



*P*hysical  
Health



# PHYSICAL HEALTH

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# A LCOHOL ABUSE MAY INCREASE SUSCEPTIBILITY TO HIV INFECTION

- *Alcohol abuse among people with the human immunodeficiency virus (HIV) is significant.*
- *Researchers used simian immunodeficiency virus (SIV) infection of rhesus monkeys to examine the combined effects of chronic, binge alcohol consumption on the primary stage of SIV/HIV infection.*
- *Binge drinking appears to increase the host's susceptibility to SIV/HIV infection.*

Alcohol abuse among people with the human immunodeficiency virus (HIV) is significant. One study found that 41 percent of HIV-infected patients met the criteria for alcoholism. Although alcohol abuse and HIV infection individually compromise immune function, the consequences of both conditions together is poorly understood. A study in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* used simian immunodeficiency virus (SIV) infection of rhesus monkeys to examine the combined effects of chronic, binge alcohol consumption on the primary stage of SIV/HIV infection. Researchers found that alcohol consumption may increase susceptibility to SIV/HIV infection.

“The prevalence of alcohol abuse among HIV-infected people is at least twice that found in the general population in the United States,” said Gregory J. Bagby, Kai and Earl Rozas professor of physiology at Louisiana State University Health Sciences Center and first author of the study. “Several studies indicate that individuals who abuse alcohol engage in risky behaviors such as unprotected sex with multiple partners. By itself this behavior would increase the chances of becoming infected with HIV. What is not known is whether alcohol intoxication or chronic alcohol consumption alters susceptibility to infection upon exposure to HIV beyond the behavioral effects of alcohol.”

Twenty-two male rhesus monkeys, four to six years of age, were given either alcohol or sucrose for four days per week for three months. The alcohol doses were individualized in order to achieve plasma alcohol concentrations of 230-250 mg/100ml (roughly the human equivalent of 6 to 10 drinks) for a five-hour period. After three months, seven alcohol-treated and seven sucrose-treated monkeys were infected with SIV; four alcohol-treated and four sucrose-treated monkeys were not. Blood samples were drawn prior to alcohol/sucrose infusions, one month prior to SIV infection, and then on days 6, 13, 20, 27, 42 and 61 post-SIV infection.

“This study had two primary purposes,” said Bagby. “First, we wanted to develop an animal model to study the interactive effects of alcohol on HIV disease transmission, pathogenesis, progression and anti-viral therapy. We adapted the primate model, using SIV, which infects rhesus monkeys in the same way that HIV infects humans and produces a disease that is very similar to the human disease that leads to an immunosuppressed state and AIDS. The second purpose was to examine the effects of alcohol consumption on what is called the primary stage of infection. This stage is extremely difficult to study in humans because it is rare to be able to identify infected people this early.”

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## LCOHOL ABUSE MAY INCREASE SUSCEPTIBILITY TO HIV INFECTION

Approximately one week after SIV infection, there was a 64-fold increase of the SIV virus in the blood of the alcohol-treated monkeys compared to the sucrose-treated monkeys. “This most likely means that either more cells are infected with virus at this early stage or that infected cells are producing more virus,” said Bagby. “If more cells are infected, it means that the alcohol increased infectivity of cells or increased the number of susceptible cells.”

Alcohol consumption also enhanced lymphocyte turnover (as assessed by expression of the cell cycle protein marker Ki67) in SIV-infected monkeys during the early stage of infection, which may have contributed to the observed increase of virus in the blood.

When a body becomes infected with a pathogen or virus, explained Bagby, certain cells in the immune system become activated and start dividing or proliferating. “The cell cycle marker Ki67 increases in cells that are proliferating,” said Bagby. “So an increase in this protein indicates that the immune system is responding to an infection. The cells that are produced are specifically designed to eradicate the infection. Furthermore, the increase in immune-cell production during a viral infection is accompanied by an increase in the number of cells that die. ‘Lymphocyte turnover’ refers to this increase in the numbers of cells that are produced and subsequently die.”

“The well-documented immune-weakening effects of both alcohol and HIV infection underscore the importance of understanding the potential interactions between these two common immune suppressive factors,” said Shirish Barve, associate professor in the department of medicine at the University of Louisville Medical Center. “The present work by Bagby and [colleagues] has established the much-needed animal model that could be effectively used in the study of HIV disease. Due to its similarity to HIV infection, [this] model [could] be extremely important in addressing and understanding the clinically relevant issues concerning the susceptibility of alcoholics to acquiring HIV infection and the effect of alcohol on the rate of HIV-disease progression in alcoholics.”

Bagby and his coauthors intend to continue studying the effects of alcohol on HIV disease transmission, pathogenesis, progression and therapy. “Our next study will examine the longitudinal effects of alcohol on SIV disease progression,” said Bagby. “We will look at the effects of alcohol and SIV infection on disease progression, muscle wasting and behavioral deficits.”

### Article is based on the following published research:

Bagby, J.G.,  
Stoltz, D.A., Zhang, P.,  
Kolls; J.K., Brown, J.,  
Bohm Jr., R.P.,  
Rockar, R., Purcell, J.,  
Murphey-Corb, M.,  
Nelson, S.  
(March 2003).

The effect of chronic  
binge ethanol  
consumption on the  
primary stage of SIV  
infection in rhesus  
macaques.

*Alcoholism: Clinical  
and Experimental  
Research,*  
27(3), 495-503.

# A LCOHOL AND CANCER

- *Drinking alcohol is linked to a greater risk of tumors in the esophagus, mouth, larynx and liver.*
- *Alcoholics also have a greater incidence of genetic damage than normal.*
- *A new study has found that alcohol contributes to the destructiveness of certain carcinogens.*
- *Acetaldehyde, the first product of alcohol metabolism, appears to play a key role in the damage.*

Cancer, the often-deadly process during which normal body cells are transformed into malignant ones, likely involves change in the genetic material of the cells known as deoxyribonucleic acid (DNA). Oncogenes are those genes that regulate cell growth, proliferation and repair of tissues. Oncogenes are also the targets of carcinogenic agents such as asbestos, ultraviolet rays of the sun and cigarette smoking. A study in the March issue of *Alcoholism: Clinical and Experimental Research (ACER)* investigates if alcohol exposure can increase the cytotoxicity (cell destructiveness) of known carcinogenic agents that could, in turn, damage DNA and lead to mutation or cancer.

