

# REPORT

## SAMe Part 3: The Liver Super-Nutrient

The evidence is definitely in. SAMe (S-adenosylmethionine) is serious medicine against liver disease. Almost a thousand published studies document the ability of this bioactive form of methionine to prevent and treat liver disorders, including cancer.

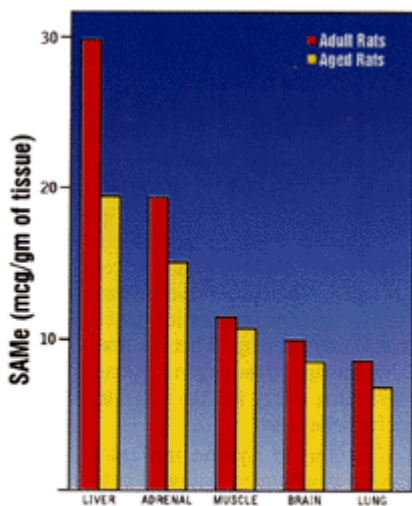


SAMe, the amazing "super-nutrient," can single-handedly normalize liver function. How? SAMe is the central player in liver biochemistry. It does two crucial things: It methylates, and it transforms itself into the liver's most vital substance, glutathione.

The liver contains the third highest amount of SAMe in the body, after the adrenal and pineal glands. SAMe is so important for liver function that it can be considered an essential nutrient for that organ. In addition to its many other functions, SAMe plays a leading role in liver regeneration. The liver has special SAMe enzymes just for regenerating tissue.

The liver has a tough job. It has to break down every chemical the body encounters, including drugs. It has to filter blood, chase after bacteria, make bile, and create various other substances such as lipoproteins. In short, there is a reason the liver is the only organ that readily regenerates: It has to.

SAMe is the product of a biochemical reaction between ATP and methionine. Half of all methionine in the body is used in the liver to make SAMe. SAMe has been compared to ATP in its importance for the body. It is used in many different cellular processes, from replication to biochemical reactions that create melatonin and phosphatidylcholine. SAMe is particularly important for the liver because glutathione is synthesized from it. Glutathione is crucial for liver function. A good portion of liver SAMe is turned into glutathione. Glutathione is the liver's natural antioxidant.



As rats age, their levels of SAMe decrease in different parts of the body. (Adapted from Stramentinoli, et al. J Gerontol 32: 391.)

SAMe has been isolated from yeast and purified. It is currently sold in Europe as an antidepressant. Many clinical studies have been conducted with this supplemental form of SAMe. It has been used in trials against depression, osteoarthritis and other conditions. Of all the published studies, the ones on the liver are perhaps the most comprehensive.

### SAME AND CIRRHOSIS

The normal liver is a real workhorse. It stores vitamins, manufactures cholesterol, filters bacteria from blood, synthesizes fibrinogen and prothrombin (blood clotters), breaks down toxic biochemicals, synthesizes proteins and bile, and makes glycogen from glucose. The liver has bacteria-killing detoxifying cells called reticuloendothelial cells, which are only found in the liver, lymph nodes and spleen. Liver health is extremely important: What goes on in the liver affects many other body systems. A person with a sick liver is a person in trouble.

Cirrhosis of the liver begins with fatty infiltration, then progresses to an organ full of nodules and ropes of connective tissue. Degeneration and regeneration of tissues also occur. Alcoholism or hepatitis virus usually causes cirrhosis of the liver, but various other

conditions also can cause it.

One of the biochemical consequences of cirrhosis is glutathione depletion. Glutathione is a very important antioxidant for the liver. The liver contains lots of fat and mitochondria, both of which generate free radicals. Without sufficient glutathione to quench them, the radicals damage the liver. Much of what is called cirrhosis is actually free radical damage from lipid peroxidation and oxidative stress.

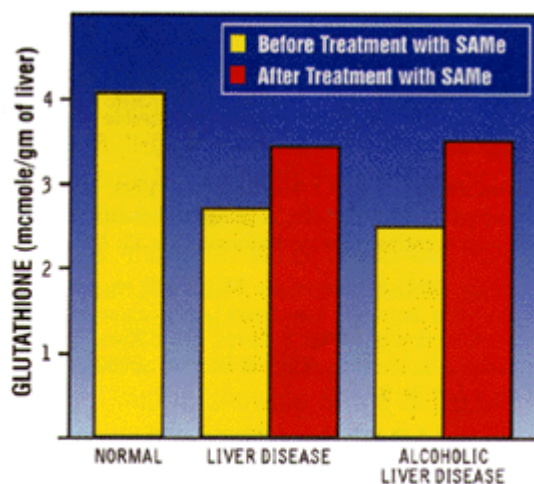
Alcohol breaks down to a product called acetaldehyde, a notorious free-radical producer. Glutathione and cysteine both bind to acetaldehyde to neutralize it. In chronic alcoholism, there is so much free radical damage to "clean up" that the antioxidant system can barely keep up. What results is massive damage to the organ responsible for screening every foreign substance that enters the body.

