Alcohol metabolism: implications for nutrution and health

Patel, V.B. and Preedy, V.R.

Chapter 10: Alcohol Metabolism: Implications for nutrition and health

Vinood B. Patel & Victor R. Preedy

Objectives

By the end of this chapter, you should be able to:

- understand the varying intake of alcohol by different population and ethnic groups, and the contribution that alcohol makes to energy intake
- explain the main features, concepts and consequences of alcohol metabolism
- understand how alcohol damages virtually all organs in the body especially the liver
- describe the principle nutritional deficiencies in alcoholism

10.1 Introduction

The term alcohol is often interchanged with the primary alcohol, ethanol and less commonly with ethyl alcohol. In the following text the word alcohol and ethanol will be used interchangeably. The consumption of alcoholic beverages is generally termed "drinking" and dates back over 9000 years ago when humans began fermenting alcoholic beverages. Today they are the most widely consumed beverages in the world and a leading cause of disability, morbidity and mortality (WHO 2014). The oxidative metabolism of ethanol produces acetaldehyde and acetate, which are the current preferred names though there may be usage of systematic names, i.e., for acetaldehyde and acetic acid these would be ethanal and ethanoate, respectively. However, the inadvertent consumption of certain alcohols such as methanol or ethylene glycol can produce toxic oxidative products, formaldehyde and oxalic acid, respectively.

Individuals will have preference for consuming different types of alcoholic beverages, for example wine, lager, ale, cider, spirits or alcopops. However, some countries, regions within countries or communities forbid the consumption of alcohol on religious, cultural or moral grounds. Individuals may gain pleasure from the psycho-pharmacological effects of alcohol whereas others may react quite badly, with flushing, nausea and palpitations due to a genetic variation in alcohol- or acetaldehyde-metabolising enzymes, producing high levels of acetaldehyde. Acute and chronic consumption of alcohol may cause malnutrition or act as a toxin and induce pathological changes in a variety of organ and tissues, such as the liver, brain, muscle, gut. By contrast, a proportion of individuals

consume moderate amounts of alcohol (1 to 2 drinks/day), comprising up to 5% of total dietary energy, and some data suggests that moderate alcohol consumption may be beneficial in reducing cardiovascular disease. However, some argue that its beneficial effect may be controversial or outweighed by its detrimental effects. Recent guidelines under review suggest the cardioprotective effect is minimal or negligible (Department of Health, 2015) and limited to women over the age of 55. Thus, it is important to take a balanced view of ethanol's effects.

Guidance on the Consumption of Alcohol by Children and Young People from the Chief Medical Officers of England, Wales and Northern Ireland has suggested that children under 15 should not drink alcohol due to a range of damaging consequences. A common feature of excessive alcohol consumption is vomiting and coma with cognitive impairment as a result of long term usage. Alcohol will lead to a lack of inhibitions, causing increased risk of drink driving accidents, crime, and risky sexual activity. Furthermore women who are pregnant or about to become pregnant should avoid heavy alcohol consumption particularly in the 1st trimester as this can lead to neurological dysfunction such as that observed in foetal alcohol syndrome disorders and low birth weight. Pregnant women should not consume more than one or two units once or twice a week or avoid drinking altogether (Department of Health 2015). Drinking alcohol whilst breast feeding should be avoided as breast milk will contain traces of alcohol and smell differently, thus affecting the baby’s nutritional intake and/or feeding patterns.

The chemical nature of alcohol

In chemistry terms an alcohol is any organic compound with a functional hydroxyl group bonded to a carbon chain. As a consequence of its combined polar (OH group) and non-polar (C_2H_5 groups) properties, and because it is relatively uncharged, ethanol is miscible with water and can cross cell membranes by passive diffusion. It has the ability to dissolve lipids, such as biological membranes and can act as a solvent for many organic compounds. Ethanol is produced from glucose via the fermentation of yeast to produce ethanol, carbon dioxide and ATP. The source of carbohydrate (glucose) dictates the type

of alcoholic beverage. For example, beer is fermented from barley, wine from grapes, cider from apples.

<Figure 10.1>

The immediate metabolite of ethanol oxidation, acetaldehyde (**Fig 10.1**), is a highly toxic and chemically reactive molecule that can bind irreversibly with proteins, DNA, RNA and other molecules. The products are called adducts. Acetaldehyde is involved in liver disease pathology, where formation of acetaldehyde-protein adducts induces an immunological reaction. Readers are referred a Novartis (formally CIBA) special publication for additional reading (Novartis Foundation Symposium and Novartis 2007). Acetate, the product of acetaldehyde metabolism, is either oxidised peripherally to CO_2 in the Krebs (citric acid) cycle or used for synthesis of fatty acids and triglycerides. Acetate *per se* also has some biological activity e.g., it dilates resistance and capacitance blood vessels. It is also thought to affect mitochondrial fatty acid oxidation, reducing ATP levels. Finally, in illicit or home brewed beverages and even in some commercially available beverages, there may be significant quantities of compounds that have putative toxic properties, i.e., congeners. These include diethylene glycol, acetaldehyde, acetone, methanol and butanol.

The contribution to the energy intake of different population groups

Energy content of alcoholic beverages and the Unit system

The chemical energy content of ethanol is 29.7 kJ (7.1 kcal) per g. In the UK, an alcoholic drink or "Unit of alcohol" contains 10 mL of ethanol by volume and is equivalent to 8 g of ethanol (**Table 10.1**). However, there remains wide international variation in the amount of alcohol in a standard drink (from 7-14 g ethanol) as not all countries use the Unit system (**Table 10.1**). The alcohol concentration of beverages can vary from 0.5% (v/v) for low alcohol beers to 35-50% (v/v) for distilled spirits such as vodka or whisky (**Table 10.2**). A Unit of alcohol (10 mL or 8 g) of alcohol, is equal to a 125 mL glass of wine containing 8% alcohol by volume or half a pint of 'ordinary' strength beer containing 3.5% by volume. However, alcohol sold in UK pubs for most beers is around 4% to 5% (2.3 Units and 3 Units respectively, per pint), whereas a can of lager/beer/cider (440 mL) is 2 Units. Wine is often sold as medium (175 mL) or large

(250 mL) servings, containing around 13% by volume (equating to around 2.3 and 3.3 Units, respectively).

<Table 10.1>

<Table 10.2>

Recommended limits for alcohol consumption

New proposed guidelines (Department of Health, 2015) by the UK Chief Medical Officers, have recommended alcohol consumption of no more than 14 Units/week for both men and women. Furthermore, the 14 Units should be spread evenly over 3 days or more, and to include alcohol free days for heavy drinkers. This new advice is in contrast to previous maximal amounts recommended by the Royal College of Physicians, of 21 Units/week for men and14 Units/week for women. Previous Governmental guidelines were based on maximum daily amounts, i.e., no more than 3-4 and 2-3 Units per day for men and women, respectively (**Table 10.3**).

<Table 10.3>

The Health Survey for England reported that in 2014, 28.9 million people (58% population) drank alcohol in the previous week of the survey; 12.9 million people drank more than 4 units in the previous week and 2.5 million drank more than 14 Units in a single day. Binge drinking which is a hazardous form of alcohol consumption is classified as consuming >8 Units/single session or >4 Units/single session for men and women, respectively. Taking the adult population as a whole, about 22% of males and 16% of females in the UK drink more than 21 or 14 Units per week, respectively, with this rate declining slightly over recent years (**Table 10.4**). Around 9 million people are drinking harmful levels of alcohol, with at least 2 million people dependent on alcohol. The National Health Service (NHS) estimates that around 9% of men in the UK and 4% of UK women show signs of alcohol dependence.

<Table 10.4>

There are ethnic variations in the extent of alcohol consumption, with 25% of Caucasian men drinking more than 21 Units/week, compared to 6% for Asian or Black men. For women, the same ethnic patterns are seen as in men.

The extent of alcohol misuse can be measured in a number of ways that is either in terms of weekly or daily guidelines. In terms of weekly guidelines 63% and 62% of men and women, drink at the lower risk levels of 21 and 14 units per week, respectively (Fuller 2015). In contrast, 22% of men and 16% of women drink more than the 21 or 14 units per week, respectively (Fuller 2015).

There are also age-related changes in drinking patterns and this may also reflect sociological and demographic changes in the elderly population. It is reported that drinking more than 21 Units a week is more common in the 65 to74 age group. In women, the highest prevalence of drinking more than 14 Units a week is in the 55 to 64 age group, where approximately one fifth exceeded the guidelines (Fuller 2015). However, different patterns emerge if alcohol misuse is considered in terms of daily amounts. In terms of drinking more than 4 or 3 Units a day, for men and women, respectively, then a greater proportion of the younger population exceeds the daily guidelines compared to the more elderly (Fuller 2015).

Recent trends have shown more people are teetotal (15% of men and 21% of women) (Fuller 2015) and binge drinking decreasing slightly in recent years (Statistics on Alcohol for England 2015). However, there are regional (North versus South) and country variations (i.e., England vs Scotland). Data obtained from surveys tend to underestimate alcohol consumption. As a result seven day drinking diaries are being used to assimilate data by Health Survey England in conjunction with one-off surveys.

Drinking in the young and gender susceptibility

The results of a UK survey (Smoking, drinking and drug use among young people in England 2013) continued to show an overall decreasing trend for “drinking for the first time” (39% in 2013, compared to 61 % in 2003) and drinking in the last week (9% in 2013, compared to 25% in 2003) in children aged 11-15. However, about 70% of 15 year olds have reported drinking for the first time, compared to 9% for 11 year olds. The mean Units/week consumed by 15 year old boys and girls is approximately 9 Units and 8 Units, respectively.

