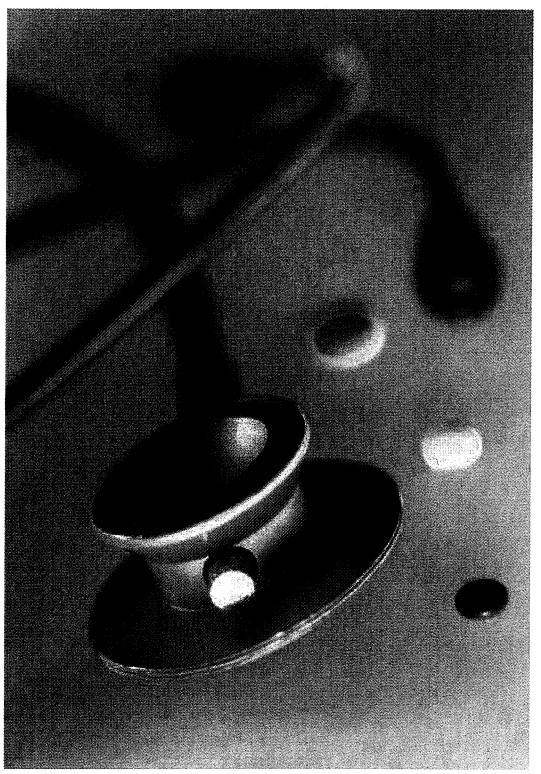
# *Alcohol in Diet and Its Impact On*



# *Human Health*

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# Contents

# Introduction

During the last century alcohol has become number one substance of use and abuse worldwide but primarily in the western world. The health problems associated with alcohol consumption costs the states and governments enormous amounts of money annually. The use of alcohol has a variety of effects on human body; the effects can be reversible or irreversible and lead to disabilities and death. The amount of alcohol use is widely dependent on culture, religion and the geographic area where we live. In some cultures and religions alcohol consumption is uncommon or even prohibited; this can be seen in Middle East and Islamic countries, whereas in other places like Europe especially in the northern hemisphere the alcohol consumption is increasing and accounts for a large number of morbidity and mortality in those areas.

Aside all the acute and chronic pathological changes in the body alcohol intoxication accounts for a large number of hospital admissions and leads to an increased workload for the already overwhelmed healthcare providers. The continuation of alcohol usage leads to alcoholism and development of dependence which except the organic changes in the body also has social and marital consequences.

Since the consequences of the increased alcohol consumption is recognized the aim of preventive measures has come to play a great role. These measures are composed of providing information to the public especially schools and youngsters where a global increase of consumption is seen. Other measures are at governmental level where new laws and regulations are passed to monitor and control the production, import and consumption. At this level the northern European countries have come further than the rest of the world by implementation of alcohol monopole where alcohol is only sold through especial stores and only people of a minimum age of eighteen can buy it.

# Pharmacodynamics of ethanol

Ethanol enters the circulation within minutes after absorption through the gastrointestinal tract after consumption and is widely distributed throughout the body. Almost all the ethanol is metabolized by the liver which contains the enzyme alcoholdehydrogenase, this enzyme converts alcohol to acetaldehyde which is further converted by another enzyme, namely, aldehydedehydrogenase to acetate.

Accumulation of acetaldehyde due to excessive consumption leads to a so called alcohol-flush reaction. The affected person experiences tachycardia, hypotension and facial flushing. These are pathophysiological changes associated with vasodilatation. These changes can be artificially induced by administration of Disulfiram, a drug used in combination with others to induce the unpleasant sensation in chronic user to promote withdrawal. Some people have a lower tolerance level; this is due to a lower level of the active form of the alcoholdehydrogenase isoenzyme. These occur in about 50% of Japanese and other Asians (1).

# Bodily impacts

## *Alcohol and the nervous system*

### Acute intoxication

Ethanol readily crosses the blood-brain barrier, and consequently, brain and blood alcohol concentrations equilibrate rapidly after drinking. Intoxication develops in non-alcoholic persons at blood alcohol levels of 10 to 35mmol per liter (50 to 150 mg per dl) and is more severe when blood levels are rising. There is usually euphoria, a loss of social inhibitions, and talkative behaviour, but sometimes intoxicated people are gloomy and aggressive. Some do not experience euphoria but only become drowsy; they rarely abuse alcohol.

At higher blood ethanol concentrations, cerebellar and vestibular function deteriorates, and lethargy and stupor may supervene. In non-alcoholic persons, blood ethanol concentrations of 110 mmol per liter (500 mg per dl) can be fatal, usually because of respiratory depression and hypotension.

Persons with alcoholism are more resistant to ethanol intoxication than non-alcoholic persons. Alcoholic "blackouts" can occur during heavy drinking and are characterized by hours of amnesia while awake. Immediate recall and long-term memory are normal, but new events are forgotten, as in patients with transient global amnesia. Although alcoholic blackouts have been related to reduced plasma tryptophan levels, ethanol inhibition of N-methyl-D-aspartate (NMDA) receptor-stimulated calcium flux in the hippocampus may be more important (1).

### Alcohol induced Wernicke-Korsakoff syndrome and dementia

The association between alcohol, thiamine deficiency and the development of amnesia has long being suspected. This relationship has recently been confirmed by improvement of neuroimaging technology, serving as a tool for further understanding of biochemistry of the brain.

The development of neurological disorder is a consequence of prolonged alcohol consumption and malnutrition giving rise to deficiency of Thiamine (vitamin B1) and other important vitamins. People with alcoholism often obtain as much as 50% of their calories from ethanol, and serious nutritional deficiencies can develop, particularly for protein, thiamine, folate, and niacin.

In addition there is direct toxic effect of alcohol. Recent evidence suggests that genetic factors contribute to the diverse toxicity of ethanol. Ethanol can also be an exogenous substrate for specific enzymes leading to the accumulation of possibly toxic abnormal products. These include phosphatidylethanol and fatty-acid ethyl esters. In addition, acetaldehyde is a possible toxin. Acetaldehyde can react with diverse proteins to form acetaldehyde-protein adducts that accumulate in proportion to the amount of ethanol consumed during chronic alcoholism. Prolonged ethanol-induced changes in receptor-stimulated second messenger production and ion channel function could also be cytotoxic, particularly for organs with little cell turnover, such as brain, muscle, and liver.

Wernicke's encephalopathy is characterized by the triad of ataxia, oculomotor abnormalities, and global confusion. On microscopic examination, demyelination, necrosis, gliosis, and vascular proliferation occur in the mamillary bodies,superior cerebellar vermis, hypothalamic

nuclei, and other gray matter regions of the diencephalon and brainstem. Because cerebellar lesions are most severe in the superior vermis, patients usually have gait ataxia with few signs of limb incoordination. Nystagmus is the most common ocular sign. Bilateral rectus palsies and horizontal conjugate defects are also common.Vertical gaze palsies occur less frequently, and complete ophthalmoplegia is rare. Other infrequent findings include ptosis, internuclear ophthalmoplegia, and loss of pupillary reflexes. The acute confusional state is characterized by inattention, disorientation, and sleepiness. Sometimes patients are agitated, but most are apathetic, indifferent, and amnestic. Impaired consciousness can be an important feature in otherwise unrecognized cases of Wernicke's encephalopathy, so that this diagnosis must be considered in patients with unexplained stupor and coma. In addition the classic triad, patients may have hypotension or hypothermia due to hypothalamic involvement.

In alcoholic patients, thiamine deficiency may result from an inadequate diet, impaired intestinal absorption, and decreased hepatic thiamine storage. Four enzymes involved in intermediary metabolism require thiamine pyrophosphate as a cofactor: pyruvate dehydrogenase, a-ketoglutarate dehydrogenase, transketolase, and branched-chain a-ketoacid dehydrogenase. The affinity transketolase for thiamine is reduced in some patients with Wemicke's encephalopathy. These patients are at greater risk for functional thiamine deficiency to develop when thiamine levels in the diet are marginal. Autopsy studies indicate that Wernicke's encephalopathy is much more prevalent than recognized during life.

Although the diagnosis is usually made on clinical grounds, computed tomography and magnetic resonance imaging (MRI) may aid in diagnosing mild or atypical cases. The volume of the mamillary bodies is reduced in chronic Wernicke's encephalepathy. Calculating the volume of the mamillary bodies by MRI can distinguish patients with Wernicke's encephalopathy from unaffected controls or patients with Alzheimer's disease. If the disease is untreated, the mortality rate is 10% to 20%. Diagnosis is critical because treatment usually corrects most or all of the abnormalities. Because patients are risk for cardiovascular collapse,

Wernicke's encephalopathy must be considered a medical emergency. Patients should be admitted to a hospital and thiamine, 100 mg per day for several days, administered parenterally toensure absorption.