Cysteine is synthesized along the SAME biochemical pathway before glutathione is made. Cysteine eventually becomes glutathione. The SAME byproduct, homocysteine, is the precursor for cysteine. (Note: antioxidant vitamins C and E are partners with glutathione: They work together to maintain levels of each other).

## PROTECTION AGAINST TOXINS

Study after rat study shows that maintaining SAME levels protects the liver. Acetaminophen (Tylenol) is notorious for causing liver toxicity. In a mouse study, deaths from high doses of acetaminophen were completely abolished if SAME was given within one hour. If given within five hours, the number of deaths was significantly reduced. Rats treated with tetrachloride develop massive free radical damage very similar to what occurs with alcohol. If the same rats are given SAME, damaging collagen deposits can be significantly reduced. How does SAME work? It works by increasing or maintaining glutathione levels.

SAME's ability to be taken up by human liver cells and converted into glutathione was confirmed by researchers in Spain in 1991. They reported in *Toxicology* that supplemental SAME maintains glutathione levels if added at the same time as alcohol (which drastically depletes glutathione).



**Total glutathione before and after 6 months treatment with 1,200 mg oral SAME. (*Gastroent* 24:407, 1989).**

Although there are hundreds of rodent studies on the protective effects of SAME on the liver, human studies are scarce. There are two good reasons for this: Liver biopsies are not popular, and SAME is not patented. Several human studies done outside the U.S. do, however, demonstrate that the rodent studies with SAME hold up in humans. Some of these were reported in a Drugs supplement entitled "Recent Advances in the Treatment of Liver Diseases," published in 1990.

In a placebo-controlled study in the *Scandinavian Journal of Gastroenterology*, 16 patients with liver disease (both alcoholic and non-alcoholic) were given 1,200 mg of oral SAME per day for six months. Liver biopsies showed a significant increase in glutathione, and a significant reduction in oxidized glutathione. In the non-alcoholic, liver-damaged subjects, alanine aminotransferase (a liver enzyme indicating damage) was reduced. In a study in which 45 patients with alcoholic liver disease were treated with intravenous SAME for 15 days, liver function improved significantly. Besides its ability to keep the liver's antioxidant system functioning, SAME works in other important ways.

## SAME AND FAT

The liver is Grand Central Station for molecules that chaperone lipids around the body (lipoproteins). It is the site where very low-density lipoproteins (VLDL) and cholesterol are synthesized. Cholesterol is the precursor for important steroid hormones such as estrogen, DHEA, androgens and the glucocorticoids. It also is part of bile, which acts as a natural detergent against dietary fat. Cholesterol has gotten a bad rap; it is actually a very important substance.

Cirrhosis of the liver causes fatty infiltration, in which pools of lipids accumulate in the liver. SAME can prevent and cure this condition. Rats were the first to experience SAME's lipid-lowering benefits. In a rodent study in *Toxicology and Applied Pharmacology*, SAME completely prevented fatty liver when given at the same time as alcohol. In a study involving 37 people with fatty liver, hepatitis and cirrhosis, 150 mg of SAME, I.V., completely obliterated the fat in three patients and substantially reduced it in all others within 15 days. Groups in Italy and a group in Spain confirmed these results.

Not only does SAME prevent fat from accumulating in the liver, it prevents cirrhosis-related lipid elevation outside the liver. The blood cells in people with cirrhosis have a high cholesterol-to-phospholipid ratio. This causes problems with the way cells function. Kidney problems, bleeding and anemia in cirrhosis patients can be traced to cell membrane problems. How well cells function depends upon how well their membrane functions. Cell membranes need just the right amount of fluidity to function well. Fluidity depends on lipids. Too much cholesterol, and they harden up. Too much phosphatidylcholine, and they spread out like watery pancakes.

People with liver disease have too much cholesterol in their cell membranes. A group in England has shown that SAME dramatically reduces cholesterol. The cholesterol-to-phospholipid ratio decreased substantially in the erythrocytes of people with

liver disease two weeks after they were treated with oral SAME (1,600 mg). SAME has been shown to decrease cholesterol in plasma as well. Thirteen patients with hyperlipidemia were given 30-minute infusions of SAME. Total lipids and cholesterol fell significantly.

