Evolutionary Anthropology 13:82–88 (2004)

Ponce de Leon and the Telomere of Youth

KENNETH WEISS

The explorer went to the ends of the earth looking for immortality. Did he only have to go to the ends of his chromosomes?

"If the drug industry has a commercial Holy Grail, it might be an anti-aging pill, one that would let you live longer and prolong your youthful vigor," wrote Gina Kolata in a recent article in the *New York Times*.[1] Genes have recently been found that have similar effects on aging processes in yeast, flies, nematodes, and humans. This suggests that aging might be an easily modifiable phenomenon and the drug industry is eager to discover the magic potion for eternal youth.

Of course the icon of the search for the Fountain of Youth is Juan Ponce, known as Ponce de Leon. A comrade of Columbus, who successfully fought the Moors and helped subjugate Hispañola as a base for Spanish conquests, Ponce became governor of Puerto Rico in the early 1500s. Later, faced with age and the fading of his glory days, he heard of crystal waters, among trees bearing golden fruit tended by lovely maidens, that bestowed eternal youth upon those who bathed in them. Who could resist? After searching in vain in the Bahamas, in 1512 Ponce followed magnolia-scented offshore breezes to what he hence named "Florida," where his search also failed—but he would return.

Figure 1. Ponce de Leon in his younger years.

In longing for long life, Ponce de Leon looked over the far horizon for simple cures for death. In the scientific age we seek our dreams on the inner horizon of our genome, and we're in an age when we can stop hypothesizing about aging-related genes and, if they exist (unlike the Fountain of Youth), find them. But before seeing what is now known about such genes, we first need to consider just what kind of phenomenon aging actually is.

WHAT KIND OF EVOLUTIONARY PHENOMENON IS "AGING"?

The fitness associated with any trait is a life-history phenomenon. Age-specific timing of reproductive maturity, fertility, and mortality determine lifetime reproductive success. Life-history traits are complex, because they can be affected by selection and drift directly, but even traits like locomotion are indirectly screened through their life-history effects. One net result is that species have characteristic aging rates, making questions like, "How long do dogs live?" evolutionarily meaningful. Perhaps the fact that lifespan is a somewhat colloquial rather than scientific term has led to the notion of that each species has what has been called a Maximum Lifespan Potential (MLP), so that individuals who avoid exogenous causes of death-like predation or infection will eventually succumb to a species-specific internal clock at its MLP, making room for a fresh generation.

We can illustrate aspects of life-history evolution by the *survivorship* curve, the age-specific probability of surviving from birth to each age (Figure 2). The impression that there is an MLP is an understandable illusion of such data (Figure 2, first 2 curves). Trends in causes of mortality over time made it seem that the survivorship curve was becoming "squared," approaching a limit—the MLP—that the rapid acceleration of mortality rates with age make it impossible to survive. The reason for the illusion, which was widely accepted by the biomedical aging research community until quite recently, was that early extrinsic causes of mortality like infection were being reduced by public health measures. If we could finally remove those causes we would have something rather squarish (curve C), because the remaining intrinsic aging processes would then predominate.

However, the MLP was far beyond ages most people ever attained, so it was always difficult for evolutionary biologists to accept the notion, in part also because one of its rather incredible implications was that the known causes of death were biologically unrelated to the determination of life-

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DOI 10.1002/evan.20008
Published online in Wiley InterScience (www.interscience.wiley.com).

