in two weeks instead of three or four does not justify the use of corticosteroids with their inherent risk of side effects. A shortening of the period of severe visual disability in bilateral cases (or in patients with unilateral optic neuritis and poor vision in the other eye), however, would be worth while. We now reserve treatment for this small group.

We are grateful to the physicians and surgeons of Moorfields Eye Hospital, City Road, for agreeing that all patients presenting to the casualty department with optic neuritis during the period of our study should be referred to our clinics. We also thank Mr H Donovan for statistical analysis of the results. A contribution from the Monnell Foundation towards the expenses of the investigation is much appreciated.

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Changing pattern of alcoholic liver disease in Great Britain: relation to sex and signs of autoimmunity

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Summary

A survey of 293 patients with alcoholic liver disease showed that women, particularly those aged under 45, had a significantly higher incidence of alcoholic hepatitis, with or without superimposed cirrhosis, than men. The long-term prognosis for both women who continued to drink and those who stopped drinking was worse than that for men. Autoantibodies were more common in women, which suggested that immune mechanisms may play a part in the pathogenesis and progression of alcoholic liver disease in women.

Introduction

The steady increase in alcohol consumption in Britain over the past 20 years, and particularly in the last decade, has been reflected by a rise in the number of offences associated with alcohol abuse.[1] There has been a parallel rise in the frequency of alcoholic cirrhosis. Thus a survey from Birmingham in 1959-64 attributed 33% of cases of cirrhosis to excessive drinking,[2] whereas the figure for 1964-9 was 51%.[3] In a recent survey in South London the proportion of alcoholics among cirrhotics had risen still further to 65%[4]; the increased incidence was particularly conspicuous among women. We reviewed the records of 293 patients who presented to a specialist referral unit for liver diseases in 1967-75. Possible changes in the pattern of alcoholic liver disease, as evidenced by clinical features and histological changes, as well as the male:female ratio, were analysed in relation to the mode of presentation and to prognosis.

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Since considerable interest has recently focused on the role of immune mechanisms in perpetuating alcoholic liver damage, we also investigated laboratory manifestations of autoimmunity.

Patients and methods

The 293 patients were admitted to the liver unit, King's College Hospital, in 1967-75 with a diagnosis of alcohol-related liver disease. Regular daily ingestion of at least 100 g ethanol could be substantiated, either on the patient's own account or by information from a relative or close friend.

The histological features of all patients were assessed by biopsy on referral and, in 45 patients, by a follow-up biopsy. The patients were classified according to the following seven histological diagnoses: (*a*) fatty infiltration alone; (*b*) fatty infiltration and portal fibrosis; (*c*) alcoholic hepatitis (with foci of lobular inflammation, spotty necrosis or hyaline inclusions, or both)[5]; (*d*) central sclerosing hyaline necrosis[6]—same pattern as in *c* with a centrilobular distribution and much tissue loss together with fibrous tissue deposition surrounding hepatic vein radicals; (*e*) cirrhosis; (*f*) cirrhosis and alcoholic hepatitis; (*g*) primary hepatocellular carcinoma, in all cases superimposed on cirrhosis.

Laboratory investigations included standard tests of liver function, measurement of serum immunoglobulin levels,[7] and tests for serum autoantibodies.[8] ^{99}Tc-scintiscanning of the liver and spleen was performed in most cases, and the splenic peak count rate was calculated as a measure of portosystemic shunting.[9]

Results

Sex ratio—There were 215 men and 78 women—a male:female ratio of 2·7:1. The mean age at presentation was similar in both sexes (men 51·7±10·2 years; women 51·9±11·1). One hundred and six patients presented in 1967-71 and the remaining 187 in 1972-5. Over the period of survey there was a significant increase in the proportion of women referred, particularly with cirrhosis or alcoholic hepatitis. Thus in 1967-71 the male:female ratio was 4·88:1 compared with a ratio of 2·11:1 in 1972-5 ($\chi^2=7·14$; $P<0·01$). Over this period the proportion of men aged under 55 who showed features of alcoholic hepatitis or cirrhosis also significantly increased (34/54 in 1967-71 and 64/76 in 1972-5; $\chi^2=6·57$; $P<0·025$).

