. The glomerulus is composed of capillary endothelium that is fenestrated. Surrounding the endothelial cells is a basement membrane.

c. Substances in the blood are filtered through capillary pores between endothelial cells (single layer). The filtrate then passes across the basement membrane and through filtration slit between the foot processes (also called pedicels) and enters the capsular space. From here, the filtrate is transported to the lumen of the proximal convoluted tubule.

Figure 2:

Proximal Tubule

The proximal tubule consists of three discrete segments: the S 1 (pars convoluta), S 2 (transition between pars convoluta and pars recta), and S 3 (the pars recta) segments (Figure 1). The formation of urine is a highly complex and integrated process in which the volume and composition of the glomerular filtrate is progressively altered as fluid passes through each of the different tubular segments. The proximal tubule is the workhorse of the nephron, as it reabsorbs approximately 60% to 80% of solute and water filtered at the glomerulus. Toxicant-induced injury to the proximal tubule therefore will have major consequences to water and solute balance. The proximal tubule contains numerous transport systems capable of driving concentrative transport of many metabolic substrates, including amino acids, glucose, and citric acid cycle intermediates.

The proximal tubule also reabsorbs virtually all the filtered low molecular- weight proteins by specific endocytotic protein reabsorption processes. In addition, small linear peptides may be hydrolyzed by peptidases associated with the proximal tubular brush border. An important excretory function of the proximal tubule is secretion of weak organic anions and cations by specialized transporters that drive concentrative movement of these ions from post-glomerular blood into proximal tubular cells, followed by secretion into tubular fluid.

Loop of Henle, Distal Tubule and Collecting Duct

The thin descending and ascending limbs and the thick ascending limb of the loop of Henle are critical to the processes involved in urinary concentration (Figure 1). Approximately 25% of the filtered Na^+ and K^+ and 20% of the filtered water are reabsorbed by the segments of the loop of Henle.

The late distal tubule, cortical collecting tubule, and medullary collecting duct perform the final regulation and fine-tuning of urinary volume and composition. The remaining Na^+ is reabsorbed in conjunction with K+ and H+ secretion in the late distal tubule and cortical collecting tubule. The combination of medullary and papillary hypertonicity generated by countercurrent multiplication and the action of antidiuretic hormone (ADH, vasopressin) serve to enhance water permeability of the medullary collecting duct. Chemicals that interfere with ADH synthesis, secretion, or action therefore may impair concentrating ability.

PATHOPHYSIOLOGIC RESPONSES OF THE KIDNEY

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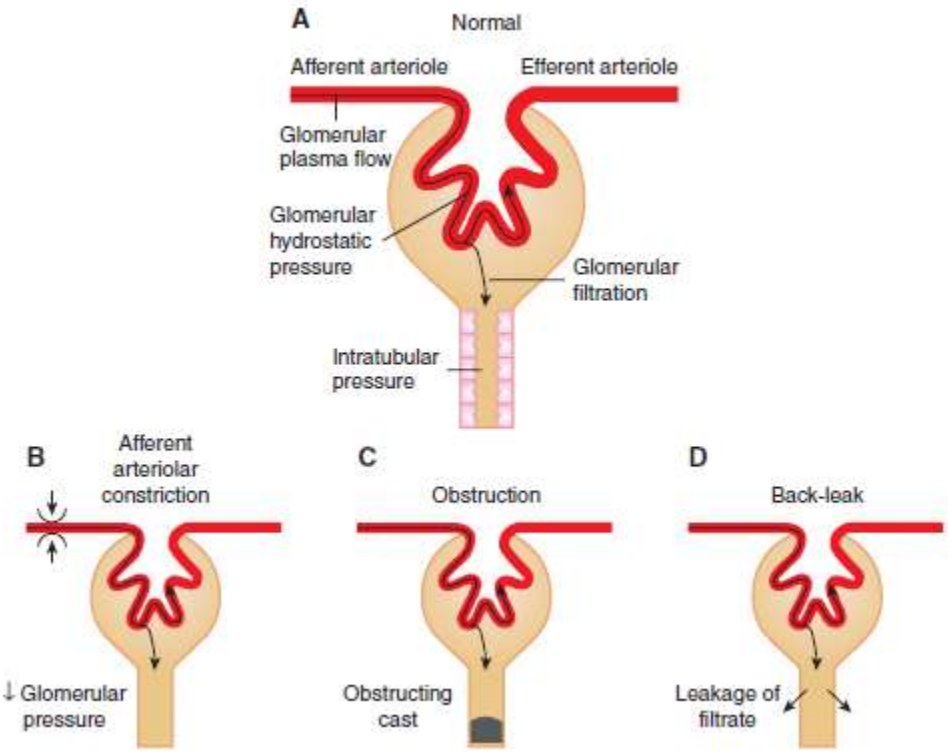

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Toxicology
SPECIFIC NEPHROTOXICANTS

Heavy Metals
Many metals, including cadmium, chromium, lead, mercury, platinum, and uranium, are nephrotoxic. It is important to recognize that the nature and severity of metal nephrotoxicity varies with respect to its form. For example, salts of inorganic mercury produce a greater degree of renal injury and a lesser degree of neurotoxicity than do organic mercury compounds. Metals may cause toxicity through their ability to bind to sulfhydryl groups. For example, the affinity of mercury for sulfhydryl groups is very high and is about 10 orders of magnitude higher than the affinity of mercury for carbonyl or amino groups. Thus, metals may cause renal cellular injury through their ability to bind to sulfhydryl groups of critical proteins within the cells and thereby inhibit their normal function.

