Progress report

Alcohol and the liver

The process . . . is commonly produced by a long habit of drinking spirituous liquors.

Matthew Baillie

The use and abuse of alcohol is almost as old as mankind itself. Appreciation of its toxic effects, especially those with more dramatic impact on the central nervous system, is only just younger. That the liver may be damaged by prolonged alcohol ingestion has been realized at least since the time of Vesalius, and the association is now so firmly accepted in popular thinking that to the layman the term 'cirrhosis' usually connotes alcoholism. The purpose of this report is to review briefly the metabolic and structural effects of alcohol upon the liver and to examine this association in the light of current concepts.

Metabolism of Ethanol

The liver is the site of metabolic degradation of approximately 95% of ingested ethanol. Initially there is oxidation to acetaldehyde which is then converted to acetyl coenzyme A. A final step is oxidation to carbon dioxide via the citric acid cycle. Until recently it was thought that the critical initial stage was catalysed solely by the cytoplasmic enzyme alcohol dehydrogenase¹. It is now known that at least one other site of oxidation exists—in this case the microsomal fraction². The relative importance of this microsomal ethanol oxidizing system is not yet known, but since microsomal enzymes are capable of adaptive increase of activity or 'induction' the existence of this alternative pathway of alcohol metabolism may explain in part the phenomenon of tolerance in the alcoholic^{3,4}. It is possible that other non-microsomal enzymes (catalases) may be involved in a small proportion of ethanol degradation. Ethanol oxidation results in alteration of the redox potential with an increase in reduced nicotinamide adenine dinucleotide (NADH), that is, an increase in the NADH/NAD ratio. This has important consequences for both fat and carbohydrate metabolism.

Metabolic Effects of Ethanol Ingestion

EFFECTS ON MICROSOMAL ENZYMES

The resultant effects of acute and prolonged ethanol ingestion are partly adaptive and partly toxic. The enhanced ability to metabolize alcohol with continuing ingestion already referred to may be related to induction of the microsomal ethanol oxidizing system. This is paralleled in the recent observations that ethanol increases the activity of pentobarbitone hydroxylase in man⁵. Hence alcohol appears to share some of the features of drugs such

as phenobarbitone which are capable of inducing microsomal enzyme systems. These findings provide an explanation for the well known observation that alcoholics not under the immediate influence of alcohol are unusually resistant to the effects of sedative drugs⁵. The interactions of ethanol with other pharmacological agents is now actively under study; the importance of such work, especially with common therapeutic drugs like anticoagulants, can hardly be over emphasized. Such adaptive metabolic changes resulting from ethanol ingestion are mirrored in some of the organelle changes visible on electron microscopy, notably increase in size of the smooth endoplasmic reticulum (microsomes)^{6,7}.

EFFECTS ON FAT METABOLISM

The widespread effects of alcohol on fat metabolism are complex and still a matter of dispute. Lack of comparability of results obtained in the rat and in man makes for difficulties in interpretation. Fatty acid synthesis is increased⁸ as also is the conversion of fatty acids to triglyceride⁹. In contrast fatty acid oxidation is reduced¹⁰. There is evidence that synthesis of lipoprotein is increased¹¹ but the release of lipoprotein from the liver cell may be impaired. Lipid peroxidation may be enhanced, and uptake by tissues of triglyceride impaired. The result of these effects is both fatty deposition in the liver and hyperlipidaemia but the relative importance of the various mechanisms is not yet understood¹². Several factors probably affect which mechanism predominates; factors such as the duration and size of the ethanol 'load', the diet and nutritional state of the subject, and, to some extent, the sex. In acute alcohol experiments most of the lipid accumulated in the liver can be shown to be of extrahepatic origin⁹. In this situation the source of fat is predominantly adipose tissue. Under more chronic conditions dietary fat is important¹³. Although defective protein synthesis with failure of the lipoprotein mechanism for clearing lipid from the liver may cause fatty liver with such toxic agents as carbon tetrachloride, there is no evidence that this mechanism is important for alcohol, except possibly with very high concentrations.

