Upsala J Med Sci 92: 315–327, 1987

# A Study of Three Groups of Urban Men from the General Population with Different Alcohol Habits and Drug Use and Their Serum Levels of Liver-related Enzymes and Haematological Variables

Sture Mützell

*Department of Family Medicine, University Hospital, Uppsala, Sweden*

## ABSTRACT

A sample of 200 men from the general population was investigated concerning alcohol consumption in relation to laboratory findings. The relation between symptoms of alcoholism (subjective relative loss of control over drinking, blackouts and morning drinks) and the alcohol consumption was also studied. The subjects were divided into three groups: (I) a group with low alcohol consumption without symptoms of alcoholism, (II) an intermediate group with low, moderate or high alcohol consumption and one or more alcohol symptoms and (III) a heavy-drinking group with two or more symptoms. The heavy-drinking group had significantly higher serum bilirubin, aspartate amino-transferase (ASAT), creatine kinase and lactate dehydrogenase values than the other two groups. Gamma-glutamyl transpeptidase (GGT) showed no relation to alcohol consumption. The use of liver-metabolized drugs was investigated. Ten of the 53 heavy drinkers were taking such drugs, because of illness, and the other 43 were not. The heavy drinkers taking drugs showed pathological laboratory values throughout, in contrast to the subjects of the other subgroups. Serum GGT was high in the drug-using groups but was not significantly elevated in the groups taking only alcohol and no drugs.

## INTRODUCTION

Poikolainen et al. (29) found no relationship between the serum concentration of gamma-glutamyl transpeptidase (GGT) and the daily alcohol intake in a study with use of the diary method and a questionnaire, but according to Kristenson et al. (15) GGT is a good marker of high alcohol intake. The purpose of the present survey was to elucidate the following questions:

1. Is heavy alcohol drinking in a population sample related to deviating liver function tests and haemopoiesis?
2. Can biomedical tests be used for screening of drinking problems?
3. Do drugs metabolized through the liver, together with alcohol, interfere with the function of the liver, and if so in what way?

## MATERIAL

The present sample of 200 men was collected as a reference group for the KARTAD project which is being carried out at the Magnus Huss Clinic of the Karolinska Hospital in Stockholm. "KARTAD", stands for the KAROlinska project for research and Treatment of Alcohol Dependence. More than 700 consecutively admitted alcoholic patients living in the same geographical area as the random control sample of men in the present study have taken part (1). The same medical, social and psychological methods were used for examination of the random controls as for the KARTAD patients.

From the National Register covering all Swedish inhabitants, a random sample of 228 men was taken from the general male population living in the urban districts of Solna and Sundbyberg, with altogether 80,000 inhabitants, in the catchment area of the Karolinska Hospital. Forty men in each of the age groups 20-29, 30-39, 40-49, 50-59 and 60-65 years were sampled in order to achieve the same degree of precision for all age groups in the estimation of different variables. The initial random sample drawn consisted of 209 men aged 20-65 years. Of this sample, two persons had died, five had moved more than 120 miles from Stockholm, and ten were living permanently abroad at the time of the investigation and were thus excluded from the sample. Nine persons refused to be examined and two to take part in the computed-tomographic (CT) and psychological investigations. Thus, of the initial sample of 209 men 181 were investigated. To increase the sample of investigated men to 200, a supplementary sample was drawn in exactly the same way as before. All men in the supplementary sample could be included in the investigation, and the final sample was thus 200. The drop-out rate in the collection of the sample was less than 10 %. The drop-outs did not differ from the examined persons in social status, age, education, civil status, work status or with respect to entry in official registers (police, social register, local health insurance office, Temperance Board register)($p > 0.05$).

The subjects were examined at the Magnus Huss Clinic of the Karolinska Hospital in Stockholm. In studies of alcohol consumption, the consumption in the last week was recorded, as it was considered that the subjects' recall would be poorer for the period further back in time. Otherwise the compliance would have been less than 100 %. In the present study the occurrence of three symptoms related to heavy drinking was recorded: Inability to cut down or stop drinking, i.e. loss of control; morning shakes and malaise relieved by drinking, i.e., morning drinks; and alcohol amnesia or memory lapse after drinking of alcohol, i.e. blackouts. The participants were first divided into three groups:

(I) A group with low alcohol consumption without symptoms of alcoholism;

(II) an intermediate group with low, moderate or high alcohol consumption and one or more alcohol symptoms; and

(III) a heavy-drinking group with high consumption and two or more symptoms (Table I).

