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AS WE SEE IT**Aging Research Becomes A Science****Why A Breakthrough Funded By The Foundation Will Lead To Therapies That Reverse Aging And Prevent Age-Related Disease**

It is 2025. Bill and Kathy have been married for 58 years. They are 85 years “old,” but look and feel younger than five years ago. In 2020, with the end-stage of their natural life span beginning to unravel before their eyes, Bill and Kathy started on a therapy to reverse aging in their bodies. They had a small computerized device (about the size of a dime) implanted in their chests. It delivers optimal levels of gene products, the production of which has been going awry as Bill and Kathy have grown older. These gene products regulate other genes that are restoring Bill and Kathy’s bodies to healthy, youthful function.

Over the past five years, Bill and Kathy have seen and felt their bodies grow younger and healthier. Cells, organs and systems, which had been deteriorating for decades, are now being rejuvenated. Their muscles are becoming stronger, their neurons more active, their skin smoother and their joints more supple. They have better coordination, more stamina, sharper minds and can fight off diseases more effectively.

Bill and Kathy are now optimistic about the future. They expect to live many more years and are making plans to travel around the world. Bill is even thinking about starting a new business, 15 years after he sold his old business. Instead of being fearful that they will have to depend upon their children, Bill and Kathy are pushing them to start aging reversal therapy themselves... so that the whole family can grow young together.

The creation of the aging reversal therapy described above began in the 1990s, when Affymetrix, a company in Silicon Valley, developed the ability to measure the expression of thousands of genes at a time with high-tech gene chips. At the same time, hundreds of scientists were hunting to identify the entire genome of mice, humans and other species.

These advances made it possible for Richard Weindruch and Tomas Prolla of the University of Wisconsin to investigate the genetic basis of aging and compare it with the genetic effects of caloric restriction (CR), the only proven method to slow aging and extend maximum life span in mammals. Weindruch and Prolla initially looked at gene expression in muscle in mice. Their findings were published in the August 27, 1999 issue of *Science*. (A copy of this paper and an exclusive interview with Weindruch and Prolla can be found in the November 1999 issue of *Life Extension* magazine.)

Several other major advances were soon made by Stephen R. Spindler of the University of California at Riverside. Dr. Spindler found that the turn-around from an aging genotype to an anti-aging genotype could be achieved in as little as several weeks of caloric restriction. He also found a pattern of aging reversal in these gene changes and that this pattern could be induced rapidly in old mice.

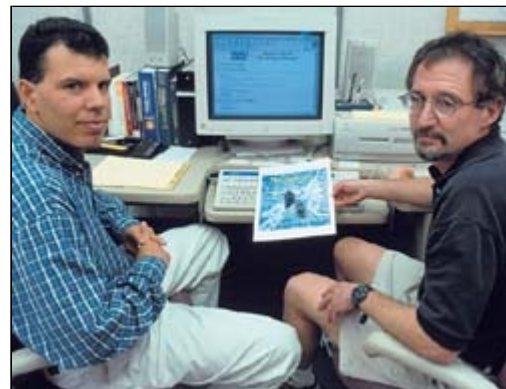
In this issue, we reprint Dr. Spindler’s paper describing his findings from the September 11, 2001 issue of the *Proceedings of the National Academy of Sciences (PNAS)* and carry an exclusive interview with him. But before we come to these items, I want to fully explain the enormous value of these recent advances and why they will lead to the kind of aging reversal therapy depicted at the beginning of the article.

The search for the fountain of youth

Throughout the 20th century, scientists and “youth doctors” searched without success for therapies to make their patients



Saul Kent



Drs. Tomas Prolla and Richard Weindruch

biologically younger. Their long run of failures came in the face of a growing body of evidence that mammals can be made radically younger in the laboratory by feeding them nutrient-rich diets restricted in calories.

The first evidence that caloric restriction (CR) can produce dramatic anti-aging effects came in the 1930s when Cornell University's Clive M. McCay published his studies with rats in the *Journal of Nutrition* and other publications. McCay found that severely restricting the caloric intake of young rats (right after weaning) produced side effects such as seizures and the prevention of sexual maturation, which, in some cases, led to the death of the animal.



Stephen R. Spindler, Ph.D.