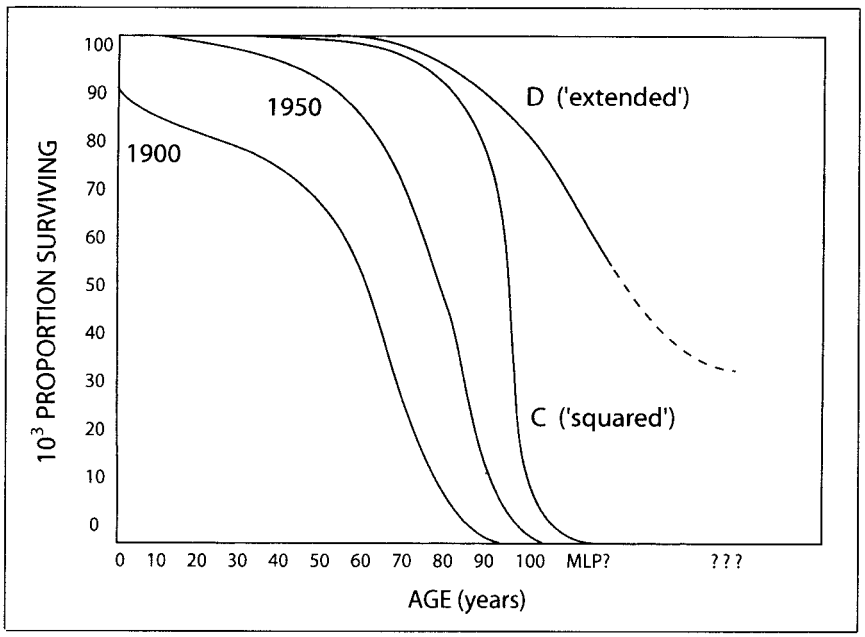

Figure 2. A survivorship history, in percent surviving from birth each succeeding age. General pattern of U.S. mortality by age in 1900, 1950, and (curve C) the continuation of that trend giving the appearance of a squared survivorship curve at the hypothetical human MLP. Curve D shows an "extended" life history without the squaring, as has been seen in recent years, leading to the suggestion that human life can be indefinitely extended. Schematic.

span, and without them we could all live in good health until our MLP[th] birthday.[2] Aging research might not make us immortal, but we'd at least be able to have a well-planned Last Supper.

Instead, and more plausibly, recent mortality data show that death rates do not rapidly accelerate at very old ages (Figure 2, "extended" curve D). This means that the oldest old do not drop off suddenly, but gradually: there is no "squaring" of survivorship. The MLP vanishes—and the unrepentant research lobby now touts its new insight that human life can be extended indefinitely. But this too is a Leonid dream. Life expectancy and health at older ages have recently increased, in part because of life-extending intervention like less physical stress, better nutrition, drugs and vaccines, bypass surgery, cancer chemotherapy, bronchial ventilators, more effective long-term and emergency room care, and the like. But a visit to a senior center reveals the sobering truth that old people are "old" in roughly the same complexity of ways as always.

Why would the idea that aging is a unified biological trait, or that there could be a simple genetic MLP-directing switch, seem plausible in the first place? One oft-cited reason is that among vertebrate species there is a systematic relationship between estimated lifespan and measures like mean body or brain size (Figure 3). Indeed, the same age-patterns of diseases that fail to support the notion of a fixed MLP to kill us, suggest that there must be some common underlying processes that evolution (or we) might play with to preserve us.

At any given age, the absolute risk of death from different causes varies by orders of magnitude. But the *change* in those risks with age are very similar (Figure 4); diverse causes rise in risk at roughly the 5th power of age. Similar diseases strike mice, monkeys, and men, who share largely the same genome, yet are scaled to each species' lifespan, indicating that evolution may somehow calibrate the overall rate of aging, rather than specifically of death. The tapering off of

