

LE Magazine February 2000**COVER STORY**

On the Frontiers of Science

Research funded by The Life Extension Foundation

The Life Extension Foundation was formed 20 years ago for the purpose of supporting research aimed at extending the healthy human life span. This article describes the research The Foundation is currently funding and highlights the obstacles that had to be overcome to get to where we are today.

On March 1, 1985, The Life Extension Foundation launched a program called PROJECT 2000 whose goal was to discover at least one major breakthrough in slowing human aging by the year 2000. The Foundation made 15 grants that represented the most promising research opportunities at the time. We initiated each research project with a down payment grant, and then agreed to pay for continuing expenses related to the research with surpluses generated by the on-going sales of vitamin supplements to members.



All of this research came to a crushing halt on February 26, 1987, when the FDA raided The Foundation's facilities. The FDA seized most of the supplements we were selling to support the research and then launched a full-scale criminal investigation and prosecution that lasted until 1996 (when the U.S. Attorney's Office dropped the case completely).

Not only did the FDA's actions economically cripple The Foundation's ability to continue funding research, but FDA agents paid personal visits to some of the scientists who had received the financial grants and told them that the money they received from us might be from the proceeds of "criminal activity", and the scientists could therefore be charged with "money laundering" for accepting our grants. One scientist was terrorized into stopping an important anti-aging project, but most of them (such as Dr. Roy Walford) were not intimidated and continued to use our grant money to further their research.

In 1988, we were able to initiate a project to investigate Dr. Donner Denckla's death hormone theory of aging, but this too had to be abandoned as the FDA took even more aggressive steps to shut us down.

It is my opinion that had the FDA not stopped the research projects we were funding in the late 1980's, there would have been substantial advances made in human aging control by now. In essence, the FDA set the most ambitious anti-aging/life extension research program of all time back by twelve years, which represents a significant portion of the projected life span of those reading this article.

PROJECTS THE FOUNDATION IS FUNDING TODAY

In 1999, The Life Extension Foundation provided more funding to scientific research than at any other time in its history.

The Foundation's policy is to award grants to scientists who are personally committed to extending the human life span, as these dedicated professionals take extraordinary steps to make their research as cost-effective as possible. We also are careful to commit our research dollars to projects that are difficult or impossible to fund with conservative government and institutional grants. This enables our grant dollars to accomplish a lot more than most government-sponsored research, which tends to be conservative, is often wasteful, and is, in some cases, entirely useless.

Drug companies spend billions of dollars developing what they know they can patent, and often convince the Federal government to subsidize research on their patented products. On the other hand, The Foundation is willing to fund anti-aging research involving unpatentable agents because we want to find out what works, whether it can be patented or not. Moreover, even when the research we fund leads to patents, these are usually for fundamental breakthrough discoveries with vast potential for extending healthy life span, rather than patents for "me-too" drugs that try to carve out a small niche in a large field already overpopulated with similar drugs.

The Life Span Project

At the University of California at Riverside (UC-Riverside) and the University of Wisconsin, The Life Extension Foundation is supporting a large-scale study of the effects on health and longevity in middle-aged mice of various combinations of nutrients, hormones and European drugs. This research is headed by Drs. Stephen Spindler of UC-Riverside and Richard Weindruch of the University of Wisconsin. The antioxidants being tested include melatonin, lycopene, vitamin E, alpha lipoic acid and procysteine. Some groups of mice are receiving mitochondrial energy-enhancing nutrients like coenzyme-Q10, carnitine and NADH. Still other groups are receiving the anti-glycosylation drug aminoguanidine or the hormone pregnenolone.

The most important aspect of this research is to maintain an age-matched control group of mice that are not receiving any supplements. Since this study was begun on middle-aged mice, the results should be more indicative of what humans might expect when they begin taking these nutrients over age 40. Drs. Spindler and Weindruch are so concerned about validating the results of their studies, that one control group of mice is calorically restricted, since this is the gold standard for life span extension. The calorie-restricted mice are expected to live the longest, and the effects of different anti-aging agents will be compared not only to a non-supplemented control group, but also to the calorie restricted group.