“We are bombarded by potential carcinogenic agents every day in our environment,” said Richard A. Deitrich, professor of pharmacology at the University of Colorado Health Science Center. “Most of these do not cause cancer, but given a boost from alcohol, some of them may.”

“Epidemiological studies have shown that drinking alcohol is associated with an increased risk of tumors in the esophagus, mouth, larynx and liver,” noted David B. Couch, associate professor of pharmacology and toxicology at the University of Mississippi and lead author of the study. “Blood cells of alcoholics also have a greater incidence of genetic damage than do members of the general population. It has been unclear, however, if alcohol itself causes these effects. The key finding of our study was to show that, in the model system used, alcohol exposure could produce effects consistent with inhibition of the base excision repair pathway.” In other words, alcohol appears to contribute to genetic damage by impairing DNA repair processes.

Researchers tested the survival capabilities of Chinese hamster ovary A10 cells by exposing them to alcohol, genotoxicants (substances that can damage DNA through mutation or cancer) and non-DNA reactive cytotoxic agents. A10 cells were chosen because they have been engineered to express alcohol dehydrogenase (ADH), which is known to convert alcohol to acetaldehyde (AcHO). AcHO belongs to a class of compounds called aldehydes (such as formaldehyde, a disinfectant and preservative), and is well-known as a highly reactive and toxic compound that can damage the cells of any living thing. Normally when people drink, alcohol is converted to AcHO in the liver. It is then rapidly metabolized to acetate, which is then further metabolized by tissues outside of the liver.

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The specific genotoxicants used in the experiment were 1-methyl-3-nitro-1-nitrosoguanidine, ethyl methanesulfonate, 4-nitroquinoline-N-oxide, ICR 170 and mitomycin C. Also used was 6-thioguanine, which damages DNA but not directly. The non-DNA reactive compounds used were ouabain, cycloheximide and colchicine. In addition, an inhibitor of ADH called 4-methylpyrazole was given to some of the A10 cells in order to establish if alcohol or its metabolite acetaldehyde was responsible for cell damage.

“The major finding of this study is that alcohol causes an increase in the mutagenicity (the capacity to induce mutations) of agents that damage DNA,” said Deitrich. “This is as a result of the metabolism of alcohol to acetaldehyde. In fact, it is clear that acetaldehyde is the major culprit in the effects noted here. The presumption is that it is acetaldehyde itself that is causing the damage, but it could be other aldehydes as well. For example, acetaldehyde may interfere with the normal cellular mechanisms designed to inactivate endogenous aldehydes, those produced in normal cellular function or those produced as a result of alcohol’s production of oxidative damage.”

“Acetaldehyde is highly reactive,” added Couch. “It can react with amino groups on proteins, which could potentially interfere with the function of the protein. Of course, acetaldehyde can also react with other cellular constituents, including DNA.”

Couch and Deitrich both noted that, even though researchers have known for a long time that alcohol increases the risk of cancer, relatively little attention has been paid to the genotoxic implications of exposure to alcohol. Deitrich had several suggestions for future research directions, some of which Couch and his colleagues already plan to pursue.

“It would seem reasonable to dissect the mechanism(s) by which DNA damage takes place,” said Deitrich. “For example, what specific DNA damage is done, and why can’t the cells repair this damage? What implications does this research have for about half of the Asian population who lack the ability to efficiently metabolize acetaldehyde? Does this relate to their greater risk of liver damage if they do drink? What implications does this have for alcoholics who are treated with Antabus (containing disulfiram) which increases the level of acetaldehyde in the body if they drink? What implications does this have for these people even if they do not drink, since Antabus inhibits the metabolism of endogenous aldehydes as well?” He added, “Perhaps the most important future research would be to demonstrate that acetaldehyde levels that are found in the normal range after alcohol consumption will also cause this damage.”

**Article is based  
on the following  
published research:**

Couch, D.B.,  
& Baker, R.C.  
(March 2002).  
Ethanol-enhanced  
cytotoxicity of  
alkylating agents.  
*Alcoholism: Clinical  
and Experimental  
Research*,  
26(3), 381-385.



# CAN HEAVY ALCOHOL USE LEAD TO SOME KINDS OF CANCER?

- *A significant proportion of Asians lack the aldehyde dehydrogenase-2 (ALDH2) gene.*
- *Acetaldehyde is produced in saliva while drinking alcohol.*
- *ALDH2-deficient individuals who drink heavily appear unable to eliminate salivary acetaldehyde.*
- *These same individuals have much higher rates of digestive tract cancers.*
- *Findings suggest that salivary acetaldehyde may be carcinogenic.*

In the June issue of *Alcoholism: Clinical and Experimental Research (ACER)*, researchers explore a potential association between high rates of alcohol use and high rates of upper digestive cancers. They used a unique group to investigate their hypothesis: individuals who lack the aldehyde dehydrogenase-2 (ALDH2) gene.

Alcohol is metabolized principally in the liver by two enzymes that act sequentially. Alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde; aldehyde dehydrogenase (ALDH) converts acetaldehyde to acetate. Acetate is then metabolized by tissues outside of the liver. As much as 50 percent of Chinese and Japanese people lack the aldehyde dehydrogenase-2 (ALDH2) isoenzyme, a deficiency which allows acetaldehyde to accumulate in the blood and tissues after drinking. These individuals experience an unpleasant response to drinking alcohol, such as facial flushing, headaches, palpitations, dizziness and nausea. They also seem to have significantly higher rates of digestive tract cancers.

