UC Irvine
UC Irvine Previously Published Works

Title
PERSPECTIVE: THE EVOLUTIONARY BIOLOGY OF AGING, SEXUAL REPRODUCTION, AND DNA REPAIR.

Permalink
https://escholarship.org/uc/item/8482p1nb

Journal
Evolution; international journal of organic evolution, 47(5)

ISSN
0014-3820

Author
Avise, John C

Publication Date
1993-10-01

DOI
10.1111/j.1558-5646.1993.tb02155.x

Copyright Information
This work is made available under the terms of a Creative Commons Attribution License, availalbe at
https://creativecommons.org/licenses/by/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

EVOLUTION

INTERNATIONAL JOURNAL OF ORGANIC EVOLUTION

PUBLISHED BY

THE SOCIETY FOR THE STUDY OF EVOLUTION

Vol. 47 **October 1993** **No. 5**

Evolution, 47(5), 1993, pp. 1293–1301

PERSPECTIVE

THE EVOLUTIONARY BIOLOGY OF AGING, SEXUAL REPRODUCTION, AND DNA REPAIR

JOHN C. AVISE

Department of Genetics, University of Georgia, Athens, Georgia 30602

Abstract.—Three recent books on the evolutionary biology of aging and sexual reproduction are reviewed, with particular attention focused on the provocative suggestion by Bernstein and Bernstein (1991) that senescence and genetic recombination are related epiphenomena stemming from the universal challenge to life posed by DNA damages and the need for damage repair. Embellishments to these theories on aging and sex are presented that consider two relevant topics neglected or underemphasized in the previous treatments. The first concerns discussion of cytoplasmic genomes (such as mtDNA), which are transmitted asexually and therefore do not abide by the recombinational rules of nuclear genomes; the second considers the varying degrees of cellular and molecular autonomy which distinguish unicellular from multicellular organisms, germ cells from somatic cells, and sexual from asexual genomes. Building on the Bernsteins' suggestions, two routes to immortality for cell lineages appear to be available to life: an asexual strategy (exemplified by some bacteria), whereby cell proliferation outpaces the accumulation of DNA damages, thereby circumventing Muller's ratchet; and a sexual strategy (exemplified by germlines in multicellular organisms), whereby recombinational repair of DNA damages in conjunction with cell proliferation and gametic selection counter the accumulation of nuclear DNA damages. If true, then elements of both the recombinational strategy (nuclear DNA) and replacement strategy (cytoplasmic DNA) may operate simultaneously in the germ-cell lineages of higher organisms, producing at least some gametes that are purged of the DNA damages accumulated during the lifetime of the somatic parent. For multicellular organisms, production of functionally autonomous and genetically screened gametic cells is a necessary and sufficient condition for the continuance of life.

Key words.—Cellular autonomy, cytoplasmic genomes, immortality, recombination, senescence.

Received March 23, 1993. Accepted April 21, 1993.

The phenomena of aging and of sexual reproduction are surely among the most counterintuitive and puzzling of widespread outcomes to have evolved under the influence of natural selection. Why should individuals of most species senesce and die when Darwinian selection seemingly would favor any genetic predisposition for greater longevity and continued reproduction? And why should individuals engage in sexual as opposed to asexual reproduction, when by so doing they not only expend time and energy in finding a mate, but also dilute (by 50%!) their genetic contribution to each offspring? Evolutionary biologists have long pondered these issues, and the theoretical and empirical results recently have been summarized eloquently in three landmark books. This commentary will address primarily the contribution by Bernstein and Bernstein (1991) on DNA repair as it relates to the evolution of aging and sexual reproduction, but for useful background some comments first will be made about the important volumes by

©1993 The Society for the Study of Evolution. All rights reserved.

Rose (1991) on aging and by Michod and Levin (1988) on sex.

Aging

Under Rose's evolutionary definition, aging is "a persistent decline in the age-specific fitness components of an organism [survival probability or reproductive output] due to internal physiological deterioration" (Rose 1991, p. 38). The central thesis of Rose's book is that the mathematical framework of evolutionary genetics has solved the paradox of aging in age-structured populations by showing that the phenomenon is an inevitable outcome of the declining force of natural selection through successive age classes. Under the formal theory that Rose cogently summarizes, natural selection is simply indifferent to problems of somatic deterioration with advancing age, because as measured by effects on fitness (representation in successive generations) these problems are trivial compared with those that might appear earlier in life. Thus, aging and death exist not for any ineluctable physiological cause, but because of "a failure of natural selection to 'pay attention' to the problem" (p. 185). Particular genetic mechanisms of aging are not specified by this evolutionary theory, but two leading candidates for which explicit theoretical treatments are available are (1) *antagonistic pleiotropy,* in which alleles tend to evolve that have beneficial effects at early ages of life but antagonistic deleterious effects later, and (2) *age specificity of gene action,* in which alleles with age-delayed deleterious somatic effects accumulate in evolution simply because they are nearly neutral in terms of fitness because of weak selection in later age classes. Regardless of the means by which aging is played out from the basic evolutionary script, the take-home message is that "given age-structured populations and genetic variation in life histories, aging is a straightforward corollary of population genetics theory" (p. 16). This theory should apply to all organisms in which there is a clear distinction between somatic cells and germ-line cells.

