Alcoholic liver injury

By MICHAEL DAVIS, *Department of Gastroenterology, Royal United Hospital, Bath BA1 3NG*

Over the past decade there has been a steady increase in the per capita consumption of alcohol in the UK (Chick, 1982). Numerous studies from many parts of the world have demonstrated a clear correlation between mortality from cirrhosis of the liver and the average quantity of alcohol drunk in that locality (Seeley, 1960; Stone *et al.* 1968; Rankin *et al.* 1975; Morgan, 1981). Population studies have shown that the prevalence of potentially hazardous drinking in a population increases in proportion to the average consumption (Rankin *et al.* 1975; Chick, 1982), and the frequency and mortality from alcohol-related diseases changes in parallel. The calculated incidence of alcoholic cirrhosis in patients presenting to Dudley Road Hospital, Birmingham, increased fivefold over the time-period 1959-1976. The incidence of cirrhosis from other causes remained essentially unchanged (Saunders *et al.* 1981*a*,*b*).

Spectrum of alcoholic liver injury

Some individuals who abuse alcohol may show no histological abnormality in the liver, although more-detailed assessment often reveals swelling of hepatocytes due to accumulation of water and protein (Orrego *et al.* 1980; Volentine *et al.* 1984). These abnormalities resolve rapidly on cessation of drinking.

Fatty infiltration of the liver is the earliest gross hepatic lesion seen in association with alcohol abuse (Rubin & Lieber, 1968). Macrovesicular fat droplets accumulate within hepatocytes because fatty acid oxidation is impaired. This is partly due to depression of the TCA cycle consequent on increased NADH:NAD resulting from the conversion of ethanol to acetaldehyde by the enzyme alcohol dehydrogenase (*EC* 1.1.1.1) (Lieber & De Carli, 1977). Damage to mitochondria by ethanol or its metabolites also probably plays a role (Arai *et al.* 1984), and a toxic effect on the hepatocyte Golgi apparatus is also likely to be important (Marinari *et al.* 1984). The quantity of fat in the diet is important in determining the degree of steatosis induced by alcohol; for a given alcohol intake, more steatosis develops with a normal-fat diet than with a low-fat diet (Lieber & De Carli, 1973). Dietary deficiencies in lipotropic factors such as choline and methionine are unlikely to be of major importance in pathogenesis of alcoholic fatty liver. The lesion cannot be prevented by massive choline supplementation in volunteer subjects (Rubin & Lieber, 1968), and furthermore the hepatic lipid composition in the two conditions is different; in alcoholic steatosis hepatic phospholipid content increases whereas in choline deficiency it decreases (Ashworth *et al.* 1961; Lieber *et al.* 1965).

Of patients who abuse alcohol, 30–50% will develop alcoholic hepatitis, a condition characterized by inflammatory cell infiltration in the liver parenchyma, hepatic necrosis and eosinophilic cytoplasmic inclusions within hepatocytes known as Mallory's hyaline. A proportion of patients with this condition will progress to cirrhosis (Rubin & Lieber, 1975).

Factors predisposing to alcoholic liver injury

Overall there is evidence that ethanol is a cumulative hepatotoxin, and there is a broad correlation between the severity of the liver lesion and the quantity and duration of heavy drinking (Pequignot *et al.* 1974; Lelbach, 1975). However, there are wide

individual variations, and the correlation is by no means an absolute one. Various factors have been invoked in an attempt to explain individual differences in the evolution of alcoholic liver injury, including the pattern of drinking, and constitutional factors such as the sex of the drinker, immunological mechanisms and nutritional status.

Pattern of drinking. Clinical studies indicate that a steady, sustained intake of alcohol is more likely to lead to development of cirrhosis than binge drinking (Brunt *et al.* 1974). A recent experimental study on rats fed on alcohol has shown that those animals which developed inflammatory changes in the liver had higher and more-sustained blood ethanol concentrations than those which did not (Tsukamoto *et al.* 1985).

