**3. Natural Products:**

include naturally occurring catecholamines hormones and cytokines, as well as animal and plant toxins.

Glucocorticoids and mineralocorticoids:

glucocorticoids include corticosterone, cortisone. and hydrocortisone(cortisol) and the mineralocorticoid (aldosterone). Both appear to stimulate cardiac fibrosis by regulating cardiac collagen expression independently of hemodynamic alterations. Furthermore, aldosterone and glucocorticoids induce hypertrophic growth and alter expression of $Na^+$, $K^+$-ATPase. activate both Na/H+ antiporter, and chloride bicarbonate exchanger of cardiac myocytes clinically relevant cardiac hypertrophy has been observed in premature infants undergoing dexamethasone treatment.

**Thyroid hormone includes thyroxin(T4) and triiodothyronine(T3):**

hypothyroid states are associated with decreased heart rate, contractility, and cardiac output, whereas hyperthyroid slates are associated with increased heart rate, contractility, cardiac output. Thyroid hormones also alter expression of cardiac SR handling proteins including increased expression of SR $Ca^{2+}$ATPase.

**Animal and plant toxins:**

Animal toxins as the venom of snake, spiders, scorpions and marine organisms have profound effects on the cardiovascular system.

**Environmental Pollutants and Industrial Chemicals:**

Solvents Industrial solvents can exert adverse effects on the heart directly or indirectly both are related to their inherent lipophilicity. Solvents may affect cardiac physiological functions such as contraction and energy production by directly dispersing into plasma membranes. the effects of solvent on the heart would be more related their action on neuro-hormonal regulation of cardiac function. Solvents may disrupt sympathetic and parasympathetic control of the heart as well as cause release of circulating hormones such as catecholamines, vasopressin, and serotonin.

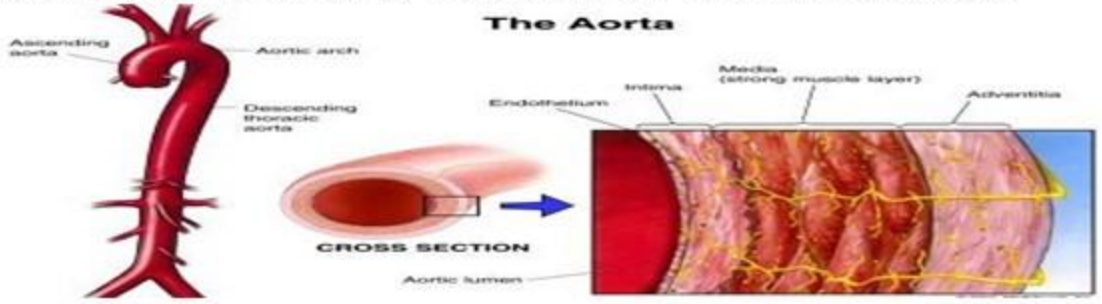
**Metal and Metalloid:**

the most common heavy metals that have been associated with cardiotoxicity are cadmium, lead, and cobalt. These metals exhibit negative inotropic and choronotropic effects and can also produce structural changes in the heart. Chronic exposure to cadmium has been reported to cause cardiac hypertrophy. Lead has an arrhythmogenic sensitizing effect on the myocardium. In addition, lead has been reported to cause degenerative changes in the heart. Cobalt has been reported to cause cardiomyopathy. The cardiotoxic effects of heavy metals are attributed to their ability to form complexes with intracellular macromolecules and their ability to antagonize intracellular $Ca^{2+}$.

Arsenic has a high affinity for sulfhydryl l proteins, which involved in multiple cellular metabolism and function.

## VASCULAR SYSTEM

The vascular system consists of blood vessels of varying size and different cellular composition. In add the lymphatic system belongs to vascular system, but it only carries plasma.




## VASCULAR SYSTEM TOXIC RESPONSES

### Mechanisms of Vascular Toxicity

(1) alterations in membrane structure and function: modulation vascular reactivity is regulated by the transfer of signals from the surface to the interior of the cell and/or direct modulation of the structure and function of contractile proteins. Usually, disorders of vascular reactivity involve disturbances of ionic regulation.

(2) oxidative metabolism of plasma lipoproteins caused initiation and progression of atherosclerosis.

(3) the capacity of target cell to detoxify the active toxin or handle prooxidant states.

