Biochemical Tests in Alcohol Abuse

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INTRODUCTION

Illness related to alcohol use has traditionally been thought of in terms of 'alcoholism' and cirrhosis of the liver, but in recent years it has become clear that there is potential for alcohol-related damage to nearly all organs or systems, and that this may occur at levels of alcohol consumption which are common in many 'Western' societies. The number of people potentially at risk from their alcohol consumption is much greater than the number conforming to the diagnosis of 'alcoholism', and so attention has been directed towards programmes to reduce alcohol consumption in heavy drinkers. This would require identification of such people at an early stage, before irreversible changes have occurred, and laboratory tests might provide an alternative or adjunct to questionnaires or clinical suspicion.

The papers cited provide a background on the frequency distribution of alcohol intake in Australia, and the prevalence of possibly harmful consumption patterns; on the reasons for believing that heavy drinking is related to mortality experience; on the search for suitable tests, either clinical signs, questionnaire responses, or laboratory tests; a selection of the laboratory tests currently available with some assessments of their strengths and weaknesses; the possible impact of tests in a population-based programme; and some indication of tests which might be more effective than those commonly available.

ALCOHOL USE AND ITS CONSEQUENCES

The first three papers report on the prevalence of various levels of alcohol consumption in Sydney.

REYNOLDS I, HARNAS J, GALLAGHER H, BRYDEN D.
Drinking and drug taking patterns of 8516 adults in Sydney.
Medical Journal of Australia 1976; 2:782-785.

The group surveyed in this paper were men and women attending for a health check at a multiphasic health screening centre, and alcohol consumption was assessed from answers given as part of a long computer-administered questionnaire. Although there are obvious problems in accepting the subjects' answers uncritically, any bias is likely to be towards an underestimation of consumption. On the basis that 80 g/day of ethanol is dangerous for men and 40 g/day for women, then about 11% of the men and about 5% of the women were at risk.

GIBSON J, JOHANSEN A, RAWSON G, WEBSTER I.
Drinking, smoking and drug-taking patterns in a predominantly lower socioeconomic status sample.
Medical Journal of Australia 1977; 2:459-461.

This study was designed to complement the previous one by using the same methods on a group of 9829 men and women selected in a different way. The conclusions are very similar, in that 8% of the men declared an alcohol intake of six drinks or more, and 4% of women three drinks or more, every day or most days.

WILLIAMS AT, HARDING BURNS F, MOREY S.
Prevalence of alcoholism in a Sydney teaching hospital.
Medical Journal of Australia 1978; 2:608-611.

A group of 457 in-patients were surveyed and it was found that 11% of the men took more than 80 g of alcohol daily and approximately 2% of the women averaged 40 g/day or more. The reasons for the patients' admission to hospital were also considered and 15% of admissions were classified as either alcohol-related (5%) or possibly alcohol-related (10%). There were a number of exclusions from this study; patients from the obstetric and gynaecological wards and from private wards were not included, nor were the (few) patients in this hospital aged less than 16 years.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GGT	Gamma-glutamyl transferase
HDL-C	High-density lipoprotein cholesterol
MCV	Mean corpuscular volume

LELBACH WK.
Epidemiology of alcoholic liver disease.
Progress in Liver Disease 1976; 5:494-515.

This review presents the evidence from various sources of the association between populations' average alcohol consumption and the incidence of cirrhosis of the liver, and discusses the social, occupational and economic factors which influence alcohol consumption. It also presents the relationships between years of drinking, daily amount of alcohol and the risk of developing cirrhosis in alcoholics which were found by Pequignot in France and which led to the view that those taking more than 80 g of ethanol per day are at risk. Recent evidence suggests that this value (80 g/day) may be too high for men and is almost certainly too high for women.

PETERSSON B, KRANTZ P, KRISTENSSON H, TRELL E, STERNBY NH.
Alcohol-related death: a major contributor to mortality in urban middle-aged men.
Lancet 1982; ii:1088-1090.