***Table 1.*** *Prevalence of symptoms associated with different alcohol consumption quartiles. Groups I - III.*

| Quartiles of alcohol consumed in previous week | No symptoms | One symptom | Two symptoms | Three symptoms |
|---|---|---|---|---|
| Quartile I (n=50) | **GROUP I** 41 | 6 | 3 | 0 |
| Quartile II-III (n=100) | **GROUP II** 57 | 23 | **GROUP III** 17 | 3 |
| Quartile IV (n=50) | 6 | 11 | 17 | 16 |

**GROUP I** Low alcohol consumption without alcohol symptoms (n=41)
**GROUP II** Intermediate group with low, moderate or high alcohol consumption with one or more alcohol symptoms (n=106)
**GROUP III** Heavy drinking alcohol group with high consumption and two or more symptoms (n=53)

These three groups were then subdivided with respect to the use of liver-metabolizing drugs:

(IA) low or moderate alcohol consumption and no use of drugs;

(IB) low or moderate alcohol consumption with use of drugs;

(IIA) high alcohol consumption with no use of drugs; and

(IIB) high alcohol consumption with use of drugs.

Subjects taking antihypertensive drugs (beta-adrenoceptor blocking agents, hydrochlorothiazide, thiazides and hydralazines) were assigned to the groups without any use of drugs. Thirteen of the 126 men in group IA and three of the 43 in group IIA used antihypertensive drugs.

## METHODS

The examination took an average of about nine hours and included a general medical examination, taking of a psychiatric and social history, blood and urine tests, X-ray of the heart and lungs, ECG and electroneurography (ENeG).

### Sociological interview

All subjects answered a questionnaire containing standardized questions pertaining to family conditions, education, smoking and physical exercise. Detailed questions were asked about the amount of alcohol consumed and the pattern of "alcohol behaviour". A sociological interview was then conducted with each subject concerning these questions. Six to 24 months later a sample of 40 men was selected randomly and answered the same

questionnaire as previously. They were also interviewed in the same way as before. This test-retest of the same questions was made to evaluate the consistency with time. The reliability of the answers to the questions concerning alcohol consumption was between 0.56 and 0.95 (22).

Medical interview

The subjects answered a standardized questionnaire concerning their previous and present health, respiratory symptoms, blackouts, epileptic fits and delirious episodes. The questionnaire consisted of a general and a cardiovascular section. Questions concerning respiratory and cardiovascular symptoms were identical to those in the questionnaire designed and tested for several years at the Department of Thoracic Medicine of the Karolinska Hospital. An interview was then conducted with all subjects concerning these questions.

Physical examination

Weight was recorded to the nearest kilogram and included light underwear. Height was measured in centimetres. The blood pressure was measured with the same mercury manometer in all subjects, between 9 and 10 a.m. This was done in the same room by the same person, and noise and chilling were avoided. The pressure was measured in the right upper arm and at least two measurements were performed. Blood pressure was recorded at the start of the examination and after 15 min of rest in complete quiet.

Laboratory tests

Blood samples were drawn in the morning after an overnight fast. Toxicological screening was carried out at the Beckomberga Hospital, where the following assays were also performed: Serum concentrations of barbiturates, other sedatives and alcohol and urinary concentrations of meprobamate, benzodiazepines, alkaloids, phenothiazines, tricyclic antidepressives, amines stimulating the central nervous system, and salicylic acid. The following were determined at the Karolinska Hospital: Erythrocyte mean corpuscular volume (MCV), blood (B) concentration of haemoglobin, and serum (S) concentrations of amylase, bilirubin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (ALP), GGT, lactate dehydrogenase (LD), creatine kinase (CK), iron and transferrin. The ethanol and metanol concentrations in the blood were assayed.

## STATISTICAL METHODS

In order to test the hypothesis of two means being equal against a two-sided alternative, the t test was used. As a measure of association between pairs of variables, Pearson's

*Table 2. Characteristics of the three groups with different drinking habits.*

| | GROUP I (n=41) | GROUP II (n=106) | GROUP III (n=53) |
|---|---|---|---|
| Age (yrs) | 44 ± 14 | 46 ± 14 | 42 ± 13 |
| Height (cm) | 178 ± 7 | 178 ± 6 | 177 ± 6 |
| Weight (kg) | 77 ± 12 | 76 ± 9 | 78 ± 10 |
| Alcohol in blood on arrival at hospital (%) | 0 | 1 | 9 * |
| Alcohol consumption 7 days before arrival at hospital (g) | 0 ± 1 | 11 ± 10*** | 34 ± 31*** |
| Smokers (%) | 46 | 42 | 62 |
| Actions by the Temperance Board (%) | 2 | 8 | 32*** |

Significance levels tested in comparison with group I by Student's t test and Chi-square test.
* p<0.05
** p<0.01
*** p<0.001