Mercury
Humans and animals are exposed to elemental mercury vapor, inorganic mercurous and mercuric salts, and organic mercuric compounds through the environment. Administered elemental mercury is rapidly oxidized in erythrocytes or tissues to inorganic mercury, and thus the tissue distribution of elemental and inorganic mercury is similar. Due to its high affinity for sulfhydryl groups, virtually all of the Hg^{2+} found in blood is bound to cells—albumin, other sulfhydryl-containing proteins, glutathione, and cysteine. The kidneys are the primary target organs for accumulation of Hg^{2+}, and the S 3 segment of the proximal tubule is the initial site of toxicity.

As the dose or duration of treatment increases, the S 1 and S 2 segments may be affected. Renal uptake of Hg^{2+} is very rapid with as much as 50% of a nontoxic dose of Hg^{2+} found in the kidneys within a few hours of exposure. Considering the fact that virtually all of the Hg^{2+} found in blood is bound to an endogenous ligand, it is likely that the luminal and/or basolateral transport of Hg^{2+} into the proximal tubular epithelial cell is through cotransport of Hg^{2+} with an endogenous ligand such as glutathione, cysteine, or albumin, or through some plasma membrane Hg^{2+} -ligand complex. Current evidence indicates that at least two mechanisms are involved in the proximal tubular uptake of Hg^{2+} (Fig. 1). One mechanism appears to involve the apical activity of γ-glutamyl transpeptidase, cysteinylglycinase, and the transport of Cys–S–Hg–S–Cys through one of more amino acid transporters. Basolateral membrane transport is likely to be mediated by the organic anion transport system.

The acute nephrotoxicity induced by $HgCl_2$ is characterized by proximal tubular necrosis and AKI within 24 to 48 hours after administration. Early markers of $HgCl_2$ –induced renal dysfunction include an increase in the urinary excretion of brush-border enzymes such as alkaline phosphatase and γ-GT, suggesting that the brush border may be an initial target of $HgCl_2$. As injury progresses, tubular reabsorption of solutes and water decreases and there is an increase in the urinary excretion of glucose, amino acids, albumin, and other proteins. Associated with the increase in injured proximal tubules is a decrease and progressive decline in the GFR.

The reduction in GFR results from the glomerular injury, tubular injury, and/or vasoconstriction. If the decline in renal function is not too severe, the remaining proximal tubular cells undergo a proliferative response and renal function returns over time. Chelation therapy with 2,3-dimercaptopropane-1-sulfonate or 2,3-mesodimercaptosuccinic acid is used for the treatment for mercury-induced nephrotoxicity.

Changes in mitochondrial morphology and function are very early events following HgCl 2 administration, supporting the hypothesis that mitochondrial dysfunction is an early and important contributor to inorganic mercury-induced cell death along the proximal tubule. Other studies have suggested that oxidative stress and disregulation of Ca^{2+} homeostasis plays an important role in $HgCl_2$ -induced renal injury.

