

How is the evolutionary biological theory of aging holding up against mounting attacks?

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(This is an invited discussion piece submitted by Dr. George M. Martin. Responses to and discussion of this piece are invited from all readers of this Newsletter for publication in the next issue.)

I cannot imagine any theoretical construct more central to biogerontology than the evolutionary biological theory of aging (SN Austad, *Why We Age*, Wiley, NY, 1997). The theory applies to age-structured populations and to ecologies that dominated the early history of particular animal species. These early nature-nurture interactions shaped the genomes so that their life histories maximized reproductive fitness. In ecologies with high hazard functions, the more optimal life history would be one that involved rapid development, large numbers of progeny beginning shortly after the attainment of sexual maturity, and relatively short life spans. For the case of low hazard environments, a different life history strategy, one involving slower rates of development, longer periods of fecundity and longer life spans, might prove to lead to greater reproductive fitness. Tom Kirkwood's formulation invokes trade offs between the need for energetic resources for reproduction versus the need for energetic resources to maintain the soma (Kirkwood and Holliday, *Proc R Soc Lond Biol Sci* 205:531, 1979)

For species that evolved in either high or low hazard environments, all phenotypes that had not reached some significant level of expression until the latter part of the life span will have escaped the force of natural selection. This is because the bulk of the gene pool passed on to subsequent generations represent alleles from the very large group of young, actively reproducing individuals, not the very small group of rather rare old survivors. These alleles that escape the force of natural selection could be "good" alleles (e.g., those that code for more robust maintenance of homeostasis in the face of endogenous and exogenous injuries) as well as "bad" alleles (e.g., those that code for relatively inefficient maintenance of homeostasis).

Surprisingly, there was very little attention given to evolutionary biology at the many meetings on the biology of aging I attended during the 1960's, 1970's and for much of the 1980's, although there were a few of us who were impressed by the ideas of Peter Medawar. (The late George Sacher, incidentally, was singularly unimpressed.) A few of us knew about the famous 1957 paper by George C. Williams. But it was Tom Kirkwood and Robin Holliday in the UK and Michael Rose (UK, Canada and US) who brought the issues up forcefully in the late 1970's and 1980's. I particularly recall the participation by Tom Kirkwood and Michael Rose at a number of meetings on the biology of aging at about that time, including Tom's participation at the Santa Barbara Gordon Conference I chaired in 1979 (<http://sageke.sciencemag.org/cgi/content/full/2002/34/re4/DC4>). Michael's educational fervor prompted him (with Graves) to publish a paper entitled "What evolutionary biology can do for gerontology" (*J Gerontol* 44:B27, 1989). As Jim Vaupel pointed out at one of our meetings, however, when most gerontologists finally understood and accepted the theory (some forty years after Medawar), demographers began to question it! This was the result of the studies of Jim Carey and colleagues on medflies and subsequent related studies with other organisms (Vaupel et al., *Science* 280:855, 1998). Given extremely large populations, it became clear that there were departures from the Gompertz curves. Age specific mortalities declined in very old animals, something that had not been pre-

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dicted by the evolutionary biological theory of aging. My simplistic and probably naïve take on this controversy is that when animals become extremely aged, they stop moving around or flying and are therefore less likely to become injured. The evidence for declines in age-specific mortality in very old humans is less striking and could reflect secular trends in the institution of unusual interventions, such as central heating and air conditioning and immunizations against pneumococcus and influenza. Moreover, extremely aged human subjects also do not move around much and are therefore less likely to break their hips and die in the hospital from some antibiotic-resistant pneumonitis. I call this my “cocoon” hypothesis!

There had been, in fact, much earlier challenges. One idea had its inspiration in the work of engineers who had to calculate the times to failure of components of complex machines such as airplanes. Some argued that we too are complicated machines and that inherent deficiencies in design were sufficient to lead to aging and failure without the necessity of invoking evolutionary theories. But one could argue, as have the Gavrilovs, that such ideas are indeed compatible with evolutionary theory (Gavrilov and Gavrilova, *J Theoret Biol* 213:527, 2001).

