Inside back cover: Old before his time, the poet in middle age - Walt Whitman, c. 1860. See Caleb E. Finch on Aging, inflammation & the body electric, pages 68-76: "One hundred and fifty years after Whitman sang 'the body electric,' we can find in Whitman's fate some clues to the nature of aging." Photograph © Corbis.
Caleb E. Finch

Aging, inflammation & the body electric

In a famous photograph of Walt Whitman taken in the 1860s (see inside back cover), the great American bard looks wizened—his hair white, his face weathered. He looks, in short, like an old man. In fact, he was only in his forties.

During the Civil War, Whitman spent hours each day in hospital wards attending to desperately sick soldiers, which exposed him to dysenteries and horribly infected wounds. As a result, a bad infection in one hand climbed up into his shoulder, and he became beset by chronic headaches and fevers.

One hundred and fifty years after Whitman sang “the body electric,” we can find in Whitman’s fate some clues to the nature of aging. For much of his adult life, he complained of chronic headaches, fevers, and weakness. At the age of 55, he suffered a stroke that paralyzed his left side. Other strokes followed, though without noticeably impairing his memory. Whitman eventually lived to the age of 72, exceeding his generation’s life expectancy by about thirty years. Yet shortly before his death, one of his doctors noted, “His apparent age was greater than his real years.”

A postmortem by experts in gross morbid anatomy showed that Whitman had long suffered from both meningitis and tuberculosis. Tuberculous meningitis may have contributed to his strokes and would have been consistent with his other reported ailments. Both infections inflame arteries at the base of the brain, which, in turn, increases the risk of infarcts and strokes that selectively damage deep brain centers in a “TB zone,” but usually spare higher cognitive functions. Although tuberculous meningitis is a rare disease, the ‘Whitman case’ points us to more general principles in aging.

Inflammation is increasingly recognized as fundamental to aging. As modern medicine has brought infectious diseases like tuberculosis and meningitis under control, successive generations have had to carry less of the inflammatory burden of such diseases— which may help account for recent improve-
ments in human longevity. Changes of the inflammatory burden may also anticipate limits ahead. Aging, of course, is an immensely complex process governed by multiple gene-environment interactions. No single factor governs aging—biogerontology is a graveyard of single-cause hypotheses.

In the past century and a half, human life spans have increased remarkably, with one year added to the life span for every three to four years of calendar time. Before the Industrial Revolution, the average life span was about thirty-five to forty years. Even if one survived the hazards of childhood to reach maturity, the remaining life span was still shorter than today’s. Currently, life expectancy in most developed countries has doubled to about eighty years and continues to climb. The result is a major shift in population age structure, from broad-based pyramids with younger groups in the majority, to skyscraper-shaped structures, which are arising everywhere because of the steadily growing rates of survival at younger ages and survival to increasingly older ages. In fact, centenarians are the fastest expanding age group. Sitting on the topmost is Jean Calment (1875–1997) who tested cognitively normal at 119. Her 122-year longevity may yet be superseded.

The decline in childhood mortality rates is yet another remarkable change that has occurred in recent generations. Not so long ago, infant and childhood mortality rates were very high almost everywhere; rates of 30 percent were very common in Europe and North America until the Industrial Revolution, when early-age mortality began to decrease. This is significant because childhood mortality trends are the strongest predictors of later mortality. In following birth cohorts over their life spans, Eileen Crimmins and I discovered that the survivors in birth cohorts with high early-age mortality rates showed much higher mortality rates at all later ages than survivors in birth cohorts with lower early-age mortality rates. Evidence from Sweden, which has kept remarkably complete records of mortality since 1750, makes a very strong case for this.

We hypothesized that this outcome was the result of chronic infections and inflammations accelerating aging processes. For example, rheumatic fever, the result of streptococcus infections, killed many children in the 'bad old days' before antibiotics. But the disease continued to affect even its survivors, who rarely lived beyond middle age, because the bacterial colonization of the valves had weakened their hearts. TB was another common scourge often acquired in childhood that shortened adult life spans. Thus, it appears that early infections have a strong connection to adult longevity.