A group of 10353 men, all aged 46-48 but otherwise unselected, were followed for a period of 0-6 years, and during this time 199 died. The cause of death was assessed in each case from all available sources. A category of 'alcohol-related death' was defined 'if high alcohol consumption was considered the major underlying cause in the chain of events leading to the death'. In this population and age-group, alcohol-related death was more common than deaths from cancers or cardiovascular disease, accounting for 30.7% of all deaths. Of these deaths, only 10 out of 61 had been recorded as alcohol-related. Official statistics considerably under-estimate deaths due to alcohol.

DETECTION OF ALCOHOL ABUSE

ANON.
Screening tests for alcoholism?
Lancet 1980; ii:1117-1118.

This editorial gives an overview from the perspective of six years ago, starting from the magnitude of the problem and discussing ways in which people with excessive alcohol intake might be detected. Interview or questionnaire techniques, which mostly concentrate on symptoms of dependence, might be supplemented by laboratory tests as objective markers of intake. Screening, however, was seen as a distant possibility because so many of the criteria laid down by Wilson and Jungner (The Principles and Practice of Screening for Disease, WHO, Geneva 1968) were far from being fulfilled. The application of questionnaires in conjunction with GGT and MCV to high-risk groups was seen as the most productive use of resources.

SKINNER HA, HOLT S, SHEU WJ, ISRAEL Y.
Clinical versus laboratory detection of alcohol abuse: the alcohol clinical index.
British Medical Journal 1986; 292:1703-1708.

A large number of clinical signs, medical history items, laboratory tests, and questionnaire responses were recorded in 131 outpatients with known alcohol problems and 131 social drinkers in order to find the items giving the best discrimination between these two groups. A group of 52 patients presenting to a general medical practice, but not drinking excessively, were also assessed. The best discrimination was given by composite indices based on the clinical features (73% sensitivity at 94% specificity) and on history items (92% sensitivity at 84% specificity), while an index based on results for GGT, MCV, HDL-C and blood alcohol gave 71% sensitivity at 90% specificity. This assessment is impressive because the various indices can be compared on the same group of patients and at the same time. The clinical features are more effective than the laboratory tests. However, the out-patient group was composed of people with severe and longstanding alcohol problems (mean alcohol intake in previous six months 130 g/day, mean duration 7.7 years). The authors commented that it remains to be seen whether the 'alcohol clinical index' maintains its superiority in different populations and clinical settings — particularly when the full range of drinking behaviour in the population is included.

JOHNSON RD, WILLIAMS R.
Prevention of hazardous drinking: the value of laboratory tests.
British Medical Journal 1985; 290:1849-1850.

This editorial, from probably Britain's leading group on liver disease, offers an interesting contrast with the 1980 Lancet editorial. After stating the problem and commenting on the need for techniques to supplement history-taking, the sensitivity and specificity of GGT, MCV, and discriminant scores from many tests are discussed. The finding that a raised GGT has been found to be predictive of increased mortality suggests that laboratory markers, even if they are not effective as screening tests for detecting hazardous drinking, may identify subjects undergoing possibly harmful metabolic changes. Further evaluation of newer tests (see below) is advocated.

RESULTS IN 'ALCOHOLICS'

ROSALKI SB, RAU D.
Serum gamma-glutamyl transpeptidase activity in alcoholism.
Clinica Chimica Acta 1972; 39:41-47.

Liver function tests were carried out on 76 patients, either in-patient alcoholics or out-patient heavy drinkers. The GGT levels were raised in three-quarters of these, compared to a third for AST and less than a fifth for ALT and alkaline phosphatase. In the

patients classified as heavy drinkers rather than alcoholics, GGT was the only enzyme to show elevation. This study showed that GGT could be abnormal in people without clinical or other biochemical evidence of liver disease, but who had a high level of alcohol intake. The authors attributed the raised GGT levels to cellular injury rather than enzyme induction.