(4) the accumulation of chemicals in the vascular wall. Aromatic hydrocarbons and other ubiquitous environmental contaminants participate in the lipid phase of the atherosclerotic plaques.

### Vascular system toxic effect:

• Nicotine: nicotine is mimics the actions of acetylcholine at nicotinic receptors throughout the body. Tobacco smoke also facilitates thrombosis by modulation of platelet function and vascular spasm.

• Psychotropic Agents: Trifluoperazine and chlorpromazine among the psychotropic drugs have been to cause intracellular cholesterol accumulation, Aside from atherogenic effects. Postural hypotension has been identified as the most common cardiovascular side effect.

• Oral contraceptive steroids: can produce thromboembolic disorders.

• Bacterial Endotoxins: are potent toxic agents to vascular system and cause a variety of toxic effects in many vascular beds. In the liver they cause swelling of endothelial and adhesion of platelets to sinusoid walls. In the lung, endotoxins produce increased vascular permeability and pulmonary hypertension.

• Vitamin D

The toxic effect of Vitamin D may be related to its structural similarity to 25-hydrocholesterol, a potent vascular toxin. The manifestations of Vitamin D hypervitaminosis include calcification of the coronary arteries and smooth muscle cell proliferation

• B-Amyloid: Accumulation of B-amyloid is a major lesion in the brain of Alzheimer's patients. B-amyloid produces extensive vascular disruption, including endothelial and smooth muscle damage, adhesion and migration of leukocytes across arteries and venules.

### Environmental Pollutants and Industrial Chemicals:

• Short-term exposure to carbon monoxide is associated with direct damage to vascular endothelial and smooth muscle cells, Injury to endothelial cells increases intimal permeability and allows the

interaction of blood constituents with underlying components of the vascular wall. The toxic effects of carbon monoxide have been attributed to its reversible interaction with hemoglobin. As result of this interaction carboxyhemoglobin decreases the oxygen-carrying capacity of blood eventually leading to functional anemia. In addition, carbon monoxide interacts with cellular proteins such as myoglobin and cytochrome c oxidase and elicits a direct vasodilatory response of the coronary circulation.

• Metals and Metalloids: waterborne elements (selenium, chromium. copper, zinc. cadmium, lead, and mercury) as well as airborne elements (vanadium and lead) involves reactions of metals with sulfhydryl, carboxyl or phosphate groups. Metals such as cobalt, magnesium, manganese, nickel. Cadmium, and lead also interact with and block calcium channels, Intracellular calcium-binding proteins.

• Lead: has been associated with hypertension in a large percentage of patients(Elevated blood pressure has also been observed during childhood lead poisoning). The direct vasoconstrictor effect of lead related to the putative hypertensive response. this effect can be complemented by the ability of This activate the renin-angiotensin- aldosterone system, lead inhibits the repair process in damaged endothelial cells and modulates spontaneous release of fibrinolytic proteins from subendothelial cells through intracellular calcium-independent pathways. Acute lead-induced neuropathy may be due to cerebral capillary dysfunction Inorganic lead alters arterial elasticity and causes sclerosis of renal vessels.

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## Toxic response of the blood

Hematotoxicology (blood as a target organ): is the study of adverse effects of drugs, nontherapeutic chemicals and other agents in our environment on blood. this characteristic makes hematopoietic tissue a particularly sensitive target for cytoreductive or antimitotic agents, such as those used to treat cancer, infection, and immune-mediated disorders. The synthesis of heme occurs in the cytoplasm and mitochondria of erythroblasts. The initial step in the pathway is the mitochondria synthesis of aminolevulinic acid, a step that is commonly affected by xenobiotics, including lead.

**Ferrochelatase:** catalyzes the incorporation of ferrous iron into the tetrapyrrole protoporphyrin, that causes inhibition of the synthetic pathway leading to the sideroblastic anemias, can cause an imbalance between iron concentration and ferrochelatase activity resulting in iron deposition within mitochondria, with its characteristic accumulation of iron in bone marrow erythroblasts. It is consider the hallmark lesion of the sideroblastic anemia.

**Xenobiotics Associated with Sideroblastic Anemia**

| | |
|---|---|
| Ethanol | Chloramphenicol |
| Isoniazid | Cooper chelation/deficiency |
| Pyrazinamide | Zinc intoxication |
| Cycloserine | Lead intoxication |

Bleeding may potentiate the risk of developing iron deficiency anemia.