EFFECTS ON CARBOHYDRATE METABOLISM

Ethanol may produce either hyperglycaemia or hypoglycaemia depending largely on the condition of the individual¹⁴. Where glycogen stores are reduced, as for instance following a period of fasting or starvation, hypoglycaemia is likely to occur. This is an important cause of unconsciousness following an ethanolic debauch which is easily overlooked. The fall-off in hepatic glucose output seems to be due to inhibition of gluconeogenesis at the pyruvate carboxylase stage which in turn is a direct result of the alteration of the cell redox potential (NADH/NAD ratio), one effect of which is to lower available pyruvate¹⁵. Since utilization of glucose in the tissues is also inhibited by ethanol, hypoglycaemia only occurs when this effect is swamped by a larger fall-off in hepatic glucose output¹⁶.

OTHER METABOLIC EFFECTS

There are many other metabolic consequences of alcohol outside the scope of this review¹⁷. One having some clinical importance is the effect on porphyrin metabolism. Moderate acute alcohol ingestion leads to coproporphyrinuria even in normal healthy subjects. Alcoholics consistently excrete coproporphyrin III¹⁸ and in a small proportion a frank acquired porphyria cutanea

tarda develops. There is skin fragility, photosensitivity, pigmentation, and hypertrichosis. The liver cells can be made to fluoresce due to large amounts of preformed porphyrins¹⁹. There is, however, no porphobilinogenuria, and no features of acute intermittent porphyria. The condition is probably the result of both endogenous factors (genetic predisposition) and the exogenous factor (alcohol). Iron overload is common in these patients and indeed iron deposition can commonly be seen in the livers of alcoholics, especially where iron ingestion is high (as in areas of high wine drinking such as France and Italy). There is some evidence that folate deficiency, a common feature of alcoholism, may be an additional determining factor in the haemosiderosis or haemochromatosis seen in alcoholics²⁰.

Forms of Ethanol-induced Liver Disease

Four main clinicopathological forms of ethanolic liver disease can be distinguished. There is considerable overlap in individual cases but the distinction has convenience.

HEPATOMEGALY

This change is probably largely an adaptive phenomenon associated as it is with the electron microscopic abnormalities already referred to, such as hypertrophy of the smooth endoplasmic reticulum and increase in size of the mitochondria with disorganization of the cristae⁷. Simple hepatomegaly is usually an incidental clinical finding and has no particular prognostic significance.

ALCOHOLIC FATTY LIVER

Accumulation of lipid—predominantly triglyceride—in the liver is a highly characteristic effect of ethanol ingestion. It occurs even when dietary fat intake is curtailed²¹, although more markedly with increasing intake. Of itself it is of little clinical significance. The evidence that simple fat accumulation of itself leads ultimately to cirrhosis is almost totally lacking and most workers do not now regard it as a 'precirrhotic' condition. The picture may, however, merge with alcoholic hepatitis when in addition to accumulation of fat there is cellular degeneration and necrosis and inflammatory cell reaction.

Sometimes alcoholic fatty liver and lipidaemia are accompanied by jaundice and haemolytic anaemia²². The distinctiveness of the association, however, is probably not great enough to justify the retention of the designation 'Zieve's syndrome'. The cause of the haemolytic anaemia is not clear. Pancreatitis may contribute to the hyperlipidaemia²³.

Occasionally alcoholic fatty liver is accompanied by marked cholestasis and extrahepatic biliary obstruction is suspected²⁴.

ALCOHOLIC HEPATITIS

In contrast to simple fatty liver alcoholic hepatitis is probably a precirrhotic condition. Histologically the progression to cirrhosis is marked by a linking up of the central hyaline necrosis and fibrosis with the inflammatory reaction in the portal tracts (expansion with fibrosis together with ductular and vascular proliferation). Acute hepatitis may occur in conjunction with an established cirrhosis. Fat is common but not invariable. When present it probably indicates that alcohol consumption has continued until very

recently. Alcoholic hyaline, described 60 years ago by Mallory²⁵, has always been considered the hall mark of alcoholic hepatitis but it is now known to be nonspecific, and indistinguishable material has been noted in active chronic hepatitis, extrahepatic obstruction, and Wilson's disease among other conditions. It remains nevertheless a helpful diagnostic feature. Its origin is still unclear. In the electron microscope it appears as a fine fibrillar mesh but with aging it becomes a dense amorphous mass^{26,27}. In cirrhosis it is said to carry a poor prognosis²⁸.

