used in different laboratories. 
In fact, when comparing our standard with that of a reference laboratory (Glostrup, Denmark), our standard was about 50% lower, the standard curve being displaced to the left. This finding is of no importance to the discussion of our findings because differences between groups are not affected, but the absolute values for P.R.A. and renin substrate will be correspondingly lower in our laboratory.

We gratefully acknowledge the help and advice on renin measurements given by Dr Jörn Giese and Dr Ric Kappelgaard, department of clinical physiology, KAS Glostrup, Denmark. This study was supported by Swedish Medical Research Council grant no. B-74-19x-3948.

Requests for reprints should be addressed to M. A.

REFERENCES

CASUAL BLOOD-ETHANOL ESTIMATIONS IN PATIENTS WITH CHRONIC LIVER DISEASE
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Sheila Sherlock D. N. Baron
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Summary
Patients attending a clinic for diseases of the liver were tested for blood-ethanol by a gas-chromatographic technique sensitive to about 5 mg/dl (1 mmol/l). Of 172 patients (51 men, 121 women) 36% gave a history of heavy drinking (>80 g ethanol/day; equivalent to 8 fl oz of whisky or 1 litre of wine) and 13% had ethanol in the bloodstream at values of 8-400 mg/dl. 42 patients (24%) had the liver-biopsy changes of alcoholic liver disease, and 17 of these had ethanol in the blood at one time or another. Nearly half (22/49) of all patients admitting heavy drinking also had detectable blood-ethanol. In all cases but 1 where blood-ethanol was found, a drinking history was admitted on first attendance, and alcoholic liver disease was nearly always found on subsequent biopsy. Blood-ethanol and admission of drinking were most constantly found in association with alcoholic steatosis and hepatitis. Both features were less commonly present in cases of alcoholic cirrhosis. Only 1 patient of 22 with "cryptogenic" cirrhosis on biopsy was found to have both ethanol in the blood and an alcoholic history, although 5 had an alcoholic history alone. The value of serial blood-ethanol estimations in the treatment of alcoholics and the detection of relapses is demonstrated. The findings confirm the relatively low frequency of alcoholism as a contributor to cirrhosis in the United Kingdom. Alcohol does not seem a major cause of cryptogenic cirrhosis. Casual blood-ethanol estimation is a useful and objective adjunct to techniques of investigating diseases of the liver.

Introduction
This year in England and Wales about 1500 people will die from cirrhosis of the liver. About a third of these deaths will be associated with alcoholism, and could have been avoided if identified and treated in time. The identification of alcoholics in a community taxes the ingenuity of both epidemiologists and clinicians, and methods to assess prevalence have included hospital-admission statistics, population studies, field surveys, and cohort studies. Alcoholics individuals are identified on the basis of clinical or historical evidence of "problem drinking"—an arbitrary concept drawn from definitions which stress the dependent nature of alcoholism. Definitions may not be objective and often exclude patients whose "social drinking" has not progressed to addiction but in whom alcohol has already led to physical damage, such as cirrhosis of the liver.

Although alcohol (ethyl alcohol, ethanol) is believed to be a direct hepatotoxin, the epidemiological relationship of excessive drinking to alcoholic liver disease is uncertain. Another problem in hepatology is the detection of problem drinking in patients who deny excessive ethanol intake. This may be important in the allocation of cirrhosis with non-specific histological features on liver biopsy to either alcoholic or cryptogenic groups.

We thought that these questions could be investigated by the assessment of blood-ethanol levels in outpatients with alcoholic, cryptogenic, and other liver diseases.

