

Alcohol—risks and mechanisms of damage

The first part of this one-day conference, held at the Royal College of Physicians in December 1993, was devoted to the relationship between alcohol consumption and the health of the nation, in particular the complex effects of alcohol intake on mortality and its widely publicised protective effect against death from coronary artery disease. This led to a discussion of the rationale for the currently recommended 'safe limits' for alcohol consumption and the controversial issue of whether, in view of the beneficial cardiovascular effects of light alcohol intake, teetotallers should be encouraged to drink. The second part of the conference dealt with the biological and biochemical effects of alcohol on the liver. While excessive alcohol consumption is clearly associated with the development of liver disease, advanced liver disease occurs in only a minority of heavy drinkers. Recent advances in our understanding of the pathogenesis of alcoholic liver disease are now beginning to offer biochemical explanations for individual susceptibility and provide a more rational basis for the design of new long term treatment modalities.

Alcohol and public health

Alcohol and the vascular system

Dr A L Klatsky (Permanente Medical Group, California, USA) gave a comprehensive review of the effects of alcohol on the cardiovascular system. Cardiomyopathy due to the dose-related toxic effects of alcohol rather than to associated thiamine deficiency (beri-beri) or to toxins present in beverages (eg cobalt) has been recognised since the early 1960s. However, although various invasive and non-invasive investigations have revealed abnormalities of cardiac structure and function in over 50% of alcoholics, clinically evident alcoholic cardiomyopathy is relatively uncommon. The precise pathogenic mechanisms are unclear but formation of fatty acid ethyl esters by the non-oxidative metabolism of alcohol may play a role [1]. Alcohol intake and withdrawal is also associated with most types of atrial and ventricular tachycardias and sudden death—the 'holiday heart syndrome', so called in view of the tendency of patients to present around holidays and weekends. The mechanism of arrhythmogenesis may be related to catecholamine

release or alternatively to autonomic neuropathy which is manifest as QT interval prolongation on the electrocardiogram. QT prolongation identifies patients with alcoholic liver disease who are at increased risk of sudden cardiac death [2].

Evidence from more than 50 cross-sectional and 10 prospective studies confirms that alcohol intake of more than three drinks (units) per day is associated with high blood pressure [3]. The mechanism for this pressor effect is unclear but it is exaggerated in 'binge' drinkers and is reversible with abstinence. The association with hypertension has been found by Dr Klatsky and colleagues to account for an increased risk of haemorrhagic stroke in individuals drinking more than three drinks per day, although Professor Marmot later referred to the British regional heart study in which an increased risk of stroke was only observed at more than six drinks per day. It is important to note that alcohol intake appears to protect against occlusive stroke, which presumably reflects its beneficial effects on haemostasis (see below) [4].

What does the J-shaped curve mean in 1993?

Professor M G Marmot (University College and Middlesex School of Medicine, London) gave an eloquent review of the complicated relationship between alcohol intake, coronary artery disease (CAD) and mortality. He considered the explanations for the widely quoted U- or J-shaped curve describing the relationship between alcohol intake and total and cardiovascular related mortality. It shows that mortality amongst light (1–9 drinks per week) and moderate (10–34 drinks per week) drinkers is lower than in abstainers and heavy drinkers. The left hand part of the U is due to an inverse relationship between death from CAD and alcohol intake, while the right hand portion is attributable to a greater risk of non-ischaemic cardiovascular deaths (arrhythmias, haemorrhagic strokes, cardiomyopathy) and non-cardiovascular deaths (accidents, suicide, cancer, liver disease) in heavy drinkers. The inverse relationship between CAD and intake is not due to 'sick quitters' because individuals who have never drunk also die more often from CAD than light/moderate drinkers; nor is it due to other potentially confounding factors such as age, sex, smoking, diabetes, hypertension, diet or social class [5].

Supportive evidence for a protective effect of alcohol on CAD and thrombotic cerebrovascular disease is provided by its biological plausibility [4]. Alcohol intake raises the level of the protective high-density lipoprotein (HDL) cholesterol, including both its HDL₂ and HDL₃ subfractions [6]. It is also associated with impaired platelet function and lower levels of plasma fibrinogen.