The histological signs of acute alcoholic hepatitis are encountered with much greater frequency than the classical clinical syndrome of the same name. This commonly follows an alcoholic debauch and is characterized by abdominal pain, jaundice, ascites, vomiting, fever, and leucocytosis; the liver is usually considerably enlarged and tender^{29,30}. The biochemical picture is commonly a combination of hepatocellular disturbance and cholestasis. Acute viral hepatitis or extrahepatic obstruction may therefore be simulated and liver biopsy can then be extremely valuable if coagulation will permit. The prognosis is generally held to be poor, death ensuing from haemorrhage, coma, or renal failure³¹. If all those patients showing the histological features of alcoholic hepatitis are included, however, the immediate mortality is probably not above 10%.

Severe portal hypertension may occur in hepatitis long before cirrhosis becomes established³². The reason is the predominantly centrilobular distribution of the necrosis, inflammatory reaction, and collagen deposition, leading to central vein compression. Edmondson and his colleagues have termed this process 'sclerosing hyaline necrosis'³³. Far from being unusual it is not uncommonly seen in alcoholic hepatitis if looked for.

CIRRHOSIS

The factors leading to increased laying down of collagen in response to injury are as yet unknown but are currently under intensive study. Some toxic agents, including ethanol, will prolong the half-life of collagen within the liver. In both cirrhosis and ethanolic hepatitis the collagen content may be four times greater than in the normal liver.

Bridging of the central and portal canals with fibrous tissue (as already described) together with focally accentuated regeneration leads to a finely nodular cirrhosis in which fat is also a common feature. This micronodular cirrhosis ('portal cirrhosis') tends to persist while progressive injury continues. The liver is commonly enlarged. With cessation of drinking there tends to be a transformation to a more coarsely nodular or irregular form—so-called macronodular cirrhosis ('postnecrotic' cirrhosis)³⁴. Here fat is usually absent and by this stage the aetiological nature of the cirrhosis may not be clear. This transformation to macronodular cirrhosis has two important clinical consequences. First, the sampling error is increased and the diagnosis is more likely to be missed on needle biopsy³⁵. Secondly, primary liver cell carcinoma (hepatoma), a complication occurring in up to 15% of alcoholic cirrhotics, is usually a feature of macronodular rather than of micronodular cirrhosis^{7,36}.

Pathogenesis of Ethanol-induced Liver Disease

For many years two questions have been central in discussion of this aspect of liver disease. What is the aetiological role of ethanol itself? Why do only a

proportion of ethanol abusers develop irreversible liver damage? Answers, albeit incomplete, can now be given to these.

THE AETIOLOGICAL ROLE OF ETHANOL

The association of irreversible liver disease (cirrhosis) with ethanol is undeniable. Early work tended to devalue the importance of ethanol itself and emphasize instead the associated dietary deficiencies. Fatty change in the rat was shown to be preventable by choline administration³⁷. In fact, since then a variety of substances, predominantly antioxidants, have been shown to share this protective role³⁸. Nevertheless, recent work by Lieber and Rubin has established beyond doubt that ethanol produces acute liver damage even in the presence of adequate dietary supplementation. This occurs in both normal subjects³⁹ as well as possibly in 'susceptible' individuals (alcoholics)²¹. An important corollary of Lieber and Rubin's work is the demonstration of the direct hepatotoxicity of pure ethanol free from impurities, additives, and congeners which have in the past been incriminated. Moreover the quantities of alcohol required to produce changes in healthy volunteers never raised the blood alcohol level above 80 mg %, ie, the 'breathalyser range'³⁹.

All clinical evidence of this kind is of necessity short-term and since it probably takes 10 years or more of drinking to produce cirrhosis the direct relationship of ethanol to this end-stage damage is difficult to show by these means. Further evidence against the primary role of nutritional deficiency in producing cirrhosis of the alcoholic is the undoubted occurrence of cirrhosis in alcoholics with very adequate dietary intake⁴⁰.

ADDITIONAL AETIOLOGICAL INFLUENCES

Estimates of the frequency with which alcohol abusers develop cirrhosis range from 1 to 30 %. Variability is due, in part, to such problems as the differing definitions of 'alcoholism'. In addition there may be a real variation in susceptibility between racial groups. There is evidence that at least four factors influence whether or not the alcohol abuser develops irreversible damage.

