

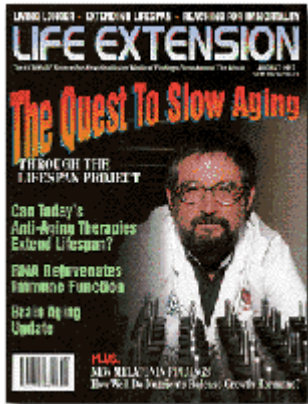
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On The COVER

Lifespan Project Launched

THE GOAL: TO FIND PRACTICAL METHODS OF RETARDING THE AGING PROCESS

By Richard Weindruch and Stephen R. Spindler



For the first time, the co-directors of the Life Extension Foundation's groundbreaking Lifespan Project discuss the newly launched, multi-year program's approaches to exploring the impact of nutrients, drugs and hormones on extending lifespan. The results may well blaze new pathways, not only in understanding how to increase longevity, but also in lending solid credibility to the emerging science of 'biogerontology.'

As Roy Walford nicely discusses in his book "Maximum Life Span," the extension of lifespan has been one of our species' oldest preoccupations and greatest dreams. Dr. Walford makes the point that, since the beginning of time, life extensionists and immortalists have been forced to deal with negative attitudes about their goals. This negativity has been expressed in various forms, including myths, literature and religious beliefs (as Walford puts it, ". . . most religions love death").

The good news is that the study of the biology of aging, sometimes called biogerontology, has now emerged as a serious and active area of scientific inquiry. It had remained a "fringe science" until relatively recent times, but this changed with the establishment of the National Institute on Aging, as part of the National Institutes of Health, in 1974. NIA's founding was a milestone event for American aging research.

Another milestone occurred on March 3, with the arrival at the animal facilities at the University of California at Riverside and the University of Wisconsin at Madison, of 300 four-week-old male mice of a particularly long-lived strain (this number ultimately will reach 1,600 mice). Their arrival launched The Lifespan Project, funded by the Life Extension Foundation to determine how nutrients, hormones and drugs now being used by life extensionists influence longevity in adult mice. We will also be testing these substances to determine their influence on certain biologic measures of the rate of aging.

The mice will be young adults at the onset of testing in August. Among the agents to be tested are alpha lipoic acid, acetyl-L-carnitine, aminoguanidine, coenzyme Q10, lycopene, melatonin, NADH, procysteine and pregnenolone. These compounds were selected on the basis of several theories of aging, discussed below.

A FUNDING DIFFICULTY

Biogerontology now attracts investigators from diverse backgrounds. This is due, in part, to increased availability of funds to conduct aging research, although the funding picture is still not good enough, with only about 10 percent to 20 percent of grants submitted to the NIA actually being funded. It is extremely difficult to obtain NIA funding for research like The Lifespan Project because peer reviewers typically judge such work to be too descriptive and non-focused. Such studies are often labeled as "fishing expeditions."

A fundamental tool in aging research is the survival curve. This graphs the percentage of a population alive as a function of age. Survival curves for humans in the United States as well as laboratory mice illustrate the nature of caloric restriction, which extends maximum lifespan, and its possible ramifications.

Consider two types of survival statistics: average lifespan, meaning the average age of death for the population, and maximum lifespan, often calculated as the average age of death for the population's longest-lived 10 percent. Looking at the survival curves for persons in the U.S. in 1900, 1940, 1980 and 1988, one sees that average lifespan has increased from about 47 years in 1900 to 75 years in 1988. Yet, despite this 60-percent rise in average lifespan, maximum lifespan has increased far less (based on some analyses, it hasn't increased at all).

MAXIMUM LIFESPAN STAGNANT

The major point is, despite this century's landmark medical and public-health advances which have produced a huge increase in average lifespan, the maximum lifespan for humans about 120 years has yet to be extended. Nor has the species-specific maximum lifespan been convincingly extended in other mammals (with rats and mice being the usual subjects), except for caloric restriction without deficiency in the intake of essential nutrients. The increase in maximum lifespan caused by caloric restriction, and the fact that restricted rodents stay biologically "younger longer," suggest to most gerontologists that at least some basic aging processes are being decelerated by caloric restriction.

Different approaches have been used to investigate the biology of aging. Among questions asked, for example, are, why does one type of mouse, called *Peromyscus*, live about twice as long as another type, *Mus*? The same questions are posed within a species; for example, what are the biochemical and behavioral traits shared by people who live beyond 100?

Perhaps the most commonly used approach is the comparison of differently aged animals. Most such studies have compared young (but sexually mature), middle-aged, and old mice or rats for some parameter deemed important by the investigator. Another approach is to study models showing certain features of accelerated aging and to determine the genetic and biochemical reasons for this acceleration.