It is important to begin therapy before feeding or administering parenteral glucose solutions because carbohydrates can precipitate or worsen the encephalopathy. Outpatient therapy should continue with at least 50 mg of thiamine per day because thiamine absorption is often impaired in patients with alcoholism. With treatment, ocular abnormalities may resolve within hours a few days; confusion and ataxia usually resolve more slowly. Sequelae include gait ataxia, nystagmus, and Korsakoff's psychosis. Korsakoff's psychosis is a chronic amnestic disorder that occurs in most patients who survive Wemicke's encephalopathy. Remote memories remain intact, but there is retrograde amnesia for recent memories, and patients are usually disoriented to place and time. Particularly striking is an inability to learn new information (anterograde amnesia).

Immediate recall is intact, but patients are unable to remember the same information several minutes later. They appear to be unaware of their deficit, and confabulation is common. Alertness and other aspects of cognitive function are unaffected. Lesions in the dorsal medial nuclei of the thalamus are probably responsible for the memory deficits. About 25% of patients never recover and require long-term care, whereas 20% recover completely over

several months. It is not clear whether thiamine is effective in treating Korsakoff's syndrome (1).

**Alcohol induced peripheral neuropathy**

Polyneuropathy is the most common neurological complication in alcoholism. Patients report paresthesias, pain, and weakness, especially in the feet. Dysesthesias can be so severe that they interfere with walking.

Examination reveals reduced pain and temperature sensation. Distal muscle weakness and atrophy are common, greater in the legs than in the arms. Deep tendon reflexes are reduced, and ankle reflexes are usually absent, even in asymptomatic patients.

Cerebrospinal fluid protein levels are usually normal or slightly elevated.Alcoholic polyneuropathy is characterized by axonal degeneration and demyelination. Although earlier clinical evidence suggested that inadequate nutrition was responsible,a specific vitamin deficiency has never been documented.

Recent evidence suggests a direct neurotoxic effect of ethanol on peripheral nerves. Alcoholic persons frequently suffer entrapment or pressure neuropathies, particularly of ulnar and peroneal nerves. Recovery in abstinent patients is slow and often incomplete, requiring weeks to months (1).

**Alcohol induced seizures**

The relation between alcohol and seizures is complex. It has been estimated that the prevalence of epilepsy in alcohol dependent patients is three times that of the general population, although the prevalence of alcoholism is only slightly higher in patients with epilepsy than in the general population. Abrupt cessation after prolonged heavy drinking may trigger alcohol withdrawal seizures, thought to be caused by abrupt decline of the brain alcohol levels. Seizures may occur before the blood alcohol content returns to zero due to partial withdrawal either during sleep or during financial limitations on the level of alcohol provision. Withdrawal seizures can occur after short bouts of drinking (1–6 days). There may be a genetic susceptibility to alcohol withdrawal seizures.

Acutely, partial seizures and epileptic EEG abnormalities are not infrequent in alcohol abusers. It has been suggested that alcohol causes between 9–25%of cases of status epilepticus. The outcome of patients with alcohol related status epilepticus appears more favourable, but recovery may be compounded by an unduly prolonged post-ictal state. Alcohol dependent patients also have seizures that occur remotely from alcohol withdrawal. The high prevalence of these seizures points to the role of alcohol toxicity in seizure genesis. It has been shown that heavy alcohol use leads to structural brain changes. Concern has been expressed that repeated cycles of alcohol exposure and withdrawal may lead to a process termed kindling, which could then precipitate seizures (2).

## *Alcohol and the cardiovascular system*

Although moderate alcohol consumption is decreasing the prevalence of coronary heart disease, an excessive and chronic use is associated with irreversible pathological changes of myocardium and a higher prevalence of coronary heart disease. These changes are complex and are composed of a combination of pathological changes, namely a decrease of synthesis of contractile proteins leading to an insufficient contractile ability of the myocardium, necrosis/apoptosis of cardiomyocytes and hypertrophy of the ventricular wall. All these changes fall into a phenomenon called alcoholic heart muscle disease (AHMD).

**Alcoholic heart muscle disease**

AHMD is defined as myocardial pathology occurring in patients in whom the sole causative agent is excessive ethanol consumption with an alcohol intake of greater than 80 grams of ethanol a day for 10 years or more, or a cumulative lifetime alcohol intake exceeding 250 kg. AHMD is characterized by cardiomegaly, dilatation of the left ventricle and ventricular hypocontractility. There are pathological alterations in left and right ventricular tissue with dysrhythmias (including sinus tachycardia, extrasystoles, or atria1 fibrillation) and complaints of fatigue or breathlessness.

Features of heart muscle changes in AHMD include histological derangements in myofibrillary architecture, mitochondrial abnormalities, widening of the gap junction and alterations in the sarcoplasmic reticulum. Fibrosis, increased lipid deposits and inflammatory infiltrates are seen, especially in the later stages. Overall the features are similar to those seen in dilated cardiomyopathy and eventually heart failure may ensue.

The changes in the heart muscle are generally complex. Electron microscopy of cardiac tissue from chronic ethanol abusers (duration of AHMD ranged from 2 to 10 years) reveals abnormalities of the contractile elements that vary from one region to another. These include separation of filaments and loss of striations. In overtly damaged myofibrils, mitochondrial abnormalities are also apparent. Although these changes are credited by the effects of chronic ethanol consumption, moderate amounts of alcohol can also cause functional impairments. This includes a reduction in the ejection fraction as little as 30 min after alcohol consumption (mean plasma ethanol levels of approx 25 mmol/l).

Some possible mechanisms contributing to the development of AHMD are as follows:

1. Nutritional factors:

There is no doubt that nutritional abnormalities or limitations induce specific heart muscle disorders. Thiamine deficiency, for example, may give rise to beriberi which is associated with congestive heart failure, although this is reversible. In general, at least in the developed countries, beriberi-associated heart muscle damage occurs very infrequently.

Alcohol-related cobalt-induced cardiotoxicity is now rare. was subsequently found that the cobalt used as a foaming agent was the cause of beer-drinkers heart.

The role of nutritional inadequacies in the etiology of most alcoholic heart muscle disease has now generally been confirmed by use of models entailing experimentally induced cardiac muscle damage in laboratory animals. In these, the feeding regimes have been strictly controlled, confirming the development of AHMD as being independent of malnutrition.

2. Biochemical factors:

Free radicals, acetaldehyde and altered endocrine status have all been implicated in the pathogenesis of liver abnormalities in alcoholism. It is probable that some of these processes may also occur in heart muscle and indeed a variety of metabolic changes occur in the heart. These include, for example, defects in the plasma membrane of the heart or increased free radical activity which may be of importance in other heart muscle diseases. Additional biochemical defects have been reviewed. However, any loss of tissue components that contain protein, such as mitochondrial and contractile elements, must be explained by changes in protein turnover.

3. Changes in protein turnover and cell death:
The process whereby ethanol might alter cardiac protein metabolism is in the following pathway: DNA-> RNA- > protein. However changes in heart protein content must be explained by both synthetic and degradative pathways. This introduces the concept of protein turnover, which is defined as the dynamic process whereby tissue (i.e., heart) proteins are continually being formed and degraded. In the steady state the rate of protein synthesis equals the rate of protein breakdown.

In many organ systems, including the heart, myocyte loss or cell death may be an important component of organ dysfunction and pathology. Cell death can result from either necrosis or apoptosis programmed cell death). There are several early reports in humans with AHMD and animal models of cardiomyopathy that support a role for myocyte loss as a mechanism underlying alcohol linduced cardiac dysfunction. In 1965, in a histopathologic examination of hearts of patients with the diagnosis of AHMD, Hibbs and colleagues reported that myocytes lost their cross-striated appearance and had pyknotic nuclei. The latter, a reduction the size of the nucleus, can be a characteristic of apoptosis. Capasso found a significant loss of myocytes in the LV from rats fed ethanol in their drinking water for 8 months.

Recently, Chen using primary neonatal myocyte cell cultures, examined the effects of acute alcohol (500 mg/dL and 1,000 mg/dL) exposure on the process of apoptosis. Apoptosis was induced by rinsing cells twice in phosphate-buffered saline solution and then replacing the medium with serum-free suspension. Both concentrations of alcohol potentiated the apoptotic effect of serum withdrawal (as measured by DNA acid fragmentation).

In addition, both alcohol concentrations increased the protein levels of the pro-apoptotic protein Bax and increased caspase-3 enzyme activity the latter is a member of a family of intracellular proteases activated in apoptosis). Interestingly, in this same experiment, the application of insulin-like growth factor (IGF)-1 attenuated the apoptotic effects of ethanol on serum withdrawal. It is interesting that IGF-1 attenuated the effects of alcohol. IGF-1 has multiple effects on the cell, some which include cell proliferation and differentiation,whereas activation of signaling components downstream to the IGF receptor are linked to the development of hypertrophy. In acute infusion of alcohol (500 mg/dL for 150 min) increased messenger RNA p21 levels. p21 is an inhibitor of cyclin-dependent kinases, and p21 may be one of the many proteins involved in the hypertrophic response (3,4).