Having established a conceptual primacy for the evolutionary theory of aging, Rose then chastises the field of gerontology for lack of this orienting foundation. For example, according to the evolutionary view, "the search for an ultimate physiological cause of aging is no more cogent than a search for a physiological cause of evolutionary adaptation would be. . . . This implies that one of the basic goals of gerontology, that of finding the physiological cause(s) of aging, is misconceived" (pp. 99–100). Rose provided extended reviews of the experimental evidence for several physiological theories for aging previously advanced (involving "wear and tear," rate-of-living considerations, hormonal influences, metabolic pathologies, and a host of others), and finds all to be wanting as universal explanations. Although many of these factors no doubt play proximate roles in the aging process, none provides the ultimate explanation for aging that is embodied in the evolutionary view.

From experimental findings as well as comparative aspects of aging across life forms, Rose concluded that there are multiple causes for aging and that these can be arranged hierarchically with regard to explanatory power. The ultimate (evolutionary) cause is the attenuation of the force of natural selection with respect to the age of gene effects in species with soma. At the penultimate level are the population genetic explanations of antagonistic pleiotropy and mutation accumulation, and at the bottom tier are the highly idiosyncratic molecular, cellular, and physiological pathways by which the genetic underpinnings of aging happen to have been executed in a particular population or species.

Rose's book is a seminal contribution because it provides one of the clearest, most coherent, and forceful documentations of why aging is not incompatible with natural selection after all. This new perspective should revolutionize the conceptual framework of gerontology, which as a discipline had remained one of the last bastions of biology relatively untouched by evolutionary thought. However, I don't quite share Rose's enthusiasm that this new theoretical orientation will revolutionize the day-to-day practice of gerontological research (any more than did Darwin's [1859] classic "On the Origin of Species by Means of Natural Selection, or the Preservation of Favored Races in the Struggle for Life" change the day-to-day practice of naming and describing species). Thus, an important empirical task in gerontology will remain the identification of particular molecular or cellular events involved in the aging process, idiosyncratic as they may be. This effort is especially important in humans or other species in which ameliorative efforts might then be contemplated. Furthermore, if the arguments by Bernstein and Bernstein (1991) (see beyond) are correct, Rose's sounding of the death knell for global molecular mechanisms underlying aging may have been premature.

Sex

Sexual reproduction entails the generation of new combinations of genes by the mixing of genomes, or portions thereof. In most evolutionary definitions, *sex* is synonymous with *genetic recombination,* although some authors emphasize usual components of the process, such as *physical recombination* (the breakage and reunion of two different DNA molecules), and *outcrossing* (the mixing of DNA molecules from separate individuals). Why should various mechanisms for genetic mixis have evolved so nearly universally across life? Michod and Levin's edited book brings together authoritative and stimulating contributions on this topic from most of the major architects of recent theories on the evolutionary significance of sexual reproduction.

These diverse hypotheses can be divided into two categories that are nearly opposite in orientation, though not necessarily mutually exclusive. The first category of theories perceives a benefit per se for sex, either at the immediate level of individual fitness or at the evolutionary level of group persistence. Thus, genetic mixis itself is the object of selection. Theories of this type are united by the theme that genetic variability arising from mixis and molecular recombination must somehow be advantageous in an ecological or evolutionary theater, such that the benefits to individuals (or perhaps to extended groups) outweigh the rather obvious and substantial costs of sex to individuals. Three advantages classically proposed for sexual reproduction are as follows: (1) to facilitate the incorporation of beneficial mutations into an evolutionary lineage; (2) to facilitate the removal of deleterious mutations (i.e., to overcome Muller's ratchet, the ineluctable process by which the mutational load in strictly asexual lineages can remain only the same or increase through time); and (3) to allow adjustments to spatial or temporal changes in the physical and biotic environment. Several chapters (by Bell, Crow, Ghiselin, Maynard Smith, Seger and Hamilton, Williams, and others) formalize and elaborate these hypotheses, all of which can rationalize the prevalence of sexual modes of reproduction. However, some of the arguments are less than fully convincing, particularly when it comes to proposed short-term benefits of sex that are required under a strictly individual-selectionist framework.