The evolutionary theory predicts a polygenic basis for aging and the likelihood that multiple mechanisms are involved. Then how, many would ask, can the theory be reconciled with the mounting evidence that single gene mutations in worms, flies and mice can lead to enhanced life spans? And how to reconcile the fact that a single environmental intervention – caloric restriction – can enhance the life spans of so many species? My answer is that the gene actions involved in these interventions have certainly not escaped the force of natural selection. They evolved as types of diapauses to permit prolonged survival in times of environmental stresses that precluded successful reproduction. Such diapauses would be eventually trumped by the evolutionary biological theory of aging.

A growing number of scientists now believe that the evolutionary biological theory might be falsified by evidence that there have been behavioral phenotypes in grandparental generations that have not escaped the force of natural selection and that these phenotypes are seen even today among elders living among primitive tribes (eg., Kaplan and Robson, *Proc Natl Acad Sci USA* 99:10221, 2002). But we really do not know how many such elders survived among our ancestral populations and how effective the behaviors of those relatively few survivors might have been in enhancing the reproductive fitness of their grandchildren. Moreover, in experimental situations with mammals living in the wild, support for the “grandmother hypothesis” was lacking (Parker, Tatar and Collins, *Nature* 392:807, 1998).

The most recent challenge has come from a field biologist, David Reznick. I was delighted to have heard his presentation at the last meeting of the American Aging Association in St. Petersburg, Florida. He presented surprising data, in his work with different populations of guppies; the predicted relationship between environmental hazards and life span (at least for the case of predation) was not holding up. (David’s paper on the subject has just appeared) (Reznick et al., *Nature* 431:1095, 2004.) His conclusions are thus quite different from what emerged from Steve Austad’s classical research on Virginia Opossums (Austad, *J. Zoology (London)* 229: 695, 1993).

The fact that such an icon as the evolutionary theory of aging is under challenge is a tribute to the viability of our field. No theory should ever be immune from new challenges. I nevertheless continue to embrace the theory as “the best game in town”. Other views would be most welcome, however!

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(cont. on page 7)

Commentary submitted by Dr. Svetlana V. Ukraintseva Duke University

“Bad” in the Young – “Good” in the Old: Is This Consistent with the Antagonistic Pleiotropy Concept?



One of central ideas linked to the evolutionary theory of aging is the concept of “antagonistic pleiotropy”. The antagonistic pleiotropy of gene action is proposed by evolutionary biologists to be a mechanism explaining origin of “age-related” diseases with the post-reproductive age of onset (Lithgow and Kirkwood 1996). The idea is that genes, which increase fitness at the reproductive period, would be saved in evolution even if they show negative effects at old ages, such as increased risks of pathologies. For example, high estrogen levels observed in female organism during the reproductive period are profitable because they support fertility, and deleterious because they are associated with higher risks of some cancers later in life. Alleles associated with the high estrogen levels are supported by the natural selection despite their disadvantageous effects because majority of cancers have a substantial latency period and are clinically manifested far after the age of climacteric. Studies of estrogen show that pre-menopausal women, who were treated with oral estrogens, have an increased risk of breast cancer of about 30 percent after fifteen and more years of exposure (Steinberg et al. 1991).

George Martin (2002) suggested more comprehensive classification of gene actions that escape the force of natural selection and, hence, are responsible for senescent phenotypes. He proposed that not only initially “good” alleles with “bad” late effects are responsible for appearance of age-related diseases in evolution. Another mechanism could be that some, initially “bad”, alleles reach a phenotypic level of expression only in advanced years of life. Suppose, some allele is affected, and, as result, amount of normal protein is reduced. The effect of such protein deficiency may accumulate over time and manifest itself in a clinical disorder of old age. The author also suggested inappropriate up-regulation of good alleles in late life as an additional cause for increased risks of elderly pathology.

This, more sophisticated, approach, however, does not cover an intriguing situation, when initially “bad” alleles become “good” later in life and so help a person to survive old age and become centenarian (Ukraintseva 2000, Yashin et al. 2001).

