ACTA MED PORT. Suppl 2: 49, 1981

ALCOHOL AND LIVER DAMAGE

Sheila Sherlock

Department of Medicine, Royal Free Hospital Medical School. (University of London). Pond Street, London. England

The association of alcohol with cirrhosis was recognised by Matthew Baillie in 1793 and later by Addison. In Western countries the incidence of cirrhosis can be directly related to the quantity of alcohol consumed. In France, between 1941 and 1947, rationing of wine from five to one litre per week led to an 80% reduction in mortality from cirrhosis (1). Cirrhosis is on the increase. In the U.S.A. it is the fourth commonest cause of death in white males. In Britain, deaths from cirrhosis have increased by approximately 25% in the last decade. The death rate in different communities correlates quite well with alcohol consumption (Table 1). The prevalence in various countries largely depends on religious and other customs and on the relation between the cost of alcohol, and the weekly wage. In France wine is cheap and cirrhosis is common. The lower the cost of alcohol, the more are lower socio-economic groups affected. Certain occupations are particularly associated with the risks of alcoholism. They include, the liquor trade, *show business* or those on expense accounts or with ready access to duty-free liquor. In Britain the patient with alcoholic liver disease tends to be the executives, Services personnel, physicians and, increasingly all over the world, their lonely wives.

Table 1

Cirrhosis mortality related to alcohol consumption

	Cirrhosis mortality per 100000 population over 25 years of age	Per capita alcohol consumption/ year (litres absolute alcohol)
France	57.2	16.4
Portugal	55.1	14.1
Italy	52.1	14.0
West Germany	39.6	11.3
Spain	38.8	11.7
USA	28.6	5.8
Canada	19.6	6.5
Sweden	15.6	5.7
Holland	7.4	4.8
UK	5.7	6.2

Women seem more susceptible than men (2). They are less likely to be suspected of alcohol abuse, they present at a later stage and are more likely to relapse after

treatment (Table 2). Each bottle of spirits contains 240G of alcohol. The *safe* daily consumption is uncertain. 160G daily used to be the limit, but now 60G in men, and a mere 20G in women may suffice (1). Alcoholics with cirrhosis have usually consumed about 190G of alcohol daily for ten years, although there are wide individual variations. Alcoholism of shorter duration may be compensated by a higher daily dose and vice versa.

Table 2

Alcoholic liver disease
Male: Females
(Morgan et al 1978)

Females Suspected	38%
Males Suspected	77%
Continued to Abuse alcohol	
Males	71%
Females	91%

The liver injury is unrelated to the type of beverage consumed. It is related only to its alcohol content. The non-alcoholic constituents of the drink — congeners — are not particularly hepatotoxic. The steady daily imbiber is much more at risk than the *spree* drinker whose total alcohol intake may be no less. This may be because the intermittent drinker gives his liver a chance to repair, and partly because his diet suffers less.

Genetics

Not everyone who drinks excessively develops liver damage. In a group of 526 unselected male alcoholics receiving treatment, liver function tests showed severe liver damage in a quarter, but no significant liver damage in one half (3). Numerous chronic alcoholics with completely normal livers pose an interesting problem. Their *hepatic resistance* might be genetically determined.

There have been associations between HLA blood groups and susceptibility of heavy drinking to chronic liver damage. This seems to have geographic variations, in the United Kingdom the association is with HLA-B8 (4), in Chile with HLA-B13 (5), and in Norway with HLA-BW40 (6).

Metabolism of Alcohol (Fig. 1) (7, 8)

Alcohol cannot be stored and obligatory oxidation must take place, predominantly in the liver. The healthy individual cannot metabolize more than 160-180 gm per day. Alcohol induces enzymes used in its catabolism, and the alcoholic, at least while his liver is relatively unaffected, may be able to metabolize more. One gram of alcohol gives 7 calories, and alcoholics literally run on spirit. These *empty* calories make no contribution to nutrition other than to give energy.