Drinking by school children and adolescents has at least six serious consequences: (a) alcohol poisoning and fatalities; (b) drinking in formative years will predict the extent of alcohol misuse or dependency later on; (c) drinking may be compounded by polydrug and other substance misuse including tobacco; (d) total lifetime intake of alcohol, rather than recent intakes, is a good predicator of alcohol-related harm (Saunders and Devereaux 2002); (e) tissues in the young are particularly sensitive to alcohol; (f) there is an association of underaged or unsupervised dinking with poor academic performance and crime.

Men consume higher amounts of alcohol than women (**Tables 10.4, 10.5)** but women are more susceptible to alcohol-induced injury such as cardiomyopathy, skeletal muscle myopathy, brain damage and liver disease. This may be related to lower clearance rates of alcohol on "first pass metabolism", as a consequence of either smaller liver size, differences in gastric alcohol metabolising enzymes, endocrine factors, body fat composition or even psycho-social factors in reporting alcohol consumption. Compared with men, women also have higher blood acetaldehyde levels following the same amount of alcohol per unit body weight. It has been estimated that whilst men will show an increased chance of developing liver disease at an intake rate of 40-60 g ethanol/day, the threshold level for women is lower at 20 g/day. A comprehensive analysis of the vulnerability of women compared to men has been reviewed and readers are referred to this work (Fernandez -Sola et al., 2005).
(**Table 10.5**)

Energy and micronutrient content of alcoholic beverages

As mentioned earlier one Unit contains 8 grams of ethanol, which is equivalent to ten mL of ethanol and thus provides 234 kJ (56 kcal). This can underestimate the true energy content of alcoholic drinks since they also contain constituents, such as unfermented carbohydrates, amino acids and fatty acids (see **Table 10.2;** Foods Standards Agency 2002) or when combined with "mixers"(carbonated beverages) or fruit juices. Depending on the alcoholic beverage, the energy composition varies from about 126-921 kJ (30-220

kcal) /100 mL. Low or zero alcohol beverages will as expected have a lower energy content although this is compensated with a higher carbohydrate content. Alcoholic beverages will also contain trace amounts of compounds that imparts flavour or characteristics of taste and smell, e.g., aliphatic carbonyls, other alcohols, monocarboxylic acids, sulphur containing compounds, tannins, polyphenols or minerals.

Ethanol's contribution to energy in the diet

The mean daily intake of alcohol in all men (19-64; consumer and non-consumers) is 18.5 g (553 kJ or 131 kcal) (29.2 g for just consumers; 868 kJ or 207 kcal) and 10.1 g (301 kJ or 72 kcal) for all women (19.2 g for just consumers; 571 kJ or 136 kcal) (National Diet and Nutrition Survey, 2014). Consideration must be taken of the non-alcoholic energy contained within the beverages as mentioned above.

Most of the consumption of alcohol in the UK is in the form of beer (men) and wine (women) (**Table 10.5**). Overall (i.e., in alcohol consumers and non-consumers) the contribution of ethanol to total energy intake in the 19-64 age group is reported to be 5.6% in men and 4.1% in women, respectively (National Diet and Nutrition Survey, 2014). In consumers, the corresponding contributions are 8.9% and 7.8%, respectively (National Diet and Nutrition Survey 2014).

However, the contribution of ethanol-derived calories is significant in dependent alcoholics. In one study, patients attending an inner city Alcohol Misuse Clinic in the UK consumed on average 160 g ethanol/day; contributing to about 60% of dietary energy intake. However, as mentioned before, alcohol consumption reporting is subject to errors. For example, underreporting is known to be commonly prevalent in all self-reporting methods (Awoliyi et al., 2014). No food frequency questionnaires have been unequivocally validated in alcohol misusers. Typical patients with chronic liver disease may consume 160-250 g ethanol/day (1140-1770 kcal/day). This has nutritional consequences as ethanol may be perceived as being "empty," i.e., having negligible or minor quantities of micro- or macronutrients. High ethanol loads also impairs the normal function of the liver and damages the intestinal tract (**see section 10.3**).

There is now growing evidence that excessive alcohol intake increases the risk of type II diabetes. Consuming five or six alcoholic drinks per day raises the risk by between 15% and 75%, with women at greater risk. The relationship between alcohol consumption and obesity is controversial and may relate to gender, genetic and dietary factors as well as the levels of alcohol consumed. Obesity is not apparent in all alcoholics but in some subjects who consume moderate to high amounts of alcohol, obesity may increase. Some of this effect may be related to appetite. For example, in one study dietary intake following ingestion of 32 g of alcohol was 5786 kJ (1385 kcal) versus 4928 kJ (1179 kcal) when 8 g of alcohol was consumed.

Systemic negative consequences of chronic alcohol ingestion.

There are as many as 200 different alcohol-related disorders or injuries (**Table 10.6**; Preedy and Watson 2005; WHO 2014) affecting the whole body. Many of the deleterious effects relate in some way to ethanol metabolism, altering cellular biochemistry either because of ethanol *per se*, or its immediate metabolite, acetaldehyde. Approximately 10-15% of chronic alcohol misusers will have cirrhosis and 30% will have gastrointestinal pathologies (**Table 10.7**). In terms of the gastrointestinal tract, all regions can be affected from the mouth to the rectum. For example, oral mucosal lesions have be shown to occur in as much as 28% of chronic alcoholics. The relative risk of rectal cancers increases about four fold in chronic alcohol misusers. Fatty liver will occur in 80% of chronic alcoholics and 50% will have bone marrow changes (perturbing red blood cell morphology). Half of chronic alcoholics will have damaged skeletal tissue (osteoporosis, osteopenia, fractures including post-fracture malunion) whereas between 20-30% will exhibit a spectrum of subclinical or clinical cardiac abnormalities (i.e., alcoholic cardiomyopathy) or other cardiovascular diseases including hypertension. A staggering 80% of subjects will have skin lesions including those of vascular, fungal, bacterial or viral origins and 40-60% will have alcoholic myopathy. Abnormal gonadal function will occur in 50% of male alcoholics.

As a rule of thumb, 50% of chronic alcohol misusers will have one or more organ or tissue abnormalities (**Table 10.8**). In England, in 2013 there were 8,416 alcohol-related deaths, of which the majority is due to alcoholic liver disease (**ONS, 2015**). Globally approximately 3.3 million (5.9 % of all deaths) are alcohol related (**WHO, 2014**). There is however under-reporting of alcohol related illnesses and conditions.

<Table 10.6>

<Table 10.7>

<Table 10.8>

Very often dependent drinkers smoke cigarettes or tobacco related products, i.e. they are addicted to nicotine and this has a greater effect on the development of disease than either addiction alone. This is particularly relevant with respect to cancers of the upper aerodigestive tract, and these synergistic effects of smoking and drinking have also been seen in the development of cirrhosis, possibly due to toxic metabolites of nicotine processed in the liver. The advent of smokeless cigarettes i.e., e-cigarettes, or vaping is a relatively new phenomena but there is little research on this in relation to alcohol consumption. However, one study showed a positive correlation between e-cigarette usage and the extent of alcohol consumption.

In Europe and the Americas, between 15-55% of people attending hospital (as either inpatients or outpatients) or primary care centres are classified as dependent or hazardous alcohol abusers. However, fewer than 5% of adults have such misuse or dependency recorded in their medical records. Prevalence rates of alcohol misuse will depend on geographical and socio-economic factors. In London (UK), a third of all acute hospital admissions are alcohol related and the prevalence of alcohol misuse in in-patients in city hospitals may be as high as 50%. In fracture clinics, 40-70% of patients score positively for alcohol-related dependency or abuse syndromes. Overall in 2014 there were over 1.5 million NHS admissions to Accident and Emergency (A & E) Departments due to alcohol consumption placing a financial burden of £3.5 billion on the NHS. This compares to the overall cost of £21 billion to the UK economy as a consequence of alcohol misuse as it not only affects health but societal factors (police, judiciary, social departments etc).

Questionnaires of alcohol misuse and impact on health.

There are several questionnaires designed to detect alcohol misuse. These questionnaires have been well validated and include The Alcohol Use Disorder Identification Test (AUDIT) Michigan Alcohol Screening Tool (MAST), Cut, Annoyed, Guilty, Eye-Opener (CAGE), Paddington Alcohol Test (PAT), Severity of Alcohol Dependence Questionnaire (SADQ) and other questionnaires. Currently the gold standard is perceived to be the AUDIT questionnaire due to its wide applicability, translation into different languages and international usage. In some circumstances these can be more useful than laboratory tests on serum, plasma, urine or saliva. However, these questionnaires do not give precise information on the amount of alcohol consumed.

Alcohol Metabolism

Many of the pathologies associated with excessive alcohol consumption are due to the damaging effects of acetaldehyde, and molecular and cellular metabolic changes (e.g., DNA methylation, redox state, anti-oxidant or endocrine status) associated with ethanol oxidation (**See Figure 10.1** for a scheme of ethanol metabolism). All biochemical pathways and cell structures have the potential to be targeted by ethanol or its related metabolites. Central to these effects is the liver, where 60-90% of ethanol metabolism occurs. Up to 90% of the substrates utilised in conventional metabolic pathways in liver may be displaced by ethanol oxidation. Ethanol ingestion can inhibit protein and fat oxidation in the body by approximately 40 and 75%, respectively. The 2.5- fold increase in oxidation of carbohydrate after a glucose load is also abolished by ethanol. Oxidation of ethanol by *gastric first pass metabolism* will account for 5-25% of ethanol oxidation and 2-10% of ingested ethanol will appear in the breath, sweat or urine.

The metabolic fate of alcohol following digestion and absorption.

Ethanol is rapidly absorbed, primarily in the upper gastrointestinal tract and appears in the blood as quickly as 5 min after ingestion. Its distribution will approximate total body water. Its elimination thereafter will approximate to Michaelis-Menten kinetics though zero-order elimination kinetics have also been described. Blood alcohol levels depend on

pathophysiological factors, such as absorption rate, *first pass metabolism*, the extent to which liver function has been altered and blood flow. The rate at which alcohol is oxidised, or disappears from the blood, varies from 6 to10 g per hour. This is reflected in plasma levels, which falls by 9-20 mg/100 ml/ hour. In response to a moderate dose of alcohol of 0.6-0.9 g/kg body weight, the elimination rate from the blood is approximately 15 mg/100 ml blood/ hour on an empty stomach though there is considerable individual variation.