Professor Marmot also considered the evidence that various types of alcoholic beverage might have different effects on CAD mortality risk, a subject of considerable recent media attention. In particular, the fact

CHRISTOPHER PAUL DAY, MD, PhD, MRCP
*Medical Research Council Clinician Scientist Fellow,
 Newcastle University*

that CAD mortality in France is lower than would be expected from the intake of saturated fat—the ‘French paradox’—has been widely publicised and has been attributed to the high consumption of red wine. A specific protective effect of wine is supported by the inverse correlation between population CAD mortality and *per capita* wine intake. Dr Klatsky reported the results of his recent study in the United States in which red and white wine drinkers were found to have a lower risk of CAD mortality than predominantly spirit or beer drinkers [7]. He attributed this finding to the presence of other potentially favourable traits with respect to CAD risk factors in wine drinkers. This may include the timing of alcohol consumption with respect to food intake, with wine drinkers achieving lower blood alcohol levels than spirit or beer drinkers due to their tendency to drink with meals. It is possible that heavy drinkers in a predominantly wine-drinking population might only attain the same blood alcohol levels as do light and moderate spirit or beer drinkers and therefore do not incur the increased risk of cardiovascular death associated with their high level of consumption. This would explain why a population in which wine is the predominant beverage would have a lower risk of CAD death than predicted from its *per capita* alcohol intake.

Safe limits: should they be redefined?

Dr P Elwood (MRC Epidemiology Unit, South Wales) reviewed the rationale for the currently recommended ‘safe limits’ of 21 units of alcohol per week for men and 15 for women. The basis for these limits appears to be studies showing that the risk of hypertension and haemorrhagic stroke is increased only in individuals drinking more than three units per day and evidence from large population studies that liver disease does not occur with consumption at or below this level [8]. Dr Elwood did, however, stress that no study had specifically addressed the effects of levels of alcohol intake on the detrimental psychosocial effects of alcohol. He also raised the important issue of whether the limits should take account of age and sex. Recent studies from New Zealand and the United States have shown that, while alcohol intake in persons over 60–65 does prevent more deaths than it causes, in younger persons it increases net mortality owing to a greater risk of unnatural death and cancer. In addition, the risk of alcohol-related cancer death, subsequently discussed by Professor Doll, appears to be greater in women than in men and this probably accounts for the higher risk of non-cardiovascular death in heavily drinking women than in men [9]. These sex- and age-related differences should be taken into account in future public health policy recommendations.

Dr Elwood’s principal concern was the effect that a misunderstanding of media coverage concerning the protective effect of alcohol on ischaemic heart disease could have upon people’s alcohol consumption. The

sale of red wine in America recently increased by 45% following a television programme discussing the ‘French paradox’. This type of publicity has led to previously contented teetotallers asking their doctors whether they should take up drinking. As far as public health policy is concerned the answer must certainly be ‘no’. The large Intersalt study of factors affecting blood pressure in 52 countries demonstrated that the prevalence of heavy drinkers in a population is closely correlated with *per capita* alcohol intake. Any increase in overall consumption in response to either medical advice or media pressure is likely to produce more ‘problem’ drinkers with the attendant unequivocal medical and psychosocial risks.

Alcohol and cancer

Prior to summing up the first part of the conference, **Professor Sir Richard Doll** (Radcliffe Infirmary, Oxford) reviewed the evidence that alcohol plays a role in the aetiology of cancer. He considered that results from several large epidemiological studies have firmly established that alcohol intake is associated with higher cancer mortality and that this makes a significant contribution to the right-hand part of the U-shaped curve. In some cancers, such as those of the oropharynx and oesophagus, the increased risk is confined to smokers but for others, such as large bowel and breast, the risk is independent of tobacco consumption. It is a sobering thought that the increased risk of breast cancer may occur at very low levels of alcohol intake. Sir Richard concluded that there was no definite indication either for changing the currently recommended safe limits or for advising teetotallers to start drinking. In an individual case, however, medical advice should take into account the age and sex of the patient, their relative risks of cancer and ischaemic heart disease and their risk of progression to heavy intake. Finally he stressed that we must be careful not to ignore the obvious beneficial non-medical aspects of alcohol consumption when advising our patients—‘Quality not just quantity of life’!

