



U.S. Department of Health
& Human Services

National Institutes of Health

National Institute on Alcohol Abuse
and Alcoholism

ALCOHOL ALERT

Number 72

April 2007

ALCOHOL METABOLISM: AN UPDATE

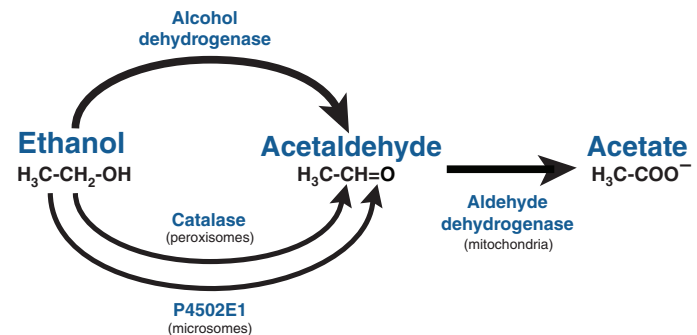
Drinking heavily puts people at risk for many adverse health consequences, including alcoholism, liver damage, and various cancers. But some people appear to be at greater risk than others for developing these problems. Why do some people drink more than others? And why do some people who drink develop problems, whereas others do not?

Research shows that alcohol use and alcohol-related problems are influenced by individual variations in alcohol metabolism, or the way in which alcohol is broken down and eliminated by the body. Alcohol metabolism is controlled by genetic factors, such as variations in the enzymes that break down alcohol; and environmental factors, such as the amount of alcohol an individual consumes and his or her overall nutrition. Differences in alcohol metabolism may put some people at greater risk for alcohol problems, whereas others may be at least somewhat protected from alcohol's harmful effects.

This *Alcohol Alert* describes the basic process involved in the breakdown of alcohol, including how toxic byproducts of alcohol metabolism may lead to problems such as alcoholic liver disease, cancer, and pancreatitis. This *Alert* also describes populations who may be at particular risk for problems resulting from alcohol metabolism as well as people who may be genetically "protected" from these adverse effects.

THE CHEMICAL BREAKDOWN OF ALCOHOL

Alcohol is metabolized by several processes or pathways. The most common of these pathways involves two enzymes—alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). These enzymes help break apart the alcohol mole-



cule, making it possible to eliminate it from the body. First, ADH metabolizes alcohol to *acetaldehyde*, a highly toxic substance and known carcinogen (1). Then, in a second step, acetaldehyde is further metabolized to another, less active byproduct called *acetate* (1), which then is metabolized into water and carbon dioxide for easy elimination (2).

Other enzymes—The enzymes cytochrome P450 2E1 (CYP2E1) and catalase also break down alcohol to acetaldehyde. However, CYP2E1 only is active after a person has consumed large amounts of alcohol, and catalase metabolizes only a small fraction of alcohol in the body (1). Small amounts of alcohol also are removed by interacting with fatty acids to form compounds called fatty acid ethyl esters (FAEEs). These compounds have been shown to contribute to damage to the liver and pancreas (3).

Acetaldehyde: a toxic byproduct—Much of the research on alcohol metabolism has focused on an intermediate byproduct that occurs early in the breakdown process—acetaldehyde. Although acetaldehyde is short lived, usually existing in the body only for a brief time before it is further broken down into acetate, it has the potential to cause significant damage. This is particularly evident in the liver, where the bulk of alcohol metabolism takes place (4). Some alcohol

metabolism also occurs in other tissues, including the pancreas (3) and the brain, causing damage to cells and tissues (1). Additionally, small amounts of alcohol are metabolized to acetaldehyde in the gastrointestinal tract, exposing these tissues to acetaldehyde's damaging effects (5).

“Differences in alcohol metabolism may put some people at greater risk for alcohol problems.”

The Chemical Breakdown of Alcohol



The chemical name for alcohol is ethanol ($\text{CH}_3\text{CH}_2\text{OH}$). The body processes and eliminates ethanol in separate steps. Chemicals called *enzymes* help to break apart the ethanol molecule into other compounds (or *metabolites*), which can be processed more easily by the body. Some of these intermediate metabolites can have harmful effects on the body.