*Table 3. Characteristics of the four groups with different drinking habits with and without drug use.*

| | GROUP IA Low alcohol No drugs (n=126) | GROUP IB Low alcohol Drugs (n=21) | GROUP IIA High alcohol No drugs (n=43) | GROUP IIB High alcohol Drugs (n=10) |
|---|---|---|---|---|
| Age (yrs) | 45 ± 14 | 46 ± 15 | 41 ± 14 | 49 ± 5 |
| Height (cm) | 178 ± 7 | 177 ± 8 | 177 ± 7 | 179 ± 4 |
| Weight (kg) | 76 ± 9 | 76 ± 12 | 76 ± 10 | 85 ± 5**** |
| Alcohol in blood on arrival at hospital (%) | 1 | 0 | 5 | 30**** |
| Alcohol consumption 7 days before arrival at hospital (g) | 8 ± 9 | 6 ± 11 | 30 ± 28**** | 39 ± 29**** |
| Smokers (%) | 42 | 52 | 60 * | 70 |
| Action by the Temperance Board (%) | 6 | 10 | 33**** | 30** |

Significance levels tested in comparison with low alcohol - no drugs group by Student's t test and Chi-square test.
* p<0.05
** p<0.01
*** p<0.001
**** p<0.0001

product-moment correlation (r) was chosen. Differences in pairs of non-continuous variables were tested for significance by the Chi-square test. Quartiles were used for grouping the sample into homogeneous groups with regard to alcohol consumption. For testing levels of significances, groups II and III were tested against group I, and groups IB, IIA and IIB against group IA.

## RESULTS

Characteristics of the three groups with different drinking habits are presented in Table 2. There was no difference in mean age between the three groups. The mean height and weight were the same. Ethanol was found in the blood of 9 % of the heavy drinkers, who had consumed 34 g of alcohol a day during the last week before the hospital examination.

*Table 4. Alcohol-related liver and pancreatic tests: Mean values of serum bilirubin, ALP GGT, ASAT, ALAT, CK, LD and Amylase.*

| | | GROUP I (n=41) | GROUP II (n=106) | GROUP III (n=53) |
|---|---|---|---|---|
| S-bilirubin | (µmol/l) | 10 ± 5 | 11 ± 7 | 12 ± 6* |
| S-ALP | (µkat/l) | 3.0 ± 1.0 | 2.9 ± 0.9 | 3.1 ± 0.9 |
| GGT | (µkat/l) | 0.8 ± 1.1 | 0.5 ± 0.4** | 0.7 ± 0.6 |
| S-ASAT | (µkat/l) | 0.36 ± 0.12 | 0.38 ± 0.12 | 0.54 ± 0.56** |
| S-ALAT | (µkat/l) | 0.44 ± 0.35 | 0.36 ± 0.22* | 0.56 ± 0.64 |
| S-CK | (µkat/l) | 2.0 ± 1.2 | 2.2 ± 1.2 | 3.3 ± 4.1* |
| S-LD | (µkat/l) | 5.4 ± 0.8 | 5.6 ± 0.9 | 6.2 ± 1.8*** |
| S-Amylase | (µkat/l) | 3.1 ± 1.3 | 3.3 ± 1.8 | 3.2 ± 0.9 |

Significance levels tested in comparison with group I by Student's t test and Chi-square test.
• p<0.05
** p<0.01
*** p<0.001

*Table 5. Alcohol-related liver and pancreatic tests: Mean values of serum bilirubin, ALP, GGT, ASAT, ALAT, CK, LD and Amylase.*

| | | GROUP IA Low alcohol No drugs (n=126) | GROUP IB Low alcohol Drugs (n=21) | GROUP IIA High alcohol No drugs (n=43) | GROUP IIB High alcohol Drugs (n=10) |
|---|---|---|---|---|---|
| S-bilirubin | (µmol/l) | 11 ± 7 | 9 ± 5 | 13 ± 6 | 8 ± 3 |
| S-ALP | (µkat/l) | 2.9 ± 0.8 | 3.3 ± 1.2* | 3.1 ± 1.0 | 3.2 ± 0.5 |
| GGT | (µkat/l) | 0.50 ± 0.43 | 1.15 ± 1.24**** | 0.57 ± 0.37 | 1.34 ± 0.93**** |
| S-ASAT | (µkat/l) | 0.38 ± 0.12 | 0.37 ± 0.13 | 0.53 ± 0.61** | 0.60 ± 0.28**** |
| S-ALAT | (µkat/l) | 0.38 ± 0.27 | 0.38 ± 0.22 | 0.54 ± 0.70* | 0.64 ± 0.28** |
| S-CK | (µkat/l) | 2.2 ± 1.2 | 1.9 ± 1.1 | 2.8 ± 2.7 | 5.2 ± 7.1**** |
| S-LD | (µkat/l) | 5.5 ± 0.9 | 5.7 ± 0.6 | 5.9 ± 1.1** | 7.1 ± 3.5*** |
| S-Amylase | (µkat/l) | 3.3 ± 1.8 | 2.7 ± 0.8 | 3.3 ± 0.9 | 2.9 ± 0.9 |

Significance levels tested in comparison with group IA by Student's t test and Chi-square test.
* p<0.05
** p<0.01
*** p<0.001
**** p<0.0001

