Normal metabolism of ethanol involves oxidation to acetic acid, conversion to acetyl CoA and processing in the usual mitochondrial respiration. Alcohol is thus a source of energy; the number usually given for caloric value is about 7 kcalories/g. Normal ethanol intake varies greatly -- averaged over the US population it is about 5% of energy intake - - and a small amount is supplied by the action of intestinal bacteria. This normal metabolism assumes a relatively balanced diet and moderate levels of alcohol (less than 10 - 20% of caloric intake).

The major reactions are:

1. Alcohol dehydrogenase: ethanol + NAD+ ----> acetaldehyde + NADH
2. Aldehyde dehydrogenase: acetaldehyde + NAD+ ----> acetic acid + NADH

High levels of alcohol may not allow the mitochondrial processing of NADH to keep up. This, especially in association with low food intake, can lead to a number of metabolic consequences.

Build-up of intermediates. Acetaldehyde from the alcohol dehydrogenase reaction is extremely toxic and may cause several kinds of damage. Aldehydes are generally reactive with amino groups and may interact with proteins. Acetaldehyde also competes for the plasma carrier of pyridoxal (vitamin B6). This can exacerbate what may already be a dietary deficiencies in vitamins.

The aldehyde dehydrogenase reaction leads to production of acetic acid. There is a limited ability to convert this to acetyl CoA and acetic acid can appear in the blood leading to acidosis. (Recall from Biochemistry that the reason ketone bodies have evolved is that they are a method for the liver to supply substrates to other tissues with a lower ratio of acid/carbon than acetic acid).

Deficiency in NAD+. Because the two oxidative reactions above require, NAD+, this form of the coenzyme can become limiting and NADH can build up. This can cause the following problems:

In order to regenerate NAD+ there will be increased anaerobic metabolism, that is, conversion of pyruvate to lactate by lactate dehydrogenase. This can lead to lactic acidosis.

pyruvate + NADH ----> lactate + NAD+

This demand for pyruvate can reduce its availability for gluconeogenesis (pyruvate -> oxaloacetate -> PEP). In combination with low food intake this can lead to
**hypoglycemia.** The TCA cycle, via the malate dehydrogenase reaction is potentially another source of oxaloacetate:

\[
\text{malate + NAD}^+ \rightarrow \text{oxaloacetate + NADH}
\]

You may remember, however, that thermodynamically the malate dehydrogenase reaction favors malate and, as noted above, you already have an excess of NADH which will push the reaction away from oxaloacetate and further repress gluconeogenesis.

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**The microsomal ethanol oxidizing system.** At a certain level of alcohol -- estimates are at 10% of caloric intake -- a second oxidizing system becomes important. There is a P450 (or microsomal) oxidizing system that is inducible and will become important as the levels of alcohol become higher. One might think of this as the point at which the body is dealing with alcohol as a toxic agent rather than a dietary source. The components of this system are inducible and account for the increased tolerance of alcohol in heavy drinkers. The caloric output in terms of NADH is less than for the normal alcohol dehydrogenase system but, more important, the system will add to the load of acetaldehyde and acetate and interfere with the normal functioning of the P450 system. This is one of the sources of problems associated with alcohol consumption while on medication since many drugs are processed through the microsomal P450 system.

**Background on the microsomal oxidizing system.**

Almost all tissues contain an oxidative system, separate from the electron transport system, that is used for a number of important reactions. This system is usually part of the endoplasmic reticulum, although there is also a mitochondrial version. Experimentally, the ER system is isolated in the microsomal fraction of cell centrifugation and it is also known as the microsomal oxidizing system. These systems contain a number of different cytochromes known collectively as the cytochrome P450 system (historically, they were first identified by a strong absorption in the visible range at 450 nm). The reaction catalyzed by this system involves oxidations, usually from carbon atoms to the alcohol level. A number of different kinds of oxidations are catalyzed however and the term *mixed-function oxygenase* is frequently used. The oxidizing agent is molecular oxygen but only one atom of oxygen is used so this is frequently also referred to as a *monooxygenase*. The other oxygen is reduced by NADPH:

\[
\text{substrate + NADPH + O}_2 \rightarrow \text{NADP}^+ + \text{substrate -(OH) + H}_2\text{O}
\]

The terms microsomal oxidizing system, cytochrome P450, monooxygenase, and mixed-function oxygenase are used more or less interchangeably.