This 'cohort morbidity' has gradually decreased during the past two centuries. Its decline began long before people understood the germ theory of infectious transmission and very long before modern medicine discovered vaccination and antibiotics. By Whitman's time, and even a century before in Sweden, societies were improving public health and personal hygiene. The stink of human waste and rotting garbage was becoming less acceptable. Governments were increasingly expected to provide clean public water, covered sewers, and sanitation squads to clean up after horses. Improving transport was also giving broader access to better food year round.

Still, it is fair to say that we do not fully understand the precise relation of the improvements in education, hygiene, and nutrition to the advance in health during the Industrial Revolution.

We do know, though, that the legacy of bad conditions can persist for several generations. Low-birth weight babies not only grow up with a higher risk of heart disease and hypertension, but also tend to produce relatively small progeny of their own. Impaired fetal growth affects the pelvic blood vessels, which may never develop optimally even with good nutrition after birth. Maternal infections may be as least as important as nutrition in impairing fetal growth; for example, women with HIV or TB, even with good diets, tend to have smaller babies. Smoking can also have trans-generational effects. If your grandmothe-r smoked during pregnancy, your risk of asthma is two times greater because the egg from which you came was fully formed (and, as a result, exposed to carcinogens) while your mother was still a fetus. We may find still other infections and environmental inflammogens with persistent effects; such factors will likely slow or limit future average increases in life span.

When Walt Whitman sang of the “body electric,” he coined a metaphor that turns out to be more literally true than he may have imagined. Our aerobic metabolism is continuously producing free radicals, ‘chemical sparks’ that attack invading microbes with their highly reactive, unpaired electrons. When microbes enter our bodies, macrophages, one of the most ancient immune cells, are rapidly activated during the ‘acute phase response.’ Enzymes in these macrophages convert oxygen to the radical superoxide and fuse with carbon, chlorine, hydrogen, and nitrogen to form other radicals. As the free radicals from activated macrophages diffuse from their cell source to attack an infection, however, they also inflict local ‘by-stander’ oxidative damage on other cells and molecules.

During systemic infections, the liver also shifts gears to secrete inflammatory proteins, e.g., C-reactive protein (CRP), cytokines such as interleukin-6 (IL-6), and complement system proteins. CRP is an ancient protein that binds to certain classes of bacteria and enhances their uptake and digestion by macrophages. IL-6 and other cytokines cause fever and also mediate the next phase of host defense, instructive immunity, which emerges days later with specifically targeted antibodies or cell defenses through B-cells and T-cells.

While free radicals play a vital role in the body’s defense as well as in the normal and essential signaling between cells, they can also cause slow yet cumulative damage to irreplaceable molecules and cells. Such multiple effects, or ‘pleiotropies,’ underlie a basic principle in aging called ‘antagonistic pleiotropy’: some mechanisms that evolved to mete immediate benefits to the young have delayed consequences that slowly emerge during aging. Another example is glucose. While an essential fuel, glucose also spontaneously reacts with the amino groups of proteins and nucleic acids. The resulting oxidative modifications, or advanced glycation end-products (AGEs), can cross-link proteins and cause DNA mutations. We know that chronic hyperglycemia, as in diabetes, accelerates AGE formation. Moreover, in diabetic neuropathy, AGEs also
cause cell death by synergizing with free radicals.

Because many chronic diseases of aging develop through inflammatory mechanisms, inflammation and aging are now merging fields of research. The case is strongest for vascular disease as an inflammatory process. Because atheromas, the raised fatty plaques in the arteries that can contribute to vascular disease, are actually hotter than surrounding vessels, the idea that the sparks within are driving aging is not just a metaphor. Atheromas are loaded with inflammatory cells and proteins—cytokines, complement factors, etc. In fact, the foam cell of atheromas, which accumulates lipids, is an activated macrophage.