Most of the ethanol in the body is broken down in the liver by an enzyme called *alcohol dehydrogenase (ADH)*, which transforms ethanol into a toxic compound called *acetaldehyde* (CH_3CHO), a known carcinogen. However, acetaldehyde is generally short-lived; it is quickly broken down to a less toxic compound called *acetate* (CH_3COO^-) by another enzyme called *aldehyde dehydrogenase (ALDH)*. Acetate then is broken down to carbon dioxide and water, mainly in tissues other than the liver.

In addition to its toxic effects, some researchers believe that acetaldehyde may be responsible for some of the behavioral and physiological effects previously attributed to alcohol (6). For example, when acetaldehyde is administered to lab animals, it leads to incoordination, memory impairment, and sleepiness, effects often associated with alcohol (7).

On the other hand, other researchers report that acetaldehyde concentrations in the brain are not high enough to produce these effects (7). This is because the brain has a unique barrier of cells (the blood-brain barrier) that help to protect it from toxic products circulating in the bloodstream. It's possible, however, that acetaldehyde may be produced in the brain

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itself when alcohol is metabolized by the enzymes catalase (8,9) and CYP2E1 (10).

THE GENETICS BEHIND METABOLISM

Regardless of how much a person consumes, the body can only metabolize a certain amount of alcohol every hour (2). That amount varies widely among individuals and depends on a range of factors, including liver size (1) and body mass.

In addition, research shows that different people carry different variations of the ADH and ALDH enzymes. These different versions can be traced to variations in the same gene. Some of these enzyme variants work more or less efficiently than others; this means that some people can break down alcohol to acetaldehyde, or acetaldehyde to acetate, more quickly than others. A fast ADH enzyme or a slow ALDH enzyme can cause toxic acetaldehyde to build up in the body, creating dangerous and unpleasant effects that also may affect an individual's risk for various alcohol-related problems—such as developing alcoholism.

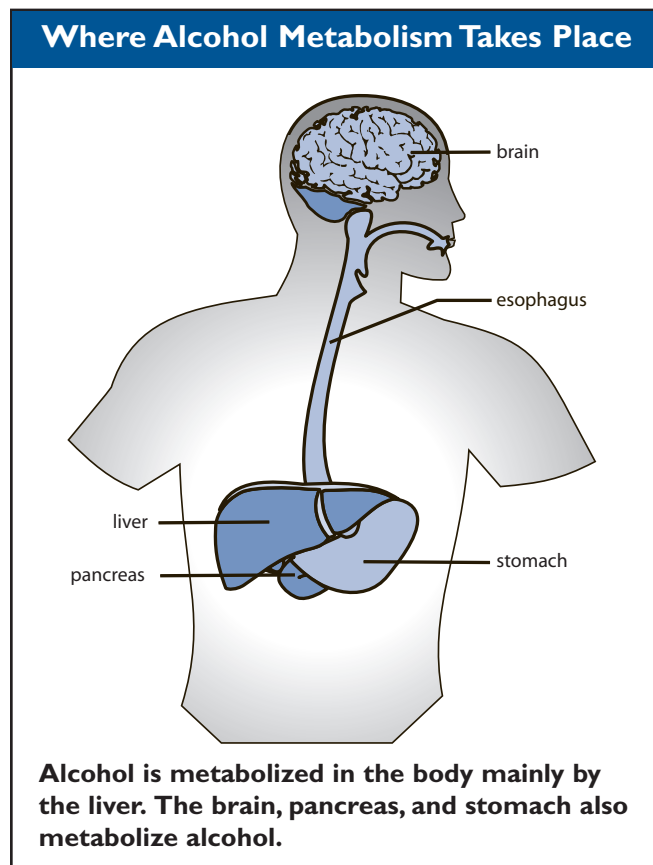
The type of ADH and ALDH an individual carries has been shown to influence how much he or she drinks, which in turn influences his or her risk for developing alcoholism (11). For example, high levels of acetaldehyde make drinking unpleasant, resulting in facial flushing, nausea, and a rapid heart beat. This “flushing” response can occur even when only moderate amounts of alcohol are consumed. Consequently, people who carry gene varieties for fast ADH or slow ALDH, which delay the processing of acetaldehyde in the body, may tend to drink less and are thus somewhat “protected” from alcoholism (although, as discussed later, they may be at greater risk for other health consequences when they do drink).