The compounds described above were carefully chosen. For example, lycopene is a member of a large class of plant pigments called carotenoids. There are more than 600 different carotenoids, but lycopene is the most efficient quencher of a particularly dangerous free radical called singlet oxygen. Unfortunately, lycopene levels in our bodies decline with age, even if we continue to eat fruits and vegetables. Lycopene increases the survival of irradiated mice, increases the resistance of mice to bacterial infections, and decreases the incidence of spontaneous and chemically induced cancers in mice. Consumption of higher levels of lycopene is associated with better human health. Thus, raising lycopene levels with dietary supplementation might prolong the life span of the mice. The same is true for the other agents in the study.

The Life Span Project mice are now 32 months old. The mice have been consuming supplements since they were about 14 months of age. As previously mentioned, supplementation began in middle age, since this corresponds to the time when most people seriously begin to take dietary supplements. About 50% of the mice are left in the life span portion of the studies. This means that the mice are remarkably healthy, and show no signs that their life spans have been prematurely shortened by disease processes. It is still too early to know for sure which of the therapies are having the greatest effects on life span and health.

The Critical Care Research Project

In 1993, The Life Extension Foundation initiated funding to a Southern California laboratory that was making significant progress in protecting against the damage that normally occurs to cells when blood flow is interrupted. As most people know, any disruption of blood flow (ischemia) causes severe cellular metabolic disturbances that often result in irreversible damage and eventual death. Nowhere is this ischemic damage more pronounced than in brain cells, where just a few minutes of blood deprivation results in cognitive dysfunction, paralysis and death.

The progress made in protecting against ischemic cellular damage has been so impressive that we've increased funding to The Critical Care Research Project every single year. We believe their work will produce a major breakthrough in protecting against the most common cause of death: lack of blood flow to the brain and other organs.

One of the great fears people have of undergoing surgical procedures is the risk of neurological impairment induced by blood flow disruption. The scientists working at The Critical Care Research Project have developed medical techniques that could greatly reduce surgical complications and neurological impairment. This new technology will also enable more victims of sudden heart attack, stroke or trauma to be revived without permanent brain damage.

When people die during surgery, it is often due to a complication that surgeons are unable to correct in time before irreversible brain damage occurs. If the technologies funded by The Life Extension Foundation were utilized in these patients, surgeons would have several hours to correct the complication, rather than just several minutes as is now the case.

It is well known that normal aging results in reduced blood flow to the brain, and that this circulatory deficit is a primary cause of diseases ranging from mild cognitive decline all the way to full-blown senility. The discoveries being made at The Critical Care Research Project have enabled The Life Extension Foundation to develop better formulas for healthy people to take today in order to protect against aging-induced reduced blood flow to the brain.

The most recent breakthrough made at The Critical Care Research Project is an Automated Liquid Ventilation System that can lower whole-body temperature extremely rapidly with an automated system that introduces cooled liquid perfluorocarbon into the lungs without causing lasting injury. What remains is to make the system portable, so that it can fit into an ambulance for use at the scene of automobile accidents, heart attacks and strokes.

A paper on the Automated Liquid Ventilation System is about to be submitted to a major medical journal for publication. The kind of rapidly-induced hypothermia that's possible with this liquid ventilation system could save the lives of large numbers of people who suffer heart attacks, strokes and severe closed head injuries. The system could also be used in-hospital to give doctors extra time to perform heavy-duty surgical procedures. We expect that this system will eventually make "Headline News" as one of the early

major medical breakthroughs of the 21st century.

The Critical Care Research Project is developing advanced methods to control death. Its scientists have restored experimental dogs to normal life after varying periods of time without blood flow and oxygen under several different conditions:

- after 17 minutes at normal body temperature
- after 5 1/2 hours at temperatures just above zero
- after 30 minutes of rapidly-induced temperature loss

The project has generated several anti-ischemia drug cocktails, an automated induced-hypothermia system, and an advanced cardio-pulmonary rescue system have the potential of saving the lives of millions of people. Key scientists working on the Critical Care Research Project: Mike Darwin, Steven B. Harris, M.D., Sandra Russell, M.S. The Project operates out of two buildings in Rancho Cucamonga, CA, is exclusively funded by The Life Extension Foundation.

