WHY WE GROW OLD

The life expectancy of Americans has nearly doubled in the past 125 years, from 40 years to 80 years. This gain is due mostly to cutting deaths of mothers in child birth and deaths of the young, particularly infants. Eliminating cardiovascular disease—the biggest killer in the U.S.—would add another 14 years of life. Getting rid of cancer, the second leading cause of death, would tack on an additional two years of life.

Though life expectancy has increased, life span hasn't. The maximum length of human life remains roughly 100 years. From its peak at age 30, the body simply declines, losing about 0.8 percent of strength and energy a year. The cause of this decline is unknown, though a host of theories try to explain it:

After 30, the body loses about 0.8% of its strength a year.

•The immunological theory: With age, the immune system's ability to make antibodies diminishes, making people more vulnerable to disease. As the immune system falls off, moreover, it's less able to discriminate between self and nonself, resulting in increased autoimmune disease.

•The neuroendocrine theory: No part of the body acts in isolation from neurons and hormones, so age changes to these systems cause widespread effects. For instance, declines in the hypothalamus affect pituitary function, which then affects the working of numerous targeted endocrine cells.

•The free-radical hypothesis: Aging is largely due to damage from free-radical reactions. A free radical reacting with a stable molecule produces another free radical, which can set off a chain reaction consuming many stable molecules. The process is especially disruptive to cell membranes.

•The cross-linkage school: Age changes occur when macromolecules become linked covalently or by a hydrogen bond. These linkages accumulate over time, moreover. DNA becomes damaged, leading to mutations or cell death. Irreplaceable molecules are reduced in number. And intracellular transport is impeded.

•The theory of waste-product accumulation: Such products build up in nondividing cells—including neurons and cells in skeletal muscle and cardiac muscle—to the point where they impede cell function, leading to age changes. At age 90, waste products occupy as much as 7 percent of intracellular volume.

•The somatic-mutation school: The build up of enough mutations in body cells produces decrements characteristic of aging.

•The program theory: An intentional sequence of events written in the genome leads to age changes. Such genetic instructions are similar to those leading to the orderly expression of developmental sequences.

•The mitochondrial theory: Accumulated errors in the mitochondria reduce cellular energy levels. This leads to a breakdown in cellular function, with high-energy tissues failing first.

Yet aging theories aren't mutually exclusive. "All or some may operate simultaneously," says Leonard Hayflick, a professor of anatomy at the University of California Medical School (San Francisco).

disease—are the same as disorders that strike seniors, except they develop earlier in diabetics. Alteon believes that glucose—which, of course, is elevated in diabetics—is key to these complications. Glucose non-enzymatically glycosylates proteins in the body, triggering a series of chemical reactions that form cross-links between adjacent proteins. Such reactions explain why structural proteins in tissue, particularly collagen, become increasingly cross-linked as people age, contributing to the stiffening characteristic of aging tissue. In diabetics, says Alteon, higher glucose levels accelerate cross-linking, thereby speeding tissue aging.

Alteon is testing a compound to prevent protein cross-linking. It expects to enter the compound, aminoguanidine hydrochloride, in combined phase II/phase III clinical trials in October for diabetes-induced kidney disease, or nephropathy. If successful, Alteon will then test the drug against other diabetic complications. It pegs the U.S. market for such complications at $500 million, with the worldwide market surging to $3 billion. "Eventually, aminoguanidine hydrochloride may also treat some of the effects of aging," says Charles Faden, Alteon's chairman and chief executive officer.

Two majors are helping to fund aminoguanidine hydrochloride development, which has already cost Alteon about $20 million. Marion Merrell Dow (MMD, Kansas City, MO) agreed last year to finance aminoguanidine hydrochloride clinical trials for up to four indications, including nephropathy, retinopathy, peripheral vascular disease, and peripheral neuropathy. In return, MMD received 8 percent of Alteon, along with co-marketing rights to the compound in North America and some European countries and exclusive rights in other markets. Yamanouchi Pharmaceutical (Tokyo) agreed in 1989 to fund preclinical trials of aminoguanidine hydrochloride, as well as other Alteon operations. It received an 8 percent stake in the company and an exclusive license to the compound in Japan, Korea, Taiwan, and China.

Yet aging will remain a mystery until more companies commit more resources to the field. "The molecular mechanism of aging is an incredibly exciting—and potentially lucrative—area to explore," says Senetek's Coppard. "Companies have to get off the sidelines. They have to take a stand."