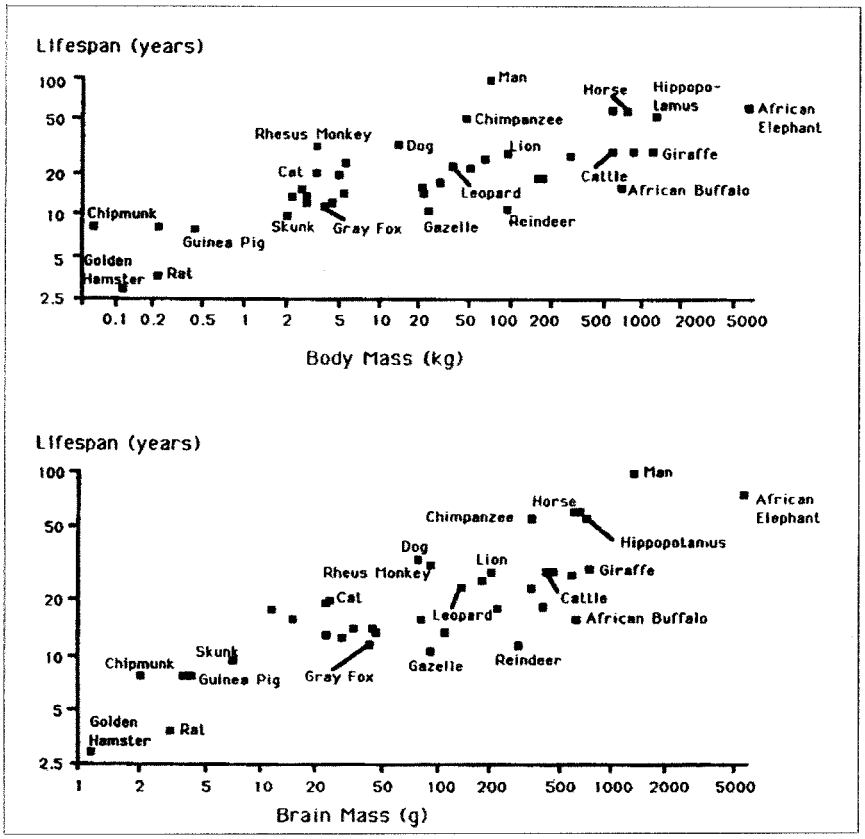

Figure 3. Age and lifespan: something's going on here. Relationship between body size and estimated lifespan among vertebrate species.