Genetic anti-aging research, University of California at Riverside

The length of an animal's life is regulated by the amount of food they eat. The more calories they eat, the faster they age. Not only do they age faster, but they are also more likely to die of cancer and develop heart disease and diabetes. The reverse also applies: the fewer the calories consumed (provided malnutrition is avoided), the slower an animal ages, the lower the death rate from cancer, and the lower the rate of heart disease and diabetes. These relationships are found in organisms as diverse as mammals, insects and worms. Even though these surprising results were originally reported back in 1935, the mechanisms of action of caloric restriction are only now beginning to be understood. It appears that calorie restriction may produce many changes in organisms that together lead to better health and to a longer life.

In Dr. Spindler's laboratory at the University of California at Riverside, one of the areas focused on is the effects of caloric restriction and eating on metabolism. Dr. Spindler has found that aging reduces the ability of the liver to function properly. Caloric restriction seems to restore the ability of the liver to carry out its functions efficiently. Research is continuing to investigate the manner in which caloric restriction achieves this restoration of function.

In other studies, Dr. Spindler has explored the effects of aging and caloric restriction on certain stress genes. One of the things he's found in old age is that stress gene expression seems to increase to a higher level, but that caloric restriction decreases this type of expression. Dr. Spindler's studies suggest that lower levels of stress gene expression may be related to less damage to the kidney and blood vessels during aging.

As you can imagine, Dr. Spindler thinks that a proper diet, supplements and under eating is very important to remaining younger longer. New research funding by the Life Extension Foundation for Dr. Spindler's lab is aimed at a method of assessing the effects on aging of drugs, nutrients and tissue transplants, and the subsequent use of this approach in the search for authentic anti-aging therapies. This research will be using the new scientific method developed by Drs. Richard Weindruch and Tomas Prolla of the University of Wisconsin to study gene expression during aging (see November 1999, Life Extension magazine). It involves assessing the expression of thousands of genes at a time with high-tech micro-array gene chips in normally-fed and calorically restricted animals. The long-term objective of this research is the development of a validated anti-aging therapy that would act to prevent cancer, heart disease, stroke and other age-related diseases, while adding years of health and youth to the human life span.

The Methylation Project

The Life Extension Foundation recently awarded a new grant to scientists at the University of Arkansas to determine if dietary methyl and zinc supplements or a SAME supplement will affect longevity, age related pathology and relevant molecular parameters in rats. This project is headed by Dr. Craig Cooney and will generate knowledge about how various supplements affect s-adenosylmethionine, homocysteine, and DNA methylation in blood. It is expected that this research will lead to improved methods of testing methylation metabolism in humans.

When people are methyl deficient, they are at much greater risk of developing cancer, cardiovascular disease, depression and a variety of neurological and other disorders. Methyl deficiency is characterized by too little s-adenosylmethionine, too much homocysteine or a loss of DNA methylation. SAME is our chief methyl donor and is used for most methylation in our cells. Methylating enzymes use SAME but are inhibited by metabolic products related to homocysteine. The buildup of homocysteine leads to inhibition of methylation reactions and can also cause cardiovascular disease. DNA methylation is absolutely essential for mammalian development and is a key mechanism in aging and carcinogenesis.

Methyl metabolism is dependent on the dietary intake of nutrients such as vitamin B12, folate, choline, trimethylglycine (TMG) and zinc. It is imperative that we get enough methyl donors and methyl cofactors as DNA methylation levels generally decrease during aging and homocysteine levels rise with age in humans.