The second category of theories proposes instead that sex is a coincidental evolutionary byproduct of other primary consequences for mixis. For example, Hickey and Rose propose that sex is an outcome of subgenomic selection on parasitic DNA sequences that "imposed" biparental sexual reproduction on host genomes to favor their own spread. Another set of scenarios in this category (chapters by Bernstein et al., Holliday, Levin, and Shields) proposes that the evolution (and perhaps maintenance) of sexual reproduction involved selection pressures favoring mechanisms for the correction of genetic errors. This leads us finally to discussion of the *DNA repair* theory of sex and aging, as further elaborated by Bernstein and Bernstein (1991).

Aging and Sex as Related Phenomena

A fundamental tenet of the Bernsteins' theory is that damages to genetic material are a universal problem for life. These damages, defined as structural irregularities in DNA that cannot be replicated or inherited (unlike mutations), are of many types: single- and double-stranded breaks, modified bases, depurinations, cross-links, and so on. They arise inevitably from insults both endogenous and exogenous to the organism (e.g., oxidative damage from the molecular by-products of cellular respiration, and UV irradiation and DNA-damaging environmental chemicals, respectively). From empirical evidence, the cumulative numbers of such damages are astounding: for example, a typical mammalian cell experiences tens of thousands of DNA damages per day! These damages, if unrepaired, interfere with gene transcription and DNA replication and can cause progressive impairment of cell function and eventual cell death. The deterioration of somatic cellular function in turn leads to organismal senescence and death.

Damages to DNA can, however, be recognized and repaired by cells (though not necessarily at a rate that keeps pace with their production). Enzymatic machineries for repair of DNA damages are evolutionarily widespread, and their molecular details have been worked out to varying degrees in several model organisms ranging from viruses and bacteria to mammals. DNA repair processes almost invariably require the replacement of damaged genetic material through use of the intact information derived from a redundant copy. One source of redundancy is the complementary strand in double-helical DNA, which can serve as a template for repair when

damage is confined to a single DNA strand. For example, all known forms of excision repair that occur regularly in somatic cells involve removal of the damaged section from one DNA strand and replacement by copying from the complementary undamaged strand.

A second source of redundancy for repair is the presence of another duplex DNA molecule with information homologous to that of the original copy. Such undamaged template appears necessary for the *recombinational repair* of double-stranded DNA damage. The Bernsteins argue that the exchange of genetic information between multiple infective phages, as well as the process of transformation whereby some bacterial cells actively take up naked DNA from the surrounding medium, are examples of primary adaptations for DNA repair in these microbes. So too they argue is meiosis in higher organisms, which is viewed as an adaptation for promoting recombinational repair of the DNA passed on to gametes. In general, all mechanisms for molecular recombination are interpreted by the authors as evolutionary adaptations that originated *and* are actively maintained by natural selection explicitly for the functions they serve in recombinational repair of DNA damage. Furthermore, in diploid multi-cellular reproductive systems with recombination, the Bernsteins suggest that outcrossing is favored because it promotes the masking of deleterious *mutations*. Thus, "DNA damage selects for recombination, and mutation in the presence of recombination selects for outcrossing" (p. 277).

According to the DNA repair theory, aging processes resulting from DNA damage should occur in all organisms, and not just those with a clear distinction between somatic tissues and germ-line cells. There appears to be a conflict of opinion (or perhaps merely a semantic distinction?) about whether senescence occurs in unicellular creatures such as bacteria, and in vegetatively reproducing multicellular creatures such as some plants and invertebrate animals. Rose concludes that "species that unequivocally lack such a separation of the soma, such as some sea anemones, some protozoa, and all known prokaryotes, appear to lack aging" (p. 90). However, the Bernsteins suggest that although populations of cells may survive indefinitely (e.g., in clonally reproducing trees and bacterial colonies), nonetheless "one would not expect to find old cells in a tree any more than one would find old cells in a growing culture of bacteria" (p. 163). To account for the persistence of such asexual populations of cells, the Bernsteins also introduce the concept of *cellular replacement,* in which lethally damaged cells are replaced by replication of undamaged ones. This strategy should work in any cell population in which "the incidence of unrepaired lethal damages is low enough at each generation to permit replacement of losses" (p. 153). Thus, the Bernsteins propose that there are two possible pathways to immortality for a cell lineage: (1) recombinational repair of DNA damages (which applies to germ cells); and (2) cellular replacement (which applies to predominantly clonal cells as in many bacteria).