Reasons for referral—Forty-four (15%) patients were asymptomatic and had been referred for investigation of suspected liver disease after abnormal liver function values or hepatomegaly had been

detected as incidental findings. Vague ill health, weight loss, and ill-defined upper abdominal pain were presenting symptoms in a further 88 (30%) patients of both sexes and occurred in patients with alcoholic hepatitis with or without superimposed cirrhosis as well as in those with fatty infiltration with or without fibrosis. Most of the other patients were referred because of the appearance of one or other of the main complications of liver disease (gastrointestinal bleeding in 50 (17%), jaundice in 35 (12%), ascites in 38 (13%), and hepatic encephalopathy in 38 (13%).

The first biopsy showed that there was a small proportion of patients with only minor hepatic abnormalities (fatty infiltration with or without fibrosis) (table I); most (170 (58%)) showed features of cirrhosis, with or without concomitant alcoholic hepatitis, on first presentation. Alcoholic hepatitis or central sclerosing hyaline necrosis without cirrhosis was present in 55 (19%) patients, while in 14 (5%) a primary hepatocellular carcinoma was superimposed on cirrhosis, which had been known to exist for at least eight years.

TABLE I—*Histological abnormalities on referral in 293 patients*

Diagnosis	No (%) of patients	No (%) with lesion		P value (men v women)
		Men	Women	
Fat with or without fibrosis	54 (18·4)	46 (21·4)	8 (10·3)	<0·05
Alcoholic hepatitis	39 (13·3)	27 (12·6)	12 (15·4)	NS
Central sclerosing hyaline necrosis	16 (5·5)	7 (3·3)	9 (11·5)	<0·025
Inactive cirrhosis	65 (22·2)	52 (24·2)	13 (16·7)	NS
Cirrhosis and alcoholic hepatitis	105 (35·8)	70 (32·6)	35 (44·9)	NS
Hepatoma	14 (4·8)	13 (6·1)	1 (1·3)	NS
Total	293 (100)	215 (100)	78 (100)	

Liver damage in relation to sex—Analysis of the type of liver damage in relation to sex showed that there was a significant preponderance of men with fatty infiltration (table I). Conversely, a significantly higher proportion of women presented with central sclerosing hyaline necrosis, and overall there was a significantly higher incidence of alcoholic hepatitis, with or without cirrhosis, among women $\chi^2 = 11{\cdot}74$; $P < 0{\cdot}001$). Of the 14 patients with hepatoma, 13 were men, and when patients with cirrhosis only were considered, this complication was found to occur nearly five times more often in men than in women (9·63% and 2·04% respectively). There was a significantly higher overall incidence of alcoholic hyaline in women (60·2%) than in men (34·8%; $\chi^2 = 16{\cdot}22$; $P < 0{\cdot}0005$). This reflected an increased incidence of hyaline in women with cirrhosis as well as the female predominance of alcoholic hepatitis already referred to. Considerable fatty deposition in the liver was more common in women than in men with cirrhosis (86% and 61·5% respectively; $\chi^2 = 9{\cdot}73$; $P < 0{\cdot}005$). In contrast, significant iron deposition was more common in men (74·8% compared with 38·7% in women; $\chi^2 = 15{\cdot}6$, $P < 0{\cdot}005$), and this applied to all histological groups except those with cirrhosis with superimposed alcoholic hepatitis.

Liver damage in relation to age—When the pattern of liver damage was analysed according to age, the female preponderance of central sclerosing hyaline necrosis was found to be confined to women under 55 (table II), particularly those aged under 45, 30·8% of whom showed this abnormality. By contrast, the overall incidence of inactive cirrhosis was lower in women aged less than 55 than in the older age group, although this difference just failed to achieve statistical significance.

TABLE II—*Histological abnormalities in 169 men and 70 women with alcoholic hepatitis and cirrhosis grouped according to age*

	No (%) with lesion			P value	
	Women		Men		
Age:	>55 (n = 28)	≤55 (n = 42)		Women >55 v those ≤55	Women v Men
Alcoholic hepatitis	6 (21·4)	6 (14·3)	27 (16·0)	NS	NS
Central sclerosing hyaline necrosis	0	9 (21·4)	7 (4·1)	0·001	0·025
Inactive cirrhosis	8 (28·6)	5 (11·9)	52 (30·8)	NS	0·025
Cirrhosis and hepatitis	13 (46·4)	22 (52·4)	70 (41·4)	NS	NS
Hepatoma	1 (3·6)	0	13 (7·7)	NS	0·006

No woman aged under 45 had inactive cirrhosis. The distribution of histological abnormalities in women over 55 was similar to that found in men. The only age-related difference for men was that all those with a hepatoma were over 50 years of age.

