

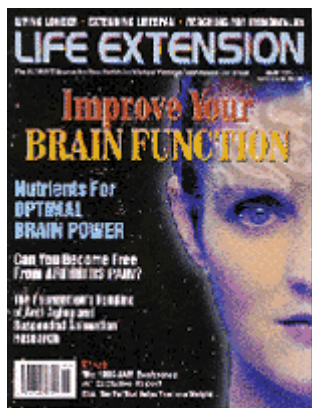
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EVENTS

The Genesis Experiment
Reversing The Aging Process:
A Quest for Authentic Rejuvenation Therapies

Fourth Annual Conference On Anti-Aging Medicine and Biomedical Technology

By Terri Mitchell



The American Academy of Anti-Aging Medicine's conference was held at the Alexis Park Resort in Las Vegas December 14-16, 1996. This year's theme was "The Future of Healthcare." Next year the conference will be held in a new 3,000-seat auditorium, presently under construction.

The future of healthcare is exciting. "Healthcare" as we know it-hospitals, drugs, doctors-is being replaced by the concept of taking care of health. The switch is from treating diseases to treating people so they don't get sick in the first place. Many illnesses occur in old age, so the idea is to prevent the degenerative changes of old age so as to prevent illness. It's working, and not only is it working, but research into how to maintain physical youth is giving important new insight into diseases and their treatment.

Hormone replacement therapy (hrt) is the hottest concept in anti-aging treatment. Researchers are beginning to realize that replacing hormones lost with aging has profound physiological effects. While melatonin basked in the sun last year, growth hormone (GH) was the star of this year's conference. GH affects many of the most vexing physical changes of old age: muscle deterioration, fat deposition, energy loss, and thinning skin. In addition, GH affects less visible signs of aging which have serious consequences: osteoporosis, insulin-resistance and decreased protein synthesis. As Dr. Aftab Ahmed put it, "GH has assumed center stage."

Many other fascinating topics were discussed this year, including treatments for heart disease and new insights into why caloric restriction increases longevity. Dr. Stanislaw Burzynski explained his anti-neoplastin cancer therapy, and Dr. Roy Smith described Merck Pharmaceuticals' new drug which makes a 69-year-old produce GH like a 20-year-old.

EFFECTS OF GROWTH HORMONE

To get things off on the right foot, Dr. Thierry Hertoghe of the Academy of General Medicine put up slides of half-naked women. Smooth, taut skin over good muscles-energy, strength-wouldn't it be great to be 20 again? We all had it at one time-what happened? What happened, according to Dr. Hertoghe, is that when GH takes a holiday, fat replaces muscle, skin sags and hair disappears. When people eat too much, they get fat all over. When they have GH deficiency, they only get fat in certain places. Hertoghe explained that fatty knees, sagging backs and bellies, and bags under the eyes are symptoms of GH deficiency. Young adults secrete 500 mcg of GH a day compared to an older person's 80 mcg a day. Of all age-related hormone deficiencies, GH seems to have the most visible consequences.

Dr. Bengt-Ake Bengtsson of the University of Goteborg described a "metabolic syndrome" that results from plummeting GH. It includes lipid abnormalities, insulin resistance, abdomen obesity, and cardiovascular problems, including hypertension. He reports that one year of GH replacement leads to a better lipid profile. After two years on GH, bone metabolism is increased with a significant increase in bone density (10-15%), blood pressure goes down, energy increases, and heart output increases.

GH REPLACEMENT IN A LARGE POPULATION

Dr. L. Cass Terry of the Medical College of Wisconsin reported on the effects of hormone replacement therapy (hrt) in over 900 patients, age 20-78, in the practice of Dr. Edmund Chein at the Palm Springs Life Extension Institute in California. According to Dr. Terry, men receiving GH (and other hormones) had a 20-point drop in total cholesterol. Self-assessments showed that people on GH have more strength, endurance, muscle, exercise tolerance, and better sexual function. In addition, they report thicker

skin with better elasticity, fewer wrinkles, and more hair. Injuries heal faster, energy and memory improve, and they become more stable emotionally. These are probably not placebo effects. As Dr. Terry points out, the average placebo effect only lasts 43 days; these assessments were taken after 6½ months. Among the adverse side effects noted were one person with elevated blood sugar (the GH dose was lowered), arthralgias, fluid retention, and carpal tunnel syndrome.