Heavy drinkers are a heterogeneous group, and those who present with physical complications such as liver disease seem to differ in many respects from those presenting with social or psychological problems. Attention was drawn to these different forms by Jellinek (1960) who defined beta alcoholics as those who were not physically dependent on alcohol, but who often succumbed to medical complications, whereas gamma alcoholics were severely dependent and suffered severe behavioural problems. Using standard criteria for alcohol dependency, Wodak *et al.* (1983) found that patients presenting with liver disease were only mildly dependent, in contrast to those presenting to a psychiatric unit who were heavily so. It is possible that the latter group are protected against development of significant liver disease by their more-sporadic drinking pattern, and the fact that they tend to come to medical attention at an earlier stage in their drinking history. In keeping with this the highly dependent group were significantly younger on initial presentation than those with liver disease.

Constitutional factors. (1) *Sex.* A number of clinical and epidemiological studies have demonstrated that women appear to be more susceptible to the severe end of the spectrum of alcoholic liver injury than their male counterparts (Pequignot *et al.* 1974; Saunders *et al.* 1981*a*,*b*). Thus, comparing cumulative lifetime alcohol consumption in patients presenting with alcoholic cirrhosis to a specialist liver unit, it was found that women had drunk significantly less alcohol per day than men (88 (SE 5) and 130 (SE 6) g ethanol equivalent/d respectively) for a significantly shorter period of time (21 (SE 1) years for males, 12·1 (SE 1·2) years for females) (Saunders *et al.* 1982). Whilst differences in body size and composition may partly be responsible for this greater susceptibility of women, these cannot provide the whole explanation, and other factors including hormonally-induced variations in ethanol metabolism and immune reactivity may well be important, although there is little information on these.

(2) *HLA type.* Many studies have demonstrated the value of HLA antigens as genetic markers in human disease (Dick, 1978), and there are now several reports in the literature seeking associations between HLA antigens and different types of alcohol-induced liver injury (Eddleston & Davis, 1982). Taken individually the results of these studies have often been conflicting and difficult to interpret. This is largely because the distribution of HLA antigens varies between ethnic groups, and it is not the HLA antigen itself which confers susceptibility to a given disease, but rather a gene to which it is closely linked. In the UK there is evidence that the histocompatibility antigen HLA B8 is associated with enhanced susceptibility to the development of alcoholic cirrhosis (Morgan *et al.* 1980; Saunders *et al.* 1982). Patients with this haplotype developed cirrhosis after a significantly shorter period of alcohol consumption compared with those without, and this effect was independent of the sex of the individual.

Ethanol metabolism. The main intermediate product of ethanol metabolism is acetaldehyde, and much attention has been focused on the possible role of this very toxic compound in the production of alcoholic liver injury (Lieber, 1980). Thus, it has been shown that acetaldehyde can increase collagen synthesis, contributing to hepatic fibrosis

(Holt *et al.* 1984; Savolainen *et al.* 1984). In experimental animal models, the development of hepatic fibrosis in response to ethanol feeding has been shown to be associated with a decrease in hepatic storage capacity for vitamin A (Mak *et al.* 1984), and a similar sequence of events has been observed in the livers of patients with alcoholic liver disease (Tozuka *et al.* 1985); it has been suggested that the fat-storing Ito cells, which also store vitamin A, undergo transformation into fibroblasts. Acetaldehyde also has the capacity to bind to hepatocyte proteins (Medina *et al.* 1985), which may lead to their denaturation and subsequent liver injury, possibly via complement activation (Barry *et al.* 1984; Barry & McGiven, 1985).

