Evolutionary Anthropology 19:4–8 (2010)

The Fixed Period

Dystopic notions darkened post-Darwinian Britain

KENNETH M. WEISS

Anthony Trollope was a prolific and highly popular Victorian novelist (Fig. 1). As with soap operas today, the public eagerly awaited each monthly installment of his latest story to see what happened to whom: Did he marry her? Was it for love or was it the money? Did they live happily ever after?

Most of his books are light romps through marriage, money, status, and society. But in his last year of life, a somber Trollope penned his only fantasy, *The Fixed Period*,[1] a dark tale of a society in which people definitely did not live happily ever after. It is not a masterpiece, but it is relevant to issues we face today.

The events unfold in the fictitious Pacific island nation of Britannula, which has recently won independence from the British Empire. President Neverbend and his closest friend, one Gabriel Crasweller, have led the Assembly to pass a unique law that seemed to be in everyone's best interests. It would relieve the manifest suffering of the decrepit elderly while also relieving the younger generation of the economic burden of caring for them. The law established a retirement "college" where people would be "deposited" at a specified age: the Fixed Period. There they would be pampered for a year with every care and comfort. Then, in a glorious ceremony, they would be eased with morphine, placed in a soothing warm bath, and their veins lanced open to drain life peacefully away.

There are ironies here. Britannula's age of deposit was 67 years, judged to be a fair societal standard even though some individuals were still in fine fettle at that age. Trollope, himself in fine authorial fettle, died of a stroke in the year he wrote the book — at the age of 67 years. Another well-known Englishman, Charles Darwin, also passed from the scene in 1882. Darwin had been an avid reader of novels, including Trollope (www.darwin-online.org.uk), whom he admired for prolific persistence comparable to his own.[2] But he died seven months before Trollope, and couldn't have read *The Fixed Period*.

Trollope knew of Darwin, but felt himself so unscientific that he wrote in a letter: "I am afraid of the subject of Darwin."[2] Nonetheless, his work and Darwin's similarly described gradual rather than sudden change, be it biological or social. The harsh inequities of Darwinism stirred strong feelings in England. Trollope's was not the only dystopian writing of the period.

The Fixed Period is fiction, but the burdens of physical decline with age are very real. The burden of care is reflected by a measure called the dependency ratio, the number of elderly per each actively productive person in the population. With our low birth rates and extended survival, an increasing dependency ratio will become a predominant social theme. Coping with the inevitable societal strains will challenge scientists, politicians, philosophers, and anthropologists alike.

FALLING IN LINE TO FALL APART

Let's journey with Trollope into fantasyland and ask what Britannula's approach might imply for the human genome. Britannula's leaders solved the dependency ratio problem directly by imposing a fixed date for the end of life. That plan was nongenetic because, to be equitable, the departures were to be universally enforced at the age of 67 years. This would remove all genotypes without regard to their function. That's not the usual Darwinian idea that life is about adaptive dynamics among competing genotypes, with those that function best faring best. But it's not so different from what we have today. Although we might last longer in good shape than did our nineteenth-century ancestors, 67 years is generally past reproduction, and hence past most, if not all, fitness effects. Of course, genotypes that interred people before the Fixed Period would continue to be selected against in the usual way, even in Brittanula.

The kind of dream-world technology promised in the daily science news will be specifically tailored to prevent all disease and therefore rescue all genotypes we deem to be defective. That means that genotypes previously culled by selection would begin to accumulate in society. It may seem silly to discuss the long-term evolutionary consequences of new protections provided by modern civilization, but the concern is not new. Darwin worried about it in *Descent of Man*[3] in 1871, a decade

Ken Weiss is Evan Pugh Professor of Anthropology and Genetics at Penn State University. E-mail: kenweiss@psu.edu

DOI 10.1002/evan20249
Published online in Wiley InterScience (www.interscience.wiley.com).