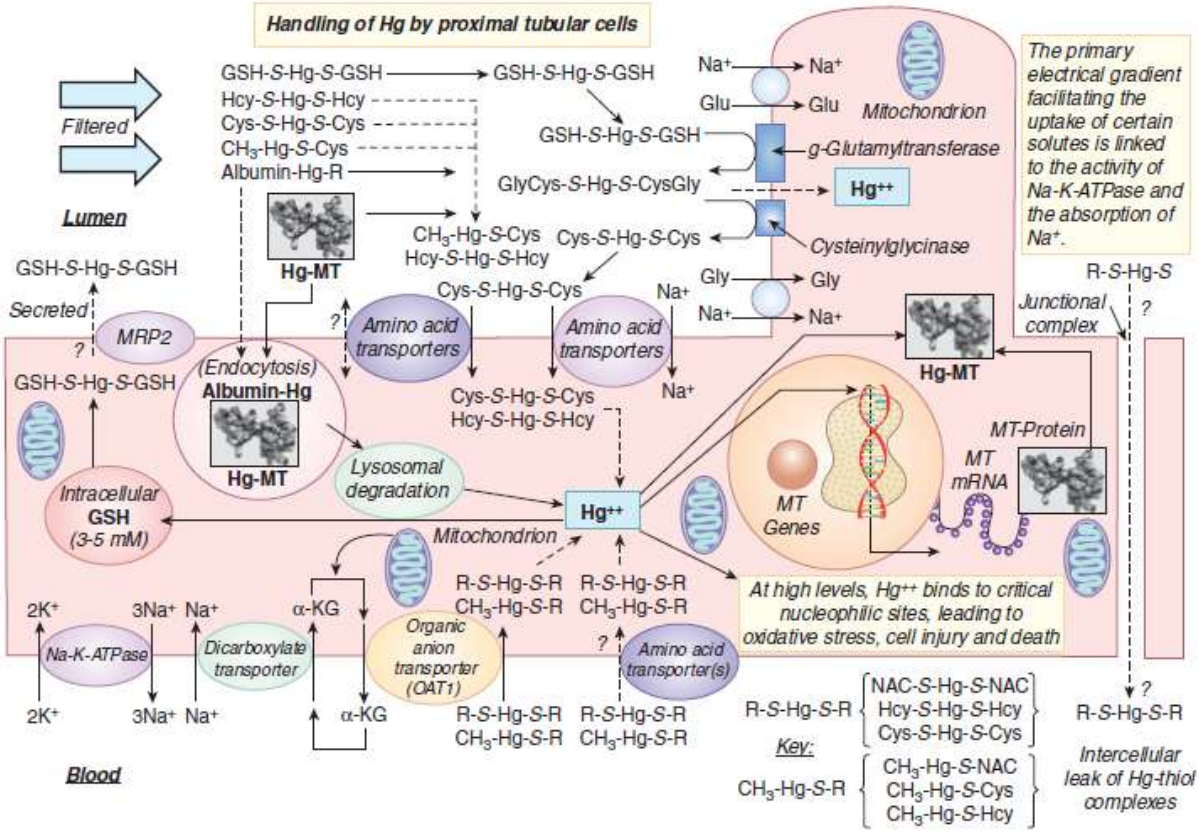

Figure 1. *Cellular transport of* Hg^{2+} *. Proximal tubular uptake of inorganic mercury is thought to be the result of the transport of* Hg^{2+} *conjugates (eg, diglutathione-Hg* $^{2+}$ *conjugate [GSHHg-GSH], dicysteine-Hg* $^{2+}$ *conjugate [CYS-HG-CYS]). At the luminal membrane, GSH-Hg-GSH is metabolized by γ-GT and a dipeptidase to form CYS-HG-CYS. CYS-HG-CYS may be taken up by amino acid transporters. It is not clear whether albumin-Hg-R conjugates are transported across the liminal membrane in vivo. At the basolateral membrane,* Hg^{2+} *-conjugates appear to be transported by organic anion transporters OAT1 and OAT3.*

Cadmium

Chronic exposure of nonsmoking humans and animals to cadmium is primarily through food and results in nephrotoxicity. In the workplace, inhalation of cadmium-containing dust and fumes is the major route of exposure. Cadmium has a half-life of greater than 10 years in humans and thus accumulates in the body over time. Approximately 50% of the body burden of cadmium can be found in the kidney and nephrotoxicity can be observed when Cd concentrations exceed 50 μg/g kidney wet weight.

Cadmium produces proximal tubule dysfunction (S 1 and S2 segments) and injury characterized by increases in urinary excretion of glucose, amino acids, calcium, and cellular enzymes. This injury may progress to a chronic interstitial nephritis. A very interesting aspect of cadmium nephrotoxicity is the role of metallothioneins. Metallothioneins are a family of low-molecular-weight, cysteine-rich metal-binding proteins that have a high affinity for cadmium and other heavy metals.

In general, the mechanism by which metallothionein is thought to play a role in cadmium and heavy metal toxicity is through its ability to bind to a heavy metal and thereby render it biologically inactive. This assumes that the unbound or "free" concentration of the metal is the toxic species. Metallothionein production can be induced by low, nontoxic concentrations of metals.

Following an oral exposure to $CdCl_2$, Cd^{2+} is thought to reach the kidneys both as Cd^{2+} and as a Cd^{2+} -metallothionein complex formed and released either from intestinal cells or hepatocytes. The Cd^{2+} -metallothionein complex is freely fi ltered by the glomerulus and reabsorption by the proximal tubule is probably by endocytosis and is limited. Inside the tubular cells, it is thought that lysosomal degradation of the Cd^{2+} -metallothionein results in the release of "free" Cd^{2+}, which, in turn, induces renal metallothionein production. Once the renal metallothionein pool is saturated, "free" Cd^{2+} initiates injury.

Halogenated Hydrocarbons

Halogenated hydrocarbons are a diverse class of compounds and are used extensively as chemical intermediates, solvents, and pesticides. Consequently, humans are exposed to these compounds not only in the workplace but also through the environment. Numerous toxic effects have been associated with acute and chronic exposure to halogenated hydrocarbons, including nephrotoxicity.

Chloroform

Chloroform produces nephrotoxicity in a variety of species, with some species being more sensitive than others. The primary cellular target is the proximal tubule, with no primary damage to the glomerulus or the distal tubule. Proteinuria, glucosuria, and increased BUN levels are all characteristic of chloroform-induced nephrotoxicity. The nephrotoxicity produced by chloroform is linked to its metabolism by renal cytochrome P450 and the formation of a reactive intermediate that binds covalently to nucleophilic

groups on cellular macromolecules. Cytochrome P450 biotransforms chloroform to trichloromethanol, which is unstable and releases HCl to form phosgene. Phosgene can react with (1) water to produce 2HCl + CO_2 , (2) two molecules of glutathione to produce diglutathionyl dithiocarbonate, (3) cysteine to produce 2-oxothizolidine-4-carboxylic acid, or (4) cellular macromolecules to initiate toxicity (see figure 2).