The major route of ethanol oxidation is by initial conversion to acetaldehyde, catabolized by the enzyme, alcohol dehydrogenase (ADH). This takes place in the cytosol. Acetaldehyde in mitochondria and cytosol may be injurious causing membrane damage and cell necrosis. The acetaldehyde is converted to acetyl CoA with acetaldehyde dehydrogenase acting as a co-enzyme. This can be further broken down to acetate which may be oxidized to carbon dioxide and water, or converted by the citric-

-acid cycle to other biochemically important compounds including fatty acids. NAD is a co-factor and hydrogen acceptor when alcohol is converted to acetaldehyde and further to acetyl CoA. The NADH generated changes the NADH: NAD ratio and the redox state of the liver. Triglyceride synthesis and lipid peroxidation are increased. The activity of the citric-acid cycle is reduced,and this may be responsible for decreased fatty acid oxidation. Lipoprotein synthesis is increased by alcohol. The NADH may serve as the hydrogen carrier for the conversion of pyruvate to lactate and blood lactate and uric acid levels rise after alcohol. Post-alcoholic hypoglycaemia and gout after alcohol ingestion may be explained by this mechanism. The conversion of alcohol to acetaldehyde also leads to inhibition of protein synthesis.

Alcohol is also metabolized by a microsomal ethanol oxidizing system (MEOS). This is induced by alcohol. This may explain the tolerance of the chronic alcoholic not only to alcohol but to other drugs metabolized by microsomal enzymes. Alcoholics not under the influence of alcohol are unusually resistant to these sedative drugs which are metabolized by microsomal enzymes. Increased testosterone metabolism may be partly responsible for feminisation and sterility.

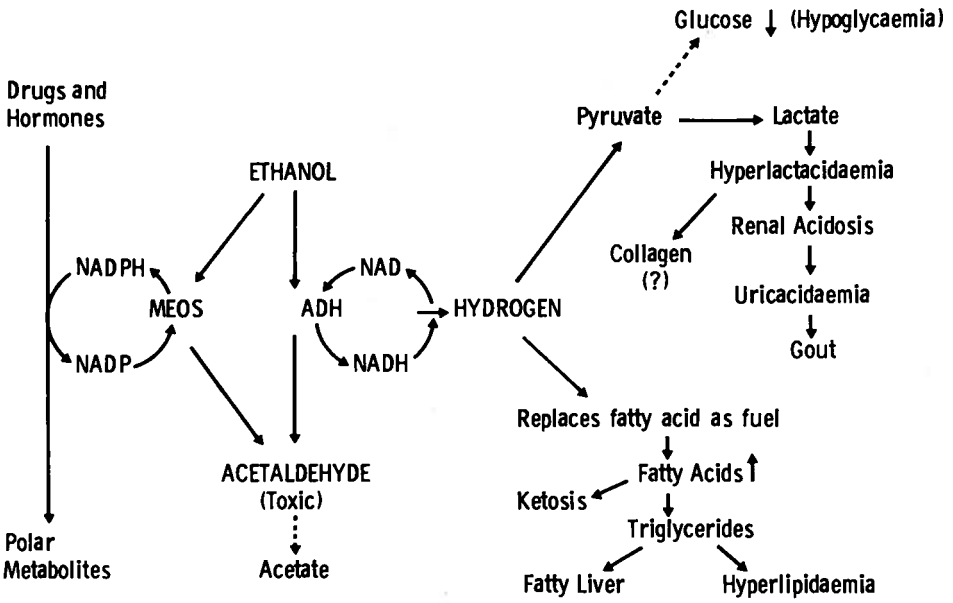

Fig. 1 — *Oxidation of alcohol in the hepatocyt. he production of acetaldehyde (toxic) is enhanced and conversion to acetate reduced. The hydrogen produced replaces fatty acids as a fuel so that fatty acids accumulate with consequent ketosis, triglyceridaemia, fatty liver and hyperlipaemia. Unwanted hydrogen is used to convert pyruvate to lactate which is produced in excess. Hyperlactacidaemia leads to renal acidosis, a rise in serum uric acid and gout. Collagen synthesis may be stimulated. Reduction of the pyruvate to glucose pathway results in hypoglycaemia. Stimulation of the MEOS drug metabolising system leads to drug and alcohol tolerance and increased testosterone metabolism may be related to feminisation and to infertility. (After Lieber, 1978). Broken lines indicate depressed pathways. Each=excess hydrogen equivalents, ADH=alcohol dehydrogenase, MEOS=microsomal ethanol oxidizing system, NAD=nicotinamide adenine dinucleotide, NADP=nicotinamide adenine dinucleotide phosphate.*