Some years ago it was demonstrated that administration of alcohol to chronic abusers of alcohol led to significantly higher blood levels of acetaldehyde compared with normal individuals (Korsten *et al.* 1975). This effect could be due to increased production or decreased detoxification of acetaldehyde, or both. Evidence for the former is scanty, and although it has been suggested that individual differences in the profile of alcohol dehydrogenase enzymes, with different affinities for catalysing the conversion of ethanol to acetaldehyde, could be important, conclusive evidence is lacking (Bosron & Li, 1986). The activity of acetaldehyde dehydrogenase, the enzyme responsible for detoxification of acetaldehyde, has also been investigated and subnormal levels have been found in liver biopsy specimens from patients with alcoholic liver disease. These rose towards normal in patients who abstained, but remained low in those who continued to drink, demonstrating that impaired degradation of acetaldehyde is secondary to alcohol-induced liver damage rather than a primary defect (Jenkins *et al.* 1984).

It has been demonstrated that acetaldehyde can bind to liver plasma membranes without damaging their functional integrity (Barry & McGiven, 1985). Such binding might, however, lead to alteration in antigenicity of the liver plasma membrane which could stimulate a cell-damaging immunological attack. Immunological abnormalities are well documented in patients with alcoholic cirrhosis (MacSween, 1986), and Neuberger *et al.* (1984) demonstrated that 43% of patients with alcoholic liver disease had circulating antibodies directed specifically against a novel antigen, which was generated in rabbit hepatocytes following chronic dosing with ethanol in vivo. The presence of the antibody, which implies the generation of a similar ethanol-related antigen in the patients' own livers, was evenly distributed between patients with fatty liver, alcoholic hepatitis and cirrhosis. In a subsequent study, it was shown that expression of the altered hepatocyte antigen could be prevented by inhibiting metabolism of ethanol to acetaldehyde by 4-methylpyrazole. Conversely, pretreatment with disulphiram to inhibit oxidation of acetaldehyde, potentiated the appearance of the new antigenic determinant (Crossley *et al.* 1986). These, and other similar studies (Poralla *et al.* 1984; Izumi *et al.* 1985) suggest that immune mechanisms directed against altered liver-cell determinants may be important in the pathogenesis of alcoholic liver disease in some patients, and that acetaldehyde or one of its metabolites is central to the antigenic alteration of hepatocytes.

Free radical-induced liver injury. Peroxidative damage to liver membrane lipids mediated via acetaldehyde has been postulated as a mechanism for the production of alcoholic hepatitis and cirrhosis (Lewis & Paton, 1982) as well as ethanol-induced fatty liver (DiLuzio & Hartman, 1967). Evidence for such a process in man comes from the demonstration that plasma levels of a marker for lipid peroxidation, namely the Δ9,11-isomer of linoleic acid, are elevated during alcohol ingestion in subjects who abuse alcohol (Fink *et al.* 1985; Thurnham *et al.* 1986*a*). This abnormality is not seen as a consequence of alcohol ingestion in normal controls, suggesting that continued high levels of intake lead to an alteration of ethanol metabolism favouring lipid peroxidation.

Subjects receiving disulphiram, which leads to the accumulation of acetaldehyde, had higher plasma levels of Δ9,11-linoleic acid than those not taking this drug, supporting a role for acetaldehyde or one of its metabolites in the peroxidative process.

Nutritional factors. Following the studies of Lieber *et al.* (1975), which demonstrated that feeding alcohol to baboons was followed by development of cirrhosis despite the intake of a nutritionally adequate diet, interest in the possible importance of nutritional factors waned. However, the body has a number of defence mechanisms against lipid peroxidation, whose integrity depends on adequate nutritional status with essential cofactors. Some of these have been investigated in patients with alcoholic liver disease and found to be impaired.

Superoxide dismutase (*EC* 1.15.1.1) protects cell membranes against peroxidative injury, and exists in two forms, one containing manganese and localized predominantly in mitochondria, and the second containing copper and zinc with a mainly cytosolic distribution. Experimental studies in monkeys (Keen *et al.* 1985) have shown a decrease in hepatic Zn concentration with a parallel reduction in activity of the cytosolic isoenzyme; there was a compensatory increase in the mitochondrial enzyme. Dietary deficiencies in Cu, Zn and Mn could therefore theoretically increase susceptibility to peroxidative injury, but this remains to be proved.

