

## Yes, Red Wine Holds Answer. Check Dosage.

By NICHOLAS WADE

November 2, 2006

**C**an you have your cake and eat it? Is there a free lunch after all, red wine included? Researchers at the Harvard Medical School and the National Institute on Aging report that a natural substance found in red wine, known as resveratrol, offsets the bad effects of a high-calorie diet in mice and significantly extends their lifespan.

Their report, published electronically yesterday in *Nature*, implies that very large daily doses of resveratrol could offset the unhealthy, high-calorie diet thought to underlie the rising toll of obesity in the United States and elsewhere, if people respond to the drug as mice do.

Resveratrol is found in the skin of grapes and in red wine and is conjectured to be a partial explanation for the French paradox, the puzzling fact that people in France enjoy a high-fat diet yet suffer less heart disease than Americans.

The researchers fed one group of mice a diet in which 60 percent of calories came from fat. The diet started when the mice, all males, were a year old, which is middle-aged in mouse terms. As expected, the mice soon developed signs of impending diabetes, with grossly enlarged livers, and started to die much sooner than mice fed a standard diet.

Another group of mice was fed the identical high-fat diet but with a large daily dose of resveratrol (far larger than a human could get from drinking wine). The resveratrol did not stop them from putting on weight and growing as tubby as the other fat-eating mice. But it averted the high levels of glucose and insulin in the bloodstream, which are warning signs of diabetes, and it kept the mice's livers at normal size.

Even more striking, the substance sharply extended the mice's lifetimes. Those fed resveratrol along with the high-fat diet died many months later than the mice on high fat alone, and at the same rate as mice on a standard healthy diet. They had all the pleasures of gluttony but paid none of the price.

***"His wife, his parents, and 'half my lab' are also taking resveratrol."***

- David Sinclair, Ph.D.

Scientists have long known that a moderate intake of alcohol, and red wine in particular, is associated with a lowered risk of heart disease and other benefits. More recently, scientists began to suspect resveratrol had particularly powerful effects and began investigating its role in lifespan.

The researchers, led by David Sinclair and Joseph Baur at the Harvard Medical School and by Rafael de Cabo at the National Institute on Aging, also tried to estimate the effect of resveratrol on the mice's physical quality of life. They gauged how well the mice could walk along a rotating rod before falling off, a test of their motor skills. The mice on resveratrol did better as they grew older, ending up with much the same staying power on the rod as mice fed a normal diet.

The researchers hope their findings will have relevance to people too. Their study shows, they conclude, that orally taken drugs "at doses achievable in humans can safely reduce many of the negative consequences of excess caloric intake, with an overall improvement in health and survival."

Several experts said that people

wondering if they should take resveratrol should wait until more results were in, particularly from safety tests in humans. Another caution is that the theory about why resveratrol works is still unproved.

"It's a pretty exciting area, but these are early days," said Dr. Ronald Kahn, president of the Joslin Diabetes Center in Boston.

Information about resveratrol's effects on human metabolism should be available a year or so, Dr. Kahn said, adding, "Have another glass of pinot noir -- that's as far as I'd take it right now."

The mice were fed a hefty dose of resveratrol, 24 milligrams per kilogram of body weight. Red wine has about 1.5 to 3 milligrams of resveratrol per liter, so a 150-lb person would need to drink 750 to 1,500 bottles of red wine a day to get such a dose.

Dr. Richard Hodes, director of the National Institute on Aging, which helped support the study, also said that people should wait for the results of safety testing. Substances that are safe and beneficial in small doses, like vitamins, sometimes prove to be harmful when taken in high doses, Dr. Hodes said.

One person who is not following this prudent advice, however, is Dr. Sinclair, the chief author of the study. He has long been taking resveratrol, though at a dose of only five milligrams per kilogram. Mice given that amount in a second feeding trial have shown similar, but less pronounced, results as those on the 24-milligram-a-day dose, he said.

Dr. Sinclair has had a physician check his metabolism, because many resveratrol preparations contain possibly hazardous impurities,

*(Continued on page 2)*

but so far no ill effects have come to light. His wife, his parents, and "half my lab" are also taking resveratrol, he said.

