Carbon Monoxide  (9-Aug-1999)

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Chapter Sections
Smoke Inhalation
Methylene Chloride
Introduction to the Toxicology of the Erythrocytes, Platelets, and Clotting Proteins

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Smoke Inhalation

<table>
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<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
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<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to 2 days, often lethal</td>
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Potential Pathophysiologic Processes

- The primary cause of death in most smoke inhalation toxicoses in small animals is believed to be carbon monoxide (CO) toxicosis.
- Thermal injury to the respiratory tract is another part of the syndrome in many cases.
- Toxic injury to the respiratory tract from noxious gases and particulates is often a third significant component of the process.
Amount of Oxygen Released from the Hemoglobin in the Tissues of the Normal Animal

Note below that the total quantity of oxygen bound with hemoglobin in the normal arterial blood (PO$_2$ of 95 mmHg) is approximately 19.4 ml. On passing through the tissue capillaries, this amount is reduced to 14.4 ml (PO$_2$ of 40 mmHg), or a total loss of about 5 ml of oxygen from each 100 ml of blood. Then, when the blood returns to the lungs, the same quantity of oxygen diffuses from the alveoli to the hemoglobin, and this too is carried to the tissues. Thus, under normal conditions, about 5 ml of oxygen is transported by each 100 ml of blood during each cycle through the tissues.
Figure 2. Oxygen-hemoglobin, oxygen-water (of the blood), oxygen-blood dissociation curves; quantity of oxygen in each 100 ml of normal blood a) bound with hemoglobin; b) dissolved in the water of the blood; and c) total oxygen in both forms.

The Utilization Coefficient: Oxygen Utilization in Normal Animals

The fraction of the hemoglobin that releases oxygen as it passes through the tissue capillaries is called the utilization coefficient. Normally, this is approximately 27% of the hemoglobin, or in round figures, the normal utilization coefficient is approximately one-fourth. During strenuous exercise, however, up to a maximum of 77% of the hemoglobin can give up its oxygen, or in round figures, the utilization coefficient is then approximately three-quarters. Nevertheless, in local tissue areas where the blood flow is very slow or the metabolic rate very high, utilization coefficients approaching 100% have been recorded - that is, essentially all the oxygen is removed.

Pathophysiology of Smoke Inhalation

Figure 3. Outline of respiratory chain oxidation. Pi, inorganic phosphate; FAD, flavoprotein; CO Q, coenzyme Q; R, proton donor; Cyt, cytochrome. Failure of oxygen delivery causes cessation of function of the cytochromes: the major source of energy (from food, etc.) conservation (in the form of ATP) in the body. Different aspects of smoke inhalation can cause a functional "asphyxia" at the tissue level by virtue of: a) reduced oxygen delivery by the blood, b) reduced exchange of gases in the lung, and/or c) direct blockade of cytochrome oxidase (cyanide).

A. Carbon Monoxide Toxicosis
Produced by incomplete combustion: therefore produced by fires in closed spaces (areas with limited oxygen)

Colorless, odorless, tasteless, and non-irritating.

Does not injure the lung but decreases the oxygen-carrying ability of blood as a result of its binding to hemoglobin.

CO also **shifts the oxygen-hemoglobin dissociation curve to the left, which impairs oxygen unloading** (by the adjacent hemoglobin molecules not bound to CO) at the tissue level. This is a **major cause of tissue hypoxia** in CO poisoning.

- **Explanation** - Hemoglobin has 4 subunits, each of which contains one heme moiety attached to a polypeptide chain. Heme is a porphyrin and one atom of ferrous (Fe++ iron). Thus, there are four sites on hemoglobin that bind one oxygen molecule (O₂) each. The hemoglobin molecule changes slightly with each oxygen atom released or taken up. This changes the affinity for the remaining oxygen atoms - and this gives rise to the oxygen dissociation curve (the plot of the relationship between percent oxygen saturation of hemoglobin and the partial pressure of oxygen in the blood). Because CO induces a shift of the oxygen dissociation curve to the left, the blood retains a higher percentage of the oxygen than normal in the tissues (higher percent saturation of hemoglobin despite lower partial pressure of oxygen in the blood). Therefore, less oxygen is delivered (released) to the tissues than normal. **Note** - That alkalization of the animal, low body temperatures, and methemoglobinemia also shift the oxygen dissociation curve to the left and are generally contraindicated with significant CO on board.