Most clinicians who give GH to reverse age-related deterioration give other hormones as well, not just GH. Testing is done before hrt is started in order to assess levels of testosterone, thyroid hormones, estrogen, progesterone, and others. Hrt involves bringing all needed hormone levels up to a "young" level.

In order to determine what effect other hormones have on GH, a study is being conducted by Dr. Marc Blackman of Johns Hopkins Bayview Medical Center in Baltimore. Funded by the *National Institute on Aging (NIA)*, the 5-year study will be unblinded in July 1998. Blackman is giving patients either GH or GH plus estrogen/progesterone (females) or testosterone (males). Mountains of data are being gathered on how hormone replacement therapy affects aging physiologically.

The "GH axis" interacts with the pituitary and the adrenals. Adrenal glucocorticoids inhibit insulin-like growth factor (IGF-1) which has an age-related decrease in step with GH. The average reduction is 50-60% from age 20-30. When clinicians want to measure how much GH a person has, they measure the amount of IGF-1. Deficits in the GH axis cause decreased IGF-1, which leads to many physiologic and immunologic deficits including: lowered antibody responses, lowered nitrogen balance, calcium imbalance, alterations in fat and carbohydrate metabolism, lowered cardiac endurance, a decrease in thickness of the left ventricle of the heart and decreased ejection, thinning skin with slower healing and less moisture, and problems involving sleep, cognition and mood. Blackman is presently looking into how GH relates to age-related sleep problems. He wants to find out whether low GH causes slow-wave sleep problems, or whether slow-wave sleep problems cause a loss of GH.

According to Blackman, the adverse side effects related to GH replacement therapy are caused by giving one big dose. When he gave 65-80-year-old men two doses-one between 8 and 9 a.m., and the other between 8 and 9 p.m.-their GH axis looked new again.

WHAT ABOUT CANCER?

Concerns have been raised that GH replacement may cause cancer. In the Chein/Terry cohort of over 900 people, four were diagnosed with cancers after beginning hrt therapy. Two of the cancers were basal cell carcinomas, one a squamous cell carcinoma of the tonsil, and the other a plasma cell cancer. The average duration was 8.7 months, with a range of 1.30+ months. The two patients with basal cell carcinomas were people who had high sunlight exposure. The overall incidence in this group of people is not greater than in people not taking the hormone, and none of these cancers can be attributed to GH itself since the patients were all taking multiple hormones. Nonetheless, the question of whether or not long-term GH replacement therapy could increase cancer risk has not been addressed in large-scale studies.

GH SECRETAGOGUES

At present, GH replacement is administered via subcutaneous injections of synthetic recombinant human growth hormone (rhGH). Besides not being much fun, injectable GH is also expensive. To most people, it is worth it, but finding an oral substitute would be an improvement.

(Note: there have been reports from England that people have contracted Cruetzfeldt Jacob ("Mad Cow") disease from injections of GH that occurred before the 1980s. These earlier forms of GH were derived from cows, and were used only in treating children with severe growth disorders. Since the early 1980s, GH has been synthesized and contains no animal products whatsoever).

One problem with GH replacement is that the injections do not mimic the body's natural secretion of the hormone, which is *pulsatile* (in bursts). While there is no doubt that GH injections are beneficial, it would be more natural to induce the body to make more of its own GH.

GH release is stimulated by growth hormone releasing hormone (GHRH), which is secreted by the pituitary gland. GH is opposed by somatostatin from the pituitary. Knowing this, researchers at Merck began looking for something that would either inhibit somatostatin or augment GHRH. Surprisingly, they found both in a peptide called Growth Hormone Releasing Peptide-6 (GHRP-6) (which was discovered in a different lab). They were quickly able to develop a drug that mimics GHRP-6 because they found that the peptide acts through a "G-protein," a fairly well-known entity. According to Dr. Roy Smith, Merck's new growth-hormone-releasing drug (MK-677) *rejuvenates the GH axis of a 69-year-old man to that of a 20-year-old*. MK-677 (and others like it) are "secretagogues" (they cause the secretion of something)-the next generation in hormone replacement therapy.