It would take decades to determine the optimal combination of methylation enhancing agents humans should take, whereas longevity studies can be done in rodents in only a few years. Nearly all previous rodent studies have measured the health of the animal over a relatively short period of time. Many tens of millions of dollars are spent each year on studies that are completed when animals are only about two years old. In these short studies we learn little or nothing about the animals that died before two

years and we never find out anything about exceptional animals that could have lived to be 30 or 36 months of age. The Methylation Study will continue throughout the animals' life span in order to determine the maximum effects that methylation supplementation can provide.

At this point, Dr. Cooney has built from scratch, a methyl metabolism and molecular biology laboratory for The Methylation Project. This includes a Bioanalytical Systems 200 HPLC with multiple detectors, quantitative PCR capacity as well as conventional capacities in microscopy, microplate analysis and centrifugation.

Dr. Cooney has developed reliable, minimally invasive ways of obtaining blood from rats. Enough blood can be obtained on a weekly basis to do several metabolic and molecular biology measures that are essential to the aging study.

On a regular basis, precise measurements of SAME in rats of different ages will be done using very small amounts of blood. These precise measurements of SAME will allow Dr. Cooney and his researchers to determine relatively subtle differences in SAME that occur with age and with supplementation. Dr. Cooney has also determined that supplemental SAME is sufficiently stable in water to be practical for supplementing rats through their drinking water.

Demethylation (the opposite of methylation) is thought by many scientists to initiate chromosome breaks, autoimmune disease, cancer and aging. Dr. Cooney's techniques will allow for the precise monitoring of methylation metabolism and the important sequences that occur with aging.

Following initial validation studies now in progress, Dr. Cooney will extend and expand to a full longevity study where rats will be maintained on control diets, methyl supplemented diets or SAME supplements and their longevity determined by time of natural death. Longitudinal blood collection will continue at regular intervals from rats of each group and the parameters of blood homocysteine, SAME and leukocyte DNA methylation will be determined.

One-year-old rats will be maintained 12 months on their respective supplements. Their age related pathology, tissue DNA methylation and other parameters will be determined by blood measures that will include homocysteine, SAME, leukocyte DNA methylation and standard blood chemistry measures such as cholesterol and glucose. These blood parameters were chosen because they are important measures in humans and will facilitate relating the data from rats to human studies.

Methyl supplements (folic acid, B12, TMG) are important to maintain low levels of homocysteine while SAME and methyl supplements are important to maintain SAME levels and DNA methylation patterns. These issues are not just important to maintain our cells now but are also important for our ability to clone and grow tissues that could be used to extend life. As important as low homocysteine is to health, maintaining high SAME and DNA methylation patterns and protecting DNA genetic structures are even more important. This is what the current studies are addressing, while the long term studies will then show how these relate to longevity itself.

Cell, Tissue and Organ Preservation Project

The Life Extension Foundation has provided extensive funding for another Southern California laboratory called 21st Century Medicine that is developing advanced methods of supercooling cells, tissues and organs for medical uses, such as kidney, heart, cornea and liver transplants. This technology will also improve the freezing of human and animal sperm for artificial insemination. The chief scientist for this project-Dr. Gregory M. Fahy-is the world's foremost cryopreservation expert. Dr. Fahy formerly worked in the American Red Cross' research laboratories. He and fellow staff-member Dr. Brian Wowk are the world's leading experts on ice control.

Drs. Fahy and Wowk have developed the first two agents ever found to block the formation of ice in concentrations as low as one part per million. It is well known that there is a critical shortage of available organs for transplant. Even a famous football star like Walter Payton could not get a liver transplant in time to save his life. The fact of the matter is that most people who need heart or liver transplants die before a suitable organ becomes available. A major reason why more organs aren't available is that the preservation methods are so archaic, that many potentially transplantable organs cannot be used. The advanced preservation methods being developed at the 21st Century Medicine laboratory in Rancho Cucamonga will enable hearts, kidneys and livers to be maintained in a viable condition for far longer time periods than current preservation techniques allow. This will result in tens of thousands of organs being transplanted into humans who would otherwise die.

