cells? Evidence obtained by treating antigen-presenting cells in vitro with specific inhibitors suggests that cysteine proteases in general—and cathepsin S in particular—may be important in the periphery. Cathepsin S inhibition induces the accumulation of a partially proteolyzed fragment of the invariant chain in association with class II molecules and inhibits peptide loading (*4*, *5*). Nakagawa *et al.* (*6*) show that in thymus of normal mice, active cathepsin S is undetectable in cortical epithelial cells but present in thymus-derived dendritic cells and peripheral antigen-presenting cells, whereas active cathepsin L has a reciprocal distribution. Thus, the terminal stages of invariant chain degradation in thymic epithelium and in bone marrow–derived antigen-presenting cells appear to be mediated by different cathepsins.

Why should the critical invariant chain processing enzyme in thymic cortical epithelial cells differ from that in bone marrow–derived antigen-presenting cells? The range of self peptides presented to T cells undergoing negative selection in the thymus should be the same as those presented in the periphery, otherwise the potential for autoimmune recognition is high. Because the cathepsins, in addition to degrading the invariant chain, are responsible for generating the class II–associated peptides, it may be important for the proteases of the negatively selecting thymic medullary cells to be similar to those in the peripheral antigen-presenting cells. Such a restriction need not be imposed on the cortical epithelial cells mediating positive selection, where the only requirement is that a broad T cell receptor repertoire be generated. Thus, the biology of the system can be said to allow the difference in cathepsin L distribution, but the reason for it remains unclear. A further complexity is that an alternatively spliced form of the invariant chain, generally expressed together with the major form and called p41, incorporates a specific cathepsin L inhibitory domain (*8*, *9*). Does this domain regulate the activity of cathepsin L in the thymus or periphery? As is often the case, this important observation raises more questions than it answers.

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AGING

The Future of Human Longevity: A Demographer's Perspective

John R. Wilmoth

One of the greatest achievements of modern civilization has been the enormous reduction in human mortality. Life expectancy at birth, among early humans, was likely about 20 to 30 years (*1*). By 1900, the average length of life in industrialized nations had doubled relative to this historical extreme. Now, as we approach the year 2000, life expectancy at birth is around 80 years in Japan and a few other countries, and its rise continues unabated.

In recent decades, the populations of developed countries have grown considerably older, because of increasing survival to older ages as well as smaller numbers of births. Consequently, both legislators and the general public have begun to consider society's role in the support of this ever-expanding elderly population. In this new demographic context, questions about the future of human longevity have acquired a special significance for public policy and fiscal planning.

Demographers claim some expertise in predicting future mortality levels. Sometimes, their method of choice is a mere extrapolation of past trends. Biologists and others are often critical of this approach because it seems to ignore underlying mechanisms. But, in fact, this critique is valid only insofar as such mechanisms are understood with sufficient precision to offer a legitimate alternative method of prediction. Although many components of human aging and mortality have been well described, our understanding of the complex interactions of social and biological factors that determine mortality levels is still imprecise. Furthermore, even if we understood these interactions and wanted to predict future mortality on the basis of a theoretical model, we would still need to anticipate trends in each of its components.

The extrapolative approach to prediction is particularly compelling in the case of human mortality. First, mortality decline is driven by a widespread—perhaps universal—desire for a longer, healthier life. Second, historical evidence demonstrates that mortality has been falling steadily, and lifespan increasing, for more than 100 years in economically advanced societies. Third, these gains in longevity are the result of a complex array of changes (standards of living, public health, personal hygiene, medical care), with different factors playing major or minor roles in different time periods. Fourth, much of this decline can be attributed to the directed actions of individuals and institutions, whose conscious efforts to improve health and reduce mortality will continue in the future.