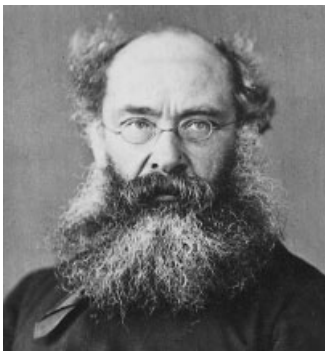

Figure 1. Anthony Trollope (1815-1882). Public domain.

before *The Fixed Period*. The same concern was central to the eugenics movement, started by Darwin's cousin, Francis Galton, which had a troublesome history over nearly a century.[4,5]

The relationships between life span and evolution can be subtle. Some species such as mayflies, which have an adult life span of less than a day, have synchronous generations, which leads to head-to-head competition for mates (though not for food, since adults are not able to eat). In a way, synchronous reproduction is non-Darwinian by being strongly conservative rather than innovative, because maturing too early or too late means that there is nobody to mate with. Developmental responses to the environment must stay within tight bounds. That's strong selective pressure to stand pat.

For simplicity, most evolutionary genetic models treat species as if they had synchronous generations, but of course mammals are not like that. Even those with fixed mating seasons, when competitive frenzy may be mayfly-like, we can live to compete in multiple seasons. Age at death may thus have been particularly important in the evolution of mammalian genomes like our own. That is why social policy related to how long one lives can affect selection, especially since males, at least, can continue to father children even at advanced ages. Primates add another aspect to the opportunity for selection by having small, often singleton litters, so that a barren mating season means a big proportionate loss of potential descendants.

The distribution of ages at death varies among mammals. However it's similar in closely related species, which suggests that longevity has been programmed by selection.[6] Believe it or not, the idea that there's a genetically evolved drop-dead age, called the Maximum Lifespan Potential (MLP), was once widespread and received bounteous research funding by NIH's National Institute on Aging (though I doubt that the bureaucrats had been inspired by Trollope). As I discussed here a few years ago,[6] an MLP always seemed evolutionarily nonsensical; it's clearly an abstraction, because it's an exact age, far beyond the reach of selection, at which almost nobody actually dies. And, like Britannula's age of deposit, it's an extreme value, which is a strange way to characterize biological traits, be they evolutionary or environmentally produced.

Various one-cause genetic reasons have been proffered to account for life span determination.[6] However, while any particular cause may contribute to aging, it can only be part of something more complex. Even if there had once been a genetic one-cause, the gene would have accumulated mutational variation over generations, resulting in a distribution of ages at death rather than a universal age of deposit. As it is, we each have our own genotype-specific calibration of the chronological age at which we reach relative wearing-out points on the aging scale. That is why we can say that some people are "young for their age."

Several specific genes have been found that affect the distribution, if not the certainty, of ages at which a given disease strikes, but there is genetic heterogeneity in every cause of adult death. Most disease risks rise with age, but that does not mean that they are functionally related to each other, because there are a lot of ways to increase over time. We may tick along at an overall rate related to our place in mammal phylogeny, but it's a highly probabilistic genetic clock, a rough evolutionary guide that tolerates large variability among us.

As a result, there is no single Fixed Period, and it's often been bleakly observed that when our time comes, we each must die alone. However, interesting recent findings suggest that our genomic fates are less lonely and more collective than we may have thought.

WHOSE GENOME?

Each of us is heavily infested with microbial tenants, including bacteria and a large chronic viral load.[7] We are hosts to an estimated ten times more bacterial cells than cells of our own. (That may seem implausible until you consider that our cells are much larger than bacteria.) Because we do not know how to culture most bacteria in the lab, we've not been able, until recently, to identify everything that is on or in us. But DNA sequencing technology is now making that possible.

Our microbiome, as it's called, can be characterized by sampling from various body tissues, extracting and sequencing all the DNA, and matching the sequences against those of known microbes (Fig. 2).[8] It turns out that our different organs are boarding houses for very different sets of guests, which vary among individuals as well. We've long known that some of our visitors, such as the *E. coli* in our gut, have always been vital to our survival. The rest seem generally benign, since the tested samples are from healthy individuals. But even if our microbiome does not leave us prostrate in bed, it does induce responses and affects our overall immune status, with implications that are not yet understood.[8]

It is not far-fetched to wonder whether studies of the genetics of aging, which consider only our own inherited genome, can be misleading. Since infectious and parasitic disease probably exert stronger and more direct selective pressure on genomes than most other factors do, the dynamics of interactions with our microbial ecosystem may have been important to longevity without having directly to do with longevity programming.