WU A, CHANARIN I, LEVI AJ.
Macrocytosis of chronic alcoholism.
Lancet 1974; i:829-830.

Increased MCV was found in 89% of alcoholics, using a rather low upper limit of normal (90 fL) based on results from hospital staff. Only a minority of these patients had low folates, and supplementation with folate did not normalise the MCV if drinking continued. Abstinence from alcohol, on the other hand, resulted in a return of red cell size to normal.

RESULTS IN UNSELECTED POPULATIONS OR IN SCREENING CLINICS

ROLLASON JG, PINCHERLE G, ROBINSON D.
Serum gamma glutamyl transpeptidase in relation to alcohol consumption.
Clinica Chimica Acta 1972; 39:75-80.

The subjects for this study were men attending a health screening centre. Of these, about 50 were selected at random from each of five alcohol consumption groups and it wa found that GGT and AST levels increased with alcohol intake. As with many subsequent papers, a correlation coefficient of around 0.3 was found for GGT and, unlike later work, also for AST. There was also a strong ($r = 0.64$) correlation between GGT and AST results. Of those admitting to more than six drinks a day, 47% had a raised GGT level, but so did 21% of those claiming to be teetotalers! The authors commented that GGT could play a part in screening for alcoholism or heavy drinking, and that, in their experience, patients could be persuaded to reduce their drinking if given evidence that it was already causing them harm.

CASTELLI WP, DOYLE JT, GORDON T et al.
Alcohol and blood lipids. The co-operative lipoprotein phenotyping study.
Lancet 1977; ii:153-155.

Information on alcohol intake, and measurements of plasma HDL-, LDL-, and VLDL-cholesterol, and of triglycerides, were gathered from five study populations in the United States. There was a consistent correlation across all five centres between HDL-cholesterol and alcohol intake ($r = 0.19$ to 0.30) and a weaker, negative correlation between LDL-cholesterol and alcohol intake. The main interest of these findings was the apparent improvement in the risk factor profile associated with higher (but still moderate) alcohol consumption. However, the authors cautioned against altering lipids by increasing alcohol intake.

WHITEHEAD TP, CLARKE CA, WHITFIELD AGW.
Biochemical and haematological markers of alcohol intake.
Lancet 1978; i:978-981.

This study reported on the frequency distributions of GGT, AST, urate, triglyceride and MCV in 2034 men aged over 40. In the whole group the GGT or AST was abnormal in 18% and these subjects also tended to have higher urates. An explanation of these results was suggested by examining data on a small sub-group (146 subjects) whose alcohol intake was known; the mean value for each of the five variables rose with increasing alcohol consumption and the effect was statistically significant for all except triglyceride. All these men were employed yet showing biochemical effects which could be attributed, in most cases, to their alcohol consumption.

WHITFIELD JB, HENSLEY WJ, BRYDEN D, GALLAGHER H.
Some laboratory correlates of drinking habits.
Annals of Clinical Biochemistry 1978; 15:297-303.

This paper is based on reported alcohol intake from a larger number of subjects and includes women as well as men. About 4500 men and 3300 women answered questions on their alcohol intake and the effects of different patterns of alcohol consumption on the frequency distributions of GGT, MCV, urate, triglyceride, AST, alkaline phosphatase, bilirubin and albumin were studied. The last three tests were minimally affected by alcohol consumption patterns in this sample but the first five, and especially GGT and MCV, showed increases in mean values with increasing alcohol consumption. The sensitivity of these tests in men taking nine or more drinks on most days was 44% for GGT, 35% for MCV, 35% for urate, 20% for triglyceride, 23% for AST. For GGT in particular, the range of values encountered increased with increasing alcohol consumption, suggesting individual differences in response.

BAGREL A, D'HOTAUD A, GUEGUEN R, SIEST G.
Relations between reported alcohol consumption and certain biological variables in an 'unselected' population.
Clinical Chemistry 1979; 25:1242-1246.