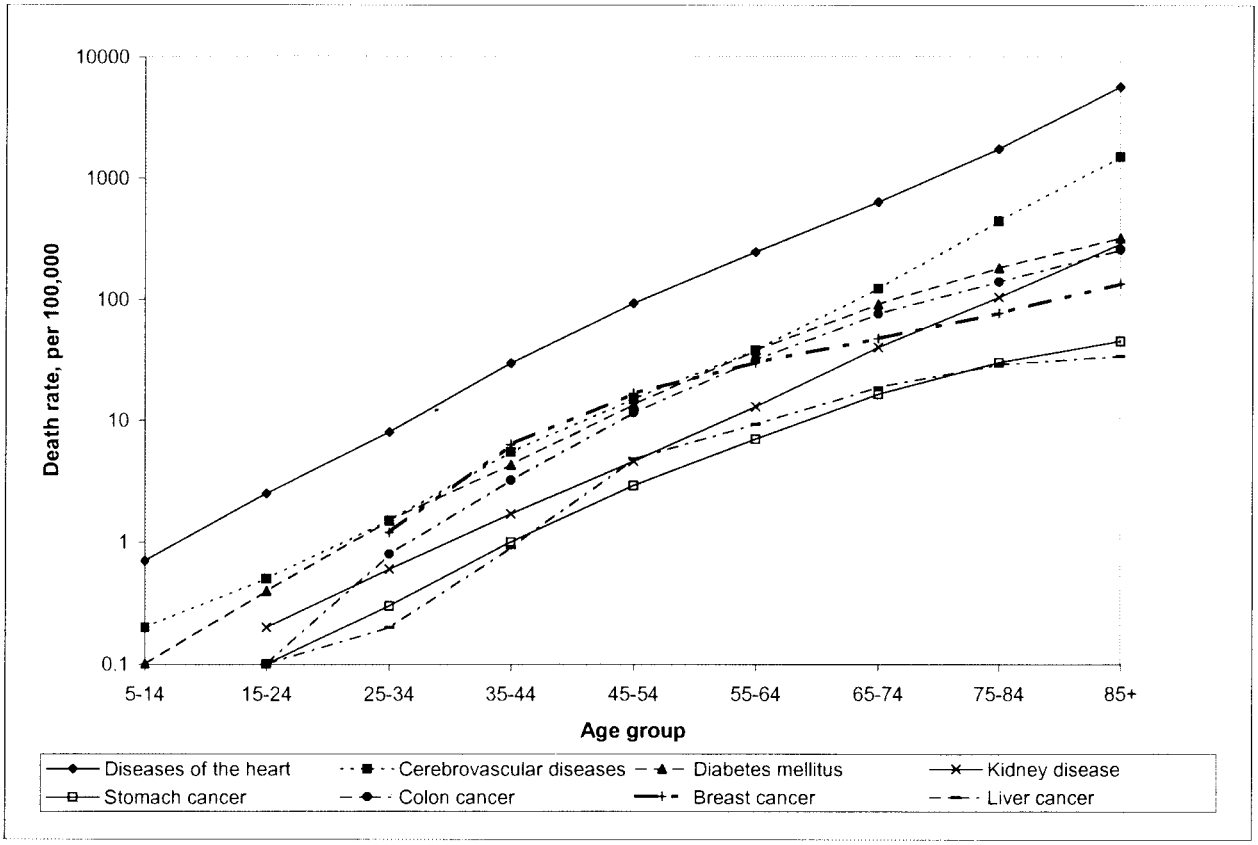

Figure 4. Different causes of death vary greatly in absolute risk but share similar patterns of acceleration with age. Risk is on a log scale. 1999–2001 U.S. mortality.[3]

some causes seen here reflects the secular trends (curve D) in Figure 3 and is due, at least in part, to the differential loss with age of individuals genetically susceptible to the various diseases. Thus, those who survive represent their own longevity, but not that of people generally.

If these data reflect an underlying aging process, that might account for another curious aspect of Figure 3, that suggests that humans live longer, by an amount roughly equaling the length of our post-reproductive survival, than a mammal our size has any right to expect. Although this could just be an artifact of multiple causes, the possibility of a common underlying cause understandably raises the hope for a Gene Therapy of Youth.

Immortality! What in the *Devil's Dictionary* Ambrose Bierce quipped that people would apply on their knees and be eternally proud to die for, is clearly possible at the cell level. Since the germ line never ages, it would seem obvious that the rest of our cells, with the same genome, don't have to wear out either. To bowdlerize James Hutton, a founder of modern geology, all life today is composed of cell lineages that are about 3–4 billion years old, with "some vestige of a beginning—no prospect of an end."

WHAT IS THE LIKELY EVOLUTIONARY EFFECT ON AGING-RELATED GENES?

Everything here seems to cut both ways. Does evolution kill us off or keep us going? One general theory for the evolution of senescence is that nothing evolved specifically to kill us off, but that the price of genes that give us plenty at twenty is to become weighty at eighty. This is known as *negative pleiotropy,* and the idea is that genes selected for early fitness can have deleterious effects in later life, when events can become just a matter of wearing-out, beyond the reach of natural selection. But wearing out does not explain our long post-reproductive *persistence,* and a variety of theories and controversies, have been advanced for that, some in the context of the broader evolution of primate life-histories.[4–7]

Evolutionary explanations almost always rest on the assumption that if aging is highly organized it must have been molded by selective forces, and the genes involved are routinely hypothesized ("Suppose a mutation increases lifespan; . . . "). I think this view of life is overdone, but it is worth considering the likely resulting impact of those forces, whatever they are.

First, however, we should not overinterpret statistical data, especially with a measure like lifespan. A species-specific lifespan or MLP is the extremum of a population phenomenon, whose estimation depends on sample size. We've observed hundreds of millions of human lifespans, vastly more

than for other species, biasing the human estimate towards the extreme of rare genotype or luck relative to what we've observed for other species. Though above the trend in Figure 3, we're not dramatically longevous for our body size, no more aberrant than rhesus, reindeer, and African buffalo, for whom no special evolutionary explanations have seemed necessary. So at least some of the excess might be simply a sample size artifact.

