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On The COVER

Business and Science
Unite to Fight
Aging

Biotech companies and scientific researchers are together reaching a critical juncture in understanding the factors that contribute to aging, and then finding ways to head them off. Via this synergy, results may not be far off.

By Gregory M. Fahy, Ph.D.

Incredibly powerful forces are being unleashed in the war against aging. The genes that control aging are rapidly being identified using a multiplicity of different approaches. Drugs have been found that appear to be extremely effective in reversing age-related changes without toxicity and are already in human clinical trials. Links among aging phenomena observed in widely divergent species such as worms, yeast and humans are becoming apparent.

Importantly, the economic implications of successful aging intervention are now palpable, which means that funding for aging intervention research has become open-ended. It appears more obvious than ever that human aging will be slowed, and it appears more likely than ever that this will happen soon enough to be of benefit to most people living today.

This was evident on December 11th and 12th, 1997, just prior to the annual meeting of the American Academy of Anti-Aging Medicine, at an exciting industry meeting in Las Vegas. The Conference on Age-Related Diseases: Exploiting Mechanisms for Drug Development, staged by International Business Conferences (IBC), brought together many new biotechnology companies whose interests include the treatment and reversal of various aspects of aging, as well as academic researchers whose results could offer major new opportunities for intervention.

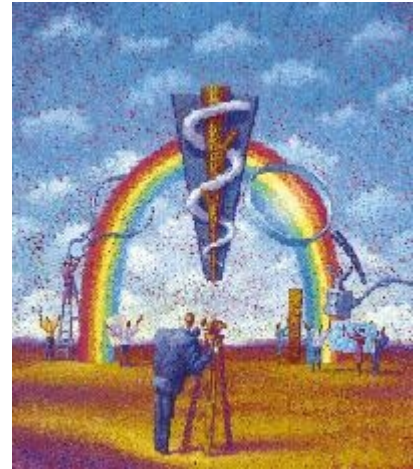
Evolutionary biologist Michael Rose described several approaches to understanding and modifying aging. He noted that one strategy for showing that a given factor causes aging is to change that factor and see if aging changes. Rose concluded that trying to accelerate aging by augmenting supposed pro-aging factors is basically useless, because one can imagine shortening life span by a multitude of mechanisms that really have nothing to do with normal aging. On the other hand, it is hard to extend life span greatly unless you slow down aging itself. Therefore, drastic life-span extension is a much more convincing proof of a given theory than life-span shortening.

As an example, Rose—a University of California, Irvine, professor, who also consults with private industry—pointed to work on the small worm, *Caenorhabditis elegans*, which showed major life span extension through a genetic mechanism (studies extensively covered by Life Extension magazine; see "Are Worm Genes the Key to Human Longevity," February 1998).

He also suggested that building molecular genetic "devices" that can insert themselves spontaneously in defined and safe locations in an organism's DNA, and that can be selectively turned on and off by investigators, might allow major increases in life span if one is lucky about choosing anti-aging genes to insert.

Rose himself has done what he terms "selective postponement of aging." Here the word "selective" refers to selection in the Darwinian sense. By choosing only older flies for reproduction, he was able to select for longevity, since short-lived flies would be sterile by the time they were allowed to reproduce. Because the selected flies pass their genes on to their offspring, the life span of the offspring is a measure of whether flies that attain great ages do so because of good luck or because of good genes.

