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EVENTS

The Roots of Aging

International conferences in Australia explored the accumulation of adverse changes that result in aging and increase the risk of death.

By Marilyn Bitomsky

Aging had been attributed to development, genetic defects, the environment, disease, and other inborn processes. In the developed countries, living conditions are now near optimum, so that aging is now the major risk factor for disease and death after about age 28. This ensures that few reach 100, and so far none exceeds about 122 years.

Two international conferences held in Adelaide, Australia, discussed the latest theories and research—the 7th Congress of the International Association of Biomedical Gerontology and Aging Beyond 2000: the World Congress of Gerontology. Many speakers at the first congress also addressed the second. The theories discussed can potentially contribute to the important practical goal of increasing the healthy, useful human life span.

Free Radicals And Spin Traps

According to the free radical theory of aging, cumulative damage caused by oxidative free radicals accounts for the dysfunctions and pathologies seen in aging. John Carney, professor of pharmacology and psychiatry at the University of Kentucky, said there are two kinds of oxidative processes, one of which is part of normal living. Another kind of oxidation is the one that causes disease. According to Carney, this pathological oxidation can be controlled.

He and his colleagues have for the last 15 years been studying compounds called free radical spin traps. In animal studies have shown that the antioxidant spin trapping compound N-tert-butyl-alpha-phenylnitron (PBN) is effective in preventing oxidative changes. Safety trials are currently being conducted before full-scale clinical trials can begin on patients who have Parkinson's disease or have suffered stroke. In a National Institutes of Health-funded study, Carney is examining the processes of Alzheimer's-associated oxidative stress, since increasing oxidative stress ultimately leads to loss of function. Carney said researchers find themselves recapitulating the mitochondrial hypothesis that Denham Harman first articulated in the 1950s.

Today Harman, convener of the IABG sessions, says much is now known about mitochondria, such as the fact that they are a source of endogenous free radical reactions, which he believes is what kills us. Not everyone is in agreement with this view, although Harman believes available data support it.

A round table discussion among conference participants considered how best to decrease the rate of progression of the superoxide radical with advancing age. According to Harman, it is just like having an X-ray machine inside of us spewing out ionizing radiation. Research conducted by the department of animal biology at Complutense University in Madrid has found that birds produce a small number of superoxide radicals, which may explain why they live comparatively longer than other animals. Akitane Mori, from Okayama University in Japan, described the same feature in the white-footed mouse. These animals divert a smaller fraction of oxygen to the superoxide radical. So, according to Harman, the question remaining is: What can we do to make our mitochondria more like those of mice or birds?

Mitochondrial Aging

The last couple of years have seen major advances in technical knowledge about mitochondrial aging, according to Kenneth



Beckman, from the department of molecular and cellular biology at the University of California at Berkeley. For example, a study published in the Proceedings of the National Academy of Sciences (Hutchin T., Cortupassi G., "A mitochondrial DNA clone is associated with increased risk for Alzheimer's disease." 1995 July 18 92[15]: 6892-5) found that the cells of people with Alzheimer's disease show a variant of mitochondrial DNA which is different from those in the general population. For some reason, it appears that there are certain mitochondrial DNA mutations.

Another major technical advance is that there have been several papers on apoptosis (programmed cell death) which showed that mitochondria are involved in that process. A protein in mitochondria called cytochrome C, the terminal electron acceptor of the electron transport chain, appears to be involved in apoptosis, Beckman said. Leakage of cytochrome C from mitochondria occurs during apoptosis. There has been a flurry of papers on that, strengthening the idea that mitochondria are important in aging, he said.

One of the main questions remaining about mitochondrial aging is whether mitochondria are the first component in cellular degeneration. "You can measure many things which deteriorate with age, but that is not evidence of their primary importance," he said.

If a single component of the cell is of primary importance, then this means it is possible to intervene pharmacologically or nutritionally. If you are trying to intervene to improve mitochondrial function and hence the function of the organism as a whole, and the mitochondria are not primary, then you are wasting your time, Beckman believes.