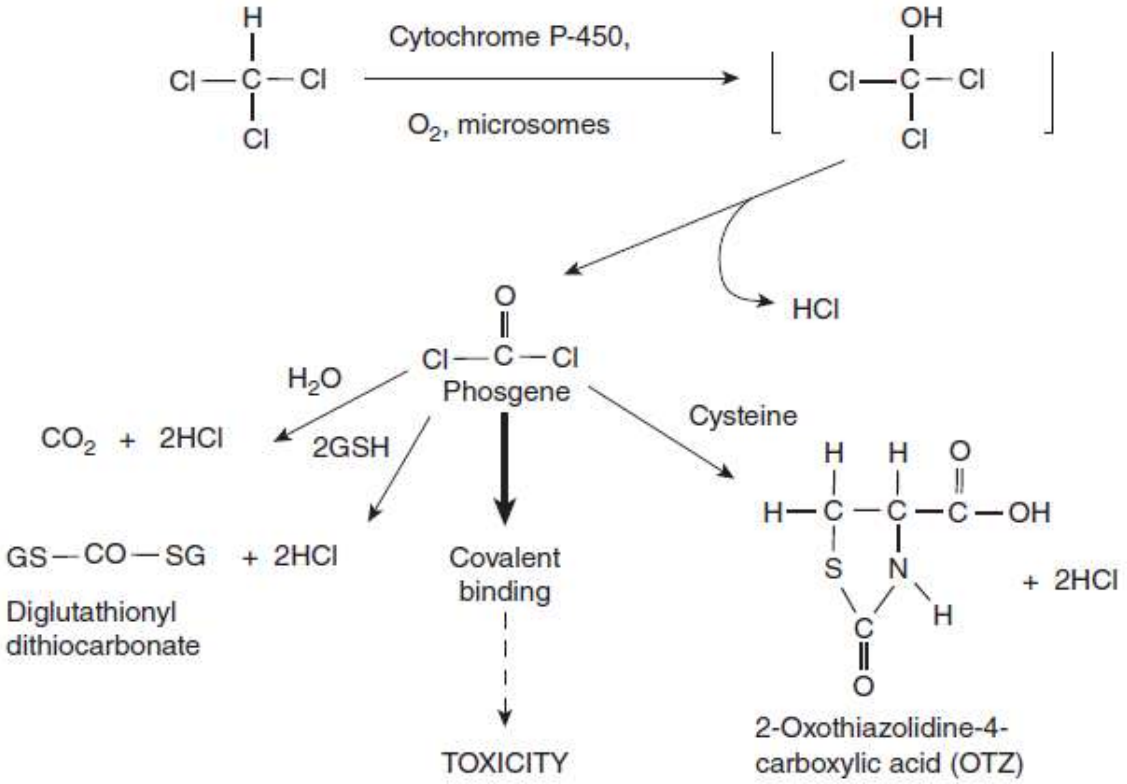

Figure 2: *Proposed mechanism of chloroform biotransformation. Chloroform undergoes cytochrome P450 - catalyzed conversion to trichloromethanol (CCl 3 - OH), which spontaneously decomposes to form phosgene. Phosgene is highly reactive and may be detoxified by reacting with sulfhydryl - containing chemicals (cysteine, glutathione [GSH]). Alternately, phosgene can react with sulfhydryl groups on protein, leading to covalent binding and possibly to toxicity.*

Therapeutic Agents:
Nonsteroidal Anti-Infl ammatory Drugs

NSAIDs such as aspirin, ibuprofen, naproxen, indomethacin, and cyclooxygenase- 2 inhibitors (eg, celecoxib) are extensively used as analgesics and anti-inflammatory drugs and produce their therapeutic effects through the inhibition of prostaglandin synthesis. At least three different types of nephrotoxicity have been associated with NSAID administration. AKI may occur within hours of a large dose of a NSAID, is usually reversible upon withdrawal of the drug, and is characterized by decreased RBF and GFR and by oliguria.

When the normal production of vasodilatory prostaglandins (eg, PGE 2 , PGI 2) is inhibited by NSAIDs, vasoconstriction induced by circulating catecholamines and

angiotensin II is unopposed, resulting in decreased RBF and ischemia. A number of risk factors (eg, renal insufficiency, congestive heart failure, hepatic cirrhosis, hemorrhage, hypertension, sepsis, diabetes) are known to facilitate the development of AKI following NSAIDs consumption.
In contrast, chronic consumption of combinations of NSAIDs and/or APAP (>3 years) results in an often irreversible form of nephrotoxicity known as analgesic nephropathy.
Impaired urinary concentration and acidification are the earliest clinical manifestations. The primary lesion in this nephropathy is papillary necrosis with chronic interstitial nephritis. Initial changes are to the medullary interstitial cells and are followed by degenerative changes to the medullary loops of Henle and medullary capillaries.