## **THE CANCER CONNECTION**

It is thought that alterations in the liver caused by alcohol, toxins and diseases can eventually cause cancer. In 1988, a group in Spain discovered that people with cirrhosis have deficiencies of two important enzymes that convert methionine to SAME, and form phospholipids (S-adenosylmethionine synthetase and phospholipid methyltransferase). Important discoveries recently have been published about SAME synthetase and cancer. Researchers at the University of Southern California report that liver cancer cells are totally lacking in liver-specific SAME synthetase. The genes for this enzyme are completely turned off in liver cancer patients.

A group at the Institute of Biomedical Investigation in Spain reported a second discovery about SAME synthetase and cancer. They found that the immune substance interleukin-2 (IL-2) turns on the SAME synthetase gene in T-cells. IL-2 is necessary for the growth of immune cells that fight viruses and cancer. Look for more research on this important enzyme in the near future as the role it plays in liver cancer is uncovered.

Many of the chemicals used to induce cancer in lab animals work by inhibiting SAME. SAME's role as a methyl donor is critical in preventing cancer (a methyl group is a biochemical entity that catalyzes important biochemical reactions in the body). The liver appears to be particularly sensitive to under-methylation.

It is well established that methyl deficiency produces liver cancer in rodents. The sequence of events has been shown in numerous studies. Methyl deficiency causes a reduction in SAME levels, and an elevation in S-adenosylmethionine homocysteine (SAH). SAH is what's left over after SAME donates a methyl group for biochemical reactions. An enzyme, SAH hydrolase, turns SAH into homocysteine. Homocysteine can be toxic if it builds up within the body, but is converted into cysteine (and eventually glutathione) if enough SAME is present.

If SAME is super-deficient, nothing gets converted, and SAH and homocysteine back up like a clogged drain. This is when cancer gets its toehold. A low SAME-to-SAH ratio is step-one in the development of liver cancer. Maintaining SAME can reverse the early changes in the process.

Certain genes must be methylated in order to keep cancer from starting. Under-methylation causes cancer. This very straightforward process is apparent in rodent models. After five weeks of a methyl-deficient diet, rats show cell changes. By the ninth week, transcripts of protooncogene genes (cancer genes c-myc and c-ras) start accumulating. It is downhill from there.

## **CANCER CELLS RUN WILD**

Cancer suppressor genes also are adversely affected by under-methylation. Researchers at the FDA's National Center for Toxicological Research have conducted research showing how under-methylation affects the p53 tumor suppressor gene. They have found that rats fed a diet deficient in SAME precursors (methionine, choline and folic acid) accumulate DNA strand breaks in certain areas of the p53 gene within days. (They also discovered areas of the p53 gene that are resistant to under-methylation). DNA strand breaks translate into a defective or non-functioning p53 protein. Without p53 to stop them, some types of cancer cells will run wild.

The prevention of liver disease is just as important as the prevention of heart disease and cancer. Like these two killers, liver diseases can be prevented by simple yet very effective dietary means. No person escapes liver damage. We are constantly assaulted by chemicals in air and water, pharmaceutical drugs, radiation, pesticides, hormones and drugs in meat, fungicides on grains, bacteria, parasites and other entities. The liver must deal with all of them on a daily basis. It generates a massive amount of free radicals during detoxification. Helping the liver is one of the simplest and most important things persons can do for their health. It is very likely that many diseases in other organs begin when the liver can't do its job.

It is not surprising that aging has an effect on liver function. A lifetime of insults takes its toll. Older people metabolize drugs differently than younger people. Their livers can't keep up. Alcohol and viruses can damage an elderly person's liver in months as opposed to years. Methylation of genes declines in older people, making cancer far more likely. Mitochondrial function declines, and lipid peroxidation increases. Glutathione levels decline, and levels of glutathione-related enzymes decline. If an older rat is fed a high cholesterol diet, cholesterol will show up in its plasma, whereas it won't in a younger rat. Changes in the way the liver synthesizes and handles lipoproteins is probably responsible for this. A study on apolipoprotein A1 ("apo" refers to the non-lipid part of the lipoprotein) indicates that lipid-related hormone receptors get faulty in old age. It also has been shown that the types of lipids within lipoproteins change in aging livers.

Free radical damage increases in old age. Researchers have not settled whether aging causes an increase in free radical

production or causes a decline in free radical scavengers. Studies on aging livers show both. One thing is certain, however: Free radicals damage DNA, and damaged DNA makes defective proteins, which lead to cells that don't function properly.