In autoimmune diseases like multiple sclerosis and juvenile-onset diabetes, our immune system is induced to attack our own tissues. The longer one lives and where one lives affect

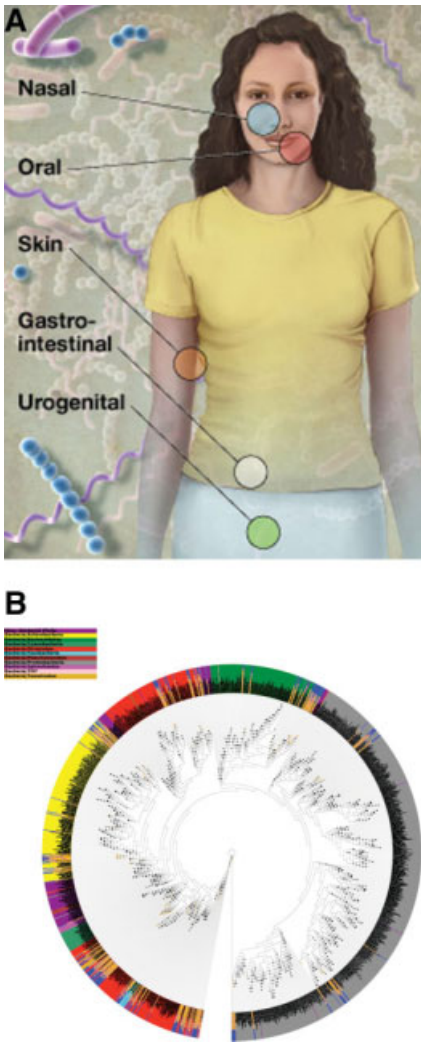

Figure 2. The NIH human microbiome project. A. Current body sampling sites. B. Phylogenetic tree of organisms identified to date, color coded by type, such as various bacterial subgroups. Details are unreadable at this resolution, but readable at the source, where site-specific data are also available. http://nihroadmap.nih.gov/hmp. (Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.)

the chance of being exposed to conditions that trick the immune system in this way. Chronic, slow-developing diseases of aging, the kind that affect adult survival and worried the Britannulians, may involve infection more than we have thought.[9] Variations in susceptibility to conditions ranging from obesity-related diseases, retinal deterioration, and bowel dysfunction involve the genetic response to inflammation.[10] That may even be true of some forms of psychosis.[11]

As far as microbiomial ecology goes, we may be helping bacteria to rapidly evolve antibiotic resistance, with obvious consequences for individual as well as collective health, regardless of any Fixed Period based in our intrinsic longevity.[12] Antibiotic-resistance genes are located on small DNA molecules that can transfer among bacterial species. Microbiome sequencing has found a plethora of antibiotic resistance genes in currently benign or quiescent pathological species. These genes are available for transfer to pathogens in our microbiomes that have been vulnerable to antibiotics. Multiple antibiotic-resistance strains are in fact showing up, for example in tuberculosis.

The immediate issue relates to pharmaceutically produced antibiotics used on us or our domesticated animals, but these bacterial communities and their transferable resistance genes were evolving long before Pfizer and Roche started urging the prolific use of their products. Indeed, the phylogenies of our invaders correspond to our place among primates, our biogeographic history, and our history of interaction with animals before and after agriculture. For example, retroviruses are capable of inserting a copy of their genes into our genomes, which are thereafter transmitted to our children (Wikipedia: retrovirus). They accumulate mutations as they go, which usually inactivates them; however, they occasionally evolve new normal human function. Today, the legacy of endogenous retroviral sequences comprises about 8% of our genomes, substantially more than our own actual genes do.[13]

By comparing the sequence variation in these sequences among individuals or species, we can estimate when they were inserted into the genome. In a recent example, a study of Malagasy lemurs found that a virus in the class that includes HIV was inserted into the genome of an ancestor of *Microcebus* lemurs around 4 million years ago, and that its mutated remains are present in multiple descendant species today. At roughly the same time, a separate event inserted the same virus in a different lemur genus, *Cheirogaleus*.[14]

We, our environments, and our miniature guests have traveled together during our evolutionary history. How directly this population ecology has affected our life-history characteristics, including fertility, how long we stay hearty, and how long we live, are subjects we can now begin to study systematically. But we don't really die alone: Our microbial guests live and die with us.