The results of genetic studies of centenarians support the possibility of a positive change in vulnerability to diseases in advanced years. Several alleles known to increase risks of a common pathology at middle and old ages are more prevalent in centenarians than in younger individuals (Shachter et al., 1994; Galinsky et al., 1997, Mannucci et al., 1997; Benedictis and Franceschi, 1998; Pepe et al., 1998). For instance, a variant of ACE which predisposes to coronary heart disease is surprisingly more frequent in centenarians (Shachter et al. 1994).

Such counterintuitive accumulation of originally harmful alleles may be easier to understand if the biological role of respective alleles in survival is taken into account. Let us consider the guanine deletion/insertion polymorphism, 4G/5G, in the promoter of the plasminogen activator inhibitor 1 (PAI-1) gene. The 4G4G genotype is associated with higher plasma levels of PAI-1 and increased risk of athero-thrombosis and myocardial infarction in middle aged men. Unexpectedly, the frequency of 4G4G genotype is higher in centenarians than in younger individuals (Mannucci et al. 1997). This apparent paradox can be explained by different physiological effects of this gene on survival of old and oldest old individuals. The 4G4G genotype is associated with high blood coagulation and increased the risk of death at old ages. Such genotype, however, may become relatively advantageous at the oldest old ages, when a recovery from injury is slow. The oldest old people have commonly decreased blood coagulating factors and higher risk of dangerous bleeding. In this situation, inherently higher level of coagulation may help to stop bleeding and decrease risk of death in emergency cases. Similar consideration can be done in

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relation to alleles increasing blood pressure in middle life: If person with the high blood pressure survives old age, he (she) can then get an advantage from these same alleles at the oldest old ages when muscular atrophy develops and blood supply of a tissue becomes worse.

That is, elderly with initially harmful genotype who nevertheless survived a dangerous period of increased risk of death from a respective pathology, may gain an advantage from the same genotype at oldest old ages. Progress of medical care improves chances of such people to survive old age, and so their proportion increases among the oldest old favoring the observed increase in longevity and centenarian proportion.

The original concept of antagonistic pleiotropy (i.e., “good” effect in the young – “bad” effect in the old) also does not take into account the fact that the same gene product may favor risk of some disease and *simultaneously* suppress development of others. Indeed, high levels of estrogens (favorable for fertility) may not only increase risks of some cancers (IARC Monographs 1999), but also decrease risks of CVD and osteoporosis.

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Dr. George M. Martin’s response:



I am most grateful for Dr. Svetlana Ukraintseva’s excellent commentary on my article. She adds an additional class of gene action to my published list of six – namely gene actions that are relatively “bad” early in the life span, but that appear to be associated with enhanced disease resistance and survival late in the life span. A caveat, of course, is that such gene actions cannot have draconian negative effects early in the life course. If they did, they could not possibly have escaped the force of natural selection. Given sufficiently long time spans, genes with even modest fitness costs should disappear, unless they are part of an evolved balanced polymorphism or escape from the competition via migration as a founding gene isolate.

Dr. Ukraintseva’s comments really address a much more general situation. Gene actions are always a function of the context in which they operate. That context includes the genetic background of the individual, of course, as well as the extrinsic environment. But it also includes the intrinsic environment, something that is steadily changing during the life course.

Now is a good time to point out that, on theoretical grounds, one can add yet another class of gene action to my initial list. A few readers of this newsletter may recall that my list included genes that undergo “adaptive silencing” during some developmental landmark, such as puberty. Once that silencing is initiated, however, the process has a “life of its own”. There is no selective pressure to “put a brake on” the process during the latter portions of the life course. But there undoubtedly exist loci that are “adaptively up-regulated” in connection with some developmental switch. Once again, there would be no selective pressure to “turn down the burner” late in the life course, when such down-regulation might conceivably be helpful for survival.

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

Commentary submitted by Drs. Leonid A. Gavrilov and Natalia S. Gavrilova

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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 "Human Biology" where their study was published.

