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**Toxicology /105447**

**Chapter 4- Hematotoxicity:**

Chemically induced hematotoxicity has been reported in the medical literature for over a century.

For example, the 1919 publication by Dr. Alice Hamilton, entitled *Industrial Poisoning by Compoundsof the Aromatic Series,* described a number of blood toxicities that were commonly encountered in occupational settings such as

* benzene-induced bone marrow suppression,
* aniline and nitrobenzene induced methemoglobinemia, and
* hydrogen sulfide–induced effects.

Exposure to hydrogen sulfide can be a significant industrial hygiene concern in the refining of petroleum products and the biological degradation of silage (fermented corn, grain, etc., used to feed livestock) and sewage. As for the number of workers affected, benzene and hydrogen sulfide probably constitute the most significant risk factors for toxicity.

Hematotoxicity is also an important concern in the administration of pharmaceuticals. For example **dapsone** (used to treat leprosy) and **primaquine** (used to treat malaria) can produce a fatal hemolytic anemia in certain genetically predisposed individuals (those with a deficiency in glucose-6-phosphate dehydrogenase). Unfortunately, individuals most likely to require primaquine or dapsone therapy livein tropical areas of Africa, Asia, and the Mediterranean and are most likely to inherit a deficiency in glucose-6-phosphate dehydrogenase.

Of widespread concern are the risks of bone marrow injury and suppression caused by cancer chemotherapeutics, complications that can often limit the administration of cancer-curing drugs.

Another longstanding problem involves carbon monoxide poisoning, which results from exposure to improperly ventilated combustion products. Outside the workplace, the most common occurrences of hematotoxicity involve carbon monoxide poisoning, due to faulty gas heating and adverse hematologic effects due to prescription medications.

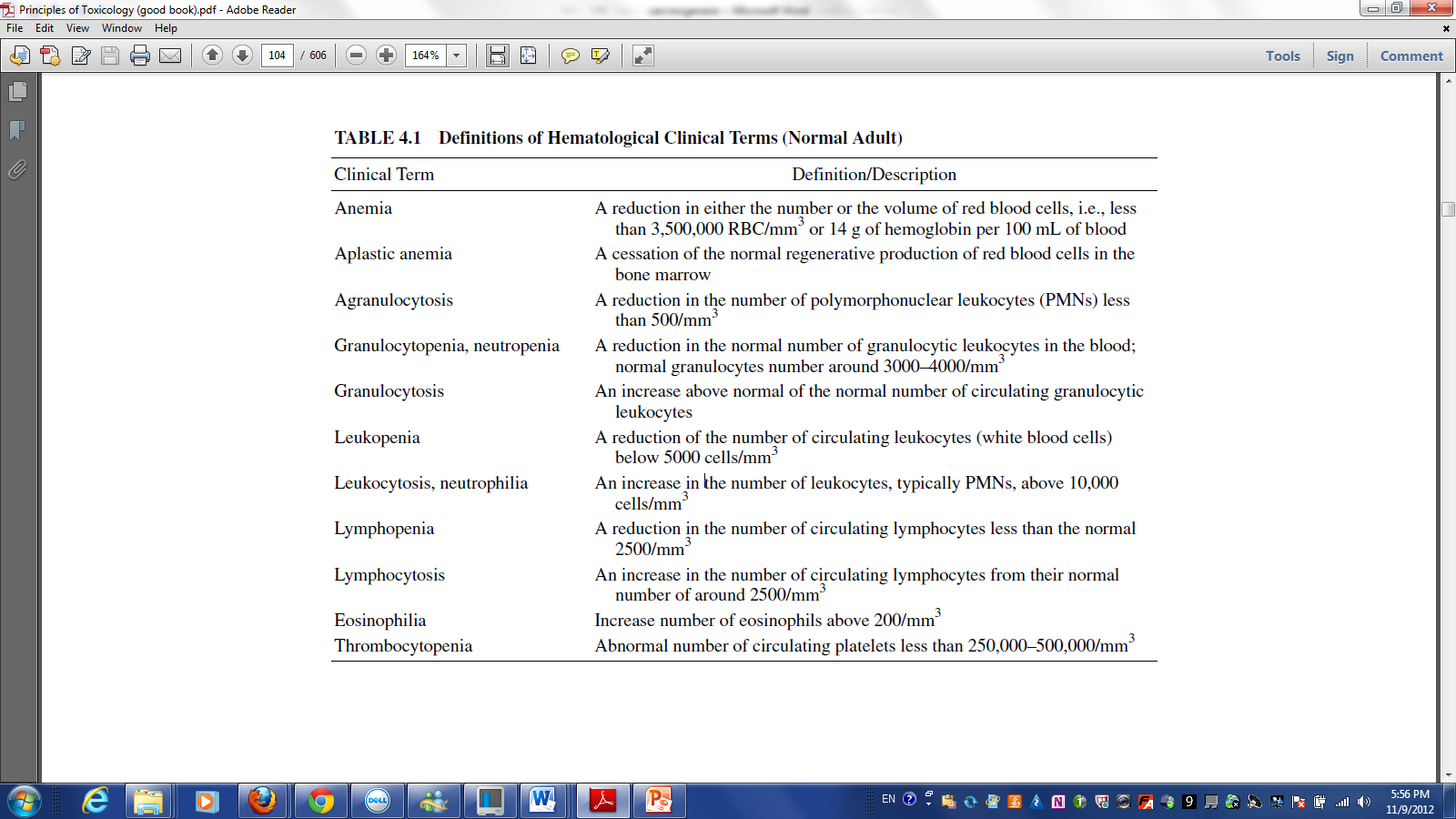
Fortunately, hematotoxicity is rarely encountered due to the resiliency of bone marrow, the redundancy of various hematologic controls and functions, and the implementation of more conservative occupational hygiene standards. However, when it occurs, it is often life threatening.