- **Note** - The fire also consumes oxygen, therefore there is less oxygen to compete for hemoglobin than would normally be the case. However, animals with CO toxicosis generally do **not** have tachypnea/hyperpnea because PO₂ levels are not low enough to trigger that sort of response. Animals may be comatose, and may develop a degree of brain (or heart) damage if the condition is sufficiently severe. The blood (antemortem or at necropsy) and muscles (at necropsy) will be bright red.

- Cardiac output is decreased - The cause **may be** CO induced cerebral hypoxia and a secondary increase in pulmonary vascular resistance.

- Result - Tissue hypoxia, hypercapnia.

- Tissue hypoxia results in lactic acidosis.

- 10% or less COHb - No clinical signs.

- 10% to 20% COHb - Shortness of breath on moderate exercise, mild dyspnea.

- 30% COHb - Increased irritability of the animal, ataxia, nausea, vomiting.

- Over 40% COHb - Confusion, collapse, possible coma.

- 50% to 60% CoHb - Respiratory failure and death may occur; possible convulsions, which are most likely to be agonal in nature.

- Half-life of CO in the body: is approximately 4 hours (in all likelihood, this is based on an assumption of normal respiratory exchange - i.e., no significant damage to the lung) (See Treatment section below).

**Combination of hemoglobin with carbon monoxide.**

- Carbon monoxide combines with hemoglobin at the same point on the hemoglobin molecule as does oxygen. Furthermore, it binds with approximately 210 - 240 times as much tenacity as oxygen, which is illustrated by the carbon monoxide-hemoglobin dissociation curve below.

![Figure 4. The carbon monoxide-hemoglobin dissociation curve.](image-url)
• This curve is almost identical with the oxygen-hemoglobin dissociation curve except that the pressures of the carbon monoxide are at a level 210 times less than those in the oxygen-hemoglobin dissociation curve shown previously. Therefore, a carbon monoxide pressure of only 0.5 mmHg in the alveoli, 210 times less than that of the alveolar oxygen, allows the carbon monoxide to compete equally with the oxygen for combination with the hemoglobin and causes half the hemoglobin in the blood to become bound with carbon monoxide instead of with oxygen. A carbon monoxide pressure of 0.7 mmHg (a concentration of about 0.1 percent) is lethal.
• A patient severely poisoned with carbon monoxide can benefit from administration of pure oxygen, for oxygen at high alveolar pressures removes carbon monoxide from its combination with hemoglobin far more rapidly than can be achieved at the low pressure of atmospheric oxygen. That is, the pressure allows the oxygen actually to force its way into the hemoglobin molecule and thereby to displace the carbon monoxide.
• The patient can also benefit from simultaneous administration of a few percent carbon dioxide because this strongly stimulates the respiratory center. The resulting increase in alveolar ventilation reduces alveolar carbon monoxide concentration and thereby increases the release of carbon monoxide from the blood.

| Table 1. Signs or Symptoms of Reduced Levels of Oxygen Due to Fire Conditions |
|-------------------|----------------------------------|
| Percent of Oxygen in Air | Signs or Symptom (Human) |
| 20 (or above) | Normal |
| 12 to 15 | Muscular coordination for skilled movements lost |
| 10 to 14 | Consciousness continues but judgment is faulty and muscular effort leads to rapid fatigue |
| 6 to 8 | Collapse occurs quickly but rapid treatment would prevent fatal outcome |
| 6 (or below) | Death in 6 to 8 minutes |