## *Alcohol and the liver*

A chronic alcohol use is associated with pathological changes of the liver, with the subsequent development of liver failure. Complications of liver failure are countless with a high mortality rate. In addition to liver failure the affected patient is subjected to an increased risk of cirrhosis and hepatocellular carcinoma.

The most serious complications are ascites, portal hypertension and the subsequent oesophageal varices, endocrine abnormality, prolonged bleeding due to a decrease of clotting factors, low levels of serum albumin leading to generalized oedema, anaemia, muscle wasting, abnormal glycogen breakdown leading to a low level of fasting glucose concentration, hepatic encephalopathy leading to coma and death, jaundice, hepatorenal syndrome with renal dysfunction, skin changes and malabsorbtion syndrome leading to a generalized wasting.

Alcoholic liver disease (ALD) is the most common liver disease in the UK causing over 20000 deaths annually. It is therefore a major cause of morbidity and mortality and a significant drain on limited healthcare resources

**Alcoholic liver disease (ALD)**

Intense research efforts over the past 20 years have highlighted several important metabolic and immunological consequences of excessive alcohol consumption that could contribute to disease pathogenesis. Defining disease mechanisms could lead to the development of novel treatment strategies, currently limited to liver transplantation for end-stage disease. It has also become increasingly clear that individuals differ in their susceptibility to ALD. Although cumulative alcohol dose undoubtedly plays a role in determining disease risk, only a small proportion of heavy drinkers go on to develop the more advanced forms of ALD – hepatitis, fibrosis and cirrhosis. Elucidating the genetic and environmental factors associated with disease progression would be a major step towards disease prevention.

The two main forms of advanced ALD are alcoholic hepatitis and cirrhosis. The former is characterised histologically by evidence of hepatocyte necrosis and apoptosis, leukocyte infiltration and perisinusoidal–pericellular fibrosis, and the presence of regenerative nodules separated by bands of scar tissue is the predominant feature of cirrhosis. It is not uncommon for both lesions to be present in the same biopsy, although the question of whether or not alcoholic hepatitis is a pre-requisite for the development of cirrhosis remains a subject of considerable debate. There is, however, little doubt that its presence increases the risk of progression to cirrhosis, even in the absence of continued alcohol intake.

Obviously, the cornerstone of treatment for both alcoholic hepatitis and cirrhosis is abstinence from alcohol. However, patients presenting with severe alcoholic hepatitis have a high mortality despite abstinence and, as yet, various pharmacological therapies have proved largely unsuccessful in improving survival. The only treatment for established cirrhosis is liver transplantation for those who develop liver failure inspite of abstinence. Until now, the development of novel treatment and preventative strategies has been hampered by the lack of detailed knowledge of the disease mechanisms. This situation might now be changing with improved insight into the pathogenesis obtained from studies that focus on the roles of metabolism, endotoxin and immunity (5,6).

**Development of ADL, susceptibility and treatment strategies**

The model discussed below encompasses all the potential mechanisms of ALD, while offering an explanation for the variability in clinical and pathological manifestations. It also offers a potential explanation for variable individual susceptibility and suggests several novel treatment strategies that might need to be tailored to particular disease phenotypes.

Gut bacteria account for around 9% of ethanol metabolism, the remainder is metabolized in the liver. As a result of this metabolism, an increase in the hepatic NADH:NAD ratio, as well as the development of oxidative stress, explains why virtually all heavy drinkers develop some degree of fatty liver.

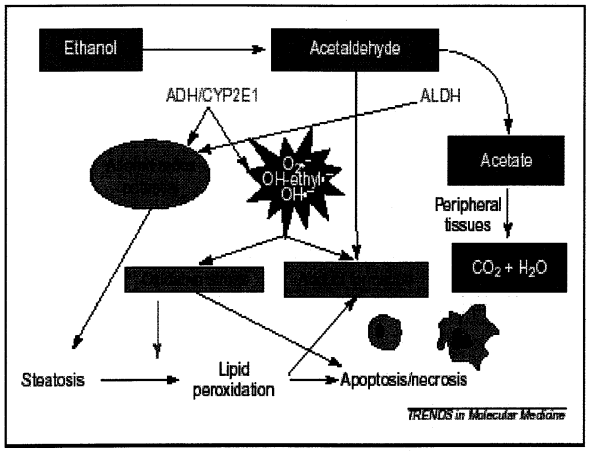


**Fig. 1.** Both steps in the metabolism of ethanol result in altered redox potential and, ultimately, steatosis. Metabolism through the CYP2E1 system is the primary source of reactive oxygen species and oxidative stress. The resulting products of lipid peroxidation, reactive oxygen species themselves and acetaldehyde all contribute to the formation of neo-antigenic adducts. Lipid peroxidation and oxidative stress themselves can lead to cell death by necrosis or apoptosis. Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P450 2E1.

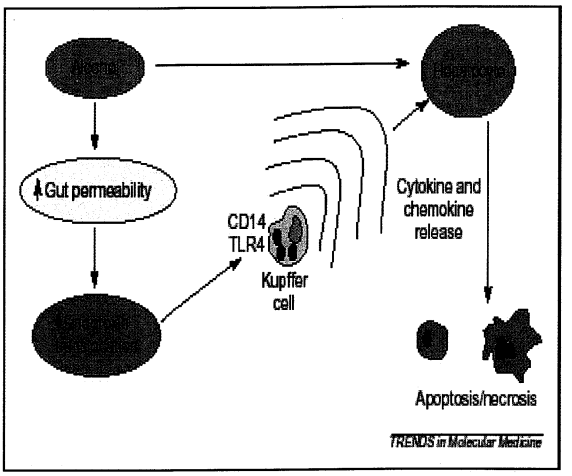


**Fig. 2.** At physiological concentrations, portal endotoxin levels result in tolerogenic levels of hepatic cytokine release. Alcohol increases gut permeability, and portal endotoxin levels rise. Kupffer cells respond by producing leukocyte chemoattractants (chemokines) and cytokines that are involved in hepatocyte apoptosis and necrosis. Abbreviation: TLR4, Toll-like receptor-4.

The severity of fatty liver will be determined by genetic and environmental factors. Functional polymorphisms in genes encoding enzymes involved in lipid metabolism are obvious 'candidate' genetic factors, however, as yet, no genetic determinants of steatosis severity have been identified. Genes influencing the development of obesity and non-insulin-dependent diabetes mellitus (NIDDM) will also be important since both are associated with steatosis. Obesity, in particular, has been strongly associated with development of steatosis in heavy drinkers and, accordingly, the environmental factor most likely to play a role in determining the severity of steatosis is diet.

The development of steatosis can be viewed as the 'first hit' in the development of liver cell injury and associated inflammation (alcoholic hepatitis). Studies in animal models of steatosis have shown that fatsensitizes the liver to a variety of potential 'second hits' triggering development of inflammation and necrosis. These second hits include oxidative stress, endotoxin, hypoxia and an immune response to protein adducts arising during ethanol metabolism, either released from necrotic hepatocytes or expressed on the surface of hepatocytes undergoing apoptosis. Individual susceptibility to alcoholic hepatitis will, again, be influenced by genetic and environmental factors. Data from animal models suggest that increased female susceptibility could be explained by oestrogen, which increases gut permeability to endotoxin.

Abstinence is obviously the most effective preventative measure. New pharmacological therapies are focussing on reducing the drive to drink in abstinent alcoholics. Determining genetic factors responsible for disease susceptibility would enable targeted counselling of high-risk individuals prior to their commencing drinking. Avoiding obesity and aggressive treatment of other conditions associated with fatty liver such as NIDDM might also be effective preventative strategies.

With regard to treatment, alcoholic hepatitis is an area of particular interest in view of its high mortality. The available animal and, more recently, human data suggest that reducing gut translocation of endotoxin with antibiotics and artificial enteral nutrition might be of benefit in these patients.

Treatment directed at the overproduction of TNFα seems a further rational approach and the recently reported beneficial short-term effect of pentoxifylline will no doubt lead to the

initiation of longer-term studies. Steroids, predominantly through their inhibitory effect on the transcription factor NF-κB, will also inhibit cytokine release by Kupffer cells and might have further beneficial effects by reducing the immune response to adducts released from hepatocytes. This effect might be more marked in individuals with an 'immune' phenotype and, if we consider alcoholic hepatitis as a potential period of sensitization to these adducts, long-term immunosuppressive agents might have a role in these susceptible patients (5,6).

## *Alcohol and the pancreas*

**Alcoholic pancreatitis (AP)**

Alcohol has long being known to be a potent causative agent of acute and chronic pancreatitis. The acute pancreatitis can develop after binge alcohol consumption or develop as a consequence of prolonged drinking. After repeated acute pancreatitis there is a risk of development of chronic pancreatitis with malabsorbtion and secondary diabetes as the consequence. The development of acute and chronic form of pancreatitis has a high degree of morbidity and mortality rate.