The rats who survived were smaller and more vigorous than McCay's normally-fed controls. The physiologic differences between the CR rats and the control rats increased as the animals grew older. While the control rats became weak and feeble, most of the CR rats remained healthy and youthful. When they neared the end of their natural life span at 32 months of age (95 years in human terms), all the controls were dead or very close to it. Most of the CR rats, on the other hand, were still alive, youthful and vigorous. McCay's oldest control rat died at 965 days, whereas his oldest CR rat lived 1,456 days (150 years in human terms). In the 1960s, CR rats in the laboratory of Morris H. Ross at the Institute For Cancer Research in Philadelphia, survived for more than 1,800 days (180 years in human terms).

For many years, CR experiments started in middle-age failed to extend life span. Then, in the 1970s, Roy Walford and Richard Weindruch of UCLA Medical Center showed that the gradual restriction of caloric intake in middle-aged mice could extend their life span. Although the extent of the life span extension achieved in these mice was less than in experiments started in youth, the results were heartening to adults of middle-age or older.

Extending maximum life span

Over the years, CR has passed every test as a treatment for aging. It prevents or postpones degenerative diseases of aging such as cancer, arthritis and atherosclerosis. It improves every measure of health, such as insulin and glucose levels, cholesterol levels, blood pressure, physical strength and stamina, immune function and cardiovascular function.

Finally, it extends maximum life span. Many therapies—including a number of antioxidants—have extended mean life span, but none except for caloric restriction have extended maximum life span. The major advances in medicine and sanitation in the 20th century added about 35 years to mean life span in humans, but not a day to maximum life span.



Biosphere II

The reason it's so much easier to extend mean rather than maximum life span is because almost all animals and humans contract diseases that kill them long before they reach the outer limits of life span. As a result, any therapy that prevents or treats any of these killer diseases effectively can extend mean life span. With maximum life span, on the other hand, we are dealing with the longest any member of the species has ever lived. . . the extreme outer limit of life span potential. The only way of extending that limit is to prevent or reverse aging, the process that defines it.

Thus far, only CR has passed this test in mice, rats or any other mammal. While other therapies have utterly failed to extend maximum life span for even a day, caloric restriction has extended it up to 80% in rats! Moreover, CR has extended maximum life span in every species studied to date. . . from insects and worms

to mice, rats and dogs. While it's too early to tell if CR will extend maximum life span in monkeys—in ongoing studies at the National Institute On Aging and the University of Wisconsin—the scientists have found the same improvements in health and vigor in the CR monkeys as in CR mice and rats.



Roy Walford, M.D.

Similar improvements in health and vigor were found in the inhabitants of Biosphere II, a man-made ecosystem. The Biospherians were forced to eat a CR diet for two years because they were unable to grow enough food to feed themselves at a normal level. Since one of them was Roy Walford of UCLA Medical Center, an authority on CR research who has medical training, the Biospherians were all tested regularly. They, too, showed across-the-board benefits in health and vigor from the CR diet.

Extended youth, vigor and energy

CR animals don't just live longer than normally-fed animals, they are also far more youthful, vigorous and energetic than their counterparts. Many CR animals go on to live in good health for months... even years... after every normally-fed animal has died. It is truly remarkable to see these supposedly "old" CR animals with your own eyes. Their youth, vigor and energy are so far beyond the norm for their age that it's hard to believe. Instead of having lethargic bodies bloated with tumors, CR mice are sleek and trim and race around their cages like youngsters. Instead

of dragging around with arthritis, CR dogs leap about and play with unbounded joy. Instead of lying around like simian "couch potatoes," CR monkeys show great curiosity and energy in interacting with humans. In short, the clinical and behavioral evidence for the extended youth of CR animals is powerful and overwhelming!

A powerful experimental tool

After more than 70 years and hundreds of CR experiments in different species, we know for certain that CR can prevent and/or reverse aging and that it can prevent the diseases that cripple and kill us. The fact that aging control can be achieved in several mammalian species tells us that it can almost certainly be achieved in humans. I don't know of a single instance in the history of medicine that such powerful evidence in animals could not be used to achieve similar success in humans.

There is a small group of life extensionists who practice caloric restriction in an attempt to retard aging and extend life span. However, the practice of CR is fraught with risks and uncertainties. Few people have the discipline to reduce their caloric intake enough to match the animal CR protocols, and practicing CR includes the risk of malnutrition, which could lower the quality of life and shorten life span.