Moreover, in brains with Alzheimer’s disease, senile plaques harbor many of the same inflammatory processes found in vascular atheroma. Senile plaques are surrounded by the brain’s special macrophage, the microglial cell. Besides the cytokines and complement factors also found in atheromas, Alzheimer plaques contain the beta-amyloid protein, which is induced by hemorrhage and inflammation.

Inflammation seems also to play a key role in the etiology of heart attacks. Elevated blood CRP and IL-6, when combined with elevated LDL, result in a fivefold or higher risk of a future heart attack. In the Honolulu Asia Aging Study, elevated blood CRP also predicted a threefold higher risk of later developing Alzheimer’s disease and vascular dementia. Tellingly, most of the known risk factors for heart attacks are also risk indicators for Alzheimer’s disease and vascular dementia.

Vascular disease typically begins decades before symptoms arise. At autopsy, soldiers killed in Korea and Vietnam often had advanced fatty plaques in their arteries. Even fetuses often have minute versions of atheromas. While these ‘prodromal’ atheromas do not block arteries they may seed further growth. Ultrasound imaging has also shown that obesity and diabetes can accelerate the growth of atheromas even in childhood. Over the course of a lifetime, the aorta and most other arteries progressively accumulate fatty deposits. Some spontaneously regress, while others balloon into full-blown intrusive plaques. In general, atheromas with many macrophages and large lipid cores are the most unstable and likely to form the thromboses (clots) that block blood flow. Besides these focal lesions, many vessels also develop thicker and more rigid walls during aging through the accumulation of AGEs. Thickening in the carotid arteries that feed the brain is a predictor of stroke.

There is growing evidence that various common infections increase the risk of heart attacks and strokes. The number of antibodies to different infections correlates with blood CRP and risk of heart attack. Hepatitis C virus (HCV) alone, for example, may heighten the risk of coronary disease up to five times. When present in a donor for cardiac transplant, HCV tripled the mortality risk from accelerated coronary disease in the grafted heart. Other common infections have modest, but potentially important, effects over the long haul. Helicobacter pylori, which leads to ulcers and a high risk of gut cancer, also increases the risk of heart attack by about 20 percent. Besides the blood vessels, the heart valves are vulnerable to microbial attack, as in rheumatic fever.

Even oral infections play a role in vascular disease. Our gums and teeth harbor an amazing diversity of bacteria as dense biofilms, which resist scrubbing.
and flossing. Tooth loss due to periodontal disease was once common: before 1900, few adults reached age 60 with any teeth. The great improvements in oral hygiene that now help us keep our bites into old age are also thought to have reduced vascular disease by lightening the load of systemic pathogens. However, it is hard to prove a particular bacteria or virus carried elsewhere in the body, particularly in low-grade infections, is a specific cause of vascular disease. The classic requirement of Koch’s postulates that the condition be transmissible with the same result may not apply to heart disease and other multifactorial conditions.

Anti-inflammatory drugs, which reduce the risk of heart attacks, give further evidence of the importance of inflammation in vascular disease. Aspirin is best known for helping prevent heart attacks. Statins also demonstrate powerful anti-inflammatory capabilities, for example, lowering blood CRP. Further, since oxidative damage is a shared mechanism in the progression of vascular disease, cancer, and Alzheimer’s disease, most drugs that retard vascular disease by acting on shared inflammatory processes also help prevent other chronic diseases. For example, aspirin reduces the risk of GI-tract cancer, though how it does so is still unclear. It is also uncertain how much of the oxidative damage is the ‘prime mover’ or a secondary effect.

Nonetheless, anti-inflammatory drugs, in reducing the activity of macrophages and other inflammatory processes, appear to lower the risk of various chronic diseases. This correlation points strongly to a connection between infections and vascular disease, one that provides modern evidence for the critical role that reducing infections and inflammation has played in the historical improvements of both childhood mortality and adult longevity rates. Animal models have supported these associations by showing that inflammation or chronic infection accelerates vascular disease, cancer, and Alzheimer’s-like changes. These modern developments also support the importance of inflammation in the historical improvements in mortality across the life span.