The main goal of research currently being conducted is to demonstrate that it is possible to cool entire organs to cryogenic temperatures, store them as long as may be desired, warm them back up, and show that they can provide useful function in the body. In addition to the synthetic ice-blockers developed by Drs. Fahy and Wowk, Foundation funds are being used to support scientists at The University of Notre Dame who have discovered a natural beetle antifreeze protein that can be the best cryoprotective agent yet discovered. This is yet another of the technologies that will be used by 21st Century Medicine to improve and perfect advanced cryopreservation methods.

A record-breaking year

In 1999, The Life Extension Foundation contributed \$2,551,000.00 for new and ongoing research projects that could lead to major medical breakthroughs in the near future, including therapies to slow the aging process. We also provided grants to facilitate the

establishment of a non-profit anti-aging medical center where the best medical care based upon the best scientific evidence would be available to patients without regard to the views of the medical and political authorities.

We spent a good part of 1999 researching and documenting the types of therapies that would be incorporated into a "life extension" medical center. A summary of these novel treatment regimens can be found in our ground-breaking book Disease Prevention and Treatment. We are currently seeking property in Arizona and/or in Europe to establish a state-of-the art facility to conduct additional laboratory research and to implement aggressive medical therapies for people who would otherwise die because of the inadequacies of conventional medicine.

Where the money comes from to support all this research

The non-profit Life Extension Foundation does not receive government funding, nor has it pursued public donations. Instead, members support the Foundation's innovative, path-breaking research projects primarily by purchasing their supplements through The Life Extension Buyers Club. The Buyers Club offers pharmaceutical-grade supplements that are years ahead of the commercial supplement industry.

Unlike commercial supplement companies that spend their profits to grow their businesses, and to line the pockets of their owners, the non-profit Life Extension Foundation uses the proceeds from product sales to support innovative scientific research to extend the healthy human life span, and to pay for legal action to protect the health freedom of Americans. Since little money is spent on advertising, The Foundation depends on its members for referrals of people they know who could benefit from the integrated disease prevention and treatment protocols we have developed over the past two decades. We received about 25,000 referrals last year. This is the primary way The Foundation continues to grow.

It is absolutely essential that The Foundation dramatically increase the amount of scientific research we fund in order to gain total control over human aging (and the diseases of aging) by the year 2020. It will be too late for most of our members if we fail to accomplish this goal by 2020. Foundation President Saul Kent will be 81 years old in 2020. He currently works 16-19 hours a day, seven days a week to oversee the scientists The Foundation is supporting in order to make sure they operate at maximum efficiency, and to find new ways to fund more research. Saul knows his life will be in great jeopardy if these scientists fail to find a cure for aging by the year 2020.

Funding PROJECT 2000

In 1985, The Life Extension Foundation launched PROJECT 2000 to research mechanisms by which human aging could be slowed. Following are the 15 initial grants that were made by The Foundation in 1985-1986:*

Richard G. Cutler, Ph.D.
National Institute on Aging, Gerontology Research Center
Baltimore, MD

Grant Total: \$38,000.00

Purpose: Dr. Cutler worked at The National Institute on Aging developing the Gerontology Research Center SOD-transgenic mouse. The purpose of such research was to enable scientists to learn about the role of SOD in aging, and whether SOD-enhancing therapies could slow aging.

Roy L. Walford, M.D.,
Prof. of Pathology
UCLA Medical Center
Los Angeles, CA

Grant Total: \$15,000.00

Purpose: Dr. Walford studied the use of a fetal thymus gland extract to rejuvenate the immune system in mice.

Joan Smith-Sonneborn, Ph.D.
University of Wyoming
Laramie, WY

Grant Total: \$42,000.00

Purpose: Smith-Sonneborn sought to apply genetic engineering techniques to the study of aging. She was striving to learn the role of DNA repair in aging and whether manipulation of DNA genes could extend life. Only recently have scientists made breakthroughs in this area that The Foundation was investigating in the mid-1980s.

Don Ingram, Ph.D.,
Research Psychologist
National Institute on Aging, Gerontology Research Center
Baltimore, MD

Grant Total: \$15,000.00

Purpose: Dr. Ingram investigated the transplantation of brain tissue from young to old animals. This research held the promise of new therapies to treat brain disorders such as Alzheimer's, Parkinson's and aging itself.

