



MALADAPTATION AND NATURAL SELECTION

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ABSTRACT

The transformations George Williams initiated in evolutionary biology seem so blindingly obvious in retrospect that they spur the question of why he saw what no one else did. While most humans are prone to see only what theory predicts, Williams sees in bold relief whatever does not fit. Not an adaptationist or an anti-adaptationist, Williams is better described as a maladaptationist. The challenge of finding evolutionary explanations for apparent maladaptations has been overlooked with casualness akin to that once typical for group selection. Suboptimal traits tend to be dismissed as illustrations of the weakness and stochastic nature of selection compared with mutation and drift. A closer look suggests that such constraints are only one of six possible kinds of explanations for apparently suboptimal designs: mismatch, coevolution, tradeoffs, constraints, reproductive advantage at the expense of the individual, and defenses that are aversive but useful. Medicine has asked proximate questions at every possible level but has only begun to ask evolutionary questions about why bodies are vulnerable to disease. Considering all six possible evolutionary reasons for apparently suboptimal traits will spur progress not only in medicine but also more generally in biology. "Williams Vision" may not yield a net benefit to the possessor, but it is invaluable for the species.

INTRODUCTION

IN 1966 George Williams published a slim volume that transformed biology. *Adaptation and Natural Selection: A Critique of Some Current Evolutionary Thought* (Williams 1966) did not report the results of clever calculations, experiments carried out with expensive machines, or even decades of field studies. Instead, it addressed a simple question with ruthless logic. Does natural selection indeed, as most biologists then believed, shape individual traits that benefit the species? The answer, in fewer than three hundred pages of clear prose, was "No." His argument was straightforward. Williams compared the genetic contributions to future generations of individuals who sacrificed reproductive success (RS) for the sake of the group to those

individuals who maximized their own reproduction. He concluded that it was theoretically possible for genes that coded for tendencies to help the group at a cost to the self to become more common if groups with more individuals with such genes succeeded in comparison with groups with fewer. In almost every actual instance, however, such group selection would be so feeble as to be inconsequential compared to the power of selection at the level of the gene or those collections of cells with identical genes that we call individuals. His critique of then-current evolutionary thought succeeded in eliminating a fundamental misconception in biology. Naïve group selection was dead.

In retrospect, his insight seems blindingly obvious. The question is how nearly everyone else in biology went along for decades oblivious to such a fundamental misconception

about how natural selection works. While others saw a benevolent Mother Nature shaping organisms for the good of species and even whole ecosystems, Williams saw contradictions in bold relief. There is something different about how he sees the world. Is this “Williams Vision” an adaptation ready to spread in the population, or a flaw or a neutral quirk? For an initial answer, consider the perfection and imperfections of the eye itself.

The vertebrate eye is the exemplar of nature’s perfection. Even a cursory examination yields admiration at the clarity of the cornea, the lens, and the vitreous fluid. The mechanism that constricts the iris in bright light is elegant. A marvelously flexible lens is exactly compressed so the eye can focus from inches to infinity. A subtle mechanism regulates intraocular pressure. The rods and cones are packed close at the fovea while the specialized motion sensitive cells monitor the periphery of the visual field. It is no wonder that Paley, among others, extolled the eye as a miracle of design (Paley 1802). Thanks to all manner of marvelous contrivances, the eye works and works well.

The eye is also, however, the poster child for the body’s imperfections. It works well when it works, but often it does not. Nearly a third of us have hereditary nearsightedness, and almost no one over 55 can read a phone book unassisted (except for those who have been nearsighted for decades!). The lovely mechanism that regulates intraocular pressure often fails, causing glaucoma. Then there is the blind spot, a manifestation of the abject design failure of nerves and vessels that penetrate the eyeball in a bundle and spread out along the interior surface instead of penetrating from the outside as in the better-designed cephalopod eye. Octopi not only have a full field of vision, but they need not worry about retinal detachment. They also need neither the tiny jiggle of nystagmus that minimizes the shadows cast by vessels and nerves on the vertebrate retina nor the brain processing mechanisms that extract the visual signal from the nystagmus noise. In short, the vertebrate eye is a masterpiece not of design, but of jury-rigged compensations for a fundamentally defective architecture. The won-

der is not the eye’s perfection, but that such a jury-rigged device works at all.