Acute pancreatitis is a consequence of inappropriate, intrapancreatic activation of zymogen enzymes. Once the zymogens are activated the process progresses rapidly and forms a mild form (oedematous type) or a much more serious necrotizing hemorrhagic type, with a much higher mortality rate. It is believed that this process occurs after many years (5-15) of heavy drinking. The mechanism of enzyme activation has been demonstrated in man, in which specific duodenal enzymes (entrokinases) which gain access into pancreatic duct by the mechanism of duodenopancreatic reflux.

Excessive alcohol intake for many years damages muscarinic cholinergic receptors, initially leading to decreased cholinesterase activity, increased sensitivity to acetylcholine which leads to increased duodenal hypertonicity, relaxation of sphincter of oddi which in normal people inhibits the reflux of duodenal content into pancreatic duct in response to food, fat and alcohol. Once this process starts it is difficult to stop and the only true treatment is abstinence. A recurrent acute inflammation if necrotizing hemorrhagic in type has a mortality rate of 25% with development of DIC (disseminated intravascular coagulation), Adult Respiratory Distress Syndrome and renal failure causing multiple organ failure (7).

## *Alcohol and Reproductive system/pregnancy*

**Drinking during pregnancy**

Alcohol consumption among women of reproductive age is widespread; a recent American national survey indicates that 75% of women aged 18 to 34 had consumed alcohol in the past year. A binge pattern of drinking appears to be a style that develops in adolescence and continues throughout high school, college and adulthood.

A 1991 national survey of randomly selected seventh to twelfth grade students found that 26% of all students have binged at least once. Surveys of colleges consistently indicate that over 40% of students self-report a binge pattern of drinking. Interestingly, the stability of binge alcohol consumption contrasts with the large declines seen from 1980 to 1990 in college students' reported use of marijuana (34% to 13%) and cocaine (6.9% to 1.2%). Recent studies examining the drinking styles of female college students reveal a significant change in

attitudes towards binge drinking. In 1977, 14% of women reported getting drunk 1 to 3 times per month and 3% were drunk weekly; in 1989, the figures escalated to 37% and 6.7%, respectively. Moreover, in 1977, 10% of women reported drinking to get drunk, whereas in 1989, 33.9% indicated intoxication as their reason for drinking.

Another trend is the increased volume females are consuming when they do binge. In a study investigating the convergence between male and female drinking styles, it was noted that in 1985, the reported volume consumed during a binge was 27% greater than in 1977. If females are beginning to imitate the typical male model of heavy binge drinking, this is particularly concerning, considering that women reach significantly higher peak blood alcohol concentrations than men do when given doses of alcohol that are standardized for body weight.

It appears that rather than being a deviant behaviour, binge drinking may be a typical social behaviour in many sociocultural domains [in a recent survey of 140 American colleges, the percentage of students reporting binge drinking was as high as 70% at the school with the high prevalence of binge drinking]. In fact, it has been described that "students who have a more normative number of binge-drinking episodes are integrated more fully into the college community than students who have no episodes or too many episodes.

Although there have been isolated reports throughout modern history suggesting the adverse effects of alcohol consumption during pregnancy, it was not until 1973 that a distinct dysmorphic syndrome associated with gestational alcoholism, the fetal alcohol syndrome (FAS), was coined and recognized in the medical literature. Alcohol is now acknowledged to be the most common human teratogen, with the number of consumers being several orders of magnitude larger than for any other teratogenic compound. The spectrum of alcohol's teratogenic impact spans a wide continuum that includes growth deficiency, central nervous system dysfunction, craniofacial anomalies, and organ/skeletal pathology; however, none of the individual deficits are pathognomonic for fetal alcohol exposure. The previous 2 decades have seen the accumulation of a large body of research on FAS and alcohol-related birth defects, yet the timing, specificity, threshold, and pathogenesis of alcohol's teratogenicity remain uncertain (8).

Full expression of FAS generally occurs only with chronic maternal ingestion of at least 2 g/kg/day of alcohol (approximately eight standard drinks per occasion, where a standard drink is equivalent to an average can/bottle of beer, glass of wine, or serving of liquor either alone or in a mixed drink). Since the inception of the term FAS into the medical literature, the major thrust of research has been the attempt to ascertain a safe limit of average daily or weekly alcohol consumption during pregnancy . It has not been until more recently that researchers using both animal and human models have begun to direct attention towards different patterns or styles of drinking rather than different daily or weekly totals.

One area of concern is the association between alcohol intoxication and unplanned or unprotected sexual activity. Studies investigating binge drinking and its associated consequences have shown that the "infrequent binge drinkers" were three times more likely than "non binge drinkers' " to report both instances of engaging in unplanned sexual activity and having unprotected sex. The "frequent binge drinkers" were seven times more likely than the "non bingers" to engage in these activities. The concern is that women who binge drink may increase their likelihood of unplanned pregnancy, and, consequently, unknowingly exposing the fetus to continued binge exposure until pregnancy is recognized.

In view of the high incidence of binge drinking among women of reproductive age, the question is, are similar levels seen during pregnancy? The answer appears to be both yes and no. It appears that similar levels may be achieved early in pregnancy but decline precipitously throughout pregnancy. In general, most women decrease their alcohol consumption during pregnancy; however, maternal drinking does not appear to be declining among those women who are smokers, unmarried, or under 25 years old.

Two groups of particular interest are alcoholics and teenagers. It has been noted that most alcoholic women decrease their alcohol consumption during pregnancy, but when they do drink they tend to binge. Considering the One area of concern is the association between alcohol intoxication and unplanned or unprotected sexual activity. Studies investigating binge drinking and its associated consequences have shown that the" infrequent binge drinkers" were three times more likely than "non binge drinkers' " to report both instances of engaging in unplanned sexual activity and having unprotected sex. The "frequent binge drinkers" were seven times more likely than the "non bingers" to engage in these activities. The concern is that women who binge drink may increase their likelihood of unplanned pregnancy, and, consequently, unknowingly exposing the fetus to continued binge exposure until pregnancy is recognized (8).

**The teratogenicity of alcohol**

Heavy drinking during pregnancy can result in serious adverse outcomes to the fetus. The Fetal Alcohol Syndrome (FAS) is a triad characterized by pre- and/or postnatal growth retardation, central nervous system damage, and typical facial dysmorphology. The insult on the brain by ethanol affects intelligence, cognitive function, and behavior. The incidence of FAS in developed countries is estimated to be as high as 0.97 cases per 1000 live births. Huge efforts and extensive resources are required for the rehabilitation, education, and integration of these children in the community (8).

Table 1. Criteria for diagnosis of fetal alcohol syndrome (2)

1. Prenatal and/or postnatal growth retardation (weight, length, and/or head circumference < tenth percentile, when corrected for gestational age).
2. Central nervous system involvement (signs of neurologic abnormality, developmental delay, or intellectual impairment, for example, mental retardation).
3. Characteristic facial dysmorphology (at least two or three of the following signs):
   a) microcephaly (head circumference < third percentile),
   b) microphthalmia and/or short palpebral fissures,
   c) poorly developed philtrum, thin upper lip, and flattening of the maxillary area.

According to the Centers for Disease Control study on the prevalence of alcohol consumption among women of childbearing age, 50% appear to consume alcohol. Fortyfive percent are defined as light drinkers (30 drinks/month), 3% as moderate (30–60 drinks/month), and 2% as heavy drinkers (60 drinks/month). The rates of drinking in North America, Europe, and Australia are similar. Although women tend to decrease their alcohol consumption during pregnancy, their actual level of drinking depends to a large extent on their drinking habits prior to conception. In many cases, the fetus is exposed to the teratogenic effects of ethanol during the critical period of organogenesis, before pregnancy is confirmed. Sixty percent of drinking women were not aware of their pregnancy until the fourth week after conception.

The fetus is more susceptible to ethanol than the mother, Offspring of rats that were fed non-toxic levels of ethanol presented with reduced growth and antioxidant activity in the liver while their mothers were not affected. Mothers of children with FAS, who are typically heavy drinkers, do not present with signs of toxicity until late in the course of alcohol abuse when impairments of the central nervous system, liver, and pancreas prevail.

The ways by which ethanol affects biochemical processes and cellular structures have been the focus of extensive research and they are still far from being completely understood. Various mechanisms have been proposed in explaining the teratogenicity of ethanol. The oxidative stress leads to peroxidation of lipids, nucleic acids, proteins, and carbohydrates. Sequelae of oxidative stress can be manifested by chromosomal abnormalities, enzymatic malfunction, and disruption of cellular membranes. The cell possesses antioxidant activity catalyzed by enzymes, such as superoxide dismutase, glutathione peroxidase, and catalase, which are capable of neutralizing reactive oxygen species (ROS). Other molecules that contribute to antioxidant activity are vitamins such as vitamin C,vitamin E, and b-carotene.