The microbiome is a source of variation relevant to fitness that throws sand in the eyes of natural selection, which might otherwise try to specify an inherited Fixed Period by screening the human genome alone. There also is another major source of genetic variation that is not inherited in the usual way and to which selection is therefore blinded, although it certainly affects how long and in what shape we live.

EVOLUTION IN CELLS AS WELL AS PEOPLE

Evolution is usually discussed in terms of the transmission of genomes from one generation of sperm or egg cells to the next, from your grandparents, to your parents, to you, and to your children. But things are rather different within each of us, in our somatic (body) cells. Their genomes evolve, too. That's where the aging that affects us as whole organisms actually occurs. We're composed of billions of semi-independent cells that undergo millions upon millions of divisions every day. There are vastly more somatic cell generations in each of us than there have ever been human germ-line transmissions in our history as a species. Each cell division is an opportunity for mutation, which, if not lethal to the cell, will in turn be transmitted to the cell's next generation within the body. The same advances in DNA sequencing technology that have enabled us to identify the cells we host is also being used to document this accumulating mutational damage in the hordes of our own cells.

Somatic mutation over our lifetimes leads cells gradually to lose the ability to behave appropriately or to

communicate with each other. That is one reason diseases in our different organ systems increase with age, accelerating our overall decrepitude and risk of death. No tissue or organ is immune to declining function of this kind. Cells lose their ability to divide or to repair damage, or they forget to stop dividing and beget cancers. Because in our bodies, as well as over evolutionary time, mutational changes are random relative to function, the mutational changes are different for every cell in every organ in every person. That is why the numbers add up differently for each of us, even for identical twins who start life with identical genomes. Environments also play a huge role in aging. In comparison, inherited variation mostly plays a bit part in this drama.

Together, these factors affect the absolute age at which each of us reaches a given physical state relative to any specified Fixed Period. For example, it has long been thought that diet and aging are related overall, beyond specific diseases like diabetes due to obesity. Reduced calorie consumption has been shown to increase the life span of experimental animals from worms to insects to rodents. That has led to predictions that the same must also apply to primates. Indeed, this has been confirmed in rhesus monkeys.[15] The longevity effect seems to involve a large set of genes in insulin-related metabolic pathways that are responsive to nutritional status, and hence to caloric consumption.[16] The mechanisms are shared among distant species and hence are phylogenetically ancient. They are directly related to survival, and thus are likely to have had more immediate and stronger fitness effects than do phenomena related to details of species-specific life span, and thus cannot, by themselves, account for such phenomena.

The rhesus story was highly touted in the media and may have scared some readers of the New York Times away from McFastFood's, at least for a while. But if calorie watching relaxes selection, the effect will be weak and distributed across a great many genes. Consequently, the main impact of such an anti-Britannulian behavior will not be genetic or evolutionary, but will simply lead to ever-larger populations of ever-slimmer people. They'll be older, too. However, the bedraggled look of the longer-lived, diet-restricted monkeys[15] seems anything but utopian, suggesting that there is a time to say farewell, and that a pleasant year in the Britannulian "college" might be a lot better!

EVOLVING A DEATH WISH

A strict Darwinian might expect organisms to evolve to die willingly after some Fixed Period, as mayflies do, making environmental room for their descendants. Should we expect humans to have evolved such a death wish, to be programmed to get out of the way when it's time to fall on our swords?

The Britannulians' policy was based on short-term societal burdens and only implicitly recognized this evolutionary duty to exit gracefully. We clearly do not have automatic mayfly genes, and one can only speculate as to why we stay around as long as we do.[6,17,18] Definitive evidence is difficult to come by, but there is no doubt we've at least evolved the ability to recognize the issues culturally, as the Britannulians did.