Predictions of future life expectancy by extrapolation yield values that are not too different from what is observed today. Recent forecasts by the U.S. Social Security Administration put life expectancy in 2050 at 77.5 years for men and 82.9 years for women, compared to 72.6 and 79.0 years in 1995 (*2*). These Social Security Administration forecasts are not true extrapolations, however, because they assume a slowdown in age-specific rates of mortality decline in the future. An independent study, based on a purely extrapolative technique, yielded more optimistic results (U.S. life expectancies at birth in 2050 of 84.3 years for both sexes combined) (*3*). Projections for Japan are only slightly higher (life expectancy at birth in 2050 of 81.3 years for men and 88.7 years for women, compared to 76.4 and 82.9 years in 1995) (*4*).

An important issue for consideration in forecasting mortality is the time frame—both the time frame of the data that form the input to an extrapolation and the time horizon of the projection itself. Although short-term fluctuations have been common, long-term mortality trends in industrialized countries have been remarkably stable. A serious yet common error is to extrapolate farther into the future than is warranted, given the length of the historical time series that forms the basis for extrapolation. When mortality decline slowed temporarily during the 1950s and '60s (in the United States and other developed countries), predictions that the rise in human life expectancy had come

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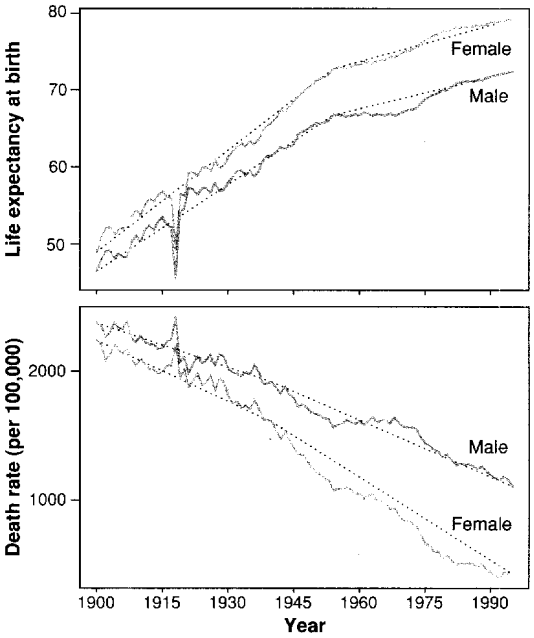
to an end were commonplace. Similarly, the unusually rapid decline of mortality rates after 1968 fostered expectations of unprecedented gains in longevity that would continue for decades. Quite simply, a projection based on less than 20 years of experience that extends 50 to 100 years into the future is imprudent, if not foolhardy.

Another common error results from an undue emphasis on trends in life expectancy. Although it continues to increase, the pace of change in life expectancy at birth has slowed in recent decades relative to the first half of the 20th century (see the graph). This observation, accompanied by an argument that predictions should be based on extrapolation, can lead to the conclusion that gains against mortality in the future will be slower than in the past. Although the increase in life expectancy has slowed down, the decline in death rates has quickened (see the graph).

These results are not contradictory. By definition, life expectancy is the average age at death for any group of individuals whose lifetime mortality experience mirrors that of the period in question. The decline in juvenile mortality in the early part of the 20th century had a greater effect on life expectancy at birth than the decline in old-age mortality is having today, for two reasons. First, the pace of decline in death rates during infancy and childhood was generally faster than anything observed to date at older ages. Second, and more important, because of the age pattern of human mortality risks (moderately high among infants and children, low in adolescence and early adulthood, rising rapidly after age 30), reductions in death rates among infants and children bring more dramatic improvements in the average length of life than do similar reductions at older ages. For example, saving an infant or child from death by infectious disease, who may then survive to age 70, yields a larger gain in life expectancy than saving a 70-year-old from heart disease, who may then survive for another decade. Thus, trends in life expectancy are deceptive, because they reflect age patterns of human morbidity and mortality as well as declines in underlying death rates.

In recent years, the extrapolative approach to mortality prediction has been challenged by assertions that future changes in average human life-span may come more or less quickly than in the past. The more optimistic view that life-span partly will increase rapidly in the near future is a result of the acceleration in rates of mortality decline among the elderly in developed countries during the past few decades (5). But from a historical perspective, this change is recent and should be extrapolated into the future with caution. If the new pattern persists for several more decades, it will then constitute strong evidence that the old trends have been replaced by new ones.