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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 Gompertzian 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).

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 manu-

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factured 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* (Curtisinger, 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>).

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Dr. George M. Martin's response:



Leonid and Natalia have given me a lovely reward for the effort of having written my little piece – a concise historical account of the literature on departures from the Gompertz formulation. I found myself thinking of what I was doing in 1939 when Greenwood and Irwin published their article in *Human Biology*. I recall that I was a 12 year old boy passionately interested in collecting free maps at the New York World's Fair, perhaps a prelude to my interest in mapping human genes that can teach us about the biology of aging and Alzheimer's disease. (In just another year or so, the adolescent hormones created new passions, however.)

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My conclusion, after reading this commentary, is that the American Aging Association should start a Committee on History and appoint Drs. Gavrilov and Gavrilova as Co-Chairs.

Commentary submitted by Dr. David Reznick

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I must agree with George Martin's statement that the traditional theories for the evolution of senescence are still the best game in town, but with some conditions. Before I define the conditions, I need to offer some background. My own results were derived from guppies (*Poecilia reticulata*) from natural populations in Trinidad where I knew from previous mark-recapture studies there were large differences among populations in mortality rate. Guppies that live with predators have much higher mortality rates than those that live without predators. The presence or absence of predators is often dictated by waterfalls that block the upstream dispersal of predators but not guppies, so these high and low predation environments can be found in close proximity to one another, in the absence of other differences in the environment. I also knew from previous work that the guppy populations are genetically different from one another and are adapted to their local environments. Guppies from high mortality rate environments mature at an earlier age, have more babies per litter, and reproduce more often. The traditional Medawar [1] and Williams[2] theories for the evolution of senescence predict that the guppies from high mortality rate environments should also start to senesce at an earlier age and should do so more rapidly yet, for the most part, senescence is slower and later in these fish relative to those from low predation environments[3]. These results began to unfold two years before the experiment was complete, so I had plenty of time to prepare myself for the difficulty of presenting the unexpected.

I reviewed the literature that deals with the evolution of senescence and found that a great deal has happened since Williams published his paper in 1957 and even since Kirkwood [4] published his first paper in 1979. There was a consistent trend of defining conditions in which the predictions from traditional theory would not apply, beginning with Brian Charlesworth's book on evolution in age-structured populations[5]. In spite of a rich diversity of hypotheses for when and why the traditional predictions would not be upheld, reviews of the evolution of senescence continued to deal almost exclusively with Medawar, Williams and Kirkwood, so these alternative ideas were not attracting any attention. I came to understand why this is. The alternatives tend to invoke complications that are hard to evaluate in nature and, in fact, have almost never been satisfactorily addressed, plus they obscured a beautiful, clear story that deserves to be true. There was also empirical evidence that they were true, coming primarily from laboratory studies of fruit flies[6], but also from some observations on natural populations, such as Austad's[7] classic work on opossums. When I was confronted by the unexpected, I felt that it was time to take these alternative ideas more seriously.

One alternative has to do with the population biology of the organism that is experiencing high or low mortality rates[5, 8, 9]. Theoreticians often model evolutionary processes by assuming that populations are growing exponentially, without any form of density regulation that would be imposed by limiting resources. Such models are often easier to work with, but lack biological realism. To make them more realistic, one often incorporates density regulation, or processes that cause population growth rate to slow, then stop as populations reach their carrying capacity. Density regulation can be caused by an increase in mortality rate, such as when food or shelter are in short supply. This increase in mortality rate may fall more heavily on some components of the population, such as the youngest or oldest individuals. Density regulation can also slow growth rate as resources become limiting, which can in turn cause an increase in the age at maturity or a decrease in birth rate. Any combination of these factors could apply to a

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particular population of organisms. Different populations or species could be regulated by different combinations of responses to density. When extrinsic mortality, such as mortality attributable to predators or disease, is imposed on such a population, then it can select for more rapid senescence, less rapid senescence, or no change in the patterns of senescence, depending on whether or not density regulation is present and on the combination of demographic changes that result in reduced population growth rate. This is what I was referring to when I said that the traditional theories are the best show in town, but with conditions. In this case, the conditions are the underlying demography of the populations that experience increased extrinsic mortality. My work thus does not disprove earlier results on opossums or *Drosophila*. It shows that those results are not universal.