But what difference does it make? Evolution of traits like longevity is glacially slow relative to the lives of individual humans and our societies. Most evolutionary change takes thousands of generations. Whole empires and their cultural traits come and go much more rapidly. In the historical context, Augustus was Emperor of Rome only a hundred generations ago, and only 500 generations have passed since agriculture was invented. Things aren't nearly stable enough for programmatic societal attempts to control evolution, much less euthanasia in old age, to make sense. The long-term implications would be wholly unpredictable. To pull off anything more systematic would take something like direct, socially pressured, population-wide genetic rather than social engineering.

Surprisingly, this has in fact been achieved, at least on a modest scale, by premarital counseling and the like to remove frank, clearly genetic causes of disease and early death such as thalassemia, a form of anemia, in Sardinia, and Tay Sachs disease among American Jews. It's a new kind of benign eugenics that hopefully could be extended to other truly genetic diseases and could have long-term evolutionary consequences. However, most genetic disease strikes early so that such measures might not affect the way we wear out later.

CRUEL BRITANNULA, BRITANNULA WAIVES THE RULES!

Darwin's message of remorseless competition darkened the utopian dreams his century had inherited from the Enlightenment. But survival instincts are not intellectual decisions made with evolutionary eons in mind, even in intellectually advanced beings such as humans.

Because of his age, Neverbend's coconspirator Crasweller was due to be the first citizen to experience the prescribed idyllic exit. But as his date of deposit approached, he stared the death wish in the eye, then blinked. He began to find reasons why he should be an exception to the new rule. His relatives naturally agreed, and schemed with the British government, which sent a gunboat to Britannula, reseized power, and abolished the mortal law, somewhat as they have just done in the Turk and Caicos Islands. President Neverbend himself sailed off to England with the Royal Navy, where he blithely lived out his natural life, and penned *The Fixed Period* as his memoir. Thus, even Britannulians were unable to subordinate their personal interests to those of society. So much for utopian dreams!

We never know, except statistically, when our own date of deposit will come. The Britannulians approximated an age at which most people were worn out, but theirs was a social rather than biological cutoff. But let's suppose that biomedical technology is able to greatly extend life, even without limit.

In fact, science raced ahead despite the Darwinian gloom and did largely conquer most early mortality in developed countries. Focus has shifted to older age, and there have been substantial improvements there as well, thanks to advances in hygiene, nutrition, and medicine. Our lives now usually last well past

Figure 3. Pillar postbox, introduced to Britain (if not Britannula) by Trollope. Source: Photo in Oxford by R.K. Weiss, sent by cell phone (faster than Royal Mail). (Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.)

Britannula's 67 years, and relatively regardless of genotype.

This rapid progress clearly shows that an evolved Fixed Period is a biological fantasy and that the biomedical community is happy to proffer utopian life virtually without end, if only we give them big research grants. Driven by hope or fear, our belief in technology seems to trump the reasonable extrapolation that even if we do continue to extend life, we'll eventually end up suffering lengthened dysfunctional dotages before passing the scene. But if the day ever comes that genomic miracle workers do make good on their promises of indefinite healthy life, we may face the hell of Sartre's play *No Exit* (1944), full of vim and Viagra but stuck with each other forever in an increasingly overcrowded room.

Before becoming a famous author, Trollope had spent many years working for the postal service. Perhaps his most recognized contribution today is not his novels, great as they are, but that he introduced the ubiquitous red pillar boxes (Fig. 3) into which Victorians posted their many letters of love and business, confession and intrigue, about which he wrote so convincingly. He entertained but didn't change people. Euthanasia is unlikely to become a societal mandate any more now than it was in Britannula.

Society seems simply unable to talk rationally about the choking demographic fact of life; that is, while there may be no death without life, there can also be no life without death. Lest we envelop the earth in global trauma, the inescapable reality is that some form of control (besides denying care to the poor, as we do now) will be inevitable in our rapidly aging society. That may include extensions of the hospice system for the terminally ill, which, after all is not that different from Britannula's hospitable "college" except that it is voluntary. But to the extent that we are genetically programmed to strive to survive, it will be as difficult for us as it was for the Britanulians to accept any legislated date-certain life span. We don't want the lengths of our lives fixed. Period.