The quirks and limits of our cognitive adaptations similarly compromise our ability to see the world accurately. At the perceptual level, Gestalt phenomena fill the gaps in partial shapes, giving the illusion of wholes. Our minds then organize perceptual data into categories that allow generalizations about members of the class, an efficient simplification that allows quick decisions, and that fosters tendencies to prejudicial assumptions that individuals all share the essential characteristics of their groups. The mind then connects these categories in theories that allow us to predict the future, often correctly, despite inherent biases and overly simple heuristics (Nisbett and Ross 1980). At each stage—perception, categorization, and theory building—our cognitive devices distort our vision. We see what we expect to see and are often blind to what does not fit our prejudices and preconceptions. Williams Vision somehow lacks these usual human foibles. Instead of seeing only what fits the theory, it sees what does not fit. To consider further if this is an adaptation or a maladaptation, we must touch on the adaptation wars.

ADAPTATIONISTS AND ANTI-ADAPTATIONISTS

Guidance comes from the first sentence in the contents of *Adaptation and Natural Selection*: “Evolutionary adaptation is a special and onerous concept that should not be used unnecessarily, and an effect should not be called a function unless it is clearly produced by design and not by chance” (Williams 1966:vii). This reluctance to call traits adaptations seems to place Williams on the anti-adaptationist side of the adaptation wars. Does this mean that Williams is reluctant to seek evolutionary functions for problematic traits? Hardly. Most of his major contributions came from the perverse tendency to seek evolutionary explanations for traits that seemed inexplicable. In the welter of words spilled about adaptationism, Williams was not in the main fray (Segerstråle 2000). The explanation may be that his views are

not simple enough to lend themselves to ready ridicule.

In contrast, much of the controversy about adaptation reflects worldviews that emerge from what scientists see in the narrow range of their daily work (Rose and Lauder 1996). Never was the hackneyed metaphor of four blind men and an elephant more apt. Geneticists track mutations appearing, drifting, and being selected in a profoundly stochastic process that leads some neutral or even deleterious genes to go to fixation, while many useful mutations either never occur or leave the gene pool without a trace. Geneticists see interactions with other genes and environments creating such phenotypic variability that it is hard to say if a gene gives a selective advantage or not. Likewise, the paleontologist's daily work involves evidence left by millions of species come and gone. Sometimes a cataclysmic event explains the departure of a species, but extinction results as often from combinations of unknown forces. Paleontologists also see traits changing over time, sometimes for good reasons, sometimes apparently just as the result of the drift of traits across the eons. Confronted with stochastic effects in their daily work, it is not surprising that the worldviews of geneticists and paleontologists tend towards suspicion about adaptation.

By contrast, the daily work of physiologists brings them face to face with adaptations (Alexander 1996). A careful examination of osmotic balance or blood pressure regulation reveals mechanisms as precise as they are robust (Vander et al. 1985). As the focus becomes more fine grained, wonderful details emerge, such as bacterial navigation strategies (Dusenbery 1996), the exquisite contrivances plants use to lure insects and anoint them with pollen (Proctor et al. 1996), and the pony fish's glow that camouflages it from deeper predators (Williams 1997). Scientists who study comparative physiology cannot help but be impressed at the diversity of adaptations even in closely related species (Schmidt-Nielsen 1990). Likewise, ethologists see adaptations at every turn (Alcock 1998). Whether their attention is on bee communication, prepared learning, bumblebee foraging, mating strategies,

or hierarchy competition, animals make remarkably sophisticated decisions (Real and Caraco 1986). Because physiologists and ethologists see exquisite adaptations in their daily work, their worldviews tend to presume good function, leaving stochastic factors for late consideration.