Genetic differences in these enzymes may help to explain why some ethnic groups have higher or lower rates of alcohol-related problems. For example, one version of the ADH enzyme, called *ADH1B*2*, is common in people of Chinese, Japanese, and Korean descent but rare in people of European and African descent (12). Another version of the ADH enzyme, called *ADH1B*3*, occurs in 15 to 25 percent of African Americans (13). These enzymes protect against alcoholism (14) by metabolizing alcohol to acetaldehyde very efficiently, leading to elevated acetaldehyde levels that make drinking unpleasant (15). On the other hand, a recent study by Spence and colleagues (16) found that two variations of the ALDH enzyme, *ALDH1A1*2* and *ALDH1A1*3*, may be associated with alcoholism in African-American people.

Although these genetic factors influence drinking patterns, environmental factors also are important in the development of alcoholism and other alcohol-related health consequences. For example, Higuchi and colleagues (17) found that as alcohol consumption in Japan increased between 1979 and 1992, the percentage of Japanese alcoholics who carried the protective *ADH1B*2* gene version increased from 2.5 to 13 percent. Additionally, despite the fact that more Native American people die of alcohol-related causes than do any other ethnic group in the United States, research shows that there is no difference in the rates of alcohol metabolism and enzyme patterns between Native Americans and Whites (18). This suggests that rates of alcoholism and alcohol-related problems are influenced by other environmental and/or genetic factors.

HEALTH CONSEQUENCES OF ALCOHOL USE

Alcohol metabolism and cancer—Alcohol consumption can contribute to the risk for developing different cancers, including cancers of the upper respiratory tract, liver, colon or rectum, and breast (19). This occurs in several ways, including through the toxic effects of acetaldehyde (20).



“The very genes that protect some people from alcoholism may magnify their vulnerability to alcohol-related cancers.”

Many heavy drinkers do not develop cancer, and some people who drink only moderately do develop alcohol-related cancers. Research suggests that just as some genes may protect individuals against alcoholism, genetics also may determine how vulnerable an individual is to alcohol’s carcinogenic effects (5).

Ironically, the very genes that protect some people from alcoholism may magnify their vulnerability to alcohol-related cancers. The International Agency for Research on Cancer (21) asserts that acetaldehyde should be classified as a carcinogen. Acetaldehyde promotes cancer in several ways—for example, by interfering with the copying (i.e., replication) of DNA and by inhibiting a process by which the body repairs damaged DNA (5). Studies have shown that people who are exposed to large amounts of acetaldehyde are at greater risk for developing certain cancers, such as cancers of the mouth and throat (5). Although these individuals often are less likely to consume large amounts of alcohol, Seitz and colleagues (5) suggest that when they do drink their risk for developing certain cancers is higher than drinkers who are exposed to less acetaldehyde during alcohol metabolism.

Acetaldehyde is not the only carcinogenic byproduct of alcohol metabolism. When alcohol is metabolized by CYP2E1, highly reactive, oxygen-containing molecules—or reactive oxygen species (ROS)—are produced. ROS can damage proteins and DNA or interact with other substances to create carcinogenic compounds (22).

Fetal Alcohol Spectrum Disorder (FASD)—Pregnant women who drink heavily are at even greater risk for problems. Poor nutrition may cause the mother to metabolize alcohol more slowly, exposing the fetus to high levels of alcohol for longer periods of time (23). Increased exposure to alcohol also can prevent the fetus from receiving necessary nutrition through the placenta (24). In rats, maternal malnutrition has been shown to contribute to slow fetal growth, one of the features of FASD, a spectrum of birth defects associated with drinking during pregnancy (23). These findings suggest that managing nutrition in pregnant women who drink may help to reduce the severity of FASD (25).

