Screening for Alcohol Abuse: Available Laboratory Tests

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This paper concentrates on laboratory tests and their performance characteristics. Although the use to which the results may be put are covered by other presentations, the use does to some extent determine the performance characteristics required.

Laboratory tests may be used to help in the detection and management of drug and alcohol problems in four main ways:

1 To detect people abusing substances who are either unaware of their problem or unwilling to admit it. This requires a test which is both sensitive (missing only a few cases) and specific (not giving false positives).
2 To determine the prevalence of abuse or use in a population in order to determine which groups are most vulnerable, or to estimate a change occurring with time or with intervention, in a way which is not influenced by variation in the reliability of self-reports of use. This application does not require high sensitivity if the sample size is large enough.
3 To monitor treatment, which will usually include either abstinence or a large reduction in use. Tests which are not sensitive can be used, but only on a proportion of cases.
4 To determine vulnerability to the medical complications of continued use. This requires validation of the test in a prospective study.

We should also consider in each case whether there are other ways of achieving the objectives, not using laboratory tests, which may be cheaper or more effective.

Two problems arise with tests for alcohol abuse, as illustrated in Figure 1.

Figure 1.

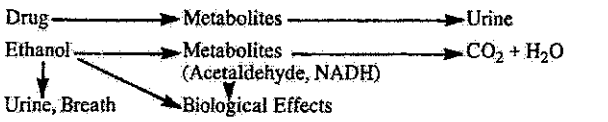

Figure 1. Alcohol metabolism is rapid and does not lead to the excretion of recognisable metabolites; assessment of alcohol consumption therefore requires detection of its medium or long-term effects.

Most illicit drugs and tobacco products are either present in the body for a considerable time or they give rise to metabolites which are slowly excreted, or both. Alcohol, on the other hand, is quickly and almost entirely metabolised to carbon dioxide and water. Practically all attempts to use laboratory tests to detect alcohol use or abuse have therefore had to rely not on actual sightings of the animal but observation of its footprints: the biological effects which alcohol produces in the body.

This introduces the major difficulty that the degree to which the biological effects occur is quite variable between people and the characteristics being measured also vary between people even in the absence of alcohol. This difficulty is only partly compensated for by the possibility that the biological effects observed can themselves be important. Changes in liver function tests, for example, may be a precursor of permanent damage to the liver.

Furthermore, the range of alcohol consumption is wide and the quantity which will cause damage is poorly defined and varies between people. Many studies have compared the results of some test in controls and 'alcoholics', finding a significant difference between these groups, but have not gone on to establish the values encountered across the entire range of drinking behaviour.

Figure 2 shows how a simple approach to questions of sensitivity, specificity, and cut-off points

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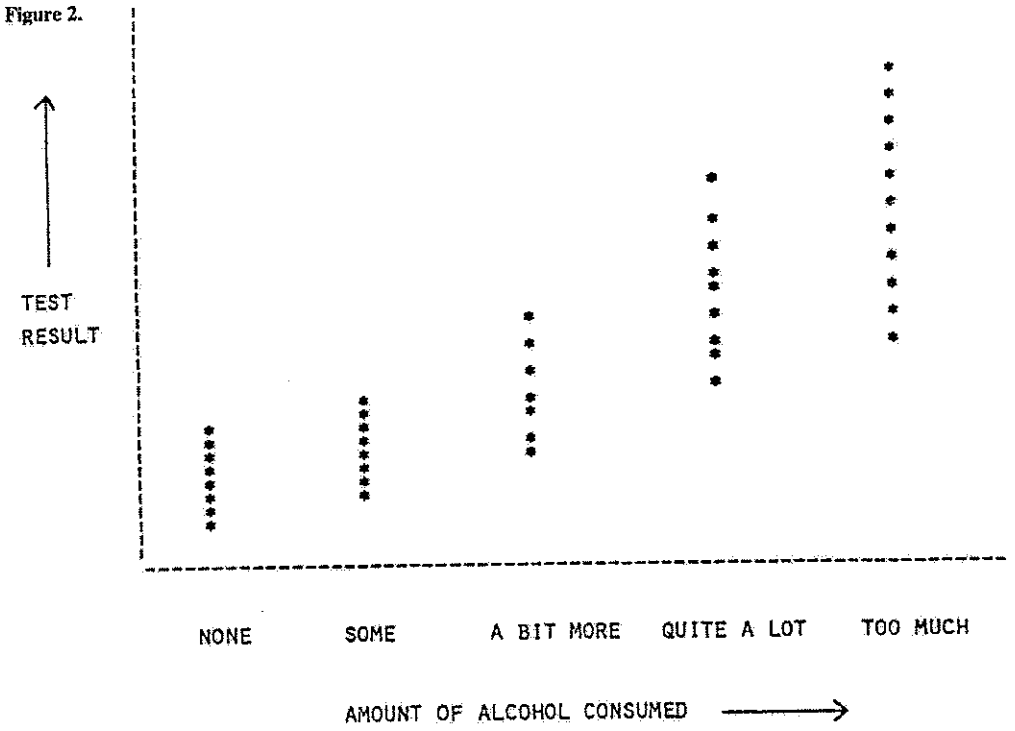