MALADAPTATIONISM

Where does this leave George Williams? Is he an adaptationist or an anti-adaptationist? He is nothing so simple. If anything, he is a *maladaptationist*. He has spent his entire career preoccupied with one apparent maladaptation after another. Very early, he wondered why senescence should exist at all. Organisms can, he pointed out, regenerate damaged tissues and even whole limbs. Maintaining a body that has already developed should surely be a simpler matter than developing a completely new soma from two strands of DNA. Why has selection not created bodies that repair themselves so they endure, if not forever, at least much longer? In a seminal paper, Williams suggested that selection would maintain the frequency of genes that gave benefits early in life even if those same genes had pleiotropic effects that caused steady and fatal damage to older organisms (Williams 1957). To illustrate this principle, he imagined a gene that changed calcium metabolism in ways that speeded bone healing but that also caused steady calcification of the coronary arteries. Even in the absence of senescence, other forces will reduce the population with age, thus making selection stronger at younger ages and magnifying the effect (Hamilton 1966; Austad 1994; Hawkes et al. 1998). Medawar had seen the same problem (Medawar 1952), but Williams made it explicit and initiated a new perspective on senescence that remains on center stage (Williams 1999; Masoro and Austad 2001).

In the same article, Williams (1957) addressed the mystery of menopause. What could be more senseless than premature failure of the female reproduction system, and what could explain survival beyond the age of reproduction? Where others saw a system simply wearing out, Williams saw a major

question. His answer was that stopping individual reproduction might maximize RS if continued reproduction at advanced ages might jeopardize the success of existing children. This provocative idea, containing the seeds of kin selection, spurs much continuing research (Austad 1994; Hawkes 2003).

My own path to Darwinian medicine began as a sophomore undergraduate when senescence suddenly struck me as a great mystery. The rate of aging is heritable and closely related species sometimes have very different life spans, so it seemed that selection should either eliminate senescence, or at least maximize life span for each species. Why does senescence persist? After several months wandering in computerless libraries with index cards in hand, I never found Williams's article from ten years previously, but I did arrive at an evolutionary answer: senescence was essential to ensure the steady turnover of individuals so that a species could evolve and not go extinct in a changing environment. This at least provided an evolutionary explanation, but over the years it kept seeming to me that this might not be quite right. In medical school, I was taught that natural selection was irrelevant; senescence is inevitable, we learned, because wear and tear damage the body. Shortly thereafter, in my quest to find a solid foundation for understanding mental disorders, I made contact with a wonderful group of evolutionary biologists at the University of Michigan. Soon, I told them about my continuing preoccupation with senescence. "What!?" they said, "You have never read Williams, 1957?!" I soon did, and the world has never looked the same since. If evolution shaped senescence, could it also help explain our vulnerability to cancer, schizophrenia, and impacted wisdom teeth? We needed to bring evolutionary biology into the medical curriculum.

First, however, I wanted to test Williams's pleiotropy theory. It should be possible to estimate the force of selection acting on senescence by comparing actual survival curves for organisms in the wild to hypothetical curves based on the assumption of no senescence. Taking the ratio of the area

under the actual curve after maturity to the area under a curve for which mortality remained constant after maturity gave a very rough estimate of the impact of senescence on reproductive success. The results for all the life tables I could find for species in the wild showed vast differences in the presumed force of selection acting on senescence in mammals compared to birds, and interestingly, for rotifers (Nesse 1987, 1988). The method is not of great practical utility, but it did inspire the idea that recent changes in the average life span for a species might result in very different numbers of genes contributing to senescence. A species that has experienced a recent decrease in life span, perhaps because of new predation risks, might well show a long span of life in the laboratory in which the effects of senescence were mediated by only a few new mutations. By contrast, a species like *Homo sapiens*, whose life span has increased rapidly, would be expected to have many modifier genes pushing the expression of many deleterious effects later and later, producing a formidable obstacle to any attempt to slow the progression of human senescence.

