

Towards a Molecular and Cellular Biodemography of Longevity

by
James W. Vaupel

Danish Center for Demographic Research, Odense, Denmark
and
Max Planck Institute for Demographic Research, Rostock, Germany

The term “biological clock” has been used in several of the presentations at this symposium, especially with regard to cellular aging. The term is a misnomer in that it misleadingly suggests a single, steady, orderly process of aging. The truth, as demonstrated by the research findings described at this symposium, is that there are multiple stochastic **ratchets** of cellular aging which involve telomere shortening, cumulative errors in nuclear DNA, increasing mitochondrial defects, mounting oxidative damage of various sorts, etc. These **ratchets**, however, appear to be only loosely coupled with lifespan (I will present evidence on this below). This is puzzling. The evidence from molecular and cellular studies of aging seems inconsistent with the evidence from biodemographic studies of aging. Research on the reasons for the apparent inconsistencies may yield important new insights. At the end of my presentation I point to some ways in which interdisciplinary research by molecular and cellular biologists working with biodemographers could prove fruitful.

For students of cellular aging it may seem astonishing that human mortality, even at the highest ages, appears to be quite plastic. Before 1950 improvements in survival

after age 80 were quite slow, but since then the pace of mortality reduction has been remarkable, especially since 1970 (Kannisto 1994 and 1996, Kannisto et al. 1994, Vaupel 1997, Vaupel et al. 1998). Let me illustrate this with several strands of evidence.

Mortality among female octogenarians fell from about 160 or 170 deaths per 1,000 in 1950 to about 80 deaths per 1,000 in 1995 in developed countries. This is shown in Figure 1 for France, Japan, and Sweden. There were also substantial, albeit less dramatic, improvements for males.

Major improvements in survival in developed countries have been achieved since the early 1950s for 60- to 100-year-olds. As shown in Table 1, annual average rates of improvement have been greatest among the younger elderly. For all these age categories, however, the pace of improvement has been comparable to and often greater than the pace of improvement at younger ages. Note that the greatest absolute improvements have been attained at the highest ages. When mortality is reduced, the number of deaths averted is proportional to the absolute decline. Although lives saved at advanced ages are generally not extended for more than a few years, the large absolute reduction in mortality among nonagenarians and centenarians is a remarkable achievement. Moreover, it is at sharp variance with the view that old-age mortality is intractable.

The substantial reductions in old-age mortality have resulted in a dramatic increase in the number of people who reach advanced old-age. In most developed countries, the number of centenarians is now growing at a rate of about 8% per year and roughly doubling every decade. This growth is largely attributable to reductions in mortality after age 80 (Vaupel and Jeune 1995). In developed countries there were 10 times as many centenarians in 1990 as in 1950 and 100 times as many as in 1850. Before

the eighteenth century centenarians were probably so exceedingly rare that in most countries in most years there may have been no instances of people who were 100 years or older (Wilmoth 1995).

An intriguing instance of the plasticity of old-age mortality has recently been found in female Mediterranean fruitflies (Carey et al. 1998). Medflies can successfully reproduce only when their diet contains protein, which is scarce in the wild. Laboratory medflies fed a diet with protein reproduce and die within 3 weeks or so. Medflies maintained on sugar and water live much longer. Death rates rise with age, but even in modest cohorts of only a few hundred individuals some survive for months. By day 90 remaining life expectancy is only a few days. But if nonagenarian medflies are given protein, their death rate falls dramatically and they start to reproduce. Mortality then rises rapidly and, like the medflies fed protein from emergence, they die within 3 weeks or so. Dietary protein on day 90 switches the medflies from survival mode to reproductive mode, which dramatically alters the subsequent trajectory of mortality. Aging is not programmed on an age-specific basis, but depends rather on whether the individual is in survival or in reproductive mode. Death rates, even at the most advanced ages, are highly plastic.

Caleb Finch, a participant in this symposium, has done extensive research on the plasticity of aging and longevity within and among species (Finch 1990). He has found that some species age very slowly whereas other species in the same genus age rapidly. He has also found that individuals in some species can experience very different rates of aging. Queen bees, for instance, live for years whereas worker bees, which have the same genome as the queens, live only a few months at most.

