THE QUARTERLY REVIEW *of* BIOLOGY

WILLIAMS'S THEORY OF THE EVOLUTION OF SENESCENCE: STILL USEFUL AT FIFTY

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ABSTRACT

George Williams indicated that he would not expect senescence to evolve in organisms that lack a distinction between germ line and soma. Escherichia coli—long assumed to lack even a hint of this distinction—is now known to senesce, posing what would seem to be a challenge to Williams's well-known theory of the evolution of senescence. However, in this review, I will show that cell division in E. coli *produces a degree of germ-soma modularity sufficient to generate age structure and antagonistic pleiotropic effects, thereby satisfying the requirements of Williams's theory. From this perspective, senescence in* E. coli *is supportive and points the way to a better understanding of the pleiotropies that connect adaptive complexity and senescence. Sexual reproduction is but one of the complex adaptations illuminated by this approach.*

INTRODUCTION

THE YEAR 2007 marked the fiftieth anniversary of the publication of George Williams's (1957) theory of the evolution of senescence. It has been an enor-mously successful theory, having stimulated and survived decades of theoretical and empirical scrutiny (e.g., Hamilton 1966; Charlesworth 1980; Rose and Charlesworth 1980; Luckinbill et al. 1984; Nesse 1988; Rose 1991;

Austad and Fischer 1991; Promislow 2004; Leroi et al. 2005). But now, indisputable evidence of senescence in bacteria (Ackermann et al. 2003; Stewart et al. 2005) has left some theorists less certain of its validity. Confidence has been replaced by a palpable uneasiness that is perhaps best summarized by Thomas Kirkwood, who asks, "Do these new findings mean that we have to tear up the rulebook and begin again?" (2005a:533).

The problem is that Williams made it clear that he did not expect bacteria to senesce (1957:403). His reason: the evolution of senescence requires the presence of a distinct soma, and the imaging technologies in use at the time gave no reason to suspect that any bacteria met this qualification. Other researchers defended this position until fairly recently (e.g., Bell 1988; Rose 1991), ardently contending that "all prokaryotes [which include all bacteria] should be free of aging, since they are strictly unicellular, without any soma or germ-plasm distinction" (Rose 1991:84).

To the contrary, I propose that, under Williams's theory, some bacteria should be expected to senesce after all because, as I will show, the assumption that all bacteria lack a germ-soma distinction is false. This claim may at first seem far-fetched, given the constraint of unicellularity, but a precedent can be found in the suggestion that some unicellular eukaryotes possess a "soma" that is distinct enough from the germ line to allow senescence to evolve for the reasons encompassed by Williams's theory. Paramecia, for example, are unicellular ciliates that have nuclei specialized to perform either somatic or germ line functions. According to Rose (1991:88–89), this segregation of function, localized to separate modules, may satisfy the requirements of Williams's theory, thus accounting for their senescence. As another example, Lai et al. (2002) have proposed that the larger, mortal mother cell in the budding yeast *Saccharomyces cerevisiae* qualifies as a soma, whereas the smaller buds, or daughter cells, are appropriately considered components of a potentially immortal germ line, therefore implying that senescence in this unicellular organism also is consistent with Williams's theory.

Not everyone, however, is reconciled to this point of view, least of all when it is applied to bacteria. Kirkwood has twice referred to Lai et al.'s (2002) interpretation of the life cycle of *S. cerevisiae* as a "stretch" (2005a:533; 2005b:444), and he has gone on to assure us that, in any case, recent descriptions of the bacterium *Escherichia coli* (as discussed in the following sections) firmly establish that senescence can evolve in the absence of any distinction between germ and soma. And Kirkwood is not the only prominent theorist to question the germ-soma distinction requirement that Williams insists is fundamental to the evolution of senescence. As early as 1993, Partridge and Barton suggested that this distinction is unnecessary, stating that "the logic of this point of view is not compelling, and it is not supported by the data" (p. 310). In its place, they propose that "The critical requirement for the evolution of ageing is that there be a distinction between a parent individual and the smaller offspring for which it provides" (Partridge and Barton 1993:310).

This challenge to Williams's theory was recently vaulted to prominence by evidence of senescence in the bacterium *Caulobacter crescentus* (Ackermann et al. 2003). Cell division in *C. crescentus* is conspicuously asymmetrical: its life cycle begins with an undifferentiated, "juvenile" swarmer cell that differentiates into a sessile, stalked "parent" cell, which then divides to once again produce undifferentiated swarmer cells. It is the differentiated stalked cells that eventually senesce; therefore, one might readily conclude, as Ackermann et al. have, that the life cycle of this organism affirms Partridge and Barton's revision of Williams's theory.