Another source of optimism about future mortality rates lies in the potential application of existing technologies (for example, nutritional supplements and reductions in smoking) or the unusual longevity of certain groups (such as Mormons and Seventh Day Adventists) (6). Such discussions may be a good way to improve health behaviors, but they are not so good at informing predictions, largely because this same sort of advocacy influenced past trends as well. For purposes of prediction, we need to ask whether future positive reforms in life-style are likely to be implemented faster or more effectively than were similar reforms in the past.



Life length. Although the rise in life expectancy slowed in the United States around the middle of the 20th century (top), the decline in death rates has accelerated, at least for women (bottom). As explained in the text, these results are not contradictory (*12*).

From time to time, technological breakthroughs provide another source of optimism about future mortality rates. Recently, the manipulation of a gene that halts the shortening of telomeres during the replication of human cells in vitro was a source of great optimism in the popular media, provoking rather extraordinary claims about the possibility of surviving to unprecedented ages in the near future (*7*). Talk of cures for cancer and vaccines against AIDS promotes similar hopes. Such discussions should not be dismissed as mere wishful thinking but should also be seen in historical perspective.

As wondrous as they may be, recent scientific advances should be compared, for example, to Koch's isolation of the tubercle bacillus in 1882—which provided confirmation of the germ theory of disease and led to a great flourishing of public health initiatives around the turn of the century—or to Fleming's discovery of the antibacterial properties of penicillin in 1928, an event that led to the antibiotic drug therapies introduced in the 1940s. Extrapolations of past mortality trends assume, implicitly, a continuation of social and technological advance on a par with these earlier achievements.

More pessimistic scenarios of the future course of human longevity are based on notions of biological determinism or arguments about practicality, yielding the now-familiar claim that life expectancy at birth cannot exceed 85 years (*8*). Some support for this view derives from evolutionary theory, which predicts a sharp rise in death rates in post-reproductive years, because deleterious genes operating at these ages have evolved with no opposition from the forces of natural selection. Existing theories say little, however, about whether this rapid rise in death rates is unalterable through human intervention (*9*).

In actual fact, current patterns of survival indicate that death rates in later life can be altered considerably by environmental influences, and there is little conclusive evidence that further reductions are impossible. Furthermore, trends in death rates and in maximal ages at death show no sign of approaching a finite limit (*10*). Nevertheless, although claims about fixed limits to human longevity have little scientific basis, a life expectancy at birth of around 85 years is within the range of values predicted by extrapolative methods for the middle of the next century. In contrast, more optimistic claims are typically much farther afield and would require a much larger deviation from past trends.

Extrapolation rides the steady course of past mortality trends, whereas popular and scientific discussions of mortality often buck these historical trends, in either an optimistic or pessimistic direction. History teaches us to be cautious. Pessimism about the continuation of mortality decline is not new, and earlier arguments about an imminent end to gains in human longevity have often been overturned, sometimes quite soon after they were put forth (*11*). On the other hand, dubious claims about the road to immortality are probably as old as human culture itself, even though they have not influenced official mortality forecasts as much as their more pessimistic counterparts.

Of course, extrapolation is not without its flaws. It could not, for example, have anticipated the rise of mortality in the former Soviet Union after 1990, the emergence of AIDS in certain populations during the 1980s, or the divergence of mortality trends between Eastern and Western Europe after 1960. However,

such observations are less an indictment of extrapolation than a demonstration that the greatest uncertainties affecting future mortality trends derive from social and political, rather than technological, factors.

Although imperfect, the appeal of extrapolation lies in the long-term stability of the historical mortality decline, which can be attributed to the complex character of the underlying process. This combination of stability and complexity should discourage us from believing that singular interventions or barriers will substantially alter the course of mortality decline in the future. In this situation, the burden of proof lies with those who predict sharp deviations from past trends. Such predictions should be based on theoretical results that are firmly established and widely accepted by the scientific community. Certainly, history can be overruled by a genuine consensus within the scientific community, but not by unproven theories, intuition, or speculation.