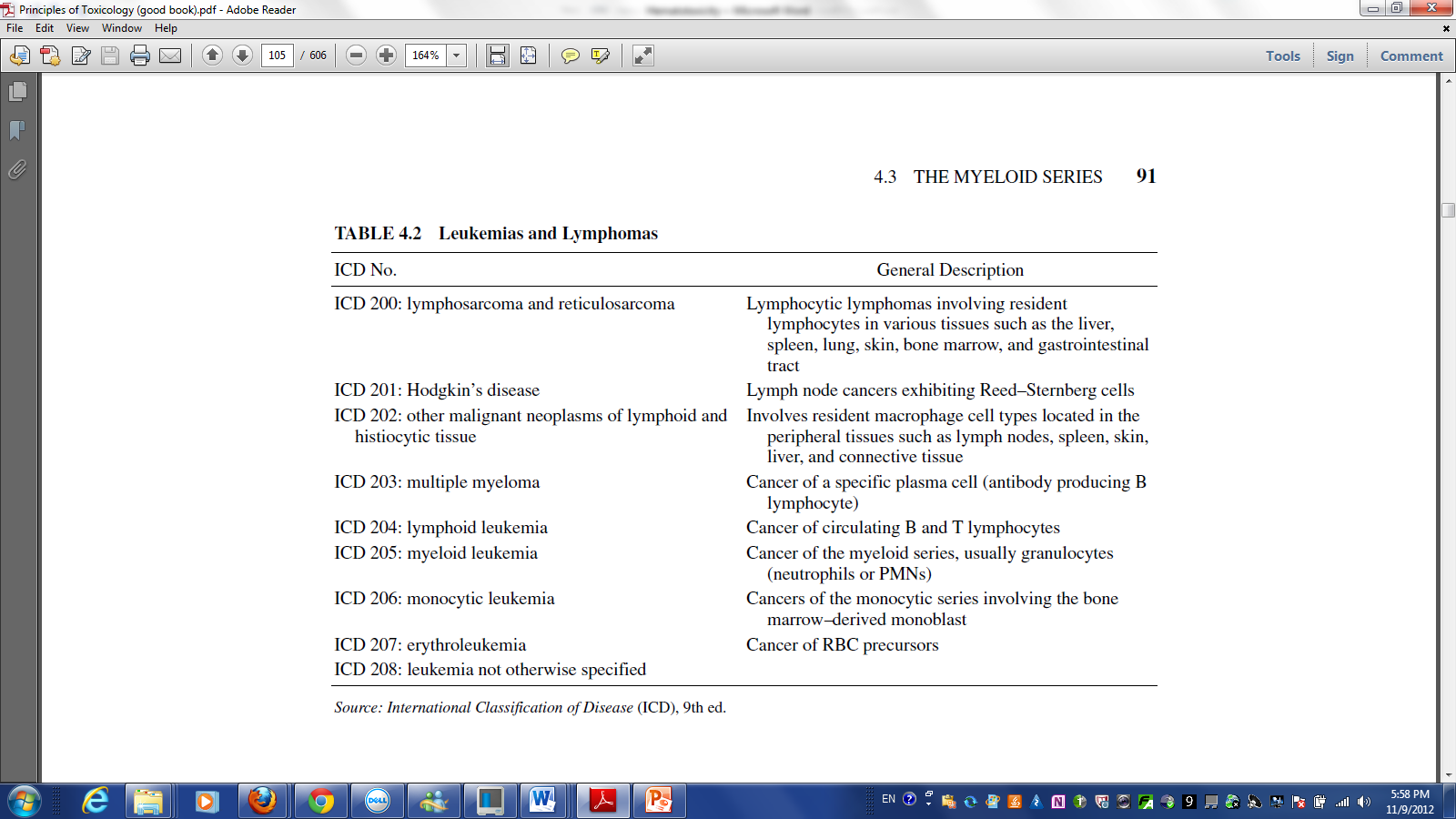
Likewise, examples of hematotoxicity resulting from exposure to environmental chemicals are relatively rare and generally involve foods or medications. Although hematotoxicity is not prevalent, it is useful for industrial hygienists, toxicologists, and occupational physicians to be aware of the chemicals that cause hematotoxicity, relevant signs and symptoms, and any antidotes and treatments that are available.