Stewart et al. (2005) have since extended the foregoing arguments, ranging even further from Williams's original position, by suggesting that it is unnecessarily restrictive to require a marked morphological or developmental distinction between parent and offspring. Specifically, in a remarkable study of the *E. coli* life cycle, they claim to have found that "a juvenile phase is not required for the process of aging any more than the presence of a germ line or a visi-

bly asymmetric division is" (Stewart et al. 2005:299). They instead hypothesize that a subtle functional asymmetry in cell division might be all that is required for senescence to evolve (see also Kirkwood 2005a), and they conclude their widely discussed article (e.g., Kirkwood 2005a,b; Khamsi 2005; Lynch 2005; Stephens 2005) with the suggestion that preventing asymmetries of the sort they identify in *E. coli* might be so costly that perhaps no form of life can avoid evolving senescence.

Senescence According to Williams

Before defending the notion that Williams's theory of the evolution of senescence is supported—not contested—by evidence of senescence in certain bacteria, I will first present a brief review of the theory's most salient features. Foremost is the expectation that the force of natural selection will tend to decline over the lifespan, beginning with the onset of reproduction. Formal analysis has demonstrated why this generally should be so (e.g., Hamilton 1966; Charlesworth 1980), but we can appreciate the point intuitively simply by recognizing that an individual with all of its reproductive potential ahead of it has greater latitude to succeed or fail than an individual that has, so to speak, already used up some of its reproduction. Without this insight, population genetics models would be unable to account for the persistence of genes that produce significant deleterious (i.e., senescent) effects.

Modeling the persistence of deleterious gene effects is relatively straightforward, however, compared to the much more vexing problem of identifying and describing all of a gene's phenotypic effects, including its effects on fitness. These are especially difficult tasks because all phenotypic effects are products of development, and development is contingent not only upon genes but also environment. Although this may seem an obvious point, it complicates matters by implying that gene effects will tend to be variable, or plastic (Schlichting and Pigliucci 1998; West-Eberhard 2003), and also inextricably intertwined. As Dobzhansky put it, "Heredity is particulate, but development is unitary" (Wiggles-worth 1961:111)—implying that all genes are both pleiotropic and epistatic. The genes that contribute to senescence are no exception, and it is important to take a moment to review Williams's view of development and pleiotropy.

According to Medawar (1952) and, later, Williams (1957), two types of genes underlie senescence: those producing exclusively detrimental effects, and those producing early beneficial effects followed eventually by detrimental effects. Williams, much more so than Medawar, emphasized the importance of the latter type, which nowadays are usually called "antagonistic pleiotropic" genes (e.g., Rose 1991). There is both direct (e.g., Leroi et al. 2005) and indirect (e.g., Nesse 1988; Promislow 2004) evidence indicating that antagonistic pleiotropic genes do indeed contribute to senescence (see also Rose 1991), but the direct evidence is minimal, and, in 1957, it was nonexistent.

Since Williams (1957) made antagonistic pleiotropy the centerpiece of his theory, one might think that being unable to identify any actual antagonistic pleiotropic genes would have been a source of consternation to him. On the contrary, he claimed that "there seems to be little necessity for documenting the existence of the necessary genes," and he gave the following justification: "Convincing examples are hard to find, because we seldom know the total survival value of a gene in a wild population, let alone its values in different parts of the life cycle. . . . [But] [p]leiotropy in some form is universally recognized, and no one has ever suggested that all the effects of a gene need be equally beneficial or harmful, or that they must be manifest at the same time." Therefore, it is reasonable to assume the existence of "genes that have opposite effects on fitness at different ages, or, more accurately, in different *somatic environments*" (Williams 1957:400, emphasis his).

We can be sure that genes encounter somatic environments that vary over the course of every individual's lifespan because even the simplest unicellular organisms grow, prepare for reproduction, acquire metabolites, and acquire or become depleted of resources. More complex organisms do the

same, but also progress through many stages of cellular and tissue differentiation, thus presenting genes with somatic environments that can be vastly different at different ages (see Leroi et al. 2005, Figure 1, for a list of categorical examples). It follows, as Williams clearly seemed to realize, that gene effects should often change with age.

Nevertheless, the difficulties inherent in conceptualizing and identifying antagonistic pleiotropic genes have left room for misunderstanding and controversy, and it is therefore illuminating to review what Williams had to say about the defining characteristics of the genes he considered most central to the evolution of senescence. In particular, he made a point of noting that "The senescence of human teeth consists not of their wearing out but of their lack of replacement when worn out" (1957:398). This would be an example of senescence mediated by antagonistic pleiotropic genes, as Williams and Nesse (1991:12–13) later clarified, only if instructions not to replace worn teeth frees up resources for more immediate purposes, such as reproduction (see Williams 1966 for a more general discussion of somatic and reproductive tradeoffs). Kirkwood and Rose (1991) have made essentially the same argument, also concluding that antagonistic pleiotropic genes must be common.