PATHOGENESIS OF LIVER INJURY

Direct Hepatotoxicity

The development of alcoholic liver damage is dependent on the duration and dose of alcohol. When volunteers, both normal and alcoholic, were, given about 10-20 ozs (300-600 ml) of 86 proof alcohol daily for about 8-12 days liver biopsy sections showed fatty change and E.M. abnormalities (9). Alcoholic hepatitis and cirrhosis have been reproduced in baboons fed alcoholic isocalorically for carbohydrate. A nutritious diet was not preventive (10).

The deleterious effect of alcohol might be accounted for by the toxicity of acetaldehyde, or by intracellular protein and water accumulation (11). There might be a microsomal activation of hepatotoxins and alterations could follow the redox state.

New Collagen Formation

This is probably the key to the progression of alcoholic hepatitis to cirrhosis. Alcohol stimulates fibrogenesis and collagen synthesis, perhaps by means of *Ito Cells* or lipocytes (12). Collagenosis may be stimulated by lactic acidosis.

Immunological

Hyper-reactivity may be responsible for progressive destruction of liver cells and development of cirrhosis. This could explain progression in spite of alcohol abstinence and a good diet. Hyaline might be the antigen concerned for alcoholic hyaline antibodies and cytotoxic lymphocytes are found in alcoholic hepatitis (13).

Hypermetabolic State

Animals chronically fed alcohol are hypermetabolic and are particularly sensitive to reduced oxygen supply (14). The increased hepatic oxygen consumption leads to a decrease in oxygen tension in centrizonal areas which are the last to receive oxygen. Hypoxia, necrosis and collagenosis are therefore predominantly centrizonal.

Nutrition and Fatty Liver

The chronic alcoholic usually eats sparingly and erratically. The diet is particularly poor in protein for such foods are costly. In contrast to other types of cirrhosis, the alcoholic shows many signs of malnutrition.

Increasing evidence that alcohol is itself hepatotoxic has shifted interest away from dietary factors as aetiological. Nevertheless, improvement in liver function does not always follow alcohol abstinence if dietary protein remains low. The alcohol oxidising enzymes and the integrity of the liver cell depend on a high level of dietary protein and other nutriments. If these are low, the capacity of the liver to metabolize alcohol and its power to synthesise the lipoprotein necessary for the transport of triglyceride-fat from the liver may be deficient.

Fatty liver is probably of little importance in relation to the development of cirrhosis. The fatty liver of Kwashiorkor, for instance, never proceeds to cirrhosis.

The increased liver fat has many sources. Most of it comes from the diet and from adipose tissue. In the liver alcohol reduces mitochondrial fatty acid oxidation (8) and increases triglyceride formation from fatty acid.

CLINICAL FEATURES

Early Recognition

This depends on a high index of suspicion on the part of the physician. A patient may present with non-specific digestive symptoms such as anorexia, morning nausea with dry retching, diarrhoea, vague right upper abdominal pain and tenderness, or pyrexia.

The patient may seek medical advice because of the effects of alcoholism such as social disruption, poor work performance, accidents, violent behavior, fits, tremulousness or depression.

The diagnosis may be made when hepatomegaly, a raised serum transaminase or macrocytosis are discovered at a routine examination, for instance at Life Insurance or during investigation of another condition.

Physical signs may be non contributory, although tender hepatomegaly, prominent vascular spiders and associated features of alcoholism may be helpful. The clinical features do not reflect the hepatic histology and biochemical tests of liver function may be normal.

Acute Alcoholic Hepatitis

This usually appears as severe hepatic decompensation after particularly heavy drinking, perhaps precipitated by vomiting, diarrhoea, an acute infection, or prolonged anorexia. The patient is pyrexial and jaundiced. Neuro-psychiatric disturbances are due not only to the alcohol ISM, but also to hepatic precoma. Subdural haematoma and Wernicke's encephalopathy must also be considered.