Merck's GH secretagogue is taken in oral form once a day. The only significant side effect is an initial cortisol increase. With chronic use, cortisol falls back to normal. The drug doesn't appear to affect receptors other than the ones that regulate GH, so there should be few, if any, adverse side effects. Merck hopes to gain approval for the drug within five years. Researchers at

Merck are anxious to find equivalent secretagogues for insulin and other important hormones.

Other companies are rushing to develop their own secretagogues. Dr. Aftab Ahmed of Gero Vita reported that his company has a peptide that may work as well as Hexalamin, a GH secretagogue being developed by Pharmacia-Upjohn. "AminoTropin-6," as it is called, "uses the body's own mechanisms" to increase GH release.

Ahmed pointed out that restoring GH and other hormones has ultimate social benefits. Thwarting physical deterioration in the elderly will help people maintain their autonomy, thus reducing healthcare costs, and easing the burden on caregivers.

DISCOVERY OF THE CENTURY

Dr. Stephen Sinatra received a call from a Ph.D. whose mother was in the hospital, dying of heart disease. Even though the son had supplied his mother's physicians with a stack of papers on coenzyme Q10 (CoQ10), they refused to give it to her. Desperate, he begged Dr. Sinatra to transfer his mother out of the hospital. The cardiologist refused, saying the woman would never survive the ambulance ride. But the Ph.D. pleaded that his mother had no chance at all if left where she was. Sinatra relented, and transported the dying woman to another hospital where she could be treated with CoQ10. She survived the ride, and Sinatra began treatment immediately. 450 mg of CoQ10 were given through her feeding tube, along with I.V. vitamins and minerals. Within days she was weaned from the ventilator, and 10 days later she walked out of the hospital.

Dr. Karl Folkers recently started calling coenzyme Q10 "Vitamin-Q10." According to his thinking, it was misnamed because Q10 is not an enzyme. It's a vitamin-a very important one. Folkers, who has 64 years of chemistry and medicine behind him, should know. He was among the first to do research on the funny orange substance, which was first discovered in beef hearts.

According to Folkers, the great value in CoQ10 is not its antioxidant activity (which is substantial) but its "bioenergetic" activity. According to Sinatra, CoQ10 is so important that if yeasts are blocked from synthesizing it, and polyunsaturated fatty acids are added to the yeasts' diet, they die. CoQ10's molecular structure is crucial for energy production in all cells. Proper energy metabolism is especially crucial for heart muscle, which is why it's such a valuable heart treatment.

Dr. Yamamura first treated a patient with a Q10-like substance in 1967. In 1972, its antioxidant properties were discovered and, in 1978, a Nobel Prize was awarded for the chemistry of Q10. Why has it taken 30 years for people to find out about this life-saving substance? Q10 can't be patented as a drug, so it doesn't fit into the treatment paradigm-a doctor's prescription. But according to Folkers, Q10 has potential for the treatment of diabetes, multiple dystrophy, AIDS, and hearing problems as well as heart disease and cancer.

Q10 IN CLINICAL EXPERIENCE

Dr. Peter Langsjoen has been conducting clinical trials with Coenzyme Q10 in heart patients since 1985. His first trial involved 19 patients in a double-blind, crossover design. Patients given 33 mg three times a day showed significant improvement over placebo. In 1990, he conducted another trial in 126 patients with idiopathic dilated cardiopathy. In this study, the dose was adjusted according to how much it took to bring the patient's blood level up to at least 2m/ml of Q10. Again, he found significant improvement (75% survival at three years compared to 25% without Q10). In 1994, he conducted another study in hypertensive patients with similar results.

One of the most consistently reported benefits of Q10 is improved diastolic blood pressure. Langsjoen explained that the diastolic function of the heart is the *energy dependent* resting phase. He believes that CoQ10 improves diastolic function because it improves energy production. He finds that patients can use 50% fewer heart drugs a few months after beginning Q10 therapy. His patients take 60 to 480 mg of CoQ10. Langsjoen has not seen adverse interactions with blood thinners or other heart medications. Langsjoen reports that Q10 increases the quality of life of elderly people, and produces results that are "dramatic and lasting," although it takes four to six months to see these results.

