Toxic response of the blood

Blood as a Target Organ

Hematotoxicology is the study of adverse effects of drugs, nontherapeutic chemicals and other agents in our environment on blood and blood-forming tissues**.** The various blood cells (erythrocytes, granulocytes, and platelets) are each produced at a rate of approximately 1 million to 3 million per second in a healthy adult; 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.

Hematotoxicity may be regarded as *primary,* in which one or more blood components are affected directly, or *secondary,* in which the toxic effect is a consequence of other tissue injury or systemic disturbances. Primary toxicity is regarded as among the serious effects of xenobiotics, particularly drugs. Secondary toxicity is exceedingly common because of the propensity of blood cells to reflect various local and systemic effects of toxicants on other tissues**.**

The production of blood cells, or hematopoiesis, is a highly regulated sequence of events by which blood cell precursors proliferate and differentiate where the bone marrow is the dominant hematopoietic organ in the latter half of gestation and the only blood cell producing organ at birth . All marrow is active, or “red marrow,” at birth . During early childhood, hematopoiesis recedes in long bones and, in adults, is confined to the axial skeleton and proximal humerus and femur **,** The marrow in the distal long bones becomes “yellow” or fatty. When demand for blood cell production is great, as with certain disease states, fatty marrow can be reactivated as sites of hematopoiesis.

Xenobiotics can affect globin chain synthesis and alter the composition of hemoglobin within erythrocytes. This is perhaps best demonstrated by hydroxyurea, which has been found to increase the synthesis of γ-globin chains. The γ-globin chains are a normal constituent of hemoglobin during fetal development, replacing the β chains in the hemoglobin tetramer (hemoglobin F, $\alpha_2\gamma_2$). Hemoglobin F has a higher affinity for oxygen than hemoglobin A and can protect against crystallization (sickling) of deoxyhemoglobin S in sickle cell disease .

.The synthesis of heme involves a series of reactions that occur in the cytoplasm and mitochondria of erythroblasts. The initial step in the pathway is the mitochondria synthesis of δ-aminolevulinic acid, a step that is commonly affected by xenobiotics, including lead. Ferrochelatase catalyzes the incorporation of ferrous iron into the tetrapyrrole protoporphyrin IX. Inhibition of the synthetic pathway leading to protoporphyrin IX,as occurs in the sideroblastic anemias, can cause an imbalance

between iron concentration and ferrochelatase activity, resulting in iron deposition within mitochondria. Mitochondrial accumulation of iron is the hallmark lesion of the sideroblastic anemias.

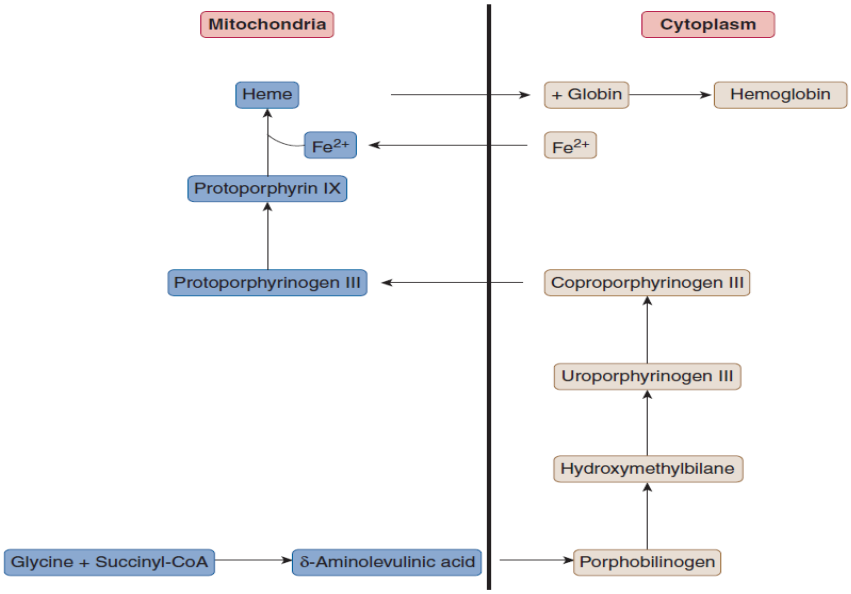


Figure 11-2. *The synthesis of heme involves a series of reactions that occur in the cytoplasm and mitochondria of erythroblasts.* The initial