Also in 1957, Williams saw another mystery, cooperation, especially in insects. He collaborated with his wife on an article that foreshadowed the revolutions of the 1960's (Williams and Williams 1957), and the solutions they proposed were close to those that reshaped our understanding of social biology. Cooperation in humans, and especially tendencies towards what appeared to be goodness, posed yet another mystery, one that Williams addressed unflinchingly (Williams 1989).

Sex was next. Before most biologists recognized that there was a problem, Williams documented the huge fitness costs of sexual versus asexual reproduction and proposed possible solutions (Williams 1975).

The pattern is clear; Williams saw the world through evolutionary lenses, but instead of fitting perceptions into the theory, the lenses highlighted every exception. Others have had this same tendency, notably Charles Darwin, whose attention was constantly drawn to facts that did not fit, whether honeybee coopera-

tion or flowers with spurs longer than the tongue of any known pollinator.

SIX REASONS FOR DISEASE VULNERABILITY

By 1986, I was preoccupied with an evolutionary perspective on disease; it made no sense that the body so well designed in some respects could be so poorly designed in others. I went looking for an evolutionary biologist to help me understand why selection had left us so vulnerable to disease. Williams, it turned out, was working on the same problem and was looking for someone who knew about disease. Our shared interest in senescence brought us together, and we soon started work on "The Dawn of Darwinian Medicine" (Williams and Nesse 1991). The magnitude of the knowledge gap in medicine soon became clear. Medical research has asked about every conceivable proximate factor that might explain why some people get sick and others do not, but evolutionary questions about disease were hardly even recognized. This now seems less surprising. The medical goals of prevention and treatment are advanced most directly by finding out what causes disease in individuals. Seeking evolutionary explanations for diseases seems, and in most cases is, of less immediate practical benefit. Furthermore, diseases represent failure, and selection shapes things that work, not things that fail, so the relevance of selection is not readily obvious. We began making progress when we changed the object of explanation from disease to vulnerability to disease. This apparently small change in perspective made all the difference. For disease after disease we asked ourselves, "Why isn't the body better designed?"

The usual answer in medicine, as well as in much of biology, has been that natural selection is an undirected process whose influence is weak because of the stochastic nature of mutations and drift, so we should not expect bodies to be anywhere near optimal. This perspective predicts that most traits in most species will be suboptimal if not severely flawed. However, examination of actual traits for specific species reveals some that are extraordinarily close to optimal, while others seem so hopelessly ill wrought that the survival of the

species seems remarkable. Geckos have toe pads covered with setae that make use of van der Waal forces of molecular attraction to allow them to walk on ceilings. Other lizards reproduce asexually in expanding clones that are fine in the short run but liable to extinction from epidemic disease. Some trees monitor the wavelength of light and allocate more resources to upward growth if the wavelength indicates the presence of nearby competitors. Others have limbs so fragile that they lose many in every wind-storm. The human body concerns us most. Our eyes are wonderful but fundamentally fragile bundles of jury-rigged design. We have heart valves that stay in an exacting leak-proof profile for a hundred years, but far earlier most of us will get Alzheimer's disease, coronary artery disease, breast cancer or prostate cancer. Near the early peak of health, we can run for miles, but at the same age we get impacted wisdom teeth, acne, and the onset of anxiety and mood disorders. These jarring contrasts between remarkable adaptations and examples of hopelessly poor design demand attention. They suggest that our thinking about maladaptation has been too casual.

Biologists have recognized the opportunities as well as the problems in the study of adaptation and maladaptation and proposed a variety of strategies to exploit them (Mayr 1983; Reeve and Sherman 1993; Rose and Lauder 1996). In particular, Crespi proposes bringing phylogeny, teleonomy, development, and genetics together in an integrated quantitative approach to the study of the selective landscapes that result in maladaptation: "Selection defines the landscape on which populations move, and to the extent that environments and selective pressures change our landscape becomes a sea where waves rise, sink and move like water in a bath" (Crespi 2000:625).

Our more medically-derived evolutionary approach to maladaptation asks why selection has not made the body better. The vagaries of a stochastic process and the constant pressure from mutation and drift are one possibility, however, there are five other reasons why selection leaves bodies with designs that appear substandard.