“We need to remember that ALDH2-deficient individuals number in the hundreds of millions,” said Mikko Salaspuro, chairman of Alcohol Diseases at the University of Helsinki, a specialist in internal medicine and gastroenterology at the Helsinki University Central Hospital and lead author of the study. “Accordingly, ALDH2 deficiency is quantitatively the most important gene mutation potentially exposing humans to an increased risk of cancer.” Salaspuro explained that high rates of digestive tract cancers among this population may be associated with high levels of salivary acetaldehyde, an association that provides strong evidence that salivary acetaldehyde is carcinogenic in humans.

Parotid glands are the main saliva-producing organs. Located next to each ear, they are connected by a duct to the upper gingival area under the upper lip. Most people produce approximately 1.5 liters of saliva per day. Usually taken for granted until it’s compromised, saliva is a clear, alkaline, semi-viscous liquid which helps in the digestion of food, and helps to keep exfoliated epithelial cells, most bacteria and food particles away from the teeth. Salaspuro’s study proposes that the parotid glands are able to metabolize alcohol into acetaldehyde.

Oral microflora may also produce acetaldehyde. Every individual has about 300 hundred different bacterial species in their mouth. That number increases exponentially in saliva, even more on tooth surfaces and even more on gingival scrapings. Everyone develops their oral

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## CAN HEAVY ALCOHOL USE LEAD TO SOME KINDS OF CANCER?

microflora within a few weeks after birth. Many live and grow in people's mouths on a platonic basis, but some are harmful, such as those producing tooth cavities or those producing acetaldehyde.

The study found that ALDH2-deficient Asians were exposed to two to three times higher salivary acetaldehyde levels than either Caucasians or Asians with normal ALDH every time they drank, and for as long as they had elevated blood alcohol levels. The ALDH2-deficiency seemed to prevent those subjects from eliminating salivary acetaldehyde. Those with the normal ALDH enzyme were able to remove the acetaldehyde, likely formed in the parotid gland, before it was secreted to their saliva. Which is not to say that normal ALDH levels completely protect heavy drinkers from salivary acetaldehyde; Salaspuro noted that Caucasians that drank heavily for a number of years had much higher rates (20 fold) of esophageal cancer.

"At higher salivary ethanol concentrations," he said, "even the individuals with normal ALDH can achieve carcinogenic acetaldehyde levels in the saliva." Salaspuro said his study's findings are important on several different levels. "We all produce potentially carcinogenic acetaldehyde in our saliva when we drink. The higher the acetaldehyde levels in the saliva, the higher the risk of digestive tract cancer. A person's risk is enhanced if, one, they drink a lot; two, if they are ALDH2-deficient; three, if they smoke or have bad oral hygiene, both of which increase the potential to produce acetaldehyde from alcohol; and four, if they have individual oral microflora characteristics that place them at higher risk."

Ting-Kai Li, distinguished professor at the Indiana University School of Medicine, agrees. "There's a high degree of suspicion or probability that acetaldehyde, which comes from alcohol, is carcinogenic, and this may be a mechanism in the higher rates of cancer among ALDH2-deficient heavy drinkers. It's not a one-to-one relationship, but it may increase the risk."

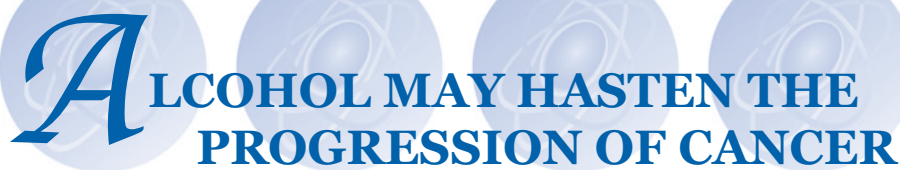
Salaspuro noted that before dietary means and cholesterol-lowering drugs were discovered, individuals with an inherited inability to remove normal blood cholesterol in their livers often died before they reached 30 years of age. He added, "Our findings open a new area, both for screening and preventive research, with respect to gastrointestinal tract cancer. I hope we will be able to one day use our findings about microbially produced acetaldehyde for the prevention of some types of cancers."



### Article is based on the following published research:

Väkeväinen, S.,  
Tillonen, J., Agarwal,  
D. P., Srivastava, N.,  
& Salaspuro, M.  
(June 2002).

High salivary  
acetaldehyde after a  
moderate dose of  
alcohol in ALDH2-  
deficient subjects:  
Strong evidence of the  
local carcinogenic action  
of acetaldehyde.  
*Alcoholism: Clinical  
and Experimental  
Research*,  
24(6), 873-877.



# A LCOHOL MAY HASTEN THE PROGRESSION OF CANCER

- *Alcohol consumption is known to compromise the body's immune system.*
- *A new study investigates the effects of alcohol consumption on mice with melanoma.*
- *Melanoma-bearing mice who received alcohol had a significant loss in body fat.*
- *The loss in body fat appears to facilitate "wasting" which, in turn, shortens survival time.*

Alcohol, the socially acceptable drug, acts upon virtually every organ system and causes a variety of physiologic and behavioral alterations. Its ability to compromise the body's immune system has been linked to the development of infectious diseases such as tuberculosis, as well as oral cancer (including the oral cavity, pharynx, larynx and esophagus), liver cancer and possibly breast cancer in women. A study in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that individuals with cancer who drink excessively may be placing themselves at risk of a more rapid death from cancer.

"Some studies have shown that alcohol consumption increases cancer metastasis," said Gary G. Meadows, director of the Cancer Prevention and Research Center at Washington State University, "while other studies have shown that alcohol consumption decreases metastasis. Thus, there is a lot more work needed in this area." Meadows, the Dorothy O. Kennedy distinguished professor, is also the corresponding author for the study.