According to Dr. Sinatra, the amount of LDL a person has is not as important as the amount of *oxidized* LDL. Free radicals produced by oxidation damage mitochondria and DNA. Both are crucial for a well-functioning heart. People who have high levels of iron and oxidized LDL, have four times the risk of heart disease than those who do not. The average cholesterol level in France is 220, yet that country has the second lowest incidence of coronary artery disease after Japan. Researchers believe that the antioxidant polyphenols in French wine protect French people from heart disease. (*Note: both white and red wine have antioxidant properties. White is not as potent as red.*)

One of the important functions of CoQ10 is that it recycles vitamin E. Vitamin E is a powerful antioxidant against lipid (fat) oxidation. According to Sinatra, adequate vitamin E will reduce LDL oxidation by 40%. Vitamin C is an important antioxidant for the heart as well. In a study in *Circulation*, 1,000 mg of vitamin C per day increased blood flow to the forearm. Importantly, it also inhibited platelet aggregation in the early morning hours. Many heart attacks occur in the morning.

According to Sinatra, CoQ10 should be taken after every meal and at bedtime. Smokers, diabetics, and people with other chronic diseases or toxic exposures need more. Patients undergoing chemotherapy should be given CoQ10 to protect from free radical damage caused by these drugs. Sinatra strives for a blood level of 2.5:/ml. He emphasizes that *clinical response is dependent on blood levels*.

Not all Q10 is well-absorbed, and Sinatra believes that some treatment failures are a result of poor absorption. Certain drugs "knock out" Q10, including the cholesterol-lowering drug, lovastatin. It is important to keep these things in mind when beginning Q10 therapy.

Magnesium, selenium, and vanadium are also important for heart health. Because of poor diet and soil conditions, it is necessary to take supplements of these trace minerals. According to Sinatra, hawthorn acts like an ACE inhibitor. Garlic lowers cholesterol and blood pressure, and cayenne inhibits LDL oxidation. All of these are heart-friendly.

ROTIFERS LIVE TWICE AS LONG ON MELATONIN

Dr. Roman Rozenzweig, who first published the melatonin theory of aging in 1987, reported on an experiment where rotifers were treated with melatonin. (A rotifer is a microscopic multi-celled organism that lives in water). Their normal lifespan is five days. With Rozenzweig's melatonin treatment, however, they lived 10.4 days. According to Rozenzweig, the pineal may be the "master gland" of aging. He believes that aging is caused by decreased melatonin, and an increased serotonin-to-melatonin ratio.

Aging causes melatonin to decrease, and serotonin to increase. This is not desirable, because serotonin antagonizes some of the good effects of melatonin. When people get older, it takes longer for the body to synthesize the enzymes necessary to process melatonin. Dr. Rozenzweig uses the serotonin-lowering drug, cyproheptadine, to reverse the age-related decline in melatonin and increase in serotonin.

LOW-CALS LIVE LONGER

The data continue to stack up on the beneficial effects of eating less. According to Dr. Richard Weindruch of the University of Wisconsin, a 20-35% calorie cut-back extends longevity in mice even when started in middle age.

According to Weindruch's (and other's) research in rodents, calorie restriction lowers oxidative stress and enhances DNA repair and protein synthesis. It protects against loss of insulin sensitivity and lowers metabolic rate. It decreases blood pressure and fasting blood sugar. All these parameters change as one ages. And many of these things relate to the so-called "diseases of aging," such as cancer and diabetes.

Eating light doesn't just help rodents. During his stint in Biosphere II, Dr. Roy Walford recorded some of the same beneficial effects in humans as researchers have seen in lab rodents. According to researchers in the field working with monkeys, where there have been similar findings, this is one instance where the rodent data will most likely hold up in humans.

