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# EVOLUTION AND MEDICINE IN UNDERGRADUATE EDUCATION: A PRESCRIPTION FOR ALL BIOLOGY STUDENTS

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**The interface between evolutionary biology and the biomedical sciences promises to advance understanding of the origins of genetic and infectious diseases in humans, potentially leading to improved medical diagnostics, therapies, and public health practices. The biomedical sciences also provide unparalleled examples for evolutionary biologists to explore. However, gaps persist between evolution and medicine, for historical reasons and because they are often perceived as having disparate goals. Evolutionary biologists have a role in building a bridge between the disciplines by presenting evolutionary biology in the context of human health and medical practice to undergraduates, including premedical and preprofessional students. We suggest that students will find medical examples of evolution engaging. By making the connections between evolution and medicine clear at the undergraduate level, the stage is set for future health providers and biomedical scientists to work productively in this**

**synthetic area. Here, we frame key evolutionary concepts in terms of human health, so that biomedical examples may be more easily incorporated into evolution courses or more specialized courses on evolutionary medicine. Our goal is to aid in building the scientific foundation in evolutionary biology for all students, and to encourage evolutionary biologists to join in the integration of evolution and medicine.**

**KEY WORDS: Biomedical research, evolution of disease, host–pathogen interactions, human genetics, medical practice, mismatch hypothesis, premedical curriculum, public health, science education.**

Application of evolutionary principles to medical research, public health, and clinical practice can improve health care, reduce suffering, and save lives. Even so, the perception that evolutionary biology and the biomedical sciences have different foci and little overlap persists (e.g., Antonovics et al. 2007; Nesse and Stearns 2008). But the potential benefits of disciplinary synthesis should be motivating to both evolutionary biologists and the biomedical community. We begin with a simple observation: humans in postindustrial and industrialized societies live in a health paradox. In these societies, we benefit from medical and public health practices that lower mortality and morbidity, we enjoy year-round access to fresh and nutritious foods, and we have leisure and resources to tend to our mental and physical well-being. Yet, we still suffer from a wide array of diseases that, in cases such as diabetes, certain cancers (melanoma and non-Hodgkin lymphomas), autoimmune diseases, and Parkinson's disease, appear to be increasing in frequency (Nesse and Williams 1994; Bach 2002; Wallace 2005; Rook 2009). Many causes underlie the so-called "diseases of civilization," but the application of evolutionary principles holds promise for reconciling and helping to solve the health paradox.

The contributions of evolution to the medical and health sciences are not limited to diseases of civilization. Evolutionary analyses of host–pathogen interactions have yielded deeper understanding of the dynamics of pathogen virulence and host resistance. Emergence of new pathogens, such as HIV, the coronavirus that caused SARS, and novel forms of influenza A virus, can be traced by phylogenetic methods. Even treatments of cancers and reproductive medicine have benefitted from new therapies arising from evolutionary perspectives. We advocate that understanding the natural history and evolutionary biology of humans and their pathogens gives perspective to the medical sciences, with the potential to inform medical practice on many levels. We also emphasize that this is a two-way street. Medical practitioners and biomedical researchers working in fields such as human physiology, biochemistry, genetics, endocrinology, immunology, pathology, and epidemiology provide a treasure trove of examples and datasets for evolutionary biologists. Exploring these can lead to new insights in evolutionary biology as well as medicine.

We do not wish to minimize the differences between how the evolutionary biology and medical communities operate, given the scientific and societal benefits each has delivered, and we acknowledge that potential conflicts can arise between the evolutionary and medical viewpoints. As evolutionary biologists, we think in terms of traits and genes in populations or lineages over time. We view traits as continuously evolving in a population context, driven by processes such as adaptation by natural selection, mutation, and genetic drift, but constrained by genetic and physiological trade-offs. We know that interactions between evolutionary forces are mediated by the effective size of populations over long time periods, and we are accustomed to seeing traits as the products of genotype-by-environment interactions. Medical doctors, on the other hand, are trained to view patients as individuals in need of care, with injuries and symptoms at a particular time. Population-level and public health concerns must be balanced with alleviating an individual patient's suffering. These apparently contradictory viewpoints need not be at odds (e.g., Childs et al. 2005). The integration of evolutionary biology into medicine, often referred to as "evolutionary medicine," provides a dynamic view of genetic, environmental, and infectious diseases. An individual patient's ailments represent a particular point in time at the convergence of ancestries, environment, and exposures, like the tips of growing and changing trees whose branches intermingle through time but stay mostly out of sight.

Evolutionary biologists who train undergraduate premedical students are in a position to teach them the fundamental evolutionary principles that underlie biology. By explicitly using biomedical examples, we can form a truly interdisciplinary science that actively engages evolutionary biologists as well as medical researchers and practitioners. This requires collaboration between the communities to develop methodologies and curricula that integrate evolutionary biology into training future generations of doctors, public health workers, and biomedical researchers.

Here, we give a brief overview of the historical relationships between evolutionary biology and medicine (Box 1), and discuss how evolutionary biologists can use medically relevant examples to teach basic evolutionary biology concepts to all undergraduates, but particularly to students preparing to enter medical professions. We frame these examples in terms familiar to evolutionary biologists, and point to resources currently available for the classroom. Our message is that evolutionary medicine is an exciting and useful field that many of our students will need to understand and

will find engaging, and that evolutionary biologists can actively connect evolutionary biology and the biomedical sciences.

## Increasing Awareness

We, the authors, contributed to a symposium on Evolutionary Medicine during the 2011 meeting of the Society for the Study of Evolution in Norman, Oklahoma, to honor seminal contributions made by George Williams, who passed away on 8 Sept 2010. Williams' writings on the evolution of senescence and life histories provided fundamental conceptual developments in evolutionary biology (Williams 1957), as did his thoughts on the role of natural selection in adaptive evolution on multiple levels from genes to individuals to groups of organisms (Williams 1966). Further, his work in collaboration with Randolph Nesse spurred interest in applying evolutionary biology to medicine and public health. The essay on "The Dawn of Darwinian Medicine" (Williams and Nesse 1991) and the book "Why We Get Sick" (Nesse and Williams 1994) are cornerstones of the synthesis between evolutionary biology and the biomedical sciences. Williams' work inspired research projects, articles, and books that have further addressed the many ways that evolutionary biology influences biomedical research and how an evolutionary approach can improve medical diagnostics and therapies (e.g., a special issue of the *Proceedings of the National Academy of Science* featuring presentations from a Sackler Symposium, held in April 2009 (Stearns et al. 2010); a special issue of *Evolution: Education and Outreach* originating in part from the SSE 2011 Evolutionary Medicine Symposium (Jenkins and Antolin 2011).

