COMMENTARIES on “How is the evolutionary biological theory of aging holding up against mounting attacks?”

Commentary submitted by Drs. Leonid A. Gavrilov, Ph.D., and Natalia S. Gavrilova, Ph.D.
Center on Aging, NORC and University of Chicago


An interesting discussion piece "How is the evolutionary biological theory of aging holding up against mounting attacks?" by Dr. George Martin is an inspiration for many possible comments. Here we focus on one particular topic raised by Dr. George Martin -- the departures of mortality trajectories from the Gompertz curve -- a paradoxical phenomenon known in scientific literature as late-life mortality deceleration, mortality levelling-off, and late-life mortality plateaus.

In many biological species, including Drosophila and humans, death rates increase exponentially with age for much of the life span (the famous Gompertz curve). However, at extreme old ages a "mortality deceleration" occurs -- the pace of mortality growth decelerates from an expected exponential curve. Sometimes this mortality deceleration progresses to the extent that mortality "levelling off" is observed, leading eventually to a "mortality plateau." Thus at extreme old ages a paradoxical situation is observed when one of the major manifestations of aging -- increasing death rate -- apparently fades away or even disappears. This phenomenon represents a challenge for many theories of aging, including the evolutionary theories (as correctly mentioned by Dr. George Martin).

It is important, however, to put the discussion of "mortality deceleration" phenomenon in a historical context. Contrary to some recent outrageous claims, the phenomenon of mortality deceleration is not a new scientific discovery, but rather an old and well documented observation, which has been known for a long time. For an excellent historical review of studies on mortality deceleration at extreme old ages, we would strongly recommend an article by S. Jay Olshansky, "On the biodemography of aging: a review essay." Population and Development Review 24, pp. 381–393, 1998.

The first person who noticed that the Gompertz curve is not applicable to extreme old ages was Benjamin Gompertz himself (see Gompertz B., Philosophical Transactions of the Royal Society, 115: 513-585,1825; reviewed by Olshansky, 1998).

In 1867, another British actuary William Makeham noted that for humans "*the rapidity of the increase in the death rate decelerated beyond age 75*" (see page 346 in Makeham, W.M. 1867. On the law of mortality. Journal of the Institute of Actuaries 13, 325-358.).

In 1919, a British statistician J. Brownlee wondered whether it is "*possible that a kind of Indian summer occurs after the age of 85 years is passed, and that conditions improve as regards length of life*" (cited from page 385 in Brownlee, J. 1919. Notes on the biology of a life-table. Journal of the Royal Statistical Society, 82, 34-77).

Later in 1932, the British actuary W. Perks observed that "*the graduated curve [of mortality] starts to decline in the neighborhood of age 84*", and suggested to substitute the Gompertz law of mortality with a logistic formula (see page 15 at Perks, W. 1932. On some experiments in the graduation of mortality statistics. Journal of the Institute of Actuaries 63, 12-57).

In 1939, the British researchers Greenwood and Irwin published a research article, "Biostatistics of Senility," with the intriguing finding that mortality force stops increasing with age at extreme old ages and becomes constant (see Greenwood, M., Irwin, J.O. 1939. "The biostatistics of senility." Human Biology, vol. 11, 1-23). Their study and findings were considered to be so important that they were featured on the front page of the academic journal

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"Human Biology" where their study was published.

This study, accomplished by the famous British statistician and epidemiologist Major Greenwood, is directly related to the topic of this discussion. The first important finding was formulated by Greenwood and Irwin in the following way: "*...the increase of mortality rate with age advances at a slackening rate, that nearly all, perhaps all, methods of graduation of the type of Gompertz's formula overstate senile mortality*" (Greenwood, Irwin, 1939, p. 14). This observation was confirmed later by many authors (see review in Gavrilov L.A., Gavrilova N.S. 1991. The Biology of Life Span: A Quantitative Approach, NY: Harwood Academic Publishers), and it is known as the “late-life mortality deceleration.”

The authors also suggested "*the possibility that with advancing age the rate of mortality asymptotes to a finite value*" (Greenwood, Irwin, 1939, p. 14). Their conclusion that mortality at exceptionally high ages follows a first-order kinetics (also known as the law of radioactive decay with exponential decline in survival probabilities) was confirmed later by other researchers, including A.C. Economos ("Kinetics of metazoan mortality," J. Social Biol. Struct. 1980, 3: 317-329). Economos demonstrated the correctness of this law for humans and laboratory animals (linear decrease for the logarithm of the numbers of survivors). This observation is known now as the "mortality leveling-off" at advanced ages, and as the "late-life mortality plateau."

Moreover, Greenwood and Irwin made the first estimates for the asymptotic value of human mortality (one-year probability of death, q_x) at extreme ages using data from the life insurance company. According to their estimates, "*... the limiting values of q_x are 0.439 for women and 0.544 for men*" (Greenwood and Irwin, 1939, p. 21). It is interesting that these first estimates are very close to estimates obtained later using more numerous and accurate human data, including recent data on supercentenarians.