Before directly exploring the topic of bacterial senescence, I have one final point to clarify. Based upon some of the articles cited earlier, one might gather that the role of asymmetrical fission in the evolution of senescence had not been appreciated until recently. This is far from true. Williams explicitly indicates his awareness of the importance of asymmetry in his discussion of both fission in flatworms and vegetative/clonal propagation in plants (1957:403–404), although he does not extrapolate to unicellular organisms. In flatworms, he identifies the asymmetry between head and tail sections as tantamount to a germ-soma distinction, and, in plants, the dedifferentiation of certain types of specialized somatic cells to germ cells, which, in turn, give rise to new "physiologically defined individuals," is presented as evidence favoring the germ-soma asymmetry requirement that lies at the heart of his the-

ory (contrast Partridge and Barton's view of dedifferentiation [1993:310]).

GERM-SOMA ASYMMETRY IN *E. COLI*

E. coli is a bacterial rod that reproduces by dividing along the short axis. Division yields two nearly same-sized daughter cells, each composed of an inherited pole (or end) and a newly synthesized pole. Inherited poles are not identical under this system; one daughter cell inherits the pole that was newly synthesized by the parent cell, while the other inherits the pole that the parent cell inherited, which must have been synthesized at least one generation prior (Nystrom 2002). By following the effects of this asymmetry over time (using automated fluorescent microscopy), Stewart et al. (2005) were able to "present conclusive evidence for aging in the old pole cell, including cumulatively slowed growth, less offspring biomass production, and an increased probability of death" (p. 296).

I believe the specific explanation that Stewart et al. (2005) offer for these findings, which was anticipated by Ackermann et al. (2003), is essentially correct. They suggest that the pattern of cell division that evolved in *E. coli* localizes accumulated damage to old pole cells, providing a means of disposal. In turn, there is a diminished need to maintain and repair damage in this localized region, thereby freeing up resources to be used for other functions. And Stewart et al. present convincing empirical support for this explanation by demonstrating that old pole cells are less fit than new pole cells because the former are senescent and the latter "show a concomitant increase in their growth and reproduction over several divisions" (2005:298).

My disagreement is not with the foregoing explanation, per se, nor is it with the compelling evidence that Stewart et al. present. Rather, I disagree with the widely trumpeted conclusion that senescence in *E. coli* has evolved in the absence of a distinction between germ and soma, and also with the implication that Williams's theory has, therefore, been superseded by an emerging theory that more properly incorporates the concept of asymmetry. I suggest that the *E. coli*

life cycle does not justify these generalizations, and the mistaken belief that it does follows from insufficiently attending to two key components of Williams's theory.

First, as alluded to earlier, the conservation of resources achieved by diminished maintenance and repair of damage is expected to generate antagonistic pleiotropic effects of exactly the sort envisioned by Williams. This is because effort diverted from maintenance and repair generally can be used for more immediate advantage (e.g., faster growth, earlier reproduction). Stewart et al. (2005), as noted, have produced evidence indicating that this type of trade-off actually occurs in *E. coli*, but they do not mention that the genes that promote it must therefore qualify as antagonistic pleiotropic genes. Second, given that the *E. coli* gene pool includes antagonistic pleiotropic genes, as the foregoing suggests it must, how were they accumulated? In short, they were accumulated for precisely the reason given by Williams in 1957: the force of selection declines over the life cycle, beginning at the onset of reproduction, thus discounting late-occurring negative effects relative to early-occurring positive effects.

But how is it possible for the force of selection to decline, other than instantaneously to zero, in an organism that seems to reproduce all at once in a single act (fission) that results in its obliteration? The answer is that reproduction does not occur all at once. Stewart et al.'s (2005) observations indicate that emerging old pole cells conserve resources by not repairing or redistributing old pole damage, thus increasing the fitness of new pole cells. This is indirect reproduction. It is an investment that, on average, increases the inclusive fitness (Hamilton 1964) of the portion of a parental cell that is in the process of becoming an old pole daughter cell. Thus, from the point of this transaction (or transactions) forward, the force of selection declines from an initial maximum. As a consequence, old pole cells emerge as independent entities that are already, to some extent, selectively irrelevant and, thus, to some extent disposable. *E. coli*, therefore, has age structure.