During the last decade, several groups of investigators have hypothesized that supplementation of antioxidants in FAS will attenuate ethanol-induced oxidative stress and thus reduce its fetal damage (9).

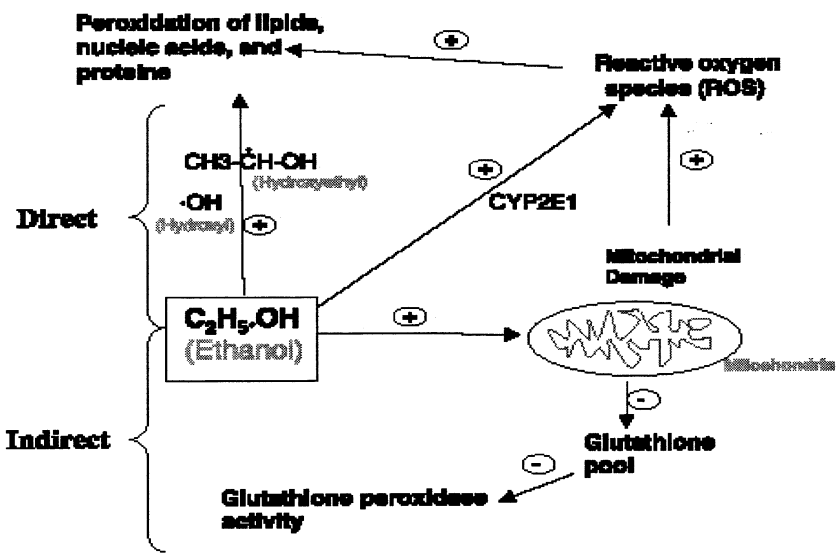


Fig. 1. Summary of ethanol-induced oxidative stress mechanisms. Pathways of oxidative stress are divided into a direct and an indirect effect. The outcome of the indirect pathway is a reduction in glutathione peroxidase activity and the outcome of the direct pathway is peroxidation of lipids, nucleic acids, and proteins through free radicals and ROS. Hydroxyethyl and hydroxyl groups = oxygen free radicals. CYP2E1 = cytochrome *P*-450 2E1. ⊕ = Excitatory effect, ⊖ = Inhibitory effect.

## *Alcohol and cancer*

### The role of alcohol in development of breast cancer

Breast cancer is the result of a complex, multi-stage process in that hereditary susceptibility, age, estrogen metabolism, tobacco smoke and alcohol consumption constitute recognized risk factors.

Recent studies confirm the significant association between alcohol consumption and breast cancer. Analysis of 322,467 women, including 4,335 cases of invasive breast cancer evaluated for up to 11 years, revealed a 41% increase in the incidence of breast cancer by alcohol consumption, and this association was dose dependent up to a dose of 30–60 g alcohol/day. This observation is consistent with several previous studies that revealed an increased risk for breast cancer by alcohol consumption ranging from 20–89%.

Alcohol consumption increases the risk for breast cancer in women by still undefined means. Alcohol metabolism is known to produce reactive oxygen species (ROS), and breast cancer is associated with high levels of hydroxyl radical (•OH) modified DNA, point mutations, single strand nicks, and chromosome rearrangement. Furthermore, ROS modification of DNA can produce the mutations and DNA damage found in breast cancer. Alcoholdehydrogenase (ADH) and xanthine oxidoreductase (XOR) are expressed and regulated in breast tissues and aldehyde oxidase (AOX) may be present as well. Mammary gland XOR is an efficient source of ROS. Recently, hepatic XOR and AOX were found to generate ROS in two ways from alcohol metabolism: by acetaldehyde consumption and by the intrinsic NADH oxidase activity of both XOR and AOX. The data obtained suggests that: (1) expression of ADH and XOR or AOX in breast tissue provides the enzymes that generate ROS; (2) metabolism of alcohol produces acetaldehyde and NADH that can both be substrates for XOR or AOX and thereby result in ROS formation; and (3) ROS generated by XOR or AOX can induce the carcinogenic mutations and DNA damage found in breast cancer.

Accumulation of iron coupled with diminished antioxidant defences in breast tissue with advancing age provide additional support for this hypothesis because both result in elevated ROS damage that may exacerbate the risk for ROS-induced breast cancer (14).

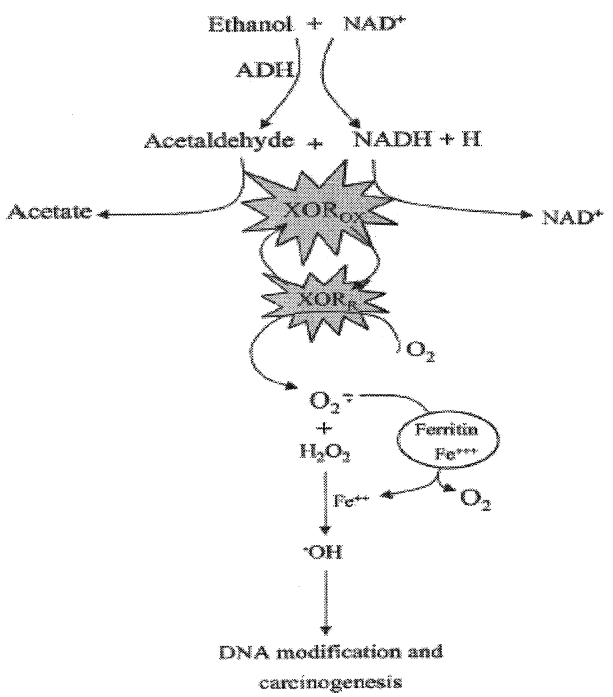


Fig. 1. The XOR hypothesis. The action of ADH on ethanol in the breast produces acetaldehyde and NADH both of which can be substrates for XOR. Reduction of XOR by either acetaldehyde or NADH results in ROS formation when XOR is subsequently oxidized by molecular oxygen. The resulting superoxide anion and hydrogen peroxide can participate in Fenton chemistry yielding hydroxyl radical, the primary ROS that produces DNA damage and mutation.

**The role of alcohol on development of oral cancer**

Chronic alcohol ingestion may be associated with the development of oral cancer in susceptible patients either alone or in synergy with other agents. The exact mechanism by which alcohol exerts such an effect is unclear and requires further investigation. However, it is likely to be due to a combination of influences, both local (e.g. direct effect on cell membranes, alteration in mucosal permeability, variation in tissue distribution and type of enzyme involved in alcohol metabolism) and systemic (e.g. nutritional deficiencies, immunological deficiencies and disturbed liver function).

The ingestion of alcoholic beverages is associated with the development of oral cancer in some patients. A recent study classified 40% of head and neck cancer patients as alcoholics. Indeed, the recent increase in oral cancer reported within a younger age group than traditionally recognized (under 40 years) parallels the increased consumption of alcohol in Britain (from 109 litres/person in 1960 to 142 litres/person in 1981).

The difficulty of assessing the influence of alcohol in the aetiology of oral cancer stems from the fact that most people who drink heavily also smoke. In addition, it can be difficult to obtain reliable information from the patients on intake of alcohol. Not least because it is actually likely to vary quite considerably from day to day. Some may 'binge' drink and others have a high daily intake.

One of the many difficulties in assessing the role of alcohol is the difficulty in accurate measurement of intake (e.g. variation in quantity, type and alcohol concentration). Data on alcohol ingestion is based on a highly subjective estimate provided by the patient. An agreed measure that is often used and that the lay person understands is that which equates half a pint of beer with one glass of wine or one measure of spirit (equivalent to 8 g of alcohol).

The Health Education Council in the United Kingdom recommended a weekly intake of no more than 14 units for women and 21 units for men. Using this criteria 1 in 4 men and 1 in 10 women in UK are believed to be drinking over this limit, with the number of habitual heavy drinkers estimated at 4 million although the legal age for drinking is 18, the average age at which drinking starts has fallen since the early 1970s from around 17 to around 11, in both boys and girls. The recent emergence of 'alcopops' (an alcoholic drink that mimics the taste of non-alcoholic drinks) appear to be widely drunk in the UK by those under 18. Alcohol is thus likely to remain a significant influence upon the oral mucosa in a substantial number of people from a relatively young age (15).

## *Alcohol and the musculoskeletal system*

**Alcoholic myopathy**

Excessive and prolonged alcohol intake causes a defined myopathic lesion characterised by selective atrophy of Type II (i.e., white or anaerobic, glycolytic fast twitch) fibres. The Type I (i.e., red or aerobic, oxidative slow twitch) fibres are relatively protected unless there is severe alcohol exposure in which case Type I fibres may also atrophy. In the initial stages of the disease there is some evidence of a Type I fibre hypertrophy, though the significance of this is unclear. These changes are accompanied by reductions in muscle mass (by an average of 22%) and body mass index (15%). Functional impairments include cramps with frequent falls and myalgic symptoms. Muscle strength is also impaired by alcohol which is related to life-time cumulative intake(16).