Nausea, repeated vomiting and fatty diarrhoea are frequent. The liver is large and painful and an arterial bruit may be heard over it. The spleen is often impalpable. Ascites may develop rapidly. Faeces are usually pale.

The peripheral blood shows a polymorph leucocytosis.

Nutritional changes include peripheral neuritis, sore red tongue, iron deficiency anaemia, scurvy, beri-beri, and ankle oedema. Folic acid deficiency may be related not only to nutritional lack, but to a direct effect of alcohol on the bone marrow.

Biochemical tests showed raised serum alkaline phosphatase and transaminase values. Serum albumin is usually low and gamma globulin raised; these return to normal as the patient improves. The serum cholesterol may be very high and the serum lipaemic. This may coincide with pancreatitis (Zieve's syndrome). Increased lipolysis may play a role as serum lipoprotein lipase is reduced, and a circulating inhibitor of the enzyme is present.

Hypokalaemia may be prominent, especially if there is diarrhoea.

An isotope scan shows virtually no hepatic uptake, the picture simulates an hepatic tumour.

Patients with acute fatty liver may die suddenly in shock, attributable to pulmonary fat emboli. Sudden deaths have also been reported in hypoglycaemia.

Gastrointestinal haemorrhage is frequently from a local gastric or duodenal lesion, and is secondary to the general bleeding tendency, rather than related to portal hypertension.

Acute alcoholic hepatitis may be confused with acute virus hepatitis. Helpful diagnostic points are the florid vascular spiders, the very large liver and the leucocytosis.

The jaundice may be markedly cholestatic. The pain, occasional pruritus, large liver and fever with leucocytosis and raised serum cholesterol and alkaline phosphatase

simulate extra hepatic biliary obstruction. Surgery must be avoided. The history of alcohol abuse, vascular spiders and, if clotting permits, liver biopsy are diagnostic. Rarely cholangitis with intraductal polymorph inflammation may be found.

Cholestasis can occasionally present with severe fatty change and minimal alcoholic hepatitis; it carries a bad prognosis(15).

Cholestasis may also be related to chronic pancreatitis with a stenosis of the intrapancreatic junction of the distal common bile duct(16) (Fig. 2). If doubt exists, endoscopic cholangio-pancreatography is mandatory. Liver biopsy showing portal zone fibrosis in the absence of severe alcoholic hepatitis suggests chronic pancreatitis as a possible cause of the cholestasis(17).

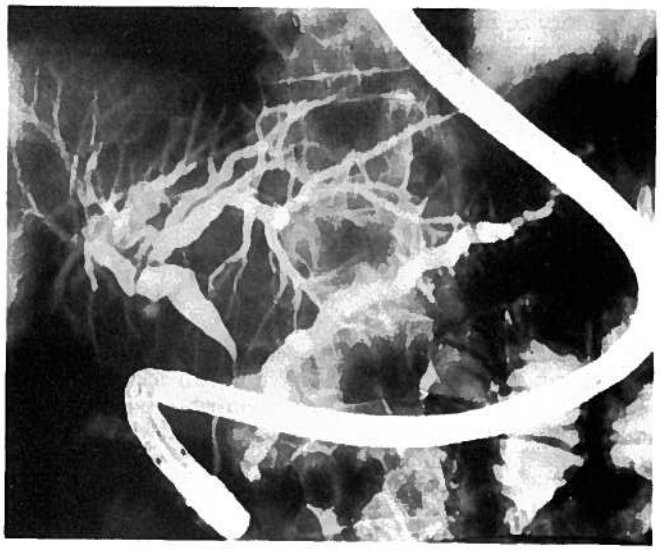

Fig. 2 — *Chronic alcoholic pancreatitis with stenosis of the distal third of the common bile duct. The main pancreatic duct is dilated and irregular. (Scott et al, 1977).*

Established Cirrhosis

This can present without acute alcoholic hepatitis ever having been recognised clinically or histologically. The cirrhosis presumably resulted from alcoholic stimulation of collagen synthesis. The picture resembles other types of end-stage liver disease. Only the history of alcohol abuse, the hepatomegaly and the associated features of alcoholism point to the aetiology.