I began the study of the evolution of senescence a few years ago as part of my interest in evolutionary biology. For me, a consequence of this work is that I am now interested in studying the demography of natural populations of guppies and to address the complexities that underlie the alternative models for the evolution of senescence. As I immersed myself in this field, I found that there are many very basic questions that remain to be answered. People have accepted the classical models because they make such good intuitive sense and because there is a modicum of data to support them. There is a wonderful diversity of alternative ideas that impress me as realistic (I review two others in my recent paper). There remain questions to be answered about issues as basic as how should one quantify senescence and by what criteria should one population or species be judged to have earlier or more rapid senescence than another. Finally, there is a wonderful diversity of organisms available for further study besides the classic model organisms.

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Dr. George M. Martin's response:



We can all be grateful to David Reznick for his insightful clarification of his position. His bottom line conclusion – that the traditional evolutionary theory is “the best game in town”, *but with some conditions*, should by now be accepted by our field.

Reading his comments about the impact of density regulation made me think about my experience with experiments on the proliferative declines of normal diploid human somatic cells in culture. While admittedly a very different model of aging, there are some intriguing parallels. First of all, simplistic models of exponential growth do not apply. There is enormous heterogeneity of growth rates, with subsets of cells exiting the cell cycle at all stages of the life history of the culture (Martin et al., *Am J Pathol.* 74:137, 1974; Abscher and Cristofalo, *J Cell Physiol.* 119:315, 1984). Secondly, a complicated phenomenon of clonal succession, first found in chromosomally marked cultures of cells from subjects with the Werner syndrome (Salk et al., *Cytogenet Cell Genet.* 30:108, 1981) may well apply to all normal diploid cultures. Thirdly, cell population density can substantially alter the response to a ubiquitous environmental stress – the oxidative stress imposed by the routine growth of cultures in ambient concentrations of oxygen (Balin, Fischer & Carter, *J Exp Med.* 160:152, 1984).

Getting back to the subject of David's commentary, my conclusion is that he should be encouraged to write a monograph on the subject. A critical update is long overdue.

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

Commentary submitted by Dr. Aubrey de Grey

Department of Genetics, University of Cambridge



George Martin provides a characteristically balanced, up-to-date, yet provocative survey of the status of the central tenet of evolutionary gerontology – the concept that the force of natural selection on any phenotype diminishes with the age at which that phenotype is manifest.

A few elaborations of what he writes seem merited, however.

First: Martin refers to but, surely only for lack of space, does not describe the concept of antagonistic pleiotropy (AP) (Williams, *Evolution* 11:398, 1957).

This idea – that some of the deleterious phenotypes not appreciably selected against because of their late age of expression might in fact be selected **for** because they arise from genetic variants that also produce beneficial phenotypes earlier in life – was for some time only tentatively supported by data, but it is now widely agreed that there are important examples of AP in nature, including in mammals. The 2002 report by Tyner et al. (*Nature* 415:45, 2002) is perhaps the most striking demonstration of AP reported to date: over-activity of p53 causes a robust resistance to cancer in mice but nonetheless reduces life expectancy by impairing highly proliferative tissues, implying that the phenomenon of cell senescence or apoptosis in response to DNA damage is a defence against cancer but is also, if done too assiduously, prejudicial to the survival of stem cell populations. In evaluating the possibility that a given result challenges the core evolutionary theory of aging it is always necessary to consider the possible role of AP in the system being explored, because even though AP is a refinement of, rather than an alternative to, Medawar's original insight it can profoundly influence predictions of how a population's aging will behave.