The proportion of smokers among the heavy drinkers was 62 %. Thirty-two per cent of the latter group were registered at the Temperance Board. In addition to consumption of a considerable amount of alcohol, the heavy drinkers showed other indications of a high alcohol intake. Characteristics of the groups who used and did not use drugs are presented in Table 3. The drug-using groups were older, but not significantly so. The ten heavy drinkers and drug-users in group IIB were significantly heavier. The recorded use of drugs was the dose prescribed by a doctor and no account was taken of possible overdosage. Ethanol was present in the blood in 30 % of the heavy drinkers using drugs, who had consumed 39 g of alcohol per day in the last week before examination in the hospital. There was almost no difference in smoking between the four subgroups. Thirty per cent of the heavy drinkers who used drugs (group IIB) and 33 % of the heavy drinkers who did not use drugs (group IIA) were registered at the Temperance Board. When consideration was paid to drug use, a number of alcohol markers were positive.

*Table 6. Haematological data: Mean values of B-haemoglobin, Ery-MCV, S-iron and transferrin saturation.*

| | | GROUP I (n=41) | GROUP II (n=106) | GROUP III (n=53) |
|---|---|---|---|---|
| Haemoglobin | (g/l) | 153 ± 9 | 152 ± 11 | 156 ± 9* |
| MCV | (fl) | 89 ± 3 | 90 ± 4 | 92 ± 6*** |
| MCV - Smokers | (fl) | 90 ± 3 | 92 ± 4 | 94 ± 6 |
| MCV - Non-Smokers | (fl) | 88 ± 3 | 88 ± 4 | 89 ± 4 |
| Serum iron | (µmol/l) | 18 ± 6 | 20 ± 7 | 22 ± 8*** |
| Transferrin saturation | (%) | 29 ± 10 | 31 ± 13 | 34 ± 14* |
| Smokers | (%) | 46 | 42 | 62 |

Significance levels tested in comparison with group I by Student's t test and Chi-square test.
- • p<0.05
- ** p<0.01
- *** p<0.001

*Table 7. Haematological data: Mean values of B-haemoglobin, Ery-MCV, S-iron and transferrin saturation.*

| | | GROUP IA Low alcohol No drugs (n=126) | GROUP IB Low alcohol Drugs (n=21) | GROUP IIA High alcohol No drugs (n=43) | GROUP IIB High alcohol Drugs (n=10) |
|---|---|---|---|---|---|
| Haemoglobin | (g/l) | 151 ± 11 | 158 ± 10** | 156 ± 9** | 155 ± 11 |
| MCV | (fl) | 89 ± 4 | 89 ± 4 | 90 ± 4 | 98 ± 8**** |
| Serum iron | (µmol/l) | 19 ± 7 | 19 ± 5 | 21 ± 7 | 25 ± 10** |
| Transferrin saturation | (%) | 31 ± 13 | 30 ± 11 | 33 ± 12 | 39 ± 19* |

Significance levels tested in comparison with group IA by Student's t test and Chi-square test.
- • p<0.05
- ** p<0.01
- *** p<0.001
- **** p<0.0001

## Liver and pancreatic tests

The heavy-drinking group (III) had significantly higher serum concentrations of bilirubin, ASAT, CK and LD than group I or II. GGT showed no relationship to alcohol consumption (Table 4). The results of alcohol-related liver and pancreas tests in the subgroups are presented in Table 5. Significantly higher serum levels of GGT, ASAT, ALAT, CK and LD were found in the heavy-drinking group using drugs (IIB) than in the other groups. In group IIA, with a high alcohol consumption and no drug use, only serum ASAT, ALAT and LD were elevated, but these values lay within the given reference ranges. GGT showed a relationship to alcohol consumption in combination with the use of drugs, but not with alcohol alone.

The third question considered in this study was whether and to what extent drugs combined with alcohol influence the laboratory findings. In the heavy-drinking subjects who used drugs (group IIB), the drugs taken included antiarrhythmic agents (quinidine, verapamil), antiepileptics (phenytoin), antibiotics (doxycycline), dextropropoxyphene, and derivatives of benzodiazepines, all of which can cause increases in liver enzymes such as GGT, ASAT, ALAT and LD. Seventy per cent of the heavy-drinking group had pathological GGT values and sixty per cent pathological values of ALAT. The most

*Table 8. Alcohol-related liver enzymes: The upper quintiles of groups I-III in per cent.*

| | Upper quintile value of liver enzymes | GROUP I (n=41) % | GROUP II (n=106) % | GROUP III (n=53) % |
|---|---|---|---|---|
| Bilirubin | 14 | 10 | 20 | 25 |
| ALP | 3.7 | 17 | 18 | 26 |
| GGT | 0.8 | 22 | 16 | 23 |
| ASAT | 0.50 | 5 | 13 | 28** |
| ALAT | 0.60 | 12 | 12 | 28 |
| CK | 3.0 | 8 | 17 | 28* |
| LD | 6.4 | 12 | 15 | 30* |
| Amylase | 3.9 | 20 | 20 | 15 |