Awareness of the potential impact of evolutionary biology on medicine is also growing beyond the biology research community, as illustrated by a joint report from the American Association of Medical Colleges and the Howard Hughes Medical Institute (AAMC-HHMI 2009), entitled *Scientific Foundations for Future Physicians*. It describes core scientific competencies that should be taught during premedical training and in medical school, and explicitly covers evolutionary biology, genetics, and genomics (download the full report from http://www.hhmi.org/grants/pdf/08–209_AAMC-HHMI_report.pdf). Nesse et al. (2010) substantially expand on these core competencies and provide further recommendations for integrating evolutionary biology into medical education. The "Future Physicians" report makes the case that because scientific knowledge and medical practice continually grow in response to new discoveries, one goal of medical school must be to train doctors to integrate and apply new clinical and scientific knowledge into their daily work, and to absorb the "fundamental scientific principles that are key to lifelong learning and biomedical scientific literacy" (AAMC-HHMI 2009, p. 3). As an integrative scientific discipline at the core of the life sciences, evolutionary biology has a role in helping physicians and biomedical researchers understand how the human body works and why it sometimes fails.

## Proximate and Ultimate Evolutionary Contexts for Disease

Human diseases are in part a reflection of the evolutionary history that shaped our genetic make-up and responses to our current environment, including the parasites and pathogenic microbes that plague us. But understanding evolutionary history provides only one perspective on disease. As pointed out by Ernst Mayr (1961) and Niko Tinbergen (1963), traits have both proximate and ultimate causes (see also Nesse and Williams 1994). Proximately, diseases arise from combinations of biochemical, physiological, and immunological responses of individuals to the environment and to pathogens. In this sense, disease can be defined mechanistically in terms of malfunctions, disorders, anatomical flaws, and infections that cause morbidity and/or death. Ultimately, however, the causes of diseases can be explained in three parts—by ancestry and common descent of organisms, by variation in the environment over time, and by ongoing genomic and evolutionary forces (Williams and Nesse 1991; Nesse and Williams 1994; Nesse and Stearns 2008). A key to understanding vulnerability to disease is that adaptive evolution increases fitness in terms of reproductive success, and not health, over many generations. Natural selection will compromise health and survival if that increases overall reproductive success, and natural selection may not keep pace with the rapid or recent environmental changes in industrial and postindustrial societies.

The viewpoint that diseases are shaped by both proximate and ultimate causes represents one of the central concepts underlying evolutionary medicine. It is important to recognize that evolution may not act to shape disease per se, but rather that evolution acts on traits that mediate vulnerability to disease. For example, the potential to form cancers is an inherent risk of multicellularity. Moreover, symptoms such as vomiting and fever may actually be defenses against disease by reducing the effects of pathogens. Legacies of evolutionary history, including interactions between an individual's genetic susceptibilities, immune system responses, and environmental exposure to poor nutrition, toxins, and pathogens, are important ultimate explanations for disease. Ongoing natural selection may also influence disease, for example, through the genomic mechanisms that underlie many cancers or parent–parent and parent–offspring conflicts for resources. These conflicts begin with different genomic contributions by the parents, and continue through prenatal development and into childhood. Further, human bodies are not optimally designed, but represent a series of developmental, biophysical, and physiological compromises driven by trade-offs that contribute

to risks of injury and disease. On another level, natural selection acts rapidly on microbes via their short generation times and high mutation rates, and microbes rapidly evolve resistance to immune defenses, drugs, and vaccines, often with tragic consequences. The evolutionary approach to the health sciences has clear implications for research on the prevalence of disease within human populations, improved public health practice, and ultimately more effective care for the sick (Nesse and Stearns 2008; Stearns and Koella 2008; Wolfe et al. 2007; Omenn 2010).

## Evolution and Medicine in the Undergraduate Curriculum

The goal of biology courses, from introductory to advanced, is twofold: for students to learn how to think scientifically, and for students to master content in biology. Understanding the nature and process of science informs personal and policy decisions, with local, regional, and global impacts, and some knowledge of biology can be helpful for everyone in making life decisions. Education research suggests that one way to support those goals is to teach with key concepts such as biological evolution (Bransford et al. 2000; Ambrose et al. 2010). This "big picture" approach helps students build a reference framework to categorize information, which facilitates building connections between new and old content, and improves student retention and ability to transfer information. The ability to categorize and connect information is one of the traits that enable experts to navigate easily through disciplinary content. The AP Biology revisions (College Board 2011) and the Vision and Change report (NSF/AAAS 2011) emphasize teaching key concepts including evolution. Evolution is an excellent theme for teaching about the nature of science (National Academy of Sciences 1998), and a poor understanding of the nature of science is correlated with a low acceptance and understanding of evolution (Johnson and Peeples 1987). Undergraduate biology educators can serve all their students well by introducing an evolutionary view into their courses, beginning with introductory biology.

Using examples from evolutionary medicine to engage all students—premedical, majors, and nonmajors—in learning about biological evolution may be a particularly effective approach to support students' development both as scientific thinkers and biologists (e.g., see Hillis 2007). As we show below, applying basic evolutionary principles to human health leads to interesting, novel, and useful conclusions. Students who are not typically excited by basic evolutionary concepts may be drawn in by focusing on human health. Exploring the research behind theories such as the "stone age diet" and the hygiene hypothesis gives students an accessible entry to discovering the nature and process of science. In particular, this approach demonstrates that premedical students should learn evolutionary biology for the same reasons they study biochemistry, physics, and mathematics—because broad scientific knowledge gives future medical practitioners the tools to understand how a patient may have developed sets of symptoms, and how to best to treat the patient.

Evolutionary medicine is easily incorporated into undergraduate curricula, through specific examples illustrating basic evolutionary concepts as well as more complex ideas. Here, we highlight key aspects of evolutionary medicine in the form of familiar evolutionary concepts. Additional examples are provided in the evolution-focused science competencies in the AAMC-HHMI Report (2009), in an expanded analysis by Nesse et al. (2010), and in Boxes 2–10. A growing number of resources are available to support advanced courses or seminars on evolutionary medicine, courses that should complement those in evolution, phylogenetics, and population genetics. These include Nesse and Williams' (1994) classic as well as more recent collections (Stearns and Koella 2008; Trevathan et al. 2008) and a textbook (Gluckman et al. 2009). The website *Evolution and Medicine Review* (http://evmedreview) provides a resource for sharing news about events and relevant articles, as well as a list of syllabi and other resources useful for educators (Box 2). The December 2011 issue of *Evolution: Education and Outreach* includes by Stearns (2011b), Omenn (2011), and Alcock and Schwartz (2011) that provide specific suggestions for courses linking evolution to medicine and public health. Other articles in the same issue provide excellent examples of the synthesis of evolution and medicine in cancer (Casas-Selves and DeGregori 2011), vaccine development (Hanley 2011), and scurvy (Buklijas et al. 2011) and highlight a new module for teaching evolution and medicine (Beardsley et al. 2011).