Figure 2. Since alcohol intake may be intermediate between clearly safe and clearly hazardous levels, a test which can distinguish between the two extremes can be difficult to interpret when applied to a population.

can be deceptive. If one only considers the distinction between 'none' and 'too much', then the hypothetical test would perform very well, but in the real world the results found in any individual would be very difficult to interpret.

Accepting the existence of these problems, what tests are available, how easy are they to perform, and what is known about the performance of each?

The first group of tests have been known for some time to be affected by alcohol consumption, are easily performed in most laboratories, and the relationship between consumption and test result has been established across the continuum of alcohol intakes and across age and sex groups. However, they are often found to be normal in people who admit to high alcohol intake and so lack sensitivity. In hospital populations they may also lack specificity, as medical conditions not related to alcohol can cause abnormalities.

These tests are plasma gamma glutamyl transferase (GGT), erythrocyte mean cell volume (MCV), and plasma urate, high-density-lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST) and triglycerides.

GGT is the most useful test, and the one about which most is known. Our data[1] come from the Medicheck centre in Sydney, and is similar to that found in several other studies from health screening centres[2,3,4,5]. We found that GGT was above the upper limit of normal in 44% of men who admitted to heavy alcohol consumption (nine drinks or more, most days), but only 26% of women taking six or more drinks when they drank alcohol.

The proportion of heavy drinkers with raised GGT was also age-dependent, with little difference in GGT values between light and heavy drinkers below the age of 30. This age-dependence is unfortunate because of the risks of traffic accidents and foetal alcohol syndrome associated with heavy drinking in young people. I have recently had the opportunity to study GGT levels and alcohol intake in teenage boys, who are a group with a worrying incidence of high alcohol consumption, but again no significant association could be found.

People who have a raised GGT associated with high alcohol consumption also tend to have other

biochemical abnormalities, especially a high AST[2,6]. The correlation between GGT and AST suggests that both these enzymes are measuring slight liver damage, and this conclusion is supported by two studies[7,8] which showed an association between plasma GGT and histological evidence of liver disease in alcoholics.

MCV was abnormal in a third of male heavy drinkers but only half that number of women; however age did not seem to make much difference to the results of this test. Other reports of the proportion of heavy drinkers showing abnormal MCVs vary widely, probably because of differences in the definition of the upper limit of normal, but most agree that MCV is the only currently available test which can complement GGT in detecting excessive alcohol use.

Like MCV, plasma urate is abnormal in about a third of male heavy drinkers but we were unable to find any association between alcohol and urate in women. This lesser biochemical response to alcohol in women is generally accepted as occurring, but it is at odds with the general clinical and epidemiological view that women are more vulnerable to alcohol-induced disease than men[9].

AST, HDL-C and triglycerides are each less sensitive than the tests discussed so far, and are not much of practical importance in the type of screening or intervention programmes we are discussing.

As far as these tests are concerned, only about half of the people whom one might wish to detect will show an abnormality. Before going on to talk about possibly more sensitive tests, however, I would like to mention one study which took a risk-factor based approach[10]. This was done in Malmo by following a cohort of middle-aged men, and some of the results are shown in Table 1.