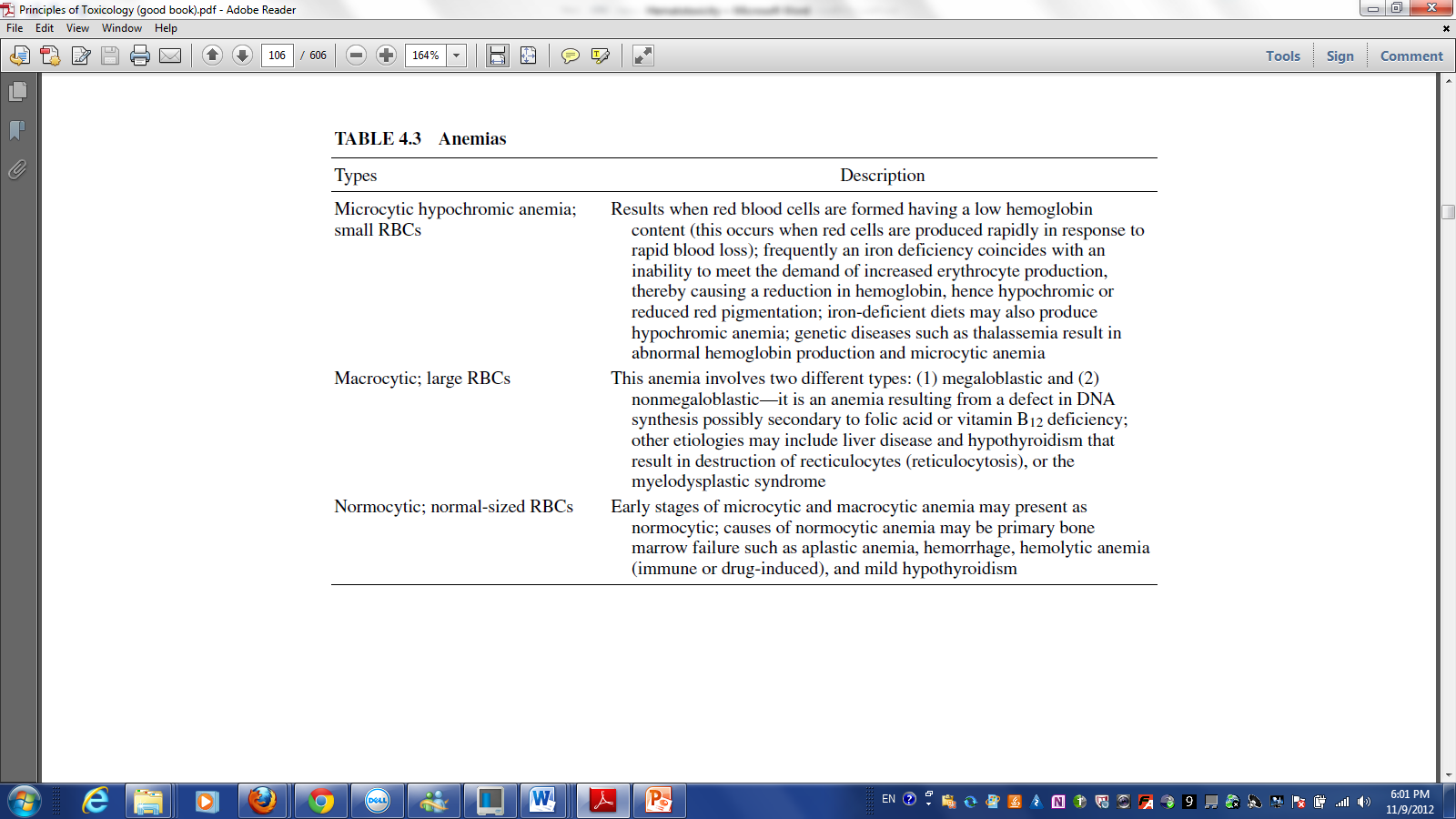
When bone marrow is injured or suppressed, the number of specific types of blood cells (or all blood cells) may decline or even disappear. The decline in the number of cells from a specific blood cell lineage has its own diagnostic term and is based on the expected normal range that exists in healthy individuals. For example, a decrease in the normal number of circulating red blood cells leads to the clinical condition of anemia, a decrease in circulating platelets is known as thrombocytopenia, and a decrease in white blood cells is called leukopenia. Table 4.1 provides definitions for various clinical terms used to describe the abnormal number of circulating red blood cells, neutrophils, lymphocytes, and platelets. Some terms describe the same condition and may create confusion when used interchangeably.

The suffix penia means an abnormal reduction, and the suffix cytosis refers to an abnormal excess. Changes in the number of circulating white blood cells provide an important diagnostic parameter for many diseases. Granulocytopenia, when the granulocyte count (primarily the neutrophils) falls to less than 1000 cells/mm3, may arise from chemical-induced bone marrow damage following administration of cancer chemotherapeutic drugs or the antibiotic chloramphenicol, antiinflammatory agents such as butazolidin, or exposure to benzene. When this occurs, an insufficient number of granulocytic cells are available to maintain the first line of defense against infectious agents, and recurrent infection is likely. Granulocytosis, or an increased number of circulating granulocytes (exceeding 10,000 cells/mm3), often occurs in patients with leukemia or can be triggered by an underlying infection. In cancers of the myeloid series, such as myelogenous leukemia, neutrophil numbers may exceed 30,000 cells/mm3. The leukemias generally consist of cells that lack the normal morphology and function of mature white blood cells (e.g., they resemble precursors of immature white blood cells found in the bone marrow).