Splenomegaly is a late feature. Portal hypertension may be related to nodular regeneration. In addition fatty liver can result in obstruction to portal flow with consequent portal hypertension which subsides as the fat disappears. Portal hypertension may also be of sinusoidal type related to central sclerosing hyaline necrosis.

The patient may present with ascites, serum albumin levels being particularly low. Portal-systemic encephalopathy has to be distinguished from alcohol withdrawal.

Associated Features

The occasional, bilaterally enlarged parotids may be analogous with that seen with other types of malnutrition. Gynaecomastia often appears after treatment and is a

frequent complication of spironolactone therapy. The testes atrophy and infertility may be a feature. Muscle mass wastes.

Dupuytren's contracture of the palmar fascia is related to the alcoholism and not to the cirrhosis.

Loss of memory and concentration, insomnia, irritability, hallucinations, convulsions, *rum-fits* and tremor may be the stigmata of alcoholism. This picture must be distinguished from early hepatic precoma.

DIAGNOSTIC TESTS

Early diagnosis often depends on the patients history which is notoriously unreliable. A laboratory test specific for alcoholism would be very helpful.

Elevated blood alcohol values indicate recent ingestion and are useful for follow-up clinics but otherwise are of limited value.

The serum aspartate transaminase (AST, GOT) or alanine transaminase (ALT, GPT) are frequent screening tests indicating liver damage. The ratio AST/ALT may be more useful. Values exceeding 2 are more often found in alcoholic than viral injury. This may be related to alcoholic damage to mitochondria or smooth muscle, with predominant release of AST.

Serum gamma glutamyl transpeptidase (gamma GT) is not specific but is a reliable test for chronic alcoholism. The enzyme is localised to the microsomal fraction of cells and may reflect the proliferation of smooth endoplasmic reticulum following chronic alcohol ingestion. Serum glutamate dehydrogenase is another reliable marker of liver cell necrosis in the alcoholic.

Serum alkaline phosphatase may be markedly increased (>4×normal) especially in those with severe cholestasis and alcoholic hepatitis.

Serum IgA values may be very high.

The plasma ratio of alpha amino-n-butyric acid to leucine (A/L) is raised in chronic alcoholics (18). This appears to be a relatively non-sensitive index of hepato-cellular damage rather than of alcoholism (19).

Non-specific serum changes in acute and chronic alcoholism include elevations in uric acid, lactate, triglyceride and reductions in glucose, phosphate and magnesium. Low serum triiodothyronine (T3) levels presumably reflect decreased hepatic conversion of T3 to T4. Levels correlate inversely with the severity of alcoholic liver disease.

Even sensitive biochemical methods may fail to reveal alcoholic liver damage, and liver biopsy must be resorted to in cases of doubt.

Needle Liver Biopsy

This confirms the presence of liver disease and identifies alcohol abuse as the likely cause. The dangers of the liver damage can be emphasised to the patient more forcibly.

Liver biopsy is important prognostically. Fatty change alone is not nearly so serious as perivenular sclerosis which is probably a precursor of cirrhosis. An established cirrhosis can be confirmed.

Diagnostic difficulties may arise when the histological picture of alcoholic liver disease is shown in a patient who denies alcohol abuse. Other causes are Indian childhood cirrhosis, gross obesity, post-jejuno-ileal bypass operation, diabetes mellitus Wilson's disease, and long-term glucocorticoid treatment.

PROGNOSIS

The prognosis in alcoholics is much better than with other forms of cirrhosis. Everything depends on whether the alcoholic can overcome his addiction. This in turn is related to family support, financial resources and socio-economic state. In a large group of working class, often skid-row type alcoholic cirrhotics studied in Boston, the mean life expectancy for men was 33 months compared with 16 months for the non-alcoholic. In a study at Yale, cirrhotic patients of a higher socio-economic class complicated by ascites, jaundice and haematemesis, showed an overall 5 year survival of 50%. If they persisted in alcoholism, this fell to 40%, whereas if they abstained, it was 60%. Very similar figures come from the United Kingdom and from Australia.