The biochemical and haematological consequences of alcohol consumption were found to be similar in France to those in England and Australia. Approximately 4000 men attending a health screening clinic showed significant correlations between alcohol intake and GGT and MCV; for GGT the correlation was slightly stronger in older men (ages over 30). The changes in GGT and MCV resulting from drinking appear to be independent of ech other. Results for women are mentioned but not presented in detail because of low declared alcohol intakes, suspected unreliability of answers, and non-significant correlations.

CHICK J, KREITMAN N, PLANT M.
Mean cell volume and gamma-glutamyl-transpeptidase as markers of drinking in working men.
Lancet 1981; i:1249-1251.

Alcohol intake over the preceding week, MCV and GGT levels were estimated in 488 men in Scotland, chosen as being in high-risk occupational groups. Both tests showed correlations around 0.35 with declared alcohol intake and sensitivities of about 50% for GGT and about 25% for MCV were found. However, this comparison of the two tests was influenced by the cut-off points chosen, which gave specifities of around 95% for MCV and 80-90% for GGT. The results were also presented in the form of conditional probabilities of being a heavy drinker; the probability rose quite sharply above a GGT value of 60 u/L and above an MCV value of 93 fL. The use of these tests is discussed and the authors feel that their main value is in alerting the physician to enquire about drinking habits. They also comment that 'Patients whose goal is reduction of drinking rather than abstinence find serial test results an aid to monitoring their consumption'.

MULTIPLE TESTS

WHITFIELD JB, ALLEN JK, ADENA M, GALLAGHER HG, HENSLEY WJ.
A multivariate assessment of alcohol consumption.
International Journal of Epidemiology 1981; 10:281-288.

Information on sixteen biochemical tests and MCV was used to produce multiple regression equations for men and for women, in the hope that these would be more effective in predicting alcohol intake than any single test. The equations were generated from part of the data and validated on the rest, to avoid the problem that multiple variables must always give a better fit to a given data set than any single one of the variables. Of the single variables, GGT and MCV showed the highest correlation with declared alcohol intake. Although equations based on GGT, MCV and urate (in men) and GGT and MCV only (in women) gave higher correlations they were not a sufficient improvement to be of practical use in classifying individuals.

SHAPER AG, POCOCK SJ, ASHBY D, WALKER M, WHITEHEAD TP.
Biochemical and haematological response to alcohol intake.
Annals of Clinical Biochemistry 1985; 22:50-61.

This paper presents a thorough analysis of the effects of drinking habits on 25 biochemical and haematological characteristics in 7735 men, aged 40-59 years, from 24 towns in England, Scotland and Wales. Nearly all test results showed a significant difference between occasional drinkers and those taking six or more drinks daily, which is not surprising with so large a sample. The most discriminatory tests (in order) were GGT, lead, MCH, HDL-C, MCV, urate and AST, with GGT being abnormal in 25% of the heavy drinkers (6 plus drinks per day) when the cut-off point was chosen so as to give 5% of the occasional drinkers above it (95% specificity). A discriminant score derived from the results for GGT, HDL-C, urate, MCH and lead gave 48% sensitivity at 95% specificity. The authors consider that the poor sensitivity is probably related to individual differences in biological response to alcohol, and suggest that the discriminant score may have a use in '... identifying those individuals who respond markedly to alcohol in biochemical and haematological terms'.

THE MALMO PREVENTIVE PROGRAMME

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.
Preventive Medicine 1980; 9:108-119.