A second question, Beckman said, is whether mitochondrial DNA itself is important. People make the assumption that mitochondrial DNA is damaged and this leads to mitochondrial dysfunction. But this is an extremely weak argument, since there is little evidence for this right now, he said.

A third question relates to improvement of mitochondrial function. Beckman's colleague, Tony Hagen, is studying potential means of improvement. Many of the studies to date have involved homogenization, grinding the tissue into a molecular soup. The problem with that, Beckman said, is that such "grind and find" chemistry may in fact cause oxidative damage. You don't know whether the damage you see occurred before the grinding or afterwards. If iron is present in the tissue, it may cause oxidation of DNA, proteins, and lipids.

One of the main differences he sees between old and young rat livers is that the cells become more heterogeneous with age. Mitochondrial function in particular seems to be very heterogeneous. Hagen is currently experimenting with various compounds to determine whether they have an effect on this heterogeneity. This is not damage per se, but rather the function of the intact cells.

DNA Deletions

Most studies examining alterations of the mitochondrial genome have focused on a particular 5 Kb deletion of mitochondrial DNA. This deletion has been shown to increase with age in many tissues. According to Judd Aiken, from the department of animal health and biomedical sciences at the University of Wisconsin, several studies on animal models, including rhesus monkeys and rodents, have shown that multiple mitochondrial DNA deletions occur with age, the highest levels being detected in highly oxidative nerve and muscle tissue. Although the mechanism by which mitochondrial DNA deletions are formed is not known, there is evidence to suggest that oxidative stress may play a role in their production.

Despite a wealth of research into free radical production, it seems there is no escaping their production by the body. And this is why attention is turning to means of "mopping them up" to prevent damage, according to Harman. Antioxidants can help, but how much is the appropriate amount, and which ones are best? Most people agree that we should be taking vitamin B complex, vitamin E, beta carotene, flavonoids, and coenzyme Q10, even though quantity is still in doubt.

Oxidant Reduction Therapy

Consideration of the progressive accumulation of mitochondrial DNA mutations with age, and the tissue cellular bioenergy decline associated with the aging process suggests the possibility of an oxidant reduction (redox) therapy for the condition, according to Anthony Linnane, from the Centre for Molecular Biology and Medicine at Epworth Hospital in Melbourne, Australia. This concept predicts that a tissue bioenergetic decline will be intrinsic to various diseases of the aged, and thereby will contribute to their pathology, particularly heart failure, degenerative brain disease, muscle and vascular diseases and other syndromes. A redox therapy based on coenzyme Q10 has demonstrated profound alteration in heart function of old rats, but no effect on young rats.

The impact of diet and specific food groups on aging and age-associated degenerative diseases has been widely recognized in recent years. Several epidemiological and clinical studies have revealed potential roles for dietary antioxidants in the age-associated decline of immune function and the reduction of risk of morbidity and mortality from cancer and heart disease. Mohsen Meydani, from the Human Nutrition Research Center on Aging at Tufts University in Boston, has found that long-term supplementation with vitamin E enhances immune function in aged animals and elderly subjects.

He found in a study of mice that after giving the animals vitamin E then infecting them with the influenza virus, the effect of the virus was much less with vitamin E. The animals on vitamin E also lost less weight during the five days of infection with the virus than did the controls. The level of vitamin E given to the animals was standard for all, 500 ppm. He has also found that the beneficial effect of vitamin E in reducing risk of atherosclerosis is in part associated with molecular modulation of the interaction of immune and endothelial cells.

Stephen Christen, from the department of molecular and cell biology at the University of California at Berkeley, noted that this is illustrated by the inverse correlation between species-specific metabolic rates and life span, and the associated exponential increase in cancer with increasing age. Consumption of large amounts of fruits and vegetables is associated with a decreased risk in cancer incidence and morbidity in general, he said. High on the "good" list are vitamin C, carotenoids and vitamin E.