The prevalence of chronic alcohol myopathy is estimated at between 45 and 70%. Regardless of the exact number of afflicted individuals, this myopathy is one of the most prominent muscle diseases and occurs more frequently than many of the hereditary myopathies. The myopathy is characterized by proximal muscle weakness and often leads to impaired ambulation, frequent falls and a generalized reduction in quality of life indices. The alcohol-induced atrophy of skeletal muscle is proportional to the total lifetime alcohol ingestion and, under severe conditions, may lead to the erosion of up to 20% of the entire muscle mass (17).

Alcoholic cirrhosis reduces muscle strength. However, alcoholic myopathy is not related to overt liver disease. Indeed, the notion that alcoholic myopathy may be mediated directly by excessive alcohol ingestion has been addressed by a number of studies and there is convincing evidence to show it occurs independently of either neuropathy, malnutrition or endocrine abnormalities such as glucocorticoid excess. Nevertheless, a modulating, rather than a causative role for some of these factors have been described (for example, for nutritional influences) (16).

Concomitant changes within the muscle include a reduction in muscle protein content, which implicates defects in protein metabolism. This is supported by the observation that muscle protein synthesis is reduced in alcoholic patients with myopathy and protein degradation may be either unchanged or reduced . Similar results have been obtained in animal models of alcoholic myopathy (16).

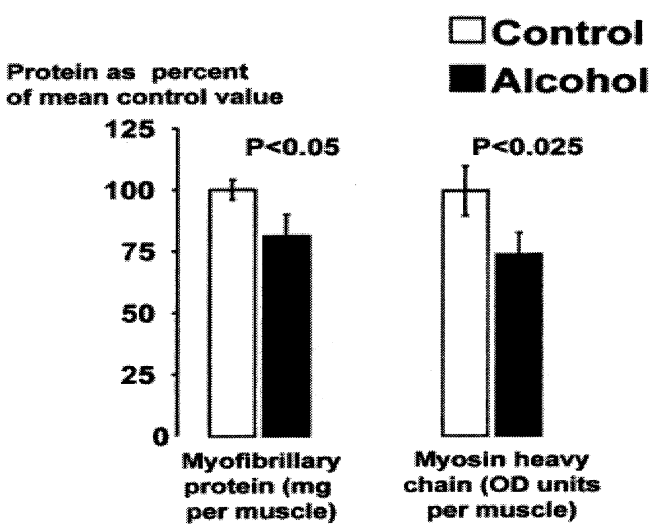


Fig. 1. Myofibrillary and myosin heavy chain protein in rats fed ethanol for 6 weeks. Total myofibrillary protein contents in plantaris muscle from 6-week glucose- and ethanol-fed male Wistar rats ($n$ = 5-6), pair-fed equivalent amounts of iso-caloric, iso-volumetric, liquid diet. Data are means ± SEM. P values are displayed over the relevant histograms. Adapted from data contained in [62].

The ability of ethanol to impair protein synthesis may be mediated directly or via acetaldehyde or acetate (e.g., active metabolites) generated by the oxidative metabolism of ethanol. Inhibition of ADH with 4-methylpyrazol (MP) did not prevent the decrease in muscle protein synthesis produced in vivo by acute alcohol intoxication. Further, none of the alcohol-induced effects on either basal or IGFI–stimulated S6K1/S6 phosphorylation are prevented by 4-MP. Hence, it is unlikely ethanol metabolism is required for alcohol to modulate protein synthesis. However, these results do not differentiate between an alcohol effect on muscle per

se versus the release of a secondary mediator from a distant organ that circulates and affects muscle in an indirect manner (17).

Different experimental approaches have been used to resolve these two possibilities. First, when ethanol is added to cultured human skeletal muscle cells protein synthesis is inhibited dose- and time-dependently. Prolonged exposure (e.g., 3 days) of myocytes to ethanol also blunted the protein synthetic response toward insulin and IGF-I. Hence, alcohol is capable of directly impairing protein synthesis in cultured muscle cells. Secondly, the direct effects of alcohol have also been assessed using the isolated perfused hindlimb muscle preparation. In this study, alcohol was included in the perfusate at a concentration comparable to that observed in vivo, and the hindlimb musculature perfused for the same time period as in vivo studies . The exposure of muscle under these conditions qualitatively recapitulates the same defects in basal and IGF-I stimulation of S6 phosphorylation as were observed in vivo suggesting that alcohol can directly decrease the translational control of muscle protein synthesis (17).

## *Alcoholic hangover*

There is no consensus definition of veisalgia ("alcohol hangover," from the Norwegian *kveis*, or "uneasiness following debauchery," and the Greek *algia*, or "pain"). Most descriptive and experimental studies have identified a set of common symptoms: headache, diarrhea, anorexia, tremulousness, fatigue, and nausea. Objective criteria have focused on decreased occupational, cognitive, or visual–spatial skill performance or on alterations in hemodynamic and hormonal measurements.

Although tachycardia, tremor, orthostasis, cognitive impairment, and visual–spatial impairment are frequently observed, they do not capture the overall experience for the patient. This remains subjective, varying from person to person and from episode to episode. To permit a uniform discussion, hangover is defined as the presence of at least two of the symptoms in **Table 1**, occurring after the consumption and full metabolism of alcohol with sufficient severity to disrupt the performance of daily tasks and responsibilities (18).

**Table 1. Symptoms of Alcohol Hangover***

| Symptom | Persons Affected, % |
|---|---|
| Headache | 66 |
| Poor sense of overall well-being | 60 |
| Diarrhea | 36 |
| Anorexia | 21 |
| Tremulousness | 20 |
| Fatigue | 20 |
| Nausea | 9 |

**Pathogenesis of Alcoholic hangover**

Part of the mystery of hangover is the set of ill defined physiologic characteristics that underlie the syndrome. One theory is that hangover is the first stage of alcohol withdrawal.

However, the hormonal and hemodynamic changes seen in hangover are distinct from those seen in alcohol withdrawal.

Although larger doses of alcohol lead to more severe symptoms, hangover is not solely dose related. Acetaldehyde, the dehydrogenated product of alcohol metabolism, might be responsible for hangover symptoms. Congeners, the byproducts of individual alcohol preparations (which are found primarily in brandy, wine, tequila, whiskey, and other dark liquors), increase the frequency and severity of hangover. Clear liquors, such as rum, vodka, and gin, tend to cause hangover less frequently, which may explain why patients with chronic alcoholism use these liquors disproportionately. In an experimental setting, 33% of patients who consumed 1.5 g/kg of body weight of bourbon (which has high congeners) but only 3% of those who consumed the same dose of vodka (which has low congeners) experienced severe hangover

The constellation of hangover symptoms (nausea, headache, diarrhea) resembles that seen in conditions related to dysregulated cytokine pathways (for example, in viral infections and after administration of interferon-a). Alcohol alters cytokine production through a thromboxane pathway. Levels of thromboxane B2 are elevated during experimentally induced alcohol hangover, and the administration of tolfenamic acid, a prostaglandin inhibitor, at the time of alcohol consumption has a small prophylactic effect in reducing hangover severity.

Several hormonal alterations have been observed in patients with hangover. Hangover severity is proportional to antidiuretic hormone concentration. Alcohol inhibits the effect of antidiuretic hormone on the kidneys, thereby inducing diuresis that is out of proportion to the volume of fluid ingested. As blood alcohol concentration decreases and dehydration persists, the serum level of antidiuretic hormone increases, maintaining water retention in dehydrated patients with hangover.

In clinical experience, hydration attenuates but does not completely relieve hangover symptoms. Serum aldosterone and renin levels also increase with hangover, but unlike antidiuretic hormone, they do not correlate well with hangover severity. The effect of alcohol consumption and hangover on glucose metabolism is incompletely understood.

Alcohol seems to inhibit the availability of glucose through an insulin-mediated mechanism. Glucagon is increased in acute alcohol intoxication, but its effect during hangover is unknown. Cortisol release is also suppressed during acute alcohol intoxication, but this effect does not persist in hangover. Levels of thyroid and growth hormone do not change during acute alcohol intoxication or hangover. Both acute intoxication and hangover cause metabolic acidosis.

Hemodynamic changes seen in the patient with hangover include increases in heart rate, left ventricular performance (as measured by ejection fraction),and blood pressure. The peripheral vasodilatation seen with acute alcohol ingestion is not observed in hangover. The increased cardiac work with normal peripheral resistance that occurs in hangover may explain the associated increased cardiac mortality rates. Patients with hangover have a diffuse slowing on electroencephalography, which persists up to 16 hours after blood alcohol level becomes undetectable. Decreased auditory evoked responses and psychomotor deficits have also been noted. These findings suggest that hangover, which manifests as "diffuse cortical depression," may be a different physiologic process than "alcohol withdrawal," which is characterized by general hyperexcitability of the brain (18).