Synthesis of heme requires incorporation of iron into a porphyrin ring. Iron deficiency is usually the result of dietary deficiency or increased blood loss. Drugs that contribute to blood loss, such as nonsteroidal anti-inflammatory agents, with their increased risk of gastrointestinal ulceration and bleeding, may potentiate the risk of developing *iron deficiency anemia* bleeding, may potentiate the risk of developing *iron deficiency anemia.* Defects in the synthesis of the porphyrin ring of heme can lead to *sideroblastic anemia*, with its characteristic accumulation of iron in bone marrow erythroblasts. The accumulated iron precipitates within mitochondria in a complex with mitochondria ferritin, causing the characteristic staining pattern of ringed sideroblasts evident on iron stains such as Prussian blue. A number of xenobiotics can interfere with one or more of the steps in erythroblast heme synthesis and result in sideroblastic anemia

Table 11-1

Xenobiotics Associated with Sideroblastic Anemia

Ethanol	Chloramphenicol
Isoniazid	Copper chelation/deficiency
Pyrazinamide	Zinc intoxication
Cycloserine	Lead intoxication

Hematopoiesis requires active DNA synthesis and frequent mitoses. Folate and vitamin B12 are necessary to maintain synthesis of thymidine for incorporation into DNA so deficiency of folate and/or vitamin B12 results in *megaloblastic anemia*

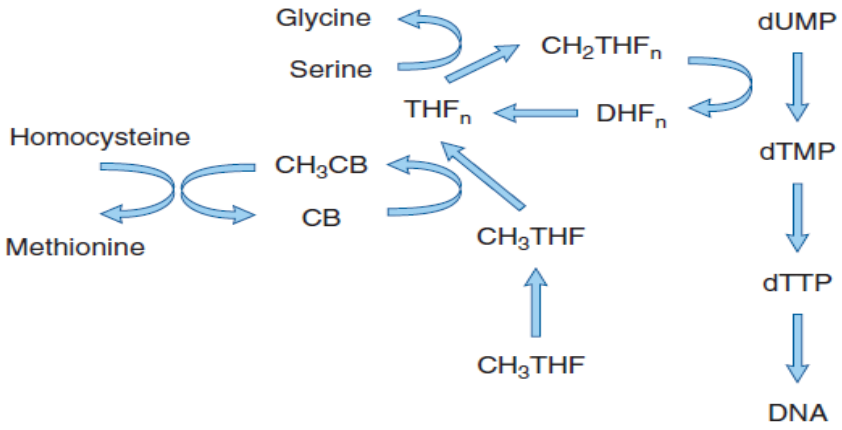


Figure 11-3. *Both tetrahydrofolate (THF) and cobalamin (CB, or vitamin B_{12}) are necessary for the synthesis of thymidine (dTMP) for incorporation into DNA.* Folate enters the cell as a monoglutamate (CH_3THF) but is transformed to a polyglutamate within the cell, a step that helps prevent leakage of folate back across the cell membrane. However, CH_3THF cannot be conjugated with glutamate. CB is necessary for demethylation of the folate, allowing formation of conjugated (polyglutamate) folate (THF_n). In the absence of CB, folate levels within the cell drop, causing a functional deficiency of folate and impairing synthesis of thymidine.

number of xenobiotics may contribute to a deficiency of vitamin B12 and/or folate

Table 11-3

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

Many of the antiproliferative drugs used in the treatment of malignancy predictably inhibit hematopoiesis, including erythropoiesis. Drug-induced *aplastic anemia* may represent either a predictable or idiosyncratic reaction to a xenobiotic. This life threatening disorder is characterized by peripheral blood pancytopenia, reticulocytopenia, and bone marrow hypoplasia