Vitamin E And Cognition

Similarly, Reinhold Schmidt noted that findings of his research were compatible with the view that vitamin E may be protective against cognitive impairment in older people. Schmidt and his colleagues from Karl Franz University in Graz, Austria, assessed the association between plasma concentrations of essential antioxidants and cognitive performance in non-demented middle-aged and elderly people. He said almost 2,000 people were assessed in this study which involved 10 naturally occurring antioxidants. He also reported another study in which there was an association between low plasma concentrations of vitamin E and a higher risk of cerebral white matter disease.



Despite the positive effects of vitamin E on the immune and cardiovascular system, Meydani found that vitamin E and several other antioxidants—namely, glutathione, melatonin, strawberry extract, and combinations of these—had no effect on extension of life from middle age. Perhaps there would have been an effect if treatments were begun earlier in life, he suggested. There is a large middle-aged population in the United States, all wondering whether antioxidants might have some effect on longevity, but Meydani found no effect on extension of life.

Commenting on Meydani's work, Russell Reiter, from the department of cellular and structural biology at the University of Texas Health Science Center, said at this stage there is no compelling evidence that taking melatonin will prolong life. Reiter said that doesn't mean melatonin is not good for many things, and it may be that the wrong studies have been done. But at present there is no solid basis for drawing the conclusion that melatonin will prolong life.

Melatonin is useful as an antioxidant in acute situations where there is tremendous oxidative stress, such as exposure to ionizing radiation, he said.

The reduction of melatonin with age may be a factor in increased oxidative damage in the elderly. Melatonin, the chief secretory product of the pineal gland, is a direct free radical scavenger and indirect antioxidant. Because of its high lipid solubility and modest aqueous solubility, melatonin is able to protect macromolecules in all parts of a cell from oxidative damage. In humans, the total antioxidative capacity of serum is related to melatonin levels.

A micronutrient supplement in modest doses for all elderly people may be the best treatment for immune problems. That is the advice of Canadian Professor Ranjit Chandra, who said aging is associated with a reduction in many immune responses.

Alterations are seen in delayed cutaneous hypersensitivity, lymphocyte response to mitogens, interleukin-2 production, and antibody response. At the same time, nutritional deficiencies are observed in at least one-third of elderly people. Dietary intake and blood concentrations of many nutrients are known to be reduced with aging. The important contributing factors to the development of nutrient deficiencies include social and psychological isolation, physical disabilities, dental problems, poverty and drug-nutrient interactions, he said.

The Necessity of Supplements

It is expensive and impractical to estimate dietary intake or blood levels of various nutrients, so a micronutrient supplement in modest doses would be the best medicine, he suggested. Such a supplement would be likely to boost immunity and reduce the burden of infection.

A high lifetime intake of vitamin C and beta carotene may protect memory functions and stave off dementia, according to the prospective Basel Longitudinal Study. Results of the study, begun in 1960, were reported to The World Congress of Gerontology

by Hannes Stahelin, a University of Basel geriatrics professor. The study followed Swiss men and women for 20 years, finding that those who had high levels of antioxidant vitamins in their blood performed better in memory function tests.

Stahelin said it seems clear that free radicals and certain related compounds advance aging, and that good antioxidants can defend the body, slow down the aging process, and protect the body from diseases such as atherosclerosis, some cancers, and mental deterioration in old age. Neurons in the brain are challenged by free radicals, he said, and the aging process itself is linked to those free radicals. Free radicals are highly reactive compounds which interact with the body's essential structures, notably the genes. Although the body has quite an elaborate defense system, in times of stress or injury, it is probably insufficient and the generation of free radicals is large, resulting in oxidative stress. At such times we need more antioxidants to maintain a healthy balance, Stahelin said. It appears that antioxidants protect the neurons from damage, although the usefulness of these vitamins is difficult to prove conclusively.

He said a Rotterdam study on dementia had shown that people with low beta carotene intake had a higher rate of dementia. That study involved testing 442 healthy elderly people aged 65 to 94 years on aspects of memory and matching the results with vitamin blood levels. It found vitamin C and beta carotene were a significant predictor of ability in tests of vocabulary, and beta carotene in tests of recognition.