First, there is the degree and duration of alcohol abuse. Péquignot has estimated that most cirrhotics have consumed in excess of 160 g of alcohol a day for many years⁴¹. He regards a daily consumption of 80 to 160 g as a potentially dangerous range and less than 80 g as 'safe'. In fact 160 g (about two-thirds of a bottle of whisky) of ethanol is approximately the maximum daily metabolic capacity for the average man⁴². Careful and extensive studies among alcoholics by Lelbach have confirmed the relationship of irreversible liver damage to absolute ethanol intake^{42,43}. The mean (admitted) duration of alcoholism in his series was 9.1 years. Absolute ethanol intake seems the important factor regardless of the type of beverage consumed.

Secondly, drinking patterns are probably important. The steady daily imbibitor is much more at risk than the 'spree' drinker whose total alcohol intake may be no less. This is partly because the latter allows his liver a chance to repair and partly because his diet suffers less. This facet is difficult to prove because alcoholics so rarely tell the truth but some supportive data do exist⁴⁴.

Thirdly, dietary intake is undoubtedly of some importance, even if in the past its role has been overemphasized⁴⁵. The addition of high protein, calorie, and vitamin supplements in malnourished alcoholic cirrhotics results in

clinical improvement even if a measure of alcohol ingestion continues^{46,47,48}. It seems reasonable to assume that dietary deficiency potentiates the hepatotoxicity of alcohol. Such potentiation has been shown in rats⁴⁹, although the findings of Hartcroft and his coworkers do not accord with this concept⁵⁰. Conversely, it is possible that alcohol in some way increases nutritional requirements of the liver⁴⁰.

Fourthly, there is the concept of inborn predisposition. Most workers accept now that hereditary factors may play some part in the development of irreversible liver disease. The genetic influences in many common conditions, though important, are small and require large accumulations of data to be meaningful. Some series^{44,51,52,53}, but not all^{54,55,56}, have shown an excess of blood group A in 'portal' cirrhosis. An original report of association with colour blindness, an X-linked trait⁵⁷, has not been subsequently supported^{54,58}. Ethnic frequency of 'portal' cirrhosis is variable⁵⁴ but in proportions not wholly related to frequency of alcoholism. Animal data in support of this are scanty⁵⁹, largely due to difficulties in finding a suitable animal model. Evidence for genetic influences is as yet slight but is accumulating.

The Natural History of Ethanolic Cirrhosis

The natural history of cirrhosis has received scant attention until recent years. Some information on the outcome of acute³¹ and chronic^{60,61} disease is available but perhaps the most significant findings are those confirming the hitherto unproven clinical impression that those alcoholics with established cirrhosis who could be persuaded to stop drinking do live longer than those who continue^{40,44}. Five-year survival can be approximately doubled by total or near total abstinence. Powell and Klatzkin⁴⁰ showed, however, that this overall improvement rate was modified by the clinical presentation. Those without jaundice, bleeding, or ascites did well anyway, while in those presenting with haematemesis it mattered little to their five-year survival whether they continued to drink or not. Nonetheless the proven worth of abstinence, together with the undoubted value of high protein and calorie diets with vitamin supplements, means that alcoholic cirrhosis can no longer be regarded as a hopeless disease and, indeed, probably carries the best potential prognosis of any cirrhosis.

The Problem and the Future

The control of alcoholic liver disease is thus essentially the control of alcoholism (or alcoholic abuse) and as such is predominantly a psycho-social problem. By all accounts it is an increasing problem. The United States has now at least 6.5 million 'problem drinkers' with a resulting estimated annual 'social cost' of two thousand million dollars⁶². Deaths from cirrhosis have increased from 10.8/100,000 in 1958 to 13.9/100,000 in 1967 and cirrhosis is now the fourth commonest cause of death in the age group between 45 and 64. No similar figures exist for alcoholism in Britain but all the evidence suggests that here also it may again be on the increase⁶³. The challenge exists to explore the epidemiology of alcoholic liver disease, to examine more closely the factors of host susceptibility, to evaluate further the role of ethanol and

nutritional factors in liver cell injury, and to find ways of minimizing the disturbances of both structure and function which ethanol produces.

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