Scientists don't know why calorie restriction increases longevity, but Weindruch is particularly interested in oxidative stress and what it does to the body's power plants (mitochondria). Anti-oxidants have been the anti-aging mantra for the past decade, but no one has shown the precise connection between free radicals and what we call "aging." Dr. Weindruch is zeroing in on what free radicals do to mitochondria, and how that relates to age-related pathologies (such as loss of skeletal muscle). He is also investigating how mitochondria from aging but healthy humans function compares to mitochondria from diseased or young, healthy humans. His investigations are an attempt to test Dr. Denham Harmon's "free radical theory of aging."

OTHER EFFECTS OF CALORIE RESTRICTION

Dr. Ron Hart of the National Center for Toxicological Research reported exciting things about caloric restriction. According to Hart, food restriction drops body temperature. Dropping the body temperature of a rodent 1.5-2.0 degrees will inhibit DNA damage 20-25%, increase free-radical-scavenging enzymes, and lower lipid peroxidation. Calorie restriction benefits cell replication. DNA strand breaks decrease and DNA repair increases. This translates into less cancer.

Eating less enhances cancer resistance in another important way: Calorie-restricted animals have a 10-fold enhancement of p53 apoptosis. Protein 53 is a hot ticket in cancer research. It kills abnormal cells (apoptosis), or stops them from growing. Cancer cells, with their mutated DNA, are normally killed by p53. But if the gene for p53 is mutated, the p53 protein can't be transcribed. Without p53 to stop them, cancer cells grow unabated. Mutations in the p53 gene are found in numerous types of cancers, as well as cancers that are resistant to treatment.

The benefits of calorie restriction are less cancer and less cardiovascular and renal disease. Hart's data show clearly that these "age-related" diseases are not an inevitable consequence of aging; they can be thwarted. If the rodent data holds up for humans,

there will be powerful evidence that how much a person puts into his or her mouth will have a profound effect at the molecular level. Less food means better cell function. Why is this? The best answer is that food ties in with the evolutionary imperative to grow up fast, reproduce and die. Food triggers changes at the molecular level that may be fine for growth and reproduction, but not so great later on, when the only thing likely to grow is cancer cells.

As beneficial as eating less is for health, eating less does not come naturally for humans. So researchers are asking, *can therapies be developed that mimic the effects of calorie restriction?* The answer is yes, and scientists like Hart are working on it. Hart has begun the first human calorie restriction study in conjunction with the University of Tennessee.

THE VIRTUES OF GETTING THINNER

The research of Hart, Weindruch and others ups the ante for getting thin. Even skinny people have an imperative to eat less. Longevity effects of calorie restriction are not automatically bestowed on thin people: they have to eat less, too. According to Dr. Roy Walford, the proper method for determining how much calorie restriction is right for you is to eat about 20% less than the amount it takes to maintain your ideal weight (a good way to achieve this is to use Dr. Walford's Diet Planner).

Even 5% weight loss has a beneficial effect on health, according to Dr. Brendan Montano of the New England Heart Center. A Body Mass Index (BMI) above 30 creates a 2-fold increased risk of dying of all causes, and a 3-fold increased risk of heart disease. Hypertension, heart disease, cancer, diabetes and stroke all increase with age, and all respond positively to calorie restriction.

Obesity is reaching epidemic proportions in the U.S. Thirty-three percent of Americans are obese, and the number is rising, especially in children. For obese people whose BMI is greater than 30, a new drug called *dexfenfluramine* has been approved by the FDA. It is being used with another weight-loss drug called *phentermine* to create what is known as "FenPhen." According to Dr. Richard Atkinson of the University of Wisconsin, "FenPhen" attacks obesity by two different mechanisms-serotonergic and andrenergic.

Both dexfenfluramine and phentermine have amphetamine-like actions. Dexfenfluramine is not for those who are simply overweight. Besides amphetamine-like side effects, it has the very serious side effect of primary pulmonary hypertension that makes the risk/benefit ratio reasonable only for the very obese. (According to Montano, the fatality rate of primary pulmonary hypertension is 55%).

DHEA AND WEIGHT LOSS

Although there are virtually no published studies on DHEA and weight-loss in humans, Dr. Judy Kameoka of the Center for Health Restoration & Metabolic Fitness reported that DHEA affects energy metabolism in ways that decrease fat, and increase muscle mass.