However, we will know that evolution has truly become an integral part of premedical scientific training when testing competency in evolution becomes part of gaining admission to medical school. The AAMC-HHMI report recommends that "assessment of the newly defined scientific competencies must be credibly and reliably accomplished by the Medical College Admission Test (MCAT®) exam" (AAMC-HHMI 2009, p. 2). The just-released (November 2011) preview of the revised MCAT® for 2015 specifically includes evolution in section 1C on *Transmission of heritable information from generation to generation and the processes that increase genetic diversity* and in section 9A on *Understanding social structure* (https://www.aamc.org/students/applying/mcat/mcat2015/). Although this is a positive step forward, indicating support from the medical community for increasing evolutionary thinking in medical education, evolution biology is still not listed as one of the "Foundations of Living Systems" or integrated throughout the lists of life sciences topics to be tested. Our undergraduate premedical students should be willing to learn evolutionary medicine, but greater synthesis is possible.

## *Biomedical Examples of Evolutionary Concepts*

With the goal of continuing development of an interdisciplinary and integrated framework for evolutionary medicine in the undergraduate curriculum, we provide some principles of evolutionary biology aligned with medical examples that students may find particularly enticing.

### GENETIC VARIATION IS THE MATERIAL FOR EVOLUTIONARY PROCESSES

Evolutionary medicine can provide engaging illustrations of the genotype to phenotype connection, and students' experience with variation in disease presentation is a familiar way to demonstrate genetic variation. In-depth genetic studies generally show that even commonly taught diseases that at first appear to have a relatively simple genetic basis are found to be more complex. Multiple functional and mutant alleles combine with environmental effects to cause variable symptoms and disease severity (Templeton 2006). This is clearly demonstrated by phenylketonuria (PKU), a condition caused by mutations in the single-copy gene encoding phenylalanine hydroxolase and tested for in neonatal health screening. PKU arises from the inability to metabolize the amino acid phenylalanine, the buildup of the amino acid and phenylketones, and eventually microcephaly, incomplete brain development, seizures, and severe learning disabilities. Although in most cases, disease can be avoided by excluding foods rich in phenylalanine from the diet, the treatment is not equally effective for all variants, and the frequencies of both functional and mutant alleles differ among human populations. This is a familiar problem to evolutionary biologists: although genetic variation is the stuff of evolution, it is seldom straightforward to map genotypic (now genomic) variability onto phenotypic differences between individuals and populations (see Boxes 3 and 4).

### COMMON DESCENT IS A RESULT OF EVOLUTION

Students often miss (or reject) this basic concept in their first introduction to evolution, but examples from evolutionary medicine can help drive this idea home. Common ancestry explains why biomedical research in animals is applicable to humans (Antolin 2009). But some caution is in order, as in the case of differences between humans and mouse strains in the P450 family of enzymes important for drug metabolism, which limits the mouse as a model for drug testing for humans (Nelson et al. 2004). Further, it is important for medical practitioners to be aware that each patient has a different ancestry (evolutionary history), and therefore a different genetic makeup, different reactions to drugs, and often different disease symptoms (Meyer 1999; Omenn 2010). In managing health care, such differences can result in life, death, or long-term disability and morbidity. Individual patients' presentation of disease will depend on complex interactions at the convergence of patients' genetic legacies, the evolutionary history of pathogens to which they are exposed, and the environmental context where the patients and pathogens meet. Combining concepts of ancestry with individual-level genetic variation culminates in the newly emerging approach of "personalized medicine" (Knight 2009; Costa et al. 2010; Jiang and Wang 2010; see Box 5).

### ADAPTATIONS WITHIN POPULATIONS ARISE THROUGH THE PROCESS OF NATURAL SELECTION IN PARTICULAR ENVIRONMENTS

A common misconception among students is that "fittest" is the biggest, strongest, or fastest. Examples from evolutionary medicine demonstrate that fitness depends on how rates of reproduction and environmental circumstances interact (see Boxes 3, 4, and 6). For example, "diseases of civilization" imply a mismatch hypothesis: alleles that cause disease in modern times may have been adaptive in the past, but produce traits that are maladaptive (mismatched) under current diet and living conditions. A corollary is that modern humans may be changing their environment more rapidly than potential responses to selection can occur. The mismatch hypothesis provides some of the best ultimate explanations for modern rates of obesity, heart disease, type-2 diabetes, breast and prostate cancer, goiter, iodine deficiency, birth defects, and aging (Harper 1975; Eaton et al. 1988; Williams and Nesse 1991; Greaves 2002; Diamond 2003; Swynghedauw 2004; Gluckman et al. 2009).

The understanding that contemporary genetic diseases and conditions may be consequences of adaptive mismatches can help explain the persistence of maladies in the face of improved sanitation and living standards. Genetic disease varies among human populations because both long-term population sizes and histories of natural selection determine how many disease-causing mutations they carry (Antolin 2009). As an example, the prevalence of specific allelic variants of the *CFTR* gene that cause cystic fibrosis, a debilitating and in the long-term fatal genetic disorder, is potentially linked to selection imposed by past outbreaks of tuberculosis (Poolman and Galvani 2007). This is similar to the long-established link between sickle cell anemia in individuals who inherit at least one copy of the *S* allele of the *HBB* globin gene, but where heterozygotes have some degree of resistance to malaria (Allison 1954). In addition to leading to better diagnoses and treatments, seeing diseases as unfortunate genetic legacies inherited from the past may also help ameliorate some of the social stigma associated with genetic diseases.

A related concept is that we are specifically adapted to the premodern environment in which humans were primarily hunter-gathers, before the domestication of plants and animals. Central to this concept is that humans are adapted to a stone-age "environment of evolutionary adaptation" (EEA). We caution against

uncritical use of the EEA, as the view is speculative, struggles to account for differences among ancestral human populations that probably experienced different environments, and ignores ongoing human evolution (also see Strassmann and Dunbar 1999; Méthot 2011). Nonetheless, the concepts of a mismatch and an EEA provide opportunities to introduce students to the scientific process, with discussion, gathering of information, and forming testable hypotheses.