Food in the stomach will delay the absorption of alcohol and blunt the peak blood alcohol concentration. The peak blood levels are the points at which the rate of elimination equals the rate of absorption. Using a standard dose of ethanol/kg body weight, it has been shown that the peak is lower after a meal compared with an empty stomach. The time to metabolise the alcohol was 2 hours shorter in the fed state than the fasted state, indicative of a post-absorptive enhancement of ethanol oxidation which can be as much as 35-50% (Jones 2000).

The type of food taken with alcoholic beverage will also alter the peak ethanol level: after a standard dose of ethanol of 0.3 g/kg, meals rich in fat, carbohydrate and protein results in peak ethanol levels of 16.6, 17.7 and 13.3 mg/100 ml, respectively (Jones 2000). Part of this variation may be due to increased portal blood flow in response to feeding which will essentially deliver more ethanol to the liver for oxidation.

The concentrations of ethanol in beverages will also influence peak blood concentration. Thus, in the fed state for a given amount of ethanol, a lower peak level is obtained with high concentrations compared with the equivalent amount of ethanol in a more dilute beverage. In fasted subjects, high and low ethanol concentrations give similar blood alcohol concentrations and areas under the curve. For example, in the fed state, beer produces higher peak blood levels compared to whisky for a given alcohol load. In the fasted state, beer produces lower mean blood alcohol concentration and areas under the curve than whisky (Roine 2000). These differences are related to one of the primary determinants of alcohol metabolism: namely the rate of gastric emptying. In simple

terms, the small intestine is the main site of ethanol absorption and food will have little effect on large volumes of ethanol-containing liquid (beer) compared to smaller volumes of high-ethanol containing liquids (whisky) (Roine 2000).

First pass metabolism and the contribution of the stomach

First pass metabolism is principally due to the liver (*hepatic first pass metabolism*), but a small proportion of alcohol is also metabolised by the stomach (*gastric first pass metabolism)*. Stomach ADH (called sigma-ADH) is a different isoform from the enzyme in the liver (**Table 10.9**). Physiological factors that influence gastric emptying will also influence the contribution of this pathway to ethanol elimination. In one study, where ethanol (0.3 g/kg body weight) was administered by different routes, it was calculated that the amount of ethanol absorbed (0.224 g/kg body weight) was 75% of the administered dose: the difference being ascribed to first pass metabolism. The rate of gastric ethanol metabolism has been reported to be about 1.8 g of ethanol per hour (Haber 2000). Reduced first pass metabolism and/or reduced gastric ADH will occur in *Helicobacter pylori* infection and during histamine H2-receptor antagonist therapy. There are also ethnic differences: those of East Asian origin have a lower stomach ADH/first pass metabolism compared with Caucasians. Chronic alcoholism reduces the capacity of this gastric route of ethanol oxidation due to the development of gastritis (which is an inflammation of the stomach).

Gender differences in alcohol metabolism

As above mentioned above, there are gender differences in the rate of ethanol elimination rates ascribed to first-pass metabolism. The activity of gastric ADH in women is also lower than in men, though this is less apparent in women over 50 years old. Compared with men, women will have higher blood ethanol levels after an equivalent load. The lower first-pass metabolism activities account for the higher ethanol levels in women, lower blood volume, and more body fat, rather than differences in gastric emptying or rate of ethanol oxidation in the liver. It has however, been proposed that women and men have comparable peak blood alcohol concentrations when dosage is based on total body water.

The speed with which alcohol is distributed in body water

Alcohol is rapidly distributed around the body as it cannot be stored. After ingestion, alcohol that is not immediately absorbed traverses the gastrointestinal tract. Very high ethanol levels occur in the small intestine compared with serum. Effectively, there is a gradient down the gastrointestinal tract. For example, a dose of 0.8 g ethanol/kg body weight (equivalent to 56 g ethanol =7 Units = 3.5 pints of ordinary beer (3.5% v/v), consumed by a 70 kg male) will result in blood ethanol levels of 100-200 mg/100 ml between 15-120 min after dosage. Maximum blood concentrations occur after about 30-90 min. Gastric levels of ethanol peak at 8 g/100 ml of luminal contents, jejunal levels are approximately 4 g/100 ml compared to approximately 0.15 g/100 ml in the ileum. Levels in the ileum reflect serum levels, i.e., from the vascular space. After about 2 hours, ethanol concentrations in the stomach and jejunum will approximate levels in serum (Mezey 1985). In the post-absorption phase, the distribution of alcohol in the body will reflect body water to the extent that, for a given dose of alcohol, blood levels will reflect lean body mass. The solubility of ethanol in bone and lipid is negligible. Whole blood levels (which includes plasma and cellular contents) of ethanol are about 10% lower than plasma levels because red blood cells have less water than plasma.

Metabolism by alcohol and aldehyde dehydrogenases and other routes

Alcohol is oxidised to acetaldehyde by three major routes (**Figure 10.1**), namely: (i) ADH (alcohol dehydrogenase; cytoplasm; (ii) MEOS, (microsomal ethanol oxidising system; endoplasmic reticulum) and (iii) catalase (peroxisomes). There are at least 6 classes of ADH and oxidised substrates include steroids and some intermediates in the mevalonate pathway as well as fatty acid ß-oxidation and retinoids (**Table 10.9;** Lieber 2000).

Alcohol metabolism via ADH leads to excess production of the reducing equivalent NADH, so that the $NADH/NAD^+$ ratio increase, with a corresponding rise in the lactate/pyruvate ratio. The metabolism of acetaldehyde to acetate via aldehyde dehydrogenase (ALDH; principally in the mitochondria), also produces NADH, so

exacerbating the elevated ratio. Changes in the cellular (via ADH) or mitochondrial (via ALDH) redox state may explain metabolic abnormalities in alcoholism such as: hyperlactacidemia, hyperuricemia, increased lipogenesis, decreased mitochondrial beta-oxidation of fatty acids, hypoglycaemia, reduced glycolysis and disturbances in the tissue responsiveness to hormones. Other contributing abnormalities include free radical damage, lipid peroxidation, iron dysregulation, adduct formation, DNA damage, epigenetic modulations, altered gene expression, apoptosis, necrosis, perturbed proteolytic cascades, translational defects, hypoxia, Kupffer cell activation, altered antioxidant status, membrane changes and alterations in cellular trafficking (Patel 2016). Extrahepatic tissues, e.g., mouth, oesophagus, duodenum, jejunum, rectum and muscle, also contain ethanol metabolising enzyme leading to localised damage.

Ethanol oxidation via peroxisomal catalase is a minor pathway and requires the concomitant presence of a hydrogen peroxide (H_2O_2) generating system (See **Figure 10.1).** When there is an increase in H_2O_2 generation, e.g., from the oxidation of long chain fatty acids in the peroxisomes, or increased mitochondrial hydrogen peroxide production, there may also be an increase in catalase-mediated ethanol oxidation.

The metabolite acetaldehyde is oxidised to acetate via NAD^+-dependent aldehyde dehydrogenase (ALDH). As with ADH, there are several classes of ALDH (**Table 10.10**). ADD GENE SENTENCE Of these the mitochondrial ALDH2 is the important in terms of alcohol related pathology. The location of ALDHs in extrahepatic tissues such as heart may be protective whereas lower levels in brain may explain the vulnerability of CNS tissues in alcoholism (Kwo and Crabb 2002).

< Table 10.10>

Acetaldehyde itself is a highly reactive toxic metabolite. As mentioned earlier, some acetaldehyde becomes bound to cellular constituents such as proteins, lipids and nucleic acids generating harmful adducts. Adduct formation not only changes the biochemical characteristic of the target molecule but the new structure may also be recognised as foreign (i.e., a neoantigen) thus initiating an immunological response (Novartis 2007).

Gene polymorphisms or ethnic variations in ADH and ALDH enzymes may explain some of the pathologies of alcoholism, and why some individuals will develop certain diseases when others do not. About 50% of East Asian origin populations (Taiwanese, Han Chinese, and Japanese) have a deficiency of ALDH2. After alcohol consumption this results in an elevation in acetaldehyde levels causing visible facial flushing (see section of facial flushing). The modified allele is designated ALDH2*2 (which has little or no metabolising activity is designated rs671 where rs is the reference SNP number) whilst the (normal) fully functional gene is ALDH2*1. If individuals with low ALDH activity continue to consume alcohol, then the high acetaldehyde levels will induce greater tissue damage. This has also been shown experimentally when agents such as cyanamide (an inhibitor of ALDH activity) can cause greater metabolic perturbations in alcohol exposed tissues.

Whilst considerable work has been carried out into polymorphisms of the ALDH2 gene, most of its relevance pertains to those of East Asian origins rather than Caucasians. Nevertheless, work has been carried out on polymorphisms relating to ADH genes (Tolstrup et al 2008). These studies show that those with fast metabolising polymorphisms (thus producing acetaldehyde levels much quickly) are less likely to be hospitalised due to the effects of alcohol, drink less and score lower on alcoholism screening tests (Tolstrup et al 2008).

Two minor but important non-oxidative pathways of ethanol metabolism result in the formation of phosphatidylethanol and fatty acid ethyl esters (FAEE) (Laposata 1998). FAEE are formed from fatty acids and ethanol in reactions catalysed by either cytosolic or microsomal FAEE synthase. In the former reaction, the immediate precursor is fatty acid, whereas the microsomal pathway utilises fatty acid CoA. The FAEE are broken down by a cytosolic hydrolase or may traverse the membrane into the intravascular space. Phosphatidylethanol is formed in a dose and time-dependent manner when ethanol becomes the polar group of a phospholipid in a reaction catalysed by phospholipase D. It is found in blood of alcoholics and due to its low metabolism, in organs exposed to ethanol, including liver, intestines, stomach, lung, spleen and muscle.

