4.1. Interaction of the Metabolism of Ethanol and Lipids

Ethanol interference with lipid metabolism may lead not only to the well-known deposition of neutral lipids in the liver (Fig. 4.1) and some other tissues but also to functional disturbances because of changes in the lipid environment of cellular membranes. Ethanol-induced lipid changes have been implicated in the pathogenesis of diseases such as pancreatitis, hemolytic anemia, cardiomyopathy, and atherosclerosis.

4.1.1. Effects of Excessive Hepatic NADH Generation

The oxidation of ethanol results in the transfer of hydrogen to NAD. During this process, the redox potential of the liver shifts to a more reduced level, indicating that the hepatocytes' capacity to handle reducing equivalents has been exceeded. The altered redox level is reflected in an enhanced NADH-to-NAD ratio, and, in turn, this excess NADH produces changes in the flux of other substrates and alters the ratio of those metabolites that are dependent for reduction on the NADH/NAD couple. It was therefore proposed that the altered NADH/NAD ratio is responsible for a number of metabolic abnormalities associated with alcohol abuse, including alterations of lipid metabolism (Lieber and Davidson, 1962).

In the absence of ethanol, the reducing equivalents utilized in the respiratory chain are provided mainly by the oxidation of fatty acids. During the oxidation of ethanol, the activity of the citric acid cycle is depressed (Forsander et al., 1965; Lieber et al., 1967), partly because of a slowing of the reactions of the cycle that require NAD. The mitochondria then use the hydrogen equivalents originating from ethanol rather than from oxidation through the citric acid cycle of two-carbon fragments derived from fatty acids. Thus, fatty acids that normally serve as the main energy source of the liver are supplanted by ethanol. Decreased fatty acid oxidation caused by ethanol has been demonstrated in liver slices (Blomstrand et al., 1973; Lieber and Schmid, 1961), perfused liver (Lieber et al., 1967), isolated hepatocytes (Ontko, 1973), and in vivo (Blomstrand and Kager, 1973). This decrease in fatty acid oxidation results in the deposition of dietary fat in the liver, when available, or fatty acids derived from endogenous synthesis in the absence of dietary fat (Lieber et al., 1966a, 1969; Lieber and Spritz, 1966; Mendenhall, 1972).

The increased NADH-to-NAD ratio is also associ-
associated with a rise in the concentration of α-glycerophosphate (Nikkilä and Ojala, 1963), which favors hepatic triglyceride accumulation by trapping fatty acids. Theoretically, lipogenesis at all levels (enhanced synthesis of fatty acid, triacylglycerols, and cholesterol and/or its esters) can be considered as metabolic systems whereby excess reducing equivalents formed during the oxidation of ethanol can be utilized. In vitro studies in rats (Gordon, 1972; Lieber and Schmid, 1961) and in humans (Holmström, 1969) have demonstrated that in the presence of ethanol, lipogenesis is increased, possibly by the elongation pathway of transhydrogenation to nicotinamide adenine dinucleotide phosphate (NADPH) (Lieber, 1968). However, this pathway may only participate in removing excess NADH under limited conditions, for in in vitro experiments in naive rats following an acute dose of ethanol, no evidence of enhanced fatty acid synthesis was observed (Guynn et al., 1973). In animals consuming ethanol for prolonged periods of time, conflicting results have been obtained. Arakawa et al. (1975) found an increase in lipogenesis, and Savolainen et al. (1977a) found no change. In monkeys, hepatic steatosis after alcohol was accompanied by increased incorporation of [14C]acetate (Vasdev et al., 1974). In vitro, addition of ethanol caused a 20% decreased incorporation of tritium into fatty acids, probably because of a decrease in the specific activity of the NADPH (Selmer and Grunnet, 1976).

The effects observed following an acute dose of ethanol and those in animals consuming ethanol for prolonged periods of time differ (Salaspuro et al., 1981). After chronic ethanol consumption, the acute inhibition of fatty acid oxidation fades (Salaspuro et al., 1981) in keeping with the attenuation of the redox change discussed previously in Chapter 1.

### 4.1.2. Interaction of Ethanol with Hepatic Microsomal Lipid Metabolism

Most of the enzymes involved in the synthesis of complex lipids (such as triacylglycerols and phospholipids) and lipoproteins are bound to the membranes of the endoplasmic reticulum. Since ethanol is also metabolized by the microsomal enzyme system, it may inter-