Alcohol and liver damage

Alcoholic fatty liver

Dr C P Day (University of Newcastle upon Tyne) considered the mechanisms important in the pathogenesis of fatty liver, the initial and most common histological finding in patients drinking excess alcohol. The severity of fatty liver in an individual correlates with the risk of progression to cirrhosis [10], suggesting either that the fat *per se* causes the development of more advanced pathology or that fatty liver and alcoholic hepatitis/cirrhosis are caused by a common injurious mechanism. Understanding the mechanisms of alcoholic fatty liver may therefore help in understanding the important mechanisms leading to progressive

liver disease and may point to the biochemical basis for individual susceptibility. Contrary to popular misconception, the redox changes that occur secondary to alcohol oxidation are not important in the pathogenesis of fatty liver. Mechanisms that are considered to play a role include: (i) increased supply of fatty acids due to increased hepatic uptake and decreased β -oxidation; (ii) direct stimulation of fatty acid esterification secondary to an increase in the activity of the enzyme phosphatidate phosphohydrolase (PAP); (iii) decreased export from the liver of synthesised triacylglycerol as very low density lipoproteins (VLDLs). Both the increased PAP activity and the impaired VLDL export are probably indirectly attributable to acetaldehyde, the principal metabolite of alcohol oxidation and the correlation between the severity of fatty liver and advanced disease may accordingly reflect the role of acetaldehyde in the pathogenesis of both types of pathology.

Alcoholic hepatitis

Professor T J Peters (King's College School of Medicine and Dentistry, London) reviewed the mechanisms considered to play a role in alcohol-related hepatocyte damage which is the central feature of the next stage of alcoholic liver disease—alcoholic hepatitis. First he referred to the potential cytotoxic effects of acetaldehyde. Acetaldehyde is highly reactive and chemically modifies phospholipids, proteins and glutathione (GSH) by covalent binding to form stable acetaldehyde adducts. These modified compounds can affect cell viability by their altered biological function and/or by becoming neoantigens initiating immunologically mediated cytotoxicity.

Two more recently identified mechanisms of alcohol-related cytotoxicity are cytokine mediated hepatocyte necrosis and free radical mediated oxidative damage. Cytokines are low molecular weight polypeptides produced by many different cells including hepatocytes, Kupffer cells and endothelial cells. They have a diverse range of mainly proinflammatory effects and some (eg tumour necrosis factor, TNF) can induce hepatocyte necrosis. Increased activity of several cytokines, including TNF and various interleukins, has been found in the sera and liver of patients with alcoholic hepatitis, and TNF levels also correlate with prognosis. The initial stimulus to TNF release may be increased portal vein levels of endotoxin secondary to the increase in gut permeability associated with chronic alcohol intake.

Free radicals are highly reactive and unique chemical species consisting of atoms or molecules characterised by an unpaired electron in the outer orbital; they can damage a wide range of cellular components, including membrane phospholipids, proteins and nucleic acids. Aerobic organisms defend themselves against free radicals by possessing protective enzymes such as superoxide dismutase and free radical scav-

engers including GSH. Recently both free radical generation and lipid peroxidation have been observed following chronic alcohol intake in animals and humans. The precise mechanisms of free radical generation following alcohol intake are unclear but acetaldehyde probably plays a role. The greater amount of iron found in the livers of 20–30% of patients with alcoholic liver disease may also be important since free iron is required for one of the key reactions involved in free radical production. Oxidative damage is further enhanced by a reduction in GSH levels due to acetaldehyde adduct formation and a decrease in the activity of the liver's protective enzymes.

