Endless Youth: The Fantasies, the Charlatans and the Science

What do vampires, Oscar Wilde and a lush mural decorating the wall of a posh Manhattan restaurant have in common? The title of this essay provides the answer. Each deals with a fantasy in which not only is death vanquished, so too is the aging process.

Popular culture seems to have, pardon the expression, an insatiable thirst for vampire tales. Vampires are capable of living indefinitely, but they may not actually enjoy endless youth. According to one “authoritative” source, “vampires do not age on a molecular/genetic level, but their life of hunting and eluding capture creates tremendous wear and tear in the form of injuries to bones and tissue” (the federal vampire and zombie agency–www.fvza.org/science2.html).

Literature has many examples of making a “deal with the devil.” Oscar Wilde’s The Picture of Dorian Gray is a variation on this theme, in this instance trading one’s soul for endless youth. The portrait’s living subject retains his youthful good looks while his portrait changes progressively, showing the ravages of age.

The Howard Chandler Christy murals that decorate the walls of the restaurant on 1 West 67th Street, formerly the Café des Artistes, now the Leopard at des Artistes, depict Ponce de Leon and his long-sought Fountain of Youth. In fact, the Spaniard was more likely searching for gold than for youth-restoring waters during his exploration of Florida, but the legend of his quest took hold, somewhat ironically, following his death. Descriptions of a fountain of youth go back at least as far as Herodotus, and are a recurrent theme in literature and art. The painting by Lucas Cranach the Elder may lack the lushness of the Christy murals, but its almost clinical depiction of the old transformed by a dip in the pool into stylish youths is unrivaled.

“Fountain of Youth” by Lucas Cranach the Elder, 1546, Staedliche Museum, Berlin.

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From this brief glimpse of just a few of the fantasies humans have created in their longing for endless youth, it is only a small step to the many ways in which some humans have tried to capitalize on that longing. Rather than just dream of a fountain of youth, why not bottle its magical waters and sell them for a handsome profit? Infused vitamin cocktails, assorted “supplements” and—a staple of many “anti-aging clinics”—hormone injections are just a few of the measures touted as preserving youthful vigor. Nir Barzilai, director of Einstein’s Institute for Aging Research, commented on treatments with testosterone, the “male” steroid hormone, and with human growth hormone in *U.S. News Health*: “What you have are a bunch of charlatans pushing treatments that not only don’t work, but are actually harming people. These kinds of treatments don’t slow aging, they accelerate it.”

Blood levels of several hormones do in fact decline with increasing age. The postmenopausal decline in estrogen in women is one of the best studied, but levels of testosterone also decline with age in some men, although generally more gradually. It seems logical to conclude that if endogenous levels of hormones such as estrogen and testosterone decline with age, replacing them would restore the beneficial, youth-preserving effects of these potent hormones. Although the FDA approved some forms of estrogen replacement therapy as early as 1941, the book *Feminine Forever* by prominent gynecologist Robert A. Wilson, published in 1966, ushered in a new era in which menopause was viewed as a disease whose ill effects could be prevented with estrogen. Wilson’s crusade, aided and abetted not only by the pharmaceutical industry but also by popular media such as *Vogue* and *Parade* magazines, promulgated the concept that short-term treatment with estrogen to relieve the vasomotor symptoms (hot flashes) of menopause was inadequate. Instead, indefinite estrogen treatment could keep women young forever and prevent heart disease, stroke, Alzheimer’s disease and osteoporosis.

All of these claims were based on what proved to be inadequate evidence from observational studies. The Women’s Health Initiative (WHI) is a multicenter, randomized controlled trial designed to test rigorously the benefits and risks of postmenopausal estrogen replacement therapy. Einstein was one of the major sites enrolling subjects in the WHI, and Sylvia Wassertheil-Smoller, principal investigator for the Einstein site, has written extensively about the findings of this ongoing study. The WHI investigators announced their first findings in 2002. Study subjects on estrogen replacement therapy actually showed an increase in the incidence of heart disease and breast cancer. Given the incessantly positive message promoting estrogen replacement therapy over the preceding decades, it’s little wonder that women and most of their physicians were confused by the WHI results. The conclusion that for many women, the adverse consequences of long-term hormone replacement therapy outweigh the benefits contradicted deeply held beliefs. Unsurprisingly, a cottage industry has sprung up taking advantage of this confusion, with the aggressive marketing of so-called “bioidentical hormones” being a prime example. The logic is that if something is “natural” and plant-derived, as opposed to synthetic, it can’t be bad for you and may be good. The occurrence in plants of some of the most potent toxins ever discovered doesn’t appear to perturb the belief system of these practitioners.