Martin notes the challenges to classical evolutionary gerontology raised by the reports from Carey et al. (*Science* 258:457, 1992) and others of the dramatic departures from the famous Gompertz relationship that are reproducibly observed in the last few percent of survivors of model organism (and indeed human) populations. Though evolutionary theory does not clearly predict an ever-accelerating mortality rate with age, it does at first sight seem to be inconsistent with a mortality rate that actually falls at extreme ages, as was reported by Carey. Remarkably, however, it turns out (de Grey, *Biochem Soc Trans* 31:452, 2002) that a deceleration in mortality rate increase, and even an eventual reduction in mortality rate with increasing age, can occur in a population within which each individual experiences the expected ever-accelerating mortality **risk** with age, simply because individuals differ in the parameters that describe the trajectory of that mortality risk (namely, the mortality risk at some convenient early age and the rate at which it increases). Thus, it is in fact unclear whether the observed shape of the “tails” of survival curves actually challenges classical evolutionary gerontology.

Martin also mentions the application of reliability theory to aging. I tend to agree with the Gavrilovs that this concept does not really merit description as a challenge to classical evolutionary gerontology.

Rather, I would say that it is a description of the same hypothesis in different terms – focusing on the typical sequences of somatic events that give rise to the selected (or not adequately selected) phenotype, while Medawar was concerned with the consequences of this viewed over evolutionary time. The diminishing redundancy discussed by the Gavrilovs (*J Theoret Biol* 213:257, 2001), for example, would naturally give rise to “late-onset phenotypes” when ob-

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served or described in terms of the behaviour of the whole system (i.e., the whole organism).

Finally, I would like to reinforce Martin's comments about caloric restriction and the various single-gene mutations that to some extent elicit the same range of phenotypes (including life extension). When Tom Johnson first reported such a mutation (*J Gerontol* 43:B102, 1988) there was considerable doubt concerning its compatibility with evolutionary theory. However, the overlap with CR that characterises nearly all the extended lifespan models in rodents and also the most extreme ones in worms has led to the appreciation that these mutations are more or less faithful phenocopies of a genuinely evolved character

– the ability to survive temporary food shortages (during which procreation is pointless, as progeny would starve to death) in a maximally youthful state. More detailed consideration of this evolutionary pressure (which, as Martin notes, is altogether distinct from the pressure to remove gene variants that predispose to rapid aging irrespective of environmental conditions) has recently led me to a rather pessimistic conclusion regarding the likely life-extension benefits of CR for humans (de Grey, *Gerontology* 51:73, 2005), even though I agree with the consensus that health benefits could be very substantial, as demonstrated by Fontana et al. (*Proc Natl Acad Sci USA* 101:6659, 2004).

In conclusion, I fully support Martin's overall conclusion that there are still numerous cases of data whose compatibility with traditional evolutionary gerontology requires careful analysis and which may even inspire refinements of that theory. In response to his comment that “no theory should ever be immune from new challenges” I would merely add that no challenge to a theory should be immune either (de Grey, *Med Hypoth* 62:1010, 2004).

Dr. George M. Martin's response:



Aubrey properly gives more attention to the notion of antagonistic pleiotropic gene action. It is a theme that will continue to survive. But I am surprised to hear some notes of pessimism from Aubrey. We are all depending upon him to elevate the level of optimism among us: yes, yes, there are things that we can fix!

Commentary submitted by Dr. David Harrison

Jackson Laboratory

I agree with Dr. Martin that it makes scientific sense to constantly refine our understanding of aging by challenging all its theories, including the evolutionary theory. While the evidence in favor of Darwin's general ideas of natural selection was strong more than 100 years ago, and has been continuously strengthened by scientific discoveries, some details by which evolution occurs are still unclear. One of these details is an explanation for aging, which occurs even though longer life would increase reproductive fitness by increasing the amount of time available for reproduction.

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

Current evolutionary theories propose that two kinds of genetic alleles cause aging, both causing deleterious effects only late in life (*Charlesworth, Genetica 91:11, 1993*):

(A) Alleles may have a selective advantage because they increase reproductive success early in life; this overbalances deleterious effects later in life, after the chances of survival are reduced (*Williams, Evolution 11:398, 1957*).