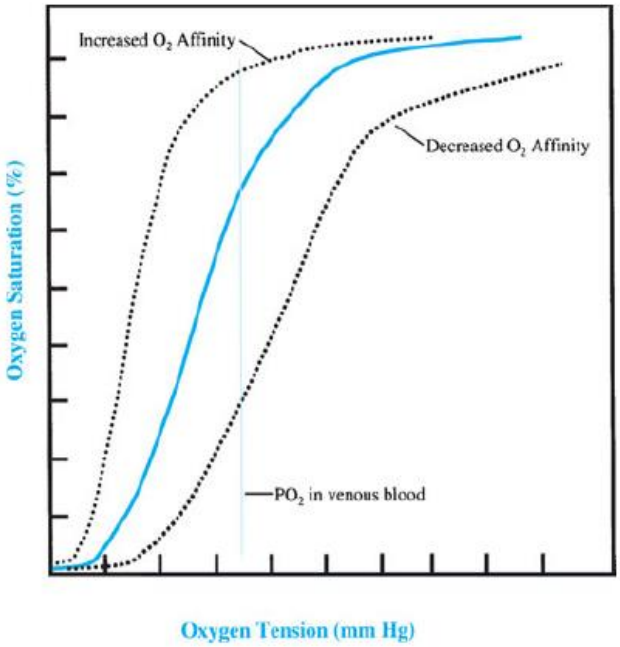
Chemicals such as benzene and radiation have a *predictable* effect on hematopoietic progenitors,and the resulting aplastic anemia corresponds to the magnitude of the exposure to these chemicals. In contrast, idiosyncratic aplastic anemia does not appear to be related to the dose of the chemical initiating the process,The mechanism of aplasia in affected patients is that Immune mechanisms have long been thought to contribute to the development of the idiosyncratic form of drug-induced aplastic anemia

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

Hemoglobin is necessary for effective transport of oxygen and carbon dioxide between the lungs and tissues. Electrostatic charges hold the globin chains of deoxyhemoglobin in a “tense” (T) conformation, characterized by a relatively low affinity for oxygen. Binding of oxygen alters this conformation to a “relaxed”



(R) conformation that is associated with a 500-fold increase in oxygen affinity. Thus the individual globin units show cooperativity in the binding of oxygen, resulting in the familiar sigmoid shape of the oxygen dissociation curve.

The ability of hemoglobin to safely and efficiently transport oxygen is dependent on both intrinsic (homotropic) and extrinsic (heterotropic) factors that affect the performance of this system.

Homotropic Effects

One of the most important homotropic properties of oxyhemoglobin is the slow but consistent oxidation of heme iron to the ferric state to form methemoglobin. Methemoglobin is not capable of binding and transporting oxygen.In addition, the presence of methemoglobin in a hemoglobin tetramer 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.

Normal erythrocyte has metabolic mechanisms for reducing heme iron back to the ferrous state; these mechanisms are normally capable of maintaining the concentration of methemoglobin at less than 1% of the total hemoglobin The predominant pathway is cytochrome b5 methemoglobin reductase which is dependent on reduced nicotine adenine dinucleotide (NADH) also known as NADH-diaphorase also an alternate pathway involves a reduced nicotine adenine dinucleotide phosphate (NADPH) diaphorase that reduces a flavin that in turn reduces methemoglobin. This pathway usually accounts for less than 5% of the reduction of methemoglobin, but its activity can be greatly enhanced by methylene blue, which is reduced to leukomethylene blue by NADPH-diaphorase. Leukomethylene blue then reduces methemoglobin to deoxyhemoglobin.

A failure of these control mechanisms leads to increased levels of methemoglobin, or *methemoglobinemia.* The most common cause of methemoglobinemia is exposure to an oxidizing xenobiotics that overwhelms the NADH-diaphorase system. A large number of chemicals and therapeutic chemicals may cause 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	

There are three **major heterotropic** effectors of hemoglobin function: pH, erythrocyte 2,3-bisphosphoglycerate concentration,and temperature.

A decrease in pH (eg,lactic acid, carbon dioxide) lowers the affinity of hemoglobin for oxygen, that is, it causes a right shift in the oxygen dissociation curve, facilitating the delivery of oxygen to tissues . As bicarbonate and carbon dioxide equilibrate in the lung, the hydrogen ion concentration decreases, increasing the affi nity of hemoglobin for oxygen and facilitating oxygen uptake.