While all the pieces of the liver puzzle have yet to be worked out, there is good evidence that SAME is a major player in liver health. Maintaining optimal SAME levels is probably the most important thing a person can do for his liver. SAME increases glutathione, and glutathione counteracts liver damage, whatever the cause. SAME is also important in the synthesis of proteins having to do with lipids that ultimately affect heart function (lipoproteins).

## **OTHER LIVER CONDITIONS RESPOND TO SAME**

It seems that almost any liver disease can be improved with SAME therapy. Cholestasis is a condition of insufficient bile. While this problem is not making headlines, it can, nonetheless, be a serious problem. Among the usual causes of cholestasis are estrogen-replacement therapy, birth control pills, certain drugs (including antidepressants) and pregnancy. Cholestasis can lead to gallstones or even death. Studies show that SAME protects against cholestasis at an oral dose of 600 to 800 mg per day.

A similar condition, biliary obstruction, can cause the same kind of liver damage as cirrhosis. Biliary obstruction occurs when bile ducts leading from the liver to the small intestine become blocked. In 1994, The Journal of Hepatology published a study that is nothing short of amazing. Biliary obstruction was surgically-induced in rats, which caused collagen deposition, mitochondrial disorganization, glycogen depletion, and lipid peroxidation...all of the hallmarks of cirrhosis. When rats were given SAME, not only were these symptoms prevented, but also glycogen went up, and bilirubin went down.

Since SAME is the bioactive form of methionine, the question arises whether persons with liver disease or cancer can elevate SAME in their liver by taking methionine. Unfortunately they can't. People with cirrhosis have impaired SAME synthetase. People with liver cancer have no liver-specific SAME synthetase. No matter how much methionine a person with liver disease takes, it will not be converted into SAME without this crucial enzyme. And without SAME, liver-protective glutathione cannot be synthesized!

What about taking glutathione? Some studies show that glutathione is bioavailable as an oral supplement; others show that it is not. Certain types of undenatured whey have been reported to elevate glutathione in rodents. A study in mice showed that an undenatured whey protein supplement enhanced liver and heart glutathione levels, and increased longevity. (Liver glutathione levels show up in the plasma part of blood, where they can be measured.) While increasing levels of glutathione through supplementation is desirable, glutathione alone cannot do the job that SAME and glutathione do together in the liver. Glutathione is a hard worker, but SAME performs many tasks, including synthesizing important enzymes. And while there are no published studies showing that supplemental glutathione prevents or cures liver disease, there are many published reports on the benefits of SAME for liver disease.

What About Betaine? Trimethylglycine (TMG or anhydrous betaine, not to be confused with betaine hydrochloride which is used as a digestive aid) is a substance made from beet sugar that increases SAME levels. Drs. Anthony J. Barak, Harriet C. Beckenhauer and Dean J. Tuma of the VA Medical Center in Omaha have done extensive testing of betaine in alcoholic rats. They have shown that rats compensate for impaired SAME synthetase by making SAME through the betaine pathway, an alternative to the methionine-plus-ATP route which depends upon SAME synthetase. Their studies show that betaine at about 15 grams per day prevents fatty liver in alcoholic rats.

According to Barak, alcohol causes a 30 to 40 percent increase in fat in the liver. He believes that it is the oxidation of this fat that causes the extensive liver damage seen in alcoholism. Increasing levels of SAME through betaine protects the liver two ways: It reduces fatty infiltration and provides the ingredients to make the free radical quencher glutathione.

Dr. Barak's group is in the process of getting human studies underway to determine whether betaine can prevent and reverse fatty liver in humans. Luckily for the participants, his group has devised a way to get the lab tests they need without subjecting people to liver biopsies, which Dr. Barak likens to being stabbed with a sword.

## **THE LIVER SUPER-NUTRIENT**

SAME is the liver super-nutrient. Nothing comes close to providing the spectrum of health benefits that SAME provides for the liver. Based on published clinical trials, elevating SAME levels can have a powerful effect on many conditions. As a preventive agent, SAME is so powerful that it can reverse the effects of chemicals and alcohol as they occur. Studies show that low SAME levels create the conditions for liver cancer, and that SAME can prevent these conditions from occurring. Anyone concerned about the effects of drugs, chemicals, alcohol and aging on their livers should look into the benefits of SAME.

PART 1 of SAME (S-adenosylmethionine)

PART 2 of SAME (S-adenosylmethionine)

PART 4 of SAME (S-adenosylmethionine)

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