The mechanism by which NSAIDs produce analgesic nephropathy is not known, but may result from chronic medullary/papillary ischemia secondary to renal vasoconstriction. Other studies have suggested that a reactive intermediate is formed in the cells that, in turn, initiates an oxidative stress, or binds covalently to critical cellular macromolecules.
The third, even though rare, type of nephrotoxicity associated with NSAIDs is an interstitial nephritis with a mean time of NSAID exposure to development of approximately five months. This nephrotoxicity is characterized by a diffuse interstitial edema with mild-to-moderate infiltration of inflammatory cells. Patients normally present with elevated serum creatinine, proteinuria, and nephritic syndrome. If NSAIDs are discontinued, renal function improves in one to three months.

Aminoglycosides

Aminoglycoside antibiotics (Figure 3), such as gentamicin, amikacin, and netilmicin, are powerful drugs for the treatment of serious gram - negative infections.
However, about 10% of patients treated with aminoglycosides will develop moderate but significant declines in glomerular filtration rate and elevations in serum creatinine concentration. The therapeutic utility of aminoglycosides is limited by nephrotoxicity, ototoxicity and neuromuscular junction blockade. Aminoglycoside nephrotoxicity is characterized by proximal tubular necrosis, proteinuria, and a profound decline in glomerular filtration rate.
Aminoglycoside antibiotics are organic polycations and carry net positive charges (Figure 3). These compounds have relatively low volumes of distribution, and the primary route of elimination is by renal excretion. Gentamicin, a typical nephrotoxic aminoglycoside, is freely filtered at the glomerulus and appears to be reabsorbed via active transport processes at the proximal tubular brush border.
Renal dysfunction by aminoglycosides is characterized by a nonoliguric renal failure with reduced GFR and an increase in serum creatinine and BUN. Nonoliguric acute renal failure appears within 5 – 7 days after aminoglycoside therapy is initiated. Polyuria is an early event following aminoglycoside administration and may be due to inhibition of chloride transport in the thick ascending limb. Within 24 hours, increases in urinary brush-border enzymes, glucosuria, aminoaciduria, and proteinuria are observed. Aminoglycosides are highly polar cations; they are almost exclusively filtered by the glomerulus and excreted unchanged.

Filtered aminoglycosides undergo proximal tubular reabsorption by binding to anionic phospholipids in the brush border, followed by endocytosis and sequestration in lysosomes of the S 1 and S 2 segments of proximal tubules (figure 4).