Alcoholic liver disease—As the chief organ responsible for the breakdown of alcohol, the liver is particularly vulnerable

to alcohol metabolism's effects. More than 90 percent of people who drink heavily develop fatty liver, a type of liver disease. Yet only 20 percent will go on to develop the more severe alcoholic liver disease and liver cirrhosis (26).

Alcoholic pancreatitis—Alcohol metabolism also occurs in the pancreas, exposing this organ to high levels of toxic byproducts such as acetaldehyde and FAEEs (3). Still, less than 10 percent of heavy alcohol users develop alcoholic pancreatitis—a disease that irreversibly destroys the pancreas—suggesting that alcohol consumption alone is not enough to cause the disease. Researchers speculate that environmental

factors such as smoking and the amount and pattern of drinking and dietary habits, as well as genetic differences in the way alcohol is metabolized, also contribute to the development of alcoholic pancreatitis, although none of these factors has been definitively linked to the disease (27).

CONCLUSION

Researchers continue to investigate the reasons why some people drink more than others and why some develop serious health problems because of their drinking. Variations in the way the body breaks down and eliminates alcohol may hold the key to explaining these differences. New

TRENDS IN RESEARCH

Investigators are studying factors that influence alcohol metabolism, such as variations in the study subjects' gender and ethnicity, genetic variations in alcohol-metabolizing enzymes, and even the food subjects consumed that day. Two methods that are helping researchers gain a better understanding of how alcohol is metabolized are the alcohol clamp method, in which alcohol is given intravenously, and the use of specially grown cells.

The alcohol clamp method. The speed at which people absorb, distribute, and metabolize alcohol varies as much as three or four times between individuals (1,2). The alcohol clamp is a method of administering alcohol intravenously to subjects, allowing researchers to circumvent variations in alcohol absorption. This technique enables researchers to administer precise doses of alcohol to achieve an exact breath alcohol concentration (a measure of how much alcohol is in the body) (3,4). The actual dose of alcohol is calculated for each individual based on his or her specific alcohol elimination rate, controlling for factors like gender and body mass. This allows researchers to compare the alcohol elimination or metabolism rates without complicating factors. For example, using the alcohol clamp method researchers were able to determine that male volunteers eliminated alcohol at significantly faster rates than did female volunteers (5–8). The alcohol clamp method also helps researchers study the genetics of alcohol metabolism, including differences in how volunteers who carry different versions of the ADH and ALDH genes metabolize alcohol (9).

Cultured cells. Cells that are grown in the laboratory (i.e., cultured cells) are an important tool in studying how alcohol damages the liver on a molecular level. Cultured cells can help to clarify the processes associated with alcohol metabolism that damage cells by allowing researchers to investigate individual metabolic pathways; to control the cells' exposure to alcohol and its byproducts; and to work with uniform, or cloned, cells (10). Additionally, because large quantities of cells can be cloned, researchers are able to repeat experiments many times in order to confirm findings.

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information will aid researchers in developing metabolism-based treatments and give treatment professionals better tools for determining who is at risk for developing alcohol-related problems.

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Resources

Source material for this *Alcohol Alert* originally appeared in a special two-part series of *Alcohol Research & Health* that examines the topic of alcohol metabolism.

- ▶ *Alcohol Research & Health* Volume 29, Number 4, 2006. This issue describes alcohol's metabolic pathways, their genetic variation, and the effects of certain byproducts, such as acetaldehyde, on a range of organs and tissues.
- ▶ *Alcohol Research & Health* Volume 30, Number 1, 2007. This issue examines how differences in metabolism may lead to increased or reduced risk among individuals and ethnic groups for alcohol-related problems such as alcohol dependence, cancer, fetal alcohol effects, and pancreatitis.

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