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REPORT

Gerontological Society Of America
Exploring The Genesis Of Aging

By Vince Cappiello

Researchers from around the world convened in Cincinnati for the 50th Annual Scientific Meeting of the Gerontological Society of America, with presentations involving therapeutic strategies in normal aging, and in such diseases of aging as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease).

Among the topics discussed by the 3,200 participants were genetic determinants of longevity and aging, growth hormone and aging, trophic factors involved in the neurodegenerative diseases of aging, and life span extension by dietary manipulation.

Again, one of the most fascinating animal models for studying longevity employs the worm *Caenorhabditis elegans*. In recent years, and as detailed extensively in Life Extension magazine, *C. elegans* has become the focus of intensive research because several mutations have been identified that significantly increase its longevity. Depending on the particular type of mutation, the longevity of these worms can be increased up to six times their normal life span.

Similar work with fruit flies (*Drosophila*) also has demonstrated that longevity can be increased by genetic manipulation. Since it appears that certain genetic determinants of longevity in lower animals have been preserved in humans, according to Dr. J. Vijg of Harvard Medical School, understanding the mechanisms involved could contribute to a better understanding of the aging process. This information could be combined with the growing body of knowledge about aging and longevity in humans that is developing in genetics, neuroscience, biochemistry, biology and medicine. Conference participants pointed out that aging is a complex process and no single avenue of research will provide the key to its understanding.

In another presentation, scientists at the Gerontology Research Center in Baltimore, including Life Extension Scientific Advisory Board member Don Ingram, and other researchers presented their findings on "Calorie Restriction in Nonhuman Primates: Relevance to Human Aging Processes and Age-Related Disease." The findings of Dr. Ingram and his colleagues are presented in expanded form elsewhere in this issue.

Dr. David Burke of the University of Michigan presented preliminary data on the mapping of mouse longevity genes in a genetically heterogeneous mouse population. Analyses of these 145 male and female mice suggested an association between the position of a gene on a chromosome (its "loci") and longevity. Future studies are planned with a larger sample in an effort to achieve statistical significance.

Human gene studies that are being used to find candidate genes and gene products for aging were discussed by Dr. Richard Cawthon of the University of Utah. The Utah Genetic Reference Project was started 14 years ago with 45 families. Currently, it is in the third generation and 450 individuals have been studied. Cell lines from these people were established so researchers could map their genetic makeup and search for those genes related to aging.

"Now that this has been done we can study specific traits," notes Cawthon. For example, traits have been identified that do not change and that have predictive value for mortality. For example, the lower the white blood cell count, the lower the risk of dying; likewise for resting heart rate. Inheritability of both conditions in twin studies was 60 percent.

Another trait being studied is telomere shortening. Telomeres, specialized structures at the tips of chromosomes, are believed to be the repository of cell longevity and have been the topic of some of the most exciting discussions on longevity so far this year.



Cawthon also discussed the use of the Utah Population Database, which was developed from descendants of the original Utah pioneers. He explained that mitochondrial inheritance is almost exclusively maternal. Mitochondria are subcellular organelles involved in cellular respiration. They are self-replicating and contain an extranuclear source of DNA. Using data from these families, long-lived females were identified, and studies of their mitochondria suggested a relationship with longevity. Cawthon is quick to state, however, that "mothers pass down many things to their daughters, including the handling of stress." He cautioned that this observed longevity could be a purely social phenomenon.

As for identifying nuclear genes that contribute to longevity, researchers are looking for effects on respiration and other cellular functions after removing mitochondria from cells in culture. Candidate genes and gene loci being sought are those that contribute to senescence and longevity.

Dr. Junko Oshima, of the University of Washington, discussed Werner's syndrome, a rare, hereditary disease of young adults characterized by short stature, early graying, cataracts, vascular disorders, and generally premature aging and death. Although it is generally felt that the clinical manifestations of Werner's syndrome mimic normal aging, Oshima noted there are important differences.

The gene responsible for Werner's syndrome is "autosomal recessive" in its pattern of inheritance-that is, in order for an offspring to develop the trait, each unaffected parent must contribute the responsible gene at the time of conception. Thus, the offspring will be "homozygous" for the gene, meaning it will have two copies of the responsible gene, an essential condition for a recessive gene to be expressed. While the parents are unaffected because they each have only one copy of the responsible gene (and thus are "heterozygous"), they will be carriers.

Male and female offspring are affected equally because the gene is carried on an autosome (any non-sex chromosome). One in four children of two unaffected parents will develop the trait. Other examples of autosomal inheritance are cystic fibrosis and phenylketonuria. Researchers have identified 24 different mutations of the Werner's syndrome gene.