## PHENOTYPIC EXPRESSION OF TRAITS OFTEN VARIES ACROSS A RANGE OF ENVIRONMENTAL CONDITIONS AND PROVIDES A PREDICTIVE FRAMEWORK FOR POTENTIAL RESPONSES TO SELECTION

Evolutionary biologists view phenotypic plasticity—the ability for organisms to display a range of phenotypes in different environments—as a way to maximize fitness under variable environmental conditions (also see Box 7). In health and medicine, phenotypic plasticity may explain why early developmental problems may lead to disease in adults (Bateson et al. 2004). An example of developmental trade-offs leading to disease in later life is increased susceptibility to heart disease in adults related to periods of nutritional deficiencies and slowed growth in fetal development and early childhood. The damage is potentially higher if subsequent weight gain (catch-up growth) is too rapid when better nutrition becomes available. In the case of growth rates and body size, adult heart disease is a cost of rapid growth following nutritional stress, and should be considered during care of low birth weight or premature babies (Bateson et al. 2004; Gluckman et al. 2009).

## LIFE SPAN EVOLVES IN THE CONTEXT OF TRADE-OFFS BETWEEN TRAITS THAT INFLUENCE FITNESS EARLY VERSUS LATER IN LIFE

Weak selection on the diseases of aging helps explain their persistence in modern times, especially as postreproductive longevity increases (also see Box 8). In evolutionary biology, fitness accrues via reproductive success summed across all stages of an individual's life history, and reproductive events early in life contribute more to fitness than do those late in life. The evolutionary theory of aging suggests that early-life fitness components including developmental rate, age at first birth, and fecundity early in life are linked by trade-offs to fecundity and mortality later in life. If these trade-offs result from the same genes acting at both life stages, selection on early-life traits will increase their frequency even if they negatively impact fitness-related traits later in life, a genetic effect called antagonistic pleiotropy (cf. Williams 1957). The role of testosterone in males provides an example. Although increased testosterone has clear benefits for maximizing male reproductive success, this may come at the expense of disease resistance because increased testosterone also reallocates immune function away from immune reactions that protect against infections (Braude et al. 1999; Bribiescas and Ellison 2007). Higher reproductive success early in life may come at the expense of disease and morbidity, especially if infections are chronic. Whether the correlation between testosterone and altered immune function represents a genetic trade-off, or whether reallocation represents adaptive phenotypic plasticity, may be determined using modern genomic analyses and association studies. Another striking trade-off is embodied in stem cells. Stem cells are essential for the differentiation and renewal of all tissues, but their genetic characteristics place them only a few mutational steps away from cancer cells, and almost all cancers originate through a short series of somatic mutation in stem cells, which are increasingly being revealed as a double-edged sword (e.g., Janzen et al. 2006; Krizhanovsky and Lowe 2009).

### *Evolutionary rate is dependent on generation times*

Exploring evolution on a microbial time scale can help students understand the roles of genetic variation and reproductive success in evolution (Box 9). Short generation time, huge populations, high mutation rate, genetic reassortment, and horizontal gene transfer in microbes and viruses ensures that infectious diseases will evade therapies and vaccines in the future, and that new diseases will continue to emerge from reservoirs in wild animals: an "arms race against an adaptable opponent" (Lederberg 2000). This dynamic view of disease accounts for the variability in human-adapted pathogens such as influenza viruses and malaria, where evolutionary escape hinders development of vaccines with long-lasting protection and results in multidrug resistance. Medical practice is directly impacted by rapid evolution of resistance to antimicrobial drugs as well as avoidance of natural and vaccine-induced immunity (Bergstrom and Feldgarden 2007; Nesse and Stearns 2008). Understanding how pathogen variability arises leads to public health interventions that may reduce exposure and limit chains of transmission (Galvani 2003).

## HUMANS HAVE COEVOLVED WITH A VARIETY OF COMMENSAL AND PATHOGENIC ORGANISMS

In our germophobic society, students need to realize that we have a long evolutionary history with microbes and parasites, and that these organisms are not always debilitating even if they cause mild disease (also see Box 10). In some cases, microbes are helpful, and removing all commensals can be unhealthy: consider the occurrence of vaginal yeast infections in conjunction with systemic antibiotic use (Eckert et al. 1998; Reid 2001). As we learn more about the complex interactions between humans and the diverse microbial species that colonize our bodies, we discover just how important commensal organisms are to our well-being (e.g., Grice and Segre 2011). Many gut bacteria play important roles in our

nutrition, such as the bacterium *Escherichia coli* in the large intestine providing us with the essential vitamin K, which we cannot produce ourselves.

Some pathogens and parasites may, paradoxically, also be necessary to our well-being. Obsession with hygiene in some industrialized societies has for the first time in our evolutionary history relieved us of our helminth parasites. Strachan (1989) first proposed the "hygiene hypothesis" that attributed the recent epidemic in asthma, allergy, and other autoimmune diseases to this loss of our old companions (Bach 2002; Osada and Kanazawa 2010). This hypothesis predicts that restoration of helminth infections, or some facsimile thereof, should relieve symptoms of at least some of these diseases. Indeed, in a clinical trial, the majority of Crohn's disease patients who ingested pig whipworm (*Trichuris suis*) experienced disease remission (Summers et al. 2005), and more studies indicating the utility of helminth infections to treat autoimmune disease have followed (Reddy and Fried 2009). Particularly, striking is the observation that patients with both multiple sclerosis and worm infections experience a much slower development of disease than do those lacking worm infections (Correale and Farez 2007). Finally, our long evolutionary history with pathogens has led to many defensive adaptations, including fever, coughing, and vomiting. Medical practitioners need to be aware of symptoms that are actually defenses, because it is possible that in some cases, treating symptoms may prolong the course of infections and opportunities for pathogen transmission (Williams and Nesse 1994; Carey 2010).