Dr. Sinclair declined to name his source of resveratrol. Many companies sell the substance, along with claims that rivals' preparations are inactive. One such company, Longevity, sells an extract of red wine and knotweed that contains an unspecified amount of resveratrol. But each capsule is equivalent to "5 to 15 5-ounce glasses of the best red wine," the company's Web site asserts.

Dr. Sinclair is the founder of a company, Sirtris Pharmaceuticals, that has developed several chemicals intended to mimic the role of resveratrol but at much lower doses. Sirtris has begun clinical trials of one of these compounds, an improved version of resveratrol, with the aim of seeing if it helps control glucose levels in people with diabetes.

"We believe you cannot reach therapeutic levels in man with ordinary resveratrol," said Dr. Christoph Westphal, the company's chief executive.

Behind the resveratrol test is a considerable degree of scientific theory, some of it well established and some yet to be proved. Dr. Sinclair's initial interest in resveratrol had nothing to do with red wine. It derived from work by Leonard Guarente of the Massachusetts Institute of Technology, who in 1995 found a gene that controlled the longevity of yeast, a single-celled fungus.

Dr. Guarente and Dr. Sinclair, who had come from Australia to work as a postdoctoral student in Dr. Guarente's laboratory, discovered the mechanism by which the gene makes yeast cells live longer. The gene is known as Sir-2 in yeast, standing for silent information regulator, and its equivalent in mice and humans is called SIRT-1.

Dr. Guarente then found that the gene's protein needed a common metabolite to activate it, and he developed the theory that the gene, by sensing the level of metabolic activity, mediates a phenomenon of great interest to researchers in aging, the greater life span caused by caloric restriction.

Researchers have known since 1935 that mice fed a calorically restricted diet -- one with all necessary vitamins and nutrients but 40 percent fewer calories -- live up to 50 percent longer than mice on ordinary diets.

This low-calorie-provoked increase in longevity occurs in many organisms and seems to be an ancient survival strategy. When food is plentiful, live in the fast lane and breed prolifically. When famine strikes, switch resources to body maintenance and live longer so as to ride out the famine.

Most people find it impossible to keep to a diet with 40 percent fewer calories than usual. So if caloric restriction really does make people as well as mice live longer -- which is plausible but not yet proved -- it would be desirable to have some drug that activated the SIRT-1 gene's protein, tricking it into thinking that days of famine lay ahead.

In 2003 Dr. Sinclair, by then in his own laboratory, devised a way to test a large number of chemicals for their ability to mimic caloric restriction in people by activating SIRT-1. The champion was resveratrol, already well known for its possible health benefits.

Critics point out that resveratrol is a powerful chemical that acts in many different ways in cells. The new experiment, they say, does not prove that resveratrol negated the effects of a high-calorie diet by activating SIRT-1. Indeed, they are not convinced that resveratrol activates SIRT-1 at all.

"It hasn't really been clearly shown,

the way a biochemist would want to see it, that resveratrol can activate sirtuin," said Matt Kaerberlein, a former student of Dr. Guarente's who does research at the University of Washington in Seattle. Sirtuin is the protein produced by the SIRT-1 gene.

Dr. Sinclair said experiments at Sirtris had essentially wrapped up this point. But they have not yet been published, so under the rules of scientific debate he cannot use them to support his position. In his Nature article he therefore has to concede that "Whether resveratrol acts directly or indirectly through Sir-2 in vivo is currently a subject of debate."

Given that caloric restriction forces a trade-off between fertility and lifespan, resveratrol might be expected to reduce fertility in mice. Dr. Sinclair said he saw no such infertility in his experiment, but he said that might be because the mice were not on a low-calorie diet.

If resveratrol does act by prodding the sirtuins into action, then there will be much interest in the new class of sirtuin activators now being tested by Sirtris. Dr. Westphal, the company's chief executive, has no practical interest in the longevity-promoting effects of sirtuins and caloric restriction.

For the Food and Drug Administration, if for no one else, aging is not a disease and death is not an endpoint. The F.D.A. will approve only drugs that treat diseases in measurable ways, so Dr. Westphal hopes to show that his sirtuin activators will improve the indicators of specific diseases, starting with diabetes.

"We think that if we can harness the benefits of caloric restriction, we wouldn't simply have ways of making people live longer, but an entirely new therapeutic strategy to address the diseases of aging," Dr. Guarente said.