Table 1. Identifiable risk factors for death in a cohort of 7948 males aged 46-48 years at entry in Malmo, Sweden[10].

	Association with deaths from:	
Risk factor	All causes (218)	Alcohol-related (55)
GGT	***	***
Alcohol abstention	NS	NS
Mm — MAST score	*	***
Smoking category	***	NS
Serum cholesterol	NS	** (Negative)
Serum triglycerides	*	NS
Systolic B.P.	**	NS
Diastolic B.P.	NS	NS
Serum creatinine	* (Negative)	*** (Negative)

* indicates significance.

There were 218 deaths from all causes, the majority from cancers, coronary heart disease (CHD), or causes related to alcohol. The expected risk factors for CHD and malignancy were revealed, but in addition it was found that GGT was a highly significant risk factor for deaths from all causes, for alcohol-related death, and even marginally significant for CHD. So maybe GGT has a significance beyond the fact that it is increased in 40 or 50% of heavy drinkers, but as far as I know no study has sought to determine whether it is a risk factor independent of alcohol intake.

In the last few years a number of other tests have been claimed to be abnormal in a high proportion of alcoholics, but have not been assessed in heavy drinkers in the community. Some of these are quite impressive. However, the methods for estimating these substances still have problems.

Transferrin has a fairly complex carbohydrate component which normally terminates with sialic acid residues. It has been shown that alcoholics' plasma contains desialylated transferrin molecules in addition to the more usual form and because the loss of sialic acid results in a charge difference this abnormal form can be separated by isoelectric focussing[11,12]. Some results for desialylated transferrin are shown in Table 2; it shows remarkably high sensitivity and specificity, and these results have been confirmed by a number of independent groups. However, the procedure is technically demanding because it involves isoelectric focussing and then either immunofixation or a second dimension of immunoprecipitation. I understand that a simpler procedure involving ion exchange and RIA has been developed in conjunction with Pharmacia[13] and may be commercially available soon; it has been reported[14] to give good results.

Table 2. Transferrin band with pI 5.7 identified by isoelectric focussing[11,12].

	Subjects with transferrin band detected at pI 5.7
Normal controls	1/100
Liver disease	0/22
Alcoholics — Abstinent	2/26
7 — 20 g/day	5/20
20 — 60 g/day	15/20
60 g/day or more	26/32

	Transferrin pI 5.7, as % of total transferrin
Controls (33)	1.6 ± 0.5 (95% below 2.4)
Alcoholics (20)	5.7 ± 2.8 (95% above 2.8)

The mitochondrial isoenzyme of AST can be separated from the cytoplasmic type by either immunoprecipitation or ion exchange chromatography, and results showing a good distinction between alcoholics and social drinkers have been described[15], as shown in Table 3. Interestingly, useful results could also be obtained in people who had liver disease, and raised total AST, of non-alcoholic origin.

Aldehyde dehydrogenase is the second enzyme of alcohol metabolism and there have been a number of reports that its activity is reduced in the liver or in red blood cells in alcoholics[16,17]. In addition to the possible diagnostic use of assays of this enzyme, a relative deficiency would be expected to lead to increased concentrations of acetaldehyde after alcohol and it has been proposed by a number of people that this aldehyde could react with amino groups on proteins in the same way that glucose reacts to form glycated haemoglobin. Most studies have used massive and unrealistic concentrations of acetaldehyde to demonstrate this reaction in vitro[18], but there is now some evidence from Toronto that the reaction can occur in vivo and they have raised antibodies to the modified protein which could be the basis for an immunoassay[19].

In conclusion, I think we are at an exciting stage in developing tests which could be used to help in the treatment of people who are drinking harmful amounts of alcohol, and even the tests which are currently available do have a place in counselling and in epidemiological studies.

Table 3. Isoenzymes of aspartate aminotransferase in plasma of alcoholics and controls with and without liver disease[15].

	Mitochondrial AST, as % of total	
	No Liver disease	Liver disease
Non-alcoholics	3.0 ± 2.4(14)	3.2 ± 1.9(14)
Alcoholics	11.6 ± 3.4(16)	12.6 ± 4.8(30)

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