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## REPORT

### Media Coverage of Anti-Aging Breakthroughs

Dr. Spindler's anti-aging breakthroughs sparked reports from print and electronic media in the U.S. and abroad—from the United Kingdom to India. These reports reflect the enthusiasm of scientists and life extensionists that we are truly moving closer to the development of new therapies to slow and reverse aging in humans. Here is a sampling of these reports.

#### Study: Lean Diet May Mean Long Life

It's never too late to cut back on the calories to prolong life, even in your later years, a study involving mice and low-calorie diets indicates.

In a study published Monday, researchers from the University of California, Riverside, said mice they put on a low-calorie regimen—even creatures put on the diet for a short period—exhibited characteristics of slowed aging.

Results from the study, published in the Proceedings of the National Academy of Sciences, suggest older humans could reap the benefits of such dietary changes as quickly as the mice, researchers said.

Research indicates that the sooner you cut back, the longer you may live, said Stephen Spindler of the university's biochemistry department. The widely held belief that restricting caloric intake extends life and health is backed up by research, he said.

"The bad news is, the longer you wait, the less time there is for the positive benefits to influence your aging," said Spindler.

Researchers put young and old mice on short- and long-term low-calorie diets, then observed changes in the genes of their liver cells, the study reported.

Restricting calories reversed the changes in several genes that were altered in aging animals, researchers noted. They also determined that older mice put on short-term, low-calorie diets demonstrated 70 percent of the anti-aging effects of the test animals that had been on a long-term reduced-calorie diet.

In other words, an old mouse on a low-calorie diet lived longer but not as long as one that started on the diet early in its life, researchers said.

The study is just the latest establishing a link between cutting back on calories and extending life.

Roy Walford, professor emeritus of pathology at the University of California, Los Angeles, has made headlines with a plan he calls CRON-Calorie Restriction with Optimal Nutrition. Walford, who's been using animals to research weight loss and health since the 1960s, has suggested that people could live 120 years or longer if they maintain a weight that varies from 10 percent to 25 percent below their "set points," or the weight to which the body naturally gravitates.

The latest findings in Monday's study should not be construed as an invitation for people to eat as much or as often as they please, then cut back late in life, said Spindler. Study findings indicate that cutting back sooner, rather than later, is the best way to extend longevity, he said.

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Short-Term Caloric Restriction Reverses Expression Of Genes Altered By Aging





In old mice, long-term caloric restriction alters genomic expression toward a slow-aging profile, according to a report in the early edition of the Proceedings of the National Academy of Sciences released on Monday. In addition, short-term caloric restriction also reversed close to 70% of the genome changes induced by age, Dr. Stephen R. Spindler told Reuters Health.

Dr. Spindler and colleagues of the University of California at Riverside manipulated the diets of female mice, then conducted genome-wide microarray expression analysis of 11,000 genes in the murine liver tissue.

In control mice fed a normal diet, the expression of 20 genes increased with age. These included genes associated with inflammation, stress response proteins, and proteins called "chaperones" associated with normal protein conformation.

Twenty-six genes exhibited decreased expression with age, including some involved in DNA replication and the cell cycle, indicating a general loss of negative cell growth

control with age. Aging also decreased expression of a group of genes with antineoplastic potential.

The treatment mice were fed a reduced calorie diet beginning at 28 days of age. After 27 months, the restricted diet appeared to prevent 70% of the age-related increases in gene expression seen in control mice. Calorie restriction partially restored hepatic drug-metabolizing and detoxifying functions of the liver.

Four weeks of caloric restriction in 34-month-old mice appeared to rapidly reverse many age-related changes in gene expression, reproducing 55% of the effects of long-term restriction.

"These results suggest that caloric restriction may rapidly ameliorate inflammation and other stresses, even in very old animals," the investigators write, as well as "rapidly reproducing the antineoplastic effects of long-term caloric restriction."

This study lays the groundwork for animal studies to identify drugs that can induce the rapid genomic effects of calorie restriction, Dr. Spindler told Reuters Health.

He suggested that short studies in humans may also be warranted. The goal would be "to see if we can change biomarkers of aging in accessible tissues back to more useful patterns of gene expression," he said. Caloric restriction may thus represent "a treatment for healthy people to prevent the onset of age-related diseases and to reduce their severity."