Paradoxically, Oshima noted that some parents of her Werner's syndrome patients are centenarians. Since these parents must be heterozygotes, one would expect that one in four of their children would develop the disease; however, the observed ratio is much higher than that. "Clearly, we're missing some genetic risk factor," Oshima says, "which requires further investigation." On another front, a team of researchers discussed the problems associated with age-related declines in the secretion of growth hormone (GH), and insulin-like growth factor-1 (IGF-1). Low levels of these factors occur in aging women and men, and are considered to be "pacemakers" of aging because they contribute to osteopenia (thin bones), muscle atrophy, and decreased exercise tolerance.

Administration of exogenous GH to older adults has shown that it can increase IGF-1 secretion, lean body mass, muscle mass and skin thickness. It has also been reported that bone "turnover"-the continual process of bone formation and resorption that takes place in normal bone-is affected, suggesting that GH could impact the onset of osteoporosis.

In this regard, Dr. Dike Kalu, of the University of Texas, discussed bone turnover and studies of the effect of GH on bone loss in aging. Although the results of these studies were conflicting, genetic factors appeared to be the greatest determinant of bone loss.



James Nelson (left) discussed calorie restriction and dietary manipulation, Dike Kalu (top) explored bone turnover, and Junko Oshima (right) reviewed findings on Werner's Syndrome.

Still, Kalu feels that GH and IGF-1 have therapeutic potential for rebuilding bone in established osteoporosis. While optimum candidates for such therapy in human osteoporosis are yet to be established, initiation of this therapy in women before menopause might be beneficial in delaying or preventing osteoporosis.

It is well known that age-related deterioration in cognitive and motor functions can be correlated with dysfunction of specific neuronal populations in the central nervous system, explained Dr. Joe Springer of the University of Kentucky. The original concept that this deterioration is due to cell death has come into question; evidence is accumulating that the neurons are undergoing subcellular change rather than death.

Current research strategies are based on the concept that in neurodegenerative diseases such as Alzheimer's, Parkinson's and ALS, normal functioning of neurons has been compromised. "So if we can administer the right exogenous neurotrophic factor, normal function may be restored; whereas, if left untreated the deterioration will progress to degeneration," notes Springer. "It is this degeneration that is observed in lesions of neurodegenerative diseases."

Springer's line of research focused on one type of neurotrophic factor called glial cell line-derived neurotrophic factor (GDNF), identified in 1993 and found to increase survival of dopamine neurons located in the substantia nigra of the brain. Dopamine neurons utilize dopamine as the neurotransmitter. It is these neurons that degenerate in Parkinson's disease.

Since motor neurons in the spinal cord depend on neurotrophic factors for survival and maintenance of function with muscles, Springer became interested in studying how GDNF contributed to these effects. GDNF is normally synthesized at very low levels in skeletal muscle. But in a mouse study in which the motor nerves to hind-limb skeletal muscles were severed, he found that GDNF-derived mRNA increased after two weeks. Springer believes this suggests a potential role for GDNF in nerve regeneration: it may act as an "attractor" for the regenerating axons.

Springer also described a study to investigate the role of GDNF in the connection between synapses, the sites where neurons transmit neurochemical communications. When GDNF was administered to mice, higher levels of GDNF-derived mRNA and GDNF protein were found in their skeletal muscles, compared with the control mice. Microscopic examination of these muscles revealed that each muscle fiber from the GDNF-treated mice had two neuromuscular junctions instead of one. A neuromuscular junction is the area of connectivity between a motor neuron and a muscle fiber.

In discussing the significance of these findings, Springer noted that during early development, multiple axon processes grow into skeletal muscle so there is more than one neuromuscular junction for each muscle fiber (polyinnervation). About two weeks after birth, however, these fall off in number until a one-to-one ratio is achieved...that is, there is only one neuromuscular junction per muscle fiber.

After the injection of GDNF into the brain, many of the Parkinsonian features improved, including speed of movement, posture and balance.

Since GDNF in this study was shown to maintain polyinnervation in adult mice, Springer believes it may affect spinal cord motor neuron function in later stages of adult life. It may also be beneficial in maintaining synaptic function.

Dr. Greg Gerhardt, of the University of Colorado, agrees with Springer in that motor deficits observed in aging and in Parkinson's disease may not be due to the death of dopamine neurons, but rather to a functional decline in the dopamine system. "GDNF has been shown to have dramatic effects on dopamine in vitro, and it shows great promise in reversing neurodegenerative changes in vivo," notes Gerhardt.