The greatest value of CR research is as a powerful experimental tool to help us discover why we grow old and die. Once we have credible scientific evidence about what causes aging, we'll be able to develop new anti-aging therapies that extend life span. Once we've developed a true anti-aging therapy, we'll be on the way to solving the overall problem of aging.

If the greatest value of CR is to help us discover why we grow old, why hasn't that happened during the past 70 years? Why haven't we been able to develop therapies that duplicate the anti-aging effects of caloric restriction? Why haven't we learned how to grow younger and healthier with the passage of time? Why are we still growing old and dying?

Lack of knowledge about the causes of aging

The major reason we've been unable to duplicate the effects of CR on aging has been our lack of knowledge about what causes aging. We know that CR has a major impact on aging because it produces multiple physiological benefits, prevents the diseases of aging, and extends maximum life span radically. Although these kinds of across-the-board effects are persuasive evidence that aging has been slowed or reversed, they make it difficult to pinpoint the crucial changes that trigger the anti-aging process. Until recently, all we've been able to do is catalog the consequences of aging rather than identify its causes.

Without adequate knowledge of the causes of aging, there has been only one credible method of evaluating the effects of therapies on aging—their effect on maximum life span. The problem with life span studies, however, is their length, high cost, and that they are only a single measure of aging. Such studies take years, even in relatively short-lived species such as mice and rats, and are impractical in long-lived species such as humans.

The result has been that there have been very few life span studies conducted and that most of them have been in strains of mice or rats with shortened life spans. For example, there have been studies showing modest increases in life span in mice receiving antioxidants, but these studies have been done in animals bred to die prematurely from cancer, autoimmune disease or other life-shortening syndromes. Life span studies should only be done in long-lived strains of mice, where extending life span would clearly be due to an anti-aging effect.

Searching for biomarkers of aging

In the 1970s, scientists concerned about the lack of a scientific method to study aging began to search for biochemical and

physiologic tests that would qualify as valid “biomarkers of aging.” Such biomarkers would be used over short periods to evaluate the effects of therapies on aging. They would serve to identify promising anti-aging therapies, which could then be tested in other ways, including life span studies.

The search for biomarkers of aging failed for several reasons. First is that most tests proposed as biomarkers have been inappropriate. If a 50-year-old “couch potato” begins to exercise regularly, which leads to a major reduction in his blood pressure by age 60, for example, it doesn’t mean that he is younger at 60 than he was at 50.

Second is that most proposed biomarkers don’t measure functions that change rapidly enough. What good is a biomarker that requires 5-to-10 years to change enough to be a valid measure of aging? What we need are major changes that occur rapidly in basic life processes. Moreover, unless these changes are confirmed by maximum life span studies, they cannot be considered valid.

Gene expression and aging

Ever since Watson and Crick described the structure of the DNA molecule in the 1950s, scientists have pursued changes in gene expression as a measure of all life functions, including aging. As the blueprints for life, genes produce the proteins that define the nature of the processes and structures in our bodies. Genes determine whether we are male or female, short or tall, large or small, smart or slow, strong or weak, healthy or sick. They define what we look like and play a major role in how we feel and behave. Every developmental change that occurs during our life span—from growth, sexual maturation, learning and memory and the physical and mental breakdowns that occur with age—are controlled by the actions of our genes. In short, we grow old, suffer and die because our genes fail to keep us alive and healthy.

But what about calorically-restricted animals? They are healthier and live much longer than normal. If aging is controlled by genes, surely these changes would be reflected by changes in gene expression in CR animals, which would lead to the discovery of genes involved in aging. Once that was done, it would lead to the ability to duplicate the anti-aging changes in gene expression by other means... perhaps a particular drug, a combination of drugs, a lifestyle change or a method of genetic engineering.

It didn’t happen that way, however, for decades. Most scientists had no experience with caloric restriction. They didn’t know about or appreciate the value of the research. The few who had done CR research either hadn’t worked with genetic techniques, didn’t understand the value of gene changes associated with CR or didn’t have the time or money to pursue the problem.

A major obstacle to genetic research into aging has been the fact that traditional techniques used to measure gene expression—such as Northern Blot Analysis, rtPCR and Luciferase Assays—are time-consuming and expensive. They only enable scientists to measure the expression of a few genes at a time at a high cost. Since there are tens of thousands of genes, it is very difficult to search for the right genes with these techniques.