For the study, pathogen-free female mice were divided into a number of study groups, each containing 20 mice. These included nontumor, water-consuming mice; nontumor, alcohol-consuming mice; with-tumor, water-consuming mice; with-tumor, alcohol-consuming mice; with-tumor, pair-fed mice that had their alcohol calories replaced with maltose-dextrin; and with-tumor, pair-fed mice that did not have their alcohol-derived calories replaced with maltose-dextrin. The mice were given water or 20% w/v alcohol in their drinking water for three weeks to six months. Some were then inoculated with melanoma cells subcutaneously into the right dorsal hip. The mice continued to consume water or alcohol, and researchers gathered a variety of biochemical data at various time periods following tumor inoculation, including body weight, body water content, tumor weight and carcass fat content.

"Alcohol consumption caused a loss in body fat in the mice with melanoma," said Meadows, "and this was associated with a decrease in survival of the melanoma-bearing mice. This could be important because cancer patients often lose a lot of weight near the end of life even if they are able to maintain their food intake. It is commonly thought that this weight loss accelerates the progression of the cancer and shortens survival. The weight loss for cancer patients is in body protein as well as body fat. However, the interesting thing about the loss of body weight in our study is that it was from fat, not protein."

"Although often regarded as socially unacceptable, fat serves a useful purpose as energy storage for the body," said Carl Waltenbaugh, professor of immunology at Northwestern University Medical School. "Chronic alcohol consumption increases leptin, a fat-cell

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(adipocyte) derived hormone that has multiple biological effects, including the ability to change lipid metabolism. Eventually, an alcoholic's body utilizes fat as a primary energy source, resulting in 'wasting' or rapid loss of body weight. Once fat reserves are exhausted, the body must rely more and more upon alcohol as an energy source. At the same time, alcohol depresses immune function, especially natural killer cells that are responsible for tumor cell elimination. This study shows that chronic alcohol consumption shortens cancer survival time for tumor-bearing patients. For alcoholics without known cancer, loss of natural killer cells means that a first line of defense is missing in these individuals, thus increasing their susceptibility to cancer in the future.

Waltenbaugh suggested that future research determine if alcohol presents a confounding factor for more cancers than melanoma, what amount and duration of alcohol consumption causes this effect, whether or not abstinence from alcohol might affect tumor progression/weight loss, and if leptin antagonists might increase chances of survival.

"Other studies have shown that abnormal leptin levels also alter immune function," he said. "Yet alcohol-induced augmentation of leptin is new to science. Elevated leptin levels and diminished immune function in alcohol-consuming individuals suggest a potential cause for increased susceptibility to infection in these individuals." Conversely, he said, this association may also allow scientists to develop ways to protect alcoholics from infection.

Another possibility for future leptin research, according to Meadows, is related to the finding that the tumor-bearing mice lost weight and fat without losing muscle mass (body protein).

"We are planning more studies in the future to see how alcohol influences fat metabolism," said Meadows. "We are very interested in finding the mechanism for the fat loss in the tumor-bearing mice, because this could lead to a new way to promote fat loss in obese people without the accompanying loss in muscle mass during dieting. In particular, we are interested in the effects that alcohol has on leptin, which also has a role in controlling obesity."



## Article is based on the following published research:

Nunez, N.P.,  
Carter, P.A., &  
Meadows, G.G.  
(May 2002).

Alcohol consumption  
promotes body weight  
loss in melanoma-  
bearing mice.

*Alcoholism: Clinical  
and Experimental  
Research,*  
26(5), 617-626.



## IS THERE A LINK BETWEEN ALCOHOL AND ALLERGIES?

- *Immunoglobulin E (IgE) is a molecule involved in allergic diseases.*
- *Serum IgE levels are influenced by genetics, allergen exposure and some environmental factors.*
- *A new study investigates if alcohol may be one such environmental factor.*
- *Low to moderate alcohol consumption was found to be associated with increased IgE levels.*

Immunoglobulin E (IgE) is a molecule involved in allergic diseases. Atopy – the genetic predisposition to develop IgE antibodies against some antigens in the environment – affects as much as 30 percent of the population, and is believed to be increasing in frequency. In addition to the influence of genetics and allergen exposure, serum IgE levels can also be increased by a number of factors that include parasitic and other infections, neoplasms (abnormal tissue growth) and exposure to certain environmental factors. A study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* investigates if alcohol may be one such environmental factor.

“In prior studies we observed that alcoholics have increased IgE values,” said Arturo González-Quintela, associate professor of internal medicine at the Complejo Hospitalario Universitario de Santiago, Spain and corresponding author of the study. “In the present study, we focused on the possible influence of minor quantities of alcohol intake, that is, ‘normal consumption’ or what is considered below the range of alcohol abuse. To our knowledge, this is the first study to focus on the association of low to moderate alcohol intake and both total and specific serum IgE levels.”

A total of 460 patients (251 males, 209 females) were recruited from an adult allergy clinic in Spain. Based on skin-prick tests to common aeroallergens, 325 (71%) were classified as atopic and 135 (29%) as non-atopic. Most of the atopic patients (253 or 78%) were allergic to house dust mites. Using 10 grams as a measure of one drink, 260 patients (57%) were found to consume a median of 30 grams of alcohol per week and 200 patients (43%) were considered abstainers. Total serum IgE was measured in all patients and serum specific IgE (for specific allergies) were measured in atopic patients.

“Our research found that regular alcohol intake higher than 70 grams per week (or more than one drink per day) was associated with increased total serum IgE levels in the patients studied,” said González-Quintela. “In patients allergic to house dust mites, regular alcohol intake was associated with increased serum levels of specific IgE against these mites.”

“These findings do not merely support the suggestion that alcohol simply is a risk factor for developing allergies,” observed Thomas R. Jerrells, professor of pathology and microbiology at the University of Nebraska Medical Center and the Omaha VA Medical Center. “The study results indicate that consumption of alcohol may result in abnormal immune responses or that the control of the immune system is affected. This leads to questions about the significance of

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the increased response to allergens by drinkers. If alcohol somehow affects the control of the immune response to these allergens, an exaggerated response would be expected.”