However, the approach that is most germane to The Lifespan Project seeks to determine if a treatment can slow the rate of aging, as evaluated by lifespan, the age of onset and incidences of the diseases of aging, and whether indicators of "biological age" are influenced by the treatment. A number of strategies have been employed in attempts to retard the aging process in different species. Research of this type is conducted either to develop an intervention that might be applicable to humans or to make clearer the root causes of aging.

Among the strategies, lowering of core body temperature has been found to retard aging and extend lifespan in cold blooded animals. But only caloric restriction has been shown to extend species-characteristic maximum lifespan in nearly all species tested, including invertebrates, fish, and warm-blooded vertebrates such as mammals.

CALORIC RESTRICTION FEATURES

The effect of caloric restriction on primate longevity, including the longevity of humans, has never been adequately tested. There are trials being conducted in rhesus monkeys subjected to a 30-percent reduction in caloric intake, a study which should provide relevant survivorship data in about 20 years. There are observations in humans (Kagawa, 1978; Albanes, 1990; Andersson et al., 1996) and data from physiologic alterations during caloric restriction in normal weight humans (Velthuis-te Wierik et al., 1995; Walford et al., 1992), which support the idea that humans will respond to reduced caloric intake in a manner similar to other animals.

In "The Retardation of Aging and Disease by Dietary Restriction" (Weindruch and Walford, 1988), we identified the salient features of caloric restriction. For the purposes of this article, five aspects of caloric restriction are important: - Calories are most critical. The lifespan-extending effects of caloric restriction depend on calorie restriction per se. The most common level of caloric restriction investigated is about 40-percent less than average unrestricted food intake. Forty percent caloric restriction produces mice and rats of very different size and body composition than their control-fed counterparts. Even mild caloric restriction (10 to 20 percent) produces some life-extension and disease-prevention effects. The strong inverse relationship between energy intake and longevity has led co-author Richard Weindruch to favor mechanisms for caloric restriction with strong links to energy metabolism. As discussed below, a major theory in this regard is the free radical theory of aging.

Restricting fat, protein, or carbohydrates without caloric reduction does not increase the maximum lifespan of rodents. Nor does overall vitamin supplementation, the antioxidants tested to date, variations in the type of diet, dietary fat, carbohydrates or protein. Again, we refer here to maximum species-specific lifespan, not merely strain-specific lifespan. In contrast, the lifespan of short-lived strains of mice and rats can be increased by dietary manipulations other than caloric restriction, probably by influencing disease susceptibility or progression, not basic aging. However, even in these strains, caloric restriction gives by far the most impressive results.

MANY SPECIES AFFECTED

- Caloric restriction is effective in diverse species. Most caloric restriction studies have been in rats or mice. However, caloric restriction also extends lifespan in single celled protozoans, rotifers, water fleas, fruit flies, spiders and fish.

- Restricted animals stay biologically "younger longer." Caloric restriction in mice and rats extends biologic youth and postpones or prevents most major diseases (cancers, kidney disease, cataracts, etc.). Accordingly, the caloric-restricted rodent provides a model to study aging with minimal distortion from diseases. About 90 percent of the 300 or so age-sensitive outcomes studied

stay "younger longer" in caloric restricted animals. For example, decreases in certain immune responses begin in normal mice at one year of age, but begin at two years of age in restricted mice.

- Caloric restriction markedly retards disease progression in short-lived mice and rats. Many mouse and rat strains are available for gerontologic studies. These can be subdivided into short-lived strains (mean lifespans less than about 15 months) and long-lived strains (mean lifespans greater than approximately 25 months). We believe that long-lived strains provide superior models and have selected one for use in The Lifespan Project.

Short-lived strains have a distinct disease profile, which results in the death of the animals prematurely, at an age considered young for the species. However, short-lived strains provide excellent models for humans who are genetically prone to certain diseases. Caloric restriction greatly retards cancers (including breast, colon, prostate, lymphoma, etc.), renal diseases, diabetes, hypertension, hyperlipidemia, lupus, and autoimmune hemolytic anemia, to name a few. These data are so convincing that disease-prone families may prove to be the source of volunteers for the first controlled clinical trials of caloric restriction.

- Caloric restriction started in middle age also retards aging. This type of caloric restriction is most germane to potential human application. We found that caloric restriction that is started in middle aged mice extended maximum lifespan by 10 to 20 percent and blocked cancer development (Weindruch and Walford, 1982). This study involving two strains of mice allowed free access to food until 12 months of age, and then gradually restricted food by about 30 percent. We will soon publish results showing caloric-restricted rats studied at 17 months of age (late middle age) and again at 30 to 32 months of age show fewer signs of aging in skeletal muscles, as compared with age-matched normally fed controls (Aspnes et al., in press).

TWO MAJOR QUESTIONS

Two major question now face investigators of caloric restriction. First, how does caloric restriction retard aging in rodents? This is a very challenging question because the most important mechanisms driving biological aging remain unidentified. The second question concerns the relevance of the rodent data to humans. This question is being addressed by studies in monkeys and humans.