Dr. Spindler emphasized, however, that "calorie restriction is not a treatment for people who are already ill." Also, because a critical aspect of caloric restriction is provision of all essential nutrients, he said it will not reverse the aging process in those who are anorexic or bulimic, or in those suffering from starvation.

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## Dieting May Slow Aging, Study Suggests

After only a month on a very low-calorie diet, the gene activity of mice in a scientific study was altered nearly as significantly as that of animals who follow such a diet on a long-term basis. The study suggests that the effects of a low-calorie diet may be enjoyed even by people starting late in life, says Stephen R. Spindler, senior author of the study, scheduled for publication next week in the Proceedings of the National Academy of Sciences.

Dr. Spindler linked the effects of cutting calories to quitting smoking, which confers benefits soon after the habit is kicked, although those who quit earlier in life experience the benefits longer.

For many years, researchers have been showing that mice live longer when fed a diet 30% to 40% lower in calories than what would normally be considered adequate. The reasons for the life extension remain poorly understood, however. Several studies have shown that the activity of dozens of genes are altered during such diets, suggesting a complex biochemical mechanism may be at work. No one knows yet if the results extend to humans.



In the current study, researchers observed the genetic "expression profile," a measure of whether genes are active at any given

time, in mouse livers. Forty-six liver genes showed drastically different levels of activity in normal, aging mice, than they did in younger mice; some were more active, others were less active. That suggests they play some role in aging.

Of the 46 genes, 27 reverted to a more youthful activity profile in mice who ate the low-calorie diet for more than a year. But only four weeks on the diet was enough to create the youthful profile in 19 of those 27 genes, or about 70% of them.

Mark Lane, an antiaging researcher at the National Institutes of Health, says the study is potentially important. But he adds that its implications are unclear because scientists haven't yet shown that mouse genes that grow more or less active during aging are really the cause of the process. "You have to study each one, and determine whether it is really related to aging," Dr. Lane says. Dr. Spindler agrees that the role of the genes in aging is unproven, but says that many are linked to known functions, such as cell death in response to damage, which could be linked to aging. A major plus of the finding, he adds, is that it should give scientists a quicker way to screen drugs that mimic the purported antiaging effects of low-calorie diets. Dr. Spindler has founded a company, LifeSpan Genetics Inc. of San Jose, Calif., to market such a screen to drug companies.

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### Low-Calorie Diet Given To Mice May Be Key To Longevity In Humans



Putting elderly mice on a very low-calorie diet for as little as four weeks reversed many of the changes in the activity of various genes that had occurred during normal aging, according to a new study.

The research, which used a new technology to pinpoint which genes are active in mice at different ages, may help scientists understand how calorie restriction extends animals' lifespan and, eventually, to develop longevity therapies for humans.

"My work shows that calorie restriction not only prevents [age-related] changes" in gene activity, "but very quickly reverses the majority of the changes that take place with age," said Stephen R. Spindler, a professor of biochemistry at UC Riverside and an author of the study.

Huber Warner, associate director of the biology of aging program at the National Institute on Aging, said the results were interesting but needed to be confirmed. Until recently, he said, scientists have been able to examine aging's effects on relatively few genes, but the new technology enables a "vast number of genes [to] be looked at" simultaneously.

Severe calorie restriction is the only treatment that consistently has been shown to extend mammals' lifespan, although its effectiveness in people is unproven. In animals, it lowers the incidence of cancer and delays the onset of other age-related diseases. Although scientists have theorized that low-calorie diets may reduce age-related cell damage and decrease levels of cancer-promoting growth factors, they have only recently been able to examine how such diets affect many of the approximately 30,000 genes in a mouse or human.

Spindler and colleagues used a method called microarray technology to analyze which of 11,000 genes were expressed-or used to provide instructions for making proteins-in the livers of young and old mice. They also tested the effect of calorie restriction on gene expression. Some mice were fed a low-calorie diet-just enough to prevent starvation-from the time they were weaned; others were switched from a normal to a low-calorie diet for four weeks starting when they were 34 months old.

The scientists found 20 genes whose expression increased with age. Several were associated with inflammation, a process that in the liver can contribute to the development of cirrhosis or cancer. In 14 of the 20 genes, long-term calorie restriction completely or partially prevented the age-related changes.

Switching mice to the low-calorie diet at 34 weeks of age reproduced about 70% of the effect of keeping animals on a low-calorie diet lifelong, Spindler said. That suggests that if there are health benefits of calorie restriction in humans, some of those benefits could be obtained by reducing calories even in old age.

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