TABLE 1
*Six Evolutionary Explanations for
 Vulnerability to Disease*

- Selection is slow
 - Mismatch between design and environment
 - Competition with a pathogen or other organism
- Selection cannot solve some problems irrespective of time
 - Tradeoffs
 - Constraints peculiar to living systems, e.g. path-dependence
- We misunderstand what selection shapes
 - Traits that increase RS at the cost of disease vulnerability
 - Aversive defenses are readily mistaken for diseases

One obvious reason for disease vulnerability is the time lag between environmental change and adaptation by natural selection. Periods of cataclysmic change, such as the past 300 years, pose challenges for most organisms (Committee to Review the U.S. Climate Change Science Program Strategic Plan 2004) and lead to mass extinctions (Thomas et al. 2004). We humans die young from heart disease thanks to diet and exercise preferences and metabolic systems shaped in an environment where constant ready access to salty, hot fatty meat was beyond imagination (Eaton et al. 2002). Certain South American plants are in even more dire straights since the extinction of the giant mammals that ate their thorny fruits and spread the seeds (Janzen and Martin 1982). Even in the absence of ecological catastrophes of the sort now unfolding, environments vary from year to year, making adaptation somewhat suboptimal for most organisms in most environments.

When the relevant environment is a pathogen or another competing organism, there is no catching up as coevolutionary arms races create cycles of escalating responses and counterresponses. Antibiotic resistance is the dramatic exemplar. Worse yet, the armaments and defenses shaped in these arms races take resources away from other essential tasks and yield mechanisms likely to be dangerous to

host as well as pathogen. For instance, autoimmune diseases arise from malfunctions of the inflammation system, and even the normal immune system exacts constant costs and accumulating damage that result in disease.

Natural selection cannot accomplish other potentially protective changes even given plenty of time. Any change that improves the performance of one trait is sure to harm another. Such tradeoffs are intrinsic to all designs, natural or human made. A car that gets 40 miles per gallon will not reach 60 miles per hour in 6 seconds. The thin distal ends of the human radius and ulna are fragile and prone to fracture. If they were thicker, however, we would not be able to rotate our wrists with such adaptive felicity.

Other limits are peculiar to living systems. Selection can only tinker with designs that already exist. Because a species cannot go into the shop for a few generations of retooling, many structures are fundamentally suboptimal with no hope that selection can fix them. The inside-out vertebrate eye is the exemplar; the human spine is another painful reminder of what selection cannot do. In addition, the process of selection is stochastic, so useful alleles are lost and disease alleles persist, causing thousands of genetic diseases. The variation in many traits, such as leg length, arises from multiple genes whose interactions with each other and environments ensures that some individuals will be at the maladaptive tails of the distribution for that trait (Houle 1992). Then there is the genetic code itself. Any information code will accumulate errors, but diploidy makes organisms intrinsically vulnerable to diseases that result from heterozygote advantage, and linkage disequilibrium guarantees that some traits will be suboptimal (Crespi 2000).

Other traits shaped by selection seem maladaptive only because our vision is self-centered. Most physicians imagine that selection shapes organisms for health and happiness. It does, when that advances the interests of the genes. However, a gene that increases RS will spread even if it reduces health, happiness, or longevity. Thus, we all age faster than we would otherwise, and young men have tendencies to do wild and dangerous things (Wilson and Daly 1985). Even more troubling, a gene that

advances its own interests at the expense of individuals will sometimes spread, despite opposing mechanisms, possibly including recombination (Burt and Trivers 1998; Haig 2002).

Finally, there are defenses. Cough, fever, pain, nausea, vomiting, pain, anxiety, and fatigue are not abnormalities, even if they do motivate people to seek medical help. They are aversive, almost certainly for good reason, but they are not themselves problems, they are solutions (Nesse and Williams 1994). The tendency to misinterpret them as problems is so pervasive it has been called "The Clinician's Illusion." Clinicians are prone to think defenses are abnormal because they are expressed in the presence of disease, and general medicine uses drugs to block them with remarkable safety. This apparent safety is partly because our environment is safer than it once was, but it is also because selection shapes regulation mechanisms according to the costs and benefits of responding versus not responding to ambiguous cues. A signal detection analysis shows that normal systems express many false alarms. This "smoke detector principle" explains why so many defenses can be blocked safely, and why we should urgently look for rare dangers from drugs that block defenses (Nesse 2005).