The binding site for 2,3-BPG is located in a pocket formed by the two β chains of a hemoglobin tetramer. Binding of 2,3-BPG to deoxyhemoglobin results in stabilization of the "T" conformation,with reduced oxygen affinity (a shift to the right of the oxygen dissociation curve). The concentration of 2,3-BPG increases whenever there is tissue hypoxemia but may decrease in the presence of acidosis or hypophosphatemia. Thus hypophosphatemia may result in a left shift of the oxygen dissociation curve. Clofibric acid and bezafibrate are capable of lowering the oxygen affinity of hemoglobin, analogous to 2,3-BPG

The oxygen affinity of hemoglobin decreases as the body temperature increases This facilitates delivery of oxygen to tissues during periods of extreme exercise, and febrile illnesses associated with increased temperature. Correspondingly, oxygen affinity increases during hypothermia, which may lead to decreased oxygen delivery under these conditions. This must be taken into consideration during surgical procedures during which there is induction of deep hypothermia**.**

Nonimmune Hemolytic Anemia

Microangiopathic Anemias Intravascular fragmentation of erythrocytes gives rise to the *microangiopathic hemolytic anemias* . The hallmark of this process is the presence of schistocytes in the peripheral blood. These abnormal cellular fragments are usually promptly cleared from the circulation by the spleen. Thus their presence in peripheral blood samples indicates either an increased rate of formation or abnormal clearance function of the spleen. The formation of fi brin strands in the microcirculation is a common mechanism for RBC fragmentation. This may occur in the setting of disseminated intravascular coagulation, sepsis, the hemolytic-uremic syndrome (HUS), and thrombotic thrombocytopenic purpura (TTP).

Infectious Diseases Infectious diseases 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. *Bartonella bacilliformis* is thought to adhere to the erythrocyte, leading to rapid removal from the circulation.

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, incluing 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. Oxygen can "capture" one of the iron electrons,resulting in the generation of methemoglobin (HgbFe3+) and superoxide (O2–) Superoxide must be detoxified or it can lead to oxidative injury within the cell. The pathways involved include superoxide dismutase , catalase , and glutathione peroxidase .

$$HgbFe^{++}O_2 \rightleftharpoons HgbFe^{++} + O_2 \quad (1)$$

$$HgbFe^{++}O_2 \rightleftharpoons HgbFe^{+++} + O_2^- \quad (2)$$

$$2O_2^- + 2H^+ \xrightarrow[\text{Dismutase}]{\text{Superoxide}} O_2 + H_2O_2 \quad (3)$$

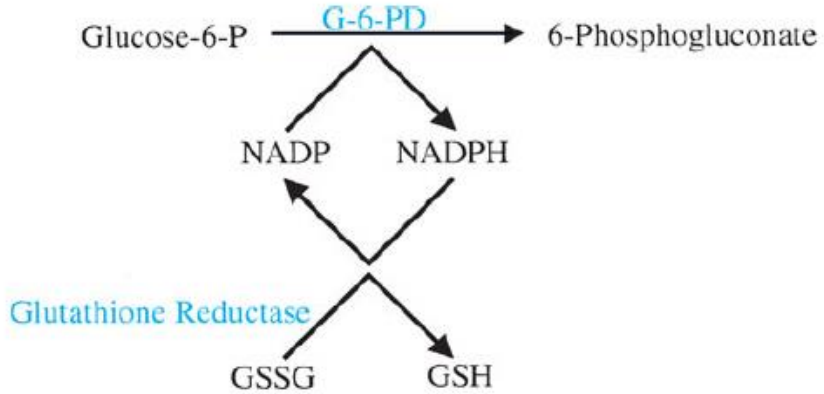
$$2\,H_2O_2 \xrightarrow{\text{Catalase}} H_2O + O_2 \quad (4)$$

$$H_2O_2 + GSH \xrightarrow[\text{Peroxidase}]{\text{Glutathione}} GSSH + H_2O \quad (5)$$

$$O_2^- + GSH \xrightarrow[\text{Peroxidase}]{\text{Glutathione}} GSSH + H_2O \quad (6)$$

A supply of reduced glutathione (GSH) is necessary to prevent excessive oxidative injury. The most common enzyme defect associated with oxidative hemolysis is glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, a sex-linked disorder characterized by diminished G-6-PD activity. It is often clinically asymptomatic until the erythrocytes are exposed to oxidative stress from the host response to infection or exposure to xenobiotics.