In summary, the joint pillars of the Bernsteins' theory are that aging is a direct consequence of the accumulation of DNA damage, and that sex where it occurs is a consequence of the need to transmit damage-free genetic information to progeny. The theory as presented does not imply that the production of allelic variation through recombination and outcrossing is unimportant for long-term evolution: "Infrequent beneficial allelic variants generated by recombination undoubtedly promote long-term evolutionary success, just as infrequent beneficial mutations do." Nonetheless, "the tendency toward randomization of genetic information that occurs with recombination and outcrossing, under general conditions, has a negative effect on fitness in the short run, just as mutations, in general, do" (p. 287).

I think that the DNA repair theory as expounded by the Bernsteins is extremely important for several reasons. First, it provides a conceptual framework for linking the widespread phenomena of aging and sex, two evolutionary subjects that more typically have been dealt with separately (as in the Rose and Michod and Levin volumes). Second, the theory appears both logically consistent internally, and eminently plausible empirically—at least as much so as many of the traditional theories on sex and aging. Indeed, much of the Bernsteins' book constitutes a detailed compilation of observations and experimental data that appear either consistent with or positively supportive of the DNA repair view. Third, the DNA repair theory envisions immediate selective advantages that apply to individuals and their offspring and not merely to longer-term group benefits.

Finally, the DNA repair theory represents a dramatic and refreshing (to me) conceptual departure from the more traditional evolutionary

theories of sex, which sometimes seem to go to rather great lengths in attempts to identify short-term benefits for the genetic variability generated by recombination. Under the Bernsteins' view, genetic variability is an immediate curse rather than a blessing, with any long-term benefits derived from recombinational variation being fortuitous epiphenomena of cellular and molecular processes that evolved under selection pressures to repair DNA damages and mask deleterious mutations. In this regard, I am reminded of the opposing world views on genetic variation expressed in another evolutionary arena—the debate between the selectionists and the neutralists. When extensive genetic variation was first uncovered in protein-electrophoretic and other molecular assays, many evolutionists assumed that the variability must be actively maintained by natural selection, and they sought hard to identify the balancing selective forces involved. But from the neutralist perspective [which grew out of the "classical" school in which genomes were perceived as heavily burdened by mutational load (see Lewontin 1974)], the overall magnitude of molecular variation was actually much lower than expected, given suspected mutation rates and effective population sizes. Thus, under the neutralist (and classicist) world views, if selection was involved appreciably in molding molecular genetic variability, it must act primarily in a diversity-reducing rather than diversity-enhancing fashion (Nei and Graur 1984).

Where does the DNA repair hypothesis fall within the hierarchical framework of causes for aging as advanced by Rose (p. 162, see above)? If correct, the theory cannot be placed at the bottom of the hierarchy as just another idiosyncratic physiological mechanism for aging, because it is general, and an explicit selective force is involved. Indeed, the hypothesis is in some respects more universal than that of the declining force of natural selection with advancing age, because it applies to all forms of life, including those without a clear distinction between somatic and germ cells. However, for organisms with soma, the DNA repair hypothesis does not appear incompatible with Rose's evolutionary view: the declining impact of natural selection with age would mean that any organismal benefits to accrue from DNA repair processes in the later cohorts of an age-structured population would provide insufficient selective force to circumvent the evolutionary appearance of senescence and somatic death.

Having heartily applauded the Bernsteins' contribution, I must add however that I seriously doubt it tells the whole story on the significance of genetic variation. Once recombinational processes had evolved (for whatever reason, of which the need for DNA repair must now be considered a leading candidate), it seems probable that the genetic variability thereby generated would have been exploited for other functions as well. For example, the extensive molecular variability in the repertoire of the immune response in higher animals is in part recombinationally derived, and undoubtedly fosters enhanced disease resistance that often must be of immediate fitness benefit. Furthermore, the increased genetic variance stemming from recombination might well allow sexual reproducers to outpersist asexual reproducers in changing environments, despite the fact that such explanations tend to be group selectionist. Finally, as emphasized by several authors in the Michod and Levin volume (e.g., Brooks, Felsenstein, Maynard Smith, Trivers, Uyenoyama, and Williams), rates and patterns of genetic recombination (and the linkage disequilibria that they entail) can vary remarkably: across different regions of the genome, between the sexes, temporally within the life cycle (e.g., in taxa with an alternation of generations between sexual and asexual modes), across populations and species, and spatially across habitats. Many of these differences have been interpreted as adaptive adjustments to varying selection regimes. As stated by Ghiselin (Michod and Levin 1988, p. 20), "The eukaryotic genome turns out to be very highly organized, and the whole apparatus shows every indication that the amount, kind, and timing of recombination, and also the release of variability, are adaptive. . . . [T]he DNA repair hypothesis suggests that there should be little correlation between what goes on and when and where it happens. Such a correlation definitely does exist."