| Table 2. Signs and Symptoms at Various Concentrations of Carboxyhemoglobin |
|-------------------|----------------------------------|
| % COHb | Signs and Symptoms (Human) |
| 0 to 10 | No signs or symptoms |
| 10 to 20 | Tightness across forehead, possible slight headache dilation of the cutaneous blood vessels |
| 20 to 30 | Headache and throbbing in the temples |
| 30 to 40 | Severe headache, weakness, dizziness, dimness of vision, nausea, vomiting, and collapse |
| 40 to 50 | Same as above, greater possibility of collapse, syncope, and increased pulse respiratory rates |
| 50 to 60 | Syncope, increased respiratory and pulse rates, coma, intermittent convulsions, and Cheyne-Stokes respiration |
| 60 to 70 | Coma, intermittent convulsions, depressed heart action and respiration leading to death within hours |
| 70 to 80 | Weak pulse, slow respiration leading to death within hours |
| 80 to 90 | Death in less than an hour |
| 90+ | Death in a few minutes |

B. Excessive Heat

- May directly injure upper respiratory mucosae: full expression of effects is often delayed.
- May result in laryngospasm, erosions, edema: possibly life-threatening.
- Mucosal burns of mouth, nasopharynx, pharynx, or larynx may lead to upper airway obstruction at any time during the first 24 hours after the burn.
- True thermal damage to the lower respiratory tract is rare unless live steam or explosive gases are inhaled.
- Airway damage may occur, however, from inhalation of superheated soot and other particles resulting from incomplete combustion.
- Ocular irritation or injury may also be present.

C. Noxious Gases and Particulates

- Full expression of effects are often delayed depending on the types of gases and/or particulates that are generated by the fire and the amounts involved.
- Gases may be carried in with superheated particulate matter.
- Toxic products may include short-chain aldehydes, acids (and oxides of sulfur and nitrogen which are converted to acids in the respiratory tract), and ketones from burning furniture, fabrics, plastics, etc. Wood smoke has 20 to 25 times the aldehydes present in smoke from burning kerosene and the former is much more lethal. Benzene or cyanide may be produced by some burning processes. One source of cyanides is burning urethanes. Benzene may act as a local anesthetic to permit deeper entry into the lung of acids and other noxious gases.
- Carbon dioxide, also produced during burning is a simple asphyxiant which further aggravates the lack of oxygen available to the cells.
- As lung damage is manifested during the first days following smoke inhalation, ventilation/perfusion abnormalities may occur possibly including intrapulmonary shunting. Compensatory tachypnea is likely in seriously affected animals.
- Pulmonary macrophages are also poisoned by smoke, which severely impairs macrophage function, which enhances the likelihood of delayed bacterial pneumonia.

Clinical Signs and Effects

- **Stage I** (during smoke inhalation).
  - Initial hyperventilation, hypoxia, hypercapnia, acidosis.
  - Decreased cardiac output, bronchospasm.
  - Carbon monoxide poisoning.
  - After several minutes, apnea may occur (this may be an effect of factors other than or in combination with carbon monoxide rather than due to CO alone).
  - Three possible outcomes when carbon monoxide alone is involved: recovery with no permanent effects, recovery with CNS damage (the brain is generally regarded as the most sensitive tissue), death.
- **Stage II** (0 to 30 minutes after removal from smoke)
  - Hypercapnia, mild hypoxia.
  - Severely depressed cardiac output.
  - Increased vascular resistance.
  - Hyperventilation.
  - Carboxyhemoglobinemia.

| Table 3. Time to Physical Incapacitation (TI) And Time to Death (TD) in CO, HCN, And CO + HCN Atmospheres |
|---------------------------------------------------------------|-----------------|-----------------|-----------------|
| Rotary Cages | HCN - 450 PPM | CO - 13,500 PPM | CO + HCN |
| TI Minutes | 4.1 ± 0.7 | 2.4 ± 0.3 | 2.0 ± 0.3 |
| TD Minutes | 10.9 ± 2.0 | 5.8 ± 1.2 | 3.7 ± 0.4 |
| Insert Cages | TD Minutes | 7.9 ± 2.0 | 6.3 ± 1.5 | 3.2 ± 0.4 |
- **Stage III** (2 to 24 hours after removal from smoke)
  - Increasing hypoxia.
  - Decreasing pulmonary compliance.
  - Altered ventilation:perfusion rations.
  - Clearing of CO.
  - Mildly depressed to normal cardiac output.
  - Pulmonary edema.
- **Stage IV** (after 24 hours)
  - If bacterial pneumonia develops, lung failure is common.
  - In the absence of bacterial pneumonia, recovery is common (do not make a prognosis too soon - i.e., hesitate for a few days at least).