Besides common infections, obesity is also a risk factor in vascular disease, cancer, and possibly Alzheimer’s disease. Again, obesity and diabetes are characterized by increased inflammation, including higher blood CRP. Conversely, animal studies consistently show health and longevity benefits in proportion to the level of caloric restriction. In laboratory rodents, reducing caloric intake by 10 to 40 percent delays many chronic diseases, lowers free radical production and oxidative damage, and reduces blood CRP. Moreover, in mice engineered with genes that cause cancer, vascular disease, or Alzheimer’s disease, caloric restriction slowed all these conditions. In these same models, obesity and diabetes accelerated many aging changes slowed by caloric restriction. Scientists have discovered that the mechanisms at work in caloric restriction include lower blood glucose and AGE formation.

The benefits of caloric restriction to lab animals, however, may be something of an artifact of their confinement. Benign lab environments do not demand the activity required in the real world for the relentless search for food and avoidance of predators. Primates in captivity tend to obesity and diabetes, making them good models of our modern couch-potato lifestyle. In humans, obesity and diabetes may be successfully treated by diet and exercise.
Would caloric restriction benefit current human aging? One widely used measure is body mass index (BMI), which adjusts body weight for height. A BMI below twenty represents extreme leanness; a BMI above thirty, obesity. A BMI below twenty may be unhealthy because of anorexia, smoking, or wasting diseases. On the other hand, a BMI above thirty increases the risk of diabetes, hypertension, and vascular disease. Most studies agree that a BMI somewhere between these extremes has little influence on mortality risk.

So would caloric restriction benefit the majority in the mid-BMI range? John O. Holloszy’s study of eighteen volunteers showed that a 20 percent caloric restriction for three or more years improved risk indicators of vascular disease. Several groups are accumulating personal data on caloric restriction, and efforts are underway to find drugs that mimic caloric restriction. But one cannot forget that Jean Calment was also known for her hearty appetite for food and wine.

The recent increase in human longevity contradicts old beliefs that life spans are fixed. The scourge of heart attacks has diminished remarkably in the past thirty years, in part because of the gradual decrease in smoking. There is growing recognition that lifestyle choices strongly influence health at later ages.

Aging is very plastic, whichever genes an individual has inherited. This plasticity implies that in past centuries earlier signs of aging accompanied the shorter life spans. To Walt Whitman, even 50 was old. In a February 12, 1867, letter, he wrote, “[I] am now in good spirits…I don’t feel a bit ‘pegged out’—only getting old—most 50, you know….” It is frustrating that we do not have reliable general markers for rates of individual aging that we can apply to earlier times. Graying hair certainly is not a good indicator of one’s state of health or future longevity. Whitman’s hair had begun to turn gray by 30, when he was in robust health. Even today, there is no consensus on which biomarkers of aging can predict the remaining life span of an individual.

Genetic vulnerabilities undoubtedly account for some of the individual differences in mortality risk—but they are not the whole story. The longevity of highly inbred laboratory rodents within the same colony, for example, differs widely. Individual rats of the same sex living in the same cage also vary widely in learning ability, reproduction, tumor incidence, and molecular damage to mitochondrial genes as they age. Within the same colony, life spans may range 50 percent about the mean, from twenty to forty months. Flies and worms also show wide individual variations in cell damage during their month-long life spans. Humans show a similar range, when calculated in proportion to life span.

From observing human twins and laboratory animals, geneticists have concluded that the heritable component of longevity is relatively modest, between 10 and 35 percent. Studies of human twins make clear the limits of genetics in aging. Menopause in identical twin pairs is typically separated by two years but can be up to twelve years apart. Chance variations in the numbers of egg cells formed in the ovary before birth may be responsible for these differences in menopause. However, after 80, the percentage of the remaining life span in twin pairs that is attributable to heredity is almost zero. At this point, the more sociable twin is likely to live longer. On average, human sociobehavioral factors also have a stronger influence than ge-
netics on an individual’s ability to survive, for example, a hip fracture.