**Economic Consequences and Prevalence**

Although hangover might be considered trivial—just deserts for the overindulgent—it has substantial economic consequences. A recent British study noted that alcohol use accounted for 2 billion pounds ($3.3 billion U.S.) in lost wages each year, most of which resulted from work missed because of hangover. Alcohol costs in Canada amount to $7.5 billion each year, and $1.4 billion is lost each year because of decreased occupational productivity caused by hangover-like symptoms.

Studies in other countries have yielded similar per capita estimates for the annual cost of alcohol ingestion: Australia, $3.8 billion; New Zealand, $331 million; and the United States, $148 billion. Greenfield recently estimated the average annual opportunity cost due to hangover as $2000 per working adult. In the workplace, the greatest cost incurred by alcohol is the decreased productivity of affected employees as a result of hangover-related absenteeism and poor job performance. In Finland, which has a population of 5 million, more than 1 million workdays are lost each year because of hangover. Light-to-moderate users of alcohol (0 to 3 drinks per day for men and 0 to 1 drink per day for women) account for most of the lost-work costs because they make up most of the work force.

Fifty-four percent of all alcohol-related problems in the workplace are caused by light drinkers, and 87% are caused by light-to-moderate drinkers. The primary morbidity that affects light-to-moderate drinkers is the hangover, not the long-term consequences of alcohol abuse, such as cirrhosis and cardiomyopathy. Chronic alcoholism is responsible for only a small proportion of the total societal cost of alcohol use.

Perhaps the most alarming feature of veisalgia is its high prevalence. In a study of college students, 25% of students reported experiencing a hangover in the previous week and 29% reported losing school time for hangover recovery. More than 75% of men and women who have consumed alcohol report that they have experienced hangover at least once, and 15% experience hangovers at least monthly. Ten percent of British men reported hangover-related problems at work at least monthly. Paradoxically, hangover is much more common in light-to-moderate drinkers (70%) than in heavier drinkers.

Although hangover may be interpreted as merely uncomfortable, the patient with hangover is at increased risk for injury and poor job performance. Patients with hangover have diminished visual–spatial skills and dexterity, even after alcohol can no longer be detected in the blood. Impairment from hangover has been experimentally demonstrated in pilots, people who drive, and skiers. Managerial skills and task completion are also adversely affected (18).

## Alcoholism

Alcoholism is characterized by addiction to alcohol. Persons with this addiction crave alcoholic beverages and develop tolerance to its intoxicating effects. When they stop drinking, neurologic signs of withdrawal develop. This withdrawal syndrome is evidence of a physical dependence on ethanol. Alcohol abuse refers to recurrent episodes of excessive drinking despite serious economic, social, or medical consequences. Alcohol abuse does not usually produce physical dependence. Alcoholism is a worldwide disorder of enormous cost to society. In the United States more than 20% of hospital admissions involve medical complications of excessive drinking, and the annual socioeconomic cost of alcoholism is about $100 billion. Persons with alcoholism have serious medical complications and

commonly have alcoholic neurologic disorders. Most of these disorders, except Wemicke's disease, appear to be due to the neurotoxicity of ethanol. Wemicke's encephalopathy is caused by thiamine deficiency, but genetic factors may play a role in affected patients (1).

**Alcoholism and tolerance**

Tolerance to alcohol can be acute or chronic. Acute tolerance to alcohol develops rapidly, after drinking several hours; a person can appear to be sober at blood alcohol levels that caused intoxication earlier. Chronic tolerance is a characteristic feature of alcoholism, and alcoholic persons can appear sober at blood alcohol concentrations of 90 to 110 mmol per liter (400 to 500 mg per dl). The highest recorded level is 330 mmol per liter (1,510 mg per dl) in an ambulatory person with chronic alcoholism who had stopped drinking three days earlier. Tolerance is caused by adaptive molecular changes in the brain (1).

**Genetic component of alcoholism**

Considerable evidence exists that genetic factors play a role in alcoholism. Alcoholism is about seven times more frequent in first-degree relatives of alcoholic persons than in the general population. In addition, 16% to 26% of fathers and 2% to 6% of mothers of alcoholic persons also have alcoholism. Identical twins have a significantly higher concordance of alcoholism than fraternal twins, even when environmental factors, such as the greater frequency of social contact between identical twins, are taken into account. The strongest evidence for heritability of alcoholism has come from adoption studies. Among alcoholic patients with severe alcohol-related behavioural or medical complications, adoptees have an average of 2.5 times greater chance of alcoholism developing if at least one biologic parent had alcoholism.

Based on the results of Swedish adoption studies, Cloninger described two subtypes of alcoholism. Type 1 is more common among men and women with female alcoholic relatives, whereas the type 2 syndrome is characteristic of male relatives of alcoholic men. Those with type 1 alcoholism tend to drink excessively later in life, usually after an extended period of social drinking. They can abstain from alcohol or engage in binge drinking. Associated personality traits in type 1 alcoholism include anxiety, high reward dependence, emotional dependence, rigidity, and perfectionism. Type 2 alcoholism is associated with antisocial personality traits such as impulsivity, fighting, drunk driving, and criminal behaviour.

Persons with type 2 alcoholism begin drinking in their teens or early adulthood, actively seek alcohol, and usually cannot abstain from drinking. Whether this classification scheme will prove to be useful in clinical and genetic studies remains to be determined.

Studies linking alcoholism with the chromosome 4q blood group marker MNS and the esterase D marker on chromosome 13q have been reported, but these results are inconclusive for substantial linkage. Recently a complementary DNA probe, which contains the last coding exon of the dopamine D2-receptor gene and 16.5 kilobases of the noncoding sequence on chromosome 11, has been used to examine brain tissue from 35 persons with and 35 without alcoholism. These results provided statistical evidence for the presence of a genetic locus of susceptibility to a severe form of alcoholism in the q22-q23 region of chromosome 11.

Several authors have criticized the criteria used for retrospectively diagnosing alcoholism in this study and have warned against over-interpreting the results from such a limited number of patients. Moreover, a subsequent study of 40 living, unrelated persons with alcoholism and two families with multigenerational alcoholism failed to confirm this linkage. Clearly, much

work is necessary to identify the gene(s) involved in alcoholism. This is likely to be a formidable problem because the contribution of a specific genotype will be complicated by the heterogeneity of alcoholism and the absence of precise diagnostic criteria. For example, in families with a history of alcoholism, some individuals with genetic risk might choose never to drink, while others without genetic risk might become alcoholic because of socioeconomic reasons. Therefore, even if a probe for a linked gene were used in linkage studies in families, it might not be possible to achieve a significant lod-score because of the heterogeneity of alcoholism. Multigenic approaches may prove to be more valuable. Also, it may be more plausible to search for phenotypic biochemical or molecular markers of alcoholism. Once a candidate phenotype is recognized, it should be possible to identify specific genes involved in alcoholism (1).

**Molecular component of alcoholism**

Acute and chronic ethanol-induced changes in membrane-dependent events appear to be related to acute intoxication, tolerance, and physical dependence. Ethanol intercalates into cell membranes, increasing membrane fluidity, but it is not clear how changes in membrane order control physiologic function. Recent evidence suggests that proteins involved in signal transduction may be more important pathophysiologic targets for alcohol. Components of signal transduction cascades that adapt to ethanol include ion channels, second messengers, neurotransmitters and their receptors, G proteins, chaperonins, and regulators of gene expression (1).

DOPAMIN AND SEROTONIN: Dopamine is implicated in neural mechanisms of reward, reinforcement, and craving, and psychoactive drugs, including ethanol, increase dopamine release from mesolimbic regions in rats. 5-Hydroxytryptamine3 (5-HT3) receptors control dopamine release, and in mesolimbic regions, dopamine release induced by ethanol is blocked by 5-HT3 antagonists. Ethanol potentiates 5-HT-receptor activation, and 5-HT3-receptor antagonists reduce ethanol intake75 and the ability to discriminate between water and alcohol. These findings suggest that serotonin, acting at 5-HT receptors, may mediate some aspects of ethanol intoxication and ethanol-seeking behaviour (1).

**Alcohol withdrawal syndrome**

When drinking is abruptly reduced or discontinued, a hyperexcitable withdrawal syndrome develops that is considered to be evidence of physical dependence. Clinical features include tremulousness, disordered perceptions, convulsions, and delirium tremens. These symptoms and signs appear to be due to adaptive neural mechanisms that are no longer opposed by the depressant effects of ethanol.Tremor is a common symptom, beginning six to eight hours after the last drink and worsening in one to two days. Sympathetic hyperactivity with elevated levels of norepinephrine and its metabolites has been documented, and treatment with sympatholytic drugs can be helpful. The calming effects of benzodiazepines, however, are more effective.