Another potential illusion is that even the modest post-reproductive survival found in contemporary tribal cultures may be misleadingly long, because they probably have far better cultural protection (arrows, sharper stone blades, metal, agriculture, maybe even antibiotics or antimalarials) than was available when our life history evolved. Studies of traits like hominid fossil dental eruption suggest that our maturation rates evolved long ago, but this need not apply at the other end of life when selection was weaker. And if the historical, anthropological, and fictional literature is any guide, in prior times people were widely seen as pretty worn out by their 50s. I've been reading *Don Quixote,* in which the Don is described as "about fifty years old, of a strong complexion, dry flesh, and a withered face." Yet people from all cultures living in modern environments like, say, Mohawks in Toronto (or knights of La Mancha in La Mancha), stay equally fit, for equally long. As anthropologists we should keep in mind the trap of viewing the world through our own cultural lenses; for example, we routinely apply skin cosmetics to prevent "premature" aging. The difference between what is possible and what actually occurred or was selected for in the past is an important distinction in evolutionary biology that may well apply here. The fact that Bonzai trees can be made does not mean trees evolved to be tiny.

How old was old in days of old is debatable,[5,7,8] but the question is what happens to those who do live to be old, and the most prevalent explanations for long human survival involve trans-generational resource transfer. An older adult has reduced needs for herself and can contribute enough food, safety, or other care to enhance the chances, and hence evolutionary fitness, of her children or grandchildren.[5] Trans-generational resource transfer is undeniable, but only a fraction of fitness remains in the Darwinian arena by the ages at which it occurs. Although the overall heritability of longevity in humans is about 25%, showing that there *is* potentially relevant variation, that heritability declines with age: genetic effects are weakest at the ages when trans-generational effects are most important. And as to the human specificity of aging, baboons have roughly the same heritability, in both sexes, and as in other mammals the pattern of senescence in baboons resembles that in humans, despite very different lifespans.

The transfer of resources to the next generation involves not the direct fitness of a parent, but her inclusive—indirect—fitness achieved via others who bear her genes. But her specific selective advantage would be less than it might seem because small local demes consisted mainly of cousin-like kin, who care for a woman's children if she dies, and communal necessity makes hunter-gatherers share resources like food, defense, tool-making technology, and so on. Ultimately culture is enabled by genes, but in the search for a biomedical elixir of youth, we seek a genetic cause of the biology of aging itself, not of the culture that protects old people.

For these reasons, late-age selection effects were probably weak, and if many different genes contribute to longevity, the net selective advantage at any one of them would have been even smaller. In our small ancestral populations this means that genetic drift would have been a stronger, if not predominant effect on the frequencies of alleles related to late-age survival. This high genetic noise-to-signal ratio in turn means that we should not expect the kind of simple genetic aging mechanism—the pharmaceutical dream—that one might expect after rapid, strong selection. But what do we actually find?

"SUPPOSE A MUTATION INCREASES LIFESPAN . . ."

In fact, genes have been found that satisfy a key requirement that an "aging" gene should affect underlying processes we associate with getting old. The first genes known to affect aging probably were those causing numerous *progerias,* including Down's syndrome. Progerias commonly affect connective tissue, which is found in skin, bone, muscle, heart, and blood vessels, and by affecting multiple traits in similar ways can appear to accelerate general aging.

Free oxygen radicals, or oxidants, interact with cellular components causing damage to any tissue, including mutations in DNA, damage that accumulates with age.[9] Various diseases, especially cancer, have been thought to be accelerated by such damage. Dietary antioxidants have been thought to reduce a variety of such diseases and hence general aging rates, and oxidant-scavenging genes are viewed as longevity-promoting candidates.

In a wide variety of experimental laboratory animals, and probably humans, modest restriction of dietary caloric intake increases the length of life (maybe the secret is not to seek the Fountain of Youth but to shun the Soda Fountain). Some genetic mechanisms are known that probably contribute to this observation. In response to calorie intake, genes in the insulin-like, pituitary, and related hormonal signaling systems can shunt metabolic energy either to growth and reproduction or, when suppressed, to extended lifespan. Genes in the *Sirtuin* gene family[10] indirectly affect these pathways by modifying the histone proteins that package DNA, affecting gene expression. One sirtuin, Sir2, affects yeast lifespan through effects on mating and cell division cycles, and in some species Sir2 affects expression in the insulin-like system. A human homolog, SIRT1, affects the cell cycle and programmed cell death.