DHEA blocks the conversion of fibroblasts to adipose (fat) tissue through the control of certain enzymes. In addition, it raises levels of serotonin (in rats), which lowers appetite. The hypothalamus is the part of the brain that is serotonin-responsive and controls appetite. One of the most interesting DHEA studies this year came out of Louisiana State University. Researchers found that if Zucker rats were given a choice, they chose 40% of their calories as fat. Giving them DHEA abolished their preference for fat, which prevented weight gain. Consistent with its fat-lowering reputation, a study out of Japan shows that DHEA lowers serum lipid levels in men.

DHEA REVIEW

For those who missed last year's conference, Dr. William Regelson presented a good review of the benefits of the neurosteroid hormone, DHEA (dehydroepiandrosterone). DHEA continues to be an exciting anti-aging therapy.

According to Regelson, DHEA can sensitize cells to insulin. Insulin desensitization is an age-related phenomenon that has deleterious effects. Diabetes can be prevented in diabetic-prone mice by DHEA, and Regelson is attempting to rejuvenate pancreatic islet cells in mice with DHEA.

One of the most important effects of DHEA is on immunity. DHEA provokes certain biochemicals known as cytokines which stimulate important immune system cells. DHEA's effect on cytokines is thought to be responsible for its ability to inhibit viruses in mice.

CURING CANCER

According to Dr. Stanislaw Burzynski, "cancer is a disease of information processing." Turn off the oncogenes, turn on the tumor

suppressor genes, and there is no cancer. He has developed peptides that do just that. They are called antineoplastons. Dr. Burzynski has been conducting research on this anti-cancer therapy for over a decade, which is extensively documented in peer-reviewed journals. He has conducted 20 Phase I studies, and is currently directing Phase II studies, seven of which are completed and 69 are ongoing. In 40 people with brain tumors who completed Phase II, 83% had a complete or partial response, while only 17% progressed.

According to Burzynski, cancer genes are turned on every day. His goal from the beginning was to find the "switch" to turn cancer genes off. According to Burzynski, a gene called the ras oncogene is involved in 40% of all cancers. It can be turned on by growth factors or cell signals. Antineoplastons inhibit the ras gene.

Another gene involved in cancer is the p53 tumor suppressor gene. According to Burzynski, p53 is involved in 50% of all cancers. The protein product of p53 will kill cancer cells if activated. But in some cancer patients, the gene is turned off and doesn't make the necessary protein. One of Burzynski's antineoplastons not only turns the gene on, but inhibits genetic mutations that keep it silent. Brain tumors are among the toughest cancers. Burzynski began treating a group of 20 patients having certain types of brain cancer with antineoplastons nine years ago. All but four are still alive.

The National Cancer Institute has reviewed some of Burzynski's data and confirmed his results. Since Burzynski's approach is to turn on and off natural "switches" that people normally have, there are few side effects. His anti-neoplastons simply induce cells to do what they ought to be doing anyway. Cancer cells die the way they naturally would (by apoptosis or by growth inhibition). *[Dr. Burzynski is currently on trial in federal court in Houston for sending his antineoplastons across state lines].*

SUMMARY OF FINDINGS

If one thing got across at the conference, it is that the utilization of hormones and other therapies to reverse aging is worth its weight in taxpayer money. Healthy older people are more self-sufficient, and spend less time in hospitals and "nursing homes." A bottle of Coenzyme Q10 costs a lot less than heart bypass surgery, and is a lot more fun. The name of the game is to *eat like a bird, exercise, and replace those hormones!* No longer is hormone replacement synonymous with estrogen and menopausal women. DHEA, pregnenolone, growth hormone, and testosterone are the new kids in hormone replacement. (DHEA and pregnenolone are hormone precursors). And they do a lot more than just stave off hot flashes.

Pharmaceutical domination of healthcare may soon cease. Supplements can no longer be dismissed as "quackery." Too many scientifically-sound studies are being published. Even that dinosaur called government has seen the light, and is funding studies on non-drug therapy. More and more people are becoming aware that prevention and non-toxic interventions work. Clinicians are taking supplements themselves, and no longer go into apoplexy when a patient expresses the desire to take vitamins instead of drugs. The quest for youth is driving a real "healthcare" industry that prevents disease, enhances the quality of life, and decreases healthcare costs. It is a force to be reckoned with.