The theme that biological response is as important as the absolute amount of alcohol ingested is also mentioned in this article. Instead of studying the effects of drinking (assessed by questionnaire, with its inherent inaccuracies) on some laboratory test measurement, the authors determined plasma GGT levels in a population-based sample of men, aged 47 to 49 years, and followed up with repeat GGT determinations, clinical examination and in-depth interviews on the men with results in the top 10%. It was estimated that heavy drinking was the most probable cause of the high GGT in three-quarters of the cases. The group with high GGT values also tended to have increases in HDL-C, both aminotransferases, cholesterol, triglycerides, plasma glucose after a glucose load, and blood pressure. This group of subjects 'was not composed of overtly alcoholic or otherwise diseased individuals' however, further investigation revealed clinical symptoms of alcohol addiction in more than 60% of the study group, including cases with no other abnormal liver tests than GGT. The authors concluded that a preventive trial was justified.

KRISTENSON H, OHLIN H, HULTEN-NOSSLIN M-B, TRELL E, HOOD B.
Identification and intervention of heavy drinking in middle-aged men: results and follow-up of 24-60 months of long-term study with randomised controls.
Alcoholism: Clinical and Experimental Research 1983; 7:203-209.

From male subjects identified by a raised GGT on two occasions (as described in the last paper) 317 were allocated to an intervention group and 268 to a control group. After some losses, 261 and 212 subjects, respectively, remained. The intervention group had monthly follow-up and counselling, including feed-back based on their GGT levels and changes in them, with the goal

of achieving moderate drinking rather than abstinence. The control group were advised by letter that they had an impaired liver test and that they should restrict their alcohol intake. The groups were compared after two and four years. There was a reduction in mean GGT values in both groups at both two and four years, but there were fewer days off work because of sickness, fewer days in hospital, and fewer deaths in the intervention group. The authors considered that discussing GGT results with the patients was very helpful, but that the most important factor in such a programme '... is not the diagnostic aids but ... patient and qualified professional manpower'.

TRELL E, KRISTENSON H, PETERSSON B.
A risk factor approach to the alcohol-related diseases.
Alcohol and Alcoholism 1985; 20:333-345.

This paper gives an overview of the screening and intervention programme in Malmo, and the importance of alcohol abuse as a factor influencing mortality in middle-aged men. The authors believe that 'risk factors' exist for alcohol-related death, just as they do for cardiovascular disease, and that since alcohol-related deaths were as common as those from cardiovascular disease or from cancer in the age-group they studied, the evaluation of detection and intervention programmes based on these risk factors is important. The risk factors for alcohol-related death which they have identified are GGT, the MAST questionnaire, creatinine and cholesterol. A combined score based on these was more successful in predicting death than the corresponding coronary heart disease risk factor function.

NEWER TESTS

STIBLER H, BORG S, ALLGULANDER C.
Clinical significance of abnormal heterogeneity of transferrin in relation to alcohol consumption.
Acta Medica Scandanavica 1979; 206:275-281.

Separation of transferrin isoforms by isoelectric focusing, followed by immunofixation, revealed a band with pI 5.7 which was present in many alcoholics but in only one out of a hundred controls. The prevalence of this band increased with increasing alcohol intake and it was present in 26 out of 32 (81%) of those who had taken more than 60 g of alcohol per day in the preceding week; 77% of this group had a raised GGT. The pI 5.7 band was not found in any of 22 patients with liver disease without current alcohol abuse. Eight healthy volunteers took 0.6 g ethanol per kg body weight daily for seven days, and a faint pI 5.7 band was detected in three. Incubation with neuraminidase to remove sialic acid from the carbohydrate sidechains converted the transferrin from normals and alcoholics to a pI 5.9 form, suggesting that the difference was in the degree of sialylation.

VESTERBERG O, PETREN S, SCHMIDT D.
Increased concentrations of a transferrin variant after alcohol abuse.
Clinica Chimica Acta 1984; 141:33-39.

The ratio of transferrin of pI 5.7 to total transferrin was determined in plasma or serum from 33 controls and 20 alcoholics (within 24 hours of drinking). In the controls this ratio was 1.55 ± 0.53% and in the alcoholics it was 5.73 ± 2.80%; 95% of the normals had results below 2.4 and 95% of the alcoholics had results above 2.8, suggesting that this test might have had very good specificity and sensitivity. GGT was also measured in most of the alcoholics and was abnormal in 11 out of 18 (61%), but there appeared to be no association between the degree of abnormality of the two tests. After hospitalisation the transferrin ratio decreased to or towards normal but data on half-life were not given.