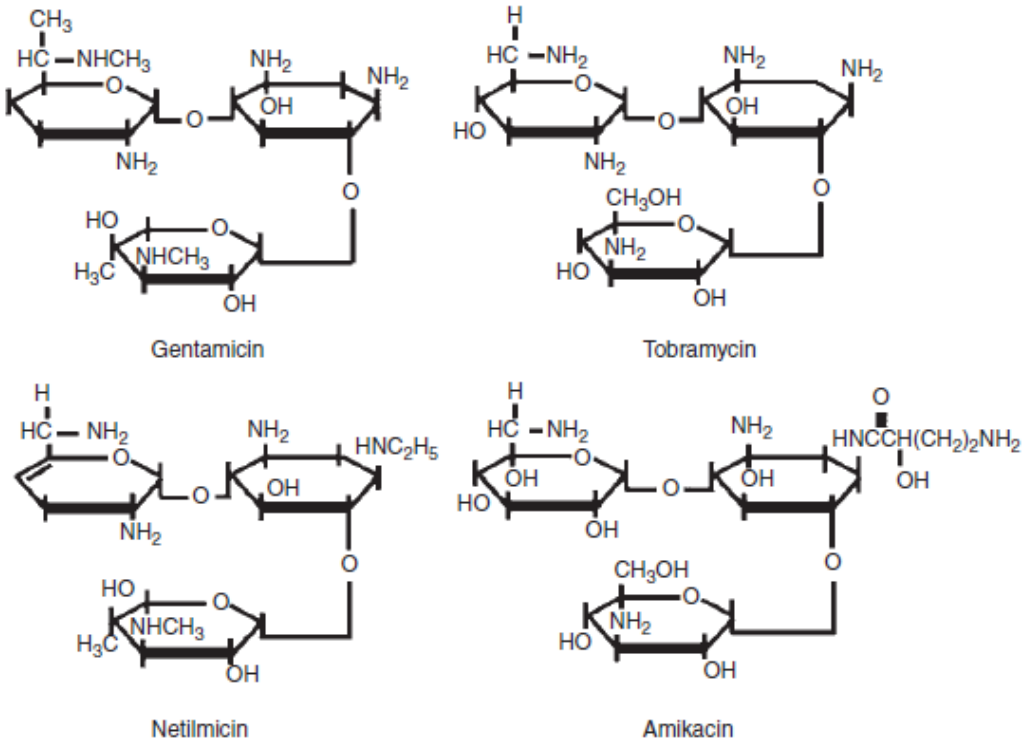

Figure 3: *Chemical structures of several aminoglycoside antibiotics*

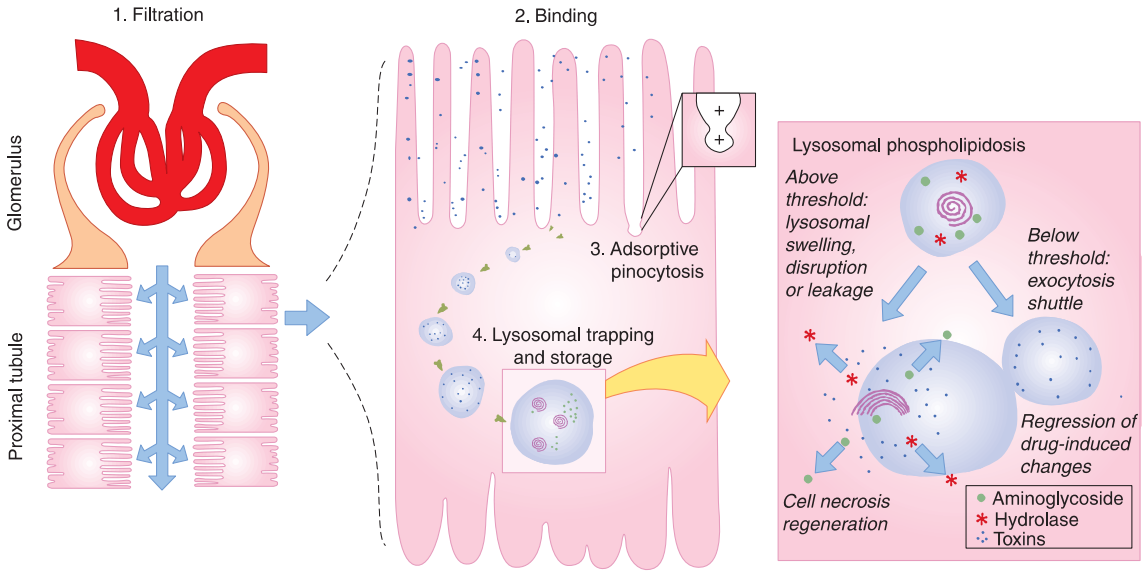

Figure 4: *Renal handling of aminoglycosides: (1) glomerular filtration, (2) binding to the brush-border membranes of the proximal tubule, (3) pinocytosis, and (4) storage in the lysosomes.*

Several mechanisms have been proposed to account for gentamicin cytotoxicity, including:
(1) lysosomal damage.
(2) Altered phospholipid metabolism.
(3) Inhibition of critical intracellular enzymes.
(4) Inhibition of mitochondrial respiration.
(5) Lipid peroxidation.
(6) Misreading of mRNA.

The earliest lesion observed following clinically relevant doses of aminoglycosides is an increase in the size and number of lysosomes. These lysosomes contain *myeloid bodies* , which are electron-dense lamellar structures containing undergraded phospholipids. The renal phospholipidosis produced by the aminoglycosides is thought to occur through their inhibition of lysosomal hydrolases, such as sphingomyelinase and phospholipases. One hypothesis suggests that the lysosomes become progressively distended until they rupture, releasing lysosomal enzymes and high concentrations of aminoglycosides into the cytoplasm (Figure 4). The released lysosomal contents can interact with various membranes and organelles and trigger cell death. Another mechanism of aminoglycoside nephrotoxicity includes a decrease in *K*f and GFR.

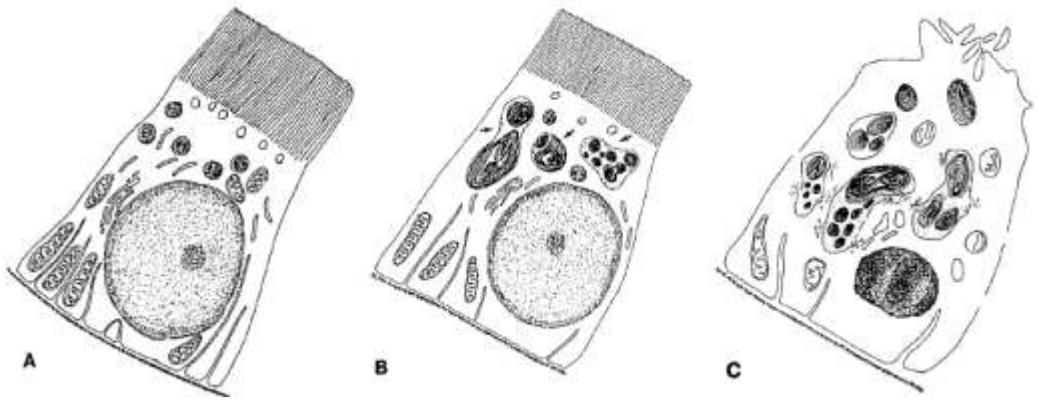

Figure 4: Ultrastructural alterations induced in proximal tubular cells during aminoglycoside treatment. (A) Control. Changes detected early on and at low doses (B) consist mainly of the enlargement of lysosomes, which most likely occurs by fusion of preexisting structures and which is caused by the progressive deposition of polar lipids which adopt a concentric lamellar disposition (myelin-like structures, most commonly referred to as myeloid bodies); the other subcellular structures are usually well preserved. Later changes or changes observed with high doses (C) include the apparent rupture of lysosomes (with the release of myeloid bodies in the cytosol), extensive mitochondrial swelling and damage, dilatation of the endoplasmic reticulum cisternae, shedding of the apical brush-border villi, pericellular membrane discontinuities, and the occurrence of apoptotic nuclei. These alterations do not necessarily coexist in all cell.