RESEARCH

THE GENESIS EXPERIMENT REVERSING THE AGING PROCESS: A QUEST FOR AUTHENTIC REJUVENATION THERAPIES

By Michael G. Darwin, Steven B. Harris, M.D., and Sandra Russell, B.A.

The Life Extension Foundation's funding of anti-aging research at 21st Century Medicine laboratories means taking different pathways in the quest to extend the lifespans of people of all ages Here, three of the researchers explain their progress to date.

Experimental gerontology seeks to understand how and why living organisms grow old and die. Gerontologists do not yet have a workable paradigm for how and why we age. As a result gerontologic research has been typically far removed from clinical application, while advances in clinical medicine often occur independently of any theoretical understanding of aging. For example, physicians did not need to understand the inflammatory "cascade" to make very good use of aspirin. Indeed, aspirin was used for nearly a century before anyone began to understand its mechanisms of action. Similarly, today we are using a variety of drugs and nutrients to fight aging and age-associated diseases without fully understanding how aging works.

Right now, the only way to find out if potential anti-aging therapies really work is to conduct lifespan studies in a relevant animal model. There are several barriers to getting this kind of research done. The first is that it takes time, considerable skill and money. The second is that many agents with anti-aging potential cannot be patented, which discourages investment in lifespan studies.

But at the Life Extension Foundation, our major concern is not how much money we can make from funding research, but how vital the research is for anti-aging purposes. To that end, the Foundation is funding long-term lifespan studies in laboratory mice (the Lifespan Project) to determine the effects of various nutrients, hormones and drugs on lifespan, aging and the diseases of

aging.

For those who can't wait to find out how to slow the aging process throughout the lifespan, we're also funding a series of studies aimed at achieving rejuvenation, called the Rejuvenation Project, on gaining a partial reversal of the aging and degenerative changes associated with advancing age. Among the agents we plan to investigate in our quest for authentic rejuvenation therapies is growth hormone, which has been proven to have potent anti-aging effects in humans, and has extended the mean lifespan of aging mice in dramatic fashion.

The first study in the Rejuvenation Project is now well underway and is expected to be completed this year. It is called the Genesis Experiment and is a classic example of research that could not be done in a university or industry setting.

For many years it has been known that adult animals (including humans) can be re-populated with missing cell types without which they would otherwise suffer death or disease. Perhaps the most common example of this is the administration of bone marrow via intraperitoneal or intravenous injection to re-populate the marrow of a patient who has undergone chemotherapy and/or radiation treatment for cancer. Similarly, fetal cell transplants have been used to repopulate neuron-depleted areas of the brains of both rats and humans with Parkinson's disease. Fetal neurons also have been used to seed the forebrains of aged animals with cholinergic neurons in an attempt to improve cognitive function.

TWO THEORIES OF AGING

Two theories of aging are the immunologic theory of aging and the finite number of cell divisions, or "Hayflick Limit," theory of aging. These two theories are not exclusive of each other. Both state that aging occurs in part or in whole as a result of a decline in the population of young, viable, dividing cells in the body as a whole, or in the immune system in particular. It would be interesting (and very useful) to know if the administration of "youthful" stem cells, the formative cells that give rise to the various differentiated tissues of the body that comprise our organs and tissues, can extend lifespan in aged animals. For many years, animal fetuses, principally from sheep, have been homogenized into cells and given to treat aging. This "cell therapy" treatment was invented by Swiss physician Dr. Paul Nihans and has been popularized by European physicians such as Hans Schmidt in Germany. Many remarkable claims have been made for this treatment, but there are theoretical and practical reasons to suspect that it does not work.

As originally put forth by Dr. Nihans, the fetal cells from sheep are supposed to "take" and colonize the elderly human host, rejuvenating him in the process. The problem is that even in the same species, each individual is genetically and immunologically unique and such foreign tissues are likely to be rejected. Indeed, even tissues from a brother or sister (unless from an identical twin) are rejected without the use of powerful and dangerous immunosuppressive drugs, such as cyclosporine, which depress immune function.