**Smoke Inhalation - Emergency Workup** (quick list; see below for details).

- Obtain arterial blood gases on room air if possible.
- Examine skin to evaluate burns, especially facial.
- Carefully examine mucosal surfaces for burns/soot.
- Perform a thorough neurologic, corneal, and funduscopic examination.
- Auscult over the upper airways and thorax.
- Examine the saliva for carbonaceous particles.
- Perform an EKG for older or more significantly affected animals.
- Utilize laryngoscopy or bronchoscopy if available for animals with significant facial burns, soot in pharynx, carbonaceous particles in saliva, dyspnea, or upper airway effects.
- Obtain baseline thoracic X-rays.

**Diagnosis and Monitoring (details)**

- Monitor for acrid smell of smoke on the haircoat.
- Ask rescuers whether the animal was able to move away from the fire on its own or not.
- Carefully examine the external animal and oral-pharyngeal area; check for laryngospasm immediately.
- Auscult thoroughly.
- Examine carefully for hoarseness, expiratory wheeze, or carbonaceous sputum which indicate serious involvement.
- Determine carboxyhemoglobin concentrations (as percent saturation of hemoglobin in the carboxyhemoglobin state) and blood gases on whole blood.
  - Venous blood samples are generally evaluated for carboxyhemoglobin and arterial samples are tested for the common blood gases pO₂, pCO₂, pH.
  - Serial carboxyhemoglobin determinations on blood are of value in monitoring respiratory function as are ordinary blood gases. When carboxyhemoglobin concentrations are comparatively high, initial assessment of paO₂ may be misleading, since the oxygen carrying capacity of the hemoglobin is reduced. The arterial partial pressure of oxygen (paO₂) can still be normal (as will the calculated value for oxygen saturation derived therefrom) even in moderately severe CO toxicosis. Thus, the paO₂ can be normal, although the O₂ content is actually dangerously low. It is, therefore, helpful to measure the oxygen saturation of the blood directly using a hemoximeter.
  - Evaluate color of blood to see if it is cherry red from CO, or less often from cyanide (usually die fast from cyanide); red color can mask actual tissue hypoxia and poor perfusion from shock.
  - Utilize radiographic evaluation: often normal for first 16 to 24 hours after a moderate to severe injury; therefore can use for comparison to subsequent radiographs. Radiographs help to reveal atelectasis, edema, hemorrhage, infection. Most often see bronchial or peribronchial densities or interstitial infiltration, indicative of edema. The presence of air bronchograms may be seen in instances of edema or pneumonia.
  - A transtracheal aspiration biopsy may be used to assess the relative numbers of necrotic and normal cells and the presence of particulate debris.
  - Bronchoscopy requires general anesthesia for 10 to 15 minutes and must, therefore, be used only when the risks are not excessive and always with caution. Can be used to assess airway changes including mucosal erythema, hemorrhage, ulceration, edema, and carbonaceous particles.
Treatment