NALPAS B, VASSAULT A, LE GUILLOU A, et al.
Serum activity of mitochondrial aspartate aminotransferase: a sensitive marker of alcoholism with or without alcoholic hepatitis.
Hepatology 1984; 4:893-896.

Four groups of patients were studied; 30 alcoholics with alcoholic liver disease and 16 with no evidence of such disease, 14 patients with viral hepatitis, and 14 healthy subjects. Serum mitochondrial AST (mAST) was measured after immunoinhibition of cytosol AST, and the ratio of mAST to total AST was also calculated. The GGT and glutamate dehydrogenase levels were also measured on the same specimens. The mAST results and mAST/total AST ratios were; non-alcoholic controls 0.43 ± 0.37 (SD) U/L and 2.98 ± 2.39% respectively; alcoholics with normal liver function 1.95 ± 0.39 U/L and 11.58 ± 3.35%; alcoholics with liver disease 10.40 ± 8.36 U/L and 12.57 ± 4.80%; viral hepatitis 7.85 ± 9.31 U/L and 3.19 ± 1.94%. The results for mAST/total AST ratio showed a good separation between the two groups of alcoholics, on the one hand, and the controls and viral hepatitis patients on the other. The ratio (with a sensitivity of over 90% in this group) was better than GGT in discriminating the alcoholics from the non-alcoholics. As well as presenting promising data on mAST as a marker of alcoholic abuse, this paper suggests that some changes affecting the mitochondria in the liver occur in all alcoholics.

HOMAIDAN FR, KRICKA LJ, WHITEHEAD TP.
Morphology of red blood cells in alcoholics.
Lancet 1984; i:913-914.

One of the most consistent findings in various papers has been that red cell size is increased in many heavy drinkers or alcoholics. These authors subjected red cells from 16 alcoholics to scanning electron microscopy and found abnormalities in their appearance. Although there were only a small number of patients and the technique is not suited to routine use, it is noteworthy that all of the alcoholics showed distinctly abnormal RBC morphology. It is not clear what changes in the cell membrane structural components occur as a result of the heavy alcohol consumption (100-470 g/day) in these subjects or whether it is related to an increase in MCV.

KORRI U-M, NUUTINEN H, SALASPURO M.
Increased blood acetate: A new laboratory marker of alcoholism and heavy drinking.
Alcoholism: Clinical and Experimental Research 1985; 9:468-471.

Ethanol clearance from the blood is increased in those who regularly take large amounts and so the rate of formation of acetate is increased. These authors have tested the hypothesis that blood acetate levels can be used to detect the 'metabolic tolerance' to alcohol and therefore detect habitual heavy alcohol consumption. Blood acetate was measured by an enzymatic method in 51 intoxicated patients admitted to an emergency department and in 53 controls who were given alcohol. The patients were further classified as alcoholics (23), heavy drinkers (17) or occasional drinkers (11). The male alcoholics and heavy drinkers had blood acetates of 0.82 ± 0.21 mmol/l while the male controls averaged 0.41 ± 0.21 mmol/l; the occasional drinkers did not differ from the controls. The sensitivity of acetate was the same as that of GGT in the alcoholics and appeared to be higher than that of GGT in the heavy drinkers. A blood acetate level may be a useful test but would probably require the administration of alcohol as a provocative procedure.

CONCLUSIONS

There are important roles for clinical biochemists to play in preventive programmes. In particular, to help determine whether biological markers are better predictors of disease or death than the measures of consumption or of alcohol dependency;and to develop the laboratory methods for the suggested newer tests to a stage where they can be performed quickly, precisely and economically in large enough numbers to allow a thorough evaluation of their usefulness.