A more appropriate animal model for cell therapy would be to administer more or less genetically identical fetal tissue to old animals. Such an experiment could answer important questions about how aging occurs, and if rejuvenation of old animals is possible by giving them young stem cells. One way to do this experiment is to use animals that are so inbred that they are nearly identical genetically. In such animals, tissues can be transplanted to any other animal of the same strain without concern about rejection.

The Fischer 344 rat is such an animal. The Fischer 344 has been inbred over hundreds of generations so that all individuals in the strain have histocompatible tissues. Another advantage to the Fischer 344 is that it is a widely used animal in biomedical research (and in gerontology) and thus old animals, or so-called "retired breeders," are readily available at a reasonable cost. Similarly, "timed pregnant" females can be ordered so that histocompatible fetal tissue is available on demand at precisely the right time.

On Sept. 24, 1996, 30 Fischer 344 male rats, 20 months of age (the human equivalent of 60 to 65 years of age) arrived at the facilities of 21st Century Medicine in Southern California. Each animal was placed in a separate cage, and on Sept. 29, the animals were randomly divided into three groups of 10 each. One group (experimental) was given complete tissue samples from fetuses removed from time-pregnant females by intraperitoneal administration.

A VERY GOOD MODEL

Another group (the control) was given the vehicle solution in which the fetal cells were prepared (Hank's Balanced Salt Solution), in the same manner as the experimental group. A third group (also a control) was given liver and spleen tissue from a non-pregnant female of the same age, as used to provide the complete fetal tissues. The purpose of this last group was to serve as a control on the sterile preparation technique used to generate the fetal tissues. The spleen of adult animals also contains many immune cells, including stem cells.

The mean lifespan of male Fischer 344 rats is about 766 days. Not surprisingly, mortality has been brisk and, four months into

the study, only 13 animals remained alive out of the 30 that were present when the study began.

We already have a pretty good idea of the effects of fetal cells administration on mortality and morbidity, but those results will not be revealed until the study is over. More importantly, we have developed what we think is a very good model for rapidly determining if an intervention is effective at reversing the aging process.

These studies are not easy to do. Every aspect of the animals' care must be tightly controlled if the data are to be meaningful. Day-night cycles, temperature, humidity, diet and husbandry must be meticulously attended to. Additionally, the animals must be weighed weekly, and also checked twice daily so that dead animals can be promptly necropsied to determine the cause of death.

Substantial upgrades to the 21st Century Medicine facility were made to carry out the Genesis Experiment, as well other experiments in the Rejuvenation Project which will follow. These upgrades have paid off handsomely. There have been no significant problems. In fact, things have gone about as well as we could have hoped for. The animals mostly are dying of cancers, with an occasional death from pneumonia or congestive heart failure. The survival curve of the animals closely matches that of the best curves in the literature. Data acquisition and animal husbandry have proceeded smoothly.

Unlike the pilot Genesis Experiment, future studies in the Rejuvenation Project will include more tests. For example, the growth hormone study will probably include laboratory evaluations of blood and more detailed measurement of the animals' physiological response to the treatment. In the Genesis Experiment, the only endpoints have been cause and time of death. Effects of treatment on lean body mass, total body fat, blood chemistries, immune function and other parameters of interest were not determined.

INCREASING THE MONITORING

However, as other agents and approaches to slowing or reversing aging in the aged adult animal are evaluated, there will be various types of functional and biochemical monitoring. In fact, one of the features built into these experiments will be to increase the frequency and scope of monitoring if a favorable response to treatment is detected. Sentinel animals not included in the core group and used to determine the effect of the treatment on lifespan will be used for blood drawing and other invasive procedures so that the effects of the treatment on lifespan can be separated from "perturbations" induced by laboratory sampling.

The Life Extension Foundation is probably the only organization in the world that will be funding this type of interventive research, which has the potential of benefiting you in the near future, in extending the lifespan of people of all ages, not just members of future generations.

Foundation president and founder Saul Kent is almost 58 years old, and many foundation members are older than he is. They are extremely interested in finding methods to extend their lifespans before it's too late. That's why the Rejuvenation Project will be an integral part of the life extension research funded by the Foundation in the years to come.

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