- Removal from the toxic environment.
- Face mask administration of oxygen at the site of the fire is very helpful in human medicine and the same would apply in veterinary medicine if possible.
- Be certain there is an adequate airway: may involve oropharyngeal suction, removal of debris, and maintenance of an unobstructed flow of air.
- With significant laryngospasm, it may be necessary to utilize endotracheal or tracheostomy intubation (don't wait until the last minute to try to intubate!); may be followed by positive pressure ventilation.
- For CO poisoning, use 100% oxygen therapy or, if available, O₂ with a few percent CO₂. The 4-hour half-life of CO in the blood when exchanged for oxygen in room air can be decreased to 30 to 40 minutes when 100% O₂ is breathed. Also, breathing 100% O₂ can result in enhanced delivery of oxygen to the tissues, since dissolved oxygen in the blood can enter the tissues even before CO is significantly displaced from hemoglobin.
- Oxygen is preferably provided in an oxygen cage, although masks may be used; it may be necessary to sedate the seriously hypoxic but difficult to manage patient and then to deliver the oxygen after intubation. Usually 8 to 12 breaths per minute are used for approximately 30 to 40 minutes.
- Positive-pressure ventilation is also of value for pulmonary edema if it is involved.
- Intravenous fluids are used in shock states to help maintain cardiac output and thereby enhance oxygen delivery to the tissues. Lactated Ringer's has been suggested as the fluid of choice. Fluid administration must be carefully monitored to avoid overhydration to avoid potentiating pulmonary edema.
- Corticosteroids are not recommended since patients with both smoke and thermal injury have experienced reduced survival rates when these drugs were used. Corticosteroids are used only for animals with serious circulatory shock.
- Antibiotics given prophylactically are not recommended although, in instances in which infection is developing, antibiotics are indicated and are generally selected on the basis of airway culture and sensitivity test. Most infections are with gram-negative organisms which should influence initial therapy while awaiting culture results.
- Bronchodilator therapy is used to alleviate reflex bronchospasms (use when patient exhibits wheezing); aminophylline (6 to 10 mg/kg IM, IV, or orally, TID) or theophylline elixir (0.4 ml/kg orally TID), or terbutaline sulfate (Brethine; 5 to 10 mg/kg orally TID may be used.
- Surface burns and the use of tracheostomy tubes increase the likelihood of secondary infections and decrease the likelihood of survival. Proper handling and use of tracheostomy tubes is essential in controlling the incidence of bronchopneumonia.
- Cats or dogs with cyanide toxicosis should be handled with care. Cats and, to a lesser degree, dogs are more susceptible than humans and large animals to agents that oxidize hemoglobin to methemoglobin (such as nitrite), so that protocols (such as nitrite + sodium thiosulfate) for humans and large animals with cyanide toxicosis may be unsafe for small animals, especially the cat.

Note - See also Vet Clin North Am, March 1990.

Methylene Chloride

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<th>Full Table for Carbon Monoxide</th>
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**Synonyms** - Dichloromethane, methylene dichloride, methylene bichloride

**Sources**

- Paint and varnish strippers
- Wood stains
- Solvent/degreasers
- Toxic exposures can result from inhalation, ingestion, or skin or ocular contact.
- **Note** - Combustion of methylene chloride can produce highly toxic phosgene gas, which may damage the lungs.

**Metabolism**

- A portion of methylene chloride is converted to carbon monoxide. At least in neonatal puppies (and probably many other species and all life stages with sufficient exposure), persistent exposure may lead to clinical carbon monoxide toxicosis.
- Mouse liver produces formaldehyde (a mutagen) from methylene chloride and mice develop DNA-protein cross links as well as liver and lung tumors following exposure to methylene chloride.
- Hamster liver did not develop DNA protein cross links following exposure to methylene chloride and hamsters did not develop liver or lung lesions as in mice.
- Rats are also resistant to methylene chloride-induced liver tumors.
- There is no epidemiologic evidence to indicate the methylene chloride is carcinogenic in human beings. Mouse, primary hepatocytes produced DNA-protein cross links, but human hepatocytes did not, following exposure to methylene chloride.

**Clinical Signs**

- Ataxia, incoordination, stupor or increased irritability.
- Nausea.
- Pulmonary edema.
- As with carbon monoxide toxicosis, animals may exhibit carboxyhemoglobin, and associated bright red blood, as well as red muscle tissues.

**Diagnosis**

- Identification of methylene chloride in source materials, digestive tract contents, and tissues.
- Elevated carboxyhemoglobin, which is more persistent after cessation of exposure than with carbon monoxide gas. This is because of continued metabolism of absorbed methylene chloride.

**Treatment**

- Prevent absorption: remove animals from in enclosed spaces in cases of inhalation or dermal exposure. Bathe with detergent to remove from skin.
- Increase oxygen available to animals with carbon monoxide toxicosis.
- Ingestion of significant amounts may be unlikely due to irritant effects on the digestive tract mucosae.
- Apparently, there are no data on the use of emetics, lavage, cathartics, and activated charcoal. However, if there are no apparent contraindications and ingestion of large amounts has recently occurred such treatments are warranted.