Patients and Methods
Patients were seen in an outpatient clinic for diseases of the liver. This was held on a Thursday morning between 9.30 A.M. and 1 P.M. An unselected sample was questioned as to drinking habits and, after skin swabbing with isopropanol, 2 ml specimens from a peripheral vein were drawn into fluoride specimen tubes. The blood-alcohol was estimated by gas chromatography with a sensitivity for ethanol of about 5 mg/100 ml (5 mg/dl, or 1 mmol/l in Systeme International units) using a Fye 'Unicam' series 104 chromatograph, in association with a present address: Department of Gastroenterology, Royal Victoria Infirmary, Newcastle upon Tyne.
BLOOD-ETHANOL AND DRINKING HISTORY IN LIVER PATIENTS

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>No.</th>
<th>Heavy drinking admitted</th>
<th>Ethanol in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic cirrhosis</td>
<td>22</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Alcoholic steatosis</td>
<td>8</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Non-specific inflammation</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>22</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Other liver diseases*</td>
<td>95</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Not available</td>
<td>8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>172</td>
<td>49</td>
<td>22</td>
</tr>
</tbody>
</table>

* Including active chronic hepatitis, secondary biliary cirrhosis, haemochromatosis, chronic persistent hepatitis, primary biliary cirrhosis, drug-induced cholestasis, idiopathic benign recurrent cholestasis, haemangiosarcoma.

Patients subsequently admitted to the ward underwent liver biopsy by the Menghini technique. The relationships between liver histology, alcohol intake, and blood-ethanol were analysed by non-parametric statistics or the Fisher-Irwin-Yates exact-probability test on 2x2 contingency tables.

Results

In the two years 1972-1974 there were 340 requests for blood-ethanol estimations from the liver clinic. These (see table) involved 172 patients (51 men, 121 women). The diagnosis, made on the basis of liver biopsy, blood-ethanol, and the drinking history, is given in the table. 36% of patients admitted drinking more than 80 g ethanol per day, equivalent to 8 fl oz (230 ml) whisky or 1 litre of wine, and 13% had ethanol detectable in their bloodstream at one time or another.

Only 1 patient with non-alcoholic or non-cryptogenic cirrhotic liver disease (chronic persistent hepatitis B) gave an alcoholic history, and ethanol was not detected in any of the 95 patients in this category. On the other hand, 17 out of 42 (41%) of patients with alcoholic liver disease had ethanol in the blood. The most constant detection of blood-ethanol occurred in the two subgroups, alcoholic hepatitis and alcoholic steatosis. All the patients in these groups admitted heavy drinking, and 13 out of 20 (65%) had ethanol in their blood.

Nearly half (22 out of 49) of all patients admitting heavy drinking had ethanol in their blood at one time or another. Only 1 patient who denied alcohol intake on first attendance was subsequently found to have ethanol in the blood. However, patients in this category tended to understate their morning's intake. An example of this is the housewife who said that she had had a light ale (300 ml) for breakfast: 3 hours later she had a blood-ethanol of 250 ml/dl, suggesting an ethanol intake equivalent to ten light ales.

5 patients with cryptogenic cirrhosis gave a history of heavy drinking, and in 1 of these ethanol was found in the blood. No patient with a positive blood-ethanol had a normal liver biopsy.

Patients with an alcoholic history with and without a positive blood-ethanol test differed from one another in only one respect—namely, the number of tests performed. The number of requests per patient was much higher in the group of patients where ethanol was detected at least once. This is reflected in fig. 1, which gives the chances (with 95% confidence limits) of detecting blood-ethanol as the number of tests per patient rises. With one to two tests, only 13% are positive, with three to five tests the proportion rises sharply to 40-50%, whilst with six to ten tests the detection-rate is 89%. The theoretical probability (from the binomial distribution) of a positive result with three tests is 29%. The observed probability of 50% suggests that drinking patients have been selectively retested. Nonetheless this number of tests is probably the least which is likely to yield a satisfactory chance of detecting problem drinking.

Blood-ethanol Levels

The distribution of blood-ethanol levels, where detected, is given in fig. 2. This corresponds to a log-normal curve with a mode at 28 ml/dl. The highest level recorded was 400 mg/dl, five times the maximum legal driving limit. Of 8 patients with ethanol levels >150 mg/dl 7 were women; of 14 patients with values ≤150 mg/dl 5 were men. There is a significant excess of women with the higher blood-alcohol readings (p<0.05). Where blood-ethanol is found the histological picture is more likely to be alcoholic hepatitis than
alcoholic cirrhosis ($p<0.01$). In general also, patients where ethanol was found in the blood tended to give daily consumption histories of greater than 120 g ethanol, equivalent to 12 fl oz (340 ml) whisky or 1500 ml of wine.