## George Williams and the Last Word

In a memoir (The Edge blog [http://www.edge.org/documents/williams_index.html], downloaded 17 June 2011), George Williams sums up why evolutionary medicine should resonate in the community of evolutionary biologists, and how evolutionary thinking can help physicians to become better practitioners:

> In twenty or thirty years, medical students will be learning about natural selection, about things like balance between unfavorable mutations and selection. They will be learning about the evolution of virulence, of resistance to antibiotics by microorganisms, they will be learning about human archaeology, about Stone Age life, and the conditions in the Stone Age that essentially put the finishing touches on human nature as we now have it. These same ideas then will be informing the work of practitioners of medicine, and the interactions between doctor and patient. They'll be guiding the medical research establishment in a fundamental way, which isn't true today. At the rate things are going, this is inevitable. These ideas ought to reach the people who are in charge—the doctors and the medical researchers—but it's even more important that they reach college students, especially future medical students, and patients who go to the doctor. They'll have questions to ask that doctor, who will have to have answers. I hope this set of ideas produces a certain amount of bottom-up influence on the medical community, via students and patients. But I hope also that there's some top-down influence—that it will be influencing the faculties in medical schools and the researchers on human disease.

George Williams' work spurred us to ask "What is the role of evolutionary biologists in promoting evolutionary thinking in medical education and practice?" We encourage evolutionary biologists working in schools of medicine and public health, as well as colleges and universities where evolutionary research and instruction occurs, to explore relationships between evolution and health. We encourage evolutionary biologists to reach out to premedical students and others preparing for the medical professions, and to directly connect evolutionary science to the intellectual development of physicians and public health practitioners at every phase of their education and training.

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## *Box 1. A brief history of links between evolution and medicine. Michael F. Antolin.*

The historic relationship between medicine and evolutionary biology has been mixed, and traditionally evolutionary biology has not played a prominent role in medical training. Even so, general natural history was part of the medical school curriculum when Charles Darwin attended Edinburgh in 1824–1826, but evolution certainly was not (Antolin 2011a,b). Darwin had familiarity with links between evolutionary biology and medicine through his grandfather Erasmus Darwin's volume "Zoonomia," which included both a Linnaean classification of disease and a clear statement about transmutation and common descent in nature (Darwin 1801). Darwin also consulted with his father, the physician Robert Waring Darwin, on human heredity and disease (Bynum 1983). The question of heredity was briefly covered issues in the "Descent of Man" (Darwin 1882) and in "Variation of Plants and Animals Under Domestication" (Darwin 1875), along with observations on the similarity of diseases (and responses to medication) in humans and apes, differing disease prevalence among human populations, effects of disease on aboriginal populations coming into contact with Europeans, and sex-limited maladies such as hemophilia and gout. As evolutionary biology developed as a field, various scientists and physicians also advocated for inclusion of evolutionary thinking in medicine (e.g., Huxley 1881; Aitken 1885; Morton 1926; see Zampieri 2009).

In the late 1800s, most applications of evolution in medicine were holistic, fitting in with the traditional medical ideas of "constitutions" and "diatheses." These were defined as tendencies to display groups of maladies in general ways, for instance "tubercular" individuals (Bynum 1983; Zampieri 2009). At the same time, the medical sciences were moving discovering specific causes for specific ailments, resulting in improved diagnosis and treatment (Porter 1998). As an example, the use of anesthesia and aseptic methods in surgery was developed during this period. The work of Pasteur, Koch, and others in identifying microbes and the birth of germ theory made it possible to identify the pathogens underlying common diseases such as whooping cough, syphilis, and cholera. Further, industrialization and concentration of human populations in cities created new public health challenges that needed attention (Porter 1998). As the mechanisms underlying evolution and genetics were explored during the late 1800s and early 1900s, so were the physiological, developmental, genetic, and microbial bases of disease.

The Flexner Report of 1910 marked a major turn toward placing medicine on a firm scientific footing. This classic of medical education explicitly called for bringing medical education onto a uniform foundation of human biology (Flexner 1910), and for experimental analysis of physiology, development, endocrinology, biochemistry, and anatomy of specific tissue and organ systems. Flexner also called for broad coverage of the general sciences as part of medical training and practice. This period saw a step toward a reductionist view of the causes of disease, diverging from previous holistic medical approaches. Although medical knowledge grew rapidly, medical applications from the emerging field of evolutionary biology were not as clear and, as a result, the evolutionary viewpoint was not broadly incorporated into medical school curricula.

Evolution was not mentioned in the Flexner Report, but one response to the report was for medical schools to establish departments of anthropology to bring human natural history, via classes in comparative anatomy and geographical medicine, explicitly into medical training (Morton 1926). This period spanning 1910 through the 1940s also saw the Modern Synthesis in evolutionary biology and breakthroughs in evolutionary research. But evolutionary biology still was not incorporated into medical training. In part, this was because the successful clinical application of antimicrobial drugs during this same period led to the idea that infectious diseases would soon to be completely manageable (Burnet and White 1972; Anderson 2004). Ironically, it is evolutionary biology that explains why pathogenic microbes remain an ongoing challenge (e.g., see Box 9).

But three serious misunderstandings and abuses of evolutionary theory resulted in evolution being expunged from medical training by the late 1940s (Porter 1998; Zampieri 2009). The first was related to the previously mentioned "constitutions," "diatheses," and "degeneracy" used to explain disease vulnerabilities in certain racial groups and in women. The misapplication of this typologically racist and sexist thinking to disease, which was wrongly tied to evolutionary principles, was largely dealt with by implementation of Flexner's (1910) recommendations. The mechanistic understanding of disease attenuated societal biases of race and gender, although social disparities in the delivery of medical treatment still persist. The second reason was the horrific application of eugenics in the first half of the 20th century

culminating in the genocidal Nazi regime in the 1930s and 1940s in Europe (Zampieri 2009). To be sure, eugenics was a malignant social policy that arose from misapplication of the science of evolution, and was discarded by evolutionary biologists after the population genetics of mutation and natural selection were better understood (J. B. S. Haldane [1964] provides an amusing essay defending mathematical theories of population genetics, including the balance between mutation and selection that was overlooked by eugenicists, and some lovely verse about his own life-ending fight with colorectal cancer). But the backlash was severe enough that even today many scientists within biomedical fields do not fully acknowledge how much evolutionary science informs medicine (Antonovics et al. 2007; Nesse and Stearns 2008). The third reason was that the dominant reductionist scientific paradigm advocated by Flexner (1910) trained scientists to reject teleological thinking, which was mistakenly conflated with the process of natural selection, a misunderstanding that persists among some to this day. Currently, few medical schools teach evolutionary topics beyond human genetic variation, drug resistance, pathogen virulence, and adaptation by natural selection (Nesse and Schiffman 2003; Downie 2004; Childs et al. 2005; Harris and Malyango 2005).