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**Introduction to the Toxicology of the Erythrocytes, Platelets, and Clotting Proteins**

1. **Development and Functions of the Red Blood Cells (RBCs)**

- Major function is to serve as a small, flexible container for hemoglobin that serves to deliver oxygen from the lungs to the tissues.
- Nucleated RBCs in fish, amphibians, reptiles, and birds.
- Non-nucleated RBCs in mammals.
- Hemoglobin contains iron (Fe⁺⁺) and has a relatively high affinity for O₂.
  - Blood with a low oxygen concentration takes on O₂ in the lungs and, because of competition for binding with 2,3-diphosphoglycerate (2,3-DPG) and protons (H⁺), oxygen is released from hemoglobin in the tissues.
  - Metabolism in the tissues and buffering of the blood (by the kidneys and lungs) creates a gradient such that the tissues are acidic relative to the blood. Thus, at the level of the capillaries, hemoglobin releases
its oxygen, which is then used by the tissues especially for oxidative phosphorylation.

- Hematopoiesis = production of blood cells.
  - Fetal and Neonatal Hematopoiesis and Fetal Blood
    - Initially hematopoiesis occurs in the yolk sac. Even in the human fetus, these are nucleated RBCs, and they contain an embryonal form of hemoglobin.
    - The liver, the spleen, and eventually the bone marrow later become sites for production of RBCs. The RBCs produced in the liver are not nucleated.
    - At birth, only the bone marrow is producing RBCs (in human beings). Still, even after birth, the liver and spleen can become sites of extramedullary hematopoiesis.
    - Human beings in utero produce fetal hemoglobin. There is a gradual transition from production of fetal to adult hemoglobin after birth so that by 6 months old babies are producing 100% adult hemoglobin.
    - Fetal hemoglobin binds 2,3-DPG less avidly than does adult hemoglobin so that the fetus can extract O2 from the maternal circulation.
    - In several species of domestic animals, fetal and adult hemoglobins are identical. The strategy in these species is simply to have less 2,3-DPG in the blood of the fetus than of the adult.
    - Erythropoietin stimulates the production of RBCs. Unlike in the adult, in the fetus, erythropoietin is produced by the liver.
  - Hematopoiesis and Blood from 6 Months of Age to Adulthood (Human)
    - Bone marrow contains multipotential stem cells that can become RBCs, megakaryocytes (precursors to platelets), or leukocytes (white blood cells = WBCs).
    - Abnormally low numbers of these elements in the blood are termed anemia, thrombocytopenia, and leukopenia, respectively.
    - Erythropoietin
      - In the adult, erythropoietin is produced by the kidney.
      - Erythropoietin causes the multipotential stem cell to become a proerythroblast, thereby committing it to a sequence of steps resulting in its becoming a RBC.
    - At the end of their lifespan, RBCs are normally removed and destroyed by the spleen. Some of the nutrients are recycled in the body, some leave via the liver and/or kidney. Removal of the spleen does not necessarily prolong the life of the RBCs, because the other parts of the reticuloendothelial system (esp. the liver and the bone marrow) take over this role of the spleen. The RBCs must pass through fine channels lined with macrophages in the spleen, and if they are deformed (e.g. if they are old cells without the energy to maintain their normal configuration, as a result of Heinz bodies, or if they are parasitized cells, they are very likely to be recognized as abnormal, engulfed, and destroyed.
    - Hemoglobin normally binds to four O2 molecules, and releases three of them in a step-wise fashion in response to a low oxygen concentration and high acidity (low pH).
    - Hemoglobin in RBCs transports O2 to the cells, and on the return trip, CO2 is carried in the RBCs in one of three forms: in the form of bicarbonate (large amount) after conversion by the enzyme, carbonic anhydrase; in simple solution (small amount); and after attaching to free amino groups of hemoglobin to form carbaminohemoglobin (R-NH-COOH) (small amount).
    - Hemoglobin is the main acceptor of hydrogen ions (H+) in the blood, accounting for about 85% of the buffering capacity of the blood.