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13. I thank R. Lee, S. Horiuchi, K. Wachter, and J. Campisi for helpful comments.

EVOLUTION

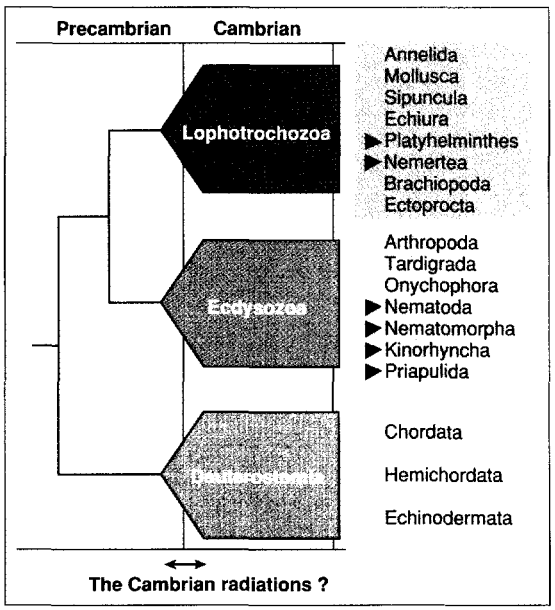
One or Three Cambrian Radiations?

Guillaume Balavoine and André Adoutte

The evolutionary phenomenon known as the "Cambrian explosion" was the sudden appearance of a modern-looking Burgess shale-like fauna with bilateral symmetry, early in the Cambrian period. This major event has increasingly attracted the interest of paleontologists and, more recently, of molecular phylogeneticists. Now, Aguinaldo *et al.* (*1*) have provided some striking new data that may allow a reinterpretation of animal phylogeny and may have a profound bearing on understanding of the Cambrian explosion.

The Cambrian bilaterians appeared shortly after the extinction of the Vendian Ediacara fauna. Vendian organisms have been described as triploblasts, diploblasts, or even multicellular organisms unrelated to metazoans (*2*). However, the few existing interpretations of some of these elusive organisms as direct relatives of the Cambrian triploblasts remain ambiguous (*3*), although trace fossils (*4*) and Precambrian embryos (*5*) suggest that triploblasts were likely to be present. What did the ancestors of the bilaterians look like, and why do they not appear more conspicuously in the Precambrian fossil record?

In traditional, morphologically based phylogenies, animals are divided into two-layered radially symmetrical animals and three-layered bilaterally symmetrical ones (or Bilateria). These Bilateria are further subdivided according to their internal organization: the Acoelomata, lacking a body cavity (mainly the platyhelminths and nemertines); the Pseudocoelomata (nematodes and some other minor phyla), which have a "primitive" internal cavity outside the mesoderm, presumably derived from the embryonic blastocoele; and the Coelomata, which have true coelomic cavities splitting the mesoderm. According to the traditional intellectual bias for increasing complexity in evolution, the acoelomates were seen as emerging at the base of the bilaterian family tree, followed by the pseudocoelomates and finally the coelomates, whose coelome allowed more complex body plans and larger sizes to evolve. These coelomates are further divided into protostome coelomates and deuterostomes, essentially according to the ontogenic origin of the mouth.



Watching an explosion. Divisions of the bilaterian family tree, showing three lineages of coelomates, among which the acoelomates and pseudocoelomates are scattered (arrows).

A new vision of the phylogenetic relationships between metazoan phyla has taken shape in the past 2 years through the investigations of the evolution of the 18S ribosomal DNA. Sequences are now available for almost all of the phyla, and a handful of recent reports, in good agreement with each other, now strikingly challenge the traditional views. In a consensual 18S ribosomal DNA tree, the Bilateria are divided in two large branches, the Deuterostomia and the Protostomia. The Protostomia are further divided in two new (and puzzling for many

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