Together, these six evolutionary explanations for vulnerability provide a powerful framework for thinking about not only disease but any apparently substandard design feature in any organism. The tendency to explain apparently suboptimal features by mentioning the vagaries of selection and its limits is casual thinking little different from the complacent acceptance of group selection. A closer look at what selection shapes requires consideration of all the possibilities for each trait in question. This challenge is difficult, especially since definitive experimental methods are rarely available. Also, evolutionary explanations for vulnerability are often multicausal and this offends human cognitive preferences. For example, our vulnerability to atherosclerosis likely arises from environmental novelties, inflammation systems shaped to protect us from pathogens, tradeoffs, constraints, and perhaps even tendencies that increase RS at the cost of health.

Medicine is adopting these ideas cautiously. They have aroused little criticism, and many expressions of surprise that all of this is not already well known. However, the fast growth of courses on evolution and disease has not been in medical schools but in biology and anthropology departments. The tight packing of the medical curriculum leaves it rigid, and medical school funding systems generally demand federally funded research that promises to help specific diseases, so it will likely be some years yet before evolution is recognized as an essential basic science for medicine.

The biggest impediment may be the tacit metaphor physicians and medical researchers use to understand the body. Descartes initiated a revolution when he described the body as a machine. Ever since, physicians have viewed disease as arising from flaws in the bodily machine. The early years of medical training make the machine seem spectacularly well-designed. In the clinic, however, it seems like a slip shod piece of work. Either way, the tendency is to view the body as a machine designed by an engineer.

The metaphor of the body as machine is now restraining progress. Bodies are not machines designed by engineers; they are somas shaped by natural selection. The vulnerabilities that lead to disease do not arise from miscopying blueprints manufacturing errors. Instead, they arise from mutations and developmental sequences shaped by natural selection. Some vulnerabilities manifest only in a modern environment, others arise from host-pathogen coevolution. Some reflect the limits of what selection can do. Some reflect our difficulty accepting that bodies are not for us, but for our genes. Those genes are not part of a single "normal genome," and no single body design defines normal for a species. Instead, collections of genes interact with environments to create variable phenotypes that are more or less successful in surviving and reproducing copies of their genetic material. An evolutionary view disappoints our human preference for essential types, and it frustrates our wish to define normal. A body is a body, not a machine.

The emphasis in the field of Darwinian medicine and this article has been on human

disease and implications for medicine. As others have noted, however, the serious investigation of apparent maladaptations offers opportunities across biology (Crespi 2000). Why is DNA repair not better? Why does the kiwi lay a single huge egg? Moreover, why, following the persisting questions asked by Williams, do sex and senescence persist despite their costs? And exactly why does the Michigan lily hold its blossom erect and open to damaging rain. Every species has dozens of apparent maladaptations ripe for study.

What about Williams Vision itself? Is it an adaptation spreading quickly, or a maladaptation ripe for study? Although the trait seems still to be rare, it does seem to offer a powerful route to scientific progress. Careful examination of phenomena that do not fit our theories usually reveals nature's subtle ways that we failed to comprehend. Occasionally, however, the fault is not with our imagi-

nation but with our theories. Whatever the outcome, maladaptationists may make faster progress than adaptationists or anti-adaptationists.

Whether Williams Vision benefits individuals is a different question. It may be rare for good reason. The route lacks the pleasures of seeing the world as a wondrous whole and calls attention to the dark side of nature. It rarely runs adjacent to vast pools of funding and does not lead to ready recognition. Williams Vision may be accurate, but there are few indications that it is an adaptation that is likely to spread soon. It seems more like a quirk, one that happens to benefit the whole species.

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