

Results of extended licensing hours may now be the subject of debate, but visions of the effect of alcohol abuse require little in the way of analysis. Here, Chris Bird and Victor R Preedy look at the spectrum of alcohol-related disease and the laboratory's role in identifying those at risk of alcohol dependency and in monitoring consumption.

Pathology of alcohol

The legs go before the liver!

There are many reasons to be interested in alcohol. The news is full of stories about alcohol-fuelled antisocial behaviour and whether or not such problems will be exacerbated by extended opening hours. Sadly, the recent death of George Best is an example of the effects of long-term alcohol abuse.

As biomedical scientists we spend much time investigating and treating alcohol-related problems. Furthermore, many of us will have consumed our fair share of alcohol over the Christmas and New Year holidays.

So, how big a problem is alcohol and what is the impact of alcohol abuse on pathology services? What tests do we use and which are likely to become available to measure alcohol abuse and its health consequences? Can we predict a genetic predisposition to alcoholism?

Scale of the problem

Alcohol creates a huge health problem. After caffeine it is the most widely used recreational drug in the world and, while moderate use by most people may have a positive health benefit, millions are damaged by alcohol overuse. Although moderate alcohol use can reduce the risk of ischaemic heart disease, this benefit must be balanced against more than 60 alcohol-related pathologies caused by overuse, particularly in individuals who are genetically susceptible to addiction or metabolically unable to deal with alcohol.

World Health Organization (WHO) data from 2000 look at the burden of various diseases in developed market economies by comparing disability-adjusted life years (DALYs). Some 10.3% of all health problems are attributed to alcohol, with 11.7% to tobacco and only 2.3% to non-prescribed drugs. Globally, 3.2% of all deaths were due to alcohol, a figure which had doubled since 1990.

However, by looking only at health issues, the effects of alcohol are seriously underestimated. Crime, antisocial behaviour, family and work problems all add to alcohol-fuelled problems and it seems clear that

alcohol is far more damaging than tobacco. Unfortunately, as with many diseases that are seen as self-inflicted, research on alcohol does not attract the funds justified by the health burden it creates.

Alcohol-related pathology

Alcohol abuse is associated commonly with liver disease but there are many other pathologies of greater importance (Table 1). Muscle damage is a particular problem, affecting smooth, cardiac and skeletal muscle. Estimates of the proportion of cardiomyopathy cases attributable to alcohol range from 21% to 32%, and alcoholic heart disease is responsible for up to half of all cases of non-ischaemic cardiomyopathy in Western society. Furthermore, although men have been the focus of most studies, women may be more susceptible to alcohol's toxic effects on the heart.

Chronic alcohol abuse causes skeletal muscle atrophy in around half of all alcohol abusers, and the entire muscle mass may be reduced by up to 30%, leading to muscle weakness, unsteady gait and frequent falls. This damage may be irreversible. Alcoholic myopathy is at least five times more common than cirrhosis and has serious consequences such as disturbances of intestinal motility (diarrhoea) and heart problems.

Alcohol is a recognised carcinogen and the incidence of many cancers is increased significantly by alcohol overuse. Cancer of the upper gastrointestinal tract may show a 12-fold increase, and even moderate alcohol use leads to significant increases in head and neck cancers, particularly in women. The incidences of breast, colon, liver and lung cancer are all increased by alcohol abuse.

The immune system is altered by alcohol, with changes in immune regulation leading to both immunodeficiency and autoimmunity. Increased susceptibility to bacterial pneumonia, tuberculosis and other infections, as well as circulating autoantibodies (particularly against the liver), is common.

Heavy drinking is often perceived as being associated with masculinity, but physiologically the reverse is true. Heavy drinking may cause a variety of hormonal disorders, including feminisation with overgrowth of mammary glands, loss of facial hair, impotency and infertility. Apart from the temporary impotence associated with heavy drinking, there can be a permanent loss of libido, shrinking of the testes and a reduction in size of the penis. Not the best advert for macho male drinks, or the men who drink them! Female drinkers can suffer masculinisation, decreased sexual drive and sterility.

Within one hour of consuming an alcoholic drink during pregnancy, the blood alcohol level of the fetus reaches that of the mother. Pregnant women who drink, and particularly those who engage in binge-drinking, place the fetus at risk of fetal-alcohol syndrome (FAS). This includes a characteristic pattern of minor facial abnormalities, growth deficiency and mental retardation. In fact,

Table 1. Problems related to regular heavy drinking or intoxication.

Fatty liver	Sexual dysfunction
Hepatitis	Infertility
Cirrhosis	Foetal damage
Pancreatitis	Haemopoietic toxicity
Cancer	Skin disease
Nutritional deficiencies	Immunodeficiency
Diabetes	Kidney damage
Cardiomyopathy	Eye pathologies
Hypertension	Dental disease
Strokes	Gastritis
Brain damage	Gout
Neuropathy	Acute alcohol poisoning
Myopathy	Oesophageal varices

FAS is thought to be the leading known cause of mental retardation in the Western world and is entirely preventable by the avoidance of alcohol by women who are pregnant.

Interaction between the various pathologies associated with alcohol is a particular problem. A patient with bleeding oesophageal varices, anaemia due to malnutrition and abnormal coagulation because of liver disease is very difficult to manage, even before we consider the possibility of heart, kidney and other problems. Many biomedical scientists will have had long days and sleepless nights preparing blood products and performing tests for such patients.