The cancer biology of the various types of leukemias (myeloid and lymphoid) and lymphomas, as well as multiple myeloma is quite complex. The types of leukemias and lymphomas are described in Table 4.2 according to the International Classification of Disease codes (frequently abbreviated the ICD). These cancers can differ in morbidity as well as clinical presentation, symptoms, management, and long-term survival.





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**Platelets:**

**Platelet aggregation: Cigarette smoke–induced arteriosclerosis** is a chemical toxicity that indirectly involves the platelets. In atherosclerosis accelerated by cigarette smoking, plaques, composed of a complex mixture of lipids (e.g., cholesterol), form underneath the normal smooth endothelial lining of the artery/arterioles. If the plaque ruptures, which it can do unpredictably, the connective tissue underneath the endothelial lining becomes exposed, and this event triggers platelet aggregation. If the platelet aggregation and fibrin deposition progresses to the point of occluding the blood vessel, an infarct occurs, and all tissue distal to the occlusion (platelet clot) dies from anoxia. The muscle that dies downstream of the clot (infarct or inclusion) is replaced by scar tissue, and hence the efficiency of the cardiac muscle is compromised.

The scar may also impact normal electrical conduction pathways in the heart. Hence, platelets are involved in the final stages of cigarette-induced atherosclerosis, a condition that can lead to vascular disease, strokes, angina, and heart attacks.

Overall, few toxicologically effects result from direct stimulation of platelet aggregation. On the other hand, aspirin and inhibitors of prostaglandin synthetase, such as ibuprofen, inhibit platelet aggregation and can prolong bleeding times. In individuals with bleeding disorders, inhibition of platelet aggregation can lead to excessive blood loss. However, the impairment of clotting is actually beneficial to individuals who are at risk of strokes, angina (ischemia of the cardiac muscle, causing pain and potential arrhythmias), and heart attacks (myocardial infarction).

The most common platelets toxicity involves suppression of normal platelet number (thrombocytopenia). **Alkylating agents** used in the treatment of cancer are notorious for causing thrombocytopenia. For many of these cancer chemotherapeutics, their dosages are limited by potentially life-threatening thrombocytopenia, which can lead to hemorrhaging and death. The oncologist will frequently regulate the dose of alkylating agents based on the patient’s platelet count. As one would anticipate, hemorrhaging from the mucous membranes of the mouth, nose, and kidneys often reveals the onset of a deficiency in platelet-controlled clotting. Sometimes it is necessary to administer platelets or whole blood to treat a cancer patient who develops serious thrombocytopenia.

**DIRECT TOXICOLOGICAL EFFECTS ON THE RBC: IMPAIRMENT OF OXYGEN**

**TRANSPORT AND DESTRUCTION OF THE RED BLOOD CELL**

Two types of toxicities essentially affect red blood cells:

(1) competitive inhibition of oxygen binding to hemoglobin and

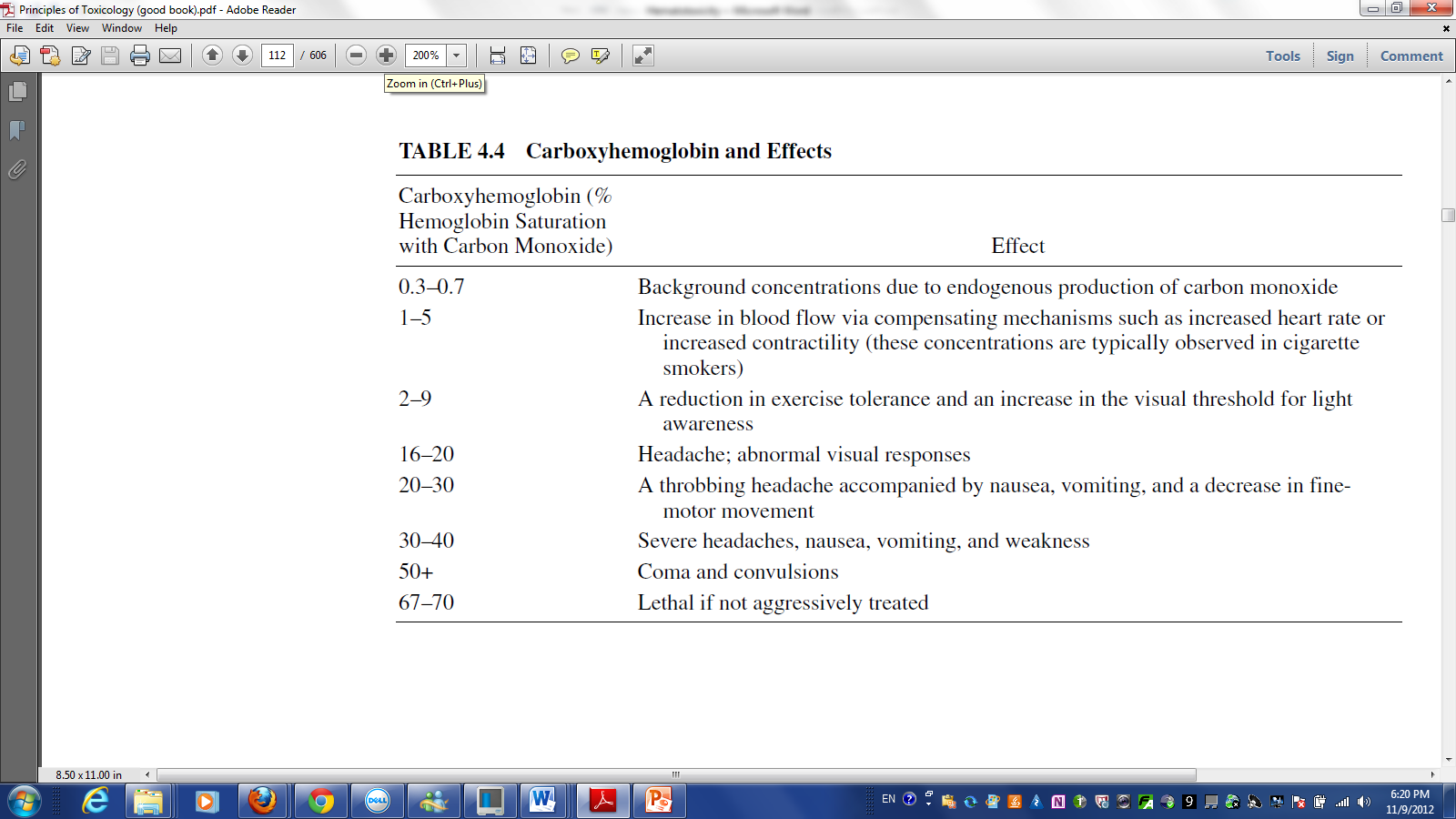
(2) chemically induced anemia in which the number of circulating erythrocytes is reduced in response to red blood cell damage. Inhibition of oxygen transport is the more commonly observed toxicity directly affecting the RBC.

**Carbon monoxide, cyanide, and hydrogen sulfide** bind to hemoglobin and can potentially interfere with its ability to transport oxygen. Carbon monoxide directly inhibits oxygen binding to hemoglobin, which can result in a spectrum of adverse effects ranging from mild subjective complaints to life-threatening hypoxia. The mechanism underlying carbon monoxide toxicity is one of the simpler toxicological phenomena, in terms of its binding to the iron molecule in hemoglobin. However, some of the consequences of carbon monoxide poisoning, such as cardiovascular and neurological effects, are much more complex and occasionally are associated with somewhat controversial outcomes (i.e., delayed neurological injury, such as memory loss, purportedly expressed as a reduction in neuropsychological

test performance).

While cyanide and hydrogen sulfide can also bind to the heme iron in hemoglobin, their significant toxic effects relate to inhibition of mitochondrial energy production.

Chemically induced methemoglobin and methemoglobinemia associated with hemolytic anemia occur by two different mechanisms. The first mechanism involves oxidation of hemoglobin (methemoglobin formation). The second mechanism involves oxidation of hemoglobin coupled to modification of RBC membrane proteins causing the RBC to be recognized as foreign by the immune system. The ultimate outcome of either type of toxicity is hypoxia.



**INORGANIC NITRATES/NITRITES AND CHLORATE SALTS**

In blood, equilibrium exists between ferrous and ferric hemoglobin. The oxygen-rich environment surrounding the RBC continually oxidizes hemoglobin to methemoglobin. Since methemoglobin doesnot bind and transport oxygen, the accumulation of methemoglobin is detrimental. Therefore, the accumulation of methemoglobin is prevented by the enzymatic reduction of ferric iron to ferrous iron via the enzyme methemoglobin reductase (also known as diaphorase). The normal concentration of methemoglobin is generally 0.5 percent or less, which produces no adverse health effects.

Methemoglobin formation results in a noticeable change in the color of blood from its normal red color to a brownish hue. In humans and animals, significant methemoglobinemia creates a bluish discoloration of the skin and mucous membranes. Mild to moderate concentrations of methemoglobin can be tolerated, and low levels of less than 10 percent may be asymptomatic, except for a slightly bluish color imparted to the mucous membranes. If blood methemoglobin concentrations achieve 15–20 percent of the total hemoglobin, clinical symptoms of hypoxia can develop, and above 20 percent, cardiovascular and neurological complications related to hypoxia may ensue.

Methemoglobin concentrations exceeding 40 percent are often accompanied by headache, dizziness, nausea, and vomiting, and levels surpassing 60 percent may be lethal. Other than supportive care to maximize oxygen transport, such as oxygen administration, little can be done to treat methemoglobinemia.

**One available antidote is the intravenous administration of methylene blue**, which provides reducing equivalents to methemoglobin reductase and thus facilitates the reduction of methemoglobin back to ferrous hemoglobin.