Phosphatidylethanol and FAEE are cytotoxic and may perturb protein synthesis and cell-signalling due to reduced phosphatidic acid production. FAEE have previously been used as a diagnostic biomarker of alcohol consumption.

Induction of microsomal cytochromes following repeated ingestion of alcohol

The MEOS is particularly important in heavy ethanol ingestion as it is an inducible pathway of ethanol metabolism. It is thus of particular significance in chronic ethanol misusers where the existing enzymes become saturated and unable to cope with the high ethanol load. The purified protein of MEOS is commonly referred to as cytochrome P450 2E1 (CYP2EI or 2EI) (although 1A2 and 3A4 are involved, see Zakhari (2006)), and its induction is due to increases in mRNA levels and its rate of translation. Acute bouts of alcohol exposure can also lead to CYP2E1 induction as well. The MEOS system utilises NADPH (**Figure 10.1)** and produces free radicals (hydroxyethyl, superoxide anion, and hydroxyl radicals), leading to increased cellular oxidative stress, particularly the endoplasmic reticulum. The MEOS has a higher K_m for ethanol (8-10 mmol/L) compared with ADH (0.2 to 2.0 mmol/L).

The metabolic basis for 'fatty liver' of chronic alcohol ingestion

Alcoholic liver disease has three consecutive stages, namely fatty liver (steatosis), alcoholic hepatitis with fibrosis, and cirrhosis, though fatty liver may progress directly to cirrhosis (Patel 2016). The ability of the liver to develop steatosis in the presence of low fat diets has led to the hypothesis that the *de novo* synthesis of triacylglycerols may arise via increases in fatty acid synthesis in the liver. Fatty liver is clinically diagnosed when the lipid content of the liver is 5-10% by weight. As mentioned earlier it occurs in about 80% of chronic alcohol misusers and is usually asymptomatic but many pro-inflammatory pathways are initiated, and with continued alcohol consumption can lead to steatohepatitis. At this stage, patients are at significant risk and may be hospitalised. In many cases of acute alcoholic hepatitis, the mortality rate is up to 35%, with a mortality rate at one month of 20%. Fatty liver, however, is not itself fatal and occurs in a variety of other conditions such as hyperlipidemia/obesity associated with insulin resistance. The biochemical features of alcoholic fatty liver are distinct from other non-alcohol fatty

liver pathologies such as those due to diabetes, reflecting their different aetiologies. However, histologically ALD is similar to diet induced non-alcoholic fatty liver disease.

Increased fatty acids in the liver present a greater biochemical "target" for the free radicals generated as a consequence of alcohol metabolism. This leads to peroxidation of fatty acids within the liver, generating lipid peroxides, malondialdehyde and 4-hydroxynonenal, which in turn can form aldehyde-protein adducts, i.e., malondialdehyde-protein adducts and 4-hydroxynonenal-protein adducts. As with acetaldehyde-protein adducts, the lipid derived protein adducts are immunogenic, promoting inflammation. The lipid in affected liver is largely triacyglycerol, which may increase between 10-50 fold; there is also a less marked increase in esterified cholesterol. Various metabolic pathways are altered leading to the development of fatty liver. These include downregulation of peroxisome proliferator-activated receptor alpha, decreased AMP-activated protein kinase activity, leptin dysregulation, and these mechanism are covered more comprehensively in Patel (2016).

Lactic acidosis resulting from alcohol ingestion.

The increased NADH/NAD^+ ratio following alcohol metabolism increases the lactate/pyruvate ratio leading to lactic acidosis in alcoholics, whereas poor nutrition/starvation, dehydration, depleted glycogen stores and increased free fatty acids in the liver promotes the ketogenic pathway producing the predominant ketone body, ß-hydroxybutyrate. These effects can cause the blood pH to fall to 7.1, and hypoglycaemia may occur. In severe cases of ketoacidosis and hypoglycaemia permanent brain damage and death may arise. However, the prognosis of alcoholic acidosis is generally good. These conditions may be exacerbated by thiamin deficiency and indeed thiamin deficiency *per se* may hasten acute episodes of lactic acidosis. The high concentration of lactic acid also impairs the kidney's ability to excrete uric acid and consequently blood uric acid levels rise (hyperuricemia), causing gout.

10.3. Toxic effects of chronic alcohol ingestion

Alcohol ingestion leads to the release of catecholamines and steroid excess

Alcohol causes increased activation of the sympathetic nervous system, with increased circulating catecholamines secreted by the adrenal medulla. Increased circulating cortisol from the adrenal cortex can, very rarely, lead to a pseudo-Cushing's syndrome with symptoms of moon face, truncal obesity and muscle weakness. These changes in circulating catecholamines and cortisol have been considered to cause some of the pathology of alcoholism, but contribute little to the major complications such as myopathy, cardiomyopathy and alcoholic liver disease.

Alcoholism also affects the hypothalamic-pituitary-gonadal axis, and these effects are further exacerbated by alcoholic liver disease. There are conflicting data regarding the changes observed. Plasma testosterone is either normal or decreased in men, and increased in women, with oestradiol levels being increased in both men and women, and rising with worsening liver disease. The production of sex hormone-binding globulin is also perturbed by alcohol, complicating the picture further. In women, these changes can cause decreased libido, disturbances in menstruation and early onset of menopause. Feminization of males, with gynecomastia and testicular atrophy tends to occur only after cirrhosis begins, and is more severe in alcoholic compared to non-alcoholic cirrhosis. Sexual dysfunction is also common in men with reduced libido and impotence. Fertility may also be reduced, with decreased spermatozoa count and motility. It is worth remembering that alcohol misuse can affect virtually every endocrine axis (Rachdaoui and Sarkar 2013).

Symptoms of excess alcohol intake

Alcohol has immediate effects on the central nervous system. These are dose dependent and begin with the so-called social modulating effects of alcohol, including increasing cheerfulness, loss of inhibitions and impaired judgement. Heavier consumption leads to agitation, slurred speech, loss of memory, with double vision and staggering. This may then progress to a depressed level of consciousness. This is of particular concern in emergency departments as when people present drunk with a depressed level of consciousness and a head injury, it can be difficult to determine whether there is co-existent pathology such as an extradural haematoma. A good rule of thumb is not to

assume that alcohol is solely responsible for any disturbance in consciousness. Ultimately loss of airway control may occur, with danger of suffocation or aspiration of vomitus and ultimately death. There is a great disparity in the effects of alcohol between individuals. This is due to varying effects of alcohol on the body, and differences in the metabolism of alcohol and products of its metabolism, including acetaldehyde.

Acute effects of alcohol on the cardiovascular system involve both the heart and the peripheral vasculature. Peripheral vasodilation causes a sensation of warmth. Although this can be interpreted by the subject as being warmer, it can be dangerous, especially in cold weather or when swimming, as heat loss is rapid but lack of awareness leaves people vulnerable to hypothermia and possibly death. Cardiac effects are usually in the form of arrhythmias, in particular atrial flutter and atrial fibrillation. These can occur whilst intoxicated or after drinking too much (i.e. the 'holiday heart' syndrome), although there is also an increase in the prevalence of these arrhythmias occurring chronically in those that have a moderate to heavy alcohol intake. This association has been demonstrated in men, but there is evidence of an association with only moderate alcohol use in women. The direct effects of alcohol on heart muscle leads to cardiomyopathy.

Effects of alcohol on skeletal muscle

Alcoholic myopathy is common, affecting 40-60% all chronic alcohol abusers, and is a major cause of morbidity. It is characterised by muscle weakness, myalgia, muscle cramps and loss of lean tissue; up to 30% of muscle may be lost. Histological assessment correlates well with symptoms, and shows selective atrophy of Type II muscle fibres. Reductions in muscle protein and RNA, with reduced rate of protein synthesis, also occur. Rates of protein degradation appear either unaltered, reduced, or increased depending on the degradation pathway investigated. Recently attention has focused on a role for free radicals in the pathogenesis of alcoholic myopathy. Cholesterol hydroperoxides are increased in alcohol-exposed muscle implying membrane damage.

Effects of alcohol on facial flushing

As mentioned previously, after consuming alcohol facial flushing of the skin is seen in approximately 40% of East Asians due to the deficiency of ALDH2. There is an accumulation of circulating acetaldehyde, with plasma levels around 20 times higher in people with this deficiency. Acetaldehyde causes increased vasodilation of blood vessels with patchy erythematous rash on the trunk and arms; individuals also feel nauseous. Flushing only rarely occurs in Europeans (<5%) and is due to other mechanisms of unknown aetiology. Acetaldehyde acts partially through catecholamines, although other mechanisms have also been implicated, including the involvement of histamine, bradykinin, prostaglandin and endogenous opioids as well as adduct formation. Administration of aspirin has been shown to block the facial flushing response in some people, implicating a role for prostaglandins. Use of naloxone (an opioid antagonist) has also been shown to reduce flushing in people in whom cyclo-oxygenase inhibitors had an effect, implicating an interaction between endogenous opioids and prostaglandins.

Effects of alcohol on dehydration.

Ethanol affects hypothalamic osmoreceptors, reducing antidiuretic hormone release, so causing reduced salt and water reabsorption in the distal tubule. This results in polyuria and may cause dehydration, especially in spirit drinkers who do not consume much water with their alcoholic drinks. A loss of hypothalamic neurones secreting antidiuretic hormone has also been described in chronic alcoholics, suggesting long term consequences for fluid balance. Increased plasma atrial natriuretic factor after alcohol consumption may also contribute to this diuresis and resultant dehydration.