The answer was that the offspring were also long-lived (had good genes), and Rose was able to generate a population of flies that lived much longer than flies in the wild. In other words, the genes for longevity were already there, and all he had to do was to sort



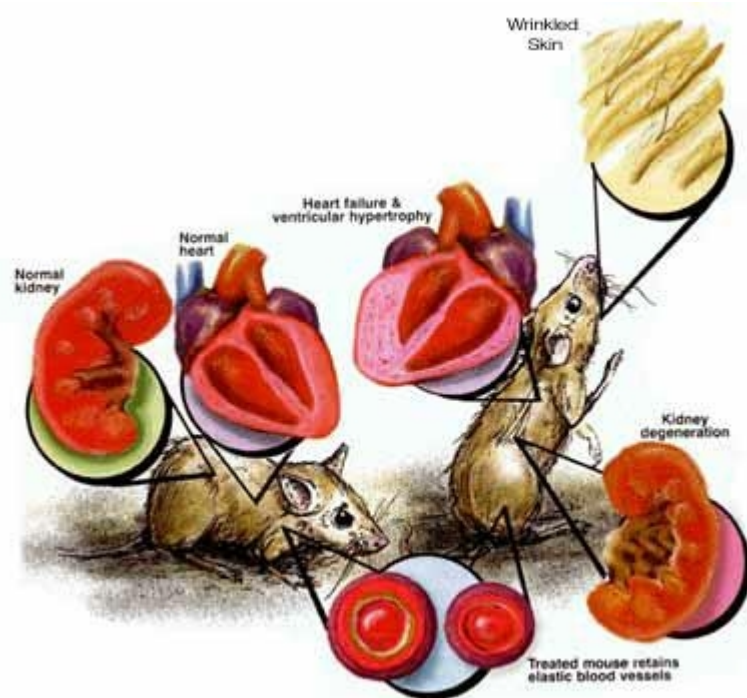
out those flies with good genes from those flies with bad genes. Further, the more he kept selecting for longevity, the longer the flies lived. There was no evidence for an immutable maximum life span. Instead, the maximum life span rose right along with the mean (average) life span. In one case, the maximum life span rose from a starting value of 67 days to a final value of 128 days.

One advantage of this approach is that, in addition to showing there are genes that govern longevity, you can compare the genes in the long-lived fly population with those in the short-lived population and find out just what the longevity genes actually are. It turned out these major increases in life span were associated with differences in only about five or six genes out of around 300 examined. Finding out more about these genes will be of major interest.

Rose then considered how to apply this approach to mammals. He has long advocated creating long-lived rodent strains, but the problem is that rodents live too long and produce too few offspring for selection experiments based on late reproduction to produce results in a reasonable time.

However, he noted that if you select flies based on their ability to tolerate stresses such as starvation, it turns out that you are also selecting flies that live a long time. For example, the 20 percent of flies that survive after the other 80 percent have died of starvation are the same flies that have naturally long life spans. This type of selection can be applied much more easily and efficiently to mice, and is therefore a feasible approach. Naturally, this approach could have spectacular commercial implications, since it could identify longevity genes that apply to humans. Rose apparently has a patent in progress along these lines. The task now, he said, is to build a "pipeline to therapy" for human beings.

Jack Egan, the senior director of pre-clinical research for Alteon Inc., a Ramsey, N.J.-based publically traded company, discussed preventing and reversing damage caused by slow spontaneous chemical reactions between blood sugar (glucose) and a variety of proteins. These unwanted chemical reactions are referred to as glycosylation or glycosylation and the products of these reactions are called advanced glycosylation end-products, or AGEs.



One of Alteon's primary drugs is Pimagedine, which used to be known as aminoguanidine, a chemical that was shown long ago to retard the unwanted irreversible attachment of glucose to body proteins. Pimagedine protects kidneys from glucose-mediated damage, as shown by reduced albumin in the urine. It even reduces blood fat levels.

One feature of aging and of diabetes is increased stiffness of blood vessels, such as the carotid artery in the neck. Egan showed that in rats, the distensibility of the carotid artery falls by more than 50 percent between 24 and 30 months of age in control animals, but falls by less than 7 percent in animals that received 50 mg/kg of Pimagedine in their drinking water. Further, over the same age interval, the rat heart-weight-to-body-weight ratio rose by about 50 percent in control animals, indicating heart failure; but the same ratio rose by less than about 7 percent in animals treated with Pimagedine. Pimagedine also normalized left ventricular stiffness and the amount of sugar attached to collagen (connective tissue protein). These are huge anti-aging effects.