Stahelin said that although antioxidants are obtained from natural sources such as fruits and vegetables, it might be necessary to consider special supplements since it is not always easy to eat fresh fruits and vegetables every day. We should adjust our diet and start to develop special, functional food which does its job more easily in certain conditions, he said. And we should increase daily intake of antioxidants above the current recommended daily intake, since we now know that higher levels might provide protection from chronic diseases.

Fruits, Vegetables And Aging

There is a correlation between the intake of fruit and vegetables and our carotenoid levels. The evidence is immensely strong that there is a relationship between the intake of fruits and vegetables and a decreased rate of age-related diseases, such as cancer and cardiovascular disease, age-related macular degeneration, and cataract, according to Norman Krinsky from the biochemistry department of the Human Nutrition Research Center on Aging at Tufts University.

Studies have now shown that supplementing the diet with beta carotene prevents cancer in humans, and there may be other effects, he said. However, he added, a recent Finnish study found an increase in lung cancer in men who were heavy smokers who also had received supplementary beta carotene. About 26,000 men were in the study, so it was not trivial. We know that smoking produces a lot of radicals which interact and alter the beta carotene, but we don't know about the impact of those products, he said.

Moreover, there is still much that is not known about the biological properties of carotenoids. They may be much more related to breakdown products such as apo-carotenoids and retinoids than to antioxidant vitamins. Much effort has gone into evaluating the relative antioxidant potency of carotenoid pigments, both in vitro and in vivo. In vitro, carotenoids can inhibit the propagation of radical-initiated lipid peroxidation. In vivo, it has been much more difficult to obtain solid experimental evidence that carotenoids act directly as biological antioxidants. In fact, in some circumstances, both in vitro and in vivo results suggest that carotenoids may function as pro-oxidants. These results can be modified by altering oxidative stress, the cellular or subcellular system, the type of animal tested, and environmental conditions such as oxygen tension.

This type of evidence raises the question whether it is still appropriate to group the carotenoids with the antioxidant vitamins such as vitamin C and vitamin E, Krinsky said. The biological properties of carotenoids may be much more related to products of the interaction of carotenoids with oxidant stress.

A cup of tea and a glass of wine may be considered just as cancer-protective as fruit and vegetables, and they may even contribute to delaying the aging process. That is the view of Ivor Dreosti, from CSIRO's division of human nutrition in Adelaide. He said the increase in cancer risk with advancing age is well recognized, and several mechanisms have been proposed as explanations. Calorie restriction, which reduces oxidative stress and effectively increases life span in animals, also seems to reduce the incidence of many cancers, possibly due to diminished mitogenesis.

Similarly, oxidative damage to DNA appears to be common to both processes, but may be more important in the mitochondria with respect to aging and in the nucleus in relation to cancer. Inadequate dietary folate and impaired DNA methylation are closely associated with increased cancer risk. Recently, defective somatic cell methylation and accumulated genetic instability have been proposed as key mechanisms contributing to senescence.

The Role of Phytochemicals

Several other well-established anti-cancer strategies, including increased fiber intake and consumption of more fruits and

vegetables, have not been studied extensively in relation to aging. However, many of the phytochemicals considered important as chemopreventive agents for cancer may well contribute to delaying the aging process.

It is clear that one can eliminate or reduce exposure to aggravating factors such as obesity, fat intake, salt intake, curing processes in food processing, spoiling because of microtoxins, and overcooking in order to reduce the risk of contracting cancer, Dreosti suggested. And there are protective factors, too, he said. Fiber has attracted a lot of attention in warding off cancer, including large bowel cancer. There are several types of fiber, including insoluble or indigestible fiber, soluble or digestible fiber, and resistant starch. This last behaves very much like insoluble fiber, which passes into the large bowel, protects the epithelium from carcinogens, and hastens digestion through the large bowel. Soluble fiber passes into the large bowel and prevents conditions that might result in cancer formation.