The revolution in aging research

Then, in the 1990s, starting with Affymetrix, companies began to develop microarray gene chips that can measure the expression of thousands of genes at a time. These chips have enabled scientists to study gene expression rapidly and effectively in mice, rats, monkeys and humans. In the year 2000, gene chips measuring the expression of 6,347 genes were used by Richard Weindruch (a CR expert) and Tomas Prolla (a geneticist) at the University of Wisconsin to compare the gene profiles of muscle in normally-fed and CR mice. They found major changes in gene expression between the two groups and their findings were published in Science. The revolution in aging research had begun.

After more than a century, aging research had finally become a science. For the first time in history, scientists could study an underlying cause of aging (gene expression) on a large-scale, enabling them to identify which genes are involved in aging and how their expression is altered by caloric restriction. It is now possible to measure in a fundamental way, the natural time-dependent process by which we deteriorate with advancing age. It is now possible to strive to reverse this process by targeting these genes for a frontal assault.

The Weindruch-Prolla method is light years beyond what has been done before, but still requires 30 months (two and a half years) to conduct an experiment. They compared normally-fed and calorically-restricted 5- and 30-month-old mice on the assumption that CR slows the aging process gradually over the life span of the animal. While their 30-month experiment showed changes in gene expression among more than 6,000 genes, it still required years to conduct, which is far from optimal for aging research.

Genetic anti-aging changes in weeks



Then Stephen R. Spindler of the University of California at Riverside made a remarkable discovery. In using Affymetrix gene chips to study the expression of 11,000 genes in the liver of young and old normally-fed and CR mice, Spindler found that 60% of the gene changes in the CR mice occurred just a few weeks after they were started on the CR diet. This finding indicates that, even if it takes years for the full effects of CR to become expressed, the genetic profile that causes the anti-aging effects of CR is developed quickly. Dr. Spindler is conducting further research to determine how quickly these changes occur and which of them are primary regulatory changes that may trigger the entire anti-aging cascade.

The use of gene chips in aging research has made it a science. The ability to study the effects of therapies on aging in weeks rather than years—through the expression of thousands of genes at a time—has made the search for anti-aging therapies practical. Scientists can now screen large numbers of potential anti-aging therapies in a reasonable time at an affordable cost. Those that show promise can then be tested more extensively over longer periods of time.

The reversal of aging

Dr. Spindler's second revolutionary finding is that caloric restriction produces a genetic anti-aging profile that largely reverses the aging changes that occur normally in mammals. CR does not prevent deleterious genetic changes gradually over the life span of the animal, but instead reverses most of them over a short period of time. This finding suggests that, although it may take much of an animal's life span for anti-aging changes to take full effect, such changes are likely to be possible in old animals (and, presumably, humans) who can only become youthful again if aging can be reversed within their bodies.

Further evidence that aging reversal may be possible in old animals is Spindler's third revolutionary finding that the rapid changeover from a genetic aging profile to an anti-aging profile occurs in old animals as well as young and middle-aged ones. This finding suggests that CR and, presumably, any therapy that mimics CR, could, potentially, reverse aging, improve health and extend life span in old animals as well as in humans.

LEF funds revolutionary anti-aging research

The revolutionary anti-aging research conducted by Dr. Spindler is being funded by the Life Extension Foundation (LEF) through a company called LifeSpan Genetics. It will lead to therapies to reverse aging and prevent the diseases of aging—either through LifeSpan Genetics or some other company. It is one of several pioneering research projects to keep you alive and healthy which are being funded by The Foundation.

Life Extension is the number one source for information about staying alive and healthy. The organization was founded by people (Bill Faloon and me) who have dedicated their lives to extending the healthy human life span. We are totally committed to extending our own lives as well as the lives of every LEF member. That's why the products we offer you are so advanced. And why the research we fund is so revolutionary.

Every time you purchase a product or make a tax deductible donation to the Life Extension Foundation, you improve your odds of staying alive and healthy. Every time we make a revolutionary research breakthrough, the chance of your living in good health for centuries goes up dramatically. Every time you stay alive and healthy for another year, you remain a player in the game with the highest payoff of all time. . . the achievement of physical immortality.

For longer life,



Saul Kent

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