## *Box 2. Exploring the nature of science with evolutionary medicine. Randolph M. Nesse.*

Much of the new interest in evolutionary approaches to medicine has come from addressing questions about why natural selection has left the body vulnerable to disease. Why does the human eye have a blind spot? Why does the appendix persist despite causing appendicitis? Why are autoimmune diseases becoming more prevalent in recent decades? Why has not natural selection shaped childbirth to be less painful and risky? Why are humans so vulnerable to drug and alcohol abuse? What is the evolutionary explanation for aging? Is menopause a life-history trait shaped by selection, or an epiphenomenon?

Students are quickly engaged in discussions about such interesting questions. The challenge for educators is to help them think critically about the questions, without getting prematurely discouraged by the substantial challenges of forming and testing evolutionary hypotheses about disease vulnerability. For many questions, such as the adaptive significance of menopause, the unknowns are so substantial that consensus remains elusive despite extensive research. Some may see this as a reason to teach simpler topics. However, students already get plenty of experience memorizing the answers to scientific questions. Topics in evolutionary medicine give them an opportunity to grapple with current questions. Students will tend to latch onto a favorite hypothesis and try to defend it. This gives educators an opportunity to emphasize the importance of considering all possible hypotheses, and strategies for determining which are correct and which are false. In contrast to proximate studies, evolutionary questions often have more than one answer, in the sense that multiple factors may be involved in accounting for a trait. Emphasizing this can help students recognize the need to consider multiple possibilities. In short, topics in evolutionary medicine are well suited to advancing a major goal of modern education—helping students to learn how to formulate hypotheses, how to go about the scientific process of testing them, and how to cope with the inevitable complexity and confusion that attend almost any scientific endeavor. Some of the more common errors are summarized in an article that lists 10 questions worth asking for any evolutionary study of disease (Nesse 2011).

## *Box 3. Environmental genome scans identify genetic variants and phenotypes that underlie differences in disease susceptibility among populations. Angela Hancock.*

Human populations span a tremendous diversity of environments, and our ability to inhabit such a broad range of habitats results in part from genetic adaptations. The availability of genome-wide data on genetic variation from diverse populations offers unprecedented opportunities to identify the loci responsible for these adaptations and elucidate the genetic architecture of human adaptive traits.

Some of the earliest and most convincing evidence of adaptation to the environment comes from correlations between phenotypes and environmental variables. Classic examples of these patterns include correlations between sickle cell anemia, β-thalassemia and malaria endemicity (Haldane 1949; Allison 1954), body mass and temperature (Roberts 1978; Katzmarzyk and Leonard 1998), skin pigmentation and solar radiation (Jablonski and Chaplin 2000), and lactase persistence and dairying (Simoons 1969). For several of these examples, the genetic variants underlying these

patterns are now known (Enattah et al. 2002; Lamason et al. 2005; Sulem et al. 2007; Tishkoff et al. 2007; Piel et al. 2010). Using genome-wide data, it is now possible to turn this approach around to scan the human genome to identify genetic variants that correlate with predicted environmental selective pressures, even without knowing the phenotypic adaptations that may drive the associations between specific alleles and the environment. Association studies of this kind have been carried out for variation related to climate, subsistence, diet, and pathogen diversity (Fumagalli et al. 2010; Hancock et al. 2010; Hancock et al. 2011). Integrating results from these environmental genome scans with studies of genotype–phenotype association and other sources reveals the relationships between disease risk and adaptation to the environment. For example, scans show that alleles correlated with diet and subsistence influence folate and energy metabolism. In addition, among genes with strong correlation with climate, many have alleles or genotypes implicated in traits such as pigmentation phenotypes and other aspects of ultraviolet radiation response, cardiovascular disease, immune response, and cancer. Together with ongoing efforts to identify variants associated with disease phenotypes in diverse populations (Rosenberg et al. 2010), environmental genome scans and scans for adaptive genetic loci can identify the genetic variants that underlie differences in disease susceptibility among populations (e.g., Nielsen et al. 2009; Pickrell et al. 2009; Grossman et al. 2010).

## *Box 4. Functional genetic variation is often geographically restricted and population specific. Andres Moreno-Estrada.*

It is repeatedly stated in medical practice that each case is unique and should be treated individually, but in most cases the underlying factors determining such variation remain poorly understood. Part of the answer however may lie in our genes and thus in our evolutionary history. For example, broad patterns of population structure among humans are largely the result of ancient demographic events. The bottleneck during the Out of Africa exodus of modern humans about 50,000 years ago contributed substantially to reduced heterozygosity in individuals living outside of Africa and remains the most remarkable demographic imprint reflected in their genomes (Cavalli-Sforza and Feldman 2003). In contrast, fine-scale population structure stems from recent demographic processes, reflecting local mating within populations living in geographically circumscribed locations. The impact of inbreeding on the frequency of rare diseases has been demonstrated in historically isolated groups, such as the Ashkenazi Jewish population (Reich and Lander 2001). If geographic regions throughout the world are finely structured, as suggested by global genomic surveys (Auton et al. 2009), it may be predicted that populations in some regions harbor disease-risk alleles that are population specific and otherwise rare in humans. For example, Acuña-Alonzo et al. (2010) recently reported that a novel cholesterol transporter ABCA1 gene variant (R230C, rs9282541) is exclusive to Native Americans and has been associated with low levels of high-density lipoprotein (HDL), obesity and type 2 diabetes in admixed populations in Mexico (Villarreal-Molina et al. 2008). The authors also identified signatures of positive natural selection around the ABCA1 variant, suggesting that R230C carriers could have had a selective advantage during the initial peopling of the Americas. Because the C230 ABCA1 protein shows decreased cholesterol efflux, the presence of this variant could favor intracellular cholesterol and energy storage, conferring an advantage during severe famine periods. However, under current westernized lifestyle, this allele may have become a major susceptibility allele for low HDL-C levels and other metabolic traits. It becomes clear that genetic variation observed today, including medically relevant variation, is the consequence of the interplay between different evolutionary forces acting over time during human population history. Therefore, medical students would benefit from learning evolution theory, as it will allow them to better understand genomic variation and its implications in health and disease.