Jerrells speculated that alcohol, either directly or indirectly through metabolites, might non-specifically activate a very complicated function of the immune system to produce IgE. An alternative possibility is that alcohol, again directly or indirectly, might activate cells that carry preformed IgE to release the IgE. Jerrells added that cells in various tissues, especially the gut, have surface IgE such as mast cells.

Nonetheless, despite results suggesting that even low to moderate alcohol consumption may affect the immune system, study authors show caution in extending these findings beyond the specific results.

“It is important to realize that it cannot be concluded,” said González-Quintela, “that alcohol intake increases the likelihood of either developing allergic sensitization to aeroallergens such as dust mites, or developing more severe symptoms in patients already sensitized. Nor can it be concluded that alcohol intake should be avoided by allergic patients.”

González-Quintela said that ongoing, unpublished studies indicate that, rather, alcohol intake is likely associated with a variable rate of sensitization to distinct aeroallergens. In other words, the sensitization rate either increases or decreases depending on the allergen considered. Furthermore, allergic sensitization depends on multiple variables – including socioeconomic conditions – that cannot be always controlled for in observational or non-experimental studies.

“Not all atopic subjects develop allergic symptoms,” he said. “In addition to a genetic background, they will also need allergen exposure. Moreover, some environmental factors more than others favor allergic or IgE-mediated immune responses. We simply need more research to improve the understanding of allergic diseases and what role alcohol consumption may play.”



### Article is based on the following published research:

Vidal, C.,  
Armisen, M.,  
Dominguez-  
Santalla, M.J.,  
Gude, F., Lojo S., &  
Gonzalez-Quantela, A.  
(January 2002).  
Influence of alcohol  
consumption on serum  
immunoglobulin E  
levels in atopic and  
non-atopic adults.  
*Alcoholism: Clinical  
and Experimental  
Research*,  
26(1), 59-64.

# How TO BUILD STRONG BONES: GET MILK, LOSE THE BOOZE

- *Alcohol consumption contributes to bone loss, and is a likely risk factor for osteoporosis.*
- *Alcohol-induced bone loss seems primarily due to reduced bone formation.*
- *An experimental drug treatment for osteoporosis called parathyroid hormone may reverse alcohol-induced bone loss in younger drinkers.*
- *Chronic adult drinkers remain at high risk of earlier and more severe osteoporosis.*

A popular bar and eatery in Austin, Texas sells t-shirts that say “Beer: It’s not just for breakfast anymore.” While the play-on-words may be initially amusing, osteoporosis is not. Alcohol consumption is known to be a significant contributing factor to bone loss, and is believed to be a risk factor for osteoporosis. Two rodent studies in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)* examine alcohol’s effects on bone. Specifically, one study investigates if these effects are reversible; another explores what differences may exist between the effects of drinking during youth versus adulthood.

“The most common form of osteoporosis occurs in elderly women and is caused by estrogen deficiency,” said Russell T. Turner, professor of orthopedics at the Mayo Clinic and lead author of one of the studies. “Bone thinning occurs as a result of a large increase in bone resorption (a loss of substance). In contrast, alcohol-induced osteoporosis is caused by decreased bone formation and is frequently observed in middle-aged men.”

Alcoholics often have bones that are less dense than normal. Less bone density means less bone strength, which can increase an individual’s risk of bone fracture. In fact, alcoholics have a high rate of non-traumatic and trauma-induced bone fractures, especially in the femoral neck. Although good nutrition is essential for maintaining bone health – and alcoholics usually have poor nutritional habits – animal studies have shown that alcohol can slow bone growth even when nutrition is maintained. This indicates that alcohol is directly responsible for at least some detrimental effects on bone health.

“Drinking cessation does not result in a spontaneous reversal of alcohol-induced bone loss,” said Turner. “This may mean that alcohol has an irreversible toxic effect on bone cells or that alcohol interferes with the normal communication between bone cells which governs the delicate balance between how much bone is formed and how much bone is resorbed.” Turner and his colleagues tested the effects of parathyroid hormone (PTH), an experimental drug treatment for osteoporosis, on rats whose bone formation had been suppressed by alcohol. The animals were the human equivalent of young adults. “The fact that they responded so vigorously indicates that alcohol-induced bone loss can be reversed,” he said.

James R. West, professor and head of the Department of Anatomy and Neurobiology in the College of Medicine and interim vice-president for research at the Texas A&M University System Health Science Center, calls this finding very interesting.

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# How TO BUILD STRONG BONES: GET MILK, LOSE THE BOOZE

However, he cautions, “PTH is also known to take calcium out of bone. So the fact that PTH can, under certain conditions, actually stimulate bone growth is a little bit unusual.” He called for longer-term studies.

Both Turner and H. Wayne Sampson, professor of human anatomy and neurobiology in the College of Medicine at the Texas A&M University System Health Science Center and lead author of the second study published in *ACER*, cautioned against adolescent drinking. “The issue of bone loss is especially critical for young people today since it is now reported that problem drinkers begin as preteens,” said Sampson. “Animal studies of an age comparable to human youth have repeatedly shown shorter bones, weaker bones and decreased bone density. Except for length, these qualities do not recover with age and, should osteoporosis occur, the bones would reach fracture threshold sooner.”

Sampson’s study is one of the first to demonstrate actual bone loss in animals that begin drinking as adults. This is an important distinction because if, as believed, alcohol has a direct effect upon osteoblasts (bone forming cells), then adults who drink heavily are causing potentially irreversible damage to their bones.

“In the younger animals tested,” said West, “you still had growth. The alcohol interferes with the growth and bone development, but when you stop the alcohol, growth resumes. Alcohol doesn’t prevent or stop the growth, it simply interrupts it. Of course, one of the dangers of growth resumption is that it gives the impression that alcohol exposure is really not a risk.” In adults, however, a grave risk of cumulative, alcohol-induced bone damage is that bone growth does not resume.

“After eight weeks,” said Sampson, “we saw nothing. But after 14 weeks, results were very dramatic. With time, alcohol had deleterious effects on adult bones. These findings indicate that if adults begin drinking chronically, they will weaken their bones and run the risk of earlier and more severe osteoporosis, should they develop the disease.”