In addition, it seems entirely reasonable to claim that, by sacrificing some of its potential to directly transmit genes to the next generation, and by doing so in a manner that benefits its contiguous sister cell, each old pole cell is, to a small degree, a specialized somatic cell. How else would one define incipient somatic cell specialization? Similarly, by virtue of benefiting from the sacrifices of old pole cells, each new pole sister cell is, to a degree, a specialized germ cell. (Note the parallels with caste evolution in social insects, including divergence in rate of senescence in queens and workers [Alexander et al. 1991].)

It is somewhat arbitrary whether the sacrifice that a parent cell/old pole cell makes to the benefit of its emerging sister cell is best described as parental investment or sibling-to-sibling nepotism. This distinction hinges upon when it becomes reasonable to think of a parent cell as two emerging daughter cells. Furthermore, since *E. coli* is not likely to be unique in its pattern of cell division and is certainly not the most ancient of bacterial rods, I suggest that wherever incipient germ-soma specialization has evolved, it is a first step leading potentially to more noticeable morphological asymmetries in cell division, such as have been described in *C. crescentus* (Ackermann et al. 2003).

Stewart et al. (2005) have asked whether any type of organism can avoid evolving senescence, and they suggest that avoidance might not be possible because of the high cost of preventing asymmetrical accumulation of cell damage, such as occurs when *E. coli* divides. If avoiding senescence requires the production of perfectly symmetrical daughter cells that are completely free of damage, then doing so is indeed prohibitively expensive. However, based upon Stewart et al.'s description of *E. coli*, as I have interpreted it, all that might be required is taking steps to avoid the systematic accumulation of effects that promote divergent specialization favoring either reproductive or somatic function.

The bacterium *Staphylococcus aureus* may be an example of a unicellular organism that directs effort toward avoiding at least the specific type of systematic germ-soma

asymmetry that has evolved in *E. coli* (see Watve et al. 2006 for a quantitative exploration of the conditions under which such a strategy would be adaptive). *S. aureus* is coccal-shaped (i.e., spherical), and it has been observed to divide along planes that alternate over three generations, with each plane being perpendicular to the one that preceded it (Dimitriev et al. 2004). *S. aureus* daughter cells are not perfectly symmetrical under this system, nor are they perfectly free of damage, but alternating planes of division would have the effect (perhaps incidentally) of distributing cell damage among lineages more equitably than has been observed in *E. coli*. Therefore, the *E. coli* model provides little or no basis for expecting senescence in *S. aureus.*

To briefly summarize, incipient germ-soma specialization in *E. coli* simultaneously produces the three requirements of Williams's theory: a distinction between germ and soma, a declining force of selection over the course of the lifespan (with concomitant selective irrelevance, or disposability), and antagonistic pleiotropic effects. With respect specifically to the latter, I suggest that there can be no more fundamental example of antagonistic pleiotropy than that which occurs when a cell or portion of a cell travels a developmental path that, by inching toward somatic cell status, trades an increment of its reproductive autonomy for some more immediate gain.

The Evolution of Complexity: A General Hypothesis

Williams erred in suggesting that bacteria should universally lack senescence, but current evidence, including the recent observation of senescence in *E. coli*, indicates that he was correct in claiming that a distinction between germ and soma is required for senescence to evolve. It therefore seems likely that, fifty years after its inception, his theory will continue to be useful—but perhaps not just as inspiration for understanding senescence. Senescence, I suggest, has an alter ego, which Williams's theory also promises to help reveal.

From this point forward, I will develop the hypothesis that senescence and complexity are the flipsides of one another, held in perpetual association by antagonistic pleiotropic genes. I will argue that complex adaptations are built out of the positive effects of accumulated antagonistic pleiotropic genes, but that negative effects eventually prevail, as Williams argued that they would, in spite of ongoing selection to attenuate or delay them. A corollary is that the evolution of complexity hinges on the extent to which organisms distinguish germ and soma.

DEFINITION

A robust definition of complexity that has had application in many fields (e.g., physics, computer science, and biology) is one that equates complexity with information content (see Adami et al. 2000 and references therein). Central to this definition is the notion that information cannot exist independently of some type of instantiation (i.e., information and, thus, complexity are physical), which in the realm of biology implies that genetic information does not exist independently of effects on phenotype (Adami et al. 2000). This is an important point, when coupled with the fact that phenotypes are always products of development, because it necessarily implies that the complexity of organisms—the amount of instantiated information—is always due to genes *and* their environmental context.