The hexose monophosphate shunt in the erythrocyte is critical for generation of NADPH, which helps maintain an intracellular supply of reduced glutathione (GSH). With a deficiency of glucose-6- phosphate dehydrogenase (G-6-PD), the rate-limiting step in this pathway,the cellular levels of GSH are reduced. Such cells show increased susceptibility to oxidative injury. Acute exposure of such cells to an oxidizing agent can result in rapid hemolysis.



Nonoxidative Chemical-Induced Hemolysis

Exposure to some xenobiotics is associated with hemolysis without significant oxidative injury, **Lead** poisoning is associated with defects in heme synthesis and a shortening of erythrocyte survival. The cause of the hemolysis is uncertain, but lead can cause membrane damage and interfere with the Na+/K+ pump. These effects may cause premature removal of erythrocytes from the circulation.

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 IgG 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" drug acting as a *hapten* and eliciting an immune response. The antibodies that arise in this type of response only bind to drug-coated erythrocytes.

Other drugs, of which quinidine is a prototype, bind to components of the erythrocyte surface and induce a conformational change in one or more components of the membrane. This type of interaction can give rise to a confusing array of antibody specificities.

A third mechanism, for which α-methyldopa is a prototype, results in the production of a *drug-induced autoantibody* that cannot be distinguished from the antibodies arising in idiopathic autoimmune hemolytic anemia ,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 inhibitors sulbactam and clavulanate

Toxicology of the Leukon

The leukon consists of leukocytes, or white blood cells, including granulocytes, which may be subdivided into neutrophils, eosinophils, and basophils; monocytes; and lymphocytes. Granulocytes and monocytes are nucleated ameboid cells that are phagocytic. They play a central role in the inflammatory response and host defense. Unlike RBCs, which reside exclusively within blood, granulocytes and monocytes merely pass through the blood on their way to the extravascular tissues, where they reside in large numbers

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. Such effects tend to be dose-related, with mononuclear phagocyte recovery preceding neutrophil recovery.Methotrexate, cytosine arabinoside, daunorubicin, cyclophosphamide, cisplatin, and the nitrosureas are toxic to resting and actively dividing cells, in which maximum effects usually are seen 7 to 14 days after exposure.where Cytokines may enhance these effects. Chemicals that affect granulocyte kinetics can cause neutropenia or neutrophilia that has variable toxicologic significance. Dexamethasone has long been known to cause neutrophilia through enhanced release of mature neutrophils from the bone marrow and demargination, with the latter being the largest contributor to the expanded circulating pool

Effects on Function

ethanol and glucocorticoids, which impair phagocytosis and microbe ingestion Iohexol and ioxaglate, components 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 on long-term methadone maintenance 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**.**

Idiosyncratic Toxic Neutropenia

Chemicals that unexpectedly damage neutrophils and granulocyte precursors—particularly to the extent of inducing agranulocytosis , which is characterized by a profound depletion in blood neutrophils **,** Idiosyncratic xenobiotic-induced agranulocytosis may involve a sudden depletion of circulating neutrophils concomitant with exposure, which may persist as long as the chemical or its metabolites persist in the circulation Hematopoietic function is usually restored when the chemical is detoxified or excreted. Toxicants affecting uncommitted stem cells induce total marrow failure, as seen in aplastic anemia, which generally carries a worse prognosis than chemicals affecting more differentiated precursors,The severity of the neutropenia often causes severe sepsis or localized infections, such as sore throat pneumonia or various cutaneous infections.

Mechanisms of Toxic Neutropenia

Toxic neutropenia may be classified according to mechanism as immune mediated or nonimmune-mediated.