In a recent study conducted in Gerhardt's laboratory, 2-year-old rats were administered GDNF into the substantia nigra of the brain. After about two weeks, spontaneous locomotor activity and the speed of movement were increased. In addition, brain levels of dopamine were increased. Similar studies in aged monkeys confirmed these findings. Future studies of this type will investigate possible gender differences, due to the fact that dopamine levels differ in males and females, and the expression of Parkinsonism in women is more prevalent than in men.

Gerhardt stresses, "We are young in the study of aging." This kind of research is just getting started because the technology was developed relatively recently. At this point, we are learning what these trophic factors do; therapeutic application of this knowledge will

come later, he says.

The neuro-restorative activity of GDNF was demonstrated by Dr. Don Gash, of the University of Kentucky, in a study using Parkinsonian rhesus monkeys. They were injected with a neurotoxin into the carotid artery on one side so that they developed Parkinson's disease on that side of the body, the other side remaining normal. They then were given GDNF by injection into the brain. Within two weeks, many of the Parkinsonian features had improved, including speed of movement, posture, balance and muscle rigidity.

Microscopic examination of the damaged side of these brains before GDNF treatment showed loss or atrophy of dopamine neurons, whereas after GDNF treatment there was restoration of neuron size and fiber density. Dopamine levels also were increased. This restorative activity of GDNF is currently being tested in patients with Parkinson's disease in a phase I clinical trial being conducted in five medical centers in the U.S.

That GDNF also has neuro-protective activity was shown by Gash's laboratory in rats pretreated with GDNF before administering a neurotoxin.

Gash is excited about the neuro-restorative and neuro-protective activity of GDNF, as well as the entry of GDNF into clinical trials in patients with Parkinson's disease. He is interested in learning whether it can also benefit people undergoing the decline in motor function that accompanies normal aging. "We are on the cutting edge of learning what role neurotrophic factors play," he says.

Experimental therapeutics with nerve growth factor (NGF) in Alzheimer's disease were reviewed by Dr. Jeff Kordower of Rush Presbyterian Medical School. Alzheimer's disease is the result of neurodegeneration exclusively in the brain. In early stages of the disease, neurochemical changes are found in the basal forebrain. The observed symptoms are due to "cholinergic" defects involved in cognition and memory—that is, relating to the nerve fibers that liberate acetylcholine at a synapse when a nerve impulse passes. Since cholinergic neurons are highly sensitive to NGF, its therapeutic potential has been recognized. According to Kordower, "Clinical trials of trophic factors to date have been failures because of delivery, delivery, delivery." That is, the failure has been due to inadequate delivery systems that induced hyperplasia, pain syndrome, herpes zoster, and other undesirable peripheral effects.

Because of these problems, he has been working with transplanted fibroblast cells that were genetically modified to secrete human NGF. In rhesus monkeys, this delivery system was used to demonstrate that NGF could rescue basal forebrain cells from injury. "So, if NGF can be delivered to the nucleus basalis in Alzheimer's patients, we may be able to affect this disease," notes Kordower.

The Impact of DHEA



There is much ongoing interest in the role that dehydroepiandrosterone (DHEA) plays in combating aging and the diseases of aging, because it has therapeutic activity in animal models of cancer, diabetes and autoimmune diseases. Similar effects are being tested in clinical trials.

For example, DHEA clearly had beneficial effects when administered to women with lupus erythematosus, a chronic inflammatory disease affecting many systems of the body. In addition to relief of symptoms, these patients required less prednisone to manage their disease. "So, the animal observations had relevance to humans," notes conference presenter Arthur Schwartz of Temple University.

However, about half the women in the lupus study developed acne because DHEA is metabolized to androgens (male hormones). Schwartz's laboratory developed a fluorinated analogue of DHEA that eliminated the androgenic effect but retained the therapeutic benefits.

A phase I, dose-escalation clinical trial of the analogue has been completed. Schwartz is very excited about the next step: phase II efficacy trials in patients with rheumatoid arthritis, type II (adult-onset) diabetes, and colon polyps. Researchers at the National Cancer Institute, with whom Schwartz has been collaborating, are also planning phase II clinical trials in colon cancer, prostate cancer, and other malignancies in which inflammation has been implicated, to determine if the abnormal multiplication of the number of cells (called hyperplasia, a condition which is preceded by inflammation) can be prevented.

Schwartz is concerned about the high dosages that were used in the animal studies. He notes, "If we can give enough of the fluorinated DHEA in clinical trials, I think it will [have an effect]."

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