Gregory M. Fahy, Ph.D.

American Red Cross

Bethesda, MD

Grant Total: \$20,000.00

Purpose: Dr. Fahy pioneered the development of a new method of low-temperature cell preservation called vitrification. This research was aimed at perfecting the long-term preservation of hearts, kidneys and livers for transplant.

Allan Goldenstein, Ph.D., Chairman, Dept. of Biochemistry

George Washington University

Washington D.C.

Grant Total: \$25,000.00

Purpose: Dr. Goldstein researched the role of the thymus gland as it related to aging and cancer. He discovered thymosin, the thymus gland hormone that plays a major role in regulating the immune system. Thymosin was approved as a drug in Europe, but rejected by the FDA.

Richard Weindruch, Ph.D.

UCLA Medical Center

Los Angeles, CA

Grant Total: \$25,000.00

Purpose: Dr. Weindruch conducted research on calorie restriction and sought methods to manipulate diet in order to prevent diseases, such as heart attacks, strokes, diabetes, hypertension, cancer and aging.

Paul Segall, Ph.D. and

Paola Timiras, Ph.D.

University of California at Berkeley

Berkeley, CA

Grant Total: \$25,000.00

Purpose: Drs. Segall and Timiras pioneered research showing a tryptophan-deficient diet early in life slowed down aging in mice. They sought to identify the mechanisms of action that enabled tryptophan-deficient mice to live longer.

Alexander S. Sun, Ph.D.

Dept of Neoplastic Sciences,

Mt. Sinai Medical Center

New York, NY

Grant Total: \$16,000.00

Purpose: Dr. Sun discovered an enzyme that is present in high amounts in normal aging cells; he sought out an inhibitor to that enzyme.

George C. Webster, Ph.D.

Florida Institute of Technology

Melbourne, Florida

Grant Total: \$16,000.00

Purpose: Dr. Webster discovered a specific chemical compound that appeared to be responsible for the loss of protein synthesis that occurs with aging. He worked on a method that would neutralize this chemical so that youthful cellular protein synthesis could be maintained throughout life.

David Harrison, Ph.D.

Research Scientist

The Jackson Laboratory

Bar Harbor, ME

Grant Total: \$25,000.00

Purpose: Dr. Harrison investigated how removal of the pituitary gland rejuvenates laboratory animals and is working to develop tests to measure aging in animals.

Mike Darwin

ALCOR Foundation

Riverside, CA

Grant Total: \$56,000.00

Purpose: Mike Darwin investigated methods of protecting brain cells against the effects of blood flow loss and on improving suspended animation techniques.

Matthew Witten, Ph.D.

Associate Professor

University of Louisville School of Medicine

Louisville, KY

Grant Total: \$15,000.00

Purpose: Dr. Witten worked on developing a computer model to measure aging.

Eugene Breznock, Ph.D.,

Prof. of Veterinary Medicine

University of California at Davis

Davis, CA

Also Director, BioSurg, Inc.)

Grant Total: \$20,000.00

Purpose: Dr. Breznock worked on developing a primate (monkey) colony to study aging and suspended animation.

Eric Drexler, Research Associate

Stanford University

Palo Alto, CA

Grant Total: \$8,000.00

Purpose: Dr. Drexler worked on molecular engineering (nanotechnology) projects as a means of extending life-span.

All of this critical research was stopped in 1987 when the FDA raided the Foundation's facilities.

The FDA also seized nutrient supplements and an entire printing of the LEF newsletter Anti-Aging News, ready to be mailed to its members.

To help our non-profit organization achieve its unprecedented goals, we ask Foundation members to tell people they know about our ambitious project of gaining control over human aging and extending healthy life span. Using The Foundation's advanced products, in conjunction with a healthful diet and exercise program, could add 10 to 15 years of healthy life to your life span, while supporting the best and most comprehensive program in the world to control aging, disease and death.

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