Adhesion molecules and alcoholic liver damage

Dr D H Adams (National Institutes of Health, USA) considered the role of leukocyte adhesion molecules in the pathogenesis of alcoholic hepatitis and cirrhosis. In both there is evidence of inflammation which seems likely to contribute to the hepatocyte damage and the subsequent fibrosis. The initial trigger for this inflammatory response is unclear; candidates include a direct effect of alcohol or its metabolites, an effect via alcohol related hepatocyte damage and endotoxin mediated TNF release. Evidence is now emerging that, whatever the initial trigger, the activation and migration of leukocytes and their interaction with target cells are all regulated by cell adhesion molecules. Leukocyte adhesion molecules and their counter-receptors might therefore play a crucial role in determining both the type and the effect of the leukocytes infiltrating the liver in alcoholic liver disease.

The predominantly neutrophil infiltration in alcoholic hepatitis is partly explained by the presence of high circulating levels and tissue expression of the endothelial adhesion molecule E-selectin, which is involved in transmigration of neutrophils into inflammatory tissue. In contrast, the predominantly mononuclear cell infiltrate in alcoholic cirrhosis may be attributed to increased expression of VCAM-1 which is the endothelial receptor for the monocyte adhesion molecule VLA-4. Both diseases are characterised by high tissue expression of ICAM-1, an adhesion ligand required for optimal transmigration of both neutrophils and mononuclear cells. In addition to determining the nature of the inflammatory infiltrate in alcoholic liver disease, adhesion molecules may play a role in inflammatory cell-mediated hepatocyte damage since they are required for cytolysis of target cells by leukocytes. In alcoholic hepatitis the leukocyte adhesion molecule (integrin) LFA-1 is upregulated on infiltrating leukocytes, and its counter-receptor, ICAM-1, is strongly induced on hepatocytes at the sites of damage. Dr Adams suggested that further clarification of the role of these pathways in the pathogenesis of alcoholic liver disease might lead to newer modes of therapy based on blocking adhesion molecules and/or their receptors.

Fibrosis and cirrhosis

Professor M J Arthur (University of Southampton) reviewed the mechanisms operative in the final stage of alcoholic liver disease—fibrosis and cirrhosis. Various data obtained from *in vitro* and *in vivo* studies have shown that quantitatively the most important cells involved in the production of collagen and other constituents of the extracellular matrix (ECM) are the lipocytes (perisinusoidal cells, fat-storing cells, Ito cells). They occupy the space of Disse, between the sinusoids and hepatocytes, and contain cytoplasmic lipid droplets composed of retinyl esters. In most species they are the principal storage site for vitamin A. When activated, lipocytes proliferate and undergo phenotypic change towards myofibroblast-like cells which have reduced quantities of vitamin A and produce increasing quantities of type I collagen rather than the predominantly type III collagen produced by quiescent cells. Activated cells also produce a type IV collagenase which leads to a further change in the composition of the normal ECM and to a perpetuation of lipocyte activation via altered lipocyte–ECM interactions. Intensive research in this field is currently being directed at determining the precise nature of the initial trigger for lipocyte activation in alcohol related liver damage. Candidates identified thus far include a plasma-membrane associated factor released by damaged hepatocytes following membrane lipid peroxidation, and a soluble factor derived from Kupffer cells recruited to the site of tissue damage. Following activation, lipocyte ECM gene transcription is stimulated by transforming growth factor β 1, released by Kupffer cells, and possibly by products of lipid peroxidation and acetaldehyde. Liver fibrosis may also be due, in part, to the observed decrease in the activity of the interstitial collagenases normally responsible for degrading type I and III collagens. Professor Arthur presented recent data showing that this may be due to the production of the collagenase inhibitor TIMP-1 by activated lipocytes.