Neglected or Underemphasized Topics

In any event, I would like to stimulate further thought and discussion about two general considerations that seemed grossly underrepresented in all three books.

(1) *Cytoplasmic genomes.*—There are two major reasons why a relative neglect of mitochondrial (mt) genomes in these volumes was surprising (similar sentiments could also be expressed about chloroplast DNA). First, in organisms as diverse as fungi and humans, else-

where there has been a tremendous resurgence of interest in the possible roles of mitochondrial DNA (mtDNA) damage in the aging process (e.g., Griffiths 1992; Wallace 1992a). In humans for example, this interest has been prompted by empirical findings that specifiable defects in mtDNA accumulate with advancing age in somatic cells, and that these defects tend to compromise physiological functions particularly in tissues and organ systems with high energy demands (e.g., the central nervous system, optic nerve, heart and skeletal muscle fibers, kidney, and liver). These are also the organ systems commonly associated with degenerative diseases and chronic illnesses of the elderly, thus suggesting a possible cause and effect relationship between mtDNA damage and the aging process (Wallace 1992b).

Further empirical and conceptual reasons exist for postulating that mtDNA might play a disproportionate role in aging. Mitochondrial DNA molecules are housed in an intracellular environment where they would seem to be especially prone to damage from oxygen radicals generated by oxidative phosphorylation (Bandy and Davison 1990). Indeed, mammalian mtDNA receives about 16-fold more oxidative damage on a per-nucleotide basis than does nuclear DNA (Richter et al. 1988, as quoted in Bernstein and Bernstein 1991). Yet ironically, animal mitochondria are thought to possess only limited DNA repair systems, and indeed this provides one conventional explanation as to why animal mtDNA evolves so rapidly at the nucleotide sequence level (Wilson et al. 1985). Animal mtDNA is packed tightly with genes crucial to the energy metabolism of cells, and for this reason, too, it would seem highly desirable for organisms to have evolved refined mechanisms for the repair of mtDNA damage. The paradox is heightened further because there are many copies of mtDNA within most cells. Thus it would seem that any repair capability should in principle be especially workable, because of the many available templates against which DNA damages might be corrected. (The hypothesis that an immunity from selection pressures stems from mtDNA redundancy and a possible excess metabolic capacity seems gratuitous and is also probably untenable evolutionarily.) Perhaps eukaryotic organisms *have* evolved more highly refined mtDNA repair mechanisms that, despite intensive searches, thus far have remained undiscovered. But if not, why not? And how can organisms have persisted evolutionarily without such enzymatic repair services for the crucial cytoplasmic genomes they depend upon for energy supplies?

A second reason for surprise over the relative neglect of mtDNA in these volumes relates to mtDNA's asexual inheritance. The transmission of mtDNA in most higher eukaryotes is predominantly uniparental, with effective genetic recombination between maternally and paternally derived molecules unknown. If meiosis and the recombinational aspects of gametogenesis provide evolutionary benefits, as surely they must (either via repair of DNA damages, and/or through generation of advantageous recombinational variation), then why doesn't mtDNA play by these rules? The entire answer cannot simply be that mitochondrial elements have been physically confined to the cytoplasm and hence unable to avail themselves of meiosis, because transfers and successful incorporations of some mitochondrial genes to nuclear chromosomes are known to have occurred over evolutionary time (see Avise 1991).

If meiosis is primarily a process for correcting DNA damages (as proposed by the Bernsteins), then mtDNA damages must be overcome by some process other than meiotic recombinational repair. One possibility is that mtDNA molecules might occasionally undergo (nonmeiotic) recombination or gene conversion within the germ line, perhaps in such a way that damage-free mtDNA templates correct faulty ones. The relatively few experimental attempts to uncover physical recombination in animal mtDNA through use of genetic markers have been hampered by the usual predominance of only one or a few detectable mtDNA clones within most individuals. More intensive searches for mtDNA recombination should be launched. Promising systems for further study involve species such as some mollusks, in which extensive paternal leakage of mtDNA into zygotes (e.g., Zouros et al. 1992) is known to have generated cell lineages jointly housing distinctive maternally and paternally derived mtDNA molecules that should provide useful genetic markers for detecting potential mtDNA recombination. Another possibility (elaborated beyond) is that processes of mtDNA replication and sorting during gametogenesis provide an alternative, strictly nonrecombinational pathway for circumventing the accumulation of genetic damages.