Amphotericin B

One compound that has been associated with distal tubular injury is amphotericin B, a polyene antifungal agent used in the treatment of systemic mycoses caused by

opportunistic fungi. Clinical utility of amphotericin B is limited by its nephrotoxicity, characterized functionally by polyuria resistant to antidiuretic hormone administration, hyposthenuria, hypokalemia, and mild renal tubular acidosis.

Amphotericin B is highly lipophilic (Figure 5) and interacts with membrane lipid sterols, such as cholesterol, to disrupt membrane permeability. Because amphotericin is freely filtered, it achieves high concentrations in distal tubular fluid and easily forms complexes with cholesterol and other lipids present in distal tubular luminal membranes. Amphotericin effectively transforms the "tight" distal tubular epithelium into an epithelium leaky to water, H^+ and K^+. Functional abnormalities observed with amphotericin B are attenuated when the antifungal agent is administered as an emulsion formulation whereby amphotericin is incorporated into lipid micelles. Antifungal activity of emulsion - formulated amphotericin B is equivalent to the standard non - emulsion formulation, whereas polyuria and hyposthenuria are significantly reduced by emulsion formulation.

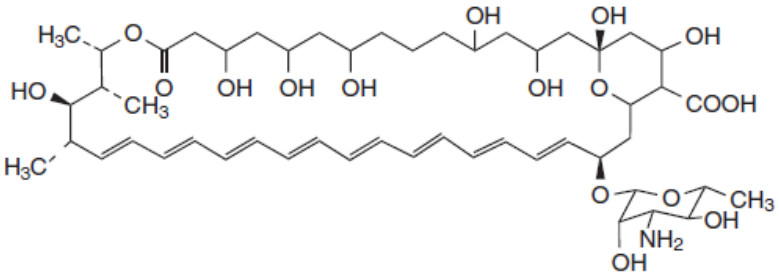

Figure 5: *Structure of amphotericin B.*

Oral hypoglycemic
Metformin

Metformin is in the biguanide class. It works by decreasing glucose production by the liver and increasing the insulin sensitivity of body tissues . Metformin treatment of people at a prediabetes stage of risk for type 2 diabetes may decrease their chances of developing the disease, although intensive physical exercise and dieting work significantly better for this purpose

It is the first-line medication for the treatment of type 2 diabetes, particularly in people who are overweight. It is also used in the treatment of polycystic ovary syndrome. Limited evidence suggests metformin may prevent the cardiovascular disease and cancer complications of diabetes. It is not associated with weight gain. Metformin is generally well tolerated. Common side effects include diarrhea, nausea and abdominal pain. High blood lactic acid level is a concern if the drug is prescribed inappropriately and in overly large doses. It should not be used in those with significant liver disease or kidney problems. While no clear harm comes from use during pregnancy, insulin is generally preferred for gestational diabetes.

Pharmacokinetics

Metformin has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly. Peak plasma concentrations (C_{max}) are reached within one to three hours of taking immediate-release metformin and four to eight hours with extended-release formulations. The plasma protein binding of metformin is negligible, as reflected by its very high apparent volume of distribution (300–1000 L after a single dose). Steady state is usually reached in one or two days .

Metformin is not metabolized. It is cleared from the body by tubular secretion and excreted unchanged in the urine; metformin is undetectable in blood plasma within 24 hours of a single oral dose. The average elimination half-life in plasma is 6.2 hours. Metformin is distributed to (and appears to accumulate in) red blood cells, with a much longer elimination half-life: 17.6 hours (reported as ranging from 18.5 to 31.5 hours in a single-dose study of nondiabetics).

Mechanism of action

Metformin's main effect is to decrease liver glucose production . Metformin decreases high blood sugar, primarily by suppressing liver glucose production (hepatic gluconeogenesis). The average patient with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one-third. The molecular mechanism of metformin is incompletely understood. Multiple potential mechanisms of action have been proposed, including; inhibition of the mitochondrial respiratory chain (complex I), activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), inhibition of mitochondrial glycerophosphate dehydrogenase, and an effect on gut microbiota . .

In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by inducing the phosphorylation of GLUT4 enhancer factor), decreases insulin-induced suppression of fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral use of glucose may be due to improved insulin binding to insulin receptors. The increase in insulin binding after metformin treatment has also been demonstrated in patients with NIDDM .

Medical uses

Type 2 diabetes : the American Diabetes Association recommend metformin as a first-line agent to treat type 2 diabetes .