2. Development and Functions of the Platelets

- The liver is the initial site of the production of platelets in the developing fetus.
- The bone marrow becomes the most important site of production thereafter.
- Platelets are the first line of defense against hemorrhage - form a "patch" over the break in a blood vessel & they help trigger the clotting cascade.
- Normally, platelets are non-sticky, but when exposed to connective tissue collagen (as a result of a break in a blood vessel), they react to release their granules and become extremely sticky, aggregate, and form a "platelet plug".
- Platelets become sticky (and small blood vessels constrict under the influence of the platelet-derived prostaglandin, thromboxane A2).
- Unlike the other non-steroidal anti-inflammatory drugs, aspirin, even at low doses, irreversibly acetylates the enzyme cyclo-oxygenase, which is the first step in the production of the prostaglandins. Thus, for the life of the platelet, its production of thromboxane is prevented. For this reason, aspirin is a useful drug to help prevent unwanted clotting that can contribute to "vascular accidents".
Production and Function of the Clotting Proteins

- The liver is the site of the production of the clotting proteins.
- Proteins are involved in two cascades: the intrinsic and the extrinsic pathway.
- These produce insoluble fibrin that reinforces the platelet plug. Eventually fibroblasts may infiltrate the area occupied by fibrin resulting in scar formation.
- A final carboxylation reaction catalyzed by vitamin-K\(_1\) serves as the activation step in the production of some of the key clotting proteins in the blood [e.g. factors II (= prothrombin), VII, IX, and X].
- Vitamin-K\(_1\) in its active hydroquinone form is essential in this process. As it functions, it is converted to its epoxide, rendering it inactive until it can be reconverted to the active form by the enzyme vitamin-K epoxide reductase.
  - Drugs used to prevent clotting, such as warfarin, natural toxins, such as dicoumarol, and rodenticides, such as brodifacoum, diphacinone, and bromadiolone inhibit vitamin-K epoxide reductase, thereby preventing the normal recycling of vitamin K to its active form and thus inhibiting the production of the active forms of the clotting proteins.
  - Compounds that inhibit vitamin-K epoxide reductase, prevent the normal frequent recycling of the vitamin from its used (inactive) epoxide form, to its active hydroquinone form.
  - Warfarin is highly protein bound in the plasma; therefore, when given with other drugs that are as tightly (or more tightly) bound, such as some sulfonamides or phenylbutazone, warfarin becomes displaced from the albumin, thereby increasing the dose that reaches the liver. This may result in marked inhibition of production of clotting proteins. This is the reason why people and animals on warfarin therapy are so prone to drug interactions that lead to severe hemorrhage.

4. Agents that Damage the Bone Marrow Stem Cells and thus Result in Depletion of All Three Series of Formed Elements (RBCs, platelets, WBCs).

- A marked deficiency of all three is termed pancytopenia.
- Pancytopenia can result from high level exposure to:
  - Radiation.
  - Benzene.
    - Metabolically activated (site unclear - liver or bone marrow?) to a cytotoxic compound, possibly benzoquinone, that is cytotoxic to the bone marrow cells.
  - Anti-cancer drugs.
  - Lindane (an organochlorine insecticide).
  - Chlordane (another organochlorine insecticide).
  - Nitrogen mustards.
  - Arsenic (rare effect).
  - Chloramphenicol (antibiotic; humans uniquely sensitive); most other species effects are more reversible. At least in some cases, seems to be mediated by an immunologic mechanism.
  - Trinitrotoluene (TNT; explosive).
  - Gold salts (used as anti-rheumatic drugs).
  - Hydantoin derivatives.
  - Phenylbutazone.
- With the above agents, sometimes one series or another may be more sensitive so that, depending on the toxicant and the dose, the problem may appear to be more of an anemia, a thrombocytopenic disorder, or a leukopenia.
- Platelet deficiency can also result from autoimmune disorders, some of which can be induced by chemicals, e.g.:
  - Quinidine (used to correct cardiac arrhythmias).
  - Phenacetin (an obsolete non-steroidal anti-inflammatory drug).