Significance levels tested in comparison with group I by Student's t test and Chi-square test.
* p<0.05
** p<0.01
*** p<0.001

*Table 9. Alcohol-related liver enzymes: The upper quintiles of groups IA, IB, IIA and IIB in per cent.*

| | Upper quintile value of liver enzymes | GROUP IA Low alcohol No drugs (n=126) % | GROUP IB Low alcohol Drugs (n=21) % | GROUP IIA High alcohol No drugs (n=43) % | GROUP IIB High alcohol Drugs (n=10) % |
|---|---|---|---|---|---|
| Bilirubin | 14 | 22 | 10 | 33 | 0 |
| ALP | 3.7 | 18 | 29 | 30 | 10 |
| GGT | 0.8 | 13 | 57**** | 21 | 70**** |
| ASAT | 0.50 | 21 | 14 | 28 | 80**** |
| ALAT | 0.60 | 17 | 14 | 28 | 60** |
| CK | 3.0 | 15 | 14 | 30* | 30 |
| LD | 6.4 | 17 | 14 | 33* | 50** |
| Amylase | 3.9 | 23 | 10 | 19 | 10 |

Significance levels tested in comparison with group IA by Student's t test and Chi-square test.
* p<0.05
** p<0.01
*** p<0.001
**** p<0.0001

important of these drugs are anticoagulants, antiepileptic agents and barbiturates (6, 14). Applying Pearson's product-moment correlation, the alcohol consumption in the heavy-drinking group using drugs was found to correlate to laboratory findings. The highest correlations were noted for serum ALAT, CK, bilirubin and LD concentrations (see Tables 8, 9). The correlation coefficient between alcohol consumption in the previous week and actions on the part of the Temperance Board was 0.43 in the heavy-drinking group with drug consumption. What is striking is that GGT only gives r=0.13.

Haematological data

The heavy-drinking group (III) had significantly higher values, though within the given reference ranges, for haemoglobin concentration, MCV, S-iron and transferrin saturation than groups I and II (Table 6). In the group of heavy drinkers using drugs (IIB) MCV, S-iron and transferrin saturation were significantly higher than in the other subgroups (Table 7).

## DISCUSSION

The heavy-drinking group in this study consumed, on the average, 34 grams of alcohol a day. In general heavy drinkers underestimate their alcohol consumption. Dissimulation as measured by the Lie Scale of the Eysenck Personality Questionnaire (4) has been found to correlate negatively with reported alcohol consumption. This means that the consumption of alcohol by the subjects of the present study was probably heavier than was recorded. In population surveys the mean alcohol intake is grossly underreported (Pernanen, 1974)(28). Nine per cent of the heavy-drinking group of the present study (group III) and 30 % of group IIB had alcohol in the blood. No linear correlation was found between the absolute serum concentration of GGT and the actual intake of alcohol as expressed in grams of pure ethanol per day in the three groups. Using both the diary method and a questionnaire, Poikolainen et al. (29) observed no relationship between GGT and daily alcohol intake. Bliding et al. (2) could not find any laboratory test that discriminated between light and heavy intake among young men, and Cushman et al. (5) reported poor sensitivity of biochemical markers of alcoholism among relatively healthy alcoholics. Poikolainen et al. concluded that markers such as GGT do not indicate the individual intake and should not therefore be used as indicators of the actual alcohol intake of a patient at a medical examination. Our data confirm their view.

The heavy-drinking group in our study had significantly higher serum concentrations of bilirubin, ASAT, CK and LD - and in the drug-using group also ALAT. Total bilirubin has been found to be moderately raised in alcoholics (12) and in alcohol-intoxicated patients (30). The investigation of hyper-bilirubinaemia in alcoholics has been limited, probably because of its multifactorial origins. Jaundice in alcoholics may be due to hepatic disease or to haemolytic disease, or both. In the present study the high-alcohol-consumption group had a high level of serum CK. Creatine kinase is found primarily in skeletal muscle, heart, and the brain. Elevated serum CK activities have been repeatedly reported in alcoholics, in association with an acute, reversible muscular syndrome (Nygren, 1966 (23); Perkoff et al., 1966 (27)). Song and Rubin (35) observed increased S-CK concentrations during a four-week period following administration of 225 g of ethanol to three non-alcoholic men. In another group of acutely intoxicated alcoholics, the initially elevated S-CK levels returned to normal during a two-week withdrawal period (24). In the present study high LD levels were found in the high-consumption group. In alcoholics, elevated LD concentrations derive from a combination of liver and muscle damage. The increases in S-CK and S-LD may be due to release following skeletal muscle damage or to myocarditis, with some enzyme leakage from the myocardium. Isoenzyme studies have revealed that the LD-1 and LD-2 isoenzymes from muscle and the LD-5 isoenzyme from the liver are frequently elevated both in intoxicated alcoholics and in healthy subjects who are given ethanol (10, 25, 26). In healthy controls acute doses of ethanol have been found to have a minimal effect on the serum LD level (9). High