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Fantasies and charlatans aside, what’s sorely needed if we are ever to understand the biological phenomenon we term “aging” is rigorous scientific research. Fundamental questions about aging beg for an explanation. What, for example, accounts for the huge difference in longevity among various species? Is there a biologically determined upper limit to longevity of species, including humans? The last few years have seen research on aging move from the “backwaters” of science into a vibrant, if still often controversial, field. Much of the recent progress in understanding the biologic basis of aging has come from studies on “model organisms” such as single-celled yeast and multicellular invertebrates such as roundworms and fruit flies. The ease of genetic manipulation in these organisms and their brief life span facilitated identification of genes and molecular pathways that, when altered, dramatically affect life span. One of the most prominent pathways is that regulated by a hormone-like substance termed insulin-like growth factor (IGF). Reduced IGF signaling in worms and fruit flies extends life. That these findings are relevant to mammals is suggested by the observation that mice with defects in the same pathway also live longer. A single “spelling” difference in the gene encoding a specific IGF, termed IGF-1, explains the size difference between virtually all small vs. large dog breeds. Since IGF-1 mediates the actions of growth hormone, this discovery itself isn’t surprising. What is provocative is the inverse relationship between size and longevity in dogs.

Einstein scientists doing important research on the IGF-1 pathway include Howard Strickler and Robert Kaplan, whose epidemiological studies point to connections among increased IGF-1 signaling, heart disease and cancer, and Yousin Suh, whose genetic studies point to connections between reduced IGF-1 signaling and increased longevity in humans.

The IGF pathway that helps regulate fuel metabolism may also be relevant to studies showing that caloric restriction (CR) prolongs life in multiple species. It’s hard to extrapolate from studies of CR in worms, flies and even mice to humans, but it’s nearly impossible to test the effects of CR on life span in humans. In an attempt to test CR’s effects in more-relevant species, studies on rhesus monkeys were initiated 25 years ago. Early results showed beneficial effects of CR on a number of surrogate markers of aging, but in the most recently reported results, there was no increase in longevity. Definitive answers to the effects of CR in humans aren’t in, but that hasn’t prevented some people from forming societies and clubs devoted to lifelong caloric restriction. The operative word in the previous sentence is “some.” The overwhelming majority of people would prefer to take a pill that provides all the putative benefits of CR without the asceticism required.

A scientifically validated anti-aging pill has not yet been developed. Doing so will require a much deeper understanding of what underlies the aging process. Genetic studies in humans, not just model organisms, will help us gain that understanding. At one extreme are rare genetic diseases, such as progeria. A “misspelling” in a single gene leads to accelerated, premature aging, with subjects rarely living past the age of 13.
At the other extreme are centenarians, such as the Ashkenazi Jewish cohort studied in Nir Barzilai’s Longenity Project. By identifying gene variants that protect these subjects from dying of the usual degenerative diseases that kill most people in their eighties, seventies or earlier, he hopes to understand the biological basis of aging. This could lead to development of therapies that mimic the effects of the protective gene variants most of us lack.

Barzilai and his colleagues, Ana Maria Cuervo and Jan Vijg, have just been awarded a large grant from the Glenn Foundation for Medical Research to establish a Glenn Center for the Biology of Human Aging at Einstein. They will take a multidisciplinary approach to discover genetic and biological mechanisms that protect against human aging and age-related diseases. Cuervo, Vijg and other Einstein colleagues, such as Richard Lipton and Joe Verghese, are each leaders in their respective fields working on aging and age-related diseases. Their collective work, and that of their other Einstein colleagues, offers our best hope to move beyond fantasies and charlatans. We may never achieve endless youth, but we can certainly do much more to improve human health through science.

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