Dreosti said fruits and vegetables are now a major emerging interest. Foods which have been associated with cancer protection include garlic, cabbage, celery, soy beans, onions—all the things which in folklore have been associated with cancer protection. A number of vegetables also have a reasonable amount of fiber in them as well. But what is in the fruits and vegetables that has this protective action? Some of those compounds are established nutrients or fiber-containing foods. Another is phytochemicals, which occur at very low levels. They don't appear to be essential nutrients, but they seem to be significant in protecting against the development of cancer.

It has long been known that dietary restriction increases the life span of rats and mice, and there is strong evidence that it does so by slowing the aging process. This anti-aging action is due to the reduction in the intake of calories rather than the reduction in intake of a specific nutrient or dietary contaminant. It was suggested that the anti-aging response to dietary restriction arose because of evolutionary advantage during periods of unpredictable short-term food shortage. Much evidence has been uncovered in support of this view (See "Calorie Restriction: Eat Less, Eat Better, Live Longer," Life Extension magazine, February 1998).

Telomeres And Telomerase

In studies of cellular aging the behavior of cultured human cells must take into account environmental treatments which can increase or reduce longevity as well as the fact that individual cells and populations derived from one primary culture vary in their life spans. Further studies on human cell senescence have revealed that there may be no correlation between donor age and replicative life span. Perhaps replicative senescence is only one of several pathways cells can take in becoming senescent.

As has been reported in Life Extension magazine, telomeres, the genetic elements that cap chromosome ends, play an important role in loss of replicative capacity and deleterious changes in gene expression in mortal normal cells. (See "Turning on Telomerase to Stop Cell Aging: The Quest for Immortality," February 1998). According to Calvin Harley, from Geron Corp. in California, the critical loss of telomeres-special DNA regions at the ends of each chromosome-signals an irreversible checkpoint arrest which contributes to the abnormal pattern of gene expression seen in old cells. The activation of telomerase—an enzyme that can reset telomeres back to their youthful lengths—slows the rate of telomere loss and hence extends the life span of progeny cells. Modulation of telomere length, telomerase activity, and senescent gene expression provide novel opportunities to develop therapies for age-related diseases, including cancer, he suggests.

Studies on diverse biological systems have revealed new insights into several fundamental aspects of what governs aging processes and longevity determination. Although we are far from a thorough understanding of either process, an appreciation of the differences between age changes and the determination of longevity seems to be emerging. Until now, the general consensus in experimental gerontology has been that the only effective means of prolonging the life span of animals is dietary restriction, and no single pharmaceutical has been shown to have such an effect. However, deprenyl, a drug originally developed as an antidepressant, is proving unique in its effects on longevity, Dr. Kenichi Kitani has found.

Deprenyl May Prolong Life

Kitani, from the National Institute for Longevity Sciences in Japan, told the International Aging had been attributed to Association for Biomedical Gerontology that deprenyl manages to raise antioxidant enzyme activities such as superoxide dismutase and catalase in selective brain regions in different animal species. Studies in mice have revealed no significant effect on longevity, while studies in rats, hamsters and dogs have proved positive.

Kitani has obtained positive effects on longevity in rats of both sexes, but two studies with different doses in mice revealed no significant positive effects. The effects on rats, mice and dogs were variable, depending on the doses used.

A recent study of deprenyl in aging beagle dogs showed a marked effect on longevity, agreeing with Kitani's superoxide dismutase results. Kitani believes the drug may at least partially prolong the life span in animals by enhancing immune system function and preventing tumor development. A study at the Life Sciences Division of the University of Toronto agreed on the significant effects of deprenyl in prolonging the remaining life expectancy of old rats treated with subcutaneous injections of the drug. This study, like that of Kitani, found no effect in mice. Reporting this study at the World Congress of Gerontology, Gwen Ivy said the variabilities of

its effect on the life spans of different animal species may stem from the variability in its optimal dose on enzyme activities.

Reflecting on the congress, Robin Holliday, at CSIRO biomedical engineering in Sydney, Australia, said most people are still focusing on theories. The free radical theory is in vogue, as is the mitochondrial theory. But aging, he says, is multi-causal. Defense against free radicals is just one maintenance mechanism. A broader view of the whole subject is necessary. Simply put, gerontologists don't yet realize how much is known about human pathologies.

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