“Demographics are changing,” said West, “and we’re seeing more osteoporosis. We need to ask ‘to what extent is alcohol abuse playing a role in this?’ People tend to think of someone who misuses or abuses alcohol as kind of a skid-row bum, but that’s not necessarily the case. There are some people out there who are drinking enough to cause organ damage and yet they’re going to work and keeping up a regular job. The cumulative, toxic effects of alcohol would surprise a lot of people.”



**Article is based  
on the following  
published research:**

Hogan, H.A.,  
Argueta, F.,  
Moe, L., Nguyen, L.P.,  
& Sampson, H.W.  
(May 2001).  
Adult-onset alcohol  
consumption induces  
osteopenia in female rats.  
*Alcoholism: Clinical  
and Experimental  
Research*,  
25(5), 746-754.

# A

## LCOHOL, SODIUM SENSITIVITY AND BLOOD PRESSURE

- *Chronic heavy drinking is known to elevate blood pressure.*
- *Sodium sensitivity also tends to raise blood pressure.*
- *New research indicates that withdrawal from heavy drinking may derange sodium metabolism in such a way that a person's sodium sensitivity is increased, leading to higher blood pressure.*

Alcohol appears to have the potential for both beneficial and toxic effects on the heart. The “French Paradox,” for example, refers to the protective properties that red wine may have vis-à-vis heart disease. Chronic heavy drinking, on the other hand, is a leading cause of several cardiovascular illnesses, including high blood pressure. High blood pressure or hypertension, increases the risk for heart disease and stroke, both leading causes of death in the United States. A study in the December issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that alcohol-induced sodium sensitivity may be one of the mechanisms underlying the association among heavy alcohol consumption, alcohol withdrawal and high blood pressure.

“We know that chronic exposure to heavy amounts of alcohol elevates blood pressure and contributes to hypertension among alcoholics,” said Cristiana Di Gennaro, a junior scientist at the University of Parma and corresponding author for the study. “We also know that sodium sensitivity is characterized by an increase of blood pressure, although not necessarily in the hypertensive range, when salt intake is elevated. In addition, sodium sensitivity has been shown to be an independent risk factor for cardiovascular disease. Our findings indicate that alcohol consumption may raise blood pressure through the induction of a sodium sensitive state.”

“There is some evidence that for heavy drinkers, even when they don’t drink, blood pressure is high,” said Maurizio Trevisan, professor and chairman of the department of social and preventive medicine at the School of Medicine, University of Buffalo. “The day after they drink, for example, their blood pressure may be higher than normal. If they drink chronically, they are in sort of a constant level of withdrawal. This can occur even in moderate drinkers, although the evidence is not as clear as it is for the heavy drinkers.” What happens during these “mini-withdrawals,” he said, is even more pronounced during extended or complete withdrawal.

Researchers examined 18 alcoholics (six females, 12 males) entering in-hospital detoxification at the University of Parma in Italy. Their blood pressure and sodium levels were assessed during their first eight days of stay. During this time, each patient was on a fixed hospital diet that provided 150 mM of sodium per day (considered normal). After one year of carefully monitored abstinence, study participants underwent a four-week phase of examination, which included measuring their blood pressure levels on three separate occasions. Then they were asked to adhere to a diet of 55 mM of sodium per day (considered low), which was later supplemented with 205 mM (for a total of 260 mM, considered high) of sodium per day.

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# ALCOHOL, SODIUM SENSITIVITY AND BLOOD PRESSURE

During the first eight days of withdrawal, alcoholics on a 'normal' diet of sodium intake demonstrated high sodium levels, weight gain and increased blood pressure. A year later, and during exposure to the dietary sodium manipulations, the same group displayed much more significant changes in blood pressure and greater sodium sensitivity when compared to a group of teetotalers. In addition, changes in blood pressure during the early withdrawal period were related to sodium sensitivity during long-term abstinence. These findings suggest that salt sensitivity plays a key role in blood pressure regulation in early withdrawing alcoholics.

"Prior to this study," said Trevisan, "we knew about some of the conditions that increase sodium sensitivity. One of them is insulin resistance, another is being overweight. Now we have [yet] another factor that appears to increase someone's sodium sensitivity, that is, heavy alcohol consumption. It looks like heavy alcohol consumption for long periods of time appears to derange your sodium metabolism in a way that makes you more sodium sensitive."

"We do not know definitely whether sodium sensitivity is an acquired trait linked to alcohol abuse," added Di Gennaro, "or a genetic trait. We do know, however, that sodium sensitivity remains significant after at least one year of alcohol abstinence in heavy alcoholics. We believe that our demonstration of an important interaction among alcohol consumption, sodium metabolism, blood pressure regulation and cardiovascular diseases extends further our knowledge about the impact of dietary and lifestyle factors on one of the most important causes of morbidity and mortality in western countries. Our findings also suggest that a dietary reduction of both alcohol and salt is warranted."

Trevisan agrees. "Everybody should benefit from a low-sodium diet anyway," he said.



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# A

## LCOHOL'S EFFECTS ON TESTOSTERONE

- *Most research has shown that alcohol inhibits testosterone secretion in male animals and humans.*
- *A new study has found that acute administration of alcohol can increase testosterone biosynthesis in some male rodents.*
- *These results provide evidence for individual differences in behavioral reactions to alcohol.*

Even though testosterone is often referred to as a “male sex hormone,” it is in actuality common to both genders of animals and humans. The overwhelming majority of research conducted in the past 25 years in both animals and humans has found that alcohol inhibits testosterone secretion. However, a new study in the January issue of *Alcoholism: Clinical and Experimental Research (ACER)* has found that acute administration of alcohol can induce a rapid increase in plasma and brain concentrations of testosterone in some rodents.

