What is aging?

Michael R. Rose1*, Thomas Flatt2, Joseph L. Graves3, Lee F. Greer4, Daniel E. Martinez5, Margarida Matos6, Laurence D. Mueller1, Robert J. Shmookler Reis7 and Parvin Shahrestani1

1 Department of Ecology and Evolutionary Biology, University of California, Irvine, CA, USA
2 Department of Biomedical Sciences, Institute of Population Genetics, Vetmeduni Vienna, Vienna, Austria
3 Joint School of Nanoscience and Nanoengineering, North Carolina A&T State University, UNC Greensboro, Greensboro, NC, USA
4 Department of Biology, La Sierra University, Riverside, CA, USA
5 Department of Biology, Pomona College, Claremont, CA, USA
6 Centro de Biologia Ambiental, Departamento de Biologia Animal, Faculdade de Ciencias da Universidade de Lisboa, Campo Grande, Lisboa, Portugal
7 Central Arkansas Veterans Healthcare System, Department of Geriatrics and Biochemistry/Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

*Correspondence: mrrose@uci.edu

Edited by:
John Tower, University of Southern California, USA

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John Tower, University of Southern California, USA

In 1991, the book *Evolutionary Biology of Aging:* a persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration (Rose, 1991). This definition has since been used by others a number of times. However, it was only a modest generalization of a definition proffered by Alex Comfort over three editions (1956–1979) of his key book *The Biology of Senescence* (Comfort, 1979): “a progressive increase throughout life, or after a given stadium, in the likelihood that a given individual will die, during the next succeeding unit of time, from randomly distributed causes.” The 1991 definition chiefly added reproductive fitness components to Comfort’s definition, while adding the qualifiers that the fitness-component decline should be persistent and should be “due to internal physiological deterioration,” where the latter phrase was meant fairly broadly. Thus increases in mortality with age due to chronic infections such as HIV/AIDS were excluded by the 1991 definition.

Yet another possibility remained, one that had been discussed in 1939 by Greenwood and Irwin (1939) in their article showing that human aging stopped demographically: lifelong heterogeneity. This is a concept that has been mathematically developed, particularly by Vaupel (Vaupel et al., 1979; Vaupel, 1988), but it is fairly easy to convey as a verbal argument. If a cohort consists of sub-cohorts that differ radically in their lifelong robustness, then the less robust will be eliminated early, leaving only the much more robust individuals. If these surviving sub-cohorts are robust enough, demographic aging should greatly slow at very late ages.

Many have looked for evidence of such an association between lifelong robustness and the cessation of aging (Khazaeli et al., 1998a,b; Drapeau et al., 2000; Mueller et al., 2005). It is possible to produce such a mortality-rate flattening by artificially constructing cohorts out of very different sub-cohorts (Brooks et al., 1994), but no one has yet found enough naturally occurring lifelong heterogeneity to generate demographic plateaus in age-specific mortality or fecundity (reviewed in Shahrzadi et al., 2009; Mueller et al., 2011). Indeed, there are good evolutionary genetic reasons to expect that such lifelong heterogeneity will rarely arise: natural selection.
will oppose the maintenance of such het-
rogenicity, whether it is due to genetic
polyorphism or extreme non-genetic
plasticity (Mueller et al., 2011, Chapter 7).
Natural selection instead favors the main-
tenance of genetic variation affecting fitness-
components when that genetic variation has
opposed effects at different ages, in other
words antagonistic pleiotropy, not lifelong
effects that are consistent in direction (Rose,
1985; Mueller et al., 2011).

Thus it appears that the cessation of
aging occurs at the individual level, and is
not just an artifact of population structure.
Yet this is clearly paradoxical, if we think
of the machinery of aging in terms of such
physiological processes as steadily cumula-
tive damage. If it is supposed that some pro-
cess of cumulative damage or disharmony is
supposed to underlie aging, why should
that process abruptly stop at the very point,
late in adult life, when it has greatly reduced
the ability of the surviving individuals to
sustain life and reproduction?

Mueller, Rauser, and Rose instead devel-
oped very different models for the evolu-
tion of late-life plateaus in mortality and
fecundity (Mueller and Rose, 1996; Mueller
et al., 2011), using the eventual plateaus in
Hamilton’s forces of natural selection as
their core explanatory principle for mor-
tality and fecundity plateaus late in adult
life. These formal mathematical models,
foundered in evolutionary genetics, show
that it is perfectly reasonable for natural
selection to produce late-life plateaus in
life-history characters, especially with finite
population sizes, once the forces of natural
selection have fallen to very low values. Of
greater significance for strong-inference
science, they further demonstrated that experi-
mental evolution can tune the timing of the
cessation of *Drosophila* aging in con-
formity with these theoretical results (Rose
et al., 2002; Rauser et al., 2006). Indeed,
the discovery that aging stops turns out to be a
powerful corroboration of Hamilton’s origi-
nal results for the forces of natural selection
(Hamilton, 1966; Mueller et al., 2011), all
the more dramatic because it was counter-
intuitive and hence unexpected.