**Case-histories**

Sequential blood-ethanol tests related to the course and events of a patient’s illness yielded some interesting (and surprising) results:

**Case 1.**—A 57-year-old counter-hand was discharged with a diagnosis of alcoholic cirrhosis. Only one of nine blood-alcohol tests over a period of 12 months was positive, at 18 mg/dl. 6 months later he was admitted with severe delirium tremens, only then confessing that he had been drinking half a bottle (380 ml) whisky and 1500 ml of wine daily for the past year. This is equivalent to 250 g of ethanol.

**Case 2.**—A 50-year-old male painter was investigated for alcoholism in 1963, when a liver biopsy demonstrated fatty change. He was referred back by his general practitioner because of seizures. In outpatients he denied excessive ethanol intake but his blood-ethanol was 21 mg/dl. Subsequently liver biopsy demonstrated alcoholic cirrhosis.

**Case 3.**—A 56-year-old housewife was admitted from the clinic with a blood-ethanol of 82 mg/dl. During her admission random blood-ethanol values were always in the undetectable range. On return from weekend leave she was found to have a blood-ethanol of 20 mg/dl. She denied drinking. On discharge she was home for 24 hours, returning to the outpatient clinic with a blood-ethanol of 112 mg/dl and has maintained similar levels since. She admits to only “the occasional gin” and refuses further inpatient treatment.

**Discussion**

The structure of the sample confirms previous impressions of the relative infrequency of alcoholic liver disease in the U.K. Among patients with liver disease about a third gave a history of heavy drinking and only 1 in 8 yielded positive blood-ethanol values.

The infrequency with which positive blood-ethanol is detected in the absence of a history of heavy drinking suggests that patients are in general frank about whether they are drinking.

The failure to detect blood-ethanol in patients who are drinking heavily is curious. This may be related to differing patterns of consumption, continuous drinkers being more likely to display a raised blood-ethanol at any one time rather than bout drinkers. Other causes of failure may be the presence of food in the stomach (delaying or retarding small-intestinal absorption by its effect on gastric emptying) and adaptive metabolism. In chronic alcoholics the fall-off of blood-ethanol from peak values is accelerated and less likely to be detected some time after administration. However, where severe liver damage has supervened, metabolism of ethanol is impaired and higher blood-levels may result from augmented gastric absorption.

A history of heavy drinking is more constantly associated with alcoholic liver disease than is the finding of blood-ethanol, especially where the patient has been frightened about attending the clinic. The blood test is a useful confirmation of clinical suspicion. This is especially true in a society where the early-morning consumption of ethanol is not the cultural norm and may well be concealed by the patient.

The chief value of blood-ethanol determination may be in the management of alcoholic patients. Cases 1–3 illustrate patterns of relapse and the efficacy of hospital admission in controlling ethanol intake. Likewise surreptitious drinking within hospital can be detected by routine blood tests. Early recognition of loss of control in alcoholics will then lead to earlier and more effective treatment.

The answers to the questions posed at the beginning of our paper seem to be as follows. Firstly, specific histological features of alcoholic liver damage are generally associated with a history of heavy drinking and detectable blood-ethanol. Secondly, heavy drinking and a positive blood-ethanol are not, in this British series, greatly associated with cryptogenic liver disease. Lastly, the finding of blood-ethanol in a patient attending a morning clinic is a useful indicator of alcoholism and possible alcoholic liver disease.

The test is a cheap and simple addition to routine techniques of investigating liver disease and should find a place in other disciplines where alcohol takes its toll.

Requests for reprints should be addressed to S. S.

**REFERENCES**


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**DINITROCHLOROBENZENE SENSITISATION TEST IN WOMEN ON HORMONAL CONTRACEPTIVES**

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**Summary**

Cell-mediated immunity was measured in women on hormonal contraceptives using the 2,4-dinitrochlorobenzene (D.N.C.B.) sensitisation test. Three groups of women were studied: forty-eight women were taking oral contraceptives of combined oestrogen/progestogen (thirty-seven of them had used oral contraceptives for a year or longer); twelve