## *Box 5. Cancer and evolution. Subhajyoti De.*

Cancers account for almost 13% of all human deaths worldwide (Jemal et al. 2011), representing a major medical problem for the modern world. It is not a single disease, but an ensemble of diseases with common principles. All cancers harbor groups of cells that show uncontrolled growth, invasion of neighboring tissues, and metastasis to distant organs (Hanahan and Weinberg 2011). Ultimately, most cancers cases result in death. Cancer arises via accumulation of mutations and selection—a case of aberrant evolution of somatic cells during the lifetime of the host, although instances of transmissible cancer are also known (Murgia et al. 2006). Although somatic cells in healthy individuals often harbor many mutations without any apparent consequences

(De 2011), cancer cells carry specific mutations that result in immortality, uncontrolled growth, and the ability to metastasize (Hanahan and Weinberg 2011). Many of the key mutagenic processes that are active in cancer cells also operate in germ-line evolution, which together with selection, gives rise to population- and species-level divergence in genomes over thousands or millions of years. Moreover, many of the genes and pathways associated with cancer are also present in other organisms such as yeast or fruit flies. For instance, the first discovery of a class of cancer genes, the rat sarcoma (RAS) family, was in rat (Harvey 1964; Kirsten et al. 1970). Therefore, much can learned about the mechanistic bases of cancer, and we may exploit weakness of cancer cells to develop better diagnostic and prognostic strategies by borrowing knowledge from germ line evolution. Genetically modified animals provide insights into cancer-related biological processes; and even today we test new cancer drugs on mice for efficacy and side effects before prescribing them to human patients. We are now moving into an era of personalized diagnostics and treatment, which will require low cost, rapid analysis using more minimal biological samples more than ever before. Evolutionary medicine can help to achieve these goals by translating knowledge from evolution into clinical strategies.

## *Box 6. Public health and evolution. Gilbert S. Omenn.*

Public health courses are emerging as popular undergraduate offerings, especially at universities with schools of public health. Evolution has shaped burden of disease in the modern world in which we practice public health (Omenn 2010). Human cultures and technologies have modified life on planet Earth and have coevolved with myriad other species, including microorganisms, plant and animal sources of food, invertebrate vectors of disease, and intermediate bird, mammal, and primate hosts. Molecular mechanisms of evolution have produced differential resistance or susceptibility to infectious agents, including malaria, plague, smallpox, TB, measles, and diarrheal and respiratory diseases. The domestication of sheep and cattle has selected for humans able to digest milk throughout life through persistence into adulthood of lactase enzyme expression in the intestine, a major story of anthropology (Itan et al. 2009). The emergence of a "Western diet" of dairy, refined cereal grains, refined sugars, vegetable oils, alcoholic beverages, salt, and omega-6-rich meats has dramatically altered glycemic load, fatty acid composition, macronutrients, acid-base balance, sodium/potassium ratio, and fiber content. The results include epidemics of atherosclerotic cardiovascular disease, obesity, diabetes, high blood pressure, osteoporosis, certain cancers, and bowel, inflammatory, and autoimmune disorders (Cordain et al. 2005). A newly recognized phenomenon is the selection of excessive hemostatic activity from platelets and the plasma-clotting proteins; what was protective against death from bleeding after injuries among hunter-gatherer, warring humans, or against pregnancy-related hemorrhage now contributes to thrombosis underlying heart attacks and strokes. Conversely, there is little pressure against hemostasis and thrombosis because deaths resulting from blood clots and coronary disease associated with hemostasis and thrombosis occur mostly after the reproductive years of life (Coller 1997). Learning about evolution over millennia for humans and over hours or days for microbes enlivens the experience of understanding evolution in public health context.

## *Box 7. Vulnerabilities to human psychiatric disorders have evolved. Bernard J. Crespi.*

Synthesis of data from multiple disciplines has led to hypotheses for understanding the evolutionary-genomic underpinnings of autism spectrum conditions and psychotic-affective spectrum conditions, mainly schizophrenia, bipolar disorder, major depression, and borderline personality disorder (Crespi and Badcock 2008). The synthesis integrates inclusive fitness theory, comparative primatology, and developmental psychology with information from mouse gene knockouts, human genomic disorders, psychiatric genetics, and human and mouse gene expression.

The primary hypotheses focus on autism and psychotic-affective conditions as diametric disorders mediated by opposite alterations to the development of human-elaborated social-brain and sexual-brain phenotypes. By this hypothesis, social-brain architecture develops predominantly in the context of mother–child interactions, whereby early, basic mother–child attachment, underlain in part by paternally expressed imprinted genes, serves as a scaffold for development of the highly social, neocortical brain. In turn, development of the highly social neocortical brain is mediated in part by effects of maternally expressed imprinted genes. Alterations to the expression of imprinted genes (genes that are silenced under inheritance from one or the other parent, and that evolve under genomic conflict, (see Haig [2004]) play important roles in early social-brain development, with

deviations toward relative paternal-gene expression increasing risk of autism. Deviations toward relative maternal-gene expression increase risk of psychotic-affective spectrum conditions (Crespi and Badcock 2008; Crespi 2011). Autism and psychotic-affective conditions are thus hypothesized to arise in part through epigenetic variation that influences maternal–paternal genomic conflicts.

More generally, the human social brain may underdevelop in childhood, manifesting as autism spectrum conditions, or selectively and relatively over-develop, usually in adolescence or early adulthood, leading to psychotic-affective spectrum phenotypes and conditions. Cognitive and affective variation between females and males strongly modulates liability to these conditions. Thus, major epidemiological and phenotypic features of autism and psychotic-affective conditions can be predicted from interactions between a male–female brain continuum and a maternal–paternal imprinting bias continuum (Crespi and Badcock 2008)

This conceptual framework spans two levels. First, the diametric nature of autism versus psychotic-affective conditions is modulated by multiple genetic, genomic, epigenetic, and social-environmental causes based in human brain evolution. Second, this diametric nature may arise from imprinted genes, which can be dysregulated in two opposite directions. The framework makes novel, testable predictions with direct implications for cognitive-behavioral and pharmacological therapy, human evolution, the molecular evolution of psychiatric risk genes, and human brain development. One important prediction, that imprinting is relatively common among genes that underlie risk of autism and schizophrenia, is supported by analyses of data from a recent genome-wide study of imprinted genes in mice (Gregg et al. 2010).