PRECEDENTS

Knowledge of the fact that selection of desirable traits yields unintended, usually negative, consequences is at least as old as farming, and much of the field of study now known as quantitative genetics has been devised to describe and understand these linkages and pleiotropies. From this twelve-thousand-year-old beginning, theorists have increasingly understood that pleiotropic effects limit evolvability and, in particular, limit the evolution of complexity (e.g., Orr 2000). Furthermore, the evolution of various types of modularity mechanisms that compartmentalize and, thus, control genetic expressions has been proposed as a general solution to this problem (e.g., Wagner and Altenberg 1996; Welch and Waxman 2003).

I suggest, along similar lines, that "germ-soma modularity" is the most fundamental of evolved mechanisms for controlling genetic expressions. As I define it, germ-soma modularity is built from processes, such as asymmetrical cell division, and/or barriers, such as cell and nuclear membranes, that each serve in some manner to distinguish or separate germ and soma. Over evolutionary time, these various processes and barriers are expected to be added or removed, changing the extent and character of germ-soma modularity. I propose that the most general function of germ-soma modularity is to give access to the early positive effects of antagonistic pleiotropic genes by acting to limit, delay, and eventually dispose of their negative effects, all while simultaneously keeping germ line genes pristine. Without means to block the intact transmission of senescent effects to offspring, the early-occurring adaptive effects of antagonistic pleiotropic genes are strictly off-limits. Therefore, increases in complexity are expected to have evolved, much of the time, in tandem with incremental increases in germ-soma modularity.

Weissman (1893) made a related point more than one hundred years ago by arguing that germ line sequestration is a prerequisite to the evolution of somatic cell specialization, but he, of course, did so without reference to antagonistic pleiotropic genes and without recognizing that germ-soma modularity evolves by increments. My main contribution here is the recognition that germ-soma modularity is a continuous variable, present in incipient form even in organisms such as *E. coli*. Later, I will identify many structures and processes in complex organisms as mechanisms that augment germ-soma modularity.

As for any trait, the extent of germ-soma modularity, as well as its precise characteristics, is expected to vary among the individuals of a species. Thus, if an individual acquires a mutation that confers both a beneficial effect and a later-occurring negative effect, the spread of this mutation is more likely, other things being equal, if it occurs in an individual with greater than average germ-soma modularity. Germ-soma modularity, therefore, would increase evolvability. This approach explicitly recognizes the contingent nature of pleiotropic expressions (a point embraced by Williams in 1957 and discussed here previously), and, as its most general point of departure, takes the view that "The architecture of the phenotype affects, and in a sense 'directs,' evolution" (West-Eberhard 2003:86).

In the two sections to follow, I will give my reasons for believing that adaptive increases in complexity are generally antagonistically pleiotropic, and I will describe the types of augmented germ-soma modularity that are required to accommodate them.

DIFFERENTIATED CELLS AND TISSUES ARE EMBODIMENTS OF ANTAGONISTIC PLEIOTROPIC GENES

I have already pointed out that any gene contributing to the pattern of cell division seen in *E. coli* is likely to have antagonistic pleiotropic effects. On the positive side, resources diverted from repairing old pole damage can be used for other purposes, but this also portends, on the negative side, that one copy of any such gene will end up in an old pole daughter cell—a cell type that, as Stewart et al. (2005) have shown, has diminished future reproductive potential. By a similar logic, I propose that all somatic specializations that develop by cellular or tissue differentiation necessarily entail some detriment to the future potential of the cell or tissue in question, implying that any gene contributing to this developmental sequence is an antagonistic pleiotropic gene. This is a broad claim, and, to illustrate it, consider the following downstream costs that are expected to accrue whenever a cell travels a differentiation pathway that increases its specialization.

1. Traveling a particular differentiation pathway should impede traveling another. This is because specialized cells are likely to have structures and processes in place that are task-specific. Undoing them inevitably requires time and energy, and probably entails risk—most notably, mistakes

leading to cancer (e.g., Campisi 2005). Any new allele that augments specialization will tend to exaggerate these costs. By analogy, a Ferrari does one thing very well, and it can be adaptive to own one if the immediate need is to go fast. However, in comparison to a less specialized vehicle, a Ferrari cannot be readily used for other purposes.

2. The expense of repairing differentiated cells should be proportional to their degree of specialization, since specialization tends to require special structures and processes. Any new allele that augments specialization will, therefore, tend to increase future repair costs. Again, Ferraris illustrate this general point well.

As an alternative to repair, damaged cells can be killed (or induced to die) and then replaced, but this is also costly, mostly because it is risky. Replacements generally must be recruited from pools of pluripotent cells that, being pluripotent and primed for replication, have a greater than average chance of becoming cancerous (Frank et al. 2003). High costs of repair and replacement, coupled with a declining force of selection over the lifespan, imply that repair and replacement will be limited—particularly in especially expensive cells. To reiterate Williams's example, past a certain age, humans tolerate wear and tear to their teeth (1957:398; see also Kirkwood 1977).