In laboratory animals the senescence-delaying effects of mutations in these genes resemble the empirical effects of calorie restriction: stretching out the survivorship curve to more like the "extended" curve D in Figure 2. This has been interpreted as showing that aging can be manipulated through only a few genetic pathways that are highly conserved among animals, and may have evolved long ago

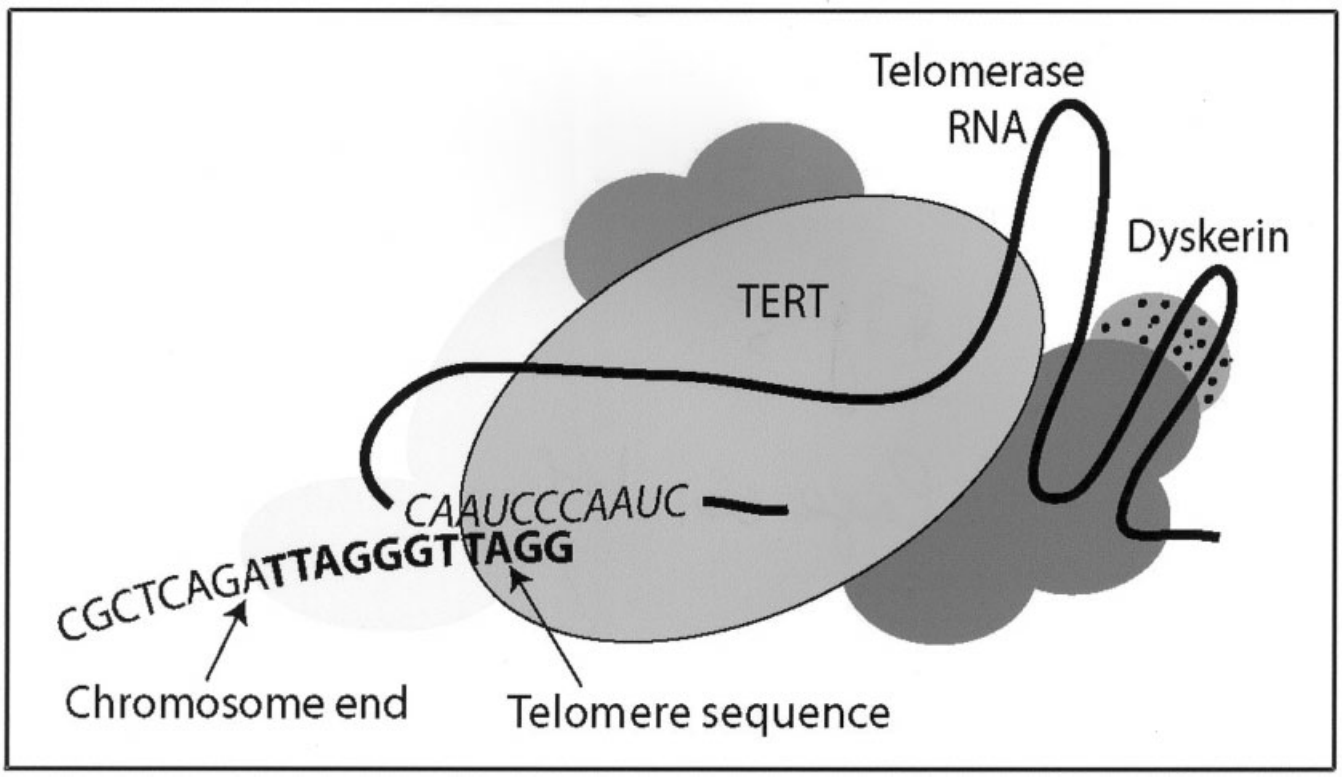

Figure 5. Telomerase complexed with proteins like TERT and dyskerin adds **TTAGGG** sequence caps to chromosomes. Modified after.[12]

as survival responses to environmental stresses.[9] But while natural and experimental mutations in these energy-related genes in laboratory animals show delayed senescence, they can also have a variety of deleterious effects,[11] some of which are also seen in naturally occurring mutations in humans (who don't gain the longevity benefits).