Genetic factors and susceptibility to alcoholic liver damage

Professor D W Crabb (Indiana University, USA) reviewed the evidence supporting a genetic explanation for the well established interindividual variation in susceptibility to the hepatic effects of alcohol. He presented evidence that alcoholism *per se* is a heritable trait. One in three alcoholics has at least one alcoholic parent, and the risk of becoming alcoholic with a parent abusing alcohol is 15% compared with 8% without such a parent. Twin and adoption studies have shown that the familial association has a significant genetic as well as environmental component. Several biochemical differences have been identified between alcoholics and matched controls, but most significant is the variation in the genes encoding the principal alcohol-metabolising enzymes, alcohol and aldehyde dehydrogenase (ADH and ALDH). The ADH isoenzyme subunits are encoded at at least seven different loci and polymorphisms have been identified in two: *ADH2* and *ADH3*. The isoenzymes arising from these different subunits exhibit widely different kinetic properties with correspondingly different rates of alcohol oxidation *in vitro*. The most important isoenzyme of ALDH is encoded at the *ALDH2* locus. Approximately 50% of orientals possess the dominant ‘null allele’ which encodes an inactive form of this enzyme. Individuals with genes encoding the more active forms of ADH or the inactive form of ALDH2 are less likely to be alcoholic than those with the least active forms of ADH and normal ALDH2, presumably reflecting their aversive reaction to acetaldehyde. These findings may, however, be less important in Caucasian populations that only vary significantly in *ADH3* genotype.

Professor Crabb then presented evidence from twin studies that there is also a genetic component to susceptibility to alcohol related liver disease. Evidence from oriental populations again suggests a role for the ALDH2 isoenzyme in this respect, with individuals heterozygous for the null allele drinking less than those homozygous for the normal allele for the same degree of liver disease [11]. With respect to Caucasian populations, two recent European studies have provided suggestive evidence that possession of the active form of *ADH3* increases the risk of cirrhosis [12]. These studies provide further support for acetaldehyde as a major mediator of alcohol related liver damage.

Hepatitis B and C and susceptibility to alcoholic liver disease

Hepatitis B and C and susceptibility to alcoholic liver disease

Dr A Parés (Hospital Clinic I Provincial, Barcelona) discussed the controversial issue of the role of hepatitis virus infection in determining the severity of alcohol related liver damage. Concerning hepatitis B virus (HBV), whilst there is no doubt that, compared with controls, patients with alcoholic liver disease have a higher prevalence of markers of current or past HBV infection, this may be explained by confounding factors such as increased numbers of blood transfusions in the alcoholics. Further evidence against a synergistic role for HBV in alcoholic liver disease is the absence of any correlation between HBV DNA levels and the histological severity of alcohol related damage [13].

The evidence concerning the role of hepatitis C virus (HCV) infection is more controversial, largely owing to problems with the specificity of the tests used to detect HCV antibodies. Dr Parés discussed the results of his own study in which patients with alcoholic liver disease who had HCV antibodies, detected with a first generation ELISA test, had worse symptoms and signs, liver function and histology than patients without HCV antibodies [14]. This difference was not

explained by confounding factors such as more hospitalisations or blood transfusions in the more severely ill patients. However, Dr Parés did not refer to a recent study from the United States which reported similar findings using a first generation ELISA test but not with a more specific RIBA test, which reduced the HCV antibody positivity rate in alcoholic patients by 80% [15]. This suggests a high degree of ELISA false positivity in patients with alcoholic liver disease, probably reflecting high levels of IgG in the most severely ill patients. The role of HCV in determining the severity of alcohol related liver damage therefore remains unresolved. This issue will have increasing therapeutic implications as more effective antiviral agents become available for the treatment of patients with chronic liver disease related to HCV infection. In contrast, there seems little doubt that both HBV and HCV play a role in increasing the risk of hepatocellular carcinoma (HCC) in patients with alcoholic liver disease. The cumulative risk of developing HCC in patients with alcoholic liver disease who have antibodies to HCV is more than twice that of similar patients without antibody [16].