**Hematopoiesis:** requires active DNA synthesis and frequent mitoses. Folate and vitamin $B_{12}$ are necessary to maintain synthesis of thymidine for incorporation into DNA so deficiency of folate and/or vitamin $B_{12}$ results in megaloblastic anemia number of xenobiotics may contribute to a deficiency of vitamin B12 and/or folate include:

**Xenobiotics Associated with Megaloblastic Anemia**

| $B_{12}$ DEFICIENCY | FOLATE DEFICIENCY |
|---|---|
| Paraminosalicylic acid | Phenytoin |
| Colchicine | Primidone |
| Neomycin | Carbamazepine |
| Ethanol | Phenobarbital |
| Omeprazole | Sulfasalazine |
| Hemodialysis | Cholestyramine |
| Zidovudine | Triamterine |
| Fish tapeworm | Malabsorption syndromes |
| | Antimetabolites |

**Drug-induced aplastic anemia:** Many of the antiproliferative drugs used in the treatment of malignancy predictably inhibit hematopoiesis, is characterized by peripheral blood pancytopenia, reticulocytopenia, and bone marrow hypoplasia. Chemicals such as benzene and radiation have effect on hematopoietic which resulting aplastic anemia corresponds to the magnitude of the exposure to these chemicals.

**Drugs and Chemicals Associated with the Development of Aplastic Anemia**

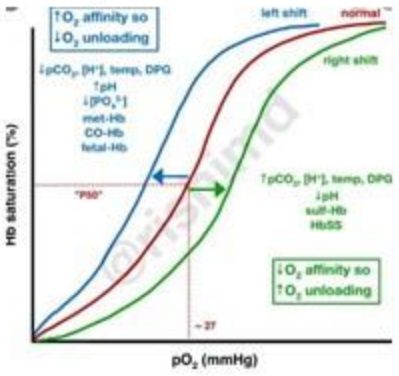
| | | |
|---|---|---|
| Chloramphenicol | Organic arsenicals | Quinacrine |
| Methylphenylethylhydantoin | Trimethadione | Phenylbutazone |
| Gold | Streptomycin | Benzene |
| Penicillin | Allopurinol | Tetracycline |
| Methicillin | Sulfonamides | Chlortetracycline |
| Sulfisoxazole | Sulfamethoxypyridazine | Amphotericin B |
| Mefloquine | Ethosuximide | Felbamate |
| Carbimazole | Methylmercaptoimidazole | Potassium perchlorate |
| Propylthiouracil | Tolbutamide | Pyrimethamine |
| Chlorpropamide | Carbutamide | Tripelennamine |
| Indomethacin | Carbamazepine | Diclofenac |
| Meprobamate | Chlorpromazine | Chlordiazepoxide |
| Mepazine | Chlorphenothane | Parathion |
| Thiocyanate | Methazolamide | Dinitrophenol |
| Bismuth | Mercury | Chlordane |
| Carbon tetrachloride | Cimetidine | Metolazone |
| Azidothymidine | Ticlopidine | Isoniazid |
| Trifluoperazine | D-penicillamine | |

**Alterations in the Respiratory Function of Hemoglobin:**

The ability of hemoglobin to safely and efficiently transport oxygen is dependent on both intrinsic (homotropic) and extrinsic (heterotropic) factors:

**Homotropic Effects:**

Methemoglobin is not capable of binding and transporting oxygen. In addition, has allosteric effects that increase the affinity of oxyhemoglobin for oxygen, resulting in a left ward shift of the oxygen dissociation curve. The combination of decreased oxygen content and increased affinity impairs delivery of oxygen to tissues when the concentration of methemoglobin rises beyond critical levels. these mechanisms are normally capable of maintaining the concentration of methemoglobin cytochrome b5 methemoglobin reductase which is dependent on reduced nicotine adenine dinucleotide (NADH) also known as NADH-diaphorase




an alternate pathway involves a reduced nicotine adenine dinucleotide phosphate (NADPH) diaphorase that reduces a flavin that in turn reduces methemoglobin. The most common cause of methemoglobinemia is exposure to an oxidizing xenobiotics overwhelms the NADH. A large number of chemicals causes methemoglobinemia.