5. Toxicoses that are Associated with Damage to RBCs or Hemoglobin, or that, via Other Mechanisms, Cause Hemoglobin to Fail to Serve as an Effective Carrier of Oxygen.

Agents that Interfere with Blood Production:

- Severe damage to bone marrow such that RBCs are not being produced is termed aplastic anemia.
- Lead: inhibits several enzymes involved in production of hemoglobin.
- Inhibits heme synthetase = the enzyme responsible for insertion of the iron atom into the protoporphyrin molecule, thus creating heme. Without heme, the hemoglobin is an ineffective carrier of oxygen. Also, the person will tend to release immature RBCs into the blood. Increased numbers of RBCs with basophilic stippling and increased numbers of nucleated RBCs are seen in the blood.
- Inhibits d-aminolevulenic acid dehydratase.

**Agents that dissolve RBC cell membranes:**

Saponins (from plants; although this effect is rarely seen); detergent-like compounds that dissolve membranes (cause digestive tract damage and upset and when absorbed in sufficient amounts cause hemolysis.

**Agents that Causes Hemolysis - Causation not Fully Worked Out:**

- Heinz bodies involved (generally related to oxidative injury).
  - Arsine (arsenic hydride) - Gas produced by charging batteries (Heinz bodies involved).
  - Stibine (antimony hydride) - Gas (Heinz bodies involved) (antimony is very toxicologically similar to arsenic in other ways as well).
  - Phenols - esp. concentrated phenol, cresol. Some old forms of Lysol® contained 0.1% of O-phenylphenol; however, it also contained 79% ethanol posing an additional toxicologic risk.
  - Propylene glycol (e.g., when given i.v.; generally not with ingestion of Sierra® antifreeze).
  - Ascorbic acid (vitamin C).
  - Ingestion of crude oil by marine birds.
  - Phenylhydrazine (intermediate in chemical industry).

**Agents that Cause Oxidative Injury to RBCs (may overlap with previous section):**

- Effects include: formation of Heinz bodies, hemolysis, and production of methemoglobinemia.
- Heinz bodies = masses of denatured hemoglobin that precipitate and become covalently bound to the interior surface of the plasma membrane of the erythrocyte. These result in recognition by the spleen as a potentially "sick" erythrocyte; spleen ruptures the RBCs thereby releasing the hemoglobin and resulting in hemolytic anemia. This type of hemolytic anemia is termed a Heinz body anemia.
- Methemoglobin: Oxidation of the ferrous iron (Fe++) in hemoglobin to ferric ion (Fe+++) creates methemoglobinemia, thereby changes the molecule from highly efficient, to a very ineffective carrier of O2.
  - Normally, some methemoglobin (i.e. hemoglobin with Fe+++) production develops in the body (up to a few % of the total hemoglobin).
  - Small amounts of methemoglobin are reduced to the normal, fully functional hemoglobin molecule (i.e. with Fe++) by the enzyme NADH methemoglobin reductase.
- Examples of agents that cause oxidative injury to RBCs (potential for Heinz bodies and serious methemoglobinemia):
  - Rape, kale, turnips (Brassica spp.): deplete glucose-6-phosphate dehydrogenase.
  - Onions and garlic (Allium spp.) also deplete this enzyme.
  - Red maple (Acer rubrum) leaves (green, red, brown, fresh or dried).
  - Acetaminophen (e.g. Tylenol®) in domestic cats.
  - Nitrite (produced from nitrate, esp. in ruminants).
  - Chlorate (rarely used as a herbicide; in some matches).
  - Naphthalene (moth balls; some moth crystals) - probably oxidative.
  - Local anesthetics especially after oral administration.

**Carbon monoxide (CO)**

- CO has a much higher (245x) affinity for hemoglobin than does O2.
- CO also decreases the tendency for hemoglobin to release to the tissues the oxygen being carried (with four binding sites, you have some sites carrying CO and other sites bearing O2).
- Neonates and animals in utero are predisposed to CO toxicosis and associated hypoxic injury.
References

Methylene Chloride


Introduction to the Toxicology of the Erythrocytes, Platelets, and Clotting Proteins


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