Medical treatment for severe alcoholic liver disease

Dr J M Neuberger (Queen Elizabeth Hospital, Birmingham) emphasised the importance of achieving abstinence which improves the prognosis in all stages of alcoholic liver disease, even in established cirrhosis with complications. When treating acute alcohol withdrawal, the dose of benzodiazepines should be reduced in patients with diminished hepatic reserve. The persisting high mortality in patients with severe acute alcoholic hepatitis, even among those who do abstain, has recently led to a search for other treatment modalities for this form of alcoholic liver disease. There now seems little doubt, from the results of several controlled trials and a subsequent meta-analysis, that steroids improve the short term survival in severely ill patients and that the benefit persists for up to two years [17]. In these trials, the decision to treat has been based either on the presence of encephalopathy or on Maddrey's discriminant function score, derived from the serum bilirubin level and the degree of prothrombin time prolongation, and shown to predict survival in prospective studies. Treatment with steroids is contraindicated in patients with evidence of active infection or bleeding. There is currently no good evidence to support any other forms of medical treatment in alcoholic hepatitis. Concerning chronic alcoholic liver disease, encouraging results have been reported both for colchicine and the antithyroid drug propylthiouracil [18], but neither has been widely adopted owing to a lack of confirmatory studies and a high drop-out rate in the colchicine trial. Both trials were of good quality and warrant further studies to refute or confirm their results.

Transplantation for alcoholic liver disease

Dr R Williams (King's College School of Medicine and Dentistry, London) reviewed the issues surrounding orthotopic liver transplantation in the treatment of alcoholic liver disease. If widely accepted, alcohol related liver disease would become the commonest indication for transplantation in the UK with at least 200 patients a year suitable for treatment. The purely medical indications for transplanting patients with alcoholic liver disease are similar to those for liver disease of other aetiologies and include worsening liver failure, complications of portal hypertension and the presence of small primary hepatocellular cancers found on routine screening. Extrahepatic complications of alcohol abuse should be specifically sought since they may have an adverse influence on the outcome of surgery.

The principal difference between considering transplantation for patients with alcohol related and other types of disease is the key issue of abstinence. First, even in patients with severe disease, abstinence can have dramatic and sometimes unpredictable effects on liver function and can therefore remove the apparent indication for transplantation in some patients. This is illustrated by a recent study from France which showed that the two-year survival in matched patients with alcoholic liver disease and a Childs-Pugh score of < 11 was no higher in those transplanted than in those managed conservatively. This suggests that patients may have received transplants who did not need them [19]. The advent of transjugular intrahepatic portosystemic stents (TIPSS) for the treatment of portal hypertension might further reduce the need to transplant alcoholics in whom this particular complication remains the only indication for transplantation following a period of abstinence.

The second issue concerning abstinence is the practice adopted in most liver units of transplanting only alcoholics considered likely to abstain following surgery. This presupposes not only that we are able accurately to identify these patients but, perhaps more important, that drinking after transplantation adversely affects outcome. Dr Williams questioned both of these assumptions. Some groups have shown that a six-months period of abstinence pre-transplant predicts the rate of recidivism following the operation [20], while others used a detailed psychosocial assessment and attendance at a rehabilitation programme to decide on the likelihood of a future return to drinking [21]. This latter group transplants only those patients perceived to be at low risk of recidivism and have used the subsequent high abstinence rate in these patients (90%) compared with the abstinence rate in the untransplanted high risk group (10%) as evidence for the efficacy of their screening programme. However, Dr Williams alluded to the 'sobering' effect of liver transplantation, and it seems probable that many 'high risk' drinkers will abstain following surgery after being

given a 'second chance'. Importantly, the only available data suggest that a return to drinking following surgery does not adversely affect survival [20]. In fact a recent report shows that it may reduce the incidence of rejection [22]!

In summary, although there is no absolute evidence for insisting on a period of abstinence pre-transplant, in non-acute cases this may help to ensure that abstinence alone will not remove patients from a high risk category requiring transplantation and may also satisfy public opinion. In more severely ill patients, in whom transplantation is the only chance of survival, there appears to be no reasonable grounds for withholding surgery whatever the perceived risk of subsequent recidivism, as this is likely to be lower than predicted and may not adversely affect prognosis.

Conclusion

Overall the conference was a success. It was well attended and provided a rare opportunity for physicians and scientists from diverse fields to discuss various aspects of alcohol related health issues. The problems and benefits of alcohol consumption are likely to be with us for the foreseeable future and the information presented at this conference can only help towards tipping the balance in favour of the latter. Of course the day was concluded by a fine dinner accompanied by precisely three glasses of red wine!

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Address for correspondence: Dr C P Day, Department of Medicine, The Medical School, Newcastle University, Newcastle upon Tyne NE1 4HH