NOTES

I welcome comments on this column: kenweiss@psu.edu. I also maintain a blog on related topics at EcoDevEvo.blogspot.com. I thank Anne Buchanan, Alan Swedlund, and John Fleagle for critically reading this manuscript. This column is written with financial assistance from funds provided to Penn State Evan Pugh professors.

REFERENCES

1 Trollope A. 1882. The fixed period. London: Blackwood.

2 Levine G. 1988. Darwin and the novelists. Cambridge MA: Harvard University Press.

3 Darwin C. 1871. The descent of man and selection in relation to sex. London: J. Murray.

4 Carlson EA. 2001. The unfit: a history of a bad idea. Cold Spring Harbor, NY: Cold Spring Harbor Press.

5 Weiss KM. 2009. Boost, don't baste, "this prodigious number of children." Evol Anthropol 18:3–8.

6 Weiss KM. 2004. Ponce de Leon and the telomere of youth. Evol Anthropol 13:82–88.

7 Virgin HW, Wherry EJ, Ahmed R. 2009. Redefining chronic viral infection. Cell 138:30–50.

8 Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. 2007. The human microbiome project. Nature 449:804–810.

9 Ewald P. 2000. Plague time: how stealth infections cause cancers, heart disease, and other deadly ailments. New York: Free Press.

10 Manolio TA, Brooks LD, Collins FS. 2008. A HapMap harvest of insights into the genetics of common disease. J Clin Invest 118:1590–605.

11 Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460:748–752.

12 Sommer MO, Dantas G, Church GM. 2009. Functional characterization of the antibiotic resistance reservoir in the human microflora. Science 325:1128–1231.

13 Belshaw R, Pereira V, Katzourakis A, Talbot G, Paces J, Burt A, Tristem M. 2004. Long-term reinfection of the human genome by endogenous retroviruses. Proc Natl Acad Sci USA 101:4894–4899.

14 Gilbert G, Maxfield D, Goodman S, Freschotte C. 2009. Parallel germline infiltration of a lentivirus in two Malagasy lemurs. PLoS Genet 5:1–12.

15 Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW and others. 2009. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 325:201–204.

16 Narasimhan SD, Yen K, Tissenbaum HA. 2009. Converging pathways in lifespan regulation. Curr Biol 19:R657–666.

17 Hawkes K. 2003. Grandmothers and the evolution of human longevity. Am J Human Biol 15:380–400.

18 Charnov EL, Berrigan D. 1993. Why do female primates have such long lifespans and so few babies? *Or* life in the slow lane. Evol Anthropol 1:191–194.

Books Received

- Ford, S.M., Porter, L.M., Davis, L.C., Eds. 2009. The Smallest Anthropoids: The Marmoset/Callimico Radiation. Developments in Primatology: Progress and Prospects. 486 pp. New York: Springer. ISBN: 978-1-4419-0292-4. $199.00 (hardcover)
- Knight, J.C. 2009. Human Genetic Diversity: Functional Consequences for Health and Disease. 352 pp. New York: Oxford University Press. $80.00 (cloth)
- O'Brien, M.J., Shennan, S.J., Eds. 2009. Innovation in Cultural Systems: Contributions from Evolutionary Anthropology. Vienna Series in Theoretical Biology. 284 pp. Cambridge: MIT Press. ISBN: 978-0-262-01333-8. $40.00 (hardcover)
- Rees, A. 2009. The Infanticide Controversy: Primatology and the Art of Field Science. 304 pp. Chicago: University of Chicago Press. ISBN: 978-0-226-70711-2. $40.00 (cloth)
- Wells, J.C.K. 2009. The Evolutionary Biology of Human Body Fatness: Thrift and Control. 382 pp. Cambridge: Cambridge University Press. ISBN: 978-0-521-88420-4. $105.00 (hardcover)