3. If repair and replacement are limited (as noted in point 2), then suboptimal function is an inevitable eventual result.

There are additional examples that illustrate the inevitability of downstream costs associated with increasing developmental complexity. Beginning first with the unicellular organism *C. crescentus*, the asymmetrically dividing bacterium described earlier, the stalk that anchors a parent cell to a substrate is a specialization that presumably confers a relatively immediate benefit. However, when the attached cell divides, it is not its stalked end that becomes a new swarmer cell. The stalk develops along a differentiation pathway that I suggest leaves its end (pole) of the cell less able to travel the developmental path that leads to the swarmer cell phenotype. In addition, due to its differentiation and concomitant increased complexity, it is likely that repair costs at the stalked end of the cell are higher than at the nonstalked end, and the potential value of repair is reduced once the stalked cell has divided for the first time because successful reproduction signals a decline in the force of selection. Consequently, disrepair is tolerated, and the eventual result is senescent decline (Ackermann et al. 2003). Genes contributing to a stalk's development are, therefore, antagonistically pleiotropic.

As noted earlier, transection experiments using flatworms reveal that tail and head segments are, respectively, germ and somatic modules. The more central point here is that germ-soma modularity makes the complexity of the head end possible. To explain this, consider a hypothetical alternative: if the worms were transected along the longitudinal axis, yielding symmetrical products, there would be no germ-soma modularity, and senescent effects that accumulate in the head would be passed intact to the next generation. Under such a system, the only way around passing senescent structures to offspring would be to repair them, but this is infeasible because sustained maintenance and repair of specialized complex structures is expensive.

Among organisms more complex than flatworms, differentiation pathways are even more constraining with respect to the future potential of the complex elements that comprise such organisms. A bone marrow cell, for example, that has differentiated into a functional memory T-cell may save its bearer from an early death by infection, but, in so doing, has essentially given up the ability to later revert to naïve T-cell status, or, if needed, to later become a neutrophil. A myocyte has lost the possibility of developing into a hepatocyte let alone an oocyte, and a fully differentiated neuron often cannot be coaxed into becoming two neurons, or to recruit a replacement if damaged, without risking mistakes that, in the worst case, result in a brain tumor. Furthermore, my right hand undoubtedly functions with the adeptness that it does because of cellular and tissue specializations that preclude later, should

it become lopped off by an ax, the ability to regenerate a new hand. The immediate benefits of these and similar complex adaptations are perhaps so glaring that they have blinded us to the fact that each step in their evolution was achieved via the sacrifice of future potential. The genes that guide their development are, therefore, incontrovertibly antagonistic pleiotropic genes in the sense proposed by Williams. Complex specialized adaptations of the type discussed here would not be possible in their absence, and neither would the organisms in which they are found.

The Incremental Evolution of Germ-Soma Modularity

As discussed previously, the early beneficial effects of antagonistic pleiotropic genes are expected to be off-limits to organisms that ineffectively isolate germ and soma to separate modules. I have suggested that many structures and processes evolved to solve this problem over the past three billion years, including the aforementioned asymmetries in division. I will now identify some additional innovations that appear to augment germ-soma modularity.

NUCLEAR ORGANIZATION

The cell nucleus and the packaging structures within it, including chromosomes and histones, as well as processes such as methylation, all confer an increased ability to regulate genes. The nucleus, therefore, greatly increases the ability of cells to have some copies of the genome working on growth and metabolism while other copies are kept pristine. That is, without the modularity afforded by the nucleus and its components, germ line genes would be more subject than they are to epistatic and epigenetic regulatory processes that guide cell growth and differentiation; as a result, their totipotency would be limited, and, over the course of a lifetime, they would be increasingly exposed to environments (extending from cytosol to ecosystem) in which negative antagonistic pleiotropic effects inevitably are expressed. Although these negative effects are tolerable in somatic modules (if they occur late

enough in the lifespan), they are not tolerable in germ modules. Thus, in short, the ability of the germ line to produce offspring free of senescent effects is enhanced by nuclear organization.

Paramecia, which have nuclei that are specialized to perform exclusively germ or somatic functions (see Rose 1991:88–89 for details), seem to support this argument rather elegantly. As possible additional support, a recent study has found that the premature aging syndrome known as progeria is due to a mutation that causes defects in the structure of the nuclear envelope (Scaffidi and Mistelli 2005).