(2) *Cellular autonomy.*—Another issue that was underemphasized in these volumes concerns the evolutionary ramifications of varying degrees of cellular autonomy. The somatic cells of an in-

dividual usually are interdependent, both structurally and functionally, whereas gametes are relatively autonomous (except perhaps in rather "trivial" respects such as the collaborative efforts required of sperm in penetrating the eggs of some species). In other words, gametes tend to be cellular free agents, whereas somatic cells (particularly in tightly organized creatures with determinate growth, such as many higher animals) are trapped in a web of interdependencies. Crow (Michod and Levin 1988, p. 68) raised an important question: "Is passing through a single-cell stage itself important? . . . Starting with a single cell, sexual or asexual, permits each generation to begin with a tabula rasa largely unencumbered by the somatic mutations from previous generations." Crow went on to lament that "I have never heard the importance of going through a single-cell stage expressed before, and would welcome comments . . . as to its possible merits."

It seems to me that many of the fundamental distinctions commonly made in discussions of aging and sex—senescence versus immortality, sexual versus asexual reproduction, somatic versus germ-line tissue, unicellularity versus multicellularity, and individuals versus groups—are inextricably related, and might profitably be viewed through a common denominator revolving on the concept of cellular autonomy, as described next.

Embellishments to the DNA Repair Theory of Aging and Sex

Here I would like to propose some possible extensions to the Bernsteins' theory of DNA repair, and by so doing suggest how concepts of cellular and molecular autonomy might usefully be added to future discussions on aging and sex.

As mentioned above, two potential pathways to immortality seem available to life. The first is predominantly or exclusively asexual and is exemplified most clearly by unicellular organisms such as bacteria. Here, cell proliferation apparently can outstrip the rate of accumulation of DNA damages and deleterious mutations, with the net result that Muller's ratchet is circumvented and an indefinite continuation of the population occurs via cellular replacement. The second pathway is sexual and is exemplified most clearly by germ-cell lineages in multicellular organisms such as vertebrates. Here, repair of nuclear DNA damages by genetic recombination supposedly operates in conjunction with cell proliferation and intercellular selection to counter the accumulation of nuclear DNA damages and deleterious mutations that would otherwise be expected.

In both routes to immortality, many cells (bacteria or gametes) may die genetic deaths (e.g., from the inevitable imperfections of any DNA repair mechanism), but these deaths do not compromise the continuance of cell lineages that happen to have escaped or repaired DNA damage. Thus, the efficacy of both pathways to immortality would seem to depend critically on the autonomy of the proliferating cells. To emphasize why this is so, consider the prospect of somatic immortality for a multicellular organism such as a vertebrate. Even if some somatic cells and tissues could keep pace with DNA damage via the nonsexual strategy of cellular replacement [as may essentially be true for epithelial cells of the digestive tract of mammals, or for hemopoietic stem cells (Bernstein and Bernstein, p. 165)], these replacements are to no avail in conferring immortality, because the final fate of these cell lineages remains inextricably tied to the remainder of the individual's soma (which as a whole inevitably senesces, as predicted by Rose's evolutionary theory). However, autonomous gametes and the genomes they contain *can* escape the sinking somatic ship.

This line of reasoning also illustrates the difficulty (semantically and otherwise) of disentangling the issue of immortality from that of the distinction between somatic and germ-line cells. Without the presence of somatic tissue, the evolutionary theory of Rose predicts no age-structure in a population, and hence no aging; but without aging, there is no compelling evolutionary stimulus for the escape of autonomous cells from a soma that inevitably deteriorates (either from DNA damage or other causes). These ruminations also point out why the distinction between an individual and a population can become rather vague in discussions of aging and immortality in unicellular taxa. A bacterial colony may survive indefinitely, but without a distinction between somatic and germ cells, what is the organismal entity to which this immortality refers? In truth, what persists are certain cell lineages, but in this sense the "individuals" or "populations" are no more well defined than are the potentially immortal germ-cell lineages in higher taxa. Furthermore, many bacterial cells inevitably die genetic deaths; but without somatic benchmarks to assess chronological age, it is debatable whether this should properly be referred to as an "aging" phenomenon.