“We have demonstrated that there are very different results in the way two different groups of male rats form testosterone after acute administration of alcohol,” said Robert H. Purdy, senior staff scientist in the Department of Neuropharmacology at the Scripps Research Institute and senior author of the study. “These differences in animals may reflect similar individual differences in humans, and provide new insights for understanding individual differences in the behavioral and endocrine pathology associated with alcohol abuse.”

Researchers injected either alcohol or 1,1-dideuteroethanol (2 g alcohol/kg body weight) into the abdominal cavities of two groups of rats, 30 un-operated and 24 adrenalectomized and castrated (ADX/GDX) Wistar males. 1,1-dideuteroethanol is a nonradioactive form of alcohol in which two of the hydrogen atoms on carbon atom #1 of ethanol have been replaced by deuterium atoms, which can then be traced. Study authors used mass spectrometry, a very precise measure of the mass and structure of compounds derived from extracts of tissues and body fluids, to determine both the amount of neuroactive steroids present and the degree of deuterium incorporation into specific neuroactive steroids isolated from brain samples.

They found that concentrations of testosterone increased fourfold in the frontal cortex and threefold in the plasma of the un-operated rats 30 minutes after alcohol administration. ADX/GDX rats had testosterone concentrations that were only five percent of those found in the un-operated rats following alcohol administration. Tracing the effects of 1,1-dideuteroethanol demonstrated that alcohol oxidation is directly linked to testosterone biosynthesis.

“Our finding of a direct link between alcohol administration and the level of the neuroactive steroid testosterone in the brain of these experimental animals was unanticipated from prior studies with another species of rats,” Purdy said.

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# A

## LCOHOL'S EFFECTS ON TESTOSTERONE

“Although many other studies clearly demonstrate that chronic consumption of high dosages of alcohol appears to be consistently inhibitory and suppresses reproductive function,” said Dennis D. Rasmussen, research associate professor in the Department of Psychiatry at the University of Washington, “this study raises the possibility that episodes of alcohol consumption may also at least temporarily increase testosterone levels, with the direction of the response likely being dependent upon a variety of factors, including dosage and personal characteristics. This particular dosage produced blood alcohol levels and behavioral responses consistent with intoxication. So, alcohol consumption, under at least some conditions and by at least some individuals, may acutely stimulate testosterone levels in the plasma and brain of both males and females and thus could elicit some of the behavioral effects associated with increased testosterone levels, such as increased libido or aggression.”

Rasmussen added that these findings join those of two other studies in which alcohol administration increased plasma testosterone levels in a gender- and dose-dependent manner. “Together these studies are important,” he said, “because they illustrate that what has become a largely accepted principal – that alcohol consumption inhibits plasma testosterone levels and reproductive function – is not universally true.”

Rasmussen suggested that future research build upon and add to previous findings regarding alcohol's effects on testosterone. “It would be important to determine whether lower dosages of alcohol, which do not induce rapid pronounced intoxication and ataxia, would also produce the acute increase in testosterone, and whether this response to lower dosages would be consistent across different strains of rats. Also, does tolerance develop with repeated administrations? Does this increase in testosterone occur following elective self-administration of alcohol? Finally, and probably most interesting, what role might the demonstrated changes in testosterone play in behavioral responses to acute ethanol consumption? Are there gender differences in these responses? And, if the responses do occur in females, are they different during different stages of a woman's cycle?”



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# M MODERATE ALCOHOL CONSUMPTION AFTER MEALS CAN DECREASE LEVELS OF INSULIN

- *Insulin is a hormone that allows blood glucose to provide energy to most of the body's cells.*
- *A lack of insulin can effectively cause some cells to "starve," leading to serious health consequences such as diabetes.*
- *New research shows that drinking a moderate amount of white wine on its own after a meal can cause levels of insulin to drop almost immediately.*

Insulin is a hormone that allows blood glucose to provide energy to most of the body's cells. New research published in the November issue of *Alcoholism: Clinical and Experimental Research (ACER)* shows that drinking a moderate amount of white wine on its own after a meal can cause levels of insulin to drop almost immediately.

"A small to moderate amount of alcohol is accepted and indeed often recommended as beneficial to one's cardiac health," said Anna Kokavec, a research psychologist affiliated with La Trobe University in Bundoora, Australia and first author of the study. "However, only a limited number of studies have assessed the effect of consuming readily available alcoholic products on major processes in the human body."

Eating foods high in carbohydrates will normally increase blood-glucose levels for several hours, which in turn, encourages insulin production by the pancreas. Insulin enables glucose, the body's chief source of energy, to gain entry into most of the body's cells located outside of the brain. A lack of insulin can effectively cause some cells to "starve," leading to serious health consequences such as diabetes.

"We know that drinking alcohol can affect the body's production of insulin," said Kokavec. "However, researchers in the past have obtained mixed results and it is only now becoming clear that the effect of alcohol on insulin may depend on the presence or absence of food. Given the discrepancy in the insulin data, the association between food and insulin production, and the important role of insulin in energy production and usage, we felt that the effect of drinking a popular alcoholic beverage such as white wine on insulin production under variable nutritional conditions warranted investigation."

Researchers examined eight non-diabetic males between the ages of 19 and 22 years. All were required to consume pizza and a soft drink for 45 minutes, and then slowly drink three standard units of white wine (10 grams of alcohol each; 30 grams total) during a 90-minute period following their meal. Plasma glucose and plasma insulin levels were assessed during and following the alcohol-consumption period.

"Our results showed that drinking a moderate amount of white wine on its own after a meal can cause the level of insulin to drop almost immediately," said Kokavec. "This was accompanied by a similar lowering of the blood-glucose level and, in some individuals, to a very dangerously low level. The level of insulin after little more than one glass of white wine was

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# M

## ODERATE ALCOHOL CONSUMPTION AFTER MEALS CAN DECREASE LEVELS OF INSULIN

similar to the level of insulin usually seen before a meal. When this is considered together with the blood-glucose finding, it suggests that drinking white wine on its own may promote a pseudo-diabetic condition, changing the way the body produces and uses glucose. This could have serious consequences because some of the cells in the body could be starved of energy, which could ultimately lead to disease.”