GAMETES

"[A]cross diverse phyla, cells that are destined to take on germ-cell fates are physically separated from potential somatic cells early in embryo-genesis, presumably to protect them from influences that would limit their potential or direct them along the path to a somatic fate" (Hubbard and Pera 2003:352). More specifically, early confinement of a germ module makes sense if the task at hand is to keep the germ line pristine, or isolated from developmental pathways occurring in the soma that limit totipotency and culminate in senescence. The evolution of multicellularity represents a great advance with respect to this task because multicellular organisms have the option of producing a separate group of cells—gametes—that, in addition to eventually transporting the germ line into the next generation, serve to isolate it from the many potentially untoward effects that occur in the juxtaposed soma.

Isolating the germ line, however, is not likely to begin and end with the production of a distinct group of gametes or their cellular precursors. A complimentary approach would be to construct the soma in ways that minimize transfer of unwanted epigenetic effects to gametes. The scrotum, an innovation evolved by mammals, may be such a construct. It provides an environment that is cooler and less metabolically active than the rest of the soma, and, at least for humans, it is well estab-

lished that testicles stored in the scrotum function much better than testicles stored in the abdomen (dysfunction manifests as sterility and testicular cancer). By a similar logic, relegating the reproductive phase of the life cycle to brief, discrete periods (e.g., to the very end of the life cycle in some organisms) might serve, at least in part, to isolate the germ line from somatic metabolism. Thus, the timing of life cycle events might in some instances, and to some extent, be designed to augment germ-soma modularity.

<div align="center">SEX</div>

In spite of the many barriers and processes that may exist to promote germ-soma modularity, it is probably not ever possible to insulate the germ line from all the unwanted epigenetic effects generated by the nearby soma. Consequently, as a countermeasure, processes are expected to have evolved that serve to reset germ lines once they have become tainted. Meiosis and sexual recombination are both known to have a rejuvenating effect on the germ line (Bell 1988; Hurst and Peck 1996), and I suggest that this might be their original, and still most important, function.

Williams was among the first to suggest that the evolution of sex represents a special problem, especially in situations entailing what has been variously referred to as "the two-fold cost of sex," "the cost of meiosis," or "the cost of males" (e.g., Williams 1975; Maynard Smith 1978). This two-fold cost accrues to females whenever they bear the full brunt of parental investment but produce offspring that carry only half of their respective genomes. A large number of hypotheses have been presented as potential explanations for the evolution and maintenance of sex under these circumstances (e.g., Kondrashov 1993), but, whether these hypotheses are viewed alone or in combination, the consensus is that sex remains largely unsolved.

Here I highlight a potential solution with roots dating at least to Ghiselin (1974): "[S]ex may become developmentally inescapable" (West-Eberhard 2003:630). And I suggest that antagonistic pleiotropic genes might be the main culprits that make sex inescapable once it has evolved.

Since the most daunting problem faced by any model purporting to account for sex is to overcome the so-called two-fold cost, I will initially bypass the issue by assuming that gametes, meiosis, and recombination evolved prior to the evolution of males. Without males there is no two-fold cost to overcome, and, therefore, the initial adaptive value of producing haploid gametes need not be very large. We might thus imagine that approximately one billion years ago there were organisms, possibly sponge-like animals, that released relatively large haploid gametes into the surrounding sea to recombine with similarly sized gametes produced by nearby conspecifics.

According to Parker et al. (1972) (see also Cosmides and Tooby 1981), however, isogametic mating systems tend to be unstable, eventually giving rise to highly dimorphic gametes (eggs and sperm). What drives this instability is that large, fertilizable gametes represent a tremendous fitness payoff to be reaped by individuals that produce smaller but more numerous gametes (Parker et al. 1972). Under the anisogamous mating systems that are, therefore, expected to evolve, the two-fold cost of sex arises and becomes increasingly common as sperm producers (males) become increasingly common. And therein lies the problem. Although Parker et al.'s model can account for the origin and initial spread of anisogamy, it does not readily account for its persistence, because it provides little basis for explaining why egg producers (females) do not regularly opt out of this exploitive system by bypassing meiosis to produce diploid gametes that do not require fertilization.

The flipside of Williams's senescence theory, however, gives the following hypothetical explanation for why opting out is rarely a viable option: meiosis augments germ-soma modularity by helping to reset tainted germ lines. Augmented germ-soma modularity allows the accumulation of new sets of antagonistic pleiotropic genes; thus, once meiosis is established in a mating system, females are

developmentally trapped into continuing to produce haploid eggs, because bypassing meiosis to produce diploid eggs would allow progeny to inherit intact some of the negative effects of the antagonistic pleiotropic genes that were accumulated during the period of evolution in which meiosis was practiced. For the same reason, bypassing gametogenesis to bud off propagules also is expected to transmit intact senescent effects to newly produced progeny, and I suggest that producing senescent progeny is likely to be more detrimental to a mother's fitness, in most situations, than paying the so-called two-fold cost of sex.