priority should be given to the discovery of new, more accurate markers of alcohol consumption. The only marker that Poikolainen et al. (29) found to be related to alcohol consumption was MCV. The heavy-drinking group in our study had a higher MCV but also slightly higher B-haemoglobin, S-iron and S-transferrin concentrations than the other two groups. It is well known that MCV has a high sensitivity in alcohol abuse, but at the same time a low specificity (11, 39, 40). The underlying reason for this has not been established, but it seems probable that it is a direct effect of ethanol on the bone marrow (18). In this context the effect of smoking must be emphasized. Eschwege et al. (7) found that MCV was increased both in smokers and in men with clinical signs of cirrhosis, and among our subjects, also, MCV was increased among smokers (Table 6). There was a non-significant increase in the numbers of smokers with increased alcohol consumption (Table 2).

The haemoglobin concentration was slightly higher in our heavy-drinking group (III), indicating that ethanol interferes with normal haeme synthesis and inhibits erythropoiesis (3). It has a disturbing effect on pyridoxine. Pyridoxine or pyridoxal phosphate is required for so called Schiff-base formation, which is necessary in the first condensation step in the synthesis of haeme, which involves activated succinic acid and glycine.

In our group III S-transferrin saturation was increased. Serum levels of transferrin are reported to be reduced in alcoholics with cirrhosis (19, 21). Murray-Lyon et al. (21) found that 35 % of a group of cirrhotic alcoholics had S-transferrin levels below the lower normal limit. This reduction in S-transferrin may be due to the diminished ability of the liver to synthesize proteins, or may be a result of the poor nutritional state of the patient.

One of the purposes of the present study was to find out whether male heavy drinkers from an urban area had deviating results of blood tests of liver function and haemopoiesis. As expected, several liver-related tests showed a relationship to alcohol habits, but not GGT.

Another question investigated was whether such biomedical tests can be used for screening of drinking problems. It was concluded that they are not reliable for this purpose. According to Kristenson et al. (15), GGT is a good marker of high alcohol intake. They found that in the group with the highest decile of GGT, 20 % had an alcohol consumption of 120 g per day and 30 % had a very low consumption. According to these authors, GGT can give both false positive and false negative results in attempts to trace latent alcoholism. Just over 25 % of their subjects had normal GGT values throughout the observation period. In the literature the reported proportion with false positive results for GGT is usually about 12 % (33). The present study provided no evidence that there are any biochemical markers today that can identify high alcohol consumers. If we select from the general population a group of subjects who abuse alcohol and also use drugs, we find pathologically increased values of GGT (Table 5). Ethanol is absorbed from the gastrointestinal tract. Only 2 to 10 % of that absorbed is eliminated through the

kidneys and lungs. The rest is oxidized in the body, principally in the liver (80 %). Extrahepatic metabolism of ethanol is small (8). The hepatocyte contains three main pathways for ethanol metabolism, each located in a different subcellular compartment: (1) the main alcohol dehydrogenase (ADH) pathway of the cytosol or the soluble fraction of the cell; (2) the microsomal ethanol oxidizing system (MEOS) located in the endoplasmic reticulum; and (3) catalase located in the peroxisomes (17). Alternate pathways for ethanol oxidation are the cytochrome P 450 dependent microsomal ethanol oxidizing system (37) and catalase in various cell fractions, including peroxisomes and microsomes (38). The quantitative role of these alternate pathways for ethanol oxidation is probably low in normal conditions. However, there is an adaptive increase in the MEOS during chronic alcohol consumption. Compared with ADH, the MEOS requires higher ethanol levels for full saturation and maximal velocity and therefore the contribution of this non-ADH pathway is strikingly increased at higher blood ethanol concentrations (36). The well-known combination of drug abuse and alcoholism emphasizes the clinical importance of ethanol and drug interactions. It is obvious that many of the central nervous effects of various drugs may be potentiated by simultaneous alcohol use. On the other hand, it is now known that the elimination rates of various drugs are influenced both by chronic ethanol consumption and by the possible liver injury. Detailed information of individual drug interactions with ethanol is discussed by Lieber (16). A chronic ethanol administration results in adaptive hypertrophy of the hepatic smooth endoplasmic reticulum. This hypertrophy is accompanied by an increased content of microsomal cytochrome P 450 (31) and of NADPH-cytochrome P 450 reductase (13). These components play a key role in the microsomal hydroxylation of various drugs and explain the well-documented enhanced clearance of such drugs as meprobamate, pentobarbitone and tolbutamide (20). This metabolic adaptation evidently contributes to the tolerance of alcoholics for drugs, including sedatives (34). Simultaneous ethanol and drug administration (e.g. ethanol and tranquillizers) results in additive or even in synergistic effects by additive action on the central nervous system and by the inhibition of drug metabolism (32). Higher GGT values are associated with a higher frequency of sick people, as indicated by higher percentages of persons receiving antiarrhytmic and epileptic treatment, with untreated hypertension, and with a pathological ECG. In attempts to find alcoholics in the population, we must keep in mind that GGT only points to a sick person and is not a proof of alcohol abuse, and that it is directly correlated to the use of drugs. Drugs which cause liver-cell damage often induce an increase in the serum GGT level above the upper normal limit.