These results call for some fundamental
re-thinking of what aging is. Twenty years
ago, evolutionary biologists imagined that
once Hamilton’s forces of natural selec-
tion reached zero, death should quickly fol-
low due to the absence of natural selection
opposing the effects of cumulative damage
and/or regulatory disharmony. Now at least
some have a very different vision (Mueller
et al., 2011). As Hamilton’s forces of natu-
ral selection decline during the first part of
adulthood, we might say that age-specific ele-
ments of adaptation are de-tuned. This de-
tuning in turn could be said to generate the
demographic phenomena of aging, as well as
the myriad physiological dysfunctions that
we know as the seemingly, but actually sec-
ondary, mechanistic foundations of aging. In
species with sufficiently severe antagonistic
pleiotropy between reproduction and adult
survival, such as Pacific salmon, soybean,
and mayflies, all members of a cohort may
die without either a well-defined period of
aging or late life, in the absence of human
intervention. But under sufficiently benign
environmental conditions, individuals from
species as disparate as humans and fruit flies
can survive a protracted aging period and
reach a subsequent late-life respite in which
fitness-component deterioration stops, a
phase permitted by the complete attenuation
of the forces of natural selection relative to
the effects of genetic drift.

The above results suggest that aging is
not inevitably a cumulative and unremit-
ting process of deterioration. Instead, aging
might be best conceived as a facet of adap-
tation, specifically its de-tuning during the
first part of adulthood. This de-tuning is
due to the steady declines in the forces of
natural selection that occur after the
start of adulthood in most populations.
Once those declines stop, aging eventually
cases, and adaptation stabilizes albeit at a
low level. There is little sign of a physiologi-
cal “momentum” that necessarily advances
aging until every member of a cohort has
died; nor is there any a priori requirement
for such constancy, despite the seductive
analog to Newtonian physics. An impor-
tant corollary is that many of the standard
biological intuitions about aging, particu-
larly those that associate it with the Second
Law of Thermodynamics, are not generally
valid. Some functional declines of physio-
logical characters continue into late-life, and
some even accelerate, whereas other func-
tional declines come to a halt (Shahrestani
et al., 2012). There is thus no scientific jus-
tification for assuming that each and every
type of physiological deterioration that has
been associated with aging must continue
without remit throughout late adult life.

This realization leads to another funda-
mental change in our thinking about “the
process of aging”; it is not actually a physi-
ological process, in and of itself. Although
it certainly involves physiological changes,
the physiology of aging is molded and con-
strained according to the dictates of natural
selection shaping adaptation. Some of the
generic foundations of adaptation serve to
sustain survival and reproduction later in
life, presumably because of age-independent
benefits (Charlesworth, 2001). Other fea-
tures of adaptation are apparently subject to
age-specific and pleiotropic genetic effects
which undermine age-specific mortality and
fecundity, together with their underlying
physiology, during middle adulthood
(Rose, 1991; Rose et al., 2002; Mueller
et al., 2011). In extreme cases of trade-offs
between survival and reproduction, contin-
ued adult survival may be wholly sacrificed
by natural selection, resulting in semelpa-
rous, univoltine, or annual life cycles (Rose,
1991). All these possibilities for patterns of
aging are permitted by evolution.

The evolutionary biology of aging
proposed in 1991 (Rose, 1991) provided
some warrant for allowing gerontologists
to conduct their research largely without
 evolutionary considerations. The falling
forces of natural selection were supposed
to ensure the cumulative and unremitting
physiological deterioration commonly
assumed by gerontologists. But now neither
that evolutionary rationale nor that type of
mechanistic thinking seem warranted, given
what we know of the cessation of aging. At
its very foundations, aging is a multifaceted
phenomenon that is a derivative feature of
the evolutionary biology of adaptation, *not
a single* physiological process, even though
adaptations generally involve physiology.

As such, aging is best studied in light of
the methodological strictures and theo-
retical scaffolding supplied by evolution-
ary biology. Some of those elements were
sketched in 1991 (Rose, 1991), but the
analysis offered then was far too simplis-
tic. We now know that aging is much more
complex than was understood then, both
genomically (Rose and Burke, 2011) and
 demographically (Mueller et al., 2011), and
it is inseparable from adaptation itself
(Rose, 2009). This makes it a hazardous
proposition to study aging without signifi-
cant attention to evolutionary genetics. An
evolutionary-genetic perspective on aging
raises several points of concern, including the difficulty of studying aging under conditions in which adaptation has been undermined or distorted, such as breeding regimes that create inbreeding depression, highly artificial genotype-by-environment interactions, and obscure evolutionary history (Rose et al., 2011). As aging is neither more nor less than the deterioration of adaptation with adult age, obscuring the features of adaptation by performing experiments with laboratory cohorts of an abnormally inbred and/or mutated strain with a poorly documented history of laboratory culture has created and will perpetuate significant difficulties of interpretation.

This vision of what underlies aging may be off-putting for some, given its theoretical complexities and difficulties for experimental design. No doubt many physicists felt the same way about the destruction of the elegant late nineteenth Century version of Newtonian mechanics by the advent of relativistic and quantum mechanics, in the period from 1905 to 1945. But paradigm transitions in science are generally like that, requiring that we abandon comfortable theories in favor of those that are significantly less wrong.

The genetics of aging cannot go on as it did before 1992. We need not jettison every lesson gleaned from past research, whether evolutionary or mechanistic, though conclusions reached under the quondam paradigm now require re-examination within our current, broader understanding. We will be able to salvage those parts that can be reintegrated within a scientific framework for the evolutionary genetics of aging, developed in light of its fundamental nature: de-tuned adaptation during the first part of adulthood. But a new evolutionary genetics of aging must now be built.

**REFERENCES**


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