Probably the most highly touted aging-related gene is one involved with the aging of chromosomes—the very heart of life—and in particular their ends, or *telomeres*. Telomeres are **TTAGGG** sequences concatenated in thousands of copies at the ends of chromosomes. These sequence caps protect the chromosomes from being chemically chewed up, as could otherwise occur during the many rounds of cell division during life. Chromosomes without telomeres cannot be replicated all the way to the ends, leading to cells that misbehave or cannot successfully divide. The gene *telomerase* is a main factor responsible for installing and maintaining telomere sequence.[12] Interestingly, telomerase does not code for a protein, but for a type of RNA that is directly active on its own, complexing with several proteins, causing the addition of the repeat sequence by complementary base-pairing, as shown in Figure 5.

A reduction of telomerase activity and shortening of telomeres occurs with age in cultured cells and because all cells have chromosomes, telomere length has been viewed as the general calibrator of longevity, and telomere loss is associated with a number of age-related diseases. But if this is a true story it is a complicated one, because mice have longer telomeres (20–50 kb) but shorter lives (2–3 yrs) than we do, and die, as we do, at comparable ages relative to their lifespans whether from telomere-related diseases or not. A further irony is that a main disease effect is that failure shut down telomerase expression allows cells to proliferate, including cancers, the archetype of age-related diseases. In this sense telomerase, by keeping cells viable, might be viewed as a gene for cellular *immortality*. Thus, therapeutic application of telomerase has been suggested as anti-aging magic, which could backfire by making small tumors more aggressive. Cell cultures that die, at least partly, because of loss of telomeres do not accurately mirror natural causes of death, in part because when a cell dies for that reason in a real organism, its place is taken by neighboring cells with sufficiently long telomeres. Viewing telomerase as a long-life gene is at least somewhat problematic.

I can't resist adding that de Leon[13] has recently confirmed an expected neurodegenerative effect, on cognition, of variation in another aging-related gene, ApoE. That's not Ponce, but it does keep it in the family!

If aging-related genes tell an aging story, it is an incomplete story, a complex story—and not the whole story. What these genes have in common is the *segmental* nature of their effects—on some but not all age-related changes. We see just what we should expect: an aggregate of many genetic effects on different aspects of aging leading to a variable, largely probabilistic, gradual aging pattern. Nonethe-