But as good as Pimagedine is, ALT-711 may be a great deal better. ALT-711 is something called an "alpha dione cleaving agent." While Pimagedine prevents permanent glucose-protein crosslinks from forming, ALT-711 reverses glucose-protein crosslinks after

they have formed. Still better, ALT-711 acts like an artificial enzyme, breaking crosslink after crosslink without itself being consumed in the reaction. It is as if ALT-711 were a "reverse free radical," setting up a chain reaction of positive, rather than negative, chemical reactions.

Interestingly, the body may attack sugar-protein crosslinks with antibodies, accounting for an increase in the amount of antibody (IgG) attached to red blood cells with age. Untreated diabetic rats steadily accumulate IgG on their red cells over time, but diabetic rats treated with oral ALT-711 at a dose of 10 mg/kg per day showed an 80 to 90 percent drop in red cell IgG in one to two weeks of treatment.

In addition, the effective dose of ALT-711 decreases with time because of the drug's enzyme-like action and the diminishing number of target crosslinks remaining to attack.

Most importantly, a dose of 1 mg/kg of ALT-711 for three weeks reversed left-ventricular stiffening and end-diastolic volume increments (indicating better heart blood pumping ability) in aged dogs. It also increased vascular distensibility throughout the vascular system and vastly increased the amount of blood pumped by the heart (cardiac output). These effects represent a reversal of lethal age-related changes.

Two-hundred times this dose of ALT-711 produced no toxicity in rats and dogs. Humans treated with ALT-711 develop a mild flu-like syndrome that goes away with discontinuation of the drug and does not recur when the drug is readministered. Of interest for those with sagging and wrinkled skin, ALT-711 significantly improved skin hydration and elasticity in animals, nearly completely reversing changes associated with sugar cross-linking.

In a counterpoint to Egan's talk, Truman Brown, scientific director of Dynamis Therapeutics Inc., made the surprising revelation that 3-deoxyglucosone (3DG) is a glycation product that is converted into AGEs, and is made not by random damage but by an enzyme involved in a lysine recovery metabolic pathway. Also, this enzyme can be blocked. Lysine apparently reacts with sugar to form a fructose-lysine (FL) molecule that is converted to 3DG, which is in turn converted to AGEs. Putting FL into the diet of rodents for eight months damages the kidney in a manner that resembles diabetes. But 3DG levels were cut by about half when an enzyme inhibitor was injected.

Jack Egan, left discusses preventing and reversing age damage caused by glucose crosslinking.



One of the most intriguing illnesses pertaining to aging is Werner's syndrome, which resembles accelerated aging. Dr. Minori Sugawara, of the Agene Research Institute Company, in Kamakura, Japan, described the molecular causes of Werner's syndrome, noting that the disease is caused by mutations in one of the three human helicase genes (the one named *wrn*) responsible for unwinding the DNA double helix so that it can function. Even though three human helicases exist, problems with just one of them cause humans to exhibit the appearance of 80-year-olds by the time they reach 38, and usually cause death by the age of 46.

Just as libraries would be useless without the ability to take the books off the shelf and read them, DNA is useless unless it can be "read" by other molecules in the cell. Helicases function like a librarian, giving access to the store of information in the genetic library. Knocking out helicase function makes the information in DNA less

available for use by the cell, and in some way this "squenching" of DNA leads to an accelerated aging syndrome. Helicases may also be involved in DNA repair.

Although six mutations in the *wrn* gene have been found, 70 percent of Japanese Werner's patients have one of two specific mutations that cause the disease. These mutations result in a complete loss of activity of the resulting helicase. Although the mutated enzyme works poorly in cells, it actually works well in a test tube. There appear to be at least two reasons for this. First, since DNA is in the cell nucleus and proteins are made outside of the nucleus, the helicase protein must move from the cytoplasm to the nucleus in order to unwind DNA. But the mutated helicase can't make this trip. Secondly, for some reason the mutated helicase mRNA (which is used to make the helicase protein) is selectively destroyed in cells, leaving very little left to make the protein, which in turn can't enter the nucleus.