Disordered perceptions may parallel the development of tremor and sympathetic hyperactivity, becoming most pronounced at 24 to 36 hours and clearing in a few days. Ordinary visual, auditory, and sensory experiences become distorted and misinterpreted.

Vivid nightmares interfere with sleep. Auditory hallucinations ("alcoholic hallucinosis") can persist for weeks, even though other manifestations of ethanol withdrawal have abated (1).

**Mechanism of alcohol withdrawal syndrome (AWS)**

1. ROLE OF EXCITATORY AMINO ACIDS:

In the nervous system, glutamate, aspartate, and their structural analogues bind to receptors that regulate ion channels or activate phosphoinositide hydrolysis. Specific receptors respond to the excitatory amino acid agonists, NMDA, kainate, ot-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or L-2-amino-4-phosphonobutanoic acid, but the NMDA receptor is particularly sensitive to ethanol.

Intoxicating concentrations of ethanol (5 to 50 mmol per liter) inhibit NMDA-activated calcium currents in rat hippocampal neurons and dorsal root sensory neurons and reduce NMDA-stimulated calcium uptake in cerebellar granule cells. Intoxicating concentrations of ethanol also inhibit cellular responses to NMDA-receptor activation, including neurotransmitter release, cyclic guanosine monophosphate production, and the generation of excitatory postsynaptic potentials.4 N-Methyl-D-aspartate receptors are important for long-term synaptic potentiation, which appears to play an important role in learning and memory. Thus, ethanol inhibition of NMDA receptors may explain cognitive defects and "blackouts" associated with intoxication and binge drinking.

Long-term exposure to ethanol causes an increased expression of glutamate receptors in the brains of alcoholic humans and synaptosomes from rats administered ethanol for two to three weeks. Recent evidence suggests that the increases also contribute to the generation of alcohol-withdrawal seizures (1).

2. ROLE OF CALCIUM CHANNELS:

Ethanol-induced changes in calcium channels may account for some of the signs and symptoms of ethanol withdrawal. Exposure to ethanol for several days increases depolarization-stimulated calcium chloride Ca uptake. Calcium flux remains elevated for several hours after the removal of ethanol and is associated with an increase in the number of binding sites for dihydropyridine calcium channel antagonists. Increases in dihydropyridine-sensitive calcium channels could induce withdrawal symptoms by promoting neurotransmitter release.

The importance of calcium channels in the pathogenesis of alcohol withdrawal syndromes is supported by evidence that calcium channel antagonists reduce the incidence of tremors, seizures, and death in alcohol-dependent mice and rats deprived of ethanol and reduce withdrawal symptoms in patients with alcoholism. Ethanol-induced stimulation of dihydropyridine binding sites is much greater in mice selectively bred for severe alcohol withdrawal seizures than in mice bred for mild signs of alcohol withdrawal. Therefore, the magnitude of alcohol withdrawal may be regulated by genetic factors that control the expression of dihydropyridine-sensitive calcium channels (1).

**How to differentiate hangover symptom from AWS:**

| Sign or Symptom | Alcohol Withdrawal | Hangover |
|---|---|---|
| Sign | | |
| Electroencephalography | Increased | Slowed |
| Auditory evoked response | Elevated | Normal to elevated |
| Hypertension | Common | Rare |
| Dehydration or orthostasis | Uncommon | Common |
| Cognitive impairment | Common | Common |
| Visual–spatial impairment | Common | Common |
| Symptom | | |
| Headache | Common | Common |
| Tremulousness | Very common | Occasional |
| Nausea | Uncommon | Common |
| Fatigue | Common | Common |
| Dry mouth | Uncommon | Common |
| Poor sense of overall well-being | Common | Common |

Data from reference (18).

**How to treat Alcohol withdrawal syndrome (AWS)**

The treatment of alcohol withdrawal syndrome is a combination of conservative and pharmacological therapy. This must be considered a medical emergency since this syndrome can have a deadly outcome for the patient.

The goal of treatment with benzodiazepines is to suppress symptoms and produce mild sedation. Generalized tonic-clonic convulsions can develop within one to two days after reducing or stopping drinking. Multiple seizures are common and usually occur over 6 to 12 hours; status epilepticus is unusual. Some attribute the development of seizures to ethanol intoxication, not withdrawal. But ethanol dependence is followed by withdrawal seizures in animals, and mice have been bred in the laboratory to have convulsions on ethanol withdrawal. Phenytoin is not useful in managing alcohol withdrawal seizures, but sedating doses of benzodiazepines are effective. Calcium channel antagonists may prove to be beneficial, but further study is needed.

Agitation, global confusion, insomnia, frightening hallucinations, and sympathetic hyperactivity characterize delirium tremens. These alarming manifestations develop abruptly several days after the occurrence of tremors and generalized hyperexcitability. This is a serious disorder, and associated electrolyte abnormalities, hyperthermia, and dehydration with circulatory collapse can be fatal. Therapy includes fluid replacement, the correction of associated electrolyte disorders such as hypokalemia and hypomagnesemia, and sedation with benzodiazepines (1).

# Prevention

The long-term treatment and prevention of alcohol dependence is best achieved by combining pharmacological agents with counselling. Research has shown that this combination leads to abstinent or at least significant reduction in alcohol use in approximately 30-50% of patients up to 2 years period from the start of intervention.

The most important factor is identification of the problem, the doctor or any other healthcare provider must upon suspicion ask the patient the CAGE questions.

The CAGE questions:

1. Have you ever tried to **C**ut down?
2. Have you ever been **A**nnoyed if somebody asks you about your drinking habits?
3. Have you ever felt **G**uilty about your drinking habits?
4. Do you feel like drinking **E**arly in the morning?

It is suggested that patient answering yes to one of these questions is a high risk patient. A successful identification can lead to helpful early intervention, namely:

- Provision of information concerning safe drinking level
- A recommendation to cut down when indicated
- Simple support and advice concerning associated problems

PSYCHOLOGICAL OPTIONS
Successful alcohol counselling involves motivational enhancement (motivational therapy), feedback, education about adverse effect of alcohol and agreeing drinking goals. A motivational approach is based on five stages of change: Precontemplation, Contemplation, Determination, Action and Maintenance. The therapist uses motivational interviewing and reflective listening to allow the patient to persuade himself along the five stages to change.

This technique, cognitive behavioural therapy and 12-step facilitation as used by AA (Alcoholics Anonymous), has all been shown to reduce harmful drinking. With addictive drinking, self-help group therapy, which involves the long-term support by fellow members of the group (e.g. AA), is helpful in maintaining abstinence. Family and marital therapy involving both the abuser and spouse may also be useful.

PHARMACOLOGICAL OPTIONS
(Naltrexone), the opioid antagonist reduces the risk of relapse into heavy drinking and the frequency of drinking. (Acamprosate ) is a drug that affects several receptors including those of GABA, noradrenaline and serotonin. There is good evidence that it reduces drinking frequency. (Disulfiram) reacts with alcohol to cause unpleasant acetaldehyde intoxication and histamine release, the acetaldehyde intoxication induces headache, nausea, vomiting etc. Trial has suggested that (Fluoxetine) a potent antidepressant drug belonging to SSRI group (Selective Serotonin Reuptake Inhibitor) is helpful in treatment of patients who have both a depressive illness and alcohol dependence (19,20).

# Conclusion

Due to its extreme reactivity, alcohol has the potential to affect virtually every organ or biochemical pathway in the human body including the liver, heart, reproductive organs, central nervous system, gastrointestinal tract, musculoskeletal system. The prevalence of some forms of cancer may also be influenced by chronic alcohol ingestion, and ingestion of alcohol may also exacerbate pre-existing cancer. These adverse changes arise because of the extreme biochemical or chemical reactivity of ethanol itself, or its reactive metabolite acetaldehyde. In addition ethanol exerts a negative impact on cell membranes which leads to cell damage. Alternatively, damage to cells or organs may arise as a result of the ensuing

secondary changes within the whole body, such as free radical generation or endocrine disruption. On the other hand there is some evidence which suggests that in moderate amounts, alcohol imparts a cardioprotective effect. This is questionable, however.

In addition to the biological effects of ethanol the psychological and socioeconomical effects are devastating for the patient in chronic alcoholism.

The prevalence of alcohol use has escalated and the age of first time drinkers has continued to decrease over the span of the century. This is a world wide problem, but differs significantly from one geographical area to another. The costs of alcohol related morbidity and mortality are enormous and is a burden for the already exhausted healthcare systems.

The aim is to change the negative trend and work in such ways as to reduce the overall consumption of alcohol. Since preventive measures are by far the cheapest option an enormous responsibility rests on our healthcare providers shoulders.

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