It is concluded that screening for drinking problems has to be based on a standardized questionnaire concerning alcohol consumption in the last week, symptoms of alcoholism (loss of control, blackouts and morning drinks) and some haematological data such as B-haemoglobin, MCV, S-iron, S-transferrin and alcohol-related liver enzymes. There is no evidence, however, that there are any biochemical markers known today that can

identify high alcohol consumers. The best method of screening is use of a standardized questionnaire of the type employed in this survey. A combination of a history of alcohol consumption, and increased MCV may be criteria for identification of an interesting homogeneous subgroup.

## REFERENCES


1. Bergman, H., Borg, S., Hindmarsh, T., Ideström, C.-M. & Mützell, S.: Computed tomography of the brain and neuropsychological assessment of alcoholic patients. In: Biological Effects of Alcohol, edited by H. Begleiter. New York: Plenum, 771-786, 1980.
2. Bliding, G., Bliding, Å., Fex, G. & Törnkvist, C.: The appropriateness of laboratory tests in tracing young heavy drinkers. Drug Alcohol Depend 10:153-158, 1982.
3. Böttiger, L.E.: Alcohol and the Blood. Scand J Haematol 10:321-326, 1973.
4. Cooke, D.J. & Allan, C.A.: Self-reported alcohol consumption and dissimulation in a Scottish urban sample. J Stud Alcohol 44:617-629, 1983.
5. Cushman, P., Jacobson, G., Barboriak, J.J. & Anderson, A.J.: Biochemical markers for alcoholism: sensitivity problems. Alcoholism 8:253-257, 1984.
6. Drug Interferences and drug Effects in Clinical Chemistry. The National Corporation of Swedish Pharmacies. 4th edition. Editors: Tryding, N. & Roos, K.-A., 1986.
7. Eschwege, E., Papoz, L., Lellouch, J., et al.: Blood cells and alcohol consumption with special reference to smoking habits. J Clin Pathol 31: 654-658, 1978.
8. Forsander, O.A. & Räihä, N.: Metabolites produced in the liver during alcohol oxidation. J Biol Chem 235: 34-36, 1960.
9. Freer, D.E. & Statland, B.E.: The effects of ethanol on the activities of selected enzymes in sera of healthy young adults; 1 Intermediate-term effects. Clin Chem 23: 830-834, 1977.
10. Hed, R., Nygren, A. & Sundblad, L.: Muscle and liver serum enzyme activities in healthy volunteers given alcohol on a diet poor in carbohydrates. Acta Med Scand 191: 529-534, 1972.
11. How, J. & Davidson, R.J.: Alcoholism and blood picture. Lancet i: 564, 1978.
12. Irsigler, K., Krypsin-Exner, K., Mildschuh, W., Pointer, H. & Schmidt, P.: Liver morphology and liver functions in delirium tremens. Dtsch Med Wochenschr 96: 9-13, 1971.
13. Joly, J.-G., Ishii, H., Teschke, R. et al.: Effect of chronic ethanol feeding on the activities and submicrosomal distribution of reduced nicotinamide adenine dinucleotide phosphate (NADPH) -cytochrome P-450 reductase and the demethylases for aminopyrine and ethyl morphine. Biochem Pharmacol 22: 1532-1535, 1973.
14. Keso, L. & Salaspuro, M: Laboratory tests in the establishment and treatment of alcohol problems. Nord Med 101: 306-312, 1986.
15. Kristenson, H., Trell, E., Fex, G. & Hood, B.: Serum gamma-glutamyltransferase: Statistical Distribution in a Middle-Aged Male Population and Evaluation of Alcohol Habits in Individuals with Elevated Levels. Prev Med 9: 108-119, 1980.
16. Lieber, C.S.: Medical Disorders of Alcoholism: Pathogenesis and Treatment. (Ed.) Lieber, C.S. Philadelphia: W.B. Saunders, 1982.
17. Lieber, C.S.: Metabolism and metabolic effects of alcohol. Med Clin North Am 68: 3-31, 1984.
18. Lindenbaum, J. & Lieber, C.S.: Haematologic effects of alcohol in man in the absence of nutritional deficiency. N Engl J Med 281: 333-338, 1969.
19. LoGrippo, G.A., Anselm, K. & Hayashi, H.: Serum immunoglobulins and five serum proteins in extrahepatic obstructive jaundice and alcoholic cirrhosis. Am J Gastroenterol 56: 357-363, 1971.