**Xenobiotics Associated with Methemoglobinemia**

| THERAPEUTIC AGENTS | ENVIRONMENTAL AGENTS |
|---|---|
| Benzocaine | Nitrites |
| Lidocaine | Nitrates |
| Prilocaine | Nitrobenzenes |
| Dapsone | Aniline dyes and aniline derivatives |
| Amyl nitrate | Butyl nitrite |
| Isobutyl nitrite | Potassium chlorate |
| Nitroglycerine | Gasoline additives |
| Primaquine | Aminobenzenes |
| Sulfonamide | Nitrotoluenes |
| Phenacetin | Trinitrotoluene |
| Nitric oxide | Nitroethane |
| Phenazopyridine | Ortho-toluidine |
| Metoclopramide | Paratoluidine |
| Flutamide | Betanaphthol disulfonate |
| Silver nitrate | |
| Quinones | |
| Methylene blue | |

**Homotropic Effects:**

**Infectious Hemolysis:**

may be associated with significant hemolysis by a direct effect on the erythrocyte or an immune-mediated hemolytic process.

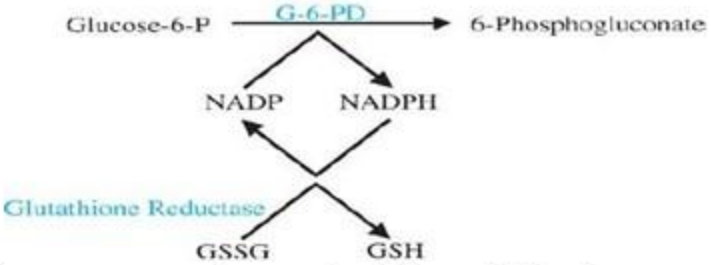
Erythrocytes are parasitized in malaria and babesiosis, leading to their destruction. Clostridial infections are associated with the release of hemolytic toxins that enter the circulation and lyse erythrocytes.

**Oxidative Hemolysis:**

Molecular oxygen is a reactive and potentially toxic chemical species; consequently, the normal respiratory function of erythrocytes generates oxidative stress on a continuous basis. Several mechanisms protect against oxidative injury in erythrocytes, including NADH-diaphorase, superoxide dismutase, catalase, and the glutathione pathway, xenobiotics Associated with oxidative Injury include Acetanilide, Naphthalene, Nitrofurantoin, Dapsone, sulfan-ilamide and Nalidixic acid, oxygen normally exchanges with the ferrous iron of deoxyhemoglobin to methemoglobin (Hgbfe3+) and superoxide (O2-). A supply of reduced glutathione (GSH) is necessary to prevent excessive oxidative injury.

**Nonoxidative Chemical-induced Hemalysis:**

Excess copper has been associated with hemolytic anemia. The pathogenesis may relate to inhibitory effects on the hexose monophosphate shunt.




**Immune Hemolytic Anemia:**

Immunologic destruction of erythrocytes is mediated by the interaction of lgG or IgM antibodies with antigens expressed on the surface of the erythrocyte. a number of mechanisms have been implicated in xenobiotics mediated antibody binding to erythrocytes. some drugs, of which penicillin is a prototype, appear to bind to the surface of the cell, with the "foreign" acting as a hapten and eliciting an immune response. The antibodies that arise in this type of response only bind to drug coated erythrocytes. Some xenobiotics are associated with nonspecific deposition of proteins on erythrocytes. This was first associated with cephalosporins but has also been seen with other drugs, including cisplatin and the beta-lactamase.

**Toxic Effects on Granulocytes**

**Effects on Proliferation :**

The high rate of proliferation of neutrophils makes their progenitor and precursor granulocyte pool particularly susceptible to inhibitors of mitosis. Agents that affect both neutrophils and monocytes pose a greater risk for infection. Methotrexate, cytosine arabinoside, daunorubicin, cyclophosphamide and cisplatin, are toxic to resting and actively dividing cells, which maximum effects usually are seen 7 to 14 days after exposure. where cytokines may enhance these effects.

**Effects on Function:**

ethanol and glucocorticoids which impair phagocytosis and microbe ingestion. lohexol and ioxaglate, ponents of radiographic contrast media, have also been reported to inhibit phagocytosis. Superoxide production, required for microbial killing and chemotaxis, has been reported to be reduced in patients using parenteral heroin as well as in former opiate abusers such as long-term uses methadone. In addition to glucocorticoids, several drugs and non-therapeutic chemicals have been shown to inhibit neutrophil chemotaxis. Examples include macrolide antibiotics, which suppress the expression of the adhesion molecule ICAM.