steatosis). The gastric changes are *acute gastritis* and *ulceration*. In the CNS, alcohol is a depressant, first affecting subcortical structures (probably the high brain stem reticular formation) that modulate cerebral cortical activity. Consequently, there is stimulation and disordered cortical, motor, and intellectual behavior. At progressively higher blood levels, cortical neurons and then lower medullary centers are depressed, including those that regulate respiration. Respiratory arrest may follow.

Chronic alcoholism affects not only the liver and stomach, but virtually all other organs and tissues as well. Chronic alcoholics suffer significant morbidity and have a shortened life span, related principally to damage to the liver, gastrointestinal tract, CNS, cardiovascular system, and pancreas.

- The *liver* is the main site of chronic injury. In addition to fatty change mentioned above, chronic alcoholism causes alcoholic hepatitis and cirrhosis, as described in Chapter 18. Cirrhosis is associated with portal hypertension and an increased risk for the development of hepatocellular carcinoma.
- In the *gastrointestinal tract*, chronic alcoholism can cause massive bleeding from gastritis, gastric ulcer, or esophageal varices (associated with cirrhosis), which may be fatal.
- *Thiamine (vitamin B_1) deficiency* is common in chronic alcoholics. The principal lesions resulting from this deficiency are *peripheral neuropathies* and the *Wernicke-Korsakoff syndrome* (see Table 9-9 in this chapter and Chapter 28); cerebral atrophy, cerebellar degeneration, and optic neuropathy may also occur.
- Alcohol has diverse effects on the cardiovascular system. Injury to the myocardium may produce dilated congestive cardiomyopathy (*alcoholic cardiomyopathy*, discussed in Chapter 12). Chronic alcoholism is also associated with an increased incidence of hypertension, and heavy alcohol consumption, with attendant liver injury, results in decreased levels of HDL, increasing the likelihood of coronary heart disease.
- Excessive alcohol intake increases the risk of *acute and chronic pancreatitis* (Chapter 19).
- The use of ethanol during pregnancy can cause *fetal alcohol syndrome*, which is marked by microcephaly, growth retardation, and facial abnormalities in the newborn, and reduction in mental functions as the child grows older. It is difficult to establish the minimal amount of alcohol consumption that can cause fetal alcohol syndrome, but consumption during the first trimester of pregnancy is particularly harmful. It has been estimated that the prevalence of frequent and binge drinking among pregnant women is approximately 6% and that fetal alcohol syndrome affects 1 to 4.8 per 1000 children born in the United States.
- Chronic alcohol consumption is associated with an *increased incidence of cancer* of the oral cavity, esophagus, liver, and, in women, possibly the breast. Acetaldehyde is considered to be the main agent associated with alcohol-induced laryngeal and esophageal cancer, in that acetaldehyde-DNA adducts have been detected in some tumors from these tissues. Individuals with one copy of the ALDH2*2 allele who drink are at a higher risk for developing cancer of the esophagus. As mentioned earlier, alcohol and cigarette smoke synergize in the causation of various cancers.
- Ethanol is a substantial source of energy (empty calories). Chronic alcoholism leads to malnutrition and nutritional deficiencies, particularly of the B vitamins.

Not all is gloom and doom, however. Moderate amounts of alcohol (about 20-30 gm/day, corresponding to approximately 250 mL of wine) have been reported to increase high-density lipoprotein (HDL) levels, inhibit platelet aggregation, and lower fibrinogen levels, providing a possible basis for protective effects against coronary heart disease. More broadly, epidemiologic studies have linked light to moderate alcohol consumption with increased overall survival as compared to teetotalers and heavy drinkers. Although it remains uncertain whether these survival benefits are due to alcohol consumption per se or to other covariates (e.g., having a lifestyle that permits one to enjoy a good glass of wine on a daily basis), it seems that the old saying is true, at least with respect to alcohol—all things in moderation!

KEY CONCEPTS

Alcohol—Metabolism and Health Effects

- Acute alcohol abuse causes drowsiness at blood levels of approximately 200 mg/dL. Stupor and coma develop at higher levels.
- Alcohol is oxidized to acetaldehyde in the liver by alcohol dehydrogenase, by the cytochrome P-450 system, and by catalase, which is of minor importance. Acetaldehyde is converted to acetate in mitochondria and utilized in the respiratory chain.
- Alcohol oxidation by alcohol dehydrogenase depletes NAD, leading to accumulation of fat in the liver and metabolic acidosis.
- The main effects of chronic alcoholism are fatty liver, alcoholic hepatitis, and cirrhosis, which leads to portal hypertension and increases the risk for development of hepatocellular carcinoma.
- Chronic alcoholism can cause bleeding from gastritis and gastric ulcers, peripheral neuropathy associated with thiamine deficiency, alcoholic cardiomyopathy, and acute and chronic pancreatitis.
- Chronic alcoholism is a major risk factor for cancers of the oral cavity, larynx, and esophagus. The risk is greatly increased by concurrent smoking or use of smokeless tobacco.

Injury by Therapeutic Drugs and Drugs of Abuse

Injury by Therapeutic Drugs (Adverse Drug Reactions)

Adverse drug reactions refer to untoward effects of drugs that are given in conventional therapeutic settings. These reactions are extremely common in the practice of medicine; an exotic, but easily seen example is discoloration of the skin caused by the antibiotic minocycline (Fig. 9-13).