Another trace element important in protecting against lipid peroxidation is selenium, a component of glutathione peroxidase (*EC* 1.11.1.9). Subnormal circulating levels of this trace metal have been demonstrated in alcoholics (Dworkin *et al.* 1985; Corpela *et al.* 1985), the extent of deficiency correlating with the severity of liver disease, although whether Se deficiency is secondary to alcohol abuse or to the hepatic damage which it produces requires further clarification.

Circulating levels of another important antioxidant, vitamin E, have also been investigated in patients abusing alcohol. A significantly higher incidence of deficiency was observed compared with normal-age and sex-matched control subjects (Thurnham *et al.* 1986*a*,*b*).

The role of glutathione in protecting liver cells against injury by free radicals and other toxic metabolites is well established. Subnormal hepatic levels of this compound have been demonstrated in the livers of patients with alcoholic liver disease, correlating with increased markers of lipid peroxidation (Shaw *et al.* 1983). Whilst glutathione depletion may arise as a result of increased demand for detoxification of ethanol-derived metabolites, there is also evidence that alcohol exerts a direct suppressive effect on hepatic glutathione synthesis (Lauterburg *et al.* 1984).

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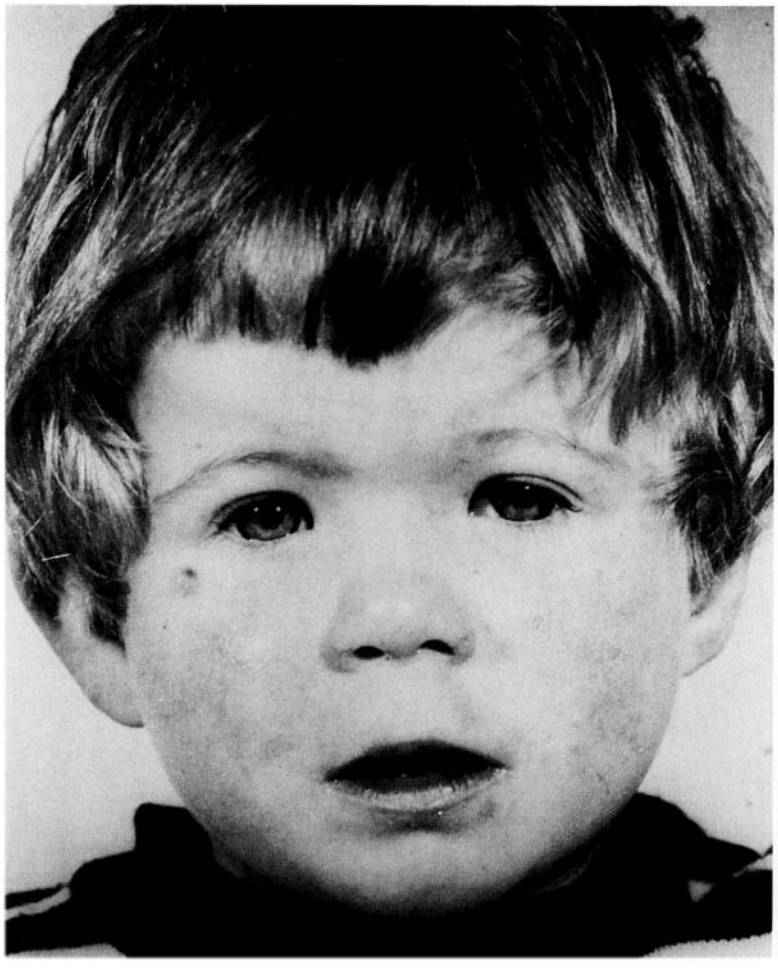

EXPLANATION OF PLATE

Plate 1. Face of toddler with fetal alcohol syndrome. The eyes are small, with epicanthic folds. The bridge of the nose is poorly formed, and the philtrum absent.

JOHN BEATTIE

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