20. Misra, P.S., Lefevre, A., Ishii, H. et al.: Increase of ethanol, meprobamate and pentobarbital metabolism after chronic ethanol administration in man and in rats. Am J Med 51: 346-351, 1971.
21. Murray-Lyon, I.M., Clarke, H.G.M., McPherson, K. & William, R.: Quantitative immunoelectrophoresis of serum proteins in cryptogenic cirrhosis, alcoholic cirrhosis and active chronic hepatitis. Clin Chim Acta 39: 215-220, 1972.
22. Mützell, S.: The reliability of anamnestic questionnaires for alcoholic inpatients. Hyg Acta Soc Med Suec 87: 310, 1978.
23. Nygren, A.: Serum creatine phosphokinase activity in chronic alcoholism in connection with acute alcohol intoxication. Acta Med Scand 179: 623-630, 1966.
24. Nygren, A.: Serum creatine phosphokinase in chronic alcoholism. Acta Med Scand 182: 383-388, 1967.
25. Nygren, A.: Studies on alcoholic myopathy with special reference to the occurrence and pathogenesis of sub-clinical myopathy. Opusc Med Suppl 21: 1-16, 1971.
26. Nygren, A. & Sundblad, L.: Lactate dehydrogenase isoenzyme patterns in serum and skeletal muscle in intoxicated alcoholics. Acta Med Scand 189: 303-307, 1971.
27. Perkoff, G.T., Hardy, P. & Velez-Garcia, E.: Reversible acute muscular syndrome in chronic alcoholism. N Engl J Med 274: 1277-1285, 1966.
28. Pernanen, K.: Validity of survey data on alcohol use. In: Gibbins, R.J., Israel, Y., Kalant, H., Popham, R.E., Schmidt, W. & Smart, R.G. (Eds.): Research Advances in Alcohol and Drug Problems, Vol. 1, New York: John Wiley & Sons, 355-374, 1974.
29. Poikolainen, K., Kärkkäinen, P. & Pikkarainen, J.: Correlations between Biological Markers and Alcohol Intake measured by diary and questionnaire. J Stud Alcohol Vol. 46. No: 5: 383-387, 1985.
30. Redetzki, H.M., Koener, T.A., Hughes, J.R. & Smith, A.G.: Osmometry in the evaluation of alcohol intoxication. Clin Toxicol 5: 343-363, 1972.
31. Rubin. E., Bacchin, P., Gang, H. & Lieber, C.S.: Induction and inhibition of hepatic microsomal and mitochondrial enzymes by ethanol. Lab Invest 22: 569-580, 1970.
32. Rubin, E., Gang, H., Misra, P.S. & Lieber, C.S.: Inhibition of drug metabolism by acute ethanol intoxication. A hepatic microsomal mechanism. Am J Med 49: 801-806, 1970.
33. Skude, G. & Wadstein, J.: Amylase, hepatic enzymes and bilirubin in serum of chronic alcoholics. Acta Med Scand 201: 53-58, 1977.
34. Soering, K. & Schuppel, R.: Wechselwirkungen zwischen Alkohol und Arzneimitteln. Dtsch Med Wochenschr 91: 1892-1898, 1966.
35. Song, S.K. & Rubin, E.: Ethanol produces muscle damage in human volunteers. Science (Wash.D.C.), 175: 327-328, 1972.
36. Takagi, T., Alderman, J. & Lieber, C.S.: In vivo roles of alcohol dehydrogenase (ADH), catalase (CAT) and the microsomal ethanol oxidizing system (MEOS) in deermice. Alcoholism 8: 123, 1984.
37. Teschke, R., Matsuzaki, S., Ohnishi, K. et al.: Microsomal ethanol oxidizing system (MEOS): current status of its characterization and its role. Alcoholism 1: 7-15, 1977.
38. Thurman, R.G. & Brentzel, H.J.: The role of alcohol dehydrogenase in microsomal ethanol oxidation and the adaptive increase in ethanol metabolism due to chronic treatment with ethanol. Alcoholism 1: 33-38, 1977.
39. Unger, K.W. & Johnson, Jr., D.: Red blood cell mean corpuscular volume: a potential indicator of alcohol usage in a working population. Am J Med Sci 267: 281-289, 1974.
40. Wu, A., Chanarin, I. & Levi, A.J.: Macrocytosis of chronic alcoholism Lancet i: 829-831, 1974.

Address for reprints

Sture Mützell
Department of Family Medicine
University Hospital
S-751 85 Uppsala
Sweden