Kokavec added that these findings also support the previously published theory that alcohol may activate a new energy system that was thought, until recently, to exist only in plants and other organisms that do not require oxygen.

“The glyoxylate cycle is an energy system that can convert fat into carbohydrate,” she said. “The glyoxylate cycle does not require thiamin, utilizes acetate as an energy source and can be switched off by glucose. If alcohol does indeed activate the glyoxylate cycle in the human liver, then this could offer an explanation for alcohol-related fatty liver, thiamin deficiency, alteration in energy metabolism under fasting conditions and lack of appetite for carbohydrates [that are] found in alcoholics, the reasons for which have baffled researchers for years.”

Furthermore, said Kokavec, “present results highlight the need to strictly control for nutritional factors when designing alcohol research as nutritional status may be a confounding factor that is contributing to variability in the alcohol literature. In addition, given the possibility that alcohol may activate the glyoxylate cycle (an energy pathway that can be switched off by glucose) it may be important for scientists to specifically control for the presence of carbohydrates when investigating the effect of alcohol.”



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# CHRONIC ALCOHOL ABUSE DAMAGES REGULATING HORMONES

- *Chronic alcohol consumption is associated with higher rates of infections, cardiomyopathy, cardiac arrhythmias, bleeding complications and liver insufficiency.*
- *New research indicates that changes in hormones that regulate electrolyte and water balance in the body may not only account for some withdrawal symptoms, but persist over long periods of strictly controlled abstinence.*

Although it is well known that alcohol abuse causes a broad range of health complications, it remains unclear how much regeneration may occur during long-term abstinence. A new study carefully monitors major water and electrolyte regulating hormones – arginine vasopressin (AVP), atrial natriuretic peptide (ANP), aldosterone and angiotensin II – from early withdrawal up to 280 days of strict abstinence. The results, published in the May issue of *Alcoholism: Clinical and Experimental Research (ACER)*, indicate that chronic alcohol abuse can cause severe alterations in hormones that regulate the body's electrolyte and water balance.

“Most available literature on regeneration from alcoholism is restricted to the first [few] days [and up to] three weeks of abstinence,” said Hannelore Ehrenreich, head of Clinical Neuroscience at the Max-Planck-Institute for Experimental Medicine and corresponding author for the study.

“Both chronic alcohol consumption and alcohol withdrawal can affect cell and homeostatic functions,” said Claudia Spies, medical associate director of the Department of Anesthesiology and Intensive Care Medicine at the University Hospital Charite Campus Mitte. “A chronic alcohol intake of at least 60g, or 1.5l beer, per day is associated with complications such as higher rates of infections, cardiomyopathy, cardiac arrhythmias, bleeding complications and liver insufficiency. During withdrawal, changes in electrolyte and water homeostasis occur.”

The consequences, however, are clear. “The hospital stay of alcoholics is prolonged compared with that of non-alcoholics,” said Spies. “A major complication is alcohol withdrawal syndrome (AWS), developed by approximately half of chronic alcoholics during their hospital stay. The majority of the patients who develop AWS have hallucinations or delirium. AWS can also be deadly. In one study, the mortality rate in patients with AWS was approximately 18 percent, whereas alcohol abusers without AWS had a mortality rate of four to six percent, and non-alcohol abusers had a mortality rate of zero percent.”

“Vasopressin, or AVP, is a hormone that is also part of the stress regulatory system,” said Ehrenreich. “In previous work, we showed that circulating levels of AVP are persistently suppressed in alcoholic patients over many weeks of abstinence. This is why we chose to further elucidate the recovery of vasopressin levels in alcoholics during long-term abstinence.”

Two groups of males participated: alcoholics (n=35), 30 to 61 years of age and controls (n=20), 25 to 50 years of age. The two groups were matched on cigarette use. “It is well known that

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## CHRONIC ALCOHOL ABUSE DAMAGES REGULATING HORMONES

acute nicotine use increases the secretion of AVP,” explained Ehrenreich. “It has to be assumed that chronic cigarette consumption also alters AVP secretion or metabolism. Therefore, we used cigarette-matched controls to exclude the influence of such an interfering variable.”

Following an inpatient detoxification period of two to three weeks, 21 of the 35 alcoholics were successfully monitored for the full length of the study period, 280 days. Researchers collected data from all of the participants on their AVP, ANP, aldosterone and angiotensin II levels, as well as measures of kidney and liver function.

They found that basal AVP levels were suppressed during the entire study period. In contrast, ANP levels were elevated for the entire time. No persistent alterations were found for aldosterone or angiotensin II. “We learned that we are dealing with profound, long-lasting alterations of key hormones of water and electrolyte balance notwithstanding at least nine months of controlled abstinence,” said Ehrenreich. “These observations imply a number of causes and consequences: they may explain excessive thirst and fluid intake, what we call diabetes insipidus; may explain how alcohol-related cardiomyopathy develops; and may show that there is a subclinically impaired renal function in these patients which clearly underlines the concept of multi-organ involvement in alcoholism. Not only are the liver and brain affected, but basically all organs are.”

Both Ehrenreich and Spies believe these results can be used to develop new therapeutic options to support abstinence. “One possibility would be to substitute AVP,” said Ehrenreich, “which might not only contribute to recovery of water and electrolyte homeostasis but also benefit cognitive functions. The findings imply that some features of craving, such as drinking behavior and thirst, might be explained by biological alterations in the regulation of salt and water homeostasis. Therefore, approaches to normalize vasopressin regulation might result in a reduction of craving-induced relapses.”

Ehrenreich added that one of the most important findings is that “chronic alcoholism is associated with long-term persistent alterations of various organs and systems. There is no immediate recovery to be expected,” she stressed. “Both for psychological and medical reasons, we need to consider that we are dealing with individuals severely compromised over many months of controlled abstinence. Detoxification treatments are necessary to overcome life-threatening withdrawal symptoms.”

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