There are at least two reasons why the results of caloric restriction studies are of major importance to The Lifespan Project: First, the need to strictly control the caloric intake of the mice used in the study; and secondly, the use of caloric restricted mice as "positive controls." Since we know that restricted mice age at a slower rate than normally-fed mice, they can be used to compare the effectiveness of other dietary changes.

Loss of body weight or slow growth can occur with antioxidant feeding (for review, see Schneider & Reed, 1985) and after adding other potential anti-aging substances to the diet L-dopa, for example (Cotzias et al., 1977; Papavasaliou et al., 1981); centrophenoxine (Hochschild, 1973); dehydroepiandrosterone (DHEA) (Nyce et al., 1984; Weindruch et al., 1984). Thus, any positive findings in animals that weigh less than controls cannot be attributed with certainty to a particular agent because inadvertent caloric restriction may have occurred. For The Lifespan Project, where rodents are fed substances having the potential to retard aging, it is crucial to make sure that all mice consume the same number of calories. We will achieve this goal by individually housing the mice and feeding them about 15-percent fewer calories than the average unrestricted intake. This will provide the added advantage of minimizing obesity in the mice.

The Lifespan Project includes a group of caloric-restricted mice to be raised at Madison. These mice will allow us to compare the agents tested (see the following story) to an intervention known to slow the rate of aging.

SEEKING OUT MAGIC BULLETS IN THE FIGHT AGAINST AGING

A wide-ranging number of nutritional agents currently are being taken by life extensionists in the hopes of retarding the aging process. The Lifespan Project will examine a number to determine their exact effects.

The agents to be tested in The Lifespan Project were chosen because there is good scientific reason to think they will block the formation or actions of free radicals and glycation end products, or reverse age-related changes in hormone action and energy production. Free radicals are produced in our bodies as a necessary by-product of life processes. A main site of free-radical production is in cell structures known as mitochondria, which serve as the cells' power plants by taking the energy derived from the breakdown of the food we eat and converting it into energy that the cell can use to do its work . . . make new proteins, pump ions, repair damage and so forth.

The production of excessive free radicals causes the slow-but-steady accrual of damage to proteins, membranes and genetic material (Weindruch, 1996; Sohal & Weindruch, 1996). The accumulation of damaged proteins contributes to cataracts, muscle deterioration and memory loss. Our bodies can repair much of this damage. We have powerful enzymatic mechanisms to detoxify them. We also have small molecules called antioxidants which "trap" free radicals by combining with them to form non-toxic by-products, which can then be eliminated safely from our bodies. Many antioxidants come from the diet.

Unfortunately our ability to repair free-radical damage decreases with age, and we make more free radicals as we age. Thus, the damage accumulates. For this reason, the consumption of antioxidants in the diet becomes increasingly important as we grow older.

LYCOPENE

There has been a great deal in the press lately about the possible anti-cancer effects of beta-carotene. But you may not have heard much about lycopene. An excellent review of the biochemistry and physiology of lycopene and its consumption by humans has been published recently (Stahl & Sies, 1996). Both lycopene and beta-carotene are members of a family of plant pigments called carotenoids. There are more than 600 different carotenoids, but lycopene and the carotenes are the most prominent.

Carotenoids are an important part of the photosynthetic complex of plants. The bright colors in leaves are covered by green chlorophyll. In the fall, during "Indian summer," the chlorophyll is degraded and the carotenoids can be seen for a time in the reds and oranges of fall leaves. They also are the pigments that give some fruits and vegetables, like tomatoes, their bright colors. In fact, tomato and tomato products are a major source of lycopene in our diet. We also get some lycopene from watermelon, guava, rose hips and pink grapefruit. Boiling tomato juice with a little corn oil greatly increases absorption of lycopene into our bodies (Stahl & Sies, 1992).

Lycopene levels are higher than beta-carotene levels in people in the United States. And lycopene is a better antioxidant than beta-carotene. Of all the plant carotenoids, lycopene is one of the most efficient quenchers of a particularly dangerous activated oxygen molecule called singlet oxygen. Equally important, lycopene is regenerated after quenching singlet oxygen, and can then detoxify toxic molecules without being destroyed itself. Unfortunately, lycopene levels in our bodies decline with age, even if we continue to eat fruits and vegetables.

The first demonstration of the biological properties of lycopene was in the late 1950s when it was shown to increase the survival of irradiated mice and to increase the resistance of mice to bacterial infections. It also decreases the incidence of spontaneous and chemically induced cancers in mice. In an Italian case-control study, high consumption of tomatoes was associated with protection from digestive-tract cancers. A prospective study of micronutrient serum levels and bladder cancer suggested that lycopene may protect against this cancer. A case-control study of pancreatic cancer found a protective effect for both lycopene and selenium. Lycopene intake is associated with reduced risk of cervical and prostate cancer. Age-related macular degeneration also is associated with low serum levels of lycopene.

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