(B) Alleles may not be removed by natural selection simply because their deleterious effects only occur late in life, when few individuals survive, so the selective disadvantage is insignificant (*Medawar, 1952. An Unsolved Problem of Biology, Lewis, London, 1952; Hamilton, J Theor Biol 12:12, 1966*).

Substantial numbers of both kinds of late acting deleterious alleles are probably present in natural populations, since the force of selection declines with increasing chances of death before deleterious phenotypes are expressed (*Rose, Evolutionary Biology of Aging. Oxford U Press, NY, 1991; Partridge and Barton, Nature 362:305, 1993*).

Life spans are determined by the first critical deleterious genetic allele that acts, and that kills the organism. Since risks of nearly all causes of death increase exponentially with a similar slope starting in mid-life, simply removing one or two deleterious mutations would not significantly increase life spans. The potentially lethal effects of all or most deleterious late acting genes must be removed, or at least simultaneously postponed, to increase fitness by increasing life spans. Therefore, as Dr. Martin states, the facts that "single gene mutations in worms, flies and mice can lead to enhanced life spans" and "a single environmental intervention - caloric restriction - can enhance the life spans of so many species" appear to contradict the theory. How can these single mutations or food restriction postpone the actions of all potentially lethal deleterious late acting alleles?

Dr. Martin answers: "...the gene actions involved in these interventions...evolved as types of diapause to permit prolonged survival in times of environmental stresses that precluded successful reproduction." I agree. In fact, J. Archer and I gave a specific example of the selective advantages of retarding reproductive aging in response to food restriction: "After a drought outlasting the maximum female reproductive lifespan, a surviving female that is still able to reproduce could repopulate huge areas once weather conditions and food supplies became favorable."

We also pointed out: "This hypothesis predicts that the beneficial effects of food restriction will be greater in species with shorter female reproductive life spans. This is required because selective pressure for mechanisms that prolong life in response to food restriction is greater for species with shorter reproductive life spans. There should be more droughts outlasting maximum reproductive life spans, the shorter such life spans are." (*Harrison & Archer, Growth, Dev Aging 53:3, 1989*).

The fact that single mutations and food restriction increase maximum life spans in mammals gives hope for designing clinical anti-aging treatments. Even if diapause permitting prolonged survival in times of stress only occur in short-lived mammals, understanding their physiological and biochemical mechanisms may suggest clinical benefits for healthful aging in human beings. Here the evolutionary theory, the "why" is inadequate. We need the "how", the underlying biological mechanisms that allow single mutations or food restriction to postpone the actions of all critical deleterious late acting alleles.

Comparisons of dwarf or food restricted mice with normal controls have shown many factors affected by the mutation and treatment. One focus is the reduction in pituitary function that occurs in these cases (*Brown-Borg et al, Nature 384:33, 1996; Flurkey et al, PNAS 98:6736, 2001*) - and even more specifically, reductions in GH and thus IGF-1 (*reviewed in Tarter et al, Science 299:1346, 2003*). Other experiments also may uncover clinically useful mechanisms, for example defining alleles found in wild-derived inbred strains that increase maximum life spans (*Klebanov et al, Exp Biol Med 226:854, 2001*), and testing hypotheses that stem cell aging is specifically retarded by dietary restriction (*Chen et al, Exp Hematol 31:1097, 2003*).

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The fact that various mammals can adapt to stress with retarded aging also suggests that the physiological changes needed to retard the actions of all deleterious late acting genetic alleles are not complex. This is consistent with another hypothesis – that similar species with widely different life spans may simply differ in a few genes that regulate aging rates. Such genes may even vary within a species; this would facilitate adaptation to new conditions under which, for example, delayed reproduction and aging increase successful reproduction. Such genes may regulate the enormous species differences in mammalian life spans. A very few genes may regulate aging rates by telling the many deleterious late acting alleles when it is late, when it is time to act.

Similar pathologies in organisms with different life spans support this hypothesis. For example, aging mice, rats, and human beings have many similar cancers and other pathologies, despite a 30-fold range in aging rates. Perhaps many late acting deleterious genes from common ancestors cause the similar pathologies, but a very few genes regulating aging rates cause mice or rats to age 30 times more rapidly than human beings.