In immune-mediated neutropenia, antigen-antibody reactions lead to destruction of peripheral neutrophils, granulocyte precursors, or both. As with RBCs, an

immunogenic xenobiotic can act as a hapten, where the chemical must be physically present to cause cell damage,or may induce immunogenic cells to produce antineutrophil antibodies that do not require the drug to be present Also like immune hemolytic anemia, drug-induced *autoimmune* neutropenia has been observed.Examples of chemicals that have been implicated include Fludarabine , propylthiouracil , and rituximab .

Some nonimmune-mediated toxic neutropenias have long been known to have a genetic predisposition Direct damage may cause inhibition of granulopoiesis or neutrophil function, Some studies suggest that a buildup of toxic oxidants generated by leukocytes can result in neutrophil damage, as with the reactive intermediates derived from the interaction between clozapine and
neutrophils. The resulting superoxide and hypochlorous acid production by the myeloperoxidase system are thought to contribute to clozapine-induced neutropenia. Accumulation of nitrenium ion, a metabolite of clozapine that causes a depletion of ATP and reduced glutathione, rendering the neutrophil highly susceptible to oxidant-induced apoptosis, is now thought to be the principal mechanism of this disorder Examples of agents associated with immune and nonimmune neutropenia/agranulocytosis INH, Rifampicin, Allopurinol,& Phenothiazines

Toxicology of Platelets and Hemostasis

Hemostasis is a multicomponent system that is responsible for preventing the loss of blood from sites of vascular injury and maintaining circulating blood in a fluid state. Loss of blood is prevented by the formation of stable hemostatic plugs. The major constituents of the hemostatic system include circulating platelets, a variety of plasma proteins, and vascular endothelial cells. Alterations in these components or systemic activation of this system can lead to the clinical manifestations of deranged hemostasis, including excessive bleeding and thrombosis. The hemostatic system is a common target of therapeutic intervention as well as inadvertent expression of the toxic effect of a variety of xenobiotics

The Thrombocyte

Platelets are essential for the formation of a stable hemostatic plug in response to vascular injury. Platelets initially adhere to the damaged wall. Activation of a pathway of several factors permits fibrinogen and other multivalent adhesive molecules to form cross-links between nearby platelets, resulting in platelet aggregation. Xenobiotics may interfere with the platelet response by causing thrombocytopenia or interfering with platelet function

Thrombocytopenia

Like anemia, thrombocytopenia may be due to decreased production or increased destruction. Thrombocytopenia is a common side effect of intensive chemotherapy because of the predictable effect of antiproliferative agents on hematopoietic precursors. Thrombocytopenia is a clinically significant component of idiosyncratic xenobiotic-induced aplastic anemia. Indeed, the initial manifestation of aplastic anemia may be mucocutaneous bleeding secondary to thrombocytopenia.

Exposure to xenobiotics may cause increased immune-mediated platelet destruction through any of several mechanisms.

1) Some drugs, such as penicillin, function as haptens, binding to platelet membrane components and eliciting an immune response that is specific for the hapten. The responding antibody then binds to the hapten on the platelet surface, leading to removal of the antibody-coated platelet from the circulation.

2) A second mechanism of immune thrombocytopenia is initiated by xenobiotic-induced exposure of a neoepitope on a platelet membrane glycoprotein. This elicits an antibody response, with the responding antibody binding to this altered platelet antigen in the presence of drug, resulting in removal of the platelet from the circulation by the mononuclear phagocytic system e.g quinidin.

3) Thrombocytopenia is an uncommon but serious complication of inhibitors of GPIIb/IIIa such as abciximab .The mechanism appears to be related to exposure of epitopes on GP IIb/IIIa that react with naturally occurring antibodies Ligand binding is known to alter the conformation of GP IIb/IIIa The GP IIb/IIIa inhibitors bind at the ligand binding site and also cause a conformational change in GP IIb/IIIa, permitting naturally occurring antibodies to bind to and initiate clearance of platelets by the mononuclear phagocytic system.

4) Heparin-induced thrombocytopenia (HIT) represents another mechanism of immune-mediated platelet destruction. This disorder is due to the development of antibodies that react with a multimolecular complex formed by the interaction between heparin and a protein, usually platelet factor 4 (PF 4), also streptokinase same mechanism.

5) Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by the sudden onset of thrombocytopenia, a microangiopathic hemolytic anemia, and multisystem organ failure, which often includes neurologic dysfunction , The pathogenesis of TTP appears to be related to the ability of unusually large vWF multimers to activate platelets, even in the absence of significant vascular damage Although these large multimers are normally secreted into blood by endothelial cells, they are rapidly processed into smaller multimers by a protease present in plasma. Acquired TTP is associated with the development of an antibody that inhibits

this protease, permitting the very large vWF multimers to persist in the circulation . Consequently, these multimers bind to platelet GP Ib/IX/V and induce platelet activation and aggregation. The organ failure and hemolysis inTTP is due to the formation of platelet-rich microthrombi throughout the circulation. The development of TTP or TTP-like syndromes has been associated with drugs such as ticlopidine, clopidogrel, cocaine,mitomycin, and cyclosporine

Toxic Effects on Platelet Function

Platelet function is dependent on the coordinated interaction of a number of biochemical response pathways. Major drug groups that affect platelet function include nonsteroidal anti-inflammatory agents; B-lactam-containing antibiotics; cardiovascular drugs, particularly beta blockers; psychotropic drugs; anesthetics; antihistamines; and some chemotherapeutic agents.

Xenobiotics may interfere with platelet function through a variety of mechanisms. Some drugs inhibit the phospholipase A_2/cyclooxygenase pathway and the synthesis of thromboxane A_2 (e.g., nonsteroidal anti-inflammatory agents). Other agents appear to interfere with the interaction between platelet agonists and their receptors (e.g., antibiotics, ticlopidine, clopidogrel). As the platelet response is dependent on a rapid increase in cytoplasmic calcium, any agent that interferes with the translocation of calcium may inhibit platelet function (e.g., calcium channel blockers). Occasionally, drug-induced antibodies bind to a critical platelet receptor and inhibit its function.

Toxic Effects on Fibrin Clot Formation

Coagulation

Fibrin clot formation results from the sequential activation of a series of serine proteases that culminates in the formation of thrombin. Thrombin is a multifunctional enzyme that converts fibrinogen to fibrin; activates factors V, VIII, XI, and XIII, protein C, and platelets; and interacts with a variety of cells (e.g., leukocytes and endothelial cells), activating cellular signaling pathways ,Most proteins involved in the coagulation cascade are synthesized in the liver. Therefore, any agent that impairs liver function may cause a decrease in the production of coagulation factors. The common tests of the coagulation cascade—prothrombin time (PT) and activated partial thromboplastin time (aPTT)—may be used to screen for liver dysfunction and a decrease in clotting factors.

Factors II, VII, IX, and X are dependent on vitamin K for their complete synthesis. Anything that interferes with the absorption of vitamin K

Conditions Associated with Abnormal Synthesis of Vitamin K—Dependent Coagulation Factors

Warfarin and analogues	Intravenous α-tocopherol
Rodenticides (e.g., brodifacoum)	Dietary deficiency
	Cholestyramine resin
Broad-spectrum antibiotics	Malabsorption syndromes
N-methyl-thiotetrazole cephalosporins	

from the intestine or with the reduction of vitamin K epoxide may lead to a deficiency of these factors and a bleeding tendency Increased Clearance of Coagulation Factors Idiosyncratic reactions to xenobiotics include the formation of antibodies that react with coagulation proteins, forming an immune complex that is cleared rapidly from the circulation and resulting in deficiency of the factor. The factors that are affected by xenobiotics most often are listed in . In addition to causing increased clearance from the circulation, these antibodies often inhibit the function of the coagulation factor

Table 11-11

Relationship between Xenobiotics and the Development of Specific Coagulation Factor Inhibitors

COAGULATION FACTOR	XENOBIOTIC
Thrombin	Topical bovine thrombin Fibrin glue
Factor V	Streptomycin Penicillin Gentamicin Cephalosporins Topical bovine thrombin
Factor VIII	Penicillin Ampicillin Chloramphenicol Phenytoin Methyldopa Nitrofurazone Phenylbutazone
Factor XIII	Isoniazid Procainamide Penicillin Phenytoin Practolol
von Willebrand factor	Ciprofloxacin Hydroxyethyl starch Valproic acid Griseofulvin Tetracycline Pesticides