**Causes:**

Inorganic nitrites such as sodium nitrite (NaNO2) and chlorates (ClO3

−) oxidize ferrous hemoglobin (Fe2+) to ferric-hemoglobin (Fe3+ or methemoglobin). Nitrite and chlorate directly oxidize hemoglobin;nitrate, however, must first be reduced to nitrite by nitrifying bacteria in the gut. Exposures to nitrates, nitrites, and chlorates occur mostly in industrial settings or from contaminated drinking water.

The typical concentrations of nitrate and nitrite found in foods and drinking water, however, do not present a risk in terms of methemoglobin production. If the rate of hemoglobin oxidation caused bynitrite/chlorate exceeds the capacity of methemoglobin reductases activity, a buildup in methemoglobin results. The oxidative conversion of hemoglobin to methemoglobin by nitrites and chlorates, combined with the reduction of methemoglobin back to ferrous-hemoglobin, is referred to as a redox cycle.

Nitrates, in addition to their conversion to methemoglobin-causing nitrite, can produce a complex array of vascular changes, such as venous pooling (reduced blood return to the right side of the heart). Episodes of as venous pooling aggravate the clinical complications of methemoglobinemia; cardiac output is reduced and tissue hypoxia is exacerbated. Thus, nitrate toxicity presents a complicated clinical picture that integrates the production of methemoglobin with a reduction in blood perfusion to tissues most in need of oxygen. The hematologic hazards regarding nitrite and chlorate, on the other hand, appear to be limited to the direct oxidation of hemoglobin to methemoglobin.

**Methemoglobin leading to hemolytic anemia: aromatic amines and aromatic nitro compounds**

Aromatic amines and nitro compounds such as aniline and nitrobenzene cause methemoglobinemia by initiating a redox cycle in the RBC. The aromatic amines and nitro compounds are important building blocks in the dye, pharmaceutical, and agricultural chemical industries. Aromatic amines are also important structural components of numerous prescription medications. By in large, amine induced methemoglobinemia and hemolytic anemia develop most often following treatment with antibiotics such as dapsone and primaquine, pharmaceuticals used to treat infectious diseases such as leprosy and malaria, respectively.

However, unlike those for nitrites and chlorates, the potential hazards of aromatic amines are not limited to methemoglobinemia. RBC changes occurring during or after methemoglobin formation may result in damage to the RBC membrane. The damaged RBCs are recognized by splenic macrophages, which remove and destroy them. Hemolytic anemia can result if the number of red blood cells destroyed exceeds the bone marrow’s capacity to replenish them; for example, by amplification of RBC production in response to increased release of erythropoietin.

Reactive metabolite(s) of the parent aromatic amine compound, formed via cytochrome P450 metabolism, are also capable of causing methemoglobinemia and hemolytic anemia. Aromatic nitro compounds, like inorganic nitrate, must first be reduced to their respective aromatic amine by gut bacteria before being metabolized to an arylhydroxylamine. It is the N-hydroxyl metabolite that is directly responsible for initiating hemoglobin oxidation via a redox cycle. The redox cycle results in the formation of reactive oxygen species in the RBC (i.e., hydrogen peroxide). The reactive oxygen species oxidize proteins in the RBC cytoskeleton and damage the RBC membrane by crosslinking adjacent proteins. The crosslinked proteins can be visualized in the form of Heinz bodies, which consist of hemoglobin covalently linked to cytoskeletal proteins on the inner side of the red blood cell membrane. RBC membrane damage may alter the normal RBC discoid morphology, depicted in Figure 4.4 for dapsone N-hydroxylamine-induced RBC morphology alteration.

These spike-shaped RBCs produced by dapsone N-hydroxylamine are known as echinocytes. Other abnormally shaped RBCs that may result from exposure to various aromatic amines include anisocytes (asymetrically shaped RBCs); spherocytes (round RBCs); elliptocytes (ellipse or egg-shaped RBCs); sickle cell–shaped RBCs (known as drepanocytes); acanthocytes, which are round RBCs with irregular spiny projections; and stomatocytes, which are RBCs with a slit-like concavity. A senescent (aging) signal may appear on the membrane of the damaged red blood cell and serve as a recognition sign for the spleen. In effect, active oxygen species produced during redox cycles appear to cause premature aging and altered morphology of RBCs, leading to their early removal from circulation. Another name for redox cycle formation of reactive oxygen species and damage to the RBC is “oxidative stress.”

Instances of aromatic amine-induced methemoglobinemia and hemolytic anemia are rather rare.

This is due to their low volatility, which reduces inhalation exposure, and the fact that many of the amines are used in the form of salts, which reduces their potential for dermal absorption. The free amines, however, are dermally absorbed and can pose a potential hazard if directly contacted by the skin. Another serious concern with exposure to aromatic amines is their potential to induce hemorrhagic cystitis (bleeding from bladder damage) and bladder cancer.

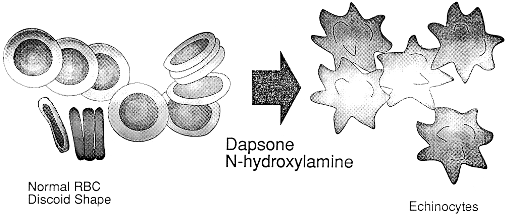


Figure 4.4 Dapsone N-hydroxylamine-induced Red Blood Cell Changes. Chemically induced damage to red blood cells is typically expressed as changes in red blood cell shape. The altered shape (morphology) results from damage to the cytoskeleton proteins or lipid membrane of the red blood cell.

Exposure to aromatic amines can be potentially life-threatening to individuals with a deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PDH). Individuals with deficiencies in G6PDH are limited in their ability to maintain sufficient levels of reduced glutathione (GSH) in their RBC.

GSH acts as a scavenger of active oxygen species such as hydrogen peroxide that are formed during the redox cycle. In the event of oxidative stress caused by an activated redox cycle, these individuals cannot withstand the oxidations of GSH to GS-SG (glutathione disulfide) or GS-S-protein, and they will suffer oxidative damage to the RBC membrane proteins at lower blood concentrations of N-hydroxy metabolites than normal people. G6PDH deficiency exists primarily among individuals of Mediterranean, African, and Asian decent. It can be tested for prior to initiation of drug therapy that may cause hemolytic anemia.

Treatment modalities for chemically induced hemolytic anemia are limited. Methylene blue may be administered to maximize the ability of methemoglobin reductase, which reduces methemoglobin back to ferrous hemoglobin. Transfusions may be necessary to replace red blood cells prematurely sequestered and destroyed by the spleen. There is no information on the use of glutathione-related antidotes such as N-acetyl cysteine. Mild conditions of chemically induced hemolytic anemia are not fatal and can be treated supportively. The extent of hemolysis induced by aromatic amines is proportionate to the amount of methemoglobin produced. Therefore, low levels of methemoglobin, in the general range of 20–30 percent or less, do not typically lead to extensive removal of red blood cells and anemia.

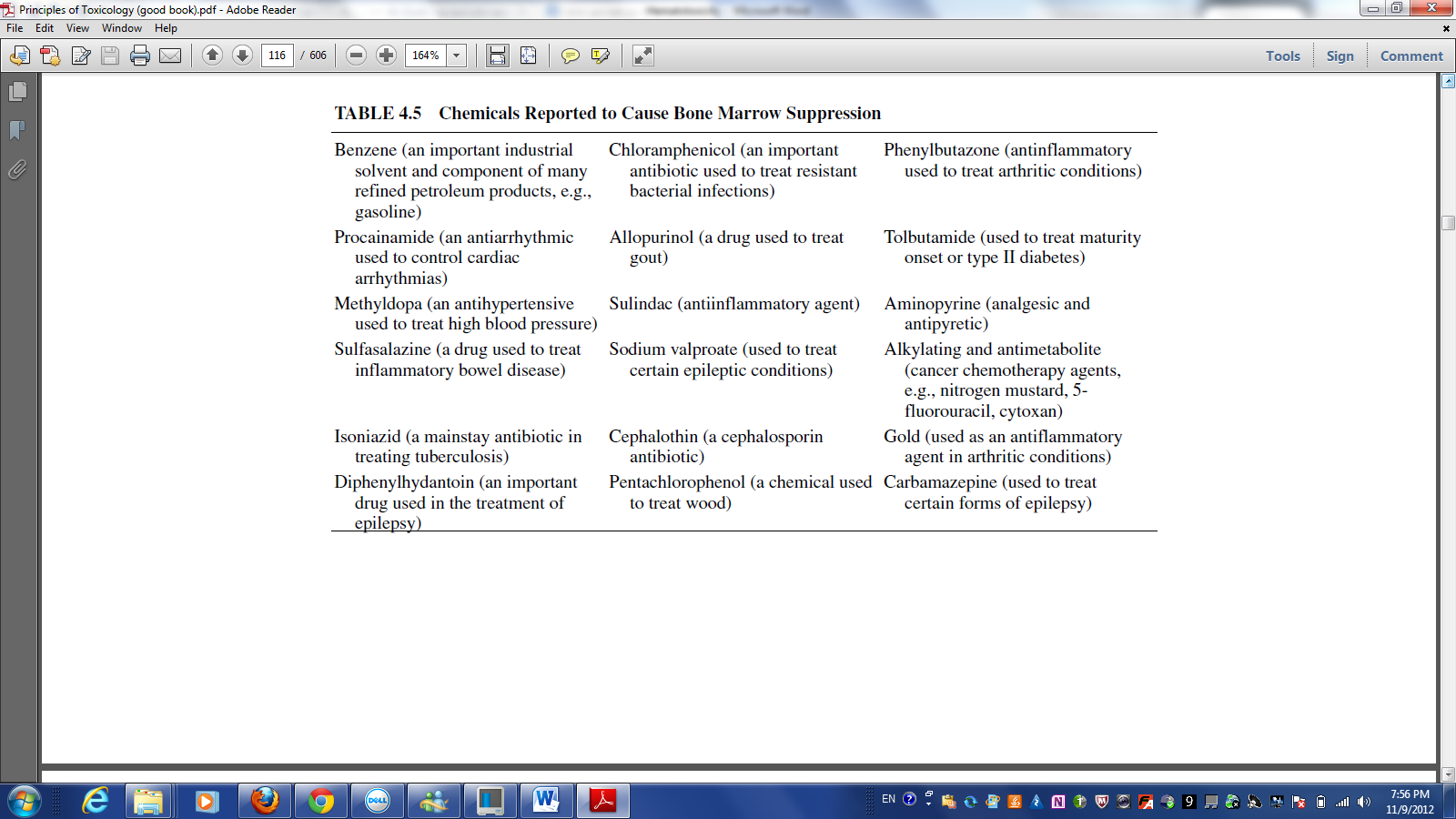
**Bone Marrow Suppression And Leukemias And Lymphomas**

**Bone Marrow Suppression**

A variety of industrial chemicals and pharmaceuticals can cause partial or complete bone marrow suppression. Pancytopenia occurs when all cellular elements of the blood are reduced. Bone marrow suppression may be reversible or permanent depending on the chemical agent and the extent of exposure. Clinical signs of bone marrow suppression include bleeding, caused by a reduction in platelet counts; anemia, which leads to fatigue and altered cardiovascular/respiratory parameters; and a heightened susceptibility to various infectious processes. The cells with the shorter lifespans are the first to disappear, such as the platelets, which have a circulating lifespan of only 9 or 10 days. Therefore, if the bone marrow injury involves the myeloid series, thrombocytopenia (i.e., reduction in the number of blood platelets) bleeding is one of the first complications to be observed. Patients with this condition are at a high risk for life-threatening internal hemorrhaging. Examples of occupational chemicals and drugs reported to cause blood dyscrasias (e.g., thrombocytopenia, neutropenia, pancytopenia) are listed in Table 4.5.

A known marrow suppressant, benzene was experimentally used decades ago to inhibit the uncontrollable production of leukemia cells. Today, the cancer chemotherapeutics are the most frequently encountered causes of bone marrow suppression.

The alkylating agents used in cancer chemotherapy are notorious for damaging the bone marrow and are often administered until the patient develops bone marrow suppression. In this event, the administration of further chemotherapy is discontinued, or more commonly, a reduction in the dose of the anticancer drug is attempted. Oncologists constantly monitor the patient’s platelet and white blood cell count in order to evaluate the bone marrow suppressive effects of the cancer chemotherapy. Chloram- phenicol is an important antibiotic used to combat strains of bacteria that are resistant to first-line antibiotics; however, it bears a well-recognized risk of bone marrow suppression. The drug phenylbutazone, once commonly used as an antiinflammatory agent for treating arthritic conditions, is now conservatively prescribed for only a few weeks at a time in order to reduce the chance of developing bone marrow suppression.



**CYANIDE (CN) POISONING**

Cyanide inhibits cytochrome oxidase, thus halting electron transport, oxidative phosphorylation, and aerobic glucose metabolism. Inhibition of glucose metabolism results in the buildup of lactate (lactic acidemia) and the increase in the concentration of oxygenated hemoglobin in venous blood returning to the heart. Increased oxyhemoglobin in the venous circulation reflects the fact that oxygen is not being utilized in the peripheral tissues. The most serious consequences of oxidative phosphorylation inhibition are related to neurological and cardiovascular problems, including adverse neurological sequelae, respiratory arrest, arrhythmia, and cardiac failure.

Cyanide exposure can occur via inhalation of hydrogen cyanide gas or through ingestion of sodium or potassium cyanide. Approximately 100 mgof sodium or potassium cyanide is lethal.

Sublethal doses of cyanide are quickly metabolized to thiocyanate via the enzyme rhodenase (a

sulfurtransferase):

Na2S2O3 + CN– → SCN– + Na2SO3

The detoxification of cyanide to thiocyanate is facilitated by adding the substrate sodium thiosulfate, which reacts with cyanide through the action of rhodenase. Thiocyanate (SCN–) is a relatively nontoxic substance eliminated in the urine.

**HYDROGEN SULFIDE (H2S) POISONING**

Hydrogen sulfide also inhibits mitochondrial respiration by inhibiting cytochrome oxidase thus halting the production of adenosine triphosphate, or ATP. Central nervous system effects ranging from reversible CNS depression to loss of consciousness and death may occur. Cardiac effects may include alterations in the rhythm and contractility of the heart. Less serious consequences of hydrogen sulfide include irritation, inflammatory changes, and edema of the mucous membranes of the eyes, nose, throat, and respiratory tract. The ppb odor threshold for hydrogen sulfide (i.e., the rotten-egg odor) in normal individuals far precedes concentrations causing adverse health effects, and for a short period of time can serve as a warning signal.

Hydrogen sulfide exposure can occur around sewers and petroleum refinery wastestreams and in situations involving natural gas production or fermentation, such as with manure or silage

(fodder for livestock stored in silos). Fortunately, most individuals are relatively sensitive to the odor of hydrogen sulfide and can detect it at ppb air concentrations, which provides an early warning. However, odor fatigue occurs with time and may result in a serious exposure if the individual remains in an area containing high or increasing concentrations of hydrogen sulfide. There are reports of individuals who are rapidly rendered unconscious and die from exposures to high levels of hydrogen sulfide, such as those exceeding 1000 ppm.