Nonetheless, the genetics and genomics of aging is a thriving, exciting field. Some centenarians carry rare genes that appear to favor longevity, including ones that mediate cholesterol metabolism. Major advances are also being made in the genetics of longevity for many different species. Mutations in metabolic pathways relevant to insulin have increased longevity in yeast cells, flies, worms, and mice. Some of these mutations, however, are less viable under more natural conditions. Dwarf mice, in particular, can live longer in certain conditions; until those conditions were discovered, they were thought to show accelerated signs of aging. What regulates the rate of oxidative damage is also mysterious—for example, why do humans live thirtyfold longer than lab mice, despite identical levels of blood glucose and body temperature?

How did aging evolve? In nature, overall mortality is vastly higher than in our current human societies. Most animal populations are dominated by young adults who do most of the reproduction needed for the perpetuation of the species. Thus natural selection is strongest against genes that impair development of young adults. According to the evolutionary theory of aging, genes that cause dysfunctions later in life are permitted to accumulate in populations because any adverse effects are delayed to minimize impact on reproduction. In effect, it is the ‘schedule of reproduction’ that determines potential longevity. If a gene mutation arose that caused heart attacks or strokes soon after puberty, this gene would be strongly selected against.

Having considered the recent improvements in longevity, let’s look further back to consider how humans became the longest-lived primate. In nature, life expectancy for monkeys at birth is about fifteen years; for great apes, it is about twenty. When protected in a zoo, primates live longer, but still not as long as humans live. The evolution of longevity in primates may have occurred in two stages; the first consisted of having fewer children per pregnancy. Among animals, great apes are distinctive for giving birth to one child at a time and providing the child parental care almost to puberty. Chimpanzees, for example, may continue to nurse for six years; orangutans, ten years. This extended care requires great apes to live longer than monkeys, whose maternal care ends after three years. For chimpanzees and monkeys in captivity, the duration of parental care is proportionate to life span; chimpanzees live to about forty-five years, monkeys to about thirty years.

Humans, who have further extended the care and training of their young to twenty years or more, also live proportionately longer. Our unusually slow maturation depends on a multigenerational support system not found in other primates. These social support systems were instrumental in evolving our tool-based cultures and effectiveness as hunters. Perhaps multigenerational support also favored survival to later ages and enhanced the evolutionary benefit of elders to their offspring. An embellished fossil jaw found in the Dmanisi site in the Transcaucasia implied such social support, even of the physically infirm, existed as long as 1.7 million years ago. However, Whitman’s paralytic stoke would have soon doomed him to be left behind by some migratory foragers.

Diet is another key difference between the great apes and humans. Anthropologists find that hunter-gatherers around
the world, like most of us, love to eat lots of meat. In this regard, humans differ hugely from the great apes, who are predominantly vegetarians with little regular intake of cholesterol—a substance not produced by plants. While some male chimpanzees avidly hunt and eat small animals, females do not eat meat during pregnancy or nursing. Because high-cholesterol diets accelerate vascular disease, cancer, and Alzheimer’s disease in laboratory animals, Craig Stanford and I have hypothesized that the evolution of greater longevity despite this new diet required our human ancestors to evolve ‘meat-adaptive genes.’

One potential meat-adaptive gene is the cholesterol carrier, apolipoprotein E, which has two common genetic variants apoE3 and apoE4. The ‘good’ apoE3 gene lowers the risk of elevated cholesterol and Alzheimer’s disease, and increases lifespan by several years. Carriers of the ‘bad’ apoE4, on the other hand, show lower frontal lobe metabolism, which could be an early stage of neurodegeneration. ApoE4 is the ancestral gene and may once have been advantageous because its proinflammatory activities may have been protective in an earlier environment. For example, people who have HCV infections but carry apoE4 have less liver damage. This double-edged impact of apoE4 can be described as an antagonistic pleiotropy, bringing advantages earlier in life, but contributing to disadvantages (e.g., Alzheimer’s disease) that emerge later. These genes were not actively selected against because so few people survived to advanced ages until recently.