The initial response to treatment is important. Precoma, persistent jaundice and azotaemia are bad signs. Such patients are very liable to develop the hepato-renal syndrome. The patient with decompensated cirrhosis improves slowly. Overt jaundice and ascites after three months carries a grave prognosis. Even total abstention may not improve the prognosis when portal hypertension is prominent. In the very late, irreversible stage where cirrhosis has developed to the stage necessitating portacaval shunt, alcohol abstinence cannot be expected to affect the prognosis. The damage has been done and there is no turning back.

Patients with acute alcoholic hepatitis often deteriorate during the first few weeks in hospital. It may take 1-6 months for resolution, and 20-50% die (20). Those with a markedly prolonged prothrombin time, unresponsive to intramuscular vitamin K, and with a serum bilirubin level greater than 20 mg, have a particularly bad outlook. A depression in serum albumin is also serious.

TREATMENT

Early Recognition

Total abstinence from alcohol is essential. A good diet must be taken and supplementary vitamins, especially B complex, supplied. Improvement is usually rapid and the patient is surprised at his well-being. After 6-12 months the question of resumption of a modest alcohol intake will be raised. The decision is based on the extent of the patients previous alcohol dependence, his life-style and psychological stability. It also depends on whether the liver biopsy showed zonal collagenosis which is pre-cirrhotic, or simply fatty change which may not be. It is preferable that all patients who have shown an adverse hepatic reaction to alcohol should abstain forever, but in some instances a small social intake may be allowed. Regular medical check-ups are essential.

Established Liver Disease

Those with acute alcoholic hepatitis or cirrhosis should abstain permanently from alcohol. The improvement following this and bed rest, may be so striking that it is virtually diagnostic of previous alcoholism. An increased protein intake hastens recovery, but this must be weighed against the possibility of producing hepatic precoma. Calories 25-30/kg and protein 0.5 g/kg are given, increasing as soon as possible to 1 g/kg. Anorexia and vomiting test the dietetic skills of the hospital. Vitamin B complex, including folic acid, are given in large doses, if necessary parenterally. Potassium chloride supplements are usually required, and some need additional magnesium and glucose.

Chlormethiazole (Heminevrin) or Chlordiazepoxide (Librium) should be given if the patient has recently been drinking heavily in order to prevent delirium tremens.

If the diagnosis is in doubt management should be conservative and needle biopsy performed as soon as possible. Laparotomy in patients with acute alcoholic hepatitis is dangerous.

The measures recommended for encephalopathy and portal hypertension should be employed. The portal venous pressure may well fall as the alcoholic hepatitis resolves. Surgery for portal hypertension should, if possible, be avoided until the maximum benefit has followed medical treatment.

Renal failure is particularly liable to follow hepatocellular failure with ascites in alcoholic patients (hepatorenal syndrome).

Corticosteroids

The high mortality of acute alcoholic hepatitis, about 50% in those with jaundice and encephalopathy, has stimulated the use of corticosteroids. These might decrease inflammation, reduce fibrosis and retard progression to cirrhosis. Controlled trials have shown variable results, sometimes beneficial, more usually not. This may be related to selection of patients. If those who are very ill and in whom liver biopsy is impossible are chosen, the results are poor. In those not so sick in whom clotting permits biopsy the results are good.

In the severely ill with deep jaundice, fever, markedly prolonged prothrombin time and electrolyte disturbances a case can be made for 30 mg Prednisolone daily for 2-3 weeks (20). This seems to decrease early mortality. Long-term corticosteroids increase mortality.

Other Measures

In view of the hypermetabolic state, propylthiouracil (300 mg day) was given short-term to patients with alcoholic hepatitis in a double-blind trial and resulted in functional improvement; hepatic histology was not studied (21). Patients with inactive cirrhosis were unaffected. Propylthiouracil is worth considering in advanced alcoholic hepatitis soon after alcohol abstention.

D-penicillamine reduces hepatic collagen, proline hydroxylase in patients with alcoholic hepatitis and may be beneficial in reducing fibrosis. It is a toxic drug and has not been fully assessed in these patients. Similarly, the use of colchicine, another toxic drug, to reduce fibrosis is only currently being evaluated.

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Address for reprints: *Sheila Sherlock*
Department of Medicine
Royal Free Hospital Medical School
Pond Street
London NW3 2 OG. England