In many plants and invertebrate animals with various asexual modes of reproduction, the usual distinctions between individuals and populations, between somatic lines and germ lines, and between aging and immortality, all become even more ambiguous (Rose). For example, vegetative cell lines of some plants can be maintained indefinitely (perhaps by the strategy of cellular replacement), whereas others appear to senesce (perhaps because cellular replacement cannot keep pace with DNA damage). The former might well be considered potentially immortal, but according to Rose they do not violate the evolutionary theory of aging because specification of germ-line tissue in these cases is problematic. Whether this is a definitional slight of hand or a bona fide consideration is unclear to me, but in any event a more critical factor may be degree of cellular autonomy displayed. Diploid cells or collections thereof that have a capacity to survive and reproduce mostly independently of other cells exhibit considerable cellular autonomy (by definition). Thus, to a vegetatively spreading plant or coral, death of a portion of the "soma" may have relatively little influence on survival and reproduction of the remaining cells of the genet (a given clonal genotype, regardless of how it is physically partitioned). This contrasts with the situation in vertebrates, in which the death of a critical tissue dooms all somatic cells within each well-demarcated individual. Thus, any cell lineages characterized by increased levels of functional and replicative autonomy carry the potential for indefinite evolutionary persistence. Whether this potential could be realized then depends on additional factors, including whether the available processes of cellular repair and replacement are adequate to control DNA damages and to circumvent Muller's ratchet.

One important consideration on whether such cellular processes are workable indefinitely concerns genomic size. Formal models indicate that Muller's ratchet may well set an upper limit on the size of the genome in asexual organisms, particularly when their populations are small (Crow, Felsenstein, and Maynard Smith in Michod and Levin 1988). Bell notes that the small size of mtDNA molecules in higher animals (≅ 16 kilobases) may be a reflection of Muller's ratchet, and furthermore the somewhat larger mtDNA molecules of yeast and plants "would have to recombine in order to maintain the integrity of their genomes, as seems to be the case" (p. 130). From this perspective, nuclear genomes are vastly too large for long-term effectiveness of a cellular proliferation strategy acting alone to compensate for accumulation of DNA damages and deleterious mutations, hence the additional requirements for sexual reproduction and recombination. Crow and others have regarded this as an important factor accounting for why species with obligate parthenogenesis or other forms of asexual reproduction "are the twigs on the phylogenetic tree, not the main stems and branches" (p. 59).

I would like to propose that elements of both the recombinational repair and replacement strategies are employed simultaneously within the germ-cell lineages of higher organisms. Under this view, recombinational repair helps purge the nuclear genome of DNA damages, and a molecular-level analogue of cellular replacement ("molecular replacement") facilitates the purging of both DNA damages and deleterious mutations in nonrecombining cytoplasmic genomes. The immediate effect of these collaborative processes is to increase the probability that at least some gametes are produced that are free from genetic defects that had accumulated during the lifetime of the parent. In turn, the zygotes and early embryos produced by such "cleansed" gametes have a higher initial likelihood of being unburdened from the load of parental DNA defects.

The molecular replacement process is proposed to operate through the replicative segregation of mtDNA molecules in the lineages of germ cells (particularly oocytes). Unlike nuclear genes in diploid organisms, each of which exists as a single allelic copy per gamete, thousands of mtDNA molecules populate most cells, and several hundred thousand copies may cohabit a mature oocyte (Michaels et al. 1982). As cells undergo mitotic or meiotic cytokinesis, particular mtDNA mutations may fluctuate in frequency because of intracellular selection (differential replication) and genetic drift. Notably, the many mtDNAs in mature oocytes probably stem from a vastly smaller pool of mtDNA molecules that survive the process of replicative segregation in earlier cytokinetic divisions of the germ-cell lineage. Evidence for this conclusion comes from the empirical generality that the vast majority of the heterogeneity in mtDNA genotypes is distributed among rather than within individuals [implying relative mtDNA population bottlenecks in germ lines (Chapman et al. 1982)], and from observed rates of mtDNA clonal sorting in the gametes and progeny of heteroplasmic females (review in Avise 1991). In any event, mtDNA molecules that survive and replicate to

populate a mature oocyte presumably have been rather scrupulously screened by natural selection for replicative capacity and functional competency in the germ-cell lineages they inhabit.