Effects of alcohol on liver function

The pathological mechanisms leading to cirrhosis occurs are complex, and are still the subject of intensive research. Fatty changes, as described earlier, arises with micro- and macrovesicle fat droplets and is generally asymptomatic. This can be detected on ultrasound, CT, MRI or fibroscan, and is associated with abnormal liver function tests (e.g., raised activities of aminotransferases in serum), although these have low diagnostic sensitivity (50-70%). Ethanol metabolism by both the MEOS and ADH pathways leads to excess free radical production in the cytosol and mitochondria, respectively. The major

cellular antioxidant glutathione (a free radical scavenger) is also reduced in alcoholics, decreasing the cell's ability to dispose of free radicals. Mitochondrial damage occurs (reduced ATP production, release of cytochrome c). These changes eventually result in hepatocyte necrosis, and inflammation. Progression to alcoholic hepatitis involves invasion of the liver by neutrophils. Gut derived bacterial endotoxin also stimulates Kuppfer cells causing the release of pro-inflammatory cytokines. Giant mitochondria are visible and dense cytoplasmic lesions, known as Mallory bodies, are seen. Acetaldehyde contributes at this stage by stimulating stellate cells to produce collagen leading to fibrosis and lowers the cellular antioxidant (glutathione) levels. Alcoholic hepatitis can be asymptomatic but usually presents with abdominal pain, fever and jaundice, and in severe acute hepatitis, patients may have encephalopathy, ascites and ankle oedema. Continued alcohol consumption may lead to cirrhosis. At this stage increasing fibrocollagenous deposition occurs spreading throughout the hepatic architecture leading to scarring. There is ongoing necrosis with concurrent regeneration. This is classically said to be micronodular, but often a mixed pattern is present. The greater amount of fibrotic tissue deposited in the liver is correlated with the severity of cirrhosis. Alcoholics usually present with one of the complications of cirrhosis such as gastrointestinal haemorrhage (often due to bleeding from oesophageal varices), ascites due to low albumin synthesis, reduced clotting factor production leading to bleeding, encephalopathy or renal failure. It is unclear why only a fraction of alcoholics develop cirrhosis. It has been suggested that there may be genetic factors, and that differences in immune response may play a role. Dietary factors may also contribute. For example, with inadequate intake of cysteine and glycine, glutathione production may be impaired. Poor intake of vitamins A, C and E, will also reduce the ability of the hepatocyte to cope with the oxidative stress imposed by alcoholism.

10.4. Alcohol and nutrition

Nutritional deficiencies are an important consideration that needs to be accounted for in alcohol misusers, with the effect on nutrition generally linked to the type of alcohol consumer. Thus it is important to distinguish between hazardous, harmful drinkers or dependant alcoholics, since this will correlate with the degree of nutritional damage.

These aforementioned terms have been classified by National Institute of Clinical Excellence but in simple terms those described as “hazardous” (heavy or binge) drinkers are at risk of physical and psychological harm, but have no overt alcohol-related pathologies. Individuals categorised as “harmful” have defined health problem or problems without demonstrable dependence but likely to develop dependence. Those who are “addicted” or “dependent” may have the same or worse pathologies as those described as harmful but at the same time exhibit a degree of psychological or physical symptoms upon withdrawal of alcohol. Dependence may be categorised as mild or severe. Thus, in general the degree of nutritional impairment is: severe dependent > mild dependent > harmful > hazardous drinker.

Altered nutritional status is due to either inadequate dietary intake, gastrointestinal damage affecting the absorption of nutrients, increased renal excretion, damage within the hepatocyte itself, or arises from the purchase of alcohol instead of food products. The consequences of nutritional deficiency are varied but can have significant effects on health. For example, circulating iron levels may be elevated in some alcohol misusers due to increased intestinal absorption, causing increased hepatic tissue iron deposition which leads to liver injury from oxidative stress. Hepatic stores of total retinoids (vitamin A) decrease in chronic alcohol misusers and correlate with severity of liver disease, whereas in very severe cases of alcoholism, classical symptoms of beri-beri and pellagra arise, though these are less common (Watson and Preedy, 2003).

There are no in depth studies measuring micronutrient intake in alcohol misusers in terms of the Lower Reference Nutrient Intake (LRNI). Of the few studies examining vitamin status in the UK, 95-100% of alcohol misusers had lower (below UK RNIs) intakes of vitamin E, folate and selenium, 50-85% of all alcoholics had low intakes of calcium, zinc, Vitamins A, B_1, B_2, B_6 and C and 45% of subjects had reduced intakes of magnesium and iron. However, intakes below the RNI itself does not imply malnutrition but studies have certainly shown that circulating levels of alpha-tocopherol and selenium are low in alcoholics compared to non-alcoholic controls. However, studies on middle-class alcoholics, free from major organ disease, suggest that when malnutrition is present it is

only mild to moderate. Alcohol will also affect the metabolism of a number of nutrients including thiamin and it has been suggested that about half of alcoholics with liver disease will have thiamin deficiency. A recent UK study showed that 45% of alcohol misusers without liver disease had either reduced activities of erythrocyte thiamin-dependent transketolase or a high activation ratio. This is of concern as Wernicke's-encephalopathy/Wernicke-Korsakoff syndrome is a frequent manifestation of thiamin deficiency, particularly in alcohol misusers. Thiamin deficiency will arise from both inadequate intakes and alcohol-induced interference of the active transport of the vitamin in the gut. Formation of thiamin pyrophosphate may also be impaired in diseased hepatic tissue in alcoholism.

Acute or chronic alcohol impairs the absorption of galactose, glucose, other hexoses, amino acids, biotin, and vitamin C. There is no strong evidence that alcohol impairs the absorption of magnesium, riboflavin or pyridoxine so these deficiencies will arise as a result of poor intakes and/or excess renal loss. Hepato-gastrointestinal damage of course may have an important role in impairing the absorption of some nutrients such as the fat-soluble vitamins, due to villous injury, bacterial overgrowth of the intestine, pancreatic damage or cholestasis.

The muscle wastage that occurs in alcoholic myopathy arises directly as a consequence of alcohol or acetaldehyde on muscle, and in not associated with malnutrition *per se*. This implies that there is a fundamental problem in assessing malnutrition in chronic alcoholics using anthropometric measures such as muscle or limb circumference due to the presence of alcoholic myopathy.

Alcoholic liver disease can be reproduced in laboratory animals fed nutritionally complete diets with alcohol, thus excluding the direct consequence of malnutrition as a causative factor. However, the concomitant presence of alcoholism and malnutrition exacerbates organ damage and/or nutritional status. Due to the effects of alcohol and acetaldehyde on nutrient metabolism, the following nutrients have been studied in greater detail due to their direct impact on liver disease pathology.

Alcohol and Micronutrients

Dietary vitamin B12 also known as cobalamin is an important vitamin responsible for haematopoiesis and memory status. It is complexed to dietary animal protein and during digestion becomes bound to intrinsic factor and taken up in the ileum, where it eventually reaches the liver. Whilst vitamin B12 deficiency is commonly associated with pernicious anaemia or intrinsic factor deficiency, in alcoholics the serum levels of vitamin B12 is thought to be normal or elevated. However, liver levels are low due to reduced uptake or storage. Thus serum levels may not be a good indicator of vitamin B12 status in alcoholics and a liver biopsy is required. Vitamin B6 or the active form known as pyridoxal 5'-phosphate is required as a co-factor for transaminase activity. Low levels of vitamin B6 can therefore affect the interpretation of alanine aminotransferase activity when assessing liver injury due to alcohol.

Since folate is not synthesised by the human body it is essential that this vitamin is derived from the diet (leafy green vegetables, brown rice) or from fortified food (in the form of folic acid e.g., breakfast cereals). Folate deficiency is a frequent occurrence in alcoholics, resulting in megaloblastic anaemia. It stems from decreased gastrointestinal absorption due to reduced transport across basolateral membranes, decreased liver folate uptake and increased renal excretion. The net effect of this are low serum and hepatic tissue folate levels.

Vitamin B deficiencies in alcoholics has a direct impact on the hepatic methionine metabolic pathway. Here, low levels of folate and vitamin B12 leads to lower methionine levels, increased levels of homocysteine and lower levels of s-adenosylmethionine (SAM) in alcoholics, the latter being an important methyl donor for histone and DNA methylation. SAM also plays a crucial role in maintaining mitochondrial function and is a precursor for glutathione synthesis, which is the main cellular antioxidant. Clinical studies have targeted SAM therapy in alcoholics, where a dose of 1 g/day for 6 months showed improvement in lower mortality rates but failed to improve on histological parameters.

Alcohol and Vitamin D

Vitamin D is a lipid soluble vitamin derived from fish oils and dairy products or synthesised in the skin. Vitamin D is transported to the liver and then to the kidneys where the active form 1,25 dihydroxyvitamin D is produced. In alcohol consumers, serum vitamin D levels has been reported to be unchanged or lower than controls. However, the main effect of alcohol appears to result in malabsorption, since administration of vitamin D to alcoholics does not raise serum vitamin D levels. Alcohol is also believed to interfere with vitamin D precursor synthesis in the liver and kidneys. Reduced sun exposure is another factor that needs to be considered as well, especially in older populations. The overall result of these perturbations results in alcoholics suffering from osteopenia leading to a greater risk of fractures, as well as osteoporosis.

Alcohol and zinc

Zinc is one of the most abundant trace elements found in the body. It is high in meat and dairy products and is stored in the liver, muscle, bone and kidneys and plays a crucial role in a range of cellular processes, through its action as zinc metalloproteins and zinc finger transcription factors. In alcoholics, studies suggest that the level of circulating zinc correlated with liver disease severity, with zinc levels 50% lower than normal healthy controls. The mechanism leading to low serum zinc levels can be attributed to low albumin levels, since zinc is mainly bound to circulating albumin. At the cellular level, poor intestinal zinc uptake, altered hepatic metabolism and increased renal excretion contribute to low serum zinc levels. Increased hepatic oxidative stress is also thought to cause zinc release from zinc proteins, leading to elevated liver zinc loss. Current research has shown promising findings in animal models where zinc supplementation prevents biochemical and histological alterations in ALD.