Alcohol consumption—No differences in alcohol consumption could be found to account for the age-related differences in the histological pattern in women (those aged under 45 took a mean (±SE of mean) of 170·6±9·3 g ethanol daily; those aged 45-55 took 175·6±9·2 g/day; and those aged over 55 took 181·1±10·6 g/day). Altogether 90·7% of men but only 65% of women admitted to a daily intake of 150 g or more ($\chi^2 = 14{\cdot}0$; $P < 0{\cdot}005$).

Immunological tests—Analysis of immunological tests showed a significant increase in the incidence of smooth muscle antibodies in women with cirrhosis and alcoholic hepatitis (45·4%) compared with the incidence in men (23·4%; $P < 0{\cdot}05$), and this was also the case for antinuclear antibodies (31·8% and 8·5% respectively; $P < 0{\cdot}05$). Mean serum IgG levels were higher in women than in men with these histological abnormalities (2·076±0·227 g/l and 1·523±0·192 respectively; $P < 0{\cdot}05$), and this was also the case for IgM (women 5·087±1·077 g/l; men 2·616±0·338 g/l; $P < 0{\cdot}02$).

Collateral shunting, as estimated from values of splenic peak count rate, was significantly greater in women with alcoholic hepatitis, with and without underlying cirrhosis (55 300±7900 cpm) than in men (27 3500±2800 cpm) ($P < 0{\cdot}0001$), indicating more severe disease in women. There was a significant correlation between values for splenic peak count rate and serum levels of IgM ($n = 77$; $n = 0{\cdot}42$; $P < 0{\cdot}001$).

Clinical outcome—Sixty-four (21·8%) of the 293 patients died within three months of presentation. This figure included all those with hepatoma, five (13%) of those with alcoholic hepatitis, five (31%) of those with central sclerosing hyaline necrosis, and 46 (27%) of those with cirrhosis. The most common factors leading to death were hepatic coma (in 26 patients (40%)) and gastrointestinal haemorrhage in 22 (34%)), with infections, including septicaemia and spontaneous peritonitis, contributing in about equal proportions. There was no significant difference in early mortality between men and women, though one woman died from hepatic encephalopathy within a month of presentation with massive fatty infiltration as the only histological abnormality.

Adequate follow-up information was available, for periods ranging from six months to eight years, on 174 of the 229 patients who survived over three months after referral.

Follow-up biopsy—Twelve of the 45 patients who underwent repeat liver biopsy claimed to have stopped drinking. Eight had shown alcoholic hepatitis on first biopsy, and reversal of this lesion was shown after eight months' to two years' abstinence. In the remaining four, who had inactive cirrhosis, no histological change was noted. Of the 33 patients who continued to drink, eight progressed from alcoholic hepatitis to cirrhosis over two to three and a half years, and this occurred particularly frequently in women. Thus of the nine women who showed alcoholic hepatitis alone on first biopsy and who continued to drink, seven developed cirrhosis, while this was the case in only one out of seven men. In only one patient (a man) did alcoholic hepatitis resolve despite his continuing to drink; this lesion persisted in 14 patients and developed in a further four who did not abstain. Six patients with inactive cirrhosis on first biopsy showed no change.

Life survival curves—Analysis of these showed that, from the time of presentation, only 41% of patients who continued to drink were alive at five years, in contrast to 60% of those who abstained ($P < 0{\cdot}05$) (fig 1). Overall men derived significantly greater benefit from stopping drinking than women. Thus all but one of the 16 men who died, in whom a drinking history was available, had continued to drink. In contrast, nine of the 20 women who died claimed to have stopped drinking ($\chi^2 = 4{\cdot}16$; $P < 0{\cdot}05$). Furthermore, cumulative mortality in women who continued to drink was significantly higher than that in men (fig 2). Thus, only 30% of the women who survived three months from first presentation were alive at five years, in contrast to 72% of men. For patients with alcoholic hepatitis and cirrhosis the average age of death in women was almost 11 years younger than that for men (51·8 years and 62·5 respectively).