Interestingly, the *wrn* mutations also alter telomere lengths in some way, in some cases accelerating telomere shortening, and in other cases having erratic effects. Telomeres consist of special DNA regions at the end of each chromosome. Each time a cell divides, it loses part of its telomeric DNA, causing telomere shortening. When telomeres become too short, cell aging may occur. So, the *wrn* mutation could act through this mechanism as well.

The most immediate question these observations raise for most people is, what happens to helicase expression with aging in normal people? Even if there is no mutation in the *wrn* gene in normal people, failure to make the helicase protein could produce the same effect as the mutations. If this happens, the gene could probably be turned back on by drugs, nutrients or other means. So what happens in the Werner's syndrome story could affect each of us.

Werner's syndrome also figured in a presentation by Leonard Guarente, professor of biology at Massachusetts Institute of Technology, in Cambridge, Mass. He provided the audience with hard evidence that appears to explain aging in yeast, and also appears to be linked intriguingly to aging in humans, and especially to Werner's syndrome.

The nucleolus is the part of the cell nucleus in which the DNA that gives rise to ribosomal RNA is located. This DNA is called rDNA, and it is required for protein synthesis. It appears this rDNA is unstable over time. With both normal aging and with accelerated aging caused by knocking out the healthy yeast analogue of the defective Werner's syndrome gene (a helicase known as *sgs1*, 43 percent identical to *wrn*), Guarente observes that the nucleolus swells and fragments. This is caused by the breakdown of the rDNA into a series of rDNA loops that float around detached from the rest of the cell's DNA. With every cell division, the number of loops increases until eventually the cell dies. The accumulation of loops may be the clock of aging in the yeast.

Young yeast have no rDNA loops. The parent cell from which other yeast cells arise, the mother cell, keeps all the loops to itself, thus sacrificing itself for the continuation of the species. Each new daughter cell, however, eventually develops a loop after dividing many times. Once this happens, deterioration becomes inevitable as the loops accumulate.

To find out if the loops are sufficient to cause aging all by themselves, Guarente introduced loops into young cells. The result was that aging was induced at a younger yeast age, resulting in a 40-percent shortening of replicative life span. Thus, loop formation is a sufficient cause of aging in yeast.

Werner's syndrome in humans involves an increase in the nucleolar damage rate, and the helicase involved in Werner's syndrome is located in the nucleolus. In the yeast, these changes in the nucleolus appear to be counteracted by a protein called *sir4*, and there is a mutation of *sir4* (*sir4-42*) that is unusually good at protecting the nucleolus from these changes, and which also extends the yeast life span by around 40 to 50 percent. Guarente did not say whether human analogues of *sir4* are known.

Guarente believes the formation of rDNA loops is due to repair of damage to rDNA. For a while, the damage is repaired without

incident, but at some point, the repair results in an rDNA loop, and the cell's fate is sealed. Once circle formation begins, sir4 migrates from the telomeres and certain other sites to the nucleolus to combat circle formation, but it cannot stop circle formation entirely. As a result, it slows but does not stop aging. When sgs1 is knocked out, sir4 migrates to the nucleolus sooner because damage gets out of control sooner.

The catch-22 is that if you do block circle formation, the cells die sooner, because circles are a by-product of rDNA repair, and the repair is needed to sustain life.

Bernard Strehler reported many years ago that, with age, the brains of dogs lose rDNA. Guarente's cells accumulate rather than lose rDNA, but the rDNA is indeed lost from its normal location-the chromosome on which it usually resides. Whether Strehler's results reflect Guarente's mechanism remains to be seen.

We know this problem is solvable, because other types of yeast are immortal. Thus, Guarente's work on yeast could reveal core aging processes that could lead to powerful anti-aging therapies for humans.

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