To adequately test this hypothesis, gerontologists should identify genes that greatly alter aging rates between similar mammals. For example, naked mole rats and mice are rodents of similar size, but the former age an order of magnitude more slowly. Gerontologists should test whether naked mole rats and mice differ in a very few regulatory genes. Research to answer this question may both improve our understanding of the evolution of aging and suggest clinical benefits for prolonged health and longer life.

Dr. George M. Martin’s response:



David Harrison makes numerous valuable points. The early insights he and his colleagues have had in understanding evolutionary biological implications of examples of diapauses are much appreciated. We have a great deal more to learn about Nature’s experiments with diapauses.

His last point, concerning the importance of variations in gene regulation in the shaping of alternative life histories, is particularly significant. My guess is that variations in structural proteins and in the catalytic efficiencies of enzymes have played a comparatively small role in the evolution of the modulation of longevity. “Tweaking” of gene regulation, leading to the speed of the response to macromolecular injury, for example, may prove to be more revealing.

Commentary submitted by Dr. Thomas B. L. Kirkwood

Institute for Ageing and Health, University of Newcastle upon Tyne

Never trust George Martin when he claims to offer a “simplistic and probably naïve take” on anything! “Naïve” and “George Martin” are terms that simply do not fit together.

George is absolutely right to point to challenges to the evolutionary theory of aging, and it is absolutely right that this theory should be challenged. No worthwhile theory is immune to challenge and it is only by repeatedly throwing awkward facts at it that we can test whether it deserves to survive.

Of the challenges listed by George in his discussion piece, each has played a part in testing and

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then ultimately strengthening the theory. The discovery of single gene mutations that increase lifespan was a particular surprise. However, what we now know is that such genes provide coordinate regulation of literally hundreds of downstream maintenance and repair processes (Murphy et al, *Nature* 424:277, 2003; Kirkwood, *Trends Endocrinol. Metabol.* 14:345, 2003). Rather than contradicting the evolutionary theory, it seems likely that we are seeing here is evidence of an additional tier of response to selection – the capacity to make short-term adjustments to altered circumstances, such as variation in food supply. This elaboration of the evolutionary theory can also account for the effects of calorie restriction (Shanley and Kirkwood, *Evolution* 54:740, 2000).

As for the apparent challenge to the evolutionary theory from the discovery of mortality plateaus, I agree completely with George that such plateaus are more likely to relate to behavioural changes or merely the mechanics of deterioration than to reveal some fatal flaw in the evolutionary logic. Mortality plateaus are interesting aspects of the biology of aging but they don't fundamentally alter our notions of why we age.

Menopause is an enigma. However, again it is one that can be accommodated within the evolutionary theory (Shanley and Kirkwood, *BioEssays* 23:282, 2001). The very fact that menopause is pretty much unique to women tells us something important about the special evolutionary circumstances of our species. Finally, David Reznick's intriguing data are just the thing to help us sharpen our evolutionary wits.

Life keeps evolving and so too must our understanding of the evolutionary basis of aging. Wouldn't it be exciting if we discovered some fact that made us rethink our ideas completely? Like George, I think this unlikely but we must keep our minds open to new developments.

I cannot think of George Martin at present without deep feelings of grief for the recent death of George's wonderful wife Julie. George, our hearts go out to you for your loss.

Dr. George M. Martin's response:



Readers new to this field of scholarship should first of all be informed that Tom Kirkwood has been among the most creative contributors to this story. That he is in agreement with essentially all of my major points is a source of great comfort to me.

I also thank Tom for remembering Julie Martin, who was my beloved wife for 52 years. Her death illustrates an important principle in gerontology – namely that, within a species, variations in the age at death may not be a valid measure of variations in rates of aging. Julie died of a glioblastoma multiforme, the result of a clonal proliferation of an aberrant glial cell. In all other respects, she was a remarkably “young” 76 year old woman.