Discussion

A notable feature of this survey was the increase over the past nine years in the proportion of patients of both sexes who presented with severe alcoholic liver injury; this increase was most pronounced in the middle-aged and younger age groups. The series was inevitably highly selected, but our figures may

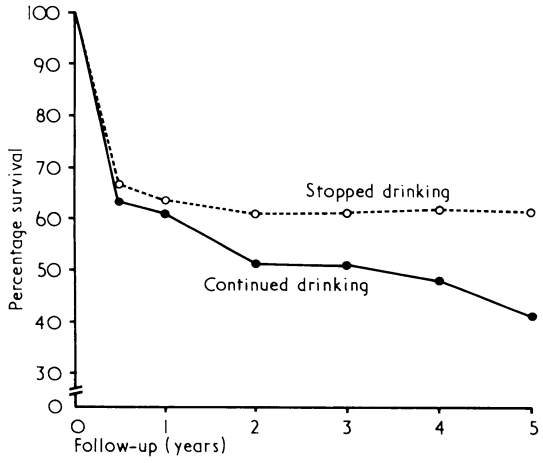

FIG 1—Effect of continuing or stopping drinking on cumulative survival from the time of presentation in 239 patients with alcoholic hepatitis or cirrhosis.

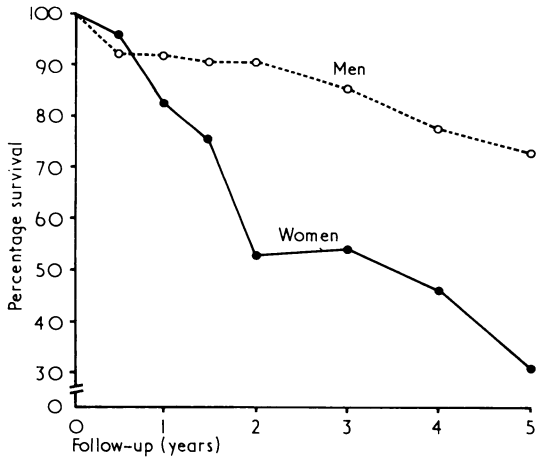

FIG 2—Sex differences in cumulative survival for patients who survived three months after presentation and who continued to drink.

be compared with those from a review of patients presenting to a specialised liver unit at the Royal Free Hospital in 1960-7. There, Brunt *et al* found cirrhosis or alcoholic hepatitis in only 40% of alcoholic patients,[10] in contrast to a figure of 80% in the present series. Many studies have shown that the severity of alcoholic liver disease is related to the quantity and duration of alcoholic consumption, and this change in pattern correlates well with national statistics for alcohol intake, which have shown a 35% increase in average per caput consumption between 1965 and 1973.[11] A similar figure was obtained in a detailed survey of drinking habits in a south London suburb in 1965-74,[12] as this increase was found to be particularly steep among women. In 1969 the male:female ratio of patients coming to the attention of the Glasgow Council on Alcoholism was 4·1:1, but by 1974 the ratio had fallen to 2·9:1—a similar change in sex ratio to that observed here.[13]

Epidemiological studies in the USA, France, and Australia have indicated that women with alcoholic cirrhosis have generally drunk less for a shorter period than their male counterparts.[14–16] The finding of a significantly higher incidence of severe alcoholic hepatitis in women, despite a lower overall incidence of heavy drinking, suggests that in England, as in other countries, they are particularly susceptible to these severe forms of hepatic damage. Our findings are unlikely to be due to a bias in favour of more men being referred with early liver lesions detected on routine medical examination, since a similar proportion of both sexes presented for this reason. It is difficult to measure alcohol intake accurately, especially in women, who may be more prone to underestimate their drinking,[17] but over 80% of our patients admitted to taking at least 150 g ethanol daily. This figure, which must represent a minimum estimate of consumption, is similar to that obtained by Lelbach from detailed interviews of alcoholic patients with liver disease.[18 19]

Clinical evidence indicates that the hepatotoxicity of alcohol is related not only to the quantity ingested but also to the pattern of drinking: a steady high intake is probably more hazardous than sporadic "binges."[20] One explanation for our findings is that the drinking habits of women may differ from those of men. Possible sex-related differences in the metabolism of alcohol to potentially toxic derivatives, such as acetaldehyde,[21] also require investigation.

We have shown that the incidences of serum autoantibodies and of alcoholic hyaline on liver biopsy are significantly higher in women, which suggests that immunological factors may also be important in the pathogenesis and progression of their liver disease. This would be in keeping with other evidence that points to immunologically mediated liver damage in alcoholism, such as that lymphocytes from patients with alcoholic hepatitis are cytotoxic to isolated hepatocytes[22] and are sensitised to extracts of alcoholic hyaline.[23] Moreover, in alcoholic cirrhosis there is a higher than normal incidence of the histocompatibility antigen HLA-B8,[24] which is also found with increased frequency in patients with autoimmune liver disease.[25] As a result younger women, who seem to be principally affected by autoimmune liver disease,[26] would be particularly vulnerable. This idea is supported by our finding of a strong female predominance among patients with alcoholic hepatitis and sclerosing central hyaline necrosis in the under-45 age group.