The P450 system is important in a number of different physiologic processes:
• **Steroid metabolism**, being associated with most of the enzymes involved in the production of steroid hormones, including the complicated first step of conversion of cholesterol to pregnenolone.

• **Detoxification** system and many foreign substances that are highly hydrophobic become hydroxylated to the point that they are more soluble and can be acted upon by enzymes that will destroy them.

• **Heme degradation** is mediated by P450 oxidations. The process involves the two step oxidation of heme to biliverdin and bilirubin. As Stryer points out, you can follow these reactions by watching color changes in a bruise. Click here for an external site (NetBiochem) with information on heme degradation.

• The P450 system is also involved in the **processing of ethanol**, especially when there is a high dietary intake (greater than 10-20 % of calories). Because it is less efficient than the normal mitochondrial system (as a food source gives roughly 5 instead of 7 kilocalories), and because it will interfere with the processes described above, the activation of this system for alcohol oxidation, is considered one of the deleterious effects of alcoholism.

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**Vitamin deficiencies in alcoholism.** Alcoholics develop nutritional deficiencies both because alcohol abuse is frequently associated with poor diet and because of the effect of ingested alcohol on either absorption or processing of nutrients. Two of the most important are B6, niacin, thiamin and folate. Alcoholism is probably the most common condition in which thiamin and folate deficiencies are seen and, in its extreme form, causes the neurologic disorders known collectively as the Wernicke-Korsakoff syndrome.

**Effects on liver lipid metabolism.** The demands on NAD+ described above also show up as an inability to metabolize fatty acids in the liver; recall that b-oxidation also uses NAD+ as one of the oxidizing agents. The results of this are fat accumulation in the liver (fatty liver) and increased VLDL. From a clinical standpoint, fatty liver and the accompanying enlargement of the liver can be reversed if alcohol is withdrawn. However, continued damage to the liver can result in alcoholic hepatitis with cell death and inflammation and this is sometimes fatal. Some drinkers, after years of abuse, can develop cirrhosis of the liver in which scar tissue is formed. Cirrhosis occurs in about 25 % of heavy drinkers although it can be caused by other factors.

**Summary.** The nutritional and biochemical consequences of alcohol abuse are due to a combination of what occurs -- the metabolism of ethanol -- and what doesn't occur -- normal intake of food and vitamins. To be metabolized, the alcohol must be oxidized to acetic acid (ultimately converted to acetyl CoA) and this requires NAD+ which can become in a limiting metabolite. The NADH that builds up will drive pyruvate to lactate which can lead to acidosis. The pyruvate is now not available for gluconeogenesis and if, as is common in serious alcoholism, the patient is not eating, hypoglycemia can result. The high NADH/NAD+ ratio will affect other processes such as b-oxidation. One clinical manifestation is liver disorders associated with alcoholism: fatty liver, alcoholic hepatitis and, sometimes, cirrhosis. The burden on oxidizing systems also leads to increased use of the P450 or microsomal oxidizing system which can have important effects on steroid
metabolism and other processes involving this system. Finally, alcoholism is frequently associated with gross malnutrition which is often seen clinically in vitamin deficiencies.

Questions for Discussion.

1. NAD+/NADH is a very important coenzyme system in biochemistry. How would you describe its general role and what part does it play in the consequences of alcoholism?

2. Describe the function of P450 oxidizing system and its role in nutritional and biochemical aspects of alcoholism.

3. Discuss the role of alcoholism in liver disease.

4. Looking at the big picture of nutrition, if you took vitamin pills, why could you not take all of your calories from alcohol? (Aside from the intoxication).