/COMMENTARY

An Age-Old Dilemma

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It's tempting to believe that such a universal phenomenon as aging requires no explanation. Our tissues, and those of all other creatures, simply wear out in time. If we survive accidents, infections, cancers, and other specific malfunctions, we die of old age. Nothing more to be said.

Except that aging is *not* an inherent feature of life. Even among the simplest systems there are exceptions and anomalies. Consider *Saccharomyces cerevisiae*. Every so often, a mother cell forms a bud that separates as a daughter cell. But it does so only for a limited time, meanwhile undergoing morphological and physiological changes characteristic of aging. Yet, the fission yeast *Schizosaccharomyces pombe* reproduces by dividing in two, and the cells never age.

Most species of life do grow old, but the list of those that don't is sufficiently large to raise questions of why and how. There is a further difficulty. The loss in fitness that accompanies aging is clearly deleterious to the individual organism. Yet natural selection operates to maximize fitness. Why then has the evolutionary scythe not eliminated aging, leaving population control largely to disease and predation? Another question is whether intervention to retard aging is feasible—other than by severe calorie restriction that is known to prolong the life of rodents. Can we hope to modify the underlying molecular processes as a means of combating degenerative conditions of the body and mind?

A decade ago, such ambitions would have seemed futile. Even four years ago the picture was confused. Writing then in *Biological Reviews* (**65**:375, 1990), Zhores Medvedev of the National Institute for Medical Research (London) reported that there were over 300 different theories of aging. Now, as indicated by a Dahlem conference held recently in Berlin, there are real grounds for optimism. Although conflicts remain, we are beginning to comprehend the molecular background of aging, and to glimpse possible avenues of intervention.

It's clear, for example, that reactive oxygen species (ROSs) and other radical oxidants damage proteins, nucleic acids, and lipids in the cell. The consequences, worsening with age, are deleterious effects on enzymes, membranes, and nuclear mitochondrial DNA. As much as 30-50% of the cellular protein in an elderly animal may be oxidized, with corresponding reductions in the activities of many enzymes. These changes could merely be an accompaniment, rather than a cause of aging. Nevertheless, it is hard to believe that cell function can be anything like normal under such enormous handicaps.

Strong supportive evidence comes from the fact that overexpression of the gene for a free radical scavenging enzyme, superoxidase dismutase, increases the life spans of fruit flies and the nematode *Caenorhabditis elegans*. Another potent antioxidant is the recently discovered vitamin pyrroloquinoline quinone—suggested at the Dahlem conference as a potential agent to combat the oxidative changes found in Parkinson's disease. The significance of DNA damage in relation to aging is underscored by the fact that patients with impaired DNA repair mechanisms have reduced life expectancy and symptoms of premature senescence.

Gerontologists are especially preoccupied at the moment with alterations in mitochondrial DNA. They are attracted to changes that have been implicated in senescence in the fungus *Podospora anserina*—notably the age-related transfer of genes from mitochondria to nuclei. This can be completely eliminated in certain mutants, which then grow indefinitely. Mitochondrial mutations have been unambiguously pinpointed in some specific diseases in recent years (for example, Leber's hereditary optic neuropathy). It remains conjectural, however, whether the one-way traffic in mitochondrial genes into the nuclei of mammalian cells is a significant factor of aging.

A second fascination stems from the fact that mitochondria, the main intracellular source of ROSs and protected from ROSs by various antioxidants, sustain much more damage than nuclear DNA. Recent discoveries of characteristic deteriorations in mitochondria from elderly organisms, including increased formation of ROSs and decreased antioxidant production, prompt the suggestion that defective mitochondria at least contribute to aging.

Although there was no consensus in Berlin concerning the precise role of mitochondrial changes, an increasingly plausible theory is that developed by Anthony Linnane at Monash University (Clayton, Australia) and Doug Wallace's group at Emory University (Atlanta, GA). They believe that a central factor in aging is a decline in the efficiency of mitochondria in releasing energy by oxidative phosphorylation. As mitochondrial DNA damage accumulates, bioenergetic efficiency falls until eventually it is inadequate to sustain normal tissue and organ function. Once the energy capacity dips below a certain threshold (the most sensitive tissues including heart, brain, and skeletal muscle) symptoms appear and worsen.

Linnane and Wallace aver that, in addition to aging itself, Parkinson's disease, Alzheimer's disease, heart and muscle disease, and many other degenerative conditions may result from what they term bioenergetic decline. There are already a few indications of appropriate therapeutic approaches—for example, concurrent treatment with coenzyme Q prevents the mitochondrial damage that occurs in animals treated with the AIDS drugs AZT.

The puzzle remains of why we need to age at all. But there are exciting foundations here for a thorough understanding of the molecular biology of aging—and perhaps for modulating the process, if that's really what we want to do. ///