Another reflection of immunological factors may be the higher serum levels of immunoglobulins in women. These abnormalities might, however, simply reflect their more severe hepatic damage, with defective sequestration of antigenic material by Kupffer cells resulting in diversion to the spleen with increased antibody production.[27] Increased levels of serum antibodies to *E coli*, predominantly of the IgM class, have been described in cirrhosis.[28] Values for splenic peak count rate on scintiscanning were higher in women than in men and correlated with serum levels of IgM, indicating that this mechanism must be at least partly responsible for the higher immunoglobulin levels in women.

The observed male predominance of primary hepatocellular carcinoma occurring with cirrhosis is similar to that reported in another British survey of patients with alcoholic cirrhosis.[3] It also agrees with other observations from this unit that this malignancy develops nearly six times more often in male cirrhotics than in women, whatever the cause of their liver disease.[29]

Like Galambos *et al*,[30] we found that the development or persistence of alcoholic hepatitis was associated with continuation of drinking, and conversely abstinence from alcohol led to resolution of this lesion. In our series alcoholic hepatitis progressed to cirrhosis only in patients who continued to drink, but other reports indicate that this may occasionally occur despite abstinence.[10 30] The beneficial effects of abstinence on long-term survival are also well shown; our five-year survival figures of 60% for those who stopped and 41% for those who continued drinking are similar to those reported by others.[10 31–33] What has not been shown before, however, is the significantly greater mortality and younger age of death among women who continue to drink, which correlates with their increased tendency to show histological progression of disease if alcohol is not withdrawn.

Furthermore, not only are women with alcoholic hepatitis and cirrhosis more susceptible than men to progression of their disease if they continue to drink: their prognosis is also worse even if they stop. The higher incidence of autoimmune markers in our women patients suggests one possible explanation for this observation—namely, that alcohol may trigger a particularly

vigorous immune destruction of hepatocytes in women, and they are less able than men to suppress this reaction once alcohol is withdrawn. We have suggested that a similar type of mechanism may be important in the pathogenesis of chronic active hepatitis.[34] Thus, while every effort must be made to recognise alcohol abuse at an early stage, and to encourage abstinence, these measures may still be inadequate to prevent the progression of liver disease in certain susceptible individuals and particularly in women.

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Study of fatal bone marrow depression with special reference to phenylbutazone and oxyphenbutazone

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Summary

The histories of 269 patients whose death certificates did not mention a drug as the cause of aplastic anaemia or agranulocytosis were investigated. Eighty-three deaths were probably caused by drugs, the most common cause of aplastic anaemia being treatment with phenylbutazone (28 deaths) and oxyphenbutazone (11 deaths). Thirteen out of 17 deaths from agranulocytosis were attributed to co-trimoxazole treatment. A separate survey of general practitioners' prescriptions enabled the mortality to be estimated. With the addition of one death due to oxyphenbutazone and four deaths due to phenylbutazone that were reported independently to the committee, the mortality from oxyphenbutazone was 3·8 per 100 000 and from phenylbutazone 2·2 per 100 000. With phenylbutazone the rates varied from under 1 death per 100 000 for men aged under 65 years to 6 per 100 000 for women aged 65 and over. Small numbers precluded estimates for oxyphenbutazone in these subgroups, although a similar trend was suggested. No particular indication for treatment seems to carry a higher risk, the main concern being the use of these two drugs in elderly patients.

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Introduction

In 1964 the Committee on Safety of Drugs (now Committee on Safety of Medicines; CSM) established a register of adverse reactions. Since then 513 reports of drug-induced fatal aplastic anaemia or agranulocytosis have been received. About half of these deaths were notified in copies of "draft entries" (derived from death certificates) that mentioned drugs as the cause of a fatal reaction, which are supplied routinely by the Office of Population Censuses and Surveys (OPCS). The remainder were reported by doctors or the pharmaceutical industry—for example, on the committee's yellow cards. The two drugs most frequently suspect are phenylbutazone (188 deaths) and oxyphenbutazone (62 deaths).

These reports cover only a proportion of the fatal drug-induced dyscrasias that actually occur, and it was therefore decided to investigate all the fatal dyscrasias identified by the OPCS, using death certificates that did not mention drugs, to obtain more realistic estimates of drug-induced dyscrasias. Because of the difficulty in establishing causality in individual cases such estimates can only be approximate, but they might be a useful guide to doctors in choosing suitable treatment for individual patients. In addition, drug-induced deaths from