To the extent that these two damage-repair processes (recombinational repair of nuclear DNA, and molecular replacement of cytoplasmic DNA) fail during gametogenesis, the metabolic functions of some germ cells will be compromised, and there will be gametic deaths. These gametic screening processes would appear to have considerable scope and impact, for at least two reasons. First, germ-line cells are highly active metabolically (Hastings 1989), such that any functional defects likely would be exposed to cellular-level selection. Second, gametes are produced in prodigious quantities by most species (e.g., males produce billions of sperm, and the number of oocytes present in a human female at birth is approximately 2,000,000; Baker 1963). Furthermore, subsequent rounds of selective screening no doubt occur at the zygotic stage and during embryonic development, as genomes from the surviving functional gametes are called upon to interact properly in diploid condition. Failures at this level would be registered as embryonic abortions, which also are known to occur at high frequency (e.g., the loss of all human conceptions has been estimated at nearly 80%; Roberts and Lowe 1975). In general, the Bernsteins interpret such observations to indicate that DNA damage is so pervasive that "recombinational repair during meiosis, as well as other repair and protective processes, may be just barely able to cope with DNA damage" (p. 260).

Summary

The Bernsteins' DNA repair theory by itself probably cannot account for all of the variety and nuances of sexual reproduction and aging processes. Nonetheless, it represents an exciting and important piece of a jigsaw puzzle whose other elements are summarized so eloquently in the Rose and Michod/Levin volumes. Furthermore, in this puzzle's emerging picture, aging and sex can be seen more clearly as interrelated phenomena, both evolutionarily and mechanistically. Undeniably, certain cell lineages in all extant life-forms have solved the problem of innate mortality (at least over the 4 billion yr of life on earth), and the strategies of genetic recombination, cellular replacement, and molecular replacement by which this has been accomplished are coming into sharper focus.

Literature Cited

Avise, J. C. 1991. Ten unorthodox perspectives on evolution prompted by comparative population genetic findings on mitochondrial DNA. Annual Review of Genetics 25:45–69.

Baker, T. G. 1963. A quantitative and cytological study of germ cells in human ovaries. Proceedings of the Royal Society of London Biological Sciences 158:417–433.

Bandy, B., and A. J. Davison. 1990. Mitochondrial mutations may increase oxidative stress: implications for carcinogenesis and aging? Free Radical Biology and Medicine 8:523–539.

Bernstein, C., and H. Bernstein. 1991. Aging, sex and DNA repair. Academic Press, New York.

Chapman, R. W., J. C. Stephens, R. A. Lansman, and J. C. Avise. 1982. Models of mitochondrial DNA transmission genetics and evolution in higher eucaryotes. Genetical Research 40:41–57.

Darwin, C. 1859. On the origin of species by means of natural selection, or the preservation of favored races in the struggle for life. John Murray, London.

Griffiths, A. J. F. 1992. Fungal senescence. Annual Review of Genetics 26:351–372.

Hastings, I. M. 1989. Potential germline competition in animals and its evolutionary implications. Genetics 123:191–197.

Lewontin, R. C. 1974. The genetic basis of evolutionary change. Columbia University Press, New York.

Michaels, G. S., W. W. Hauswirth, and P. J. Laipis. 1982. Mitochondrial DNA copy number in bovine oocytes and somatic cells. Developmental Biology 94:246–251.

Michod, R. E., and B. R. Levin, eds. 1988. The evolution of sex. Sinauer, Sunderland, Mass.

Nei, M., and D. Graur. 1984. Extent of protein polymorphism and the neutral mutation theory. Evolutionary Biology 17:73–118.

Richter, C., J.-W. Park, and B. N. Ames. 1988. Normal oxidative damage to mitochondrial and nuclear DNA is extensive. Proceedings of the National Academy of Sciences, USA 85:6465–6467.

Roberts, C. J., and C. R. Lowe. 1975. Where have all the conceptions gone? Lancet i:498–499.

Rose, M. R. 1991. Evolutionary biology of aging. Oxford University Press, New York.

Wallace, D. C. 1992a. Mitochondrial genetics: a paradigm for aging and degenerative diseases? Science 256:628–632.

———. 1992b. Diseases of the mitochondrial DNA. Annual Review of Biochemistry 61:1175–1212.

Wilson, A. C., R. L. Cann, S. M. Carr, M. George, Jr., U. B. Gyllensten, K. M. Helm-Bychowski, R. G. Higuchi, S. R. Palumbi, E. M. Prager, R. D. Sage, and M. Stoneking. 1985. Mitochondrial DNA and two perspectives on evolutionary genetics. Biological Journal of the Linnean Society 26:375–400.

Zouros, E., K. R. Freeman, A. O. Ball, and G. H. Pogson. 1992. Direct evidence for extensive paternal mitochondrial DNA inheritance in the marine mussel *Mytilus*. Nature 359:412–414.

Corresponding Editor: G. Vermeij