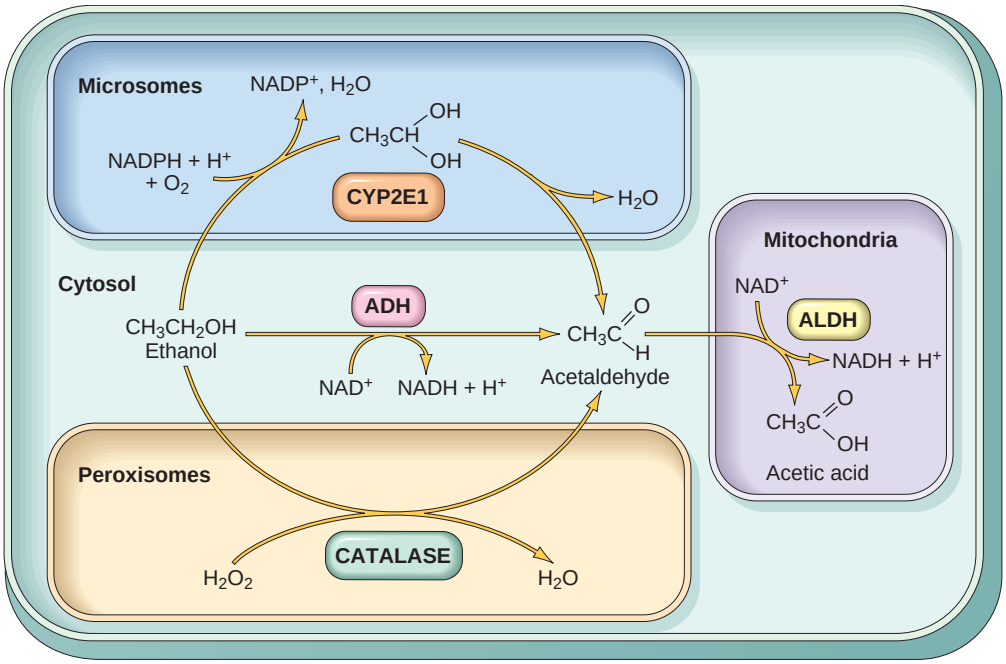

Figure 9-12 Metabolism of ethanol: oxidation of ethanol to acetaldehyde by three different routes and the generation of acetic acid. Note that oxidation by ADH (alcohol dehydrogenase) takes place in the cytosol; the cytochrome P-450 system and its CYP2E1 isoform are located in the endoplasmic reticulum (microsomes), and catalase is located in peroxisomes. Oxidation of acetaldehyde by ALDH (aldehyde dehydrogenase) occurs in mitochondria. ADH oxidation is the most important route; catalase is involved in only 5% of ethanol metabolism. Oxidation through CYPs may also generate reactive oxygen species (not shown). (From Parkinson A: Biotransformation of xenobiotics. In Klassen CD [ed]: Casarett and Doull's Toxicology: The Basic Science of Poisons, 6th ed. New York, McGraw-Hill, 2001, p 133.)

produced by alcohol metabolism is converted to *acetate* by acetaldehyde dehydrogenase, which is then utilized in the mitochondrial respiratory chain.

The microsomal oxidation system involves CYPs, particularly CYP2E1 located in the smooth endoplasmic reticulum. Induction of CYPs by alcohol explains the increased susceptibility of alcoholics to other compounds metabolized by the same enzyme system, which include drugs, anesthetics, carcinogens, and industrial solvents. Note, however, that when alcohol is present in the blood at high concentrations, it competes with other CYP2E1 substrates and delays drug catabolism, potentiating the depressant effects of narcotic, sedative, and psychoactive drugs in the CNS.

The oxidation of ethanol produces toxic metabolites and disrupts certain metabolic pathways, the most important of which include the following:

- *Acetaldehyde*, the direct product of alcohol oxidation, has many toxic effects and is responsible for some of the acute effects of alcohol and for the development of oral cancers. The efficiency of alcohol metabolism varies between populations, depending on the expression levels of alcohol dehydrogenase and acetaldehyde dehydrogenase isozymes, and the presence of genetic variants that alter enzyme activity. About 50% of Asians have very low alcohol dehydrogenase activity, due to the substitution of lysine for glutamine at residue 487 (the normal allele is termed ALDH2*1 and the inactive variant is designated as ALDH2*2). The ALDH2*2 protein has dominant-negative activity, such that even one copy of the ALDH2*2 allele reduces acetaldehyde dehydrogenase activity significantly. Individuals homozygous for the ALDH2*2 allele are completely unable to oxidize acetaldehyde and cannot tolerate alcohol, experiencing nausea, flushing, tachycardia, and hyperventilation after its ingestion.
- Alcohol oxidation by alcohol dehydrogenase causes the reduction of nicotinamide adenine dinucleotide (NAD) to NADH, with a consequent decrease in NAD and increase in NADH. NAD is required for fatty acid oxidation in the liver and for the conversion of lactate into pyruvate. Its deficiency is a main cause of the accumulation of fat in the liver of alcoholics. The increase in the NADH/NAD ratio in alcoholics also causes lactic acidosis.
- Metabolism of ethanol in the liver by CYP2E1 produces reactive oxygen species, which cause lipid peroxidation of hepatocyte cell membranes. Alcohol also causes the release of endotoxin (lipopolysaccharide) from gram-negative bacteria in the intestinal flora, which stimulates the production of TNF (tumor necrosis factor) and other cytokines from macrophages and Kupffer cells, leading to hepatic injury. However, it must be said that the mechanisms by which alcohol causes liver injury remain to be completely defined.

The adverse effects of ethanol can be classified as acute or chronic.

Acute alcoholism exerts its effects mainly on the CNS, but it may induce hepatic and gastric changes that are reversible if alcohol consumption is discontinued. Even with moderate intake of alcohol, multiple fat droplets accumulate in the cytoplasm of hepatocytes (*fatty change* or *hepatic*