Prediabetes:- Metformin treatment of people at a prediabetes stage of risk for type 2 diabetes may decrease their chances of developing the disease, although intensive physical exercise and dieting work significantly better for this purpose. In a large U.S. study known as the Diabetes Prevention Program, participants were divided into groups and given either placebo, metformin, or lifestyle intervention and followed for an average of three years

Polycystic ovary syndrome :- Antidiabetic therapy has been proposed as a treatment for polycystic ovary syndrome (PCOS), a condition frequently associated with insulin resistance, since the late 1980s. The use of metformin in PCOS was first reported in 1994, in a small study conducted at the University of the Andes,

Venezuela. The United Kingdom's National Institute for Health and Clinical Excellence recommended in 2004 that women with PCOS and a body mass index above 25 be given metformin for anovulation and infertility when other therapies fail to produce results. However, two clinical studies completed in 2006–2007 returned mostly negative results, with metformin performing no better than placebo, and a metformin-clomifene combination no better than clomifene alone. Reflecting this, subsequent reviews large randomized controlled trials in general have not shown the promise suggested by the early studies. UK and international clinical practice guidelines do not recommend metformin as a first-line treatment or do not recommend it at all, except for women with glucose intolerance. The guidelines suggest clomiphene as the first medication option and emphasize lifestyle modification independently from the drug treatment .

Gestational diabetes :- Several observational studies and randomized, controlled trials found metformin to be as effective and safe as insulin for the management of gestational diabetes. Nonetheless, several concerns were raised and evidence on the long-term safety of metformin for both mother and child is lacking.

Metformin is safe in pregnancy and women with gestational diabetes treated with metformin have less weight gain during pregnancy than those treated with insulin. Babies born to women treated with metformin have been found to develop less visceral fat, making them less prone to insulin resistance in later life

Female infertility:- In a dissenting opinion, a systematic review of four head-to-head comparative trials of metformin and clomifene found them equally effective for infertility. Four positive studies of metformin were in women not responding to clomifene, while the population in the negative studies was drug-naive or uncontrolled for the previous treatment. Metformin should be used as a second-line drug if clomifene treatment fails. Another review recommended metformin unreservedly as a first-line treatment option because it has positive effects not only on anovulation, but also on insulin resistance, hirsutism and obesity often associated with PCOS. A Cochrane Collaboration review found metformin improves ovulation and pregnancy rates, particularly when combined with clomifene, and tentative evidence that it may increase the number of live births

Signs and symptoms of metformin overdose

The most serious potential adverse effect of biguanide use is metformin-associated lactic acidosis (MALA). Though the incidence for MALA about nine per 100,000 person-years, this is not different from the background incidence of lactic acidosis in the general population. A systematic review concluded no data exists to definitively link metformin to lactic acidosis . Lactic acidosis can be fatal

Metformin overdose associated with lactic acidosis presents with nonspecific symptoms and includes severe nausea, vomiting, diarrhea, epigastric pain, thirstiness, lost appetite, lethargy and hyperpnoea. Hypotension, hypothermia, acute renal failure, coma and cardiac arrest also represent significant clinical features. Estimated mortality rate of metformin associated lactic acidosis is between 30 and 50%, but can be high as 80%. The condition occurs most commonly in patients with substantial underlying medical problems (predominantly renal insuffiency). Mortality is not in complete correlation with either metformin or lactate levels . Hyperglycemia linked to metformin overdose has occasionally been reported, although less common than hypoglycemia. Such hyperglycemia has been linked to acute pancreatitis in several cases of metformin toxicity from both therapeutic dosing and intentional overdose. Another potential complication is the elevated osmolal gap (without exposure to toxic alcohols).

Contraindications

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (arbitrarily defined as creatinine levels over 150 μmol/l (1.7 mg/dl) lung disease and liver disease. According to the prescribing information, heart failure (in particular, unstable or acute congestive heart failure) increases the risk of lactic acidosis with metformin. A 2007 systematic review of controlled trials, however, suggested metformin is the only antidiabetic drug not associated with any measurable harm in people with heart failure, and it may reduce mortality in comparison with other antidiabetic agents.

Metformin is recommended to be temporarily discontinued before any radiographic study involving iodinated contrast agents, (such as a contrast-enhanced CT scan or angiogram), as the contrast dye may temporarily impair kidney function, indirectly leading to lactic acidosis by causing retention of metformin in the body. Metformin can be resumed after two days, assuming kidney function is normal

Interactions

The H2-receptor antagonist cimetidine causes an increase in the plasma concentration of metformin, by reducing clearance of metformin by the kidneys both metformin and cimetidine are cleared from the body by tubular secretion, and both, particularly the cationic (positively charged) form of cimetidine, may compete for the same transport mechanism. A small double-blind, randomized study found the antibiotic cephalexin to also increase metformin concentrations by a similar mechanism theoretically, other cationic medications may produce the same effect.

Clinical Effect

GIT : nausea , vomiting , diarrhea , cramps and heamatemesis .

CNS : agitation , confusion , convulsion and coma .

RS : rapid deep breathing , pulmonary hypertension .

CVS : Tachycardia and hypotension .

Diagnosis

Elevation of lactate / pyruvate ratio .

Elevation of 3-hydroxyburate concentration .

Blood glucose change .

leukocytosis , thrombocytopenia .

Elevated serum creatinine and albuminuria .

treatment

ABC

Decontamination

Treatment of hypoglycemia .

Treatment of acidosis

Treatment of hypotension

Hemodialysis