Interestingly, Greenwood and Irwin suggested the same explanation for mortality levelling off, as it was offered by Dr. George Martin in his "cocoon" hypothesis: "*With advancing years the disabilities, forcefully described by a large number of poets whom it is needless to quote, restrict activities. Even the juvenile of 60, if ordinarily intelligent, eschews the violent exercises of the child of 40. Centenarians rarely appear in public. A statistical rate of mortality might show no increase with age, if the demands made on the vital forces diminished pari passu with the decay of vigor.*" (cited from page 14 in Greenwood, M., Irwin, J.O. 1939. "The biostatistics of senility." Human Biology, vol. 11, 1-23).

In 1960, journal Science published an article on a "General theory of mortality and aging" that listed some *"... essential observations which must be taken into account in any general theory of mortality.*" (Strehler & Mildvan, 1960, p.14). The first of these essential observations was the Gompertz law of mortality, while the second essential observation stated that "*the Gomperzian period is followed by a gradual reduction in their rate of increase of the mortality*" (see page 14 in Strehler, B. L., & Mildvan, A. S. 1960. General theory of mortality and aging. Science, 132, 14-21).

Biologists and biogerontologists became well aware of mortality levelling-off since the 1960s. For example a biologist P.J. Lindop (1961) applied the Perks (logistic) formula in order to account for mortality deceleration at older ages in mice (Lindop P.J. Growth rate, lifespan and causes of death in SAS/4 mice. Gerontologia, 5: 193-208, 1961). George Sacher (1966) believed that the observed mortality deceleration in mice and rats can be explained by population heterogeneity: "*one effect of such residual heterogeneity is to bring about a decreased slope of the Gompertzian at advanced ages. This occurs because sub-populations with the higher injury levels die out more rapidly, resulting in progressive selection for vigour in the surviving populations*" (see page 435 in Sacher G.A. The Gompertz transformation in the study of the injury-mortality relationship: Application to late radiation effects and aging. In: P.J. Lindop and G.A. Sacher (eds.) Radiation and ageing, 1966, pp. 411-441, Taylor and Francis, London).

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This observation of mortality deceleration was confirmed in 1979 for several other biological species including Drosophila and nematode *C. elegans* (Economos, A.C. 1979. A non-Gompertzian paradigm for mortality kinetics of metazoan animals and failure kinetics of manufactured products. AGE, 2, 74-76). The author concluded "*...that after a certain species-characteristic age, force of mortality and probability of death cease to increase exponentially with age ... and remain constant at a high level on the average for the remainder of the life span.*" (page 74). The author called these findings "*a non-Gompertzian paradigm for mortality kinetics*" (Economos, 1979, p. 74). A year later the same author analyzed data for thoroughbred horses (mares), Dall mountain sheep, houseflies and some other species, and came to a conclusion that "*Gompertz's law is only an approximation, not valid over a certain terminal part of the lifespan, during which force of mortality levels off.*" (see page 317 in Economos, A.C. 1980. Kinetics of metazoan mortality. Journal of Social and Biological Structures, 3, 317-329).

Prior to 1990 the most popular explanation of mortality plateaus was based on the idea of initial population heterogeneity, suggested by British actuary Robert Eric Beard (1911-1983). Beard developed a mathematical model in which individuals were assumed to have exponential increase in their risk of death as they age (Gompertz law), but their initial risks differed from individual to individual and followed a gamma distribution (Beard, R. E. 1959. Note on some mathematical mortality models, In: *The Lifespan of Animals,* G. E. W. Wolstenholme and M. O’Connor, eds. Little, Brown, Boston). This model produces a logistic function for mortality kinetics that is very close to the exponential function at younger ages, but then mortality rates decelerate and reach a plateau in old age. This compositional interpretation of mortality plateaus explained them as an artifact of mixture, perhaps reducing their intrinsic interest to biologists.

The situation changed in 1991, when it was found that the general theory of systems failure (known as reliability theory) predicts an inevitable mortality levelling-off as a result of redundancy exhaustion, even for initially identical individuals (Gavrilov L.A., Gavrilova N.S. The Biology of Life Span: A Quantitative Approach, NY: Harwood Academic Publisher, 1991, 385p.). Thus, a testable prediction from this theory was that mortality deceleration should be observed even for genetically identical individuals kept in strictly controlled laboratory conditions. This prediction was confirmed later for inbred strains of Drosophila melanogaster (Curtsinger, J.W., et. al., 1992. Demography of genotypes: Failure of the limited life-span paradigm in Drosophila melanogaster. Science, 258, 461-463).

In conclusion, we agree with Dr. George Martin that the evolutionary theory of aging needs to be reconciled with many empirical observations, including the late-life mortality deceleration. In 2002, we reviewed the evolutionary theories of aging, and came to the following conclusion: "*Evolutionary theories of aging are useful when they open new opportunities for research by suggesting testable predictions, but they should never be used to impose limitations on aging studies. This is because the evolutionary “theories” of aging are not in fact completed theories, but rather a set of ideas that themselves require further elaboration and validation.*" (see page 353 in Gavrilov, L.A., Gavrilova, N.S. Evolutionary theories of aging and longevity. The Scientific World JOURNAL, 2002, 2: 339-356. Available: http://longevity-science.org/Evolution.htm).

Leonid A. Gavrilov, Ph.D., and Natalia S. Gavrilova, Ph.D.
Center on Aging, NORC/University of Chicago
1155 East 60th Street
Chicago, IL 60637-2745

Fax: (773) 256-6313, Phone: (773) 256-6359

Website: http://longevity-science.org/

Dr. Martin will respond to this commentary in our May issue.