Alcohol and selenium

Selenium, like zinc is another important essential trace element. It is found in a variety of foods (meat, fish, dairy products, cereals) but in high doses, mainly as a dietary

supplement can be toxic. Selenium plays an important role in the catalytic activity of selenoproteins, particularly the antioxidant enzyme glutathione peroxidase. In alcohol consumers, serum selenium levels are reported to be lower, postulated due to lower intestinal absorption. The lower selenium levels contribute to ALD pathology due to reduced glutathione peroxidase activity, leading to increased hepatic oxidative stress. Selenium supplementation in models of liver disease have shown protection against alcohol-induced oxidative injury (Patel 2016)

It is now widely recognised that the treatment of alcoholism should cover an assessment for malnutrition. The type of treatment will depend on the severity of the disease and any underlying nutritional abnormalities.

Recent clinical trials have also examined enteral and parenteral nutrition for the treatment severe alcoholic hepatitis. Of the few random clinical trials undertaken the majority have shown a benefit to ALD patients in terms of nutritional status and liver function. However, the long term benefit remains unclear due to small sample sizes. Parenteral nutrition, whilst more costly, also carries greater risk than enteral nutrition due to complications such as infection. There has been mixed responses in alcoholic hepatitis or alcoholic cirrhotic patients following parenteral nutrition, where nutritional status and survival rates have shown either an improvement or no change. It is likely the small sample size and heterogeneity of the sample population is part responsible for this effect.

10.5 Links between alcohol intake and risk of cardiovascular disease

A range of epidemiological studies have indicated that light to moderate amounts (1-3 Units per day) of alcohol is cardioprotective and reduces coronary heart disease particularly in middle-aged men and post-menopausal women. There is a J or U shaped mortality risk curve correlated with increasing alcohol consumption. Here, a protective effect is observed at low levels of alcohol intake, around 20 g/day (approx. 1-2 Units/day). Increases in alcohol consumption from one drink per week or less to one to six drinks per week over 7 years is associated with a decrease in the risk of

cardiovascular disease. The extent of this protection is variable and is attributed to increased HDL cholesterol levels, reducing circulating levels of fibrinogen, factor VII and plasminogen activator, inhibiting platelet aggregation and thus decreasing clot formation, and lower LDL cholesterol oxidation in arterial walls. The reported cardioprotective effects of alcohol may be due to anti-oxidants or other substances in the beverages such as polyphenols in red wine (although it is now believed that all forms of alcohol can convey a cardioprotective effect). Indeed, large quantities of red wine containing catechins, quercetin or resveratrol would need to be consumed to correlate with *in vitro* studies. However, more recently UK guidelines suggest that the cardioprotective of alcohol effect is minimal.

These benefits need to be weighed up with other risk factors that are interlinked with alcohol consumption, such as smoking and obesity. Furthermore, there is a substantial body of evidence to support the notion that the total cumulative intake of ethanol (i.e., over a lifetime) will predict disease severity particularly of the heart, muscle and liver. Clearly the best advice is for abstinence and approach a healthier lifestyle by exercising combined with a well-balanced diet.

As mentioned above, the risk-benefit of alcohol consumption can be seen in a J or U shaped mortality curve. Once consumption goes beyond the threshold of 20 g/day and rises to 72 g/day, no benefit is obtained, whilst consumption of greater than 89 g/day is associated with an increased risk of coronary heart disease. The harmful effect of alcohol increasing cardiovascular mortality is distinct from the direct toxic effects on cardiac muscle, which leads to alcoholic cardiomyopathy. The main feature is a dilated left ventricle, causing reduced systolic contraction and lower cardiac output. The mechanisms are due to a reduction in cardiac contractile protein synthesis, (particularly myosin heavy chain) and the toxic effects of acetaldehyde and fatty acid ethyl esters. Management of this disorder, without heart failure ensuing, can be obtained if alcohol abstinence/reduced alcohol intake is followed.

Some studies have shown a linear (White and Black men) or J-shaped (Asian men) relationship between alcohol consumption and blood pressure, but a J-shaped relationship in women. The mechanism for hypertension that occurs after >2 drinks per day, is possibly due to increased sympathetic over activity that occurs from alcohol withdrawal after heavy drinking. Heavy drinking is associated with an increased risk of stroke. However the precise relationship between ischaemic and haemorrhagic stroke and alcohol is less clear, but some studies suggest haemorrhagic stroke has a greater occurrence and the pattern is thought to follow a U or J-shaped relationship. Binge or heavy alcohol drinking is also associated with atrial fibrillation. This association has been demonstrated in men, but there is evidence of an association with only moderate alcohol use in women (Klatsky 2015).

10.6 Links between alcohol intake and risk of cancers

Various research organisations have confirmed that alcohol poses a real significant risk to the development of several types of cancer, including the mouth, pharynx, larynx, oesophagus, colon, breast and liver. The International Agency for Research on Cancer has stated that alcohol is a carcinogen, with 3.6% of all cancers attributed to chronic alcohol drinking. The carcinogenic properties of alcohol have been proposed due to the toxic effects of acetaldehyde causing the formation of, protein adducts, increased induction of cytochrome P450 2E1 leading to reactive oxygen species causing membrane peroxidation, altered histone acetylation/methylation and DNA methylation, and increased DNA adduct formation. The latter product is thought to display high mutagenic properties, and leads to less cells undergoing apoptosis. The World Cancer Research Fund suggests 1 in 5 cases of breast cancer can be prevented by avoiding alcohol. Alcohol increases the levels of circulating oestrogen levels in women alcoholics, and stimulates oestrogen receptor signalling in breast cancer cells and nuclear transcription of oestrogen response genes. Studies suggest that the neurotoxic substance salsolinol derived from acetaldehyde and dopamine may be the agent responsible for these effects. Drinking alcohol >5 units a day increase the association with hepatocellular carcinoma. Liver cancer usually arises from the development of cirrhosis however the

direct toxic effects of acetaldehyde following chronic alcohol consumption also needs to be recognised.

The risk of these cancers appears linear, with higher amounts of alcohol consumption associated with increased risk. There is no evidence of a 'safe threshold' or 'J shaped curve'. The form in which the alcohol is consumed has only a small impact, with beer and spirit drinkers having more cancers of the upper gastrointestinal tract than wine drinkers.

Acknowledgements: With thanks to Professor Timothy J. Peters and Dr Ross Hunter for providing original material.

Key Points

Alcohol misuse is common: in the UK at least 9 million people drink more than recommended guidelines, with at least 2 million dependent on alcohol.

- The young (school children and adolescents) and women are particularly vulnerable or susceptible to the deleterious effects of alcohol and its metabolites.
- In the UK, the overall contribution of ethanol (consumers and non-consumers) to total energy intake is 5.6% in men and 4.1% women.
- In alcohol misusers, the overall contribution of ethanol to total energy intake may rise to 60% or higher.
- Alcohol absorption and metabolism is affected by a number of variables, including gastric alcohol-metabolising enzymes, ethnicity, gender, presence of different foods and body size.
- There are at least 200 different alcohol-related disorders or tissue injuries.
- Alcoholic myopathy is particularly prevalent affecting 40-60% of chronic alcoholics.
- Organic brain disease and cirrhosis only occurs in about 10-15% of chronic alcoholics.
- 50% of chronic alcohol misusers will have one or more organ or tissue abnormalities

- There are a number of routes of ethanol metabolism. The microsomal ethanol oxidising system (MEOS) is particularly important in chronic alcoholism.
- The immediate metabolite of ethanol oxidation, acetaldehyde is highly toxic.
- All pathways and cell structures have the potential to be targeted by ethanol or its related metabolites.
- The metabolic basis for 'fatty liver' in chronic alcohol ingestion involves several metabolic pathways.
- The effects of alcohol or acetaldehyde on the body are due to many processes, such as adduct formation, changes in protein, carbohydrate and lipid metabolism, membrane dysfunction, increased gut permeability, altered cytokines and impaired immunological status, perturbations in gene expression, enhanced apoptosis, reactive oxygen species/oxidative stress and changes in intracellular signalling. Many of these will be exacerbated by malnutrition.
- About 50% of alcoholics will have nutritional deficiencies and these can arise via a number of processes including poor dietary intakes, displacement of foods (empty calories theory), maldigestion, malabsorption, reduced liver uptake and increased renal excretion.

References and further reading

Awoliyi S, Ball D, Parkinson N, Preedy VR 2014 Alcohol misuse among university staff: a cross-sectional study. PLoS One. 9:e98134. doi: 0.1371/journal.pone.0098134. eCollection.

Department of Health 2015. Alcohol Guidelines Review – Report from the Guidelines development group to the UK Chief Medical Officers. Department of Health: London

Fernandez –Sola J, Nicolas J M, Estruch R M, Urbano-Marquez 2005 A Gender differences in alcohol pathology. In: Alcohol Related Pathology Volume 1. Editors Preedy, V. R., and Watson, R. R. Elsevier Academic Press. Amsterdam. Pp 261-278

Foods Standards Agency 2002 McCance and Widdowson's The Composition of Foods. Royal Society of Chemistry: Cambridge.

Freeman T L, Tuma D J, Thiele G M, et al 2005 Recent advances in alcohol-induced adduct formation. Alcoholism – Clinical and Experimental Research 29: 1310-1306
Gluud C 2002 Endocrine system. In 'Ethanol and the Liver. Mechanisms and Management'. D. I. N. Sherman, V. R. Preedy, and R. R. Watson eds. pp. 472-494. Taylor and Francis: London

Fuller E 2015 Adult alcohol consumption. Health Survey England. The Health and Social Care Information Centre.

Haber P S 2000 Metabolism of alcohol by the human stomach. Alcoholism: Clinical & Experimental Research **24**: 407-408.

HSE 2014 Health Survey for England 2014. Trend Tables Commentary and Volume 2: Methods and documentation. Health and Social Care Information Centre.