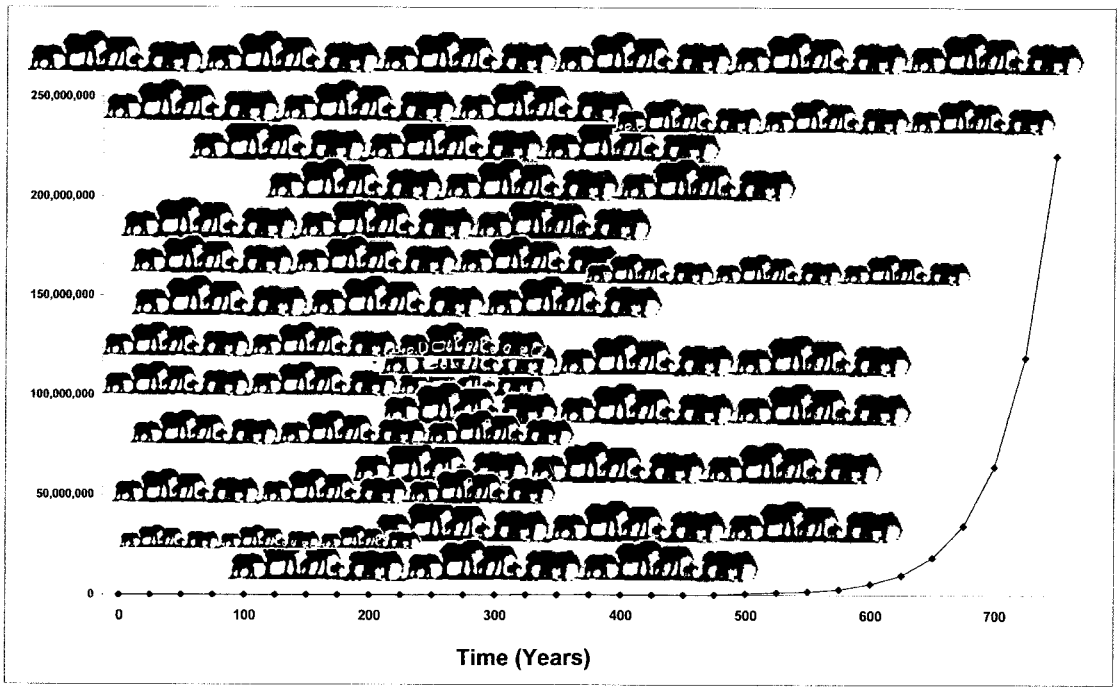

Figure 6. Darwin's Study in Grey: elephants on Malthusian parade (population growth at an annual rate of 2.5%).

less, these "aging" genes suggest how life-history events could be broadly calibrated by natural selection trimming alleles that lead to deaths so early as to affect fitness. The resulting net species-specific aggregate of effects reduces the *probability* of survival with age until it becomes so low as to generate the illusion of a death-switch at that age.

WHEN ENOUGH IS TOO MUCH

There is another point worth making. We *already* have a built-in fountain of youth. This is because the main social transfer of dotage benefits goes the other way, from children *to* their parents when they become too old to defend or feed themselves—Golden Years on Golden Pond without any help from our genes. Even today, a child's death can threaten the life of its parents.

Life can doubtlessly be even further extended by biomedical manipulation. But whether the *quality* of life can be comparably extended is less clear, and Ponce de Leon's dream is just a REM cycle away from a nightmare. Our dietary surfeit allows us to live long, healthy lives in which we can survive infection, trauma, and other forms of stress for decades, but pays us back later in the form of heart disease, hypertension, and diabetes. Grants are nutrition for scientists who are happy to feed the public hunger for a genetic life-extension Teflon so we can safely eat at will and smoke like chimneys. As the *Times* article noted, if such pills were available "The market would be huge." I have the image of force-fed insect queens and Sumo wrestlers, and that would not be all.

Against the Church's defense of an Earth-centered universe, Galileo observed that "Those who so greatly exalt incorruptibility, inalterability, etc. are reduced to talking this way, I believe, by their great desire to go on living, and by the terror they have of death. They do not reflect that if men were immortal, they themselves would never have come into the world." This personal nightmare suggests the real-world tragedy that, like an ET, lies within the womb of any Fountain-of-Youth dream. Because that dream incubates a Malthusian horror. Malthus estimated that unconstrained human populations were capable of doubling in 25 years, an annual growth rate of 2.5%, and Darwin calculated that a single pair of elephants, the slowest of breeders, would produce 19 million descendants in only 750 years (he was innumerate and changed his numbers in different editions of *Origin* but got them wrong anyway, so Figure 6 illustrates a growth rate of 2.5%).

That's assuming the elephants eventually died! The genetically engineered near-immortality often promised for the 21st century would be Malthusian growth without Malthusian checks. If we think 6 billion . . . 12 billion . . . 18 billion immortals on Earth would be paradise on Earth, even if it were possible, we're more deluded than Ponce de Leon. Maybe that was why the Amerindians met him when he arrived at the Florida coast in 1521 to resume his search for eternal life—and killed him.

We may yearn for immortality forever. But because of the way evolution works, there is no simple Fountain of Youth, and in the complex seasons of life, no eternal spring.

NOTES

I welcome comments on this column: kenweiss@psu.edu. I have a

feedback page at http://www.anthro.psu.edu/weiss lab/index.html where additional references can be found. I thank John Fleagle and Anne Buchanan for editorial assistance.

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