Students of cellular aging may also find it puzzling that mortality decelerates at older ages for all species for which large population cohorts have been followed to natural death (Vaupel et al. 1998). If each species had a characteristic maximum lifespan, governed, say, by some inexorable process of cellular aging, then survival would fall to zero at this age. Even for genetically-homogeneous cohorts of individuals reared under similar conditions, however, the survival curve gradually peters out, with no evidence for a cliff at some maximally attainable age (Curtisinger et al. 1992, Vaupel et al. 1998). For several species—including medflies, several other species of true fruit fly, a species of parasitoid wasp, perhaps yeast in stationary phase, and possibly humans—death rates actually fall at the most advanced ages.

These findings come out of the emerging field of biodemography, that is, out of conversations and research conducted jointly by biologists and demographers (Wachter and Finch 1997; Vaupel et al. 1998). Several people at this symposium—including Caleb Finch, Thomas Johnson, Michel Jazwinski, Thomas Kirkwood, and Claudio Franceschi—are involved in this endeavor.

It seems to me that cellular biologists in particular should start taking an interest in biodemography. It is clear from earlier presentations at this symposium that populations of cells—as well as populations of chromosomes and mitochondria within cells—are heterogeneous. These heterogeneous populations can be classified into sub-populations based on, e.g., telomere lengths, mitochondrial status, or nuclear DNA damage. The proportion of cells (or chromosomes or mitochondria) in different sub-populations changes stochastically with time (and age).

Demographers, according to a classic definition, analyze the structure and dynamics of populations. “Structure” refers to the classification of a population into sub-populations. “Dynamics” refers to stochastic changes over age and time in the proportions of the population in various sub-populations. That is, demographers are interested in and have the tools to think systematically about processes that are of direct relevance to the research of cellular biologists.

At this symposium, I have had the opportunity to discuss one such process with Judith Campesi, Calvin Harley, and Maarten Linskens. Telomere shortening depends on two stochastic, population processes involving the number of times a cell has divided and the cumulative loss of telomere material at the end of individual chromosomes. It is possible to develop a biodemography of telomere lengths and Campesi, Harley, Linskens and I may try to take a first step toward doing so.

Molecular biologists interested in how genetic polymorphisms affect longevity can also gain from collaborative research with biodemographers. Some such research— involving Claudio Franceschi and myself as well as Anatoli Yashin and others not present at this symposium—has already begun. If a genetic polymorphism increases the chance of survival to old age, then this polymorphism will be more common among the old than among the young. Hence, changes with age in the frequency of a polymorphism can shed light on how significant this polymorphism is for longevity.

Figure 1: Deaths per 1000 octogenarian women in France, Japan, and Sweden from 1950 to 1995. (Source: Adapted from Vaupel et al. 1998).

Table 1. Female central death rates in 1950-54 and 1990-94, the annual rate of improvement in these rates since 1950-54, and the absolute change in these rates since 1950-54 for sexagenarians, septuagenarians, octogenarians, nonagenarians, and centenarians in the United States, Japan, and the Northwestern European aggregation of Denmark, Norway, Sweden, and the Netherlands. Statistics for centenarians in the United States and Japan are not included because of concerns about data quality, especially for 1950-54. (Source: Own calculations from data in the Kannisto-Thatcher Oldest-Old Database, which is maintained at Odense University in Denmark and at the Max Planck Institute for Demographic Research in Rostock, Germany).

	Death rates in % in		Annual rate	Absolute
	<u>1950-54</u>	<u>1990-94</u>	of improve- <u>ment in %</u>	improve- <u>ment in %</u>
Sexagenarians				
United States	2.1	1.3	1.1	0.8
Japan	2.6	0.7	3.1	1.9
N.W. Europe	1.8	1.1	1.3	0.7
Septuagenarians				
United States	5.2	3.0	1.3	2.2
Japan	6.7	2.2	2.7	4.5
N.W. Europe	5.6	2.9	1.6	2.7
Octogenarians				
United States	12.3	7.6	1.2	4.7
Japan	16.4	7.5	1.9	8.9
N.W. Europe	14.8	8.8	1.3	6.0
Nonagenarians				
United States	25.9	18.8	0.8	7.1
Japan	34.2	20.5	1.3	13.7
N.W. Europe	31.9	23.3	0.8	8.6
Centenarians				
N.W. Europe	70.8	50.1	0.9	20.7

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