## *Box 8. Can any organisms be potentially immortal? Staphen C. Stearns.*

Weismann (1882) suggested that only organisms with a soma and germ line would age, and that organisms that divided symmetrically would not age. Recent experiments have shown just how precisely symmetric that division would have to be. Their results suggest that all known organisms must age, for even a bacterium like *E. coli* divides into two nonidentical cells, one of which contains older parts than the other and ages faster (Stewart et al. 2005). The lineages with the old parts suffer a fitness disadvantage and disappear, and the lineages with the young parts persist. The goal of potential immortality (barring accidents) may also be unattainable if another basic claim of the evolutionary theory of aging remains unrefuted: aging and death result not from a single mechanism that can be repaired but from the diffuse degradation of multiple processes across the entire genome and body (Williams 1957). Repair of one problem will simply reveal the next in line, and that process will repeat hundreds or thousands of times. The byproducts of repair are also expected to connect through trade-offs to costs paid in other traits. Recently, some genes with major effects on aging have been discovered in other organisms, but they are involved in trade-offs with reproductive performance early in life, and whether those trade-offs can be compensated remains to be seen (Stearns 2001a). The evolutionary view of aging is not optimistic about life-extending genetic therapies, but it may provide some needed wisdom about the human condition.

## *Box 9. Why does antibiotic resistance persist after antibiotic use stops? Carl T. Bergstrom.*

The evolution and spread of antibiotic resistance powerfully illustrates the basic process of natural selection. Bacterial populations manifest variability in antibiotic susceptibility; some of this variation is heritable; in the presence of antibiotics, less-susceptible strains survive and reproduce more rapidly. The inevitable result—as we have seen with every antibiotic yet introduced—is the evolution of resistance in bacterial populations (Genereux and Bergstrom 2005).

A related phenomenon offers an opportunity to teach more subtle aspects of evolutionary biology and population genetics (Bergstrom and Dugatkin 2011). When antibiotic use is terminated in a community, what happens to antibiotic resistance in the bacterial populations? Given that antibiotic resistance commonly imposes some cost to bacteria that express it, we might predict that when a particular antibiotic is discontinued, resistance to that antibiotic should decline. Although this sometimes occurs (e.g., Seppälä et al. 1997), it is by no means guaranteed. Sometimes resistance to the drug persists long afterward. One example is sulfonamide resistance in Great Britain, which has not declined even though sulfonamides were essentially discontinued in the mid-nineties (Bean et al. 2005). Why?

A number of multilocus evolutionary processes may contribute, including the phenomenon of associated

linkage selection (Levin et al. 1997). Because bacteria have haploid genomes and limited opportunities for recombination, most bacteria exhibit strong linkage along the entire circular chromosome. As a result, hitchhiking and related processes are very important. In the process of associated linkage selection, resistance to a new drug arises on a chromosome or plasmid carrying resistance alleles for older drugs. This generates positive linkage disequilibrium between the new and old resistance alleles. Even if an older drug is discontinued, the resistance alleles to this drug may be indirectly favored by selection for resistance to the newer drug. Associated linkage selection can thus explain why older resistant strains are not outcompeted by unrelated sensitive strains: those sensitive strains are less likely to carry resistance to whatever new drugs are currently in use.

But associated linkage selection does not explain how resistant strains are able to avoid being replaced by mutants that retain resistance to the new antibiotic but revert to sensitivity to the old one. To make sense of this, we turn to another phenomenon: compensatory mutation. Although resistance mechanisms impose fitness costs, compensatory mutations can ameliorate these costs and restore fitness of a resistant strain—in the absence of the antibiotic—to near that of the sensitive strain (Schrag and Perrot 1996; Andersson and Hughes 2010). An obvious consequence is that compensatory mutations reduce the selective difference between resistant and sensitive strains in the absence of antibiotic use, and thus slow the rate at which sensitive strains are able to replace resistant ones.

Many compensatory mutations have a more subtle effect as well. They make it difficult for bacteria to revert to full sensitivity, by creating a fitness valley between the resistant, compensated strain and the sensitive uncompensated strain (Levin et al. 2000). This occurs because the compensatory mutation, while beneficial in the presence of the resistance mutation, is deleterious in its absence. Because it is easy to "get in" to the resistant compensated state in the presence of the antibiotic but difficult to get out in its absence, this phenomenon has been described as an evolutionary lobster trap (Tanaka and Valckenborgh 2011).

## *Box 10. How evolution can make, or break, a live-attenuated virus vaccine. Kathryn H. Hanley.*

Although the negative impacts of rapid microbial evolution are well understood, humanity has turned the evolutionary lability of viruses into a means of fighting disease. "Applied evolution" has been used to generate many live-attenuated virus vaccines, including those against measles, mumps, rubella, varicella (chickenpox), influenza, and poliovirus (FDA 2011). In this classical approach, pioneered by Pasteur in his effort to create a rabies vaccine, wild-type virulent viruses are serially passaged in a novel host or in a novel temperature regime. The resulting adaptations to the new environments results in loss of fitness in the original host (Plotkin 2001). A successfully attenuated virus shows decreased virulence in humans while retaining the ability to stimulate an immune response. This process can require as few as 28 passages, as for the varicella vaccine (Takahashi et al. 2008), or hundreds, as was needed for the yellow fever vaccine (Monath et al. 2008). However, one of the drawbacks of classical vaccine design is that the phenotype of the virus, that is, its attenuation, determines genotype. Thus, although it is clearly desirable to secure attenuation by multiple or large attenuating mutations (Burch et al. 2003), the mutations responsible for attenuation of many live-attenuated virus vaccines are either unknown or, in the case of the three strains of the oral poliovirus vaccine (OPV) (Kew et al. 2005), few in number.

Predictably, ~1 in every 750,000 children receiving their first dose of OPV experience vaccine-associated paralytic polio due to reversion of virulence in the vaccine (Kew et al. 2005). Revertant strains may be transmissible between humans and thus threaten the success of the global effort to eradicate polio. In contrast, the nasal influenza vaccine carries attenuating mutations on four of its eight genomic segments, and to date has never reverted to virulence within a vaccinee (Tosh et al. 2008). Fortunately, reverse genetics (rational vaccine design) informed by evolutionary thinking suggest novel approaches to safeguard the attenuation of live vaccine viruses. For example, Vignuzzi et al. (2008) have attenuated poliovirus by enhancing the fidelity of its RNA-dependent RNA polymerase and thereby slowing its mutation rate. Because this virus is less likely to mutate, it is less likely to revert to a less-faithful, and more fit, polymerase. Finally, live vaccines may not only evolve themselves but may also shape the evolution of their wild-type counterparts. There is evidence that some veterinary vaccines are driving the evolution of antigens in their wild-type targets (Park et al. 2011), but the impacts of such evolution on virulence and transmission are not yet known. At the extreme, vaccines have the potential to eradicate their wild-type targets, potentially creating an empty niche into which new viruses may emerge from human or zoonotic reservoirs (Rieder et al. 2001; Rimoin et al. 2010; Vasilakis et al. 2011).