Pathology tests

Alcohol abuse is monitored by a variety of laboratory tests in addition to the measurement of blood alcohol levels. When raised, liver enzymes such as γ -GT, ALT and AST can all indicate liver damage caused by alcohol. Erythrocyte mean cell volume (MCV) is also affected by excessive alcohol consumption. Unfortunately, however, none of these tests is specific to alcohol. Even more sophisticated tests such as carbohydrate-deficient transferrin (CDT), which can be a longer-term indicator of alcohol abuse in much the same way that glycosylated haemoglobin is used to monitor diabetic control, is not totally specific.

New tests are becoming available for biomarkers that measure alcohol consumption and its metabolites rather than alcohol-mediated damage. Alcohol is metabolised to acetaldehyde, which is bound by haemoglobin in erythrocytes and can be

measured by high-performance liquid chromatography (HPLC). This measurement, called whole blood-associated acetaldehyde (WBAA), is a highly specific and sensitive indicator of alcohol consumption and has been used by the US insurance industry for more than a decade.

Ethyl glucuronide (EtG) can be detected in urine up to 80 hours after alcohol consumption, long after the alcohol itself has been metabolised. Phosphatidyl ethanol (PEth), another metabolite of alcohol, can be measured in blood up to three weeks after alcohol consumption. Another group of metabolites, the fatty acid ethyl esters (FAEEs), appear in blood 12–18 hours after alcohol consumption and are deposited in hair, where they can be detected several months later. The only way to remove them is to shave off all body hair!

Proteomics has also made a contribution by identifying proteins associated with heavy drinkers. Fragments of both fibrinogen and apoprotein A have been identified as possible biomarkers that are reduced by alcohol consumption.

Clearly, these new tests will be useful to clinicians in monitoring alcohol abuse and alcohol consumption levels in their patients. However, they are also attracting interest from the police, insurance companies and employers. The police would find it invaluable to detect and measure alcohol consumption several days or even weeks after an accident. Insurance companies are also interested in establishing whether or not alcohol played a part in an accident. Employers such as airlines and hauliers have

a clear duty to identify pilots and drivers who may have a drinking problem.

Identifying those at risk of becoming dependent on alcohol can help prevent alcoholism or enable people to seek early treatment. Several genes seem to be associated with alcoholism. Adenyl cyclase (AC) activity is inherited and is lower in alcoholics, even when they abstain. Unfortunately, AC level is also affected by other drugs, including marijuana.

β -endorphin, an opioid produced in the pituitary, provides natural pain relief and a feeling of exhilaration. Alcoholics and their children seem to have lower levels of β -endorphin and fewer receptors. There are also inherited differences in serotonin metabolism and its transporter molecules between alcoholics and non-alcoholics.

Clearly, in the future, clinicians may have a battery of sensitive and specific tests to identify people at risk of alcohol dependency and to monitor alcohol consumption in their patients. ■

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Why is alcohol so harmful?

Alcohol is metabolised by two main pathways. First, alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde, a very toxic chemical. The second pathway, the microsomal ethanol oxidising system (MEOS), also produces acetaldehyde. Unfortunately, this pathway is highly inducible by chronic alcohol consumption; thus, heavy drinkers become tolerant to alcohol and their bodies produce even higher levels of acetaldehyde.

The toxic effects of acetaldehyde can be seen very clearly in people who lack ALDH2, an enzyme responsible for converting acetaldehyde to acetate. Around 25–50% of Asians have a mutation in the gene encoding this enzyme so it does not work, and even small quantities of alcohol can cause flushing, tachycardia, headaches and nausea. The symptoms can be so unpleasant that drugs which inhibit ALDH2 are used to help alcoholics avoid drinking.

As if this was not bad enough, the MEOS cytochrome systems generate toxic free radicals and also increase activity by other microsomal systems. These, in turn, activate scores of biological compounds to

highly toxic and carcinogenic metabolites, which helps to explain the widespread pathology of alcohol overuse.

Can we drink safely?

Moderate consumption of alcohol has social advantages with which most of us will be familiar. Furthermore, there are health benefits associated with the antioxidants present in some drinks, particularly red wine. Antioxidants reduce the release of pro-inflammatory cytokines (eg interleukin-1 β , interleukin-6 and tumour necrosis factor- α), which are involved in the pathogenesis of atherosclerosis. Red wines and some white wines protect against low-density lipoprotein (LDL) oxidation, giving some protection against cardiovascular disease. However, antioxidants are present in some fruits and vegetables as well as virgin olive oil.

The 1992 White Paper *Health of the Nation* suggested that men should consume no more than 21 units of alcohol (a unit being 10 mL pure alcohol), and women no more than 14 units, per week. In 1995, in recognition of the specific risks of excessive drinking in a single session, the sensible drinking message was changed to focus on daily guidelines. It suggests a maximum

intake of two to three units per day for women and three to four for men, with two alcohol-free days after heavy drinking. Continued alcohol consumption at the upper level is not advised.

Clearly, some groups, such as pregnant women and those engaging in potentially dangerous activities, should drink less or even nothing at all. However, recent research suggests that total lifetime intake is the key predictor of the health consequences of alcohol consumption. With people drinking more and starting at a younger age there are likely to be serious health problems ahead.

Alcohol has been a part of our diet and that of our primate predecessors for millions of years. In fact, we are probably genetically programmed to associate the taste and odour of fermenting fruit with food sources. We may be attracted to alcohol in the same way we are attracted to carbohydrate-rich fats and sugars that were a valuable and scarce resource in our evolutionary past. Modern society provides rich foods and concentrated alcoholic drinks in abundance. Obesity is the visible consequence of the former, while the latter produce less visible but extremely serious pathology.