It is also possible that anisogamy itself might augment germ-soma modularity, adding to the developmental trap-effect of sex. That is, one might suspect, on mechanical grounds alone, that stripping genes of much of their cytoplasm, as occurs in spermatogenesis, can also strip them of at least some unwanted epigenetic effects, thus helping to reset the germ line. It follows, if this suggestion is correct, that evolution under anisogamous mating systems will lead to the accumulation of antagonistic pleiotropic genes that could not have been accumulated under isogamous systems. Thus, backwards evolution that bypasses anisogamy is likely to immediately produce offspring with less than the usual vigor.

Much evidence supports the prediction that bypassing the mechanisms of sex immediately yields weak and ineffective offspring (e.g., Hurst and Peck 1996; Corely et al. 2001), which provides a point of contrast with most competing models that predict that bypassing sex will lead, only after some delay, to declines in the fitness of offspring (e.g., via the slow accumulation of deleterious mutations).

Plants may, at first glance, seem to challenge the foregoing hypothesis, since they usually do not seem to be trapped by sex. Plants that reproduce sexually often can switch to vegetative propagation, bypassing the mechanisms of sex, and yet offspring (clones) do not as a rule inherit the senescent traits of the parent from which they are derived.

Williams (1957), as already noted, has suggested that the pattern of senescence in plants fits well with his theory so long as physiologically defined individuals (e.g., the cellulose edifices constituting particular trees, which are expendable) are not confused with clonal lineages, which are essentially immortal germ lines. Furthermore, he notes that the ability of roots, shoots, leaf tips, and other such plant parts to become propagules derives from the ability of specialized plant cells to dedifferentiate, thus reacquiring germ cell status. From the perspective being argued here (the flipside of Williams's senescence theory), plant cells have the capacity to dedifferentiate, whereas animal cells generally do not, because even the most specialized plant cells tend to be less differentiated and less complex than animal cells (Valentine et al. 1991). Fewer and shorter differentiation pathways imply that dedifferentiation is less costly in plants (cf. the analogy to Ferraris, stated earlier). It is less costly in terms of time and energy, but, more importantly, it is less costly with respect to the risk of mistakes leading to cancer. This is because "plant cancer," which may be a misnomer (Doonan and Hunt 1996), is fundamentally different from animal cancer in at least three respects. First, it is almost always caused by organisms such as viruses and bacteria and is usually eliminated by removal or destruction of these pathogens; second, plant cancer does not metastasize because plants lack the circulatory systems typical of animals; and third, plant cancer rarely kills its host, probably in large part because metastases do not occur. It is due to these factors, I believe, that plant cells have been able to evolve the capacity to dedifferentiate, and, because they can dedifferentiate to a totipotent germ cell state, they escape from the senescent effects acquired by their parents, even when they bypass sex.

A General Test: The Lansing Effect

As already stated, the barriers and germ line resetting mechanisms that I have identified as contributing to germ-soma modularity are not expected to function perfectly. Therefore, all other things being

equal, the longer the germ line is exposed to the soma, the more tainted it should become, and, in turn, progeny of older parents should generally be less fit than progeny of younger parents. This finding has been widely reported and is often referred to as the "Lansing effect" (Lansing 1947, 1954).

In spite of past challenges to its validity (e.g. Bell 1988; Rose 1991), a recent review by Priest et al. (2002), along with their own experiments with fruit flies, has lent the Lansing effect new credence. Nevertheless, little is known about the precise mechanisms by which acquired senescent characteristics might be transferred from parent to offspring. One candidate is the transfer of senescent enzymes to offspring via egg cytoplasm. Another is unintended methylation of germ line genes—which may be inevitable, given enough exposure to the developmental processes continually occurring in nearby somatic cells. Regardless of the precise mechanisms, the existence of epigenetic transfer of negative effects to offspring cannot be doubted. A heightened risk of offspring developing certain types of cancer is clearly attributable to epigenetic processes that originate in prior generations (Frank 2007). This type of evidence leaves no doubt that germ lines can become tainted (i.e., have their intended developmental programs altered) through exposure to phenomena occurring in the soma. Accordingly, there is also little doubt that germ-soma modularity plays a role in preventing unwanted transfers. From *E. coli*, to flatworms, to people, senescence may be the effect that a parent would least want to transfer to offspring. Therefore, we should expect to find that many traits and characteristics of organisms have evolved to solve this problem.

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