ApoE genes also influence response to injury. ApoE3 minimizes many inflammatory responses; thus, in head trauma, for example, apoE3 carriers show less damage. Conversely, because of premature Alzheimer’s changes, the punch-drunk boxer’s condition (dementia pugilistica) is more common among apoE4 carriers. Although we do not think of head trauma as very common, soccer players who ‘head’ the ball frequently have higher risks of cognitive losses in middle age. This should put ‘soccer parents’ on alert for the future brain health of their kids who often emulate the pros in ‘heading’ the ball. Given the consistent evidence that apoE4 increases the risk for delayed brain dysfunctions, it is not far-fetched to think that athletes in contact sports may soon care to consider apoE4 and other genetic risk factors.

ApoE gene variants may also influence brain development. When engineered into mice, the human apoE4 decreases the complexity of neurons, relative to human apoE3. Thus, the evolution of the apoE3 variant several hundred thousand years ago may have supported greater brain development as well as longevity in our species before we left Africa.

Further increases in human longevity seem likely through improving ‘gerotechnology.’ New drugs are being developed to reduce obesity, possibly as mimetics of caloric restriction. If we find drugs that give normal humans longevity benefits equal to caloric restriction in rodents, then life expectancy could grow to 110 and possibly beyond 150 (which should give those political or religious organizations that elect their heads for life pause). Other drugs may broadly protect against Alzheimer’s disease or arrest it at early stages. We may also achieve cancer prevention someday, despite increasing exposure to carcinogens.

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Many also look to regenerative medicine. One day, we may engineer stem cells to replace cells lost in diseased organs. Current debates about embryo stem cells will sooner or later fade as research discovers ways to reprogram an individual’s own skin or marrow cells for new functions. Still there is a long way to go before neuronal stem cells can restore neurological damage from traumatic injury or Alzheimer’s disease. We may also find new ways of repairing vascular damage, through engineered cells or circulating micro-robots (vaso-robots?) that are sent on patrol to repair unstable atheromas. Of course, such future regenerative medicine will be very expensive because of the huge cost of development, limiting access to those who can afford it. If the current U.S. political climate is any guide, these costly wonders will not soon be available to those with low incomes.

Beyond these anticipated biomedical advances, we need a broader view of the ecology of human aging. A starting point for modeling future population age structures is a more comprehensive account of aging that includes the load of infections and environmental inflammogens. We must also consider social dynamics such as the change in multigenerational support for the elderly that is sweeping across developed countries. The ecology of human aging must also consider the genetic changes evolved from our great-ape ancestors who were largely vegetarian and had limited multigenerational interactions. We should also expect greater demographic diversity, both of life spans and health during the later years. The fortunate who grew up with little childhood illness and maintain optimum body weight through diet and exercise could live even longer than present cohorts.

However, new risks are appearing. Obesity and diabetes are more prevalent, even among children. Maternal diabetes, moreover, heightens the risk of obesity in children. This fatty trend, if it continues to grow, could reverse historical gains. Air pollution is also on the rise. Small particles from internal combustion engines and various industrial sources inflict cardiovascular inflammatory damage; animal studies have shown that airborne pollutants activate lung macrophages and increase oxidative stress.

Also important to consider is the gap between rich and poor. Not far from the healthiest and most affluent elite in any large city are many who experience the onset of diabetes, hypertension, and other chronic diseases earlier. Epidemiologists associate the poor health of those of lower socioeconomic status with higher exposure to infections and pollution, poor diet, and limited health care. In migrant workers, TB is at least five times more prevalent than in other groups. Moreover, the spread of HIV increases the risk of TB and other infections that shorten life. Thus, poverty both dooms the disadvantaged to higher morbidity and shorter life spans, and increases the reservoirs of infectious agents that can spread to the advantaged. Sooner or later, voters must see that the potential for longer, healthier lives depends on much higher standards of health for the whole population.