Jones A W 2000 Aspects of in-vivo pharmacokinetics of ethanol. Alcoholism: Clinical & Experimental Research 24, 400-402.

Klatsky A L 2015 Alcohol and cardiovascular diseases: where do we stand today? J Intern Med 278: 238–250.

Kwo P Y, Crabb D W 2002 Genetics of ethanol metabolism and alcoholic liver disease. In 'Ethanol and the Liver. Mechanisms and Management'. D. I. N. Sherman, V. R. Preedy, and R. R. Watson eds. pp. 95-129. Taylor and Francis: London.

Laposata M 1998 Fatty acid ethyl esters: Nonoxidative metabolites of ethanol. Addiction Biology **3**, 5-14

Lieber C S 2000 Alcohol: Its metabolism and interaction with nutrients. Annual Review of Nutrition 20:395-430

Mezey E 1985 Effect of ethanol on intestinal morphology, metabolism and function. In 'Alcohol related diseases in gastroenterology'. H. K. Seitz and B. Kommerell Eds. pp. 342-360. Springer-Verlag: Berlin.

National Diet and Nutrition Survey 2014. Headline results from Years 1,2,3 and 4 (combined) of the Rolling Programme (2008/2009 – 2011/12). Public Health England.

Novartis 2007 Acetaldehyde-Related Pathology: Bridging the Trans-Disciplinary Divide (Novartis Foundation Symposia) by Novartis Foundation. John Wiley and Sons Ltd. Chichester. UK

ONS 2015 Alcohol-related Deaths in the United Kingdom, Registered in 2013. Statistical Bulletin. Office for National Statistics. London

Patel V B 2016 Molecular Aspects of Alcohol and Nutrition. Elsevier, Academic Press Oxford.

Peters T J, Preedy V R 1998 Metabolic consequences of alcohol ingestion. Novartis Foundation Symposium 2**16:**19-24.

Preedy V R, Watson R R 2005 Comprehensive handbook of alcohol related pathology. Volumes 1-3. Academic Press, San Diego, USA.

Rachdaoui N and Sarkar DK 2013 Effects of alcohol on the endocrine system. Endocrinol Metab Clin North Am. 2013 42:593-615. doi: 10.1016/j.ecl.2013.05.008.

Roine R 2000 Interaction of prandial state and beverage concentration on alcohol absorption. Alcoholism-Clinical and Experimental Research 24: 411-412.

Royal Colleges 1995 Alcohol and the heart in perspective. Sensible limits reaffirmed. A Working Group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. *Journal of the Royal College of Physicians of London* 29: 266-271.

Saunders J B, Devereaux B M 2002 Epidemiology and comparative incidence of alcohol-induced liver disease. In 'Ethanol and the Liver. Mechanisms and Management'. D. I. N. Sherman, V. R. Preedy, and R. R. Watson eds. pp. 389-410. Taylor and Francis: London.

Tolstrup J S, Nordestgaard, BG, Rasmussen, S, Tybjærg-Hansen A and Grønbæk M 2008 Alcoholism and alcohol drinking habits predicted from alcohol dehydrogenase genes. The Pharmacogenomics Journal 8, 220–227.

Watson RR, Preedy VR 2003 Nutrition and alcohol: linking nutrient interactions and dietary intake. CRC press: London.

WHO 2014 Global status report on alcohol and health 2014. World Health Organization.

Zakhari S 2006 Overview: How Is Alcohol Metabolized by the Body? Alcohol Research and Health, 29, 245-254.

Further reading

Institute of Alcohol Studies 2008 Statistics on Alcohol: England. (http://www.ias.org.uk/)

Statistics on Alcohol England, 2015. Health and Social Care Information Centre (http://www.hscic.gov.uk/catalogue/PUB17712)

World Cancer Research Fund http://www.wcrf-uk.org/uk/preventing-cancer/ways-reduce-cancer-risk/alcohol-and-cancer-prevention

Table 10.1. **The Unit system**

A.
The Unit system of alcohol consumption

One Unit
Half a pint of beer at 3.5%
218 mL of beer at 4.5% (common alcohol concentration by volume)
One glass (125 ml) of wine at 8%
76 mL of wine at 13% (common alcohol concentration by volume)
One measure (50 ml) of fortified wine (sherry, port)
One measure (25 ml) of spirits (whisky, gin, vodka etc)

B.
Ethanol comprising one Unit

UK	8 g
Australia and New Zealand	10 g
USA	12 g
Japan	14 g

Legend to Table
The Unit system of alcohol ingestion is a convenient way of abstracting the amount of ethanol consumed by individuals and offers a suitable means to give practical guidance. The amount of alcohol in each Unit will vary, for example depending on geographical location. Except for bars, the majority of UK bottled alcoholic beverages now contain the total number of units, allowing consumers to be aware of the percentage volume by alcohol correlating with the total units.

Table 10.2. Composition of alcoholic beverages

	Per 100 ml (all as g except energy)					
	Kcal	**kJ**	**Alcohol**	**Protein**	**Fat**	**Carbohydrate**
Alcohol free lager	7	31	Trace	0.4	Trace	1.5
Low alcohol lager	10	41	0.5	0.2	0	1.5
Lager	29	131	4.0	0.3	Trace	Trace
Special strength lager	59	244	6.9	0.3	Trace	2.4
Bitter	30	124	2.9	0.3	Trace	2.2
Cider (dry)	36	152	3.8	Trace	0	2.6
Wine (red, dry)	68	283	9.6	0.1	0	0.2
Wine (white, dry)	66	275	9.1	0.1	0	0.6
Wine (white, sweet)	94	394	10.2	0.2	0	5.9
Sherry (dry)	116	481	15.7	0.2	0	1.4
Spirits (various; 40% proof)	222	919	31.7	Trace	0	Trace

	Per 100 ml (all as g)									
	Na	**K**	**Ca**	**Mg**	**P**	**Fe**	**Cu**	**Zn**	**Cl**	**Mn**
Alcohol free lager	2	44	3	7	19	Trace	Trace	Trace	Trace	0.01
Low alcohol lager	12	56	8	12	10	Trace	Trace	Trace	Trace	0.01
Lager	7	39	5	7	19	Trace	Trace	Trace	20	0.01
Special strength lager	7	39	5	7	19	Trace	Trace	Trace	20	0.01
Bitter	6	32	8	7	14	0.1	0.001	0.1	24	0.03
Cider (dry)	7	72	8	3	3	0.5	0.04	Trace	6	Trace
Wine (red, dry)	7	110	7	11	13	0.9	0.06	0.1	11	0.10
Wine (white, dry)	4	61	9	8	6	0.5	0.01	Trace	10	0.10
Wine (white, sweet)	13	110	14	11	13	0.6	0.05	Trace	7	0.10
Sherry (dry)	10	57	7	13	11	0.4	0.03	N	14	Trace
Spirits (various; 40% proof)	Trace	Trace	Trace	Trace	Trace	Trace	Trace	Trace	Trace	Trace

	Per 100 ml (all as g)							
	Ribo-flavin (mg)	**Niacin** (mg)	**Trypt/60** (mg)	**B6** (mg)	**B12** (μg)	**Folate** (μg)	**Panto-thenate** (μg)	**Biotin** (μg)
Alcohol free lager	0.02	0.6	0.4	0.03	Trace	5	0.09	Trace
Low alcohol lager	0.02	0.5	0.3	0.03	Trace	6	0.07	Trace
Lager	0.04	0.7	0.3	0.06	Trace	12	0.03	1
Special strength lager	0.04	0.7	0.3	0.06	Trace	12	0.03	1
Bitter	0.03	0.2	0.2	0.07	Trace	5	0.05	1
Cider (dry)	Trace	0	Trace	0.01	Trace	N	0.04	1
Wine (red, dry)	0.02	0.1	Trace	0.03	Trace	1	0.04	2
Wine (white, dry)	0.01	0.1	Trace	0.02	Trace	Trace	0.03	N
Wine (white, sweet)	0.01	0.1	Trace	0.01	Trace	Trace	0.03	N
Sherry (dry)	0.01	0.1	Trace	0.01	Trace	Trace	Trace	N
Spirits (various; 40% proof)	0	0	0	0	0	0	0	0

Legend to Table

This table only gives an estimate of some of the compounds that will be present in alcoholic beverages. In addition, there will also be other compounds, which are not tabulated, such as fluoride, polyphenols and other organic and non-organic compounds that impart characteristics of taste and smell. Data from Foods Standards Agency (2002).

Table 10. 3. **Categorisation of weekly alcohol consumption using Units**

	Men	**Women**
Low risk	0-21	0-14
Increasing risk	22-50	15-35
***Harmful**	**>50**	**>35**

Summary of Department of Health (UK) recommendations

Men:

- Weekly: No more than 14 Units/week
- Spread drinking of 14 Units over 3 days
- Not advised: consistently drinking 4 or more Units a day

Women:

- Protection: 1-2 Units day, possibly protection against heart disease (past menopause)
- Weekly: No more than 14 Units/week
- Not advised: consistently drinking 3 or more Units a day
- Harmful: more than 1 or 2 Units of alcohol, once or twice a week when pregnant or about to become pregnant. Safest to avoid drinking during pregnancy.

Legend to Table

Guidelines are designed to limit harm (Department of Health 2015). *Harmful effects can also be obtained by binge drinking i.e., > 5 Units on a single day.

Table 10.4. **Alcohol consumption level (Units per week), in the UK, by gender, 1988 to 2014**

Percentages and weekly Units

	Alcohol consumption level (Units per week)				
	1998	**2006**	**2008**	**2010**	**2014**
Men aged 16 and over					
Non-drinker	7	11	11	13	15
Up to 21 Units (lower risk)	67	58	61	61	63
22 - 50 Units (increased risk)	20	22	20	20	17
51 Units and over (higher risk)	6	9	7	6	5
Mean weekly Units	16.4	18.9	16.8	15.9	16.8
Percent drinking more than 21 Units	**27**	**31**	**28**	**26**	**22**
Women aged 16 and over					
Non-drinker	14	17	19	19	22
Up to 14 Units (lower risk)	72	63	61	63	62
14-35 Units (increased risk)	13	15	15	10	12
36 Units and over (higher risk)	2	6	5	3	4
Mean weekly Units	6.4	9.2	8.6	7.6	8.8
Percent drinking more than 14 Units	**12**	**20**	**19**	**17**	**16**

Legend to Table

This table is designed to illustrate the variable nature of alcohol consumption in the UK. Small proportions of individuals do not drink alcohol-containing beverages at all, 15% for men and 22% for women, whereas nearly over a fifth of the male adult population drinks excessively as defined by the limits of 21 Units/week. Adapted from Institute of Alcohol Studies report 2008 & Health Survey for England 2014 Trend Tables Commentary and Volume 2: Methods and documentation report.

Table 10.5. **Consumption rates of different alcohol beverages**

	Consumption rates (units/week)	
	Men	**Women**
Spirits	1.8	1.6
Wine	4	5.4
Fortified wine	0.1	0.2
Normal strength beer/lager/cider	7.3	1.5
High strength beer & lager/cider	2.0	0.4
Alcopops	0.3	0.4

Legend to Table

Table showing the variation in consumption of different alcohol beverages in the UK including low or no (zero) alcohol drinks. Variations in the consumption rates of different alcoholic drinks are often subject to socio-economic and cultural factors. Note from 2008, consumption is calculated in units preventing direct comparison to previous data. Adapted from Health Survey for England, 2013 – Trend Tables. Health and Social Care Information Centre report.

Table 10.6. **Systems and tissues affected by alcohol misuse**

[1] Hepato-Pancretobiliary
Hepatomegaly - fatty liver, alcoholic hepatitis and fibrosis
Cirrhosis and hepatocellular carcinoma
Acute and chronic relapsing pancreatitis - malabsorptive syndrome

[2] Central, peripheral and autonomic nervous systems
Acute intoxication
Progressive euphoria, incoordination, ataxia, stupor, coma and death
Alcohol withdrawal symptoms including delirium tremens, morning nausea, retching and vomiting, nightmares and night terrors, blackouts and withdrawal seizures

Nutritional deficiencies
Wernicke-Korsakoff syndrome
Pellagra
Tobacco-alcohol amblyopia

Others
Cerebral dementia, cerebellar degeneration
Demyelinating syndromes - central pontine myelinolysis,
Marchiafava-Bignami syndrome, associated with electrolyte disturbances
Fetal alcohol syndrome - full-blown syndrome, mental impairment, attention deficit and hyperkinetic disorders, specific learning difficulties

Peripheral nervous system
Sensory, motor and mixed neuropathy
Autonomic neuropathy

[3] Musculoskeletal
Proximal metabolic myopathy, principally affecting Type II (white) fibres
Neuromyopathy secondary to motor nerve damage
Atrophy of smooth muscle of gastrointestinal tract, leading to motility disorders
Osteopenia - impaired bone formation, degradation, nutritional deficiencies (e.g. calcium, magnesium, phosphate, vitamin D)
Avascular necrosis (e.g. femoral head)
Fractures - malunion

[4] Genitourinary
IgA nephropathy
Renal tubular acidosis.
Renal tract infections
Female and male hypogonadism, subfertility
Impotence
Spontaneous abortion
Fetal alcohol syndrome

[5] Cardiovascular
Cardiomyopathy, including dysrrhythmias
Hypertension
Binge strokes
Cardiovascular disease (including stroke)

Myocardial infarction

[6] Dermatological
Skin stigmata of liver disease - rosacea, spider naevi, palmar erythema, finger clubbing
Skin infections - bacterial, fungal and viral
Local cutaneous vascular effects
Psoriasis
Discoid eczema
Nutritional deficiencies (including pellagra)

[7] Respiratory
Chronic bronchitis
Respiratory tract malignancy
Asthma
Postoperative complications

[8] Oro-Gastrointestinal
Periodontal disease and caries
Oral infections, leukoplakia and malignancy
Alcoholic gastritis and haemorrhage
Alcoholic enteropathy and malabsorption
Colonic malignancy

[9] Haematological
RBCs - macrocytosis, anaemia because of blood loss, folate deficiency and malabsorption, haemolysis (rarely)
WBCs - neutropenia, lymphopenia
Platelets - thrombocytopenia

Legend to Table
This table is designed to show that diseases associated with alcohol misuse are not confined to only the liver and brain. Virtually all tissues and organs systems can be adversely affected with only some life threatening. Furthermore, not all individuals will develop a disease possibly due to inherent protective, dietary or genetic factors (Adapted from Peters and Preedy 1998).

Table 10.7 Prevalence of alcohol-induced pathologies in chronic alcohol abusers

	(%)
Skin disorders	80
Alcoholic myopathy	50
Bone disorders	50
Gonadal dysfunction	50
Gastroenterological disorders	30
Cirrhosis	15
Neuropathy	15
Cardiomyopathy	10
Brain disease (organic)	10

Legend to Table

The prevalence of alcohol-related disorders relate to chronic alcohol-dependent subjects. (Preedy and Watson 2005; WHO, 2014).

Table 10.8. **Rule of thumb in alcohol misuse**

The five "rules of thumb" for alcohol induced pathologies

1. All tissues and organ systems have the potential to be affected by alcohol or its immediate metabolites.

2. Alcohol or its immediate metabolites has the potential to affect all biochemical pathways, subcellular organelles and other cellular systems and/or structures.

3. Not all individuals will suffer the consequences of alcohol ingestion due to cellular, nutritional or genetic protective systems.

4. 50% of alcoholics will have one or more organ or tissue pathologies.

5. 50% of alcoholics will have a deficiency of one or more micro- or macro-nutrient.

Legend to Table.

The above rules of thumb are gross generalisations and one should take into account differences due to gender, socio-ethnicity, geographical and regional variations in alcohol ingestion.

Table 10.9 **Ethanol metabolising enzymes**

Class	**Subunit**	**Location**	**Km (mM)**	**Vmax**
Class I				
ADH1A	α	Liver	4.0	30-54
*ADH1B*1*	β_1	Liver, lung	0.05	4
*ADH1B*2*	β_2	Liver, lung	0.09	450
*ADH1B*3*	β_3	Liver, lung	40	300
*ADH1C*1*	γ_1	Liver, stomach	1.0	90
*ADH1C*2*	γ_2	Liver, stomach	0.6	40
Class II				
ADH4	π	Liver, cornea	30-34	20-40
Class III				
ADH5	χ	Most tissues	>1000	100
Class IV				
ADH7	σ, μ	Stomach, oesophagus, other mucosae	20-30	1510-1800
Class V				
ADH6	-	Liver, stomach	-	-

Legend to Table

Adapted from Kwo and Crabb (2002); Zahari (2006).

Table 10.10 **Aldehyde-metabolising enzymes**

Class	**Structure**	**Location**	**Km (μM)***	
Class 1				
ALDH1	α4	Many tissues: liver>kidney	30	
Class 2				
ALDH2	α4	Low levels in most tissues Liver>kidney>muscle>heart	1	
ALDH5	?	Low levels in most tissues Liver>kidney>muscle	?	
Class 3				
ALDH3	α2	Stomach, liver, cornea	11	-
Other enzymes				
ALDH9	σ4	Liver	30	
ALDH6-8	?	?	?	

Legend to Table

From Kwo and Crabb (2002). *Km for acetaldehyde (these enzymes also metabolise other substrates).

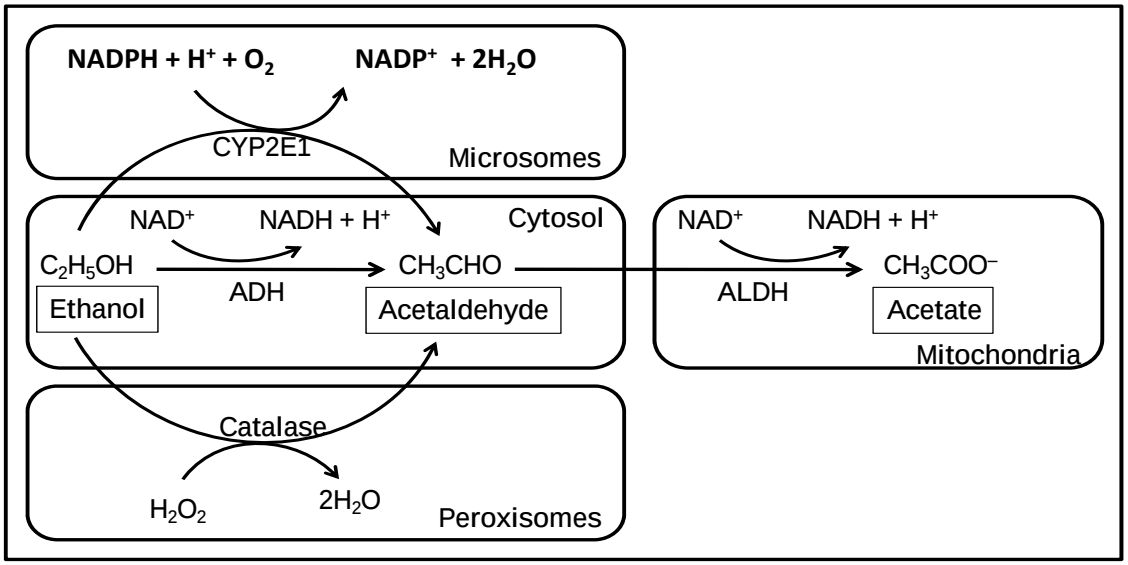

Figure 10.1 **Oxidative Pathways of Alcohol Metabolism**

Legend to Figure. Three major route of ethanol oxidation depicting the conversion of alcohol to acetaldehyde and then acetate.