form of contraception that protects against unwanted pregnancies.

Anabolic Steroids

The use of steroids to increase performance by baseball players, track-and-field athletes, and wrestlers has received wide publicity during the past decade. Anabolic steroids are synthetic versions of testosterone, and for performance enhancement they are used at doses that are about 10 to 100 times higher than therapeutic indications. The high concentration of testosterone and its derivatives inhibits production and release of luteinizing hormone and follicle-stimulating hormone by a feedback mechanism, and increases the amount of estrogens, which are produced from anabolic steroids. Anabolic steroids have multiple adverse effects including stunted growth in adolescents, acne, gynecomastia, and testicular atrophy in males, and growth of facial hair and menstrual changes in women. Other effects include psychiatric disturbances and an increased risk of myocardial infarction. Hepatic cholestasis may develop in individuals receiving orally administered anabolic steroids.

Acetaminophen

Acetaminophen is the most commonly used analgesic in the United States. It is present in more than 300 products, alone or in combination with other agents. Hence, acetaminophen toxicity is common, being responsible for more than 50,000 emergency room visits per year. In the United States, it is the cause of about 50% of cases of acute liver failure, with 30% mortality. Intentional overdose (attempted suicide) is the most common cause of acetaminophen toxicity in Great Britain, but unintentional overdose is the most frequent cause in the United States, representing almost 50% of the total intoxication cases.

At therapeutic doses, about 95% of acetaminophen undergoes detoxification in the liver by phase II enzymes and is excreted in the urine as glucuronate or sulfate conjugates (Fig. 9-14). About 5% or less is metabolized through the activity of CYPs (primarily CYP2E) to NAPQI (*N*-acetyl-*p*-benzoquinoneimine), a highly reactive metabolite. NAPQI is normally conjugated with glutathione (GSH), but when acetaminophen is taken in large doses unconjugated *NAPQI* accumulates and causes hepatocellular injury, leading to *centrilobular necrosis* that may progress to *liver failure*. The injury produced by NAPQI involves two mechanisms: (1) covalent binding to hepatic proteins, which causes damage to cellular membranes and mitochondrial dysfunction, and (2) depletion of GSH, making hepatocytes more susceptible to reactive oxygen species-induced injury. Because alcohol induces CYP2E in the liver, toxicity can occur at lower doses in chronic alcoholics.

The window between the usual dose (0.5 gm) and the toxic dose (15 to 25 gm) is large, and the drug is ordinarily very safe. Toxicity begins with nausea, vomiting, diarrhea, and sometimes shock, followed in a few days by evidence of jaundice. Overdoses of acetaminophen can be treated at its early stages (within 12 hours) by administration of *N-acetylcysteine,* which restores GSH levels. In serious overdose liver failure ensues, starting with centrilobular necrosis that may extend to entire lobules; in such circumstances liver transplantation is the only hope for survival. Some patients also show evidence of concurrent renal damage.

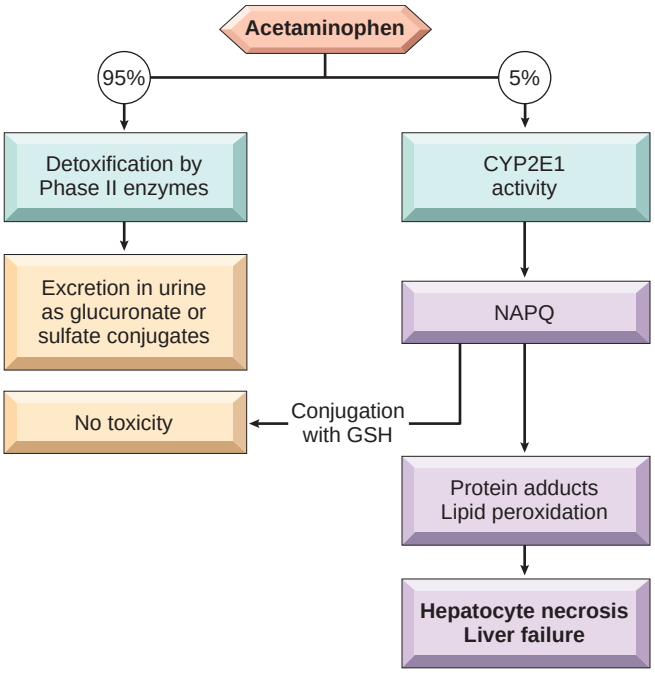

Figure 9-14 Acetaminophen metabolism and toxicity. (See text for details.) (Courtesy Dr. Xavier Vaquero, Department of Pathology, University of Washington, Seattle, Wash.)

Aspirin (Acetylsalicylic Acid)

Aspirin overdose may result from accidental ingestion of a large number of tablets by young children; in adults overdose is frequently suicidal. Much less commonly, salicylate poisoning is caused by the excessive use of ointments containing oil of wintergreen (methyl salicylate). Acute salicylate overdose causes alkalosis as a consequence of the stimulation of the respiratory center in the medulla. This is followed by metabolic acidosis and accumulation of pyruvate and lactate, caused by uncoupling of oxidative phosphorylation and inhibition of the Krebs cycle. Metabolic acidosis enhances the formation of non-ionized forms of salicylates, which diffuse into the brain and produce effects from nausea to coma. Ingestion of 2 to 4 gm by children or 10 to 30 gm by adults may be fatal, but survival has been reported after ingestion of doses five times larger.

Chronic aspirin toxicity (salicylism) may develop in persons who take 3 gm or more daily for long periods of time for treatment of chronic pain or inflammatory conditions. Chronic salicylism is manifested by headaches, dizziness, ringing in the ears (tinnitus), hearing impairment, mental confusion, drowsiness, nausea, vomiting, and diarrhea. The CNS changes may progress to convulsions and coma. The morphologic consequences of chronic salicylism are varied. Most often there is an acute erosive gastritis (Chapter 17), which may produce overt or covert gastrointestinal bleeding and lead to gastric ulceration. A bleeding tendency may appear concurrently with chronic toxicity, because aspirin acetylates platelet cyclooxygenase and irreversibly blocks the production of thromboxane A_2, an activator of platelet aggregation. Petechial hemorrhages may appear in the skin and internal viscera, and bleeding from gastric ulcerations may be exaggerated. With the recognition of gastric ulceration